Roland Seifert

Basic Knowledge of Pharmacology

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Preface

Numerous excellent pharmacology textbooks in English language are available. These books are particularly useful for obtaining well-validated information on a specific topic. However, for a student who needs to learn the principles of pharmacology, these books have become too voluminous as the result of the explosion in knowledge. In addition, most textbooks are multi-author books, entailing different writing styles, foci, didactic concepts, and terminology.

Already, during my tenure as associate professor for Pharmacology and Toxicology at the University of Kansas, Lawrence, KS, USA (1998–2004), students had asked me to develop my lecture overheads into a concise textbook. But research kept me too busy to tackle this task. Later, at the University of Regensburg (2004–2008), I taught all aspects of basic and clinical pharmacology, and students kept on asking me to write a textbook. Again, research was a priority and prevented me from writing the book. During my tenure as professor for Pharmacology at the Hannover Medical School, teaching further professionalized with sophisticated pathophysiology- and pharmacotherapy-oriented PowerPoint slides, the plan to write "the textbook" consolidated. I made the book my priority. In August 2018, the German textbook entitled *Basiswissen Pharmakologie* appeared, and students and colleagues have adopted the book quickly.

Talking to pharmacology professors from around the world, the view corroborated that internationally there is, indeed, also the need for a concise textbook, particularly for the medical students. Based on the positive feedback from the German medical students and colleagues, I decided to develop the international textbook entitled *Basic Knowledge of Pharmacology*.

The book is primarily written for medical students, but it is certainly also useful for pharmacy students. The book is designed to complement a semester or 4–5-week block course of pharmacology (lectures in the morning, afternoon free for studying) and focuses on pharmacotherapeutic principles based on pathophysiology.

▶ Chapters 1, 2, 3, and 4 deal with the basic principles of pharmacology, drug allergy, and drug intoxications. The book covers about 400 selected drugs, discussed according to integrative systems (▶ Chaps. 5, 6, 7, 8, 9, 10, 11, and 12) and indications (▶ Chaps. 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34 and 35). Clinical cases are presented as well (▶ Chap. 36). Various drug classes are discussed in different contexts (learning spiral). In the text, figures, and tables, cross-references to related content are provided. This facilitates jumping from one chapter to another. Lastly, I included a chapter (37) on 100 important drugs that every physician should know well, regardless of the specialization. With these 100 drugs, many important diseases can be treated effectively and economically.

Each chapter contains an abstract, key points, tables on the most important drugs and diseases, pathophysiology- and pharmacotherapy-oriented figures, selected key references for further reading, case studies, and MCQ exam questions. Where appropriate, tables and figures also contain key take-home messages in the legends. In the appendix, a list of drug classes and generic drugs is provided, arranged according to ▶ Chaps. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34 and 35.

In the figures, green color indicates pathophysiological changes, blue color indicates pharmacotherapeutic interventions, and

red color points to toxic interventions or adverse reactions. In the book, drugs are classified according to their mechanism of action or, where more appropriate, according to their chemical properties. Traditional but imprecise, biased or outdated terms are avoided (see ▶ Chap. 1 and list of generic drugs). The book uses abbreviations (see abbreviation list) throughout. At first, the student may have to adapt to the abbreviations. But soon, the student will realize that the acronyms are helpful for precisely defining drug classes, specific drugs, drug targets, diseases, indications, adverse drug reactions, and interactions.

Pharmacology is interdisciplinary, and the knowledge in the field has expanded tremendously during the past 10 years. Very sadly, as a result of the specialization of medicine and "modernization" of curricula, in several universities, pharmacology departments have disappeared, and pharmacology has been integrated into lectures on specific organs and diseases. While this "integrative" approach is now widely adopted, the focus on pharmacology gets lost, and it just becomes an "add-on" to the clinic. However, an in-depth understanding of the mechanisms of actions of drugs is essential for understanding indications, adverse drug reactions, and drug interactions. Hopefully, this concise textbook is helpful at maintaining and enriching still existing pharmacology courses for the medical students and leads to their reinstitution when already dissipated.

I am aware of the cultural dimension of pharmacology, i.e., pharmacotherapy is performed differently in various countries. Therefore, I did not strictly adhere to clinical guidelines by particular learned societies but rather tried to explain the basic principles. Each professor is invited to adapt the principles laid out in this book to her/his particular situation in a given country. I also realize that it is impossible to generate a list of drugs that is unanimously approved by all pharmacologists. However, the proposed list of drugs covers all major indications except for tropical diseases. I plan to cover the latter topic in the next edition of the book.

After studying this book, the student should have a good overview on the most important drug classes and should be able to critically assess their value for the treatment of important diseases. I welcome any suggestions and critique to improve future editions of this book.

Roland Seifert
Hannover, Germany
April 2019

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About the Author

Photo: Karin Kaiser, Hannover

Roland Seifert, MD, PhD

studied medicine at the Free University of Berlin (Germany) and obtained his PhD (habilitation degree) in Pharmacology and Toxicology in 1992 in the Pharmacology School of Günter Schultz. From 1995 to 1998, he was a postdoc at Stanford University, CA, USA, with Brian K. Kobilka. From 1998 to 2004, he was associate professor for Pharmacology and Toxicology at the University of Kansas, Lawrence, KS, USA. From 2004 to 2008, he served as director of the Institute of Pharmacology and Toxicology of the University of Regensburg (Germany). Since 2008, he has been the director of the Institute of Pharmacology and since 2019, additionally, director of the Research Core Unit Metabolomics at the Hannover Medical School (Germany). He is author of more than 240 peer-reviewed original papers and 40 reviews, predominantly in the fields of GPCRs and cyclic nucleotides. He is editor of several books, including two volumes of the *Handbook of Experimental Pharmacology*, and is the editor in chief of the oldest existing pharmacological journal, *Naunyn-Schmiedeberg's Archives of Pharmacology*. In 2018, he published his textbook *Basiswissen Pharmakologie* which he has now developed for an international audience. Seifert has been teaching all aspects of pharmacology to medical, pharmacy, and natural science students since 1986. He has received numerous teaching awards, both in the USA and Germany, for his continued outstanding teaching.

Abbreviations

AA	Arachidonic acid
AC	Adenylyl cyclase
ACE	Angiotensin-converting enzyme
ACEI	ACE inhibitor (ACE, angiotensin-converting enzyme)
ACh	Acetylcholine
AChE	Acetylcholinesterase
ACS	Acute coronary syndrome
ACTH	Adrenocorticotropic hormone
AD	Alzheimer's disease
ADHS	Attention deficit hyperactivity syndrome
ADME	Absorption, distribution, metabolization, elimination
ADPKD	Autosomal dominant polycystic kidney disease
ADR	Adverse drug reaction
AF	Atrial fibrillation
AICAR	5-aminoimidazole-4-carboxamide ribonucleotide
AMD	Age-related macular degeneration
AP	Angina pectoris
5-ASA	5-aminosalicylic acid
AR	Androgen receptor
ASA	Acetylsalicylic acid
AT_1R	Angiotensin-II receptor, subtype 1
ATO	Arsenic trioxide
ATRA	All-trans retinoic acid
$\alpha_x AR$	α-adrenoceptor (x, subtypes 1 and 2)
BBB	Blood-brain barrier
BK_2R	Bradykinin receptor, subtype 2
BP	Blood pressure
BPH	Benign prostatic hyperplasia
$\beta_x AR$	β-adrenoceptor (x, subtypes 1–3)
CAD	Cationic amphiphilic drug
CAH	Carbonic anhydrase
cAMP	Cyclic AMP (a second messenger)
CaSR	Calcium-sensing receptor
CB_1R	Cannabinoid receptor, subtype 1
CCB	Calcium channel blocker
CCK_2R	Cholecystokinin receptor, subtype 2
CCR5	CC chemokine receptor 5
CD	Crohn's disease
CDK	Cyclin-dependent kinase
CFTR	Cystic fibrosis transmembrane conductance regulator
cGMP	Cyclic GMP (a second messenger)
$[Ca^{2+}]_i$	Intracellular free calcium concentration
CGRP	Calcitonin gene-related peptide
CGRPR	Calcitonin gene-related peptide receptor
CHD	Coronary heart disease
CHF	Chronic heart failure
CKD	Chronic kidney disease
CO	Cardiac output
COMT	Catechol-O-methyltransferase
COPD	Chronic obstructive pulmonary disease
COX	Cyclooxygenase (subtypes 1 and 2)
CPB	Cardiopulmonary bypass
CTZ	Chemoreceptor trigger zone
CYP	Cytochrome-P_{450} isoenzyme (CYPXXX; subtype classification with combination uppercase letter - Arabic number - uppercase letter)
$CysLT_1R$	Leukotriene D_4 receptor
DA	Dopamine
DAT	Dopamine transporter
DM	Diabetes mellitus
DOAC	Direct-acting oral anticoagulant
DOR	δ-opioid receptor
DPP4	Dipeptidyl peptidase 4
D_2R-mGPCR antagonist	Antagonist at multiple GPCRs with preference for D_2R
D_xR	Dopamine receptor (x, subtypes 1–5)
DVT	Deep vein thrombosis
EC_{50} (ED_{50})	Concentration (dose) at which an agonist reaches 50% of its maximum effect
ECL	Enterochromaffin-like
ED	Erectile dysfunction
EE	Ethinylestradiol
EGF	Epidermal growth factor
EMB	Ethambutol
EPI	Epinephrine (adrenaline)

EPR	E-type prostaglandin receptor
EPS	Extrapyramidal symptom
ER	Estrogen receptor (subtypes α and β)
ET_AR	Endothelin receptor, subtype A
FI	Fusion inhibitor (HIV therapy)
FPR	F-type prostaglandin receptor
FSH	Follicle-stimulating hormone
5-FU	5-fluorouracil
GABA	γ-aminobutyric acid
$GABA_AR$	γ-aminobutyric acid receptor, subtype A
G-CSF	Granulocyte colony-stimulating factor
GC	Glucocorticoid
GCR	Glucocorticoid receptor
GERD	Gastroesophageal reflux disease
GFR	Glomerular filtration rate
GI	Gastrointestinal
GLP-1	Glucagon-like peptide 1
GLP-1R	Glucagon-like peptide 1 receptor
GPCR	G-protein-coupled receptor
GTN	Glyceryl trinitrate
$G_{(x)}$ protein	Heterotrimeric guanine nucleotide-binding protein (x, subtype s, i, o, or q)
HA	Histamine
HAART	Highly active antiretroviral therapy
HCMV	Human cytomegalovirus
HCN4	Hyperpolarization-activated cyclic nucleotide-gated channel 4
HCV	Hepatitis C virus
HDC	Histone deacetylase
HER2	Human epithelial growth factor receptor 2
HERG channel	Human ether-à-go-go-related gene channel
HIT	Heparin-induced thrombocytopenia
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HMG CoA reductase	3-hydroxy-3-methylglutaryl-coenzyme A reductase
HR	Heart rate
HRT	Hormone replacement therapy
HSV	Herpes simplex virus
5-HT	5-hydroxytryptamine (5-HT, serotonin)
$5\text{-}HT_xR$	5-hydroxytryptamine (5-HT, serotonin) receptor (x, subtypes 1–7)
H_xR	Histamine receptor (x, subtypes 1–4)
I	Inhibitor (of an enzyme or of a cytokine)
IC_{50} (ID_{50})	Concentration (dose) at which an antagonist or an enzyme inhibitor reaches 50% of its maximum inhibition
IGCR	Inhaled glucocorticoid receptor agonist
IFN	Interferon
IL-X	Interleukin; X designates the specific interleukin
i.m.	Intramuscular
INH	Isoniazid
INI	Integrase inhibitor (HIV therapy)
INN	International nonproprietary name
INR	International normalized ratio (this parameter is used to adjust VKA therapy)
IOP	Intraocular pressure
IPR	Prostacyclin (PGI_2) receptor
IUD	Intrauterine device
i.v.	Intravenous
KOR	κ-opioid receptor
LABA	Long-acting β_2-adrenoceptor agonist (controller)
LAMA	Long-acting M_3R antagonist
LH	Luteinizing hormone
LMWH	Low-molecular-weight heparin
LOX	Lipoxygenase
LSD	Lysergic acid diethylamide
LT	Leukotriene
LTRA	Leukotriene receptor antagonist
MAO	Monoamine oxidase (subtypes A and B)
MAOI	Monoamine oxidase inhibitor
MCP	Metoclopramide
MCR	Mineralocorticoid receptor
MCRA	Mineralocorticoid receptor antagonist
mGPCR antagonist	Antagonist at multiple GPCRs
MHV	Mechanical heart valve
MI	Myocardial infarction
MOR	μ-opioid receptor

6-MP	6-mercaptopurine
MRP	Multidrug resistance protein
MRSA	Multidrug-resistant *Staphylococcus aureus*
MS	Multiple sclerosis
mTOR	Mechanistic target of rapamycin
MTX	Methotrexate
M_xR	Muscarinic acetylcholine receptor (x, subtypes 1–5)
nAChR	Nicotinic acetylcholine receptor
NE	Norepinephrine (noradrenaline)
NE/5-HT enhancers	Drugs enhancing the effects of norepinephrine and serotonin
NEP	Neprilysin
NET	Norepinephrine transporter
NIPE	Neuron inhibitor with pleiotropic effects
NK_1R	Neurokinin receptor, subtype 1
NMDA	N-methyl-D-aspartate
NNRTI	Non-nucleoside reverse transcriptase inhibitor (HIV therapy)
NO	Nitric oxide
NPC1L1	*Niemann-Pick C1-like protein*
NR	Nuclear receptor
NRTI	Nucleoside reverse transcriptase inhibitor (HIV therapy)
NSMRI	Nonselective monoamine re-uptake inhibitor
NT	Neurotransmitter
OAT	Organic anion transporter
OR	Opioid receptor (subtypes M (μ), D (δ), and K (κ))
OTC	Over the counter
PAD	Peripheral arterial disease
PAH	Pulmonary arterial hypertension
PAI	Platelet aggregation inhibitor
PAR1	Protease-activated receptor 1 (thrombin receptor)
PARP-1	Poly(ADP ribose) polymerase 1
PCSK9	Proprotein convertase subtilisin/kexin type 9
PDE	Phosphodiesterase (subtypes 3, 4, and 5 are clinically important)
PE	Pulmonary embolism
PI	Protease inhibitor (HIV and HCV therapy)
PG	Prostaglandin
PK	Protein kinase
PLA_2	Phospholipase A_2
PLC	Phospholipase C
p-mGPCR antagonist	Antagonist at multiple GPCRs with pleiotropic effects
PML	Progressive multifocal leukoencephalopathy
p.o.	Per os (peroral)
PP	Proton pump
PPAR	Peroxisome proliferator-activated receptor (receptor subtypes α and γ)
PPI	Proton pump inhibitor
PR	Progesterone receptor
PTH	Parathyroid hormone
PTHR	Parathyroid hormone receptor
PUD	Peptic ulcer disease
$P2Y_{12}R$	Purinergic receptor for ADP predominantly expressed on platelets
PZA	Pyrazinamide
R	Receptor
RAAS	Renin-angiotensin-aldosterone system
Raf	Rapidly accelerated fibrosarcoma protein kinase
RANK	Receptor activator of nuclear factor κB
RANKL	Receptor activator of nuclear factor-κB ligand
RMP	Rifampicin
ROS	Reactive oxygen species
RTK	Receptor tyrosine kinase
SABA	Short-acting β_2AR agonist (reliever)
SAMA	Short-acting M_3R antagonist
s.c.	Subcutaneous
SCB	Sodium channel blocker
SERM	Selective estrogen receptor modulator
SERT	Serotonin transporter
sGC	Soluble guanylyl cyclase
SGLT-2	Sodium/glucose cotransporter 2
SJS	Stevens-Johnson syndrome
SM	Streptomycin
SNP	Sodium nitroprusside
s/p	Status post
$S1P_1R$	Sphingosine-1-phosphate receptor, subtype 1

SSNRI	Selective 5-HT/NE re-uptake inhibitor
SSRI	Selective 5-HT re-uptake inhibitor
SVR	Systemic vascular resistance
t ½	Half-life
T3	Liothyronine
T4	Levothyroxine
TB	Tuberculosis
TD_{50}	Dose at which a drug (active component) reaches 50% of its maximum toxic effect
TDM	Therapeutic drug monitoring
TdP	*Torsade-de-pointes* arrhythmia
TEN	Toxic epidermal necrolysis
THC	Tetrahydrocannabinol
TIVA	Total intravenous anesthesia
TK	Tyrosine kinase
TMP	Trimethoprim
TNF	Tumor necrosis factor
TOPO	Topoisomerase
TPO	Thyroid peroxidase
TPR	Thromboxane A_2 (TXA_2) receptor
TSH	Thyroid-stimulating hormone
TX	Thromboxane
UC	Ulcerative colitis
UFH	Unfractionated heparin
URAT1	Urate transporter 1
VEGF	Vascular endothelial growth factor
VKA	Vitamin K antagonist
V_2R	Vasopressin receptor, subtype 2
VT	Ventricular tachycardia
VZV	Varicella zoster virus
XO	Xanthine oxidase

General Principles

Contents

Introduction and Pharmacodynamics

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1

Pharmacologically active substances comprise drugs and poisons. Drugs possess therapeutically beneficial, and poisons possess deleterious effects. Drugs should be named by their INNs and not by their brand names. There are substantial cultural differences in the use of a given drug in various countries. Drugs should be classified according to their mechanism of action, and traditional slang terms should be avoided. Medicines are pharmaceutical preparations of drugs for use in humans. Development of a drug into a medicine comprises preclinical and clinical development. The latter is divided into three phases. Pharmacodynamics analyzes the effects of pharmacologically active substances on the human organism. Receptors, enzymes, ion channels, and transporters are the most important target classes for drugs. Receptors are divided into GPCRs, ligand-gated ion channels, TK-linked receptors, and NRs. Receptors are activated by agonists. Antagonists block the effects of agonists. The function of enzymes and transporters is reduced by inhibitors. Ion channel function is reduced by blockers and increased by activators. Complete concentration-response relationships are required to assess the effects of drugs with the parameters EC_{50}, IC_{50}, and intrinsic activity. The therapeutic index is a measure for the safety of a drug. Many drugs have a small therapeutic index and should, therefore, be dosed prudently. Some drugs with a small therapeutic index are even available OTC.

Key Points

1. Drugs have beneficial effects; poisons have deleterious effects.
2. The classification of a pharmacologically active substance as drug or poison depends on the specific pathophysiological context.
3. INNs of drugs should be used to avoid dependence on brand names that often have a suggestive character.
4. The word ending of an INN often provides information on the mechanism of action of a drug.
5. Slang names for drug classes such as "betablocker" or "antihistamine" should be strictly avoided.
6. Many traditional names of drug classes such as "DMARDs," "NSAIDs," "antidepressants," "antiepileptics," and "antipsychotics" lack scientific rigor and focus on a particular clinical use without being comprehensive.
7. Whenever possible, drugs should be classified according to their mechanism of action or, where more appropriate, according to their chemical properties.
8. The classification of drugs according to their mechanism of action is neutral and allows for expansion of indications without irritation or bias.
9. A mechanism-based drug nomenclature improves precise pharmacotherapy and drug safety.
10. The indications of many drug classes, specifically psychiatric drugs, have expanded substantially over the past 10 years.
11. Globally, there are substantial cultural differences in the use of individual drugs.
12. Development of a drug comprises a preclinical and clinical phase.
13. In the clinical development of drugs, it is critical to include a standard therapy as reference whenever possible.
14. Pharmacodynamics analyzes the effects of pharmacologically active substances on the human organism.
15. Receptors, enzymes, transporters, and ion channels are the most important target classes for drugs.
16. Potency designates the concentration of a drug at which its stimulatory or inhibitory effect is half-maximal.
17. Intrinsic activity describes the maximum effect of an agonist at a receptor.
18. Partial agonists possess a lower intrinsic activity than agonists; antagonists possess no intrinsic activity.
19. Long-term therapy with GPCR agonists can result in tolerance due to receptor desensitization.
20. The therapeutic index is a measure for the safety of a drug.
21. In order to ensure therapeutic efficacy, in life-threatening diseases, a smaller

therapeutic index must be accepted than in non-life-threatening diseases.
22. Some drugs with a small therapeutic index are available OTC.
23. Accordingly, even OTC drugs can cause serious intoxications when abused.

1.1 Drugs and Poisons

Pharmacology is the science that analyzes the interactions of substances with the human organism. Pharmacodynamics describes the effects of substances on the organism, whereas pharmacokinetics analyzes the effects of the organism on substances and the path of drugs through the organism (see ▶ Chap. 2). Pharmacology is situated at the interface between physiology and pathophysiology. Pharmacology aims at curing diseases or at least mitigating disease symptoms on the basis of pathophysiologically validated concepts. For certain diseases such as hypertension (see ▶ Chap. 15), very effective and economical pharmacological treatments are available. In contrast, other diseases such as arrhythmias are much more difficult to treat pharmacologically (see ▶ Chap. 17). Accordingly, the focus for such diseases is to avoid their occurrence and particularly to avoid drugs causing arrhythmias.

Pharmacologically active substances are all chemical compounds that influence body functions. The term "pharmacologically active substance" makes no predictions about the benefit or harm of its effects. Drugs possess beneficial (therapeutic) effects, whereas poisons have deleterious (toxic) effects. The definition of a pharmacologically active substance as drug or poison depends on the dose, mode of application, and the clinical situation.

As an example, if a small child accidentally ingests fruits from the deadly nightshade which contains atropine in large amounts, a muscarinic syndrome develops (see ▶ Chaps. 4 and 5). In this situation, atropine is a poison. In contrast, for bradycardia during surgery, atropine is a drug. In patients suffering from depression, NSMRIs can be mood-lifting and increase motivation. However, when large amounts of an NSMRI are ingested suicidally, the drug acts as poison and can induce severe hypotension due to M_xR and α_1AR antagonism (see ▶ Chaps. 4 and 28).

1.2 Drugs and Medicines

Medicines are pharmaceutical preparations of drugs for use in humans. In addition to the drug, a medicine also contains pharmaceutical excipients that keep the drug in solution and accelerate or delay its absorption (controlled release formulations). Medicines can cause allergic reactions (see ▶ Chaps. 3). Medicines comprise non-coated and coated tablets for oral administration, suppositories for rectal administration, transdermal systems for controlled release of a drug, and solutions for i.v., s.c., and i.m. injection, capsules for sublingual administration ensuring rapid systemic absorption and ointments, creams, eye drops, nose drops and sprays for local administration.

Medicines without drug can exert therapeutic effects as well, specifically in situations with a psychological component. Such medicines are referred to as placebos. In headache, the response rate of placebos ranges between 30 and 70% (see ▶ Chap. 10), for GI disturbances between 20 and 60% (see ▶ Chap. 12), and for insomnia between 50 and 80% (see ▶ Chap. 25). The effects of placebos are due to the suggestive power of the physician, expectations of the patient, and behavioral conditioning. Placebos can also exhibit ADRs (nocebo effect). Sleepiness, abdominal pain, and headache are typical nocebo effects and occur in up to 50% of all patients treated with placebos.

The effects of a given medicine in humans are not always identical but may differ substantially, depending on a multitude of factors. Ethnicity, sex, age, reproductive function, dietary habits, comorbidities, ethanol consumption, liver and kidney function, hormonal status, co-medication with other drugs, and genetic polymorphisms of receptors and enzymes all affect drug efficacy. While it is impossible to discuss all these variables systematically within the constraints of this basic text, important examples where these factors act will be discussed where appropriate.

1.3 International Nonproprietary Names (INN) Versus Brand Names

The international nonproprietary names (INNs) are the universal drug names. These names are used globally. There are only few exceptions from this rule. For example, in the USA and the UK, the β_2AR

agonist salbutamol is also referred to as albuterol. In these countries the non-MOR agonist paracetamol is also referred to as acetaminophen. In this book, drugs are exclusively designated by their INNs.

In many cases, one can derive the mechanism of action of a drug from its INN. For example, the ending _olol designates β_xAR antagonists, the ending _triptan designates 5-HT_{1D}R agonists, the ending _stigmine designates reversible AChEIs, and the ending _pril designates ACEIs (see list of drugs in appendix). However, there are also many exceptions from this general rule, specifically concerning long-established drugs for which the mechanism of action was not yet known when the INN was allocated. Unfortunately, the student has to "learn by heart" certain drug names such as paracetamol, metamizole, diphenhydramine, and phenprocoumon or warfarin.

A medicine is marketed either as registered trademark under a brand name or, after patent expiration, as generic drug under the INN. Brand names are fantasy names that quite often have a suggestive character to increase sales. Table 1.1 lists some examples of brand names with suggestive character including indications and ADRs. The name "Acomplia" points to a drug without complications

Table 1.1 Examples of suggestive brand names: indications and ADRs

Brand name	Drug (INN)	Drug class	Indication	ADRs	Further contexts in Chaps.
Acomplia® (withdrawn from the drug market)	Rimonabant	CB_1R antagonists	Type 2 DM, obesity	Depression, suicidality	
Addyi® (on the drug market in the USA)	Flibanserin	5-HT_{1A}R agonists/ 5-HT_{2A}R antagonists	Female hypoactive sexual desire disorder (may not be a true disease)	Hypotension, dizziness, sleep disorders	6
Bonviva®	Ibandronate	Bisphosphonates	Osteoporosis	GERD when applied incorrectly, jaw bone necrosis	20
Champix®	Varenicline	Partial nAChR agonists	Nicotine addiction	Depression, suicidality, aggressive behavior	5
Gerodorm® (on the drug market in Austria)	Cinolazepam	Benzodiazepines	Sleep disorders in elderly people	Paradoxical reactions, synergism with ethanol and MOR agonists, heavy falls, anterograde amnesia, difficulties to drive a car	25, 30
Halcion®	Triazolam	Benzodiazepines	Difficulties falling asleep	See Gerodorm®	25, 30
Regulax® Picosulfate	Picosulfate	Laxatives	Constipation	Water and electrolyte loss, deterioration of constipation when abused chronically	13
Stelara®	Ustekinumab	IL-12/IL-23 inhibitors	Psoriasis	Increased risk of TB and certain malignant tumors, encephalopathy	11

Beware of suggestive brand names. Brand names do not tell you the truth about a drug! Brand names may differ in various countries. In communication with health professionals and patients alike, always use the INN! These names very often contain crucial information on the mechanism of action of a drug! Brand names do not contain mechanistic information on drugs. In a globalized world, the use of INNs is very helpful

and a drug accomplishing its goal. The name "Addyi" implies that the drug is adding something to you. In other words, without the drug, you are incomplete. Thus, "Addyi" is a must-have. "Bonviva" points to a good life. "Champix" promises a life like a champion and with champagne. "Gerodorm" alludes to good sleep for elderly people, and with "Halcion," happiness is there. "Regulax" proposes to regulate your bowel movements, and "Stelara" is supposedly a stellar drug. These brand names emphasize positive properties of the drugs but do not critically assess efficacy in comparison to other drugs, drug interactions, or ADRs. Brand names can differ considerably from country to country, depending on the specific language. Thus, for international communication among physicians and scientists, brand names are not suitable.

As a general rule, medicines sold under a brand name are considerably more expensive than generic drugs. Following patent expiration, the price of a brand medicine containing a specific drug decreases. Whenever possible, a physician should aim at prescribing generic drugs because in ageing societies, increasing costs for medicines constitute a serious financial threat for healthcare systems.

1.4 Cultural Differences in Drug Use

There is consensus in the scientific and medical communities about the pharmacological profile of a drug with respect to mechanism of action, pharmacokinetic properties, drug interactions, and ADRs. However, when it comes to the clinical use of a drug, opinions often diverge. As a result, there are substantial cultural differences in the use of individual drugs in various countries. Numerous factors including the historical development of each country, lobbying by drug companies, different clinical approaches to a disease, and different evaluation of the safety of a drug influence these uses (see ▶ Chap. 37). National and international guidelines for pharmacotherapy of diseases are not unambiguous as well. Commercial interests sometimes play a significant role in such guidelines. For example, it makes a big difference in terms of the number of "patients" to be treated on how hypertension (see ▶ Chap. 15) and hypercholesterolemia (see ▶ Chap. 22) are defined and interpreted as risk factors for cardiovascular morbidity and mortality.

Table 1.2 lists some examples of drugs for which cultural differences in clinical use exist. One of the most striking examples for these differences is the non-MOR agonist metamizole (also referred to as novaminsulfon or dipyrone). In many countries metamizole is not available because of (rare) agranulocytosis, whereas in others it is a prescription drug with increasing popularity (e.g., Germany), and in other countries the drug is even available OTC. The excessive and uncritical use of MOR agonists in the USA has resulted in the "opioid crisis," aggressive marketing by drug companies, and de-emphasis of ADRs being some relevant factors. In contrast, in many other countries, MOR agonists are used more reluctantly, and accordingly, these countries do not suffer from an opioid crisis.

1.5 Mechanism-Oriented Nomenclature of Drug Classes

Whenever possible, drug classes should be named according to their mechanism of action. Such a nomenclature is neutral with respect to the indications of a drug class that may change or broaden over time. In the scientific literature and in daily medical language, many problematic slang terms are used. Table 1.3 lists some problematic terms. For example, the term "blocker" should be replaced by the term "antagonist" along with the corresponding receptor. Terms containing the syllable "anti" should be avoided as well in many cases. Instead, the precise target (in most cases a receptor) and the precise mechanism (in most cases antagonism) should be used. The term "aspirin" is problematic because it is actually a brand name. However, many generic preparations of ASA are available as well. The term "cardiac glycoside" is misleading because it focuses just on the drug effects on the heart. However, these drugs inhibit a universally expressed enzyme (Na^+/K^+-ATPase) and affect every organ function. The term "DMARDs" is misleading as well because it assumes a common mechanism of action of the drugs. However, the mechanisms of action of DMARDs are actually highly diverse.

The term "neuroleptic drugs" is unprecise, alluding to an "easing effects of the drugs on the nerve." However, many drugs including NSMRIs, SSRIs, anesthetics, and analgesics possess such effects. Currently, the term "antipsychotics" is

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Table 1.2 Examples of cultural differences in the use of drugs

Drug (INN)	Drug (class)	Indication	Cultural difference	Further contexts in Chaps.
Digoxin	Na^+/K^+ ATPase inhibitors	AF, CHF	Traditionally extensive use in Germany (now strongly declining); much less commonly used in the UK and USA	16, 17
Halothane	Inhalation anesthetics	Inhalation anesthesia	Listed in the WHO list of essential medicines; no longer used in developed countries due to ADRs but still broadly used in developing countries because of its lower price compared to other inhalation narcotics	27
Heroin	MOR agonists	Very serious pain; substitution in MOR agonist addiction	Used as analgesic in several countries including the UK, USA, and Canada; not used as analgesic in Germany; relatively liberal use in the Czech Republic	2, 4, 10
Metamizole	Non-MOR agonists	Serious pain	Very broadly used in Germany; forbidden in many countries including the USA, the UK, Scandinavian countries, and Japan because of the (very low) risk of agranulocytosis. Available OTC in many countries including Russia, Poland, Mexico, Israel	3, 10, 23, 32
Phenprocoumon	VKAs	Thromboembolic diseases	Broadly used in German-speaking countries but not in the USA	18
Sildenafil	PDE5 inhibitors	ED	Prescription drug; in Poland 25 mg size OTC; discussion about OTC status in other countries	9
Spiroperidol	Highly potent D_2R-mGPCR antagonist	Schizophrenia	Licensed in Japan, not marketed in other countries	29
Warfarin	VKAs	Thromboembolic diseases	Broadly used in the USA but not in Germany; most clinical studies were performed with warfarin. The drug can be prescribed in Germany, but few physicians actually do this because the market leader phenprocoumon (Marcumar®) has engraved its name even in language: A patient is "marcumarized".	18

Be aware that in different countries, different drugs are used differently! This differential drug use may lack a scientific basis and is often deeply rooted in "tradition". Hence, always dare to ask the question whether a certain use of drugs is scientifically justified or not

used broadly, but this term is not unproblematic either. Specifically, antipsychotics are now used in many psychiatric indications and in pain therapy. In addition, the term "antipsychotic" may cause fears in the patient that she/he suffers from a psychosis which is often not the case. The same fears are relevant for chronic pain patients treated with "antiepileptics." These patients do not suffer from epilepsy, but they may actually feel worse because of the treatment with such a "strong" drug.

The term "NSAIDs" is problematic because it suggests that the drugs can be used for long-term therapy of autoimmune diseases associated with inflammation (like GCR agonists). However, the long-term use of these drugs is very dangerous. Instead, they should be used only for short peri-

Table 1.3 Problematic traditional pharmacological terms not used anymore in this book und their replacements

Problematic traditional pharmacological term	Unabbreviated replacement used in this book	Abbreviated replacement in this book	Further contexts in Chaps.
Alpha blockers	α-Adrenergic receptor antagonists	α_xAR antagonists[a]	5
Angiotensin receptor blockers (ARBs)	Angiotensin-II-receptor subtype 1 antagonists	AT_1R antagonists[a]	12, 15, 16
Anticholinergic drugs	Acetylcholine receptor antagonists	AChR antagonists (either nAChR antagonists or M_xR antagonists)	4, 5
Antidepressants	Norepinephrine/serotonin enhancers	NE/5-HT enhancers	28
Antiepileptics	Neuron inhibitors with pleiotropic effects	NIPEs	25
Antihistamines	Histamine receptor antagonists	H_xR antagonists[a]	3, 7
Antipsychotics (atypical)	Antagonists at multiple GPCRs with pleiotropic effects	p-mGPCR antagonists[a]	29
Antipsychotics (general)	Antagonists at multiple GPCRs	mGPCR antagonists[a]	29
Antipsychotics (typical)	Antagonists at multiple GPCRs with preference for D_2R	D_2R-mGPCR antagonists[a]	29
Aspirin®	Acetylsalicylic acid	ASA	18
Beta blockers	β-Adrenergic receptor antagonists	β_xAR antagonists[a]	5, 15, 16, 17
Cardiac glycosides	Na^+/K^+ ATPase inhibitors	Na^+/K^+ ATPase inhibitors	16, 17
Disease-modifying antirheumatic drugs (DMARDs)	Specific drug or drug class with corresponding mechanism is used; e.g., inhibitors of the mechanistic target of rapamycin, inhibitors of the effects of TNF	Suitable mechanism-driven abbreviation has been generated for every drug and drug class; e.g., mTOR inhibitors, TNF inhibitors	11, 13, 14
H2 blockers	H_2-receptor antagonists	H_2R antagonists[a]	7, 13
Inhaled corticosteroids (ICSs)	Inhaled glucocorticoid receptor agonists	IGCR agonists	14
Insulin sensitizers	Specific drug or drug class with corresponding mechanism or chemical properties is used; i.e., agonists at the peroxisome proliferator-activated receptor γ, biguanides	Suitable mechanism-driven abbreviation has been generated for every drug and drug class; i.e., PPRA-γ agonists, no abbreviation for biguanides	19
Mood stabilizers	Specific drug or drug class with corresponding mechanism or chemical properties is used; i.e., neuron inhibitors with pleiotropic effects, alkali metal ions	Suitable mechanism-driven abbreviation has been generated for every drug and drug class; i.e., NIPEs, no abbreviation for alkali metal ions	28

(continued)

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Table 1.3 (continued)

Problematic traditional pharmacological term	Unabbreviated replacement used in this book	Abbreviated replacement in this book	Further contexts in Chaps.
Neuroleptics (synonym for antipsychotics)	Antagonists at multiple GPCRs	mGPCR antagonists[a]	28
Non-opioid analgesics	Analgesics not acting via μ-opioid receptor agonism (negative mechanistic definition)	Non-MOR agonists	10
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Cyclooxygenase inhibitors	COX inhibitors	4, 10, 11, 12, 13, 15, 16
Opioid analgesics	μ-Opioid receptor agonists (positive mechanistic definition)	MOR agonists[a]	10
Parasympatholytic drugs	Muscarinic receptor antagonists	M_xR antagonists[a]	4, 5, 28, 29
Parasympathomimetic drugs (directly and indirectly acting)	Muscarinic receptor agonists (directly acting); acetylcholine esterase inhibitor (indirectly acting)	M_xR agonists[a] (directly acting); AChEI (indirectly acting)	5, 30
Tricyclic antidepressants (TCADs)	Specific drug class with corresponding mechanism is used; i.e., nonselective monoamine re-uptake inhibitors; drugs chemically related to nonselective monoamine re-uptake inhibitors but acting through different mechanisms	NSMRIs, non-NSMRIs (these drugs are actually mGPCR antagonists)	28

[a]This term ensures consistent, logical, and practical nomenclature across all clinically relevant GPCRs. See also abbreviation list at the beginning of the book and list of drug classes and drugs at the end of the book.
Table 1.4 provides the rationale why certain pharmacological terms are used in this book. A detailed discussion on the topic of pharmacological nomenclature has been presented recently (Seifert 2018). The terms listed here are broadly used and deeply rooted in language, but they are not scientifically correct

ods of time. The term "COX inhibitors" is much more neutral in this respect and makes no biased assumptions about clinical uses.

The term "parasympatholytic drugs" should be replaced by the term M_xR antagonist because the inhibitory effect of these drugs on sweat production actually belongs to the sympathetic nervous system. For similar reasons, the term "parasympathomimetic drugs" should not be used anymore.

Table 1.4 provides the rationale for the use of several mechanism-based names of drug classes in this book that have not been traditionally used. In many cases (alkali metal ions, biguanides, D_2R-mGPCR antagonists, mGPCR antagonists, NE/5-HT enhancers, NIPEs, and p-mGPCR antagonists) the substantial expansion of indications beyond their traditional uses renders a new mechanism-based nomenclature necessary to ensure unbiased pharmacotherapy. In some case, ADRs and uncritical use (COX inhibitors and Na^+/K^+ ATPase inhibitors) call for a renaming of drug classes. Lastly, in some cases (GCR agonists, MOR agonists, non-MOR agonists, non-NSMRIs) inconsistencies in context with the correct naming of related drug classes had to be corrected.

Table 1.4 Rationale for using certain terms for drug classes in this book

Term for drug class (abbreviations)	Representative drugs	Rationale	Further contexts in Chaps.
Alkali metal ions	Lithium	Traditionally, lithium has been designated as mood stabilizer for treatment of bipolar disorder. However, it is also used in severe depression (lithium augmentation) and schizophrenia. Lithium reduces suicidality and may have neuroprotective effects in AD. Thus, the term "mood stabilizer" is too narrow to describe the established and emerging clinical uses of lithium. The term "alkali metal ions" is neutral with respect to indications and focuses on chemical properties because lithium has multiple mechanisms of action.	28, 29
Biguanides	Metformin	Traditionally, metformin has been designated as "insulin sensitizer." however, metformin has multiple mechanisms of action and pleiotropic effects. It is used for indications beyond type 2 DM including polycystic ovarian syndrome. In addition, other indications for metformin such as AD, TB, type 1 DM, and various malignant tumors are currently been explored. Thus, the term "insulin sensitizer" is too narrow to describe the established and emerging clinical uses of biguanides. The chemical class term "biguanides" is neutral with respect to indications. Because of the multiple mechanisms of action of biguanides, it is not easy to coin a practical mechanism-oriented class designation at the time being. Hence, the class name focuses on chemical properties.	19
COX inhibitors	Ibuprofen, diclofenac	The traditional term "NSAIDs" suggests the use of these drugs in arthrosis and rheumatoid arthritis for long-term management of pain and inflammation and better tolerability than "steroids" (GCR agonists). However, long-term use of NSAIDs can lead to severe ADRs (hypertension, PUD, GERD, CKD). Thus, COX inhibitors should only be used for short periods of time for various types of inflammatory pain. The term COX inhibitor is neutral and not suggestive for a specific indication or length of therapy.	10, 12, 13, 15
D_2R-mGPCR antagonists	Levomepromazine, haloperidol	The term "typical antipsychotics" was coined to describe that these drugs cause EPSs, while the "atypical antipsychotics" were assumed not cause these ADRs. However, this assumption is not correct. In addition, the individual drugs within the group of "typical antipsychotics" differ substantially in their pharmacological profile and clinical effects. Moreover, the uses of "typical antipsychotics" now go well beyond traditional psychoses (schizophrenia) and include chronic pain, tumor pain, anxiety disorders, personality disorders, and obsessive-compulsive disorders. Thus, the term "typical antipsychotic" is too narrow to describe the current indications. The term "D_2R-mGPCR antagonist" is more neutral and readily allows for further expansion of the indications for these drugs without causing confusion.	9, 29

(continued)

Table 1.4 (continued)

Term for drug class (abbreviations)	Representative drugs	Rationale	Further contexts in Chaps.
IGCR agonists	Budesonide, fluticasone	Traditionally, the term "ICSs" has been extremely widely used, "C" being the acronym for corticosteroid. However, the term corticosteroid encompasses both natural glucocorticoids (GCR agonists) acting via the GCR and mineralocorticoids (MCs) acting via the MCR. For the anti-inflammatory effects of "ICSs," only GCR is relevant. The "ICSs" do not activate the MCR in clinically relevant concentrations. In addition, "ICSs" are synthetic, not natural. Hence, it is logical to use the term IGCR agonists, specifically in view of the fact that for systemically used GCR agonists, the term "glucocorticoid" (GC) is common. Changing the term as suggested helps to clarify that "ICSs" and "GCR agonists" act via a common receptor, the GCR.	11, 13, 14
mGPCR antagonists	Levomepromazine, haloperidol, clozapine, risperidone	The umbrella term "antipsychotics (neuroleptics)" was traditionally used to describe drugs used for the treatment of schizophrenia. The term was designated at a time when the molecular mechanism of these drugs (antagonism at multiple GPCRs) was not yet known. In addition, the use of "antipsychotics" has now expanded very broadly into many psychiatric and nonpsychiatric indications. Thus, the term "antipsychotics" is too narrow to cover the current and broadening use of these drugs. The term mGPCR antagonists is more neutral in this regard. In addition, the term alerts to the fact that via antagonism at multiple GPCRs, numerous ADRs have to be expected. And this is, indeed, the case.	9, 29
MOR agonists	Morphine, fentanyl, buprenorphine	Traditionally, the term "opioid analgesics" has been used for decades. The term had been coined before the molecular mechanism of these drugs was known. However, it is now clear that the MOR is the main target of opioid analgesics to mediate therapeutic effects and ADRs (including respiratory depression and addiction!). This is highlighted by integrating the receptor abbreviation "MOR" into the term. In addition, for the sake of consistency with drugs acting as agonists at other GPCRs, e.g., D_xRs, H_xRs, and M_xRs (see also abbreviation list and Table 1.3), the specific target receptor must be named in the drug class designation. Lastly, MOR agonists are also used for several other indications not related to pain including diarrhea, dry cough, dyspnea in acute heart failure, neonatal abstinence syndrome, and substitution in heroin addiction. These uses are not reflected by the term "analgesic." the term MOR agonists is neutral with regard to clinical uses of these drugs.	10, 13, 16

Table 1.4 (continued)

Term for drug class (abbreviations)	Representative drugs	Rationale	Further contexts in Chaps.
Na^+/K^+-ATPase inhibitors	Digoxin, digitoxin	Traditionally, these drugs have been designated as cardiac glycosides. However, this term focuses just on the heart and does not consider the fact that these drugs inhibit a ubiquitously expressed enzyme in the organism. This is an important fact because the Na^+/K^+-ATPase inhibitors have many serious ADRs, a very small therapeutic index and questionable clinical efficacy. Therefore, the term Na^+/K^+-ATPase inhibitor is much more neutral and alerts physicians to the fact that these drugs inhibit a housekeeping enzyme, causing multiple ADRs and serious intoxications.	4, 16, 17
NE/5-HT enhancers	Amitriptyline, imipramine, trimipramine, citalopram, venlafaxine, tranylcypromine	Traditionally, the umbrella term "antidepressants" has been used to cover NSMRIs, non-NSMRIs, SSRIs, SSNRIs, α_2AR antagonists, and MAOIs. However, during the past 10 years, the spectrum of use of these drugs has broadened very broadly beyond depression. Specifically, NSMRIs are used, e.g., for neuropathic pain, migraine prophylaxis, and nocturnal enuresis. SSRIs, SSNRIs, and α_2AR antagonists are used for anxiety disorders, obsessive-compulsive disorders, panic disorders, phobia, and post-traumatic stress disorder and as adjunct therapy for schizophrenia. Even the MAOIs are used for additional indications including refractory anxiety and panic disorders.	5, 6, 28
NIPEs	Carbamazepine, lamotrigine, pregabalin, valproic acid	Traditionally, these drugs have been placed under the umbrella term "antiepileptics." However, during the past 10 years, the indications for these drugs have broadened very substantially. Carbamazepine is used, e.g., for bipolar disorder, schizophrenia, and trigeminal neuralgia. Lamotrigine is used, e.g., for bipolar disorder, cluster headache, migraine prophylaxis, borderline personality disorder, post-traumatic stress disorder, polyneuropathy, and depersonalization disorder. Pregabalin is used, e.g., for polyneuropathy, fibromyalgia, and restless leg disorder, and valproic acid is used, e.g., in bipolar disorder, schizophrenia, and migraine prophylaxis. Thus, the term antiepileptic is too narrow to cover the new indications of these drugs. The molecular mechanisms of action of "antiepileptics" are pleiotropic, but all drugs have in common that they ultimately inhibit the function of pathologically active neurons. Accordingly, the term NIPEs is more neutral and makes no restrictions about indications of NIPEs.	25

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Table 1.4 (continued)

Term for drug class (abbreviations)	Representative drugs	Rationale	Further contexts in Chaps.
Non-MOR agonists	Ibuprofen, paracetamol, metamizole	Traditionally, the "non-opioid analgesics" were opposed as a group to the opioid analgesics. Since it is logical, for the sake of consistency with other drugs acting at GPCRs, to drop the term "opioid" and instead use the term "MOR," this same rule has then also to be applied to the "non-opioid analgesics." this group of drugs is not defined by a common mechanism of action, but just by a negative mechanism, i.e., no agonism at MORs. In fact, the mechanisms of actions of non-MOR agonists are heterogeneous and comprise COX inhibition (ibuprofen) and various complex mechanisms in the CNS (paracetamol, metamizole). These different mechanisms of actions are also reflected in the ADRs.	10
Non-NSMRIs	Trimipramine, opipramol	Although chemically very closely related to the NSMRIs, these drugs do not inhibit NE and 5-HT re-uptake at therapeutic concentrations. These drugs are antagonists at multiple GPCRs and, therefore, could also be placed into the group of mGPCR antagonists. In fact, the non-NSMRI (mGPCR antagonist) trimipramine possesses also some antipsychotic effects in schizophrenia.	28, 29
p-mGPCR antagonists	Clozapine, olanzapine, quetiapine, risperidone	Historically, the atypical antipsychotics have been opposed to the typical antipsychotics, assuming that the former drugs do not have EPSs. However, this assumption turned out to be incorrect. In addition, the group of antipsychotic drugs is very heterogeneous in terms of their pharmacology, the common denominator being that the drugs are antagonists at multiple GPCRs. Originally, the drugs were used to treat schizophrenia, but during the past 10 years, the spectrum of indications has broadened, and pleiotropic therapeutic effects are used. For example, olanzapine is also used for bipolar disorder. Quetiapine is used for bipolar disorder, depression, Tourette syndrome, and anxiety disorders. Risperidone is used in chronic pain, bipolar disorder, autism, and compulsive-obsessive disorder. Thus, the term p-mGPCR antagonist is neutral with respect to indications.	29

The abbreviations for the drug classes are defined in Table 1.3. The rationale for using other terms not discussed in this Table is presented in Seifert (2018). Try to use a mechanism-based drug classification whenever possible

1.6 Drug Development

Development of a drug into a medicine is time-consuming and expensive. It can easily take 10–20 years before a drug becomes an approved medicine. Nowadays, identification of a pharmacological target is mostly the first step of drug development. This target should play a key role in a given disease process. Often, identification of targets is accomplished by knockout models. In these models, mostly mice, a certain gene is inactivated, resulting in pathophysiological changes that allow for conclusions about the relevance of a particular target. Following identification of a target, in the next step pharmacologically, active compounds are developed that change the function of the target.

Drug development is the task of a discipline referred to as medicinal chemistry, an important field of pharmacy and chemistry. In general, one

aims at developing drugs that modulate the target with high selectivity, i.e., with no or minor effects on other targets. Along the way to a drug, thousands of substances have to be studied. Nowadays, crystal and electron microscopical structures of targets and use of computer-assisted methods (structure- and ligand-based design) constitute integral parts of the drug development process. Drug candidates are extensively analyzed in preclinical studies encompassing studies with recombinant proteins, cell cultures, organ models, and intact animals. Once these studies are successfully completed, the risky and costly phase of clinical development begins.

In phase 1 of clinical development, drug candidates are examined in healthy volunteers to assess safety, tolerability and pharmacokinetics. In phase 2, the drug candidate is examined for the first time in patients in terms of pharmacokinetics and efficacy. In these studies, quite often surrogate parameters are determined. Surrogate parameters are assumed to allow predictions on the long-term efficacy of drugs. The biggest hurdles in the drug development process are phase 3 studies. In these studies, the efficacy of a drug is examined in large patient cohorts with respect to valid end points. It is critical that in phase 3 studies, whenever possible, control groups with placebo and a standard therapy are included to determine true therapeutic progress. In order to obscure the lack of therapeutic progress by a new medicine, it is often stated that it is not less effective than the old medicine.

After successful completion of the phase 3 studies, the new medicine is approved to enter the drug market. However, even after approval of the new medicine, it has to be critically assessed with regard to efficacy and ADRs, because the therapeutic environment of the clinic and the doctor's office (real-world situation) often differ quite substantially from the conditions in well-controlled clinical studies. It does not happen rarely that a new medicine is being withdrawn from the drug market shortly after approval because efficacy is lower than expected or serious ADRs occur. Therefore, in general, it is a wise policy for the physician to primarily focus on well-established and inexpensive drugs and to have a critical eye on expensive "innovations."

Repurposing known drugs for new indications is another successful strategy for drug development. This strategy is broadly and effectively applied to many known neuropsychiatric drugs by testing them (often initially off-label) in various new indications for which no treatment has been available so far (see ◘ Table 1.4 and see ▶ Chaps. 25, 28, and 29). This successful development has resulted in a dramatic expansion of the indications for "antidepressants" (NE/5-HT enhancers), "antiepileptics" (NIPEs), and "antipsychotics" (mGPCR antagonists) rendering necessary renaming of these drug classes to avoid confusion among physicians and patients alike (see ◘ Tables 1.3 and 1.4 and ▶ Chaps. 25, 28, and 29).

1.7 Pharmacological Targets: Receptors, Enzymes, Transporters, and Ion Channels

Receptors, enzymes, transporters, and ion channels are the most important pharmacological target classes. In addition, DNA (see ▶ Chap. 32) and cytokines (see ▶ Chap. 11) constitute pharmacological targets. Anti-targets are targets that must not be affected by a drug because otherwise serious ADRs can result. HERG channels represent a clinically relevant anti-target because their blockade by drugs such as terfenadine (prodrug of the H_1R antagonist fexofenadine) can result in life-threatening arrhythmias (see ▶ Chaps. 7 and 17). 5-HT_{2B}R antagonists such as the anorectic drug fenfluramine can cause valvular heart defects.

◘ Table 1.5 provides an overview of receptors as pharmacological targets. Receptors bear binding sites for ligands that function according to the lock and key principle. Receptors and ligands possess conformational flexibility, i.e., they can adapt to each other. Thus, it may be more appropriate to use the terms "rubber lock" and "rubber key" principle. Due to their variability of conformations and the option to form alternative and additional contacts, receptors possess the ability to bind various ligands, enabling the development of drugs with different pharmacological profiles. Most clinically relevant drugs interact non-covalently with their receptors, using ion pair bonds (salt bridges), dipole-dipole interactions, hydrogen bonds, van der Waals, and hydrophobic interactions. Non-covalent drug-target binding is reversible. On the one hand, this limits the duration of action if the drug concentration decreases due to pharmacokinetics. On the other hand, it becomes easier to adjust a therapy according to clinical needs and to avoid the risk of intoxica-

Table 1.5 Receptors as pharmacological targets

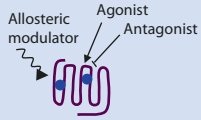
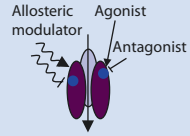
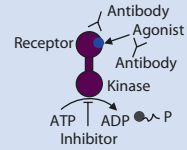
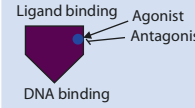
Parameter	G protein-coupled receptors (GPCRs)	Ligand-gated ion channels	Receptor tyrosine kinases (RTKs)	Nuclear receptors (NRs)
Localization	Plasma membrane	Plasma membrane	Plasma membrane	Cytosol; after ligand-binding translocation into the cell nucleus
Accessibility for drugs	Very good, hydrophilic, and lipophilic drugs	Very good, hydrophilic, and lipophilic drugs	Hydrophilic drugs (antibodies) block receptors; lipophilic drugs block the TK domain	Active substances must pass the plasma membrane; this is why drugs must be lipophilic
Characteristic structures and ligand-binding domains	Seven transmembrane domains; orthosteric ligand-binding domain for agonists and antagonists; allosteric ligand-binding domains only in few cases (cinacalcet, maraviroc) of therapeutic relevance	Oligomeric with central ion pore; orthosteric ligand-binding site for agonists and antagonists; of particular significance: Allosteric ligand-binding sites, e.g., nAChR, $GABA_AR$, and NMDAR	One transmembrane domain, extracellular ligand binding, intracellular kinase domain; protein ligands for extracellular domain with agonistic effect, antibodies against receptors and ligands; ATP-binding site in TK domain is important in tumor therapy	Protein with a ligand-binding domain and a DNA-binding domain; ligand-binding site for agonists and antagonists; receptor isoforms in various tissues and with different ligand specificity (especially suited, e.g., for treatment of mammary carcinoma and osteoporosis)
Schematics and drug targets (symbols in figures)				
Signal transduction	Activation of G proteins with subsequent activation or inhibition of effectors	Direct opening of an ion channel (receptor and effector located in the same protein); leads to hyperpolarization (chloride channel) or depolarization (sodium channel)	Complex protein-tyrosine phosphorylation cascades with multiple ramifications	Change in gene transcription with subsequent change in protein biosynthesis
Onset of action of ligands	Within seconds (fast); well suited for emergency situations	Within milliseconds (very fast); well suited for emergency situations	Within minutes to hours (moderately fast – Slow); rather for long-term therapy (exception: Insulin for treatment of hyperglycemia)	Within hours – Days (slow); long-term therapy

Table 1.5 (continued)

Parameter	G protein-coupled receptors (GPCRs)	Ligand-gated ion channels	Receptor tyrosine kinases (RTKs)	Nuclear receptors (NRs)
Examples of clinically relevant agonists	5-HT_{1D}R agonists in acute migraine; EPI in anaphylactic shock (where α_1ARs and β_xARs are relevant)	Benzodiazepines (allosteric ligands) to treat status epilepticus and to induce sedation; depolarizing muscle relaxants for short-term anesthesia	Insulin analogs with different pharmacokinetic properties to treat type 1 DM; EPO analogs for renal anemia	ER and PR agonists as components of oral contraceptives; GCR agonists to treat autoimmune diseases; SERMs to treat osteoporosis
Examples of clinically relevant antagonists	β_1AR antagonists for treatment of cardiovascular diseases; mGPCR antagonists for treatment of various psychiatric diseases	Non-depolarizing muscle relaxants for surgical interventions; allosteric NMDAR antagonists for treatment of AD	TK inhibitors for treatment of oncological diseases; TNF inhibitors (antibodies against TNF or TNFR) for treatment of autoimmune diseases	PR antagonists for abortion; MCRAs in CHF; SERMs to treat ER-positive mammary carcinoma
Further contexts in Chaps.	3, 5, 6, 15, 16, 17, 20, 29, 34	5, 25, 26, 30	11, 12, 19, 32	11, 16, 24, 32

tions at high drug doses. A clinically important example for this important concept is the possibility to rapidly annihilate the respiratory depression caused by morphine using the MOR antagonist naloxone (see ▶ Chaps. 4 and 10).

Nonetheless, there are cases in which a drug interacts covalently and irreversibly with its receptor. Irreversible blockade of the $P2_{Y12}$R by clopidogrel is an example resulting in effective inhibition of platelet aggregation (see ▶ Chap. 18).

An important task of a receptor is to ensure selectivity of the interaction with endogenous ligands. In this context, selectivity is relative. Certain receptors exhibit high selectivity, i.e., just one endogenous ligand activates receptors (examples, M_xRs, 5-HT_xRs and H_xRs; see ▶ Chaps. 5, 6, and 7). But there are also receptors that bind several ligands such as α_xARs and β_xARs that can bind EPI, NE, and DA (see ▶ Chaps. 5 and 8). In many cases such as in the therapy of asthma with β_2AR agonists (see ▶ Chaps. 5 and 14) and acute migraine attack with 5-HT_{1D}R agonists (see ▶ Chap. 6), it is desirable to use receptor ligands with high selectivity. In contrast, in other cases, such as therapy of schizophrenia with p-mGPCR antagonists (see ▶ Chap. 29), therapeutic efficacy is dependent on the interaction of the drug with multiple receptors. Another important property of receptors is that relations between drug dose/concentration and biological effect are quantitative (see ▶ Sect. 1.8). By exploiting this quantitative relationship, therapeutic efficacy of a drug can be titrated individually for each patient.

With 800 genes, GPCRs constitute the largest gene family in the human genome. GPCRs regulate virtually every body function and are readily accessible localized in the plasma membrane. So far, just few GPCRs are used clinically. GPCRs possess seven transmembrane domains connected by three extracellular and three intracellular loops, an extracellular N-terminus, and an intracellular C-terminus. GPCRs activate G proteins that modulate the activity of various effectors such as enzymes or ion channels. GPCRs mediate signaling within a few seconds. As a consequence, in many cases, rapid pharmacological effects can be achieved with GPCR ligands. Rapid-onset effects of GPCR ligands can be exploited in emergency situations. Examples for these applications are the treatment of anaphylactic shock with EPI (activation of α_xARs and β_xARs) (see ▶ Chaps. 3 and 5) or treatment of the excruciating pain in MI with the MOR agonist morphine (see ▶ Chaps. 10 and 16).

1

GPCRs possess an orthosteric binding site for the endogenous ligand and, in some cases, an allosteric site for ligands that modulate the function of the orthosteric site. Currently, ligands for the orthosteric site dominate pharmacotherapy. There are two major classes of ligands at the orthosteric site. Agonists stabilize an active conformation of the receptor, and antagonists block the effects of agonists without possessing an effect on their own (see ▶ Sect. 1.8). Examples for clinically relevant allosteric GPCR modulators are cinacalcet (see ▶ Chap. 12) and maraviroc (see ▶ Chap. 34).

Figure 1.1 shows β_xAR signal transduction and pharmacological interventions. β_xARs are activated by the first messengers EPI and NE. β_xARs couple to the G protein G_s and mediate AC activation. AC generates the second messenger cAMP from ATP. PKA is the most important cAMP-dependent effector. PKA phosphorylates target proteins that alter cell functions. In cardiomyocytes, PKA mediates positive chronotropic, dromotropic, and inotropic effects. In smooth respiratory tract muscle cells, PKA mediates relaxation (see ▶ Chap. 5). cAMP inactivation is accomplished by PDEs. EPI is used in anaphylactic shock (see ▶ Chap. 3), the β_2AR agonist salbutamol is used in asthma attacks (see ▶ Chaps. 5 and 14), and the β_1AR antagonist metoprolol is used in hypertension, CHD, and CHF (see ▶ Chaps. 15 and 16).

At the level of G_s, no therapeutically relevant interventions exist. Cholera toxin from *Vibrio cholera* causes irreversible G_s activation in intestinal epithelial cells, resulting in massive loss of

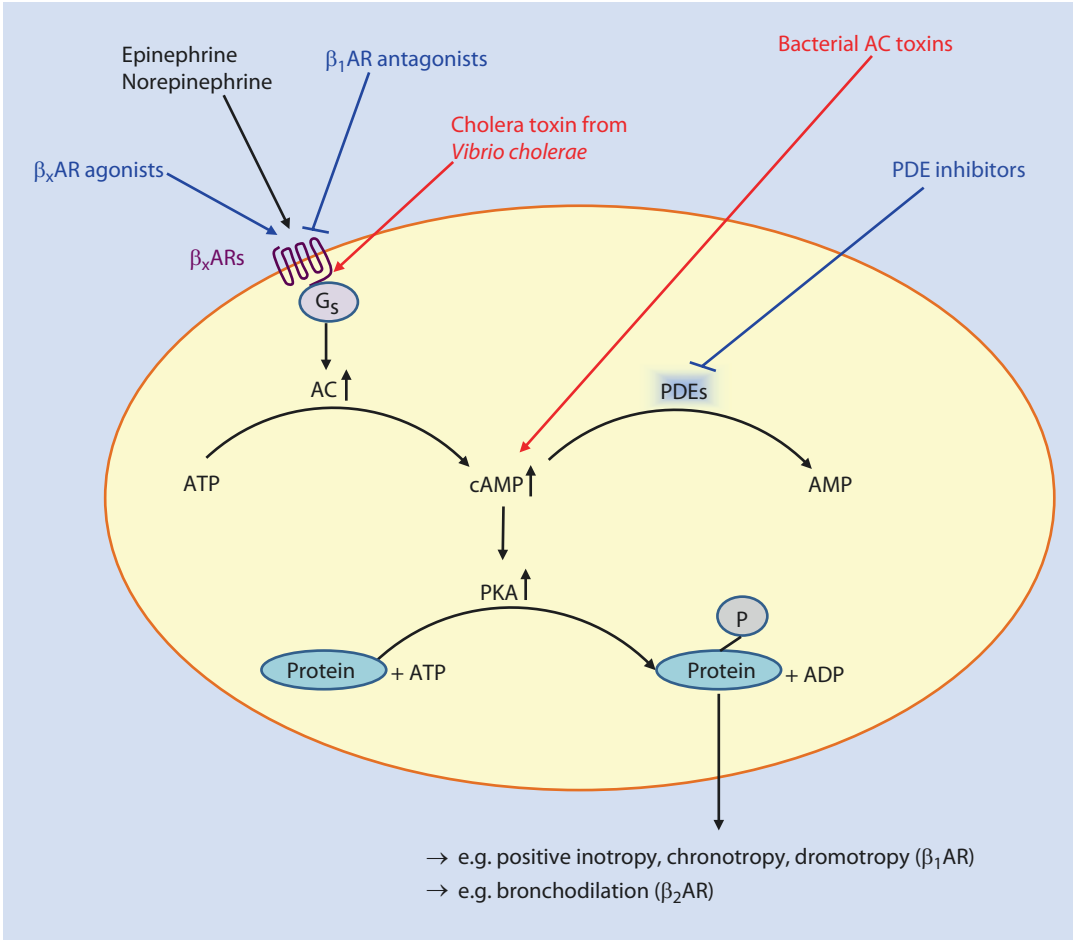


Fig. 1.1 Pharmacological modulation of GPCR-mediated signal transduction using β_xARs as example. GPCRs are excellent drug targets because they regulate almost every cell function and are readily accessible in the plasma membrane! Agonists cause desensitization, but antagonists do not. Thus, in general, long-term treatment with GPCR antagonists is less problematic than long-term treatment with GPCR agonists

water and electrolytes. The clinical manifestation, cholera, is treated with water and electrolyte substitution (see ▶ Chap. 13). AC is activated by forskolin, a diterpene from the roots of the Indian plan *Coleus forskohlii*. Forskolin is broadly advertised as "natural" drug for the treatment of obesity. Pharmacotherapeutically, forskolin does not have a role. Because of the ubiquitous expression of AC, serious ADRs result. There are also several bacterial AC toxins such as CyaA from *Bordetella pertussis*, causing whooping cough, and edema factor from *Bacillus anthracis*, causing anthrax. These bacterial AC toxins flood cells with cAMP and, thereby, cause disease symptoms. In contrast to G_s and AC, PDEs constitute well-established drug targets. PDE4 is predominantly expressed in the airways. Therefore, PDE4 inhibitors increase cAMP in bronchi and can be used for treatment of COPD (see ▶ Chap. 14). Currently, there are no clinically relevant pharmacological interventions at the level of PKA.

Tolerance due to receptor desensitization constitutes a major problem in the long-term treatment with GPCR agonists. Tolerance manifests itself as reduced efficacy of agonists following repeated administration. Long-term exposure of GPCRs to agonists leads to phosphorylation of the receptor C-terminus with subsequent binding of the adapter protein β-arrestin, uncoupling from G proteins, and sequestration of receptors in intracellular compartments. Termination of GPCR exposure to agonist results in receptor resensitization and re-translocation of the receptors to the plasma membrane. Tolerance can occur, e.g., during long-term therapy with α_1AR agonists (see ▶ Chap. 5), D_xR agonists (see ▶ Chap. 8), β_2AR agonists (see ▶ Chaps. 5 and 14), and MOR agonists (see ▶ Chap. 10). Tolerance is reversed by termination of agonist treatment. In the interval between termination of agonist therapy and receptor resensitization, the patient suffers from withdrawal symptoms and feels ill, requiring implementation of supportive therapy. In asthma, PDE inhibitors and GCR agonists can be used instead of β_2AR agonists. If the efficacy of MOR agonists decreases, non-MOR agonists and co-analgesics can be used. Long-term therapy with GPCR antagonists does not result in tolerance.

Like GPCRs, ligand-gated ion channels are localized in the plasma membrane and are readily accessible for drugs (see ◘ Table 1.5). Ligand-gated ion channels are composed of several subunits. Because the ligand-binding site and the ion channel are localized in the same protein, signal transduction is accomplished within milliseconds. Accordingly, the effects of drugs are rapid in onset which is of great relevance for emergencies and anesthesia. Currently, allosteric binding sites in ligand-gated ion channels are of greater importance than in GPCRs. An example for this notion is the benzodiazepine binding site at the $GABA_A$R that incorporates a chloride channel. Following administration of benzodiazepines, neuronal hyperpolarization occurs within very short time, resulting in sedation, muscle relaxation, and anxiolytic and antiepileptic effects. These effects of benzodiazepines are used in anesthesia (e.g., sedation and anxiolysis) and emergency medicine (e.g., treatment of status epilepticus) (see ▶ Chap. 25).

In contrast to GPCRs and ligand-gated ion channels, signal transduction via RTKs is slower, i.e., within the time frame of minutes to hours, because complex and branched phosphorylation cascades take place before the onset of biological effects. RTKs possess a single transmembrane domain (see ◘ Table 1.5). In many cases, RTKs form dimers. The extracellular domain of these receptors contains the binding site for the ligand which is a peptide or protein, mostly a growth factor. The intracellular TK is either a TK domain directly linked to the transmembrane domain or a TK non-covalently associated to the receptor. As a result of mutations, constitutively active intracellular TK (e.g., BCR-ABL) can be generated which play a major role in supporting tumor growth (see ▶ Chap. 32).

The function of RTKs can be pharmacologically modulated in both domains. In some cases, RTK agonists such as insulin and insulin analogs are used as drugs. The physicochemical properties of insulin analogs are modified in such a way that they are slowly or rapidly absorbed from the injection site. Accordingly, insulin analogs possess a long or a short duration of action (see ▶ Chap. 19). In general, it is very difficult to develop RTK antagonists because the interaction area between ligand and receptor is very large. Therefore, antibodies against ligands or receptors are used. Clinically important examples are TNF inhibitors and TNFR inhibitors that are used in the therapy of autoimmune diseases (see ▶ Chap. 11). An additional option for pharmacological intervention is inhibition of the TK activity by drugs that bind to the ATP-binding site in the catalytic cen-

ter. TK inhibitors play an important role in the therapy of tumors (see ▶ Chap. 32).

For NRs, signal transduction is much slower than for the other receptors (see ◘ Table 1.5). NRs consist of a ligand-binding domain and a DNA-binding domain. These receptors are localized in the cytosol. Upon ligand binding, they are translocated into the nucleus where they bind to specific DNA segments and activate or inhibit gene transcription. Therefore, it takes hours to days, until a pharmacological effect becomes apparent following drug administration. Accordingly, the relevance of drugs acting at NRs for emergency situations is low. The mechanism of action of NRs is also important for patient education. It must be clearly communicated to the patient that there is a latency between drug administration and onset of effect that should not be interpreted as lack of efficacy of the drug and should not lead to discontinuation of the therapy. Clinically important NRs are the thyroid hormone receptor (see ▶ Chap. 21), the GCR (see ▶ Chap. 11), the MCR (see ▶ Chaps. 15 and 16), and the sex hormone receptors (see ▶ Chap. 24). For NRs, both agonists and antagonists are available. The liver also expresses NRs that are activated rather unspecifically by xenobiotics and lead to the induction of drug-inactivating CYP (see ▶ Chap. 2).

While receptors are activated by agonists and their activation is prevented by antagonists, for enzymes, transporters, and ion channels, inhibition is the most important pharmacological intervention. ◘ Table 1.6 provides some important examples of enzymes, transporters, and ion channels as drug targets. For enzymes and transporters, the term inhibitor is used; for ion channels the term blocker is common (see list of drugs, appendix). Most drugs inhibit these targets reversibly.

However, there are also examples of clinically relevant irreversible enzyme and transporter inhibitors. With low-dose ASA (about 100 mg per day) TXA_2 formation and, thereby, platelet aggregation can be inhibited very effectively (see ▶ Chaps. 16 and 18). Irreversible inhibition of the H^+/K^+-ATPase (PP) in parietal cells of the stomach results in effective inhibition of proton secretion and is used in the therapy of GERD and PUD (see ▶ Chaps. 7 and 13). The irreversible inhibition of MAO-A and MAO-B is relevant for the therapy of resistant depression (see ▶ Chaps. 5, 6, and 28). In contrast, irreversible inhibition of AChE by phosphorylating compounds is only of toxicological relevance (see ▶ Chaps. 5, 6, and 28). Minoxidil is an example of a clinically relevant ion channel activator. It activates potassium channels and is used in resistant hypertension (see ▶ Chap. 15). Ziconotide is an example of a clinically relevant snail toxin that is used in pain therapy.

While it is always desirable to know a molecular target for a drug, there are also some important drugs for which we do not know the mechanism of action. Nonetheless, such drugs can be clinically highly effective. Examples listed in ◘ Table 1.6 are the biguanide metformin, used in type 2 DM, the alkali metal ion lithium, used in severe depression and bipolar disorder, and the analgesics paracetamol and metamizole. Probably, these drugs do not have a single mechanism of action but pleiotropic mechanisms. The therapeutic effects of these drugs were not identified by modern drug development strategies but rather by serendipity and clinical observations.

1.8 Concentration-Response Relations: Agonists and Antagonists

Concentration-response curves or dose-response curves are conventionally shown in half-logarithmic scale (see ◘ Fig. 1.2). The concentration/dose of a drug is given in logarithmic scale on the x-axis, and the pharmacological effects of the drug are shown in linear scale on the y-axis. An advantage of this procedure is that one can depict a broad range of concentrations/doses. From such curves, the inflection point (point at the sigmoidal concentration/dose at which the drug reaches its half-maximal effect) and the plateau (maximum effect of the drug) can be visualized easily, and multiple drugs can be conveniently compared with each other. Concentration/response curves are assessed when the concentration of a drug in solution can be determined precisely, e.g., in experiments with recombinant proteins, isolated cells, or organs. In case of effects of a drug in the intact organism, dose-response curves are shown, with the reference being the dose of the applied drug.

At receptors, there are two major classes of ligands, i.e., agonists and antagonists. Agonists bind to a receptor and stabilize an active conformation that allows for signal transduction (G pro-

Table 1.6 Examples of enzymes, transporters, and ion channels as pharmacological targets

Drug target class (symbols in figures)	Specific drug target	Representative drug	Drug effect	Indication	Further contexts in Chaps.
Enzymes	AChE	Neostigmine	Reversible inhibition	Myasthenia gravis	5
	COX	Ibuprofen	Reversible inhibition	Pain, inflammation, fever	10, 11
	COX-1	ASA (low dose)	Irreversible inhibition	Inhibition of platelet aggregation in CHD	18
	HMG-CoA reductase	Simvastatin	Reversible inhibition	Hypercholesterolemia	22
	MAO	Tranylcypromine	Irreversible inhibition	Refractory depression	6, 28
Transporters	5-HT transporter	Sertraline	Reversible inhibition	Depression	6, 28
	H^+/K^+-ATPase (PP)	Pantoprazole	Irreversible inhibition	PUD, GERD	7, 13
Ion channels	Potassium channels	Glibenclamide	Reversible blockade	Type 2 DM	19
	Potassium channels	Minoxidil	Reversible activation	Refractory hypertension	15
	Calcium channel (L-type)	Amlodipine	Reversible blockade	Hypertension	15
	Calcium channel (N-type)	Ziconotide	Reversible blockade	Refractory pain	10
Unknown target	Unknown, pleiotropic	Paracetamol	Analgesic, antipyretic	Mild-moderate pain	10
Unknown target	Unknown, pleiotropic	Metamizole	Analgesic, antipyretic, spasmolytic	Moderate-severe pain, colic pain	10
Unknown target	Unknown, pleiotropic	Metformin	Overall improved glucose metabolism	Type 2 DM	19
Unknown target	Unknown, pleiotropic	Lithium	Mood stabilization, mood lift, reduced suicidality	Refractory depression, bipolar disorder	28

In case enzyme inhibition causes ADRs, enzymes are highlighted with red background in all subsequent figures. The table also shows four important drugs for which the exact target is unknown

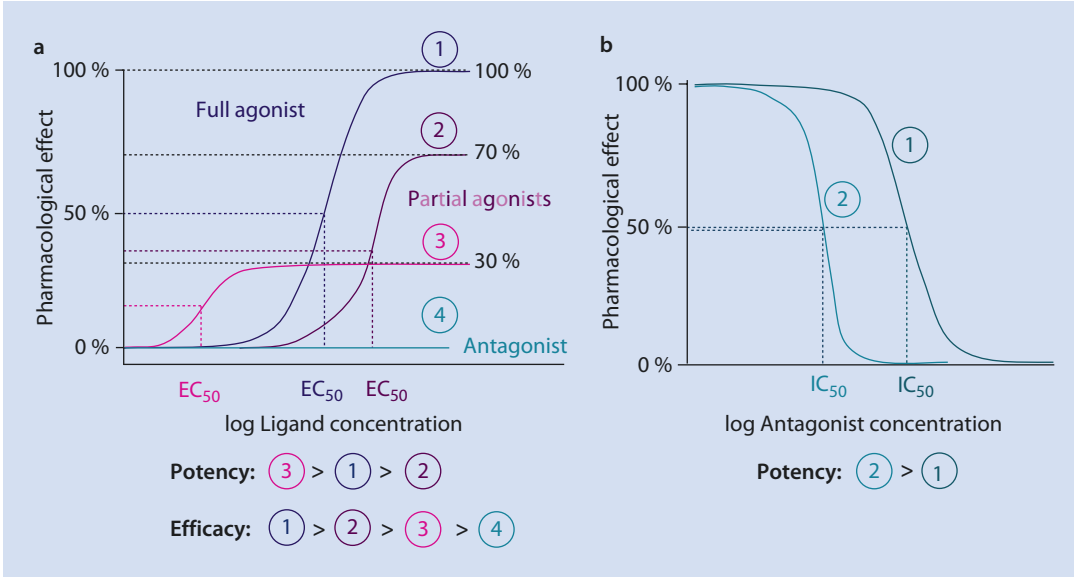


Fig. 1.2 **a, b** Concentration-response curves for agonists and antagonist at receptors. **a** Comparison of full agonists, partial agonists, and antagonists. **b** Effects of antagonists in the presence of an agonist. See also Figs. 10.2, 25.2, and 29.2. Never confuse potency with intrinsic activity (efficacy)! You always need full concentration/dose response curves to properly assess the effect of a drug. Always ask these two questions: 1. Where am I with my drug dose on the drug/response curve? 2. Is it really true that the new drug possesses a "better" clinical efficacy than the old drug or is it just a matter of having chosen drug doses that do not allow a fair comparison? And do not forget: High potency of a drug for a receptor does not automatically imply that the drug is clinically more effective! This is a crucial figure for understanding pharmacology

tein activation, ion channel opening, TK activation, gene transcription). With a few exceptions, the endogenous ligands at receptors are full agonists, i.e., they are able to maximally activate a given system. This property is used for calibration because the maximum effect of a full agonist, referred to as intrinsic activity, is defined as 100%. Receptors in the human organism are regulated by modulating the concentration of the endogenous agonist. As a consequence, mechanisms that lead to release and inactivation of an endogenous agonist are physiologically and, hence, pharmacologically important.

Antagonists also bind to receptors, but they do not stabilize an active conformation. Antagonists possess an efficacy (intrinsic activity) of 0%, i.e., in the absence of an agonist, an antagonist exhibits no effect. Partial agonists are less effective than full agonists at stabilizing an active receptor conformation. The intrinsic activity of a partial agonist is <100% and >0%. In Fig. 1.2 drug 1 possesses the highest intrinsic activity (full agonist), followed by agonists 2 and 3 (partial agonists). Drug 4 is an antagonist and does not possess intrinsic activity. Several clinically used drugs are partial agonists. Examples are the β_2AR agonist salbutamol (treatment of asthma attack; see ▶ Chaps. 5 and 14), the MOR agonist buprenorphine (treatment of moderately severe pain; see ▶ Chap. 10), the D_xR agonist bromocriptine (treatment of advanced PD; see ▶ Chap. 9), and the CB_1R agonist THC which is used for treatment of muscle spasms in MS and for pain in tumor patients (see ▶ Chap. 10).

The inflection point of the curves shown in Fig. 1.2a corresponds to the concentrations/doses at which the agonistic drugs exhibit their half-maximal effects. In case of concentrations, the term EC_{50}, in case of doses, the term ED_{50} is used. In addition to the terms EC_{50}/ED_{50}, the term potency is used, particularly for the comparison of various drugs. Drug 3 possesses the lowest EC_{50} value, followed by drug 1 and then drug 2. In other words, drug 3 is more potent than drug 1 which, in turn, is more potent than drug 2. The concentration/response curves show that the parameters intrinsic activity and potency do not have to go in parallel. Drug 3 possesses the lowest intrinsic activity but the highest potency. For an accurate comparison of various drugs, it

is essential to generate complete concentration-response curves.

When doses of various drugs are compared, it is important to know whether saturation is reached or not. Unfortunately, these prerequisites are not always fulfilled in clinical studies comparing various drugs. This can result in misinterpretations, specifically when judgements about assumed better clinical efficacy of a new drug compared to an established drug are being made. The term "better/greater clinical efficacy" does not clearly state whether it refers to potency or intrinsic activity.

As already stated above, an antagonist does not possess intrinsic activity, but antagonists are successfully used in the treatment of various important diseases such as hypertension (β_1AR antagonists; see ▶ Chap. 15), CHF (MCR antagonists; see ▶ Chap. 16), or schizophrenia (mGPCR antagonists; see ▶ Chap. 29). The clinical effects of antagonists are due to the fact that they block the actions of endogenous agonists.

Concentration-response curves for antagonists are also generally shown in half-logarithmic scale (◘ Fig. 1.2b). In case of antagonists, the biological system has first to be activated by the endogenous agonist, before an antagonist effect becomes apparent. Antagonists inhibit agonist effects according to sigmoidal concentration/dose-response curves. The inflection point of the curve corresponds to the IC_{50} or ID_{50} value at which the antagonist possesses its half-maximal inhibitory effect. At sufficiently high concentrations/doses, an antagonist can completely inhibit the effect of the endogenous agonist. The IC_{50} values of antagonists can also be compared with each other. The IC_{50} of antagonist 2 is lower than that of antagonist 1. Thus, antagonist 2 is more potent than antagonist 1. However, with respect to the maximum effect at the receptor, i.e., complete suppression of the stimulatory effects of the agonist, the two drugs do not differ from each other. For antagonists, the term potency is also used for classification of certain drugs.

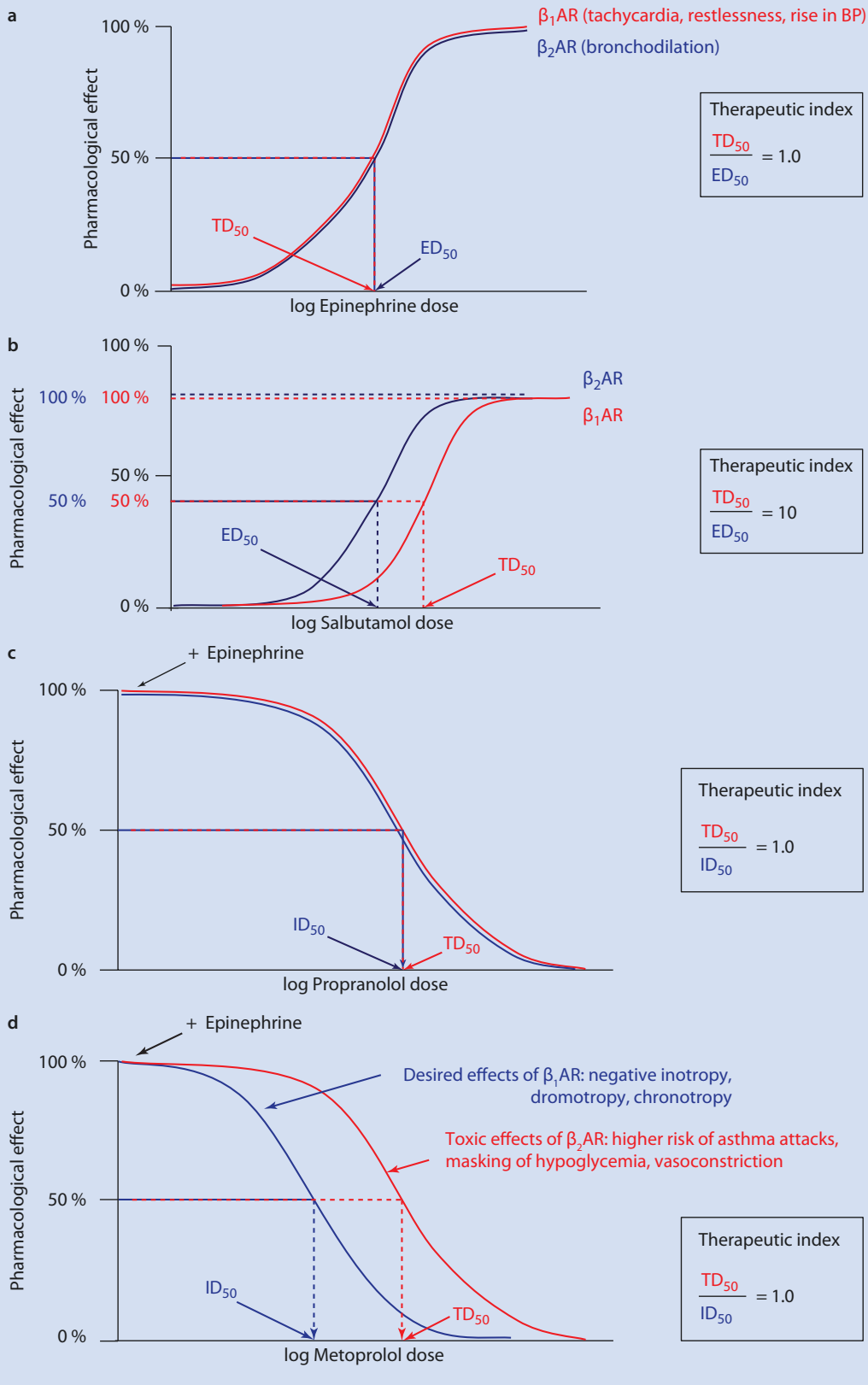
For example, drugs that antagonize the D_2R with low IC_{50} values are referred to as high-potency D_2R-mGPCR antagonists, whereas drugs that antagonize the D_2R with high IC_{50} values are classified as low-potency D_2R-mGPCR antagonists. With regard to the maximum antipsychotic effect, high- and low-potency D_2R-mGPCR antagonists do not differ from each other. It is just a matter of the drug dose at which the antipsychotic effect becomes apparent (see ▶ Chap. 29). H_2R antagonists are another example for this concept. The order of potency is famotidine > ranitidine > cimetidine, but the maximum possible inhibition of proton secretion by the drugs is comparable (see ▶ Chap. 7).

In principle, the curves for receptor antagonists shown in ◘ Fig. 1.2b can be transferred to enzyme inhibitors. In case of irreversibly acting receptor antagonists or enzyme inhibitors, the effect of the drug cannot be overcome by an increase of the agonist and substrate concentration, respectively. One has to wait until the irreversibly modified receptor/enzyme is regenerated by de novo synthesis. As a result, irreversibly acting receptor antagonists and enzyme inhibitors possess a long duration of action.

1.9 Therapeutic Index: Drug Safety

The goal of medicine in general and of pharmacology in particular is to cure diseases or at least to mitigate disease symptoms without harming the patient. The therapeutic index is a measure for the safety of a drug. In case of life-threatening diseases (e.g., tumors; see ▶ Chap. 32), a smaller therapeutic index has to be accepted than in case of non-life-threatening diseases. In order to determine the therapeutic index of a drug, one has to assess dose-response curves for the desired therapeutic effect and the toxic effect (ADRs). Such studies should only be performed in animals in order to avoid toxic drug effects in humans a priori.

Via the β_2AR, the endogenous ligand EPI mediates relaxation of smooth muscle cells (see ◘ Fig 1.1). Because EPI is a full β_2AR agonist, the hormone, in principle, could be used for treatment of an asthma attack. However, the problem is that EPI activates the β_2AR and β_1AR with the same potency (◘ Fig. 1.3). Via the β_1AR, EPI induces tachycardia which can lead to AP, arrhythmias, and MI. The therapeutic index is calculated as ratio of the dose causing 50% of the toxic effect (TD_{50}) and the dose causing 50% of the therapeutic effect (ED_{50}, E standing for therapeutic efficacy). In case of EPI, the toxic effect is tachycardia, and the therapeutic effect is bronchodilation. Since the therapeutic index for EPI with respect to asthma attack equals 1 (a small value), EPI is not used clinically for this indication.


a
β1AR (tachycardia, restlessness, rise in BP)
β2AR (bronchodilation)
Therapeutic index
TD50 / ED50 = 1.0
100 %
50 %
0 %
Pharmacological effect
TD50
ED50
log Epinephrine dose
b
β2AR
β1AR
Therapeutic index
TD50 / ED50 = 10
100 %
100 %
50 %
50 %
ED50
TD50
log Salbutamol dose
c
+ Epinephrine
Therapeutic index
TD50 / ID50 = 1.0
ID50
TD50
log Propranolol dose
d
+ Epinephrine
Desired effects of β1AR: negative inotropy, dromotropy, chronotropy
Toxic effects of β2AR: higher risk of asthma attacks, masking of hypoglycemia, vasoconstriction
Therapeutic index
TD50 / ID50 = 1.0
ID50
TD50
log Metoprolol dose

It is the goal of drug development for asthma to identify drugs that activate the β_2AR with much higher potency than the β_1AR. Chemical modification of EPI resulted in the synthesis of salbutamol. This drug activates the β_2AR with an about tenfold higher potency than the β_1AR (Fig. 1.3b). Thus, the therapeutic index for salbutamol in asthma treatment equals 10 (a large value). However, a disadvantage of the increased therapeutic index is the fact that salbutamol is only a partial β_2AR agonist. Accordingly, in a severe asthma attack, the efficacy of salbutamol is not sufficient. However, in mild to moderate asthma attacks, salbutamol can accomplish good bronchodilation without tachycardia. ADRs can occur when a patient suffers from severe asthma and uses too high doses of salbutamol although at saturation, an increase in salbutamol does not further enhance bronchodilation because the maximum intrinsic activity has already been reached. The only result of increased salbutamol dosing is enhanced activation of the cardiac β_1AR resulting in tachycardia. Such tachycardias can also occur when the patient does not take into consideration the fact that after inhalation, the drug has first to penetrate the bronchial mucosa before bronchodilation takes place. This results in a delay of a few minutes between drug application and onset of action, leading to accidental application of too high drug doses.

If the therapeutic index of a drug is very large, it can be considered to hand it in the pharmacy OTC, i.e., without prescription. An example for such a drug is ranitidine which is used for self-medication of GERD and PUD (see ▶ Chap. 7). Ranitidine antagonizes the H_1R, resulting in sedation, only at doses that cannot be achieved clinically.

β_xAR antagonists can also be used to explain the concept of therapeutic index. Via β_1AR antagonism, valuable therapeutic effects in hypertension, CHD, and CHF are achieved (see ▶ Chaps. 15 and 16). Propranolol antagonizes the β_1AR and β_2AR with similar potency (Fig. 1.3c). However, via β_2AR antagonism, serious ADRs such as cold fingers and risks of undetected hypoglycemia in DM patients and of asthma attacks are mediated. Therefore, propranolol is obsolete for the treatment of cardiovascular diseases. Chemical modification of propranolol resulted in the development of metoprolol that antagonizes the β_1AR with tenfold higher potency than the β_2AR (Fig. 1.3b). Thus, metoprolol possesses a lower ADR risk than propranolol with respect to the aforementioned problems that are mediated via the β_2AR. However, also metoprolol should be used with caution. In order to avoid β_2AR-mediated ADRs, the dose of metoprolol should only be increased incrementally.

The examples for therapeutic indices for agonists and antagonists discussed here show that for the assessment of this parameter, complete concentration-response curves are needed. A comparison of drugs at a single dose without detailed knowledge of the respective positions on the dose-response curves can be very misleading. In order to increase drug safety, drugs with a small therapeutic index should be avoided. If such drugs are unavoidable, TDM should be performed, and the patient should be carefully monitored for ADRs. Avoidance of the administration of multiple drugs (polypharmacy) is important as well. In addition, synergistically acting drugs deteriorating ADRs should be avoided.

Table 1.7 lists some drugs with a small therapeutic index. Among these drugs is the classic cytostatic drug cyclophosphamide for treatment of malignant tumors. Botulinum neurotoxin is a deadly toxin resulting in botulism with respiratory paralysis when applied systemically. However, when applied locally and cautiously, the toxin can be used for treatment of dystonia. Digoxin inhibits the Na^+/K^+-ATPase in every cell and was broadly used in certain countries for treatment of AF and CHF. However, due to the very small therapeutic index, ADRs are very common. Therefore, the use of digoxin is largely declining

Fig. 1.3 **a–d** Therapeutic index as measure for drug safety. **a**, **b** Comparison of EPI and salbutamol concerning their agonism at the β_1AR and β_2AR. **c**, **d** Comparison of propranolol and metoprolol concerning their antagonism at the β_1AR and β_2AR. See also Fig. 10.2. Sometimes metoprolol is also referred to as "cardioselective beta blocker." This is a very poor term which must be avoided! In fact, metoprolol mediates important pharmacological effects via RAAS inhibition! Keep in mind that you need to titrate the dose of metoprolol carefully. In higher doses the "cardioselectivity" of metoprolol gets lost! You may antagonize the β_2AR and get serious ADRs. Cardioselectivity is a wrong advertisement

Table 1.7 Examples of drugs with very small therapeutic index

Drug	Drug class	Indication	ADRs	Further contexts in Chaps.
Cyclophosphamide	Classic cytostatics (alkylating agents)	Malignant tumor diseases (high dose); autoimmunopathies (low dose)	Nausea, vomiting, anemia, granulocytopenia, thrombopenia, mucositis, hair loss, fatigue, secondary malignant tumors, teratogenicity. Nausea and vomiting can be reduced with 5-HT_3R antagonists. Fatigue can be improved with a moderate exercise program. In low-dose therapy, cyclophosphamide is much less toxic than in high-dose therapy.	32
Botulinum neurotoxin	Inhibitors of ACh release	Dystonias (local)	Paralysis of skeletal muscles lasting for months. In case of systemic intoxication botulism requiring mechanical ventilation. When used for cosmetic reasons and applied incorrectly, botulinum toxin can cause long-lasting paralysis of the mimic musculature so that no more emotional expressions are possible for months. The use of botulinum toxin for "rejuvenation" is medically highly questionable and dangerous but a very profitable business.	5, 37
Digoxin	Na^+/K^+-ATPase inhibitors	CHF, AF; clinical use should be avoided because clinical studies are not convincing!	The function of every organ can be compromised due to the ubiquitous expression of the Na^+/K^+-ATPase. Green-yellow vision is pathognomonic. The summer paintings from Vincent van Gogh nicely illustrate how vision is impaired in intoxication with Na^+/K^+-ATPase inhibitors. Every type of arrhythmia may occur. CNS and GI disturbances are common. Toxicity is enhanced by electrolyte alterations (potassium, calcium).	16, 17
Haloperidol	D_2R-mGPCR antagonists	Schizophrenia, acute mania, chronic pain	EPSs, cardiovascular problems (tachycardia, hypotension), TdP; particularly during rapid i.v. injection). I.v. injection of haloperidol must be performed very slowly and under ECG control.	10, 29
Lithium	Alkali metal ions	Bipolar disorder, suicidality, refractory depression, schizophrenia	Toxic effects in virtually every organ system, most notably the CNS, cardiovascular system, thyroid gland, and kidney. In addition, lithium is teratogenic. Nonetheless, despite its small therapeutic index, therapy can be successfully performed by tight TDM and monitoring of ADRs.	28
Paracetamol (OTC drug!)	Non-MOR agonists	Mild pain	Hepatotoxicity can occur if <8 g (just twice the maximum daily dose!) of paracetamol are ingested. Keep paracetamol out of reach of children! In some countries, paracetamol can be purchased in virtually unlimited quantities.	4, 10
Phenobarbital	Allosteric $GABA_A$R modulators	Drug of last resort in refractory epilepsies	Very high risk of respiratory depression, coma, and death, particularly in combination with other sedating drugs and ethanol. For these reasons, the use of phenobarbital has decreased dramatically. Various NIPEs are more effective and safer in epilepsies.	25

Table 1.7 (continued)

Drug	Drug class	Indication	ADRs	Further contexts in Chaps.
T4	Thyroid hormones	Hypothyroidism, hyperthyroidism (+ TPO inhibitors)	Hyperthyroidism and thyrotoxic crisis. Every organ can be affected. Effects in the CNS (agitation), and cardiovascular system (hypertension, tachycardia) and hyperthermia are particular dangerous.	21

The clinical use of a drug with small therapeutic index depends very much on the particular disease and pharmacotherapeutic alternatives that you may or may not have! You have to analyze each drug individually. Even OTC drugs may have a small therapeutic index

and now discouraged by a large fraction of the medical community.

Haloperidol is an mGPCR antagonist with a small therapeutic index and many ADRs. Accordingly, haloperidol must be dosed very cautiously, constantly monitoring ADRs, particularly EPSs. The thyroid hormone thyroxine also possesses only a small therapeutic index, overdosing resulting in hyperthyroidism and underdosing resulting in hypothyroidism. Therefore, therapy with T4 must be performed with tablets containing clearly defined doses, constantly assessing the clinical status of the patient and checking laboratory parameters.

As further example, paracetamol is globally used as an analgesic. In many countries, the drug is available as OTC drug. However, just doubling of the maximum analgesic dose (4g/day) can result in serious liver damage, i.e., paracetamol possesses a very small therapeutic index. This is an example of the fact that OTC drugs are not necessarily safe but potentially dangerous. In fact, liver intoxications with paracetamol are very common. Nonetheless, paracetamol is still very easily accessible to patients.

For some drugs such as phenobarbital, the small therapeutic index has resulted in almost complete disappearance from clinical use, because alternative drugs (NIPEs) with higher efficacy and fewer ADRs are available (see ▶ Chap. 25). In contrast, another drug with small therapeutic index, lithium, is widely used in bipolar disorder because it reduces suicidality (see ▶ Chap. 28). In this case, the impressive clinical effects compensate the serious ADRs, and in most patients, the situation can be controlled by tight TDM. Thus, a small therapeutic index of a drug does not preclude its broad clinical use. It all depends on the specific disease and pharmacotherapeutic alternatives.

Table 1.8 lists representative drugs with a large therapeutic index. Tiotropium and sumatriptan are classified in this category because they bind to their target receptors with high selectivity relative to other receptors. Accordingly, the ADRs of these drugs are very modest. Ranitidine also exhibits high selectivity for its target receptor, but the drug has now been largely superseded by more effective drugs, the PPIs. The WHO rehydration solution is very safe for oral rehydration of patients with diarrhea. In the clinic, underdosing rather than overdosing of the solution constitutes a common problem, resulting in insufficient rehydration. Glucose administered p.o. or i.v. is very effective and safe for treating life-threatening hypoglycemia (CNS damage). In contrast, the health risks of an accidental acute overdosing of glucose resulting in transient hyperglycemia are negligible. Lastly, penicillin G and all other β-lactam and monobactam antibiotics possess a very large therapeutic index because their target, an enzyme catalyzing bacterial cell wall synthesis, does not exist in human cells. Unfortunately, these drugs possess high allergenic potential (see ▶ Chap. 3), requiring critical use as well.

Table 1.8 Examples of drugs with large therapeutic index

Drug	Drug class	Indication	ADRs	Further contexts in Chaps.
Tiotropium	M_3R antagonists	COPD	Xerostomia if applied incorrectly (deposition in mouth)	5, 14
Sumatriptan	5-$HT_{1D}R$ agonists	Migraine attack	Chest tightness, not to be confused with AP! Few ADRs; therefore, several sumatriptan formulations are available OTC.	6
Ranitidine	H_2R antagonists	GERD (self-therapy)	Rebound hypergastrinemia if abused for long time. Because of the few ADRs (no H_1R antagonism!), ranitidine is available OTC. The main risk is actually that due to self-therapy, diagnosis of GERD and PUD is delayed.	7, 13
WHO rehydration solution	Oral rehydration solutions	Diarrhea	If applied correctly, no ADRs. Excessive use (very rare) can lead to hyperhydration. The solution is available OTC and can be prepared from pure chemical constituents in large scale in epidemics due to infections with *Salmonella, Shigella*, or *Vibrio cholerae*.	13
Glucose p.o., i.v.	Glucose	Hypoglycemia	None. Hyperglycemia does virtually never occur unless huge amounts of glucose are ingested or administered.	19
Penicillin G	Benzylpenicillins	Infections with sensitive pathogens	The most important ADR is disturbance of the GI microbiota resulting in diarrhea or, rarely, in pseudomembranous enterocolitis. The risk of allergic reactions is minimized when the patient is asked for penicillin allergies prior to treatment.	3, 33

1.10 Questions and Answers

Questions

Which statement on pharmacodynamics is correct?

A. Poisons do not possess therapeutically useful effects.
B. The smaller the therapeutic index is, the larger is the safety of a drug.
C. Intrinsic activity of an agonist constitutes a measure for the therapeutic index.
D. Partial agonists possess a higher intrinsic activity than antagonists.
E. Potency is a measure for the maximum effect of a drug.

Answers

A. Poisons can possess therapeutically useful effects if they are applied properly. The poison of the deadly nightshade, atropine, can be used for the therapy of bradycardia during surgery. Botulinum neurotoxin can be used for treatment of muscle spasms, and ziconotide can be used for the therapy of very severe pain.

B. The therapeutic index is defined as the ratio TD_{50}/ED_{50}. The larger the ratio is, the larger is the difference between therapeutic and toxic effects of a drug.

C. Intrinsic activity is a measure for the maximum effect of an agonist. There are full agonists with an intrinsic activity of 100%, antagonists with an intrinsic activity of 0%, and partial agonists with an intrinsic activity <100% and > 0%.

D. Partial agonists possess an intrinsic activity <100% and > 0%. Antagonists possess an intrinsic activity of 0%.

E. Potency describes the EC_{50} or ED_{50} of an agonist. The lower the EC_{50} or ED_{50} is, the higher is the potency of the agonist. Potency also describes the IC_{50} or ID_{50} of an antagonist. The lower the IC_{50} or ID_{50}, the higher the potency of the antagonist.

Answer **D** is correct.

1.11 Exercises

A 65-year-old patient with lung carcinoma and bone marrow metastases suffers from severe pain. The patient is treated with a partial MOR agonist. After several weeks, the efficacy of the therapy decreases.

Questions

1. Which drug was most likely given to the patient?
2. Why did the efficacy of the therapy decrease?
3. What are the next steps to alleviate the pain of the patient?
4. What has to be done if the patient again complains of pain despite improved therapy?

Answers

1. Most likely, the patient was treated with buprenorphine.
2. Most likely, the disease process progressed so that the intrinsic activity of buprenorphine was not sufficiently large anymore. It is less likely that already under therapy with buprenorphine, MOR desensitization took place.
3. In the next step, the patient is placed under a regimen with the full MOR agonist morphine. Morphine possesses a higher intrinsic activity than buprenorphine. In addition, the patient should be treated with non-MOR agonists such as ibuprofen or metamizole.
4. Further progression of the disease process and/or receptor desensitization could have occurred. Receptor desensitization can at least partially be compensated by increased morphine doses. However, physicians are often afraid of a dose increase because of anticipated dependence. In case of a deleterious disease, dependence is irrelevant. In addition to morphine, co-analgesics such as NSMRIs and/or p-mGPCR antagonists can be applied.

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Pharmacokinetics

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2

Pharmacokinetics analyzes the path of drugs through the organism and the effects of the organism on drugs. The pharmacokinetic properties of a drug are described by the ADME parameters. To ensure good intestinal absorption and BBB penetration, a drug must be of low molecular mass, neutral, and lipophilic. The first-pass effect describes inactivation of a drug during the first liver passage. CYP inhibition enhances the effects of drugs that are inactivated via the same CYP, whereas CYP induction reduces drug effects. A large distribution volume points to a deep compartment in which a drug accumulates. Prodrugs are inactive precursors of a drug which are metabolically converted to the active drug. The enterohepatic circulation is a cyclic process of biliary elimination and consequent intestinal reabsorption of a drug. In general, a drug for oral administration should possess good bioavailability, a moderately sized distribution volume, and a plasma half-life that allows for good controllability, but no enterohepatic circulation. For treatment of CNS diseases, drugs must penetrate the BBB, whereas for treatment of non-CNS diseases, a lack of BBB penetration is desirable.

Key Points

1. Most drugs are absorbed and eliminated according to first-order kinetics following oral administration.
2. The first-pass effect can be exploited for pharmacotherapy.
3. The properties of the BBB can be exploited to reduce ADRs in the CNS.
4. With a first-order kinetics, steady-state concentration of a drug is achieved after 4–5 plasma half-lives.
5. High plasma protein binding of a drug, via competition with other drugs, can lead to ADRs.
6. TDM increases drug safety.
7. The best way to minimize drug interactions is to avoid polypharmacy.
8. CYP polymorphisms can increase or reduce drug effects.
9. Liver failure and CKD can prolong drug effects and cause ADRs.
10. MRPs contribute to resistance against classic cytostatics.
11. In meningitis, babies and toddlers, xylometazoline, MCP, and loperamide are risky due to ADRs in the CNS.
12. Amiodarone is a problematic drug with an extremely long plasma half-life, substantial risk of accumulation, and many ADRs.
13. RMP, carbamazepine, phenytoin, phenobarbital, St. John's wort, and nicotine are classic CYP inducers.
14. Ciprofloxacin, azole antimycotics, erythromycin, clarithromycin, and grapefruit juice (naringin) are classic CYP inhibitors.
15. Therapy with drugs possessing a small therapeutic index such as mGPCR antagonists, theophylline, ciclosporin, and phenprocoumon are prone to CYP interactions.

2.1 ADME Parameters: Pharmacotherapeutic Relevance

Pharmacokinetics describes the path of drugs through the organism and the effects of the organism on the drug. Pharmacokinetics comprises the parameter absorption, distribution, metabolism, and elimination. These parameters influence the pharmacological effects of a drug in the organism. Pharmacokinetic processes follow zero-order or first-order kinetics. In a zero-order kinetics, a constant amount of drug is absorbed or eliminated per time interval. The classic example of a zero-order absorption is the i.v. infusion of a drug. The classic example of a zero-order elimination is the degradation of ethanol by ethanol dehydrogenase. In a first-order kinetics, drugs are absorbed or eliminated concentration-dependently; the kinetics follows an exponential function.

The plasma half-life is the time interval in which the concentration of a drug is reduced by 50%. Accordingly, after two half-lives, the concentration is reduced to 25%, after three half-lives to 12.5%, and after four half-lives to 6.25%. In an open system like the human organism, with first-order absorption and elimination kinetics, after 4–5 plasma half-lives, an equilibrium

between absorption and elimination is reached, resulting in a steady-state drug concentration.

Figure 2.1 provides an overview of the ADME parameters. In most cases, a drug is administered orally. The most important organ for absorption is the small intestine. To avoid inactivation of drugs by low pH in the stomach, many drugs are applied as acid-resistant formulations. Drug therapy should be as convenient as possible for the patient. Whenever possible, drugs should be given once daily. For many chronic diseases such as hypertension (see ▶ Chap. 15), CHF (see ▶ Chap. 16), and hypo- and hyperthyroidism (see ▶ Chap. 21), it is important to achieve a constant drug effect. Therefore, many drugs are applied as extended-release formulations. Most drugs are absorbed by diffusion. Prerequisites for absorption by diffusion are low molecular mass (<300 Dalton), sufficient lipophilicity, and neutral form of the drug. In several cases, drug absorption can be improved by application of a lipophilic prodrug. Following absorption in the intestine, the prodrug is cleaved in the organism and the active drug is liberated. Many prototypical prodrugs are esters that are hydrolyzed by esterases.

GI absorption is influenced by many factors. An accelerated intestinal passage (co-application of laxatives or prokinetics, antibiotic-associated diarrhea, inflammatory bowel diseases; see ▶ Chap. 13) can reduce drug absorption. This can lead, e.g., to the loss of effectiveness of oral contraceptives (see ▶ Chap. 24). Fat food may delay drug absorption. For some drugs (thyroid hormones, ▶ Chap. 21; bisphosphonates, ▶ Chap. 20; PPI, ▶ Chap. 13) it is essential to apply them on an empty stomach in order to ensure good intestinal absorption. Certain drugs, most notably tetracyclines (see ▶ Chap. 33) and bisphosphonates (see ▶ Chap. 20), interfere with calcium absorption and must not be taken together with calcium or milk. GCR agonists for the therapy of autoimmune diseases are given in the morning to suppress the hypophysis function as little as possible (see ▶ Chap. 11).

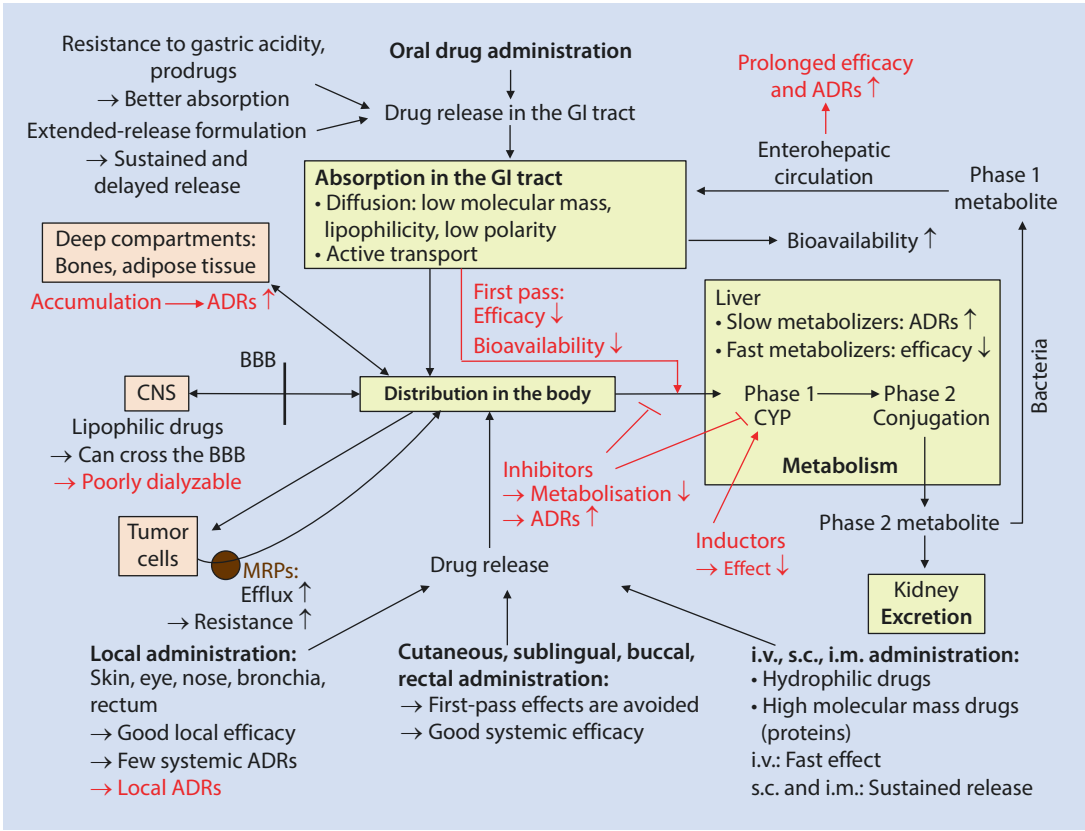

Fig. 2.1 Overview of pharmacokinetics of drugs in the organism: Pharmacotherapeutic relevance of the ADME parameters. Many ADRs are due to unfavorable ADME parameters

High-molecular mass drugs (most notably proteins such as insulin and therapeutic antibodies; see ▶ Chaps. 11, 19, and 32) and very hydrophilic drugs like ions have to be administered parenterally (mostly s.c.). Common ADRs of s.c. injection are local allergic reactions and tissue induration (see ▶ Chaps. 3, 11, 19, and 32). I.m. injections are used for application of certain sex hormones (see ▶ Chap. 24) and mGPCR antagonists (see ▶ Chap. 29). For therapy of eye diseases (see ▶ Chap. 31), respiratory tract diseases (see ▶ Chaps. 5, 7, and 14), vaginal diseases (see ▶ Chaps. 24 and 35), skin diseases (see ▶ Chap. 11), and rectum diseases (see ▶ Chap. 13), local drug administration is feasible in many cases. Advantages are that high local drug concentrations can be achieved and that in general, ADRs are just of local nature.

Following absorption in the small intestine, the drug reaches the liver. Metabolism of the drug begins already during the first liver passage. Inactivation of a drug during the first liver passage is referred to as the first-pass effect. Because of its high clinical relevance, the first-pass effect is dealt with in a separate section (see ▶ Sect. 2.2). The percentage of an orally applied drug that reaches the systemic circulation after the first liver passage is referred to as bioavailability. In general, bioavailability of a drug should be high. Following i.v. injection bioavailability amounts to 100%. The onset of drug action after i.v. injection is fast and reliable. This is routinely exploited in anesthesia and emergency medicine (see ▶ Chaps. 3, 5, 10, 16, 17, 19, and 27). However, i.v. application of drugs can also result in problems such as TdP (see ▶ Chap. 17) and should therefore be performed slowly.

After the first liver passage, the drug is distributed in the organism and reaches its target organs, unless the liver is the primary target (see ▶ Chaps. 22 and 34). Distribution depends on the physiochemical properties of the drug (charge, lipophilicity, molecular mass), pH, binding to plasma proteins, organ perfusion, membrane permeability, age, and nutritional status. Local anesthetics are an example of pH-dependent drug distribution (see ▶ Chap. 26). White adipose tissue constitutes a large compartment in which lipophilic drugs accumulate. As a consequence, in many obese patients, drug doses must be increased.

The distribution volume is a virtual volume, describing the apparent volume in which the drug is distributed. A distribution volume of 4 l implies that the drug is distributed in the intravasal space; a distribution volume of 12.5 l implies that the drug is distributed in the extracellular space. A distribution volume of 70–80 l indicates that the drug is distributed in the entire organism and a distribution volume > 80 l points to deep compartments. For pharmacotherapy, deep compartments are problematic because they point to retention of a drug in the organism (e.g., in adipose tissue or bone) and can be the cause of long-term ADRs. A drug is mobilized only slowly from deep compartments. A classic example is the class I–IV antiarrhythmic drug amiodarone (see ▶ Sect. 2.4 and ▶ Chap. 17). Tetracyclines form complexes with calcium and, when applied to a pregnant woman, can accumulate in the bones and teeth of the fetus (see ▶ Chap. 33). Another example of a drug accumulating in a deep compartment is thiopental (see ▶ Chap. 27). After i.v. injection, thiopental rapidly reaches the CNS, followed by redistribution into the skeletal muscles and later the adipose tissue. From the latter compartment, thiopental is released slowly. Thus, following a single long-term application or repeated administration, thiopental can cause prolonged sedation. In case of bisphosphonates (see ▶ Chap. 20), the deep compartment (accumulation in osteoclasts) contributes to the long-term protective effects in osteoporosis.

Binding of a drug to plasma proteins reduces the percentage of the free drug that is pharmacologically active. If two drugs with high plasma protein binding compete against each other, a small therapeutic index of one of the drugs becomes problematic. As a result, the free concentration of this drug increases, and serious ADRs can occur. A classic example is competition of the VKA phenprocoumon (see ▶ Chap. 18, plasma protein binding >99%) that competes with other strongly protein-bound drugs such as ASA (see ▶ Chap. 18) or the oral antidiabetic glibenclamide (see ▶ Chap. 19). Via displacement from plasma proteins, phenprocoumon becomes more effective at inhibiting the synthesis of active coagulation factors, ultimately increasing the risk of serious hemorrhage. This risk is further increased by ASA because this drug inhibits platelet aggregation (see ▶ Chap. 18). Therefore, for pharmacodynamic and pharmacokinetic reasons, the combination of a VKA and ASA is contraindicated. If glibenclamide is displaced from plasma proteins

by phenprocoumon, serious hypoglycemia can result. Thus, the combination of drugs with high plasma protein binding should be avoided.

The goal of tumor therapy is to selectively destroy tumor cells without harming normal cells (see ▶ Chap. 32). Via exploitation of specific receptors, enzymes, and biochemical mechanisms, it is now possible to discriminate between tumor cells and normal cells at least to a certain degree. However, tumor cells possess efficient mechanisms to evade the deleterious effects of tumor therapeutics. MRPs expressed at the plasma membranes are of great relevance for tumor resistance. MRPs export many classic cytostatic drugs from tumor cells and, thereby, reduce drug efficiency. Unfortunately, it is not yet possible to selectively inhibit MRP in tumor cells to avoid export of classic cytostatics. To circumvent the problem, various drugs are combined, delaying the selection of tumor cells with high MRP activity.

The liver is the main organ for drug metabolism. Drug metabolism is divided into two phases. In phase 1, the drug is oxidized, reduced, or hydrolyzed. Phase 1 metabolites can be pharmacologically active or inactive. In phase 2, the phase 1 metabolite is conjugated with glucuronic acid, acetic acid, sulfuric acid, or an amino acid. Via conjugation, the phase 1 metabolite (with few exceptions; morphine-6-glucuronide; see ▶ Chap. 10) becomes inactive and water-soluble. The phase 2 metabolite is then excreted via the kidney and/or bile.

In liver diseases such as hepatitis C (see ▶ Chap. 34), liver cirrhosis, and intoxication with hepatotoxic drugs such as paracetamol (see ▶ Chaps. 4 and 10) and in newborns, the metabolic capacity of the liver is reduced. Accordingly, the duration of action of drugs is increased and the drug dose must be reduced.

CYPs play a major role in phase 1 metabolism. CYPs are hemoproteins with monooxygenase activity. CYPs also play an important role in steroid hormone metabolism (see ▶ Chaps. 24 and 35). The human genome possesses more than 50 CYP genes. CYPs are classified with a *number-letter-number* code. The first number designates the gene family, the letter describes the gene subfamily, and the last number designates the individual gene.

CYP expression is regulated by NRs such as the pregnane X receptor (PXR) (see ▶ Chap. 1) which binds many xenobiotics including drugs, stimulates CYP expression, and, as a result, promotes drug inactivation. CYP activity shows substantial interindividual variations.

There are CYP polymorphisms with very high enzymatic activity (ultrafast metabolizers) and polymorphisms with very low activity (poor metabolizers). CYP polymorphisms play a major role in the responsiveness of individual patients to drugs. For example, in an ultrafast metabolizer for CYP2D6, tamoxifen is inactivated very rapidly and hence ineffective (see ▶ Chaps. 24 and 32). Conversely, in a poor metabolizer for CYP2C9, VKAs and COX inhibitors are inactivated more slowly, resulting in more serious ADRs (see ▶ Chaps. 10 and 18). Therefore, in case of unexpected lack of drug efficacy or serious ADRs, TDM is indicated. CYP interactions are clinically so important that there are being dealt with in a separate section (see ▶ Sect. 2.5).

The bile is an important elimination pathway for drugs. Biliary eliminated phase 2 metabolites reach the intestine where bacteria can deconjugate the drugs to more lipophilic phase 1 metabolites. These metabolites can be reabsorbed and become pharmacologically active. In this way, an enterohepatic circulation is established, prolonging drug action. In general, enterohepatic circulation is undesirable because it increases the risk of ADRs, specifically in cases of overdosing. Enterohepatic circulation can be interrupted by absorbents (see ▶ Chaps. 4 and 22). Digitoxin (see ▶ Chap. 16), tamoxifen (see ▶ Chaps. 24 and 32), carbamazepine (▶ Chap. 28), leflunomide (see ▶ Chap. 11), and NSMRIs (see ▶ Chap. 28) are drugs with large enterohepatic circulation.

The kidney is the major organ for drug elimination (phase 2 metabolites). Elimination is accomplished via glomerular and tubular secretion. In CKD, drug elimination is delayed, and accordingly, drugs can accumulate and serious ADRs can occur. This requires individually adapted dose reduction. CKD is so important for drug therapy that it is discussed in a separate chapter (▶ Chap. 12).

2.2 Significance of the First-Pass Effect

Table 2.1 summarizes the properties of some drugs with high first-pass effect. For p.o. administration, a high first-pass effect is disadvantageous because the drug cannot act sys-

Table 2.1 Significance of the first-pass effect for drug effects: examples

Drug	Route of administration	Pharmacological properties and pharmacotherapeutic consequences	Further contexts in Chaps.
Budesonide	Inhalation, rectal	Local anti-inflammatory and immunosuppressive effect in asthma and/or UC. After systemic absorption the drug is rapidly metabolized in the liver; therefore systemic ADRs are rare.	11, 13, 14
Estradiol	Transdermal (patch, gel)	Estradiol is the most important physiological ER agonist and is effective in treating peri- and postmenopausal symptoms. Administered orally, estradiol is inactivated to a large extent when it passes through the liver. Applied dermally, estradiol can systemically exert its effects.	24
GTN	Buccal, sublingual, rectal, i.v.	Via these routes, rapid inactivation of GTN in the liver is circumvented, and a short-term relaxing effect on smooth muscle cells is achieved, which can be used in emergency situations.	9
Scopolamine	Transdermal (patch)	Prolonged drug administration through the skin resulting in a prolonged antiemetic effect (e.g., during boat cruises).	5, 7
Simvastatin	p.o.	Simvastatin inhibits HMG-CoA reductase in the liver and thus synthesis of cholesterol. As simvastatin is rapidly metabolized in the liver, systemic ADRs can be minimized (low risk of rhabdomyolysis, provided no CYP3A4 or OATPB1 inhibitors are administered at the same time).	22

The first-pass effect is not always "a problem," but can be exploited for effective pharmacotherapy

temically. However, there is one important exception: HMG-CoA reductase inhibitors that are effective in the therapy of dyslipidemia (see ▶ Chap. 22) primarily exert their effects in the liver. HMG-CoA reductase inhibitors with high bioavailability possess a high risk for rhabdomyolysis. The risk of systemic ADRs of HMG-CoA reductase inhibitors is increased by simultaneous administration of CYP3A4 inhibitors or OATB1 inhibitors that reduce hepatic drug uptake.

GTN is a classic example of a drug with high first-pass effect. GTN does not act systemically upon oral administration. However, the smooth muscle-relaxing effect of GTN can be used in various emergency situations such as AP, hypertensive emergency, and colic pain (see ▶ Chaps. 9, 10, 15, 16, and 23). Several preparations of the drug such as sublingual sprays are available to circumvent the first-pass effect. Compared to sublingual application, the onset of action is delayed upon rectal administration to avoid the first-pass effect. The specific formulation has to be commensurate to the specific indication. Although the liver is circumvented upon buccal, sublingual, dermal, rectal or i.v. application, nonetheless, the liver will be reached soon and drug inactivation commences. As a result, the duration of action of GTN is very limited, i.e., about 30 minutes, but this time interval is sufficient to initiate further therapeutic measures.

Scopolamine is an M_xR antagonist and causes an antimuscarinic syndrome at high doses (see ▶ Chaps. 4 and 5). However, at low doses, scopolamine possesses a good antiemetic effect in kinetosis (see ▶ Chap. 6). Due to its high first-pass effect, this effect cannot be exploited therapeutically when scopolamine is administered p.o. Instead, scopolamine is applied as patch behind the ear. From this depot, scopolamine is released over a long period of time to exert its therapeutic effects while at the same time at least partially circumventing the liver.

Glucocorticoids (GCR agonists) are effective anti-inflammatory and immunosuppressive drugs that are used in autoimmune diseases and asthma and for prevention of organ rejection following

transplantation (see ▶ Chaps. 11, 13, and 14). A major problem in the clinical use of GCR agonists is that these drugs exhibit global effects on metabolism and electrolytes, resulting in serious ADRs (see ▶ Chap. 11). It is the goal of a GCR agonist therapy to focus the drug effects on the diseased organ. This goal can be accomplished on the one hand via local administration (see ▶ Chaps. 13 and 14) and on the other hand by application of GCR agonists that are rapidly inactivated in the liver following systemic absorption.

Additionally, sex hormones (estrogens, gestagens, and androgens) are rapidly inactivated in the liver following oral administration. One option to compensate for the first-pass effect is to administer high drug doses (e.g., gestagens). Another strategy is to apply the drugs locally via patches, thereby circumventing the first-pass metabolism at least partially (see ▶ Chap. 24).

2.3 Significance of the Blood-Brain Barrier (BBB)

The BBB constitutes a physiological barrier between the systemic circulation and the CNS. Tight junctions between endothelial cells prevent paracellular diffusion of drugs. Accordingly, drugs have to penetrate both endothelial membranes. Endothelial cells are located above the basal membrane. On the contralateral side of the basal membrane are glia cells that provide an optimal milieu for neurons and protect them from toxic compounds. Drugs can penetrate the BBB via diffusion and via transport processes.

Table 2.2 shows how differential BBB penetration impacts on the therapeutic use of various drugs. For treatment of CNS diseases (see ▶ Chaps. 25, 28, 29, and 30) and for anesthesia (see ▶ Chap. 27), it is essential that drugs penetrate the BBB. Most drugs reach the CNS via diffusion. Prerequisites for diffusion are low molecular mass (< 300 Dalton), sufficient, but not too high lipophilicity, and neutral drug species. A disadvantage of high lipophilicity of CNS-active drugs is that in case of intoxication, they cannot be rapidly eliminated, e.g., via dialysis (see ▶ Chap. 4). The presence of too many polar groups and a high molecular mass impede with the penetration of the BBB. In meningitis, permeability of the BBB is increased. This facilitates therapy with antibiotics that normally do not penetrate well into the CNS, most notably β-lactam antibiotics (see ▶ Chap. 33).

In some cases, transport of hydrophilic drugs across the BBB is clinically relevant. Levodopa is transported across the BBB via an amino acid carrier and converted into DA in the CNS. This mechanism is exploited in the therapy of PD (see ▶ Chap. 8). In contrast to levodopa, the DOPA decarboxylase inhibitor carbidopa is not transported into the CNS. Thus, peripheral ADRs caused by levodopa can be reduced by simultaneous application of carbidopa.

In the area postrema, the BBB is leaky so that in this region even hydrophilic drugs can reach the CNS. This is of (patho)physiological significance because activation of various receptors in the CTZ of the area postrema induces vomiting. Accordingly, antagonism of these receptors with hydrophilic drugs that otherwise penetrate the BBB only poorly results in antiemetic effects. The D_2R antagonists domperidone and MCP, the NK_1R antagonist aprepitant, and the $5\text{-}HT_3R$ antagonist ondansetron belong into this group of drugs (see ▶ Chap. 6).

In babies and toddlers, the BBB is not yet fully established physiologically. This implies that drugs that do not penetrate the BBB in school children, adolescents, and adults can reach the CNS very well in babies and toddlers and cause serious ADRs. Babies and toddlers quite often suffer from viral infections of the upper airways. For symptomatic therapy, decongestant nose drops containing α_1AR agonists (prototype xylometazoline) are applied (see ▶ Chap. 5). However, these drugs can penetrate into the CNS and cause hypertension. To avoid this ADR, it is crucial that in babies and toddlers, only nose drops with an approved low drug concentration are applied. In addition, these age groups often suffer from GI tract infections (see ▶ Chap. 13). Whereas in adolescents and adults, short-term symptomatic treatment with antiemetics and prokinetics such as MCP and the peripherally acting MOR agonist loperamide can be performed, these drugs are contraindicated in babies and toddlers. Like antipsychotically acting mGPCR antagonists (see ▶ Chap. 29), these drugs can cause EPSs (acute dyskinesias). Dyskinesias are reversible but are worrisome for the parents. Loperamide, otherwise activating only MOR outside the CNS, can

Table 2.2 Significance of the BBB for drug effects: examples

Drug	BBB penetration	Pharmacological properties and pharmacotherapeutic consequences	Further contexts in Chaps.
AChEIs			
Donepezil	Very good	Donepezil is uncharged and therefore easily penetrates the BBB. In the CNS, donepezil reversibly inhibits AChE and is symptomatically used in the treatment of AD.	30
Neostigmine	Very poor	Neostigmine is a quaternary amine and predominantly positively charged at physiological pH. Thus, it hardly penetrates the BBB and can be used without ADRs in the CNS in the treatment of myasthenia gravis.	5
M_xR antagonists			
Atropine	Moderate	Atropine is a tertiary amine. At high doses in the CNS, atropine can cause confusion, hallucinations, unconsciousness, and respiratory paralysis. Therefore, atropine has to be administered with care in anesthesia. Atropine intoxication in children is observed when they confuse the fruits of the deadly nightshade with similarly looking cherries. For treatment of a CNS atropine intoxication, the AChEI physostigmine, which also penetrates the BBB, can be applied.	4, 5, 17
Butylscopolamine	Very poor	Butylscopolamine is a quaternary amine and predominantly positively charged at physiological pH. Therefore, it hardly penetrates the BBB and can be used without ADRs in the CNS in the treatment of smooth muscle spasms.	5, 13
Scopolamine	Very good	Scopolamine is a tertiary amine. It is predominantly used to prevent motion sickness.	5, 7
Tiotropium	Very poor	Tiotropium is a quaternary amine and predominantly positively charged at physiological pH. Therefore, it hardly penetrates the BBB and can be used without ADRs in COPD therapy.	5, 14
Dopaminergic drugs			
Carbidopa	None	In contrast to levodopa, carbidopa is no substrate for the amino acid transporter and, therefore, cannot enter the CNS. This is why carbidopa effectively inhibits the transformation of levodopa into DA in peripheral organs, thereby reducing peripheral ADRs.	8
Levodopa	Very good	Levodopa passes through the BBB by means of an amino acid transporter and is converted in the CNS to DA. Levodopa is used in the treatment of PD.	8

Table 2.2 (continued)

Drug	BBB penetration	Pharmacological properties and pharmacotherapeutic consequences	Further contexts in Chaps.
MOR ligands			
Heroin (morphine prodrug, MOR agonist)	Excellent	Heroin is highly lipophilic due to the acetylation of two hydroxyl groups of morphine. It, therefore, ultrarapidly and effectively penetrates the BBB, which results in an excellent analgesic effect when administered intravenously. Having reached the CNS, heroin is rapidly mono- or dideacetylated. In some countries (e.g., UK), heroin is approved for pain management. Because of the rapid onset of effects, there is a high risk of heroin addiction.	10
Methylnaltrexone (MOR antagonist)	Very poor	Methylnaltrexone is a quaternary amine and predominantly positive at physiological pH. Therefore, it hardly crosses the BBB. Methylnaltrexone is used to relieve MOR agonist-induced constipation without attenuating the central analgesic effect.	10, 13
Morphine (MOR agonist)	Poor - moderate	Because of moderate lipophilicity and rapid glucuronidation, the CNS penetration of morphine is only poor to moderate. Particularly p.o. administration is associated with a slow onset of the analgesic effect, which is no problem in long-term pain management. However, in cases of acute pain, morphine has to be administered i.v. As morphine only slowly penetrates the BBB, the risk of addiction is only low, particularly when morphine is administered p.o. in pain management.	10
Naltrexone (MOR antagonist)	Excellent	Naltrexone is a tertiary amine and predominantly positively charged at physiological pH. It is relatively lipophilic and easily penetrates the BBB. Naltrexone antagonizes the agonist effects at the MOR. Because of its long duration of action, naltrexone is predominantly used in relapse prevention after morphine/heroin withdrawal treatment.	10

The BBB can be exploited for effective pharmacotherapy and minimization of ADRs

cause respiratory depression in babies and toddlers (see ▶ Chap. 13).

Atropine is an example of a drug with moderate BBB penetration. Atropine is primarily used in anesthesia and cardiology for treatment of bradycardia (see ▶ Chaps. 5 and 17). There is no therapeutic application of atropine for CNS diseases; for the CNS, atropine is just a poison. Introduction of an isopropyl group into atropine yields isopropylatropine (ipratropium). Due to the quaternary amino group, the latter drug does not penetrate into the CNS and can be applied via inhalation for the treatment of asthma and COPD without the risk of ADRs in the CNS. With further chemical modifications, keeping the quaternary amine function, ipratropium was developed into tiotropium that possesses a particularly long duration of action (see ▶ Chap. 14).

The BBB is also exploited with another M_xR antagonist. Scopolamine is a tertiary amine that penetrates the BBB well and is used for the treatment of kinetosis (see ▶ Chap. 6). Via butyrylation scopolamine is converted into butylscopolamine. This drug does not penetrate the BBB but can be effectively used to treat colic pain caused by the contraction of smooth muscle cells (GI tract, gall bladder, and ureteric colic and menstrual pain) (see ▶ Chaps. 5, 13, and 23). The positive charge

also reduces absorption following p.o. administration. Therefore, for severe colic pain, butylscopolamine is administered i.v.

One feature of AD is degeneration of cholinergic neurons (see ▶ Chap. 30). Accordingly, one therapeutic strategy aims at improving the function of the remaining cholinergic neurons. This can be accomplished by the AChEI donepezil that penetrates the BBB. In contrast to AD, in myasthenia gravis it is important to inhibit AChE exclusively in the periphery to enhance the function of the remaining nAChR and the neuromuscular end plate (see ▶ Chap. 5). This goal can be accomplished by administration of AChEIs that possess a quaternary nitrogen (prototype neostigmine) and, therefore, cannot penetrate the BBB. A disadvantage of the latter drug class is that GI absorption is suboptimal so that GI colic pain can result.

Drugs that exert their effects via MOR (see ▶ Chap. 10) also differ from each other with respect to BBB penetration. The MOR agonist morphine penetrates the BBB only moderately because of its two hydrophilic hydroxyl groups. As result, particularly after p.o. administration, morphine exhibits only a relatively slow onset of analgesic effect. In long-term pain therapy, these properties are actually desired because the risk of addiction and tolerance is particularly high upon rapid accumulation of the drug in the CNS following i.v. injection. Acetylation of the two hydroxyl groups of morphine gives rise to the lipophilic prodrug diamorphine or, briefly, heroin. Following i.v. injection, heroin rapidly accumulates in the CNS and is also rapidly converted in its two active metabolites, monoacetyl morphine and morphine. Following i.v. injection, heroin induces effective analgesia and a short-lasting dreamlike state with euphoria. Therefore, heroin possesses a much higher risk of addiction and tolerance than morphine. For these reasons, in many countries, heroin is not approved for pain therapy. However, in certain countries, e.g., the UK, heroin can be prescribed for severe pain. This is an example of culture-dependent differences in pharmacotherapy in different countries.

To prevent relapse of morphine/heroin addiction following detoxification, the BBB-penetrating MOR antagonist naltrexone is used. Methylation of the tertiary amine results in the formation of methylnaltrexone. This drug does not penetrate the BBB but acts only peripherally. This effect of methylnaltrexone is used in the therapy of morphine-induced constipation which is mediated via intestinal MOR (see ▶ Chaps. 10 and 13).

2.4 Significance of the Plasma Half-Life

After five plasma half-lives, a drug is virtually eliminated from the organism. The plasma half-life is of great importance for pharmacotherapy because it determines the duration of action of many drugs. ◘ Table 2.3 provides examples of drugs with widely different plasma half-lives and implications for pharmacotherapy.

The plasma half-life can range very widely, e.g., from 1 to 2 minutes for remifentanil to 2.5 months for amiodarone. The importance of the plasma half-life depends on the specific indication. For example, because of its extremely short half-life, the MOR agonist remifentanil is excellently suited for intraoperative analgesia with a very short postoperative recovery period (see ▶ Chaps. 10 and 27). The drug is applied as i.v. infusion, and the dose can be rapidly adjusted according to individual requirements. For long-term therapy of chronic pain, p.o. administered morphine in extended-release formulation having a duration of action of 8–10 hours is suitable (see ▶ Chap. 10).

For symptom-oriented therapy of pain, the COX inhibitor ibuprofen with its short plasma half-life of 2 hours is well suited (see ▶ Chap. 10). Because of this property, ibuprofen is widely used in the treatment of acute pain such as toothache, postsurgical pain, and pain after injuries to flexibly adapt the drug dose to the extent of pain. Another advantage of the short plasma half-life of ibuprofen is that ADRs, specifically in the GI tract and kidneys and on blood pressure, are transient. For long-term treatment of chronic pain such as in rheumatic diseases, ibuprofen is not feasible because of its pharmacokinetic properties.

For the treatment of chronic diseases, it is important to ensure a constant drug effect. A good example for this concept is the long-term therapy of hypertension with dihydropyridine-type CCBs (see ▶ Chap. 15). The first CCB of this class, nifedipine, exhibits a good relaxing effect on vascular smooth muscle cells, but its effect is only transient due to the short plasma half-life. Fluctuations in BP and reflex tachycardia result, ultimately lead-

Table 2.3 Significance of the plasma half-life for drug effects: examples

Drug	Plasma half-life	Route of application	Pharmacological properties and pharmacotherapeutic consequences	Further contexts in Chaps.
Analgesics				
Ibuprofen (non-MOR agonist)	2 hours	p.o., rectal, i.v.	Because of its short plasma half-life, analgesic therapy is well controllable, particularly in acute pain management.	10
Remifentanil (MOR agonist)	1–2 minutes	i.v., infusion	Because of its ultrashort plasma half-life, TIVA is very well controllable. Rapid postoperative recovery.	10, 27
CCBs				
Amlodipine	35–50 hours	i.v.	Long-acting dihydropyridine. Because of its long plasma half-life, the drug can be taken once daily and – contrary to nifedipine with its short plasma half-life – a constant BP reduction can be achieved. Because of their constant long-term effects, long-acting dihydropyridines are often used in hypertension treatment.	15
Nifedipine	1–2 hours	buccal, p.o., i.v.	Short-acting dihydropyridine. Because of its short plasma half-life, nifedipine is well suited for the treatment of hypertensive emergency. Long-term hypertension therapy should be avoided because BP fluctuations and reflex tachycardia may occur. For long-term therapy, extended-release formulations are available which, however, have been widely replaced by long-acting dihydropyridines.	15
Antiarrhythmic drugs				
Amiodarone	14–100 days	p.o., i.v.	Class I–IV antiarrhythmic drug which is effective in the treatment of AF and VT, but cumulates in many organs (liver, lung, nervous system, cornea) where it can cause severe ADRs. Moreover, amiodarone can cause long-term drug interactions by inhibiting CYP2C9 and CYP3A4. Iodine, which is contained in amiodarone, can lead to thyroid gland diseases. Amiodarone is individually administered and requires a high patient adherence.	17, 21
Dronedarone	12 hours	p.o.	Class I–IV antiarrhythmic drug that had been developed to obtain a drug with properties similar to amiodarone, but with improved efficacy and less ADRs. This aim has only been achieved in part. Dronedarone is less effective, and its ADRs and drug interactions (CYP3A4 inhibition) have to be carefully considered.	17

(continued)

Table 2.3 (continued)

Drug	Plasma half-life	Route of application	Pharmacological properties and pharmacotherapeutic consequences	Further contexts in Chaps.
Thyroid hormones				
T3	24 hours	p.o.	Because of the short half-life time of T3, the desired effects (and ADRs) of a T3 therapy are subject to larger fluctuations than those of a T4 therapy. This is why T3 is not appropriate for long-term therapy of hypothyroidism. Because of its rapid onset of action, T3 is only used to manage emergency situations.	21
T4	7 days	p.o.	After p.o. administration, T4 is converted in the body to T3. Because of the long half-life of T4, its pharmacological effect is very constant and well-tolerated by the patient. In takes some time until adjustments in T4 dosage result in desired (and undesired) effects. Because of this favorable pharmacological profile, T4 is the standard drug in the treatment of hypothyroidism.	21
Interferons				
IFN α-2a	4 hours	s.c.	Stimulation of T cells and, thus, of the immune system to respond to viral infections, especially hepatitis C. Traditional IFN injections have to be administered every other day. Variations in drug concentration result in variable antiviral effects. Adherence problems are due to the required long-term therapy (24–48-72 weeks), frequent administration, and ADRs (e.g., influenza, hair loss, weight loss).	34
Peginterferon α-2a	40 hours	s.c.	Coupling of IFN to polyethylene glycol results in protein stabilization and slower degradation. As a result, the drug has to be injected only once a week and the drug effect is more constant. The therapy is less expensive with better adherence.	34

The half-life of a drug must match its intended clinical use

ing to AP and orthostatic hypotension. This pharmacokinetic problem was partially solved by the development of extended-release formulations of nifedipine, but the duration of action was still not sufficiently long. As a consequence, dihydropyridines with a long plasma half-life (12–50 hours) were developed. These long-acting dihydropyridines ensure constant BP decrease and are well suited for long-term therapy of hypertension with only a low incidence of reflex tachycardias.

Pharmacotherapy with thyroid hormones highlights the advantages of a long plasma half-life as well (see ▶ Chap. 21). In the long-term therapy of thyroid gland diseases, exclusively T4 is used because it possesses a long plasma half-life (7 days) and, as a consequence, a very constant effect. This is therapeutically relevant because thyroid hormones modulate the function of virtually every cell type, and fluctuations in thyroid hormone action are uncomfortable for the patient. For this reason, T3, which is the active metabolite of T4 and possesses a much shorter half-life, is not used for chronic treatment. The clinical use of T3 is restricted to the rare but life-threatening hypothyreotic coma in which rapid drug effects are required.

An extremely long plasma half-life can be very problematic. A paradigm for this case is the class

I–IV antiarrhythmic drug amiodarone. In AF and VT, amiodarone shows good clinical efficacy (see ▶ Chapt. 17), but it possesses an extremely long and variable plasma half-life. The long plasma half-life also entails that only after many weeks, steady-state plasma concentrations are reached. In order to avoid this problem, a saturation therapy with initially high drug doses is often performed. Moreover, absorption following oral administration fluctuates, and there are relevant CYP interactions. These properties render individual titration of a patient with amiodarone quite difficult. TDM can partially alleviate this situation. Furthermore, due to its lipophilicity, amiodarone accumulates in many organs (deep compartments) and can cause serious ADRs. Due to its accumulation in organs, amiodarone cannot be eliminated from the organism via dialysis. Therefore, the physician and the patient have to wait for many weeks to months, until the ADRs, if at all, disappear. Because of these problems, dronedarone, an amiodarone-like drug with better pharmacokinetic properties and a greater therapeutic index, was developed. Although dronedarone possesses a much shorter plasma half-life than amiodarone, hopes for greater clinical efficacy of dronedarone were not fulfilled (see ▶ Chap. 17).

In pharmacotherapy, biologicals (recombinantly produced proteins) are of increasing importance. Insulin and insulin analogs are the classic examples of biologicals. Via the specific exchange of single amino acids, the pharmacokinetic properties of insulin are changed in such a way that it is absorbed either rapidly or slowly from the site of injection (subcutaneous fat tissue). As result, insulin possesses either a short or a long duration of action (see ▶ Chap. 19). EPO is another example of a protein in which the duration of action has been varied. By exchanging defined amino acids, the glycosylation pattern of EPO is changed, resulting in delayed degradation and prolonged duration of action (EPO versus darbepoetin) (see ▶ Chap. 12). Another way of stabilizing a protein and prolonging its duration of action in the organism is pegylation, i.e., the attachment of polyethylene glycol (PEG) groups to the protein. IFN-α-2a, which is used in the treatment of hepatitis C, is an example for this concept (see ▶ Chap. 34). IFN-α-2a has to be injected every other day. As a result, both the antiviral effects and ADRs (flu-like symptoms) fluctuate, resulting in adherence problems. As consequence of IFN pegylation, the patient needs to inject the drug less frequently, and the therapeutic effects are more consistent. Moreover, the required drug doses and treatment costs can be reduced.

The duration of action of certain drugs is not determined by their plasma half-life. Mostly drugs that irreversibly modify target proteins belong to this class of drugs. The de novo synthesis of the target protein terminates drug action. The PPIs (see ▶ Chap. 13), irreversibly acting MAOIs (see ▶ Chap. 28), $P2Y_{12}R$ antagonists, and ASA (see ▶ Chap. 18) belong to this class of drugs. ASA (as salicylic acid) possesses a plasma half-life of 2–4 hours, but inhibition of platelet aggregation as a consequence of irreversible COX-1 acetylation lasts up to 1 week. Drugs that exert their effects via NRs and altered gene expression (e.g., thyroid hormones, sex hormones, mineralocorticoids and GCR agonists) possess a much longer duration of action than would be expected from their plasma half-life (see ▶ Chaps. 1, 11, 21, and 24).

2.5 Significance of CYP Inducers and CYP Inhibitors

CYP3A isoenzymes (55% of all drugs), CYP2D6 (30% of all drugs), and CYP2C isoenzymes (10% of all drugs) are the most important enzymes for drug metabolism. Activity of CYP isoenzymes is modulated by drugs, herbal medicines, and food ingredients. In principle, two ways of modifying CYP activity exist. First, a drug can inhibit the activity of one (or more) CYP(s). Secondly, a drug, via NRs (see ▶ Chap. 1), induces the activity of one (or more) CYP(s) and, thereby, increases enzyme activity. CYP induction can already become a problem when a drug induces the activity of the specific CYP that inactivates the drug because this process reduces drug efficacy during long-term therapy. This problem is particularly relevant for antiepileptic therapy (see ▶ Chap. 25). Accordingly, during long-term therapy with a CYP inducer, the drug dose has to be increased in order to ensure a constant therapeutic effect.

Physiologically, CYP induction is a useful mechanism to protect the liver from potentially toxic effects of xenobiotics. Phenytoin, carbamazepine, and phenobarbital (see ▶ Chap. 25) and

the tuberculostatic drug RMP (see ▶ Chap. 33) are drugs that effectively induce CYPs. Additionally, St. John's wort components and nicotine are effective CYP inducer. Classic CYP inhibitors are the azole antimycotics (see ▶ Chap. 35) and the macrolide antibiotics erythromycin and clarithromycin (see ▶ Chap. 33). Moreover, quinolone antibiotics such as ciprofloxacin (see ▶ Chap. 33), the COX-2 inhibitor celecoxib (see ▶ Chap. 10), the SSRIs fluoxetine and paroxetine (see ▶ Chap. 28), the CCB diltiazem and verapamil (see ▶ Chap. 17), and protease inhibitors for HIV and HCV treatment (see ▶ Chap. 34) can inhibit CYP. Furthermore, the bitter substance naringin from grapefruit juice and constituents of goji berries, uncritically advertised as "superfood," inhibit CYPs.

Effects of CYP inducers and CYP inhibitors manifest themselves as drug interactions when the inducer or inhibitor is co-administered with another drug that is metabolized via the same CYP. The interactions are particularly critical when the inducer or inhibitor changes the effects of a drug with small therapeutic index. mGPCR antagonists (see ▶ Chap. 29), the PDE inhibitor theophylline (see ▶ Chap. 14), the VKA phenprocoumon (see ▶ Chap. 18), and the immunosuppressant ciclosporin (see ▶ Chap. 11) are representative drugs with small therapeutic index.

When a patient is treated with two drugs, in general, there is one possibility of CYP-related interaction. However, when a patient takes four different drugs (or two drugs, an herbal medicine and a critical food), there are already at least six possibilities. The number of possible interactions increases exponentially with the number of administered drugs. It is likely that polypharmacy results in ADRs that trigger the prescription of additional drugs to "treat" the ADRs. Therefore, the most important measure to reduce ADRs and the risk of drug interactions is to reduce the number of drugs as far as possible. Discontinuation of drugs, also referred to as deprescribing, quite often improves the health and well-being of a patient. Therefore, every physician and pharmacist is strongly encouraged to critically review the prescription list of a patient suffering from ADRs.

Table 2.4 shows examples of drug interactions of CYP inducers and CYP inhibitors with CYP substrates. It is rather common that psychiatric patients smoke with the goal to stabilize their psychological situation. However, constituents of cigarette smoke can effectively induce CYPs and, thereby, reduce the efficacy of mGPCR antagonists such as clozapine (see ▶ Chap. 29). The loss of efficacy of mGPCR antagonists can, in turn, deteriorate the psychological situation of the patient, triggering increased cigarette smoking. Therefore, psychiatric patients have to be informed about the deleterious consequences of smoking on the effectiveness of psychopharmacological treatment. The physician has also to ensure that the patient actually takes the prescribed medicine. For surveillance of drug effectiveness and adherence, quite often TDM has to be performed.

Many patients with advanced COPD are treated with the bronchodilator theophylline (see ▶ Chap. 14). Theophylline possesses a small therapeutic range and many ADRs that can limit drug therapy. Quite often, patients with COPD get pneumonia. For pneumonia, quinolone antibiotics are commonly prescribed. The prototypical quinolone ciprofloxacin effectively inhibits metabolism of theophylline, thereby augmenting its ADRs. β-Lactam antibiotics which do not inhibit CYPs, therefore, constitute an alternative to ciprofloxacin. For theophylline, TDM and dose adjustment have to be routinely performed. As an alternative, the patient can be treated with the PDE4 inhibitor roflumilast which possesses a higher therapeutic index than theophylline.

Ciclosporin is an immunosuppressant for treatment of autoimmune diseases and prevention of transplant rejection (see ▶ Chap. 11). The therapeutic index of ciclosporin is small as well. Many patients who are treated with ciclosporin also receive GCR agonists for immunosuppression. However, GCR agonists can cause depression (see ▶ Chap. 28). Often, these patients try to treat the depression themselves with St. John's wort extracts, avoiding consultation of a psychiatrist. But most patients are not aware of the fact that these herbal medicines contain potent CYP inducers that accelerate ciclosporin inactivation. Consequently, the immunosuppressant effects of ciclosporin decrease, deteriorating the autoimmune disease or causing transplant rejection. Therefore, all patients receiving ciclosporin have to be informed about the interaction potential of the drug. In any case, to ensure drug efficacy, TDM has to be performed.

Phenprocoumon inhibits vitamin K-dependent carboxylation of coagulation factors in the liver and

Table 2.4 Significance of CYP inhibitors and CYP inducers for drug effects: examples

Drug 1 (CYP substrate)	Active substance 2 and function at CYP	Modified effect of drug 1	Strategy to solve the problem	Further contexts in Chaps.
CYP inducers (active substance 2)				
Ciclosporin, CYP3A4 substrate	St. John's wort, CYP3A4 inducer	Attenuates immunosuppressive effect of ciclosporin; deterioration of autoimmune disease/transplant rejection	The patient has to be informed that certain herbal medicines and ingredients in food and beverages are not as harmless as they seem and can cause severe ADRs due to CYP interactions; discontinue St. John's wort; perform TDM and adjust the dose; switch to other immunosuppressive drugs, if required	11
Clozapine, CYP1A2 substrate	Nicotine, CYP1A2 inducer	Antipsychotic effect is reduced	TDM. The patient has to be informed that tobacco consumption interferes with clozapine treatment; try nicotine withdrawal; adjust the dose; switch to another mGPCR antagonist, if required	5, 28
CYP inhibitors (drug 2)				
Clopidogrel, CYP2C19 substrate	Pantoprazole, CYP2C19 inhibitor	No metabolic activation of clopidogrel and no inhibition of platelet aggregation; higher risk of stent thrombosis, MI and stroke	Check whether pantoprazole medication is required; dose adjustment of clopidogrel based on platelet function testing	18
Haloperidol, CYP2D6 substrate	Celecoxib, CYP2D6 inhibitor	Enhanced ADRs, particularly EPSs or TdP	TDM and dose adjustment; patient has to be informed about possible interactions with other drugs; avoid fast i.v. injection of haloperidol if the patient is "highly agitated" to prevent life-threatening TdP; use biperiden as antidote against EPSs	4, 17, 29
Phenprocoumon, CYP3A4 substrate	Clarithromycin, CYP3A4 inhibitor	Dangerous hemorrhage	In case of emergency, substitution therapy with coagulation factor concentrates. Vitamin K only slowly antagonizes the effect of phenprocoumon; dose adjustment based on INR monitoring; inform the patient about drugs that interfere with phenprocoumon; check patient's medication and discontinue problematic drugs; switch to a DOAC if required; consider higher treatment costs	18

(continued)

Table 2.4 (continued)

Drug 1 (CYP substrate)	Active substance 2 and function at CYP	Modified effect of drug 1	Strategy to solve the problem	Further contexts in Chaps.
Simvastatin, CYP3A4 substrate	Grapefruit juice, CYP3A4 inhibitor	Rhabdomyolysis with myoglobinemia and acute renal failure	Inform the patient about possible drug interactions between simvastatin and ingredients of food and beverages; instruct the patient on initial symptoms of rhabdomyolysis (muscle pain); adjust the dose and avoid other drugs that can cause rhabdomyolysis (e.g., fibrates)	22
Theophylline, CYP1A2 substrate	Ciprofloxacin, CYP1A2 inhibitor	Enhanced ADRs of theophylline (e.g., tachycardia, diarrhea, agitation)	TDM and dose adjustment; replace ciprofloxacin with another effective antibiotic that does not inhibit CYP1A2 (e.g., β-lactam antibiotics, where applicable); replace theophylline with a more specific PDE4 inhibitor (roflumilast), if required	14

Avoid the hazzle of CYP interactions by minimizing the number of drugs that you prescribe

is used for the treatment of thromboembolic diseases (see ▶ Chap. 18). Phenprocoumon is metabolized via CYP3A4 and CYP2C9. As a consequence, there are many opportunities for interactions, either decreased drug effects (risk of thromboembolism) or increased drug effects (risk of hemorrhage). In case that the patient is treated with a macrolide antibiotic because of a respiratory tract infection, CYP3A4 inhibition can result in life-threatening hemorrhage, whereas treatment with CYP3A4 inducers such as NIPEs or St. John's wort can cause thromboembolism. Therapy with phenprocoumon requires information of the patient, good adherence, and monitoring of drug efficacy.

The HMG-CoA reductase inhibitor simvastatin is used for treatment of dyslipidemia (see ▶ Chap. 22). However, when the bioavailability of simvastatin is increased, rhabdomyolysis can occur (see ▶ Sect. 2.2). This serious risk is increased by co-administration of CYP3A4 inhibitors. Macrolide antibiotics, azole antimycotics, and the bitter substance naringin are CYP inhibitors. Therefore, the consumption of grapefruit juice by patients who receive drugs metabolized via CYP3A4 should be avoided.

Clopidogrel is an irreversible $P2Y_{12}R$ antagonist for secondary prevention of MI and stroke (see ▶ Chaps. 16 and 18). In contrast to many other drugs, CYPs do not inactivate but rather activate clopidogrel. Hence, clopidogrel can be considered as a prodrug. Metabolic activation of clopidogrel occurs via CYP2C19. In some patients, the efficacy of clopidogrel is low. Possible reasons are that the patients possess CYP2C19 with low activity (poor metabolizer) or also receive the PPI pantoprazole that inhibits CYP2C19 (see ▶ Chap. 13). Unfortunately, it has become almost a routine practice to prescribe patients receiving a PAI an additional PPI as long-term therapy to "protect the stomach" (see ▶ Chap. 13). However, the long-term use of PPI has to be viewed very critically due to interactions and ADRs, and the use of gastrotoxic COX inhibitors should be avoided.

2.6 Question and Answers

Questions

Which statement on pharmacokinetics is *NOT* correct?

A. Transporters can contribute to resistance against tumor therapeutics.
B. The first-pass effect describes the effect of a drug in the CNS following i.v. injection.
C. A prodrug is the inactive precursor of a drug.

D. The enterohepatic circulation constitutes a cyclic process of secretion of metabolized drugs into the bile and subsequent intestinal absorption.
E. In a zero-order kinetic, a constant amount of drug is administered or eliminated per time interval.

Answers

A. MRPs can export tumor therapeutics from tumor cells. Selection of tumor cells with high MRP activity can render the tumor resistant against a particular drug.
B. The first-pass effect is defined as inactivation of a drug during the first passage through the liver.
C. Prodrugs are used with the goal to increase absorption of a drug in the GI tract or facilitate penetration through the BBB. In general, prodrugs are more lipophilic than the actual drug. Often, prodrugs are esters that are cleaved in the organism by esterases, thereby releasing the active drug.
D. The enterohepatic circulation prolongs the therapeutic effects and ADRs of a drug. In general, the enterohepatic circulation decreases the controllability of pharmacotherapy.
E. I.v. infusion of a drug is an example for zero-order absorption. Oxidation of ethanol by ethanol dehydrogenase in the liver constitutes an example for zero-order elimination.

Statement **B** is not correct.

2.7 Exercises

A 54-year-old patient has been treated for 3 months with a combination of INH + EMB + RMP for TB. Because of a newly diagnosed type 2 DM, the patient is additionally treated with glibenclamide, but despite adherence to an appropriate diet, hyperglycemia is not improved.

Questions

1. How do you explain the therapeutic failure of glibenclamide?
2. Which other pharmacotherapeutic options do you have to treat the type 2 DM?
3. Is the effect of RMP on CYP2C9 induction reversible?

Answers

1. RMP is an effective CYP inducer, e.g., for CYP2C9. Glibenclamide is metabolized via CYP2C9. Thus, increased glibenclamide inactivation is most likely the reason for its lack of effect on DM.
2. Metformin constitutes the first choice for treatment of type 2 DM. This drug is eliminated via the kidneys without metabolism. Therefore, there is no risk for interaction with RMP at the pharmacokinetic level.
3. After termination of the tuberculostatic therapy, CYP induction by RMP will disappear, and the reduced effectiveness of drugs metabolized via CYP1A2, CYP2C9, CYP2C19, CYP2D16, and CYP3A4 normalizes.

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Drug Allergy

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Drugs and pharmaceutical excipients contained in medicines can cause allergic reactions that are potentially life-threatening. Type I reactions are the result of mast cell degranulation and can lead to anaphylactic shock and death within a very short period of time. I.v. epinephrine (EPI) injection by the physician or the i.m. EPI injection by the patient (auto-injector) constitute the most important therapeutic measures. Type II reactions are characterized by immunologically mediated destruction of blood cells. Type III reactions are characterized by immune complex deposits that result in rheumatic symptoms. In type IV reactions, the HLA system is dysregulated, resulting in clinically heterogeneous autoimmunological reactions. SJS and TEN are particularly dangerous. Certain HLA polymorphisms predispose for type IV reactions.

Key Points

1. Drug allergies can occur unexpectedly and can be life-threatening.
2. Type I reactions comprise a broad spectrum of symptoms, ranging from harmless reactions to death.
3. Application of epinephrine is the most important measure in anaphylactic shock.
4. Morphine, non-depolarizing muscle relaxants, contrast media, COX inhibitors, and ACEI can cause pseudoallergic reactions that are treated like type I reactions.
5. Type II reactions are often caused by immunological destruction of blood cells.
6. Type III reactions are characterized by immune complex deposits causing rheumatic symptoms.
7. Type IV reactions are caused by cell-mediated immune reactions and are clinically heterogeneous.
8. SJS and TEN are the most important type IV reactions.
9. Prevention of drug allergies has high priority.
10. Certain HLA polymorphisms increase the risk of type IV reactions.

3.1 Pathophysiological Background

Many ADRs of drugs can be explained by their mechanism of action and are predictable (see ▶ Chap. 1). In contrast, drug allergies are not due to the mechanism of action and not predictable. Drug allergies can be life-threatening and, therefore, have to be avoided. A drug, its metabolites and pharmaceutical excipients, can cause allergies. These compounds, in general, have a low-molecular mass and act as haptens and, following binding to proteins, as immunogens. They induce allergic reactions in which antibodies or sensitized T cells are generated. Sensitization occurs within days to months after drug exposure and is symptomless. Re-exposure to the drug results in allergic reactions of types I–IV (◘ Table 3.1).

Certain drugs possess a particularly high risk for allergic reactions. Among these drugs are the sulfonamides (see ▶ Chaps. 33 and 35) which have a risk of cross-sensitization with sulfasalazine (see ▶ Chap. 13), ester-type local anesthetics (see ▶ Chap. 26), CAHI (see ▶ Chap. 31), and certain preservatives. Therefore, the use of sulfonamides should be minimized.

Penicillins possess a high risk for allergic reactions as well (see ▶ Chap. 33). However, because of their good antibacterial effectiveness when used for the proper indication, these drugs have a much better risk-benefit ratio than sulfonamides. The risk of sensitization to penicillins is particularly high when these drugs are applied onto the skin or mucosal surfaces. Accordingly, local administration of penicillins must be avoided.

Prior to every pharmacotherapy, the history of drug prescriptions and allergic reactions has to be recorded to minimize the risk of allergic reactions. If a patient has a known and defined allergy, this has to be documented in an allergy card.

The general therapeutic principle for drug allergies is to immediately stop exposure to the allergy-causing medicine and treat the allergy symptomatically, depending on the specific manifestations. Therefore, precise classification of drug allergies is essential.

Table 3.1 Overview of drug allergies and therapeutic principles

Type	Mechanism	Symptoms	Typical drugs/drug classes	Therapeutic principles	Further contexts texts in Chaps.
Type I	IgE-mediated mast cell degranulation and/or pseudoallergic immune reaction caused by CADs	Urticaria, angioedema, itching, anaphylaxis	Penicillins, cephalosporins, metamizole, sulfonamides, CADs (e.g., morphine, suxamethonium, thiopental, non-depolarizing muscle relaxants)	EPI i.v. and/or i.m.; supportive treatment with GCR agonists and H_1R antagonists; avoid CADs, COX inhibitors, and ACEIs in hypersensitive patients; BK_2R antagonists for treatment of angioedema	10, 33, 35
Type II	IgG-/IgM-mediated cell destruction	Hemolysis, thrombopenia, agranulocytosis	Penicillins, methyldopa, TPOIs, sulfonamides	Symptomatic: Substitution of missing blood cells and/or administration of growth factors (EPO, G-CSF)	15, 21, 33, 35
Type III	IgG/IgM immune complex formation	Vasculitis, arthritis, glomerulonephritis, serositis	Penicillins	Symptomatic: GCR agonists and other immunosuppressants to reduce inflammation symptoms; dialysis in case of renal insufficiency	33
Type IVa	Th1 immune reaction (monocytes)	Allergic contact dermatitis, fixed drug reaction	Barbiturates, tetracyclines, COX inhibitors, sulfonamides	Preventive HLA characterization; local administration of GCR agonists	10, 25, 27, 33, 35
Type IVb	Th2 immune reaction (eosinophilia)	Drug-related eosinophilia with systemic symptoms (DRESS)	NIPEs, allopurinol, sulfonamides	Preventive HLA characterization; symptomatic: Fever reduction with COX inhibitors, H_1R antagonists against itching, organ monitoring, water and electrolyte substitution, infection prophylaxis	23, 25, 33, 35
Type IVc	Immunological destruction of keratinocytes	Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)	NIPEs, allopurinol, sulfonamides	Preventive HLA characterization; regulation of water and electrolyte balance in ICU, infection prophylaxis, GCR agonists, TNF inhibitors, other immunosuppressants, immune globulins	23, 25, 33, 35
Type IVd	Activation of neutrophilic granulocytes	Acute generalized exanthematous pustulosis (AGEP)	Penicillins, cephalosporins	Preventive HLA characterization; infection prophylaxis, GCR agonists, and other immunosuppressants	33

For all types of allergy, renewed exposition of allergens has to be strictly avoided. Avoid the use of sulfonamides whenever possible. These drugs are highly allergenic, and in many cases, you have pharmacotherapeutic alternatives!

3.2 Overview on Type I to Type IV Drug Allergies

Type I allergies are immediate reactions that manifest themselves seconds to minutes after drug exposure. Every physician must be capable of diagnosing and treating type I reactions and to discriminate them from type IV reactions. Type I reactions are characterized by IgE-mediated mast cell degranulation (see ▶ Chap. 7). Urticaria, edema (e.g., angioedema, lip and larynx edema), and anaphylactic shock are the cardinal symptoms of type I reactions (see ▶ Sect. 3.3).

Type II and type III reactions develop within minutes to days. In type II reactions, antibodies from the IgG and IgM class are formed, resulting in destruction of hematopoietic cells. Hemolysis, thrombopenia and granulocytopenia are easy to diagnose. Type II reactions are treated by withdrawal of the drug and substitution of the missing blood cells. Type III reactions are caused by deposits of immune complexes containing IgG and IgM in organs, resulting in rheumatic symptoms such as vasculitis, serositis, arthritis, and glomerulonephritis. Again, the therapy is to withdraw the causative drug and to treat organ symptoms. It is critical that in every patient who presents with unclear rheumatic symptoms, the possibility of a drug allergy is taken into consideration.

Like type II and type III reactions, type IV reactions manifest themselves with a delay. They are caused by a cellular response of the immune system in which the HLA system plays a critical role (see ▶ Sect. 3.4). The manifestations and degrees of severity of type IV reactions are heterogeneous. Type IVa reactions are characterized by a Th1-dominated immune reaction with monocyte activation and secretion of IFN-γ and IL-2. Allergic contact dermatitis and fixed drug reactions are typical and non-life-threatening manifestations of type IVa reactions. Type IVb reactions present themselves as Th2-dominated immune responses with eosinophilia and secretion of IL-4, IL-5, and IL-13 that are accompanied by generalized exanthemas, fever, and impaired liver and kidney function.

Type IVc reactions are caused by keratinocyte destruction by cytotoxic T cells. SJS presents with painful blisters in the mouth, pharynx, and genitals and erosive conjunctivitis. In addition, the general condition of the patients is poor, and they have fever. In the even more dangerous TEN, large blisters are formed over the entire epidermis, resulting in disintegration of the entire integument (syndrome of burned skin). As a consequence, large water and electrolyte losses occur, and the risk of infections is very high. The patients suffer from high fever.

In type IVd reactions, IL-8 and granulocyte/macrophage colony-stimulating factor cause massive activation of neutrophils. Therapy of type IV reactions is symptomatic (antipyretics, substitution of water and electrolytes, treatment of infections, inhibition of inflammation with GCR agonists). Due to the limited therapeutic options for type IV reactions, prevention is of high importance (▶ Sect. 3.4).

3.3 Pathophysiology and Therapy of Type I Reaction and Pseudoallergic Reactions

In type I reactions, IgE antigen complexes induce the release of HA, bradykinin, and LTD_4 from mast cells (Fig. 3.1a). These mediators cause symptoms in the skin, GI tract, airways, and the cardiovascular system that deteriorate in a vicious cycle. Type I reactions are divided into four stages. Stage 1 is characterized by itching, urticaria, and angioedema. In stage 2, nausea, colic pain in the GI tract, hoarseness, dyspnea, tachycardia, hypotension, and arrhythmias constitute additional symptoms. As a consequence of larynx edema and bronchospasm, cyanosis with subsequent O_2 depletion develops in stage 3, resulting in shock and loss of consciousness. In stage 4, apnea and death occur.

For successful therapy of type I reactions, it is critical to recognize early symptoms and to insert a peripheral venous catheter. The catheter serves to inject EPI in doses commensurate with the clinical symptoms. Via the β_2AR, EPI inhibits mediator release from mast cells and relaxes bronchial smooth muscle cells (see ▶ Chap. 5). Via the α_1AR, EPI mediates vasoconstriction and detumescence of edema in the face, mouth, and larynx. Via the β_1AR, EPI enhances cardiac function. Patients with known severe type I allergies (also against other antigens than drugs such as grass pollen or food constituents) have to be equipped with an EPI auto-injector. Upon injection into the

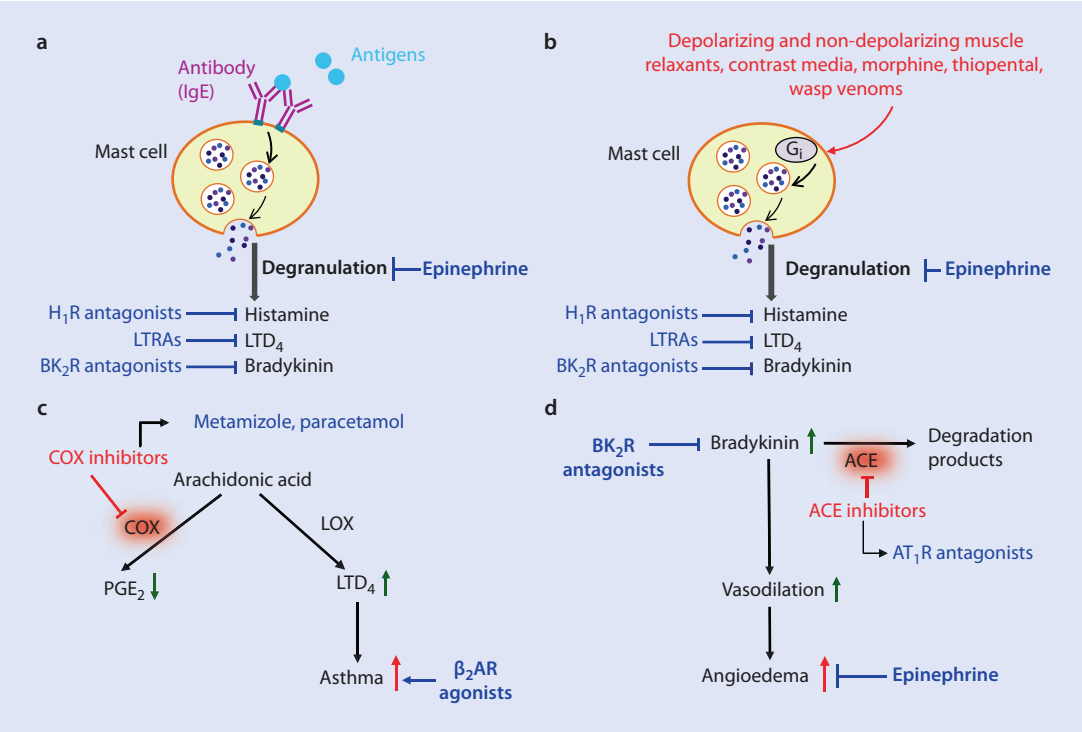

Fig. 3.1 **a–d** Allergic and pseudoallergic drug reactions. **a** Type I reaction (anaphylaxis, IgE-mediated). **b** Pseudoallergic reaction – direct G protein activation by CADs. **c** Pseudoallergic reaction – analgesic asthma caused by COX inhibitors. **d** Pseudoallergic reaction – ACEI intolerance (see also Fig. 7.2). Analyze the cause of an allergic reaction only after you have treated it properly. EPI is the most important drug, not GCR agonists and not H_1R antagonists

thigh muscles, the auto-injector provides sufficient EPI to moderately alleviate allergic symptoms until an emergency physician can treat the symptoms professionally. Auto-injectors can also be used by trained relatives of patients or physicians who do not have routine in the treatment of type I reactions. Since the EPI dose in auto-injectors is smaller than in EPI preparations for i.v. application and the absorption into the systemic circulation is slower, the maximum effect of the auto-injectors is smaller than that obtained with i.v. preparations of EPI. However, the risk of cardiac complications is smaller as well.

For fear of cardiac complications in anaphylaxis, EPI is still widely underused. Instead, H_1R antagonists are used very frequently (see ▶ Chap. 7). They can mitigate itch and urticaria, but their effects on severe edema in the face, mouth, and larynx are insufficient, and asthma is not influenced at all. The frequent use of H_2R antagonists in anaphylaxis to protect the stomach from "stress ulcer" is questionable as well. It is also common practice to inject high doses of GCR agonists in anaphylaxis. In single high doses, GCR agonists cause membrane stabilization and may prevent relapse of anaphylaxis, but their onset of action in acute anaphylaxis is much slower than that of EPI. LTRAs are used in prophylaxis of asthma but not in anaphylaxis. BK_2R antagonists (prototype icatibant) are predominantly used in hereditary angioedema that is characterized by massive bradykinin release, but in anaphylaxis, BK_2R antagonists are not routinely used.

Symptoms of type I allergies can not only be induced by IgE. Certain CADs such as morphine (see ▶ Chap. 10), non-depolarizing muscle relaxants (see ▶ Chap. 5), contrast media (see ▶ Chap. 12), the injection narcotics thiopental and propofol (see ▶ Chap. 27), and the solubilizer Cremophor EL (see ▶ Chap. 32) can stimulate mast cells following i.v. injection via receptor-independent G protein activation (Fig. 3.1b) (see ▶ Chap. 7). The therapy of pseudoallergic reactions does not differ from the therapy of allergic reactions. The i.v. injection of

EPI and the immediate interruption of supply of the causative drug are critical.

Analgesic asthma is a milder form of a pseudoallergic reaction that occurs in about 25% of all patients with chronic urticaria and 10% of all patients with asthma (Fig. 3.1c). If these patients are treated with COX inhibitors, PGE_2 synthesis decreases, and fever and pain are mitigated, but at the same time, AA metabolism is shifted toward LOX. LOX produces LTD_4 that deteriorates asthma. Therefore, COX inhibitors must be used with caution in asthma patients to avoid pseudoallergic reactions. If asthma attacks occur, they can be treated with β_2AR agonists. In asthma patients with analgesic asthma, paracetamol and metamizole can be used. For pain therapy, orally applied MOR agonists constitute an option (see ▶ Chap. 10).

ACEI can cause symptoms of a pseudoallergic reaction as well, particularly edema in the face, mouth, and larynx (Fig. 3.1d). ACEI inhibits the degradation of bradykinin and, thereby, enhance its proinflammatory effects. If patients treated with ACEI develop angioedema spontaneously or after insect stings, EPI is the drug of choice to treat the symptoms. The symptoms caused by bradykinin under ACEI therapy can also be alleviated by BK_2R antagonists, but the therapy is expensive. Therefore, patients suffering from angioedema under ACEI therapy should be switched to AT_1R antagonists. These drugs do not interfere with bradykinin degradation but possess similar effectiveness as ACEI in cardiovascular diseases (see ▶ Chaps. 15 and 16).

3.4 Pathophysiology and Prevention of Type IV Reactions

As already mentioned in ▶ Sect. 3.2, SJS and TEN are life-threatening without availability of a causative therapy. Therefore, prevention of type IV allergies is of particular importance. Although their manifestations are heterogeneous and although different immune cell populations are involved (Table 3.1), a common mechanism underlies all type IV allergies (Fig. 3.2). Human leukocyte antigens (HLAs) possess important functions in immune defense against bacterial and viral infections. Immune cells degrade both endogenous and exogenous proteins to peptides. These peptides bind to intracellularly localized HLAs. Following translocation to the plasma membrane, HLAs that are bound to exogenous peptides are recognized by CD8-positive T cells and initiate an immune reaction directed toward defense against infections. HLAs bound to endogenous peptides do not initiate an immune response. HLAs possess allosteric binding sites to which certain drugs can bind. Binding of drugs to allosteric sites in HLAs alters their conformation. The immune system recognizes these allosterically modified HLAs as exogenous (foreign) and, depending on the specific immune cell types involved, initiates a particular immune reaction. Thus, type IV reactions represent drug-induced autoimmunological processes.

HLAs exhibit interindividual variability. This is of clinical relevance because certain HLA polymorphisms favor binding of specific drugs and, hence, initiation of type IV reactions. The HLA allel B*5701 is a typical example. If this allel is present, patients will develop a type IV reaction with a probability of 90% when treated with the HIV drug abacavir, an NRTI (see ▶ Chap. 34). The abacavir hypersensitivity reaction (ABC-HSR), characterized by maculopapular exanthemas and impaired general condition, can be avoided if the presence of the specific HLA allel is excluded prior to therapy. There are also HLA polymorphisms that favor the occurrence of type IV reactions under treatment with the uricostatic drug allopurinol (see ▶ Chap. 23) or the NIPE carbamazepine (see ▶ Chap. 25). Thus, by analysis of HLA polymorphisms, the risk of type IV reactions can be reduced, representing an example of individualized drug therapy.

3.5 Question and Answers

Questions

Which statement on drug allergies is *NOT* correct?

A. In type I reactions, EPI alleviates edema and bronchospasm.
B. Type IV reactions can be effectively treated with EPI.
C. Type IV reactions are characterized by dysregulation of HLA antigens.
D. Type I reactions can result in death within few minutes.
E. Because of the high risk of allergies, sulfonamides should be avoided.

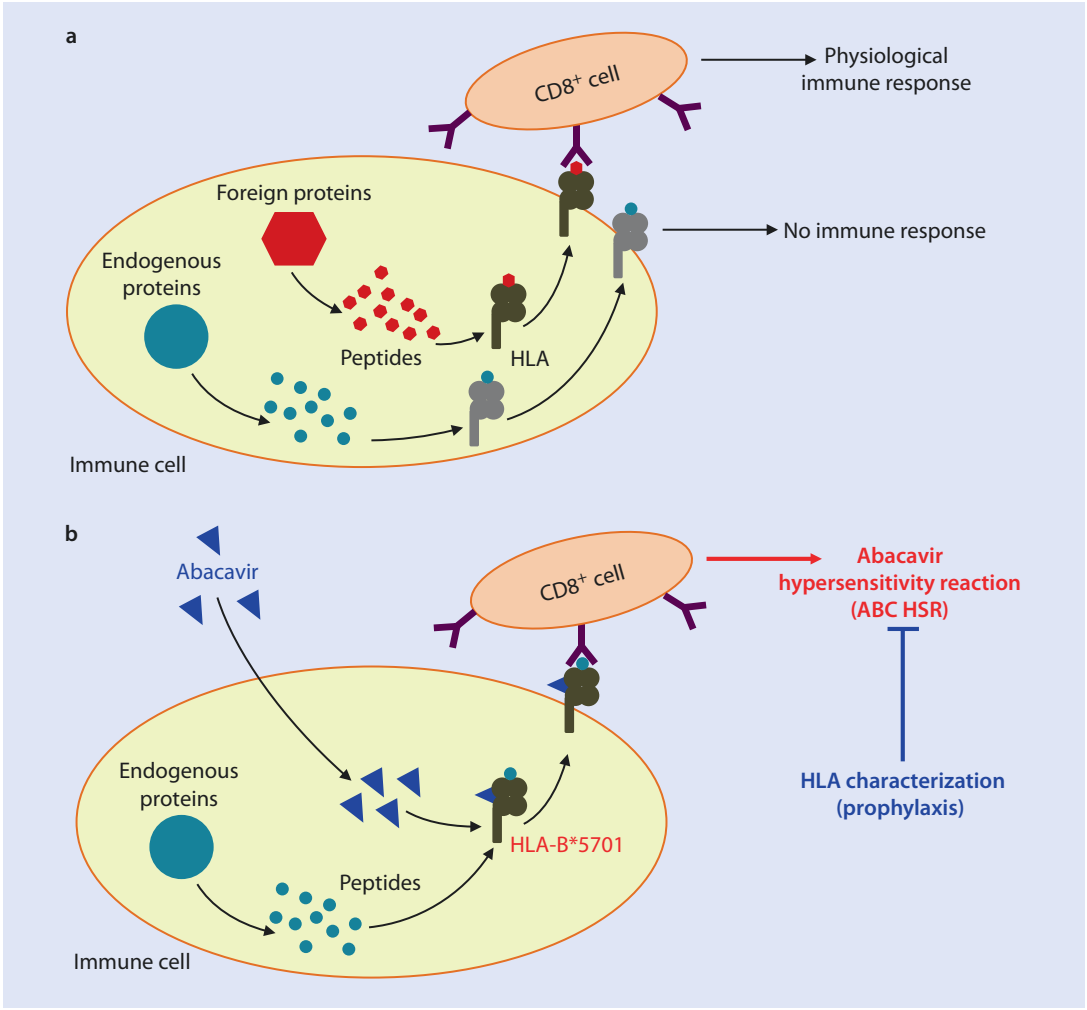

Fig. 3.2 **a**, **b** Pathophysiology of type IV reactions illustrated for abacavir (ABC-HSR). **a** No type IV reaction in the absence of abacavir. **b** ABC-HSR in the presence of abacavir. The ABC-HSR cannot be treated with EPI! You must be able to differentiate a type I reaction from a type IV reaction. These reactions are treated very differently

Answers

A. Via the α_1AR, EPI induces vasoconstriction, and via the β_2AR, EPI induces bronchodilation.

B. It is of eminent clinical importance to distinguish between type I and type IV reactions because type IV reactions cannot be treated with EPI.

C. Type IV reactions are characterized by a drug-induced allosteric conformational change in HLA antigens which results in the modified antigens being recognized as exogenous (foreign) by immune cells, triggering an immune reaction.

D. Via severe bronchospasm and anaphylactic shock, type I reactions can be lethal within few minutes, requiring immediate treatment (EPI administration). Type II–IV reactions are delayed in onset.

E. Sulfonamides belong to the drugs with the highest risk of allergic reactions. Therefore, the clinical use of sulfonamides should be restricted to indications where there is no other therapeutic alternative, i.e., bacterial infections with positive antibiogram with no other antibiotic being effective or infections with *Pneumocystis jirovecii*.

Statement **B** is not correct.

3.6 Exercises

A 61-year-old woman with CHF has been stung into the mouth by a bee and develops a severe edema of the face, lips, tongue, and larynx. The patient is treated with ramipril, metoprolol, and furosemide.

Questions

1. Which drug is most likely the cause for the angioedema?
2. What is the emergency treatment for the patient?

Answers

1. Ramipril is the most likely cause for the angioedema. This drug belongs to the class of ACEIs which inhibit bradykinin degradation. In insect sting reactions, bradykinin is released, causing severe angioedema when its degradation is inhibited. Therefore, the patient should be switched to an AT_1R antagonist (e.g., candesartan). This class of drugs does not inhibit bradykinin degradation.
2. The emergency physician slowly injects EPI i.v. This drug rapidly alleviates the life-threatening angioedema via α_1AR-mediated vasoconstriction. The EPI dose is adjusted according to the observed clinical effect. If a patient is known to have a propensity for angioedema, regardless of the specific cause, the patient should be given an EPI auto-injector. EPI is applied i.m. into the thigh muscles. EPI-applied i.m. does not act as rapidly as EPI-applied i.v., but the time between onset of angioedema and arrival of the emergency physician can be bridged. Only after injection of EPI, other pharmacotherapeutic measures such as application of GCR agonists at high does and H_1R antagonists should be considered.

Further Reading

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Treatment of Drug Intoxications

R. Seifert, *Basic Knowledge of Pharmacology*, https://doi.org/10.1007/978-3-030-18899-3_4

Drug intoxications are common. Drug ingestion mostly occurs orally. In adults, suicidal intoxications dominate, in children accidents. After recording the specific circumstances of the intoxication, primary poison elimination should be performed using absorbents. If the poison has already been absorbed into the organism, secondary poison elimination is conducted. Repeated application of absorbents, forced diuresis, dialysis, and plasmapheresis can be applied, but the effectiveness of these measures is very different for individual drugs. For certain drugs, specific antidotes are available. However, in most cases, therapy of drug intoxications is symptomatic. Because drug intoxications are so common, preventive measures such as avoidance of polypharmacy, adherence to dosing schemes, and recognition of suicidality in depressive patients are of eminent importance.

Key Points

1. Drug intoxications are common, mostly occur orally, and often have a suicidal background.
2. Key questions: Who? Why? When? Which drug? Which dose? Which circumstances? How?
3. Maintaining vital functions and primary poison elimination have the highest priority.
4. In case of poison absorption, secondary poison elimination is implemented.
5. Some intoxications are characterized by typical cardinal symptoms.
6. For some intoxications, specific antidotes are available.
7. Many intoxications can only be treated symptomatically.
8. The prevention of intoxications has high priority.

4.1 General Aspects on Intoxications

Intoxications account for about 2–15% of treatment cases in the emergency room. Most of these intoxication cases are due to drugs and most result of oral administration. In adults, suicidal intoxications dominate, while in children, accidental intoxications prevail. About 10% of all intoxications are due to illicit drugs (e.g., heroin, cocaine, methamphetamine, CB_1R agonists), and about 5% of all cases are due to excessive ethanol consumption. This chapter focuses on the treatment of drug intoxications. ◘ Table 4.1 provides a summary of important drug classes that can cause intoxications, of cardinal symptoms, and of therapeutic measures.

For effective treatment of intoxications, recording of the specific circumstances is essential. The following questions must be answered:

1. *Who* ingested the drug (age, sex)?
2. *Why* was the drug ingested (accident, suicide, attempted homicide, medication error)?
3. *When* was the drug ingested? Answering this question is important for assessing the effectiveness of primary and secondary poison elimination procedures.
4. *Which drug* was ingested? Packages, blister packs with missing tablets, individual tablets, and medication package inserts have to be secured.
5. *Which dose* was ingested? Information gathered under point 4 may help answering this question.
6. *Which circumstances* resulted in the intoxication? Temporal and spatial reconstruction of the intoxication may yield important information.
7. *How* was the drug ingested? In most cases, the drug was ingested orally, but inhalation, transdermal application, i.v. injection, and nasal application have to be considered as well.

In parallel to answering the above questions, the vital functions of the patients (respiration, cardiovascular function) must be maintained. It is also important that the physician protects himself against cross-intoxication. However, this issue is more relevant for intoxications with gases and chemicals than with drugs. Since many drugs induce nausea and vomiting in high doses, it is essential to prevent aspiration by placing the patient into a stable side position.

Because many intoxications can only be treated symptomatically, prevention is of particular importance. The basic rule to keep drugs out

Table 4.1 Cardinal symptoms, treatment, and antidotes for important drug intoxications

Drug class	Typical drug(s)	Cardinal symptoms	Treatment	Further contexts in Chaps.
AChEIs	Neostigmine, pyridostigmine, irinotecan	Muscarinic syndrome: increased secretion of tears, saliva, sweat, and bronchial mucus, GI and bladder spasms, miosis	Antidote: atropine	5, 32
Alkali metal ions	Lithium	Ataxia, unconsciousness, dehydration, epileptic seizures, coma, TDM to confirm diagnosis	Dialysis (natriuresis)	12, 28
Alkylating agents	Cyclophosphamide	Acrolein-induced hemorrhagic cystitis	2-Mercaptoethane sulfonate (MESNA); binds acrolein	32
Antiemetics	MCP	Acute dyskinesia particularly in toddlers whose BBB is not yet fully developed	Antidote: biperiden	2, 8, 13
Antithrombin III activators	UFHs	Prolonged hemorrhage time after injuries, spontaneous hemorrhage of inner organs	Antidote: protamine (binds heparin via electrostatic interactions); protamine is NOT an antidote for LMWHs	18
Anti-TB drugs	INH	Vitamin B_6 deficiency	Antidote: vitamin B_6	33
β_xAR antagonists	Propranolol, metoprolol	Bradycardia, AV block, hypotension, sedation (plus hypoglycemia after propranolol administration)	Antidote: EPI; symptomatic treatment	5
Benzodiazepines	Diazepam, midazolam. In combination with ethanol or morphine, the effects are potentiated	Sedation, unconsciousness, respiratory depression, hypotonia of the skeletal muscles	Antidote: flumazenil (only short duration of action, repeated injections are required); mechanical ventilation in case of respiratory depression	25
D_2R-mGPCR antagonists	Haloperidol	Acute dyskinesias, tremor, disorders of consciousness	Antidote: biperiden in acute dyskinesias; otherwise symptomatic treatment	29
Depolarizing muscle relaxants, haloethers	Suxamethonium, sevoflurane, desflurane	Malignant hyperthermia	Antidote: dantrolene; sedation with propofol	27

(continued)

Table 4.1 (continued)

Drug class	Typical drug(s)	Cardinal symptoms	Treatment	Further contexts in Chaps.
DHFR inhibitors	MTX	Growth inhibition of rapidly proliferating cells (mucositis, diarrhea, bone marrow suppression)	Antidote: folinic acid (replaces the missing product of the enzymatic reaction)	32
Diverse drug classes	Classic cytostatics, TPOIs, metamizole, clozapine	Agranulocytosis	The drug that causes agranulocytosis should be discontinued; administration of G-CSF (filgrastim)	10, 21, 29, 32
Factor Xa inhibitors	Rivaroxaban	See thrombin inhibitors	Antidote: andexanet, replacement of coagulation factors in acute and severe hemorrhage	18
First-generation H_1R antagonists	Diphenhydramine	Antimuscarinic syndrome	Physostigmine, symptomatic treatment	7
MOR agonists	Morphine, heroin (in case of drug abuse, look for needle marks on the whole body)	Respiratory depression, sedation, constipation, miosis (heroin addicts often use mydriatic eye drops to conceal the drug abuse!)	Antidote: naloxone (only short duration of action; repeated injections are required), mechanical ventilation, treatment of withdrawal symptoms with clonidine	10
M_xR antagonists	Atropine (black nightshade poison, drug used in anesthesia), scopolamine (drug against motion sickness)	Antimuscarinic syndrome: reduced secretion of tears, saliva, sweat, and bronchial mucus, constipation, urinary retention, mydriasis	Antidote: physostigmine	5
Na^+-/K^+-ATPase inhibitors	Digoxin, digitoxin	Yellow-green vision, any type of arrhythmias, confusion, nausea, vomiting	Antidote: F_{ab} antibody fragments, symptomatic treatment; avoid use of Na^+-/K^+-ATPase inhibitors as intoxication prophylaxis	16
Non-depolarizing muscle relaxants	Vecuronium, alcuronium	Respiratory paralysis	Antidote: neostigmine	5
Non-MOR agonists	Paracetamol	Liver failure (nausea, vomiting, abdominal pain, icterus, increased hemorrhage risk) and early symptoms are unspecific	Antidote: acetylcysteine (replaces missing glutathione)	10
	ASA	Tinnitus, fever, nausea, vomiting, respiratory paralysis, shock	Urine alkalinization (dialysis)	10

Table 4.1 (continued)

Drug class	Typical drug(s)	Cardinal symptoms	Treatment	Further contexts in Chaps.
NSMRIs	Amitriptyline	Agitation, hallucinations, epileptic seizures, arrhythmias, hypotension, antimuscarinic syndrome	Symptomatic treatment	28
PDE inhibitors	Theophylline (nonselective PDE inhibitor)	Nausea, vomiting, tachycardia, BP drop, tremor, agitation, seizures	Symptomatic treatment (β_1AR antagonists)	14
	Sildenafil (PDE5 inhibitor). The combination with GTN is dangerous	Blue vision, hypotension, tachycardia, flush, constipated nose	Symptomatic treatment	9
SSRIs	Sertraline	Serotonin syndrome (seizures, hallucinations, nausea, vomiting, tachycardia, hypertension)	Symptomatic treatment (NIPEs, mGPCR antagonists, 5-HT_3R antagonists, β_1AR antagonists)	6, 28
Thrombin inhibitors	Dabigatran	Prolonged hemorrhage time after injuries, spontaneous hemorrhage of inner organs	Antidote: idarucizumab (binds dabigatran), replacement coagulation factor therapy in case of acute severe hemorrhages	18
Thyroid hormones	T_4, also bovine desiccated thyroids ("natural" thyroid hormones)	Tachycardia, hypertension, nausea, vomiting, hyperthermia	Antidote: metoprolol (β_1AR antagonist); plasmapheresis, symptomatic treatment (benzodiazepines for agitation)	21
VKAs	Phenprocoumon	Prolonged hemorrhage time after injuries, spontaneous hemorrhage of inner organs	Antidote: vitamin K, but delayed onset of action, replacement coagulation factor therapy in case of acute severe hemorrhages	18

Analyze the cardinal symptoms in (suspected) drug intoxications! They provide you with valuable information about the possible cause and, hence, treatment!

of reach of children, e.g., in lockable cabinets, but not in bathroom or kitchen drawers or on night stands, is, unfortunately, not followed generally. In addition, lack of adherence to medication plans constitutes a relevant clinical problem. Errors can occur at the level of physicians, pharmacists, nurses, relatives, and the patient himself. Clearly written medication plans and medication aids are important for the prevention of drug intoxications.

Patients with psychiatric diseases, most notably patients with depression, are at particularly high risk for drug intoxications (see ▶ Chap. 28). The physician has to assess the suicide risk of patients while recording the medical history. Patients with high suicide risk have to be admitted to the hospital or closely supervised by the physician and relatives. Explicit suicidal thoughts must be taken seriously. Suicidal patients never must be handed out large packages of NE/5-HT enhancers, mGPCR antagonists, benzodiazepines, or MOR agonists because these drug classes can cause severe intoxications (see ◘ Table 4.1).

The consideration of concomitant diseases can reduce the risk of drug intoxications as well. For example, in patients with CKD, the emergency antihypertensive drug SNP should be avoided since in these patients, the risk of cyanide intoxication is particularly high (see ▶ Chap. 12). In patients with liver diseases, the non-MOR agonist paracetamol should only be used very cautiously because this drug is hepatotoxic (see ▶ Chap. 10). In patients suffering from epilepsy, theophylline, NSMRIs, and mGPCR antagonists should be administered only at low doses because these drugs can induce or aggravate seizures (see ▶ Chap. 25).

The combination of certain drugs can cause intoxications as well. Combination of the PDE5 inhibitor sildenafil with the NO donor GTN can cause life-threatening hypotension and MI (see ▶ Chap. 9). If a patient under therapy with the VKA phenprocoumon is additionally treated with the macrolide antibiotic erythromycin because of an intercurrent bacterial infection, life-threatening hemorrhage can occur because certain macrolides inhibit phenprocoumon inactivation via CYP3A4 (see ▶ Chaps. 2 and 18). Therefore, it is very important that all physicians involved are fully informed about the patient's medication plan. This also includes OTC medicines and herbal medicines.

4.2 Primary Poison Elimination

If the time interval between drug ingestion and arrival of the physician is only short, primary poison elimination is indicated and often successful. Historically, induced vomiting with syrup of ipecac (onset of effect within 10 minutes) or D_2R agonists like apomorphine had been performed. However, the risk of aspiration and esophagus cauterization had been so substantial that the procedure is no longer used. Currently, gastric lavage with isotonic solutions under endotracheal intubation is the measure of choice. To avoid vagal reactions, atropine is applied i.v. (see ▶ Chap. 5). Intestinal lavage with isotonic fluids is an alternative to gastric lavage.

Application of activated charcoal (0.5–1 g/kg body weight), in isotonic drinks or by gastric lavage, constitutes a component of every drug intoxication treatment regimen. Activated charcoal is very porous and possesses an absorption area of 1.000–2.000 m^2 per g. This antidote absorbs most drugs non-specifically. However, activated charcoal does not work in intoxications with organic solvents, acids, bases, and salts. If activated charcoal is applied just in water and not with isotonic solutions, there is a risk of hypotonic electrolyte imbalances.

4.3 Secondary Poison Elimination

Even after poison absorption has taken place, therapy with activated charcoal is performed. Activated charcoal absorbs drugs or drug metabolites in the intestine that were secreted into the bile. Hence, activated charcoal interrupts the enterohepatic circulation. Via urine alkalization, ASA elimination can be enhanced (see ▶ Chaps. 10, 11, and 18). ASA is a weak acid and predominantly in the protonated (uncharged) state in the usually acidic urine. As a result, ASA can diffuse across the tubules back into the organism. At alkaline urine pH, however, ASA is predominantly in the deprotonated negatively charged state and is eliminated at a higher rate.

The alkali metal ion lithium, used in depression and bipolar disorder, possesses only a very small therapeutic index (see ▶ Chap. 28) and can be eliminated from the organism via dialysis. However, dialysis cannot be used for drugs with high plasma protein binding. In these cases,

special elimination procedures have to be applied. In plasmapheresis, plasma proteins are separated from blood cells through membranes or via centrifugation, and contaminated proteins are replaced by drug-free proteins. These procedures are expensive and risky, though.

4.4 Cardinal Symptoms, Treatment, and Antidotes for Important Drug Intoxications

In many cases, the symptoms of a drug intoxication can be explained by the mechanism of action of the drug (see ◘ Table 4.1). Drugs with small therapeutic index possess a particularly high risk for intoxication. Among these drugs are lithium and NSMRIs (see ▶ Chap. 28), mGPCR antagonists (see ▶ Chap. 29), T4 (see ▶ Chap. 21), VKAs (see ▶ Chap. 18), and Na^+/K^+-ATPase inhibitors (see ▶ Chap. 16). Therefore, under therapy with lithium, NE/5-HT enhancers, mGPCR antagonists, and Na^+/K^+-ATPase inhibitors, often TDM is performed. In case of a T4 therapy, thyroid gland function is assessed by determination of the TSH concentration in plasma; in case of VKA therapy, effectiveness is monitored by measuring the INR.

The accessibility of a drug plays a role in the frequency of intoxications. For example, paracetamol is available OTC in many countries. However, at doses >8–10 g, paracetamol can cause serious liver intoxication (see ▶ Chap. 10). Hepatotoxicity of paracetamol results from depletion of glutathione. Usually, coupling of paracetamol to glutathione is the major metabolic pathway. Once glutathione is depleted, an alternative pathway is used in which a reactive paracetamol metabolite is formed. If a paracetamol intoxication is diagnosed early, acetylcysteine can be applied i.v., serving as substitute for glutathione and preventing formation of toxic metabolites. In late stages of paracetamol intoxication, liver damage is irreversible and acetylcysteine is without effect.

Certain H_1R antagonists that are available OTC as hypnotics can cause an antimuscarinic syndrome via M_xR antagonism (see ▶ Chaps. 5 and 7). This syndrome can also be caused by atropine (e.g., deadly nightshade intoxication), scopolamine (e.g., inappropriate use of transdermal systems for kinetosis), NSMRIs, and mGPCR antagonists (see ▶ Chaps. 5, 6, 28, and 29).

Because of their small therapeutic index, barbiturates that allosterically enhance the activity of the $GABA_A$R have disappeared from general medical use except for special indications (see ▶ Chaps. 25 and 27). Barbiturates can cause respiratory depression and lack the anxiolytic component of benzodiazepines. In contrast, benzodiazepines, which enhance $GABA_A$R function via another allosteric site than barbiturates, are used frequently because of their anxiolytic, sedative, and muscle-relaxing effects. Compared to barbiturates, benzodiazepines possess a much lower risk for respiratory depression, but in combination with ethanol, respiratory depression can be lethal. The depressing effects of benzodiazepines on respiration can be rapidly reversed by the specific antagonist flumazenil which, however, has only a short duration of action. Therefore, it must be administered repeatedly in benzodiazepine intoxication cases to avoid reoccurrence of respiratory depression.

MOR agonists like morphine, which are of great importance in the treatment of severe pain (see ▶ Chap. 10), can cause respiratory depression when overdosed. The uncritical use of MOR agonists has resulted in a dramatic increase in fatal intoxications in the USA (opioid crisis). In MOR agonist intoxications, the MOR antagonist naloxone can be administered. Again, the short duration of action of the antagonist has to be taken into account, requiring careful monitoring of the patient and reapplication of naloxone.

Visual disturbances can provide important information toward the elucidation of drug intoxications. Miosis is a typical sign of MOR agonist intoxication. However, heroin addicts often dilate their pupils with atropine-containing eye drops to conceal their dependency. Blue vision is typical for intoxication with the PDE inhibitor sildenafil (see ▶ Chap. 9), whereas yellow-green vision is proving intoxication with Na^+/K^+-ATPase inhibitors (see ▶ Chap. 16).

The M_xR antagonist biperiden can be used as antidote for acute dyskinesia as a result of overdosing MCP (particularly in children; see ▶ Chap. 2) and D_2R-mGPCR antagonists (particular following i.v. injection; see ▶ Chap. 29). M_xR antagonists can also be used to treat intoxication symptoms of AChEIs used in the treatment of myasthenia gravis (see ▶ Chap. 5) and AD (see ▶ Chap. 30).

T4 intoxication can result in thyrotoxic crisis (see ▶ Chap. 21). Since T4 regulates virtually

every organ function, symptoms are complex. Unfortunately, no T4R antagonist exists that could act as antidote. But even if such an antagonist were available, the onset of action would be delayed because T4 exerts its effects via altered gene transcription. However, at least a major portion of the cardiovascular symptoms of T4 intoxication that are the result of enhanced β_1AR expression can be alleviated with β_1AR antagonists such as metoprolol.

The onset of action of antidotes is quite variable. Some antidotes such as atropine, biperiden, metoprolol, and naloxone are GPCR antagonists which exhibit rapid onset of action via competition with the toxically acting agonist, particularly following i.v. injection (see ▶ Chaps. 1 and 2). The AChEI physostigmine acts rapidly as well when applied as antidote for antimuscarinic syndrome (see ▶ Chap. 5). F_{ab} antibody fragments can rapidly bind Na^+/K^+-ATPase inhibitors. Via ion pair bond formation, the positively charged protamine rapidly binds and functionally inactivates the negatively charged heparin, and antibodies against thrombin inhibitors neutralize the drug within short time and, thereby, restore thrombin function (see ▶ Chap. 18). In benzodiazepine intoxication, flumazenil exhibits a rapid onset of action as well (see ▶ Chap. 25). Other antidotes such as vitamin K possess a delayed onset of action (see ▶ Chap. 18). In case of severe hemorrhage under VKA therapy, coagulation factors have to be substituted i.v. to bridge the time until resynthesis of carboxylated endogenous coagulation factors. Moreover, folinic acid exhibits a delayed effect in MTX intoxication (see ▶ Chap. 32).

Unfortunately, specific antidotes are not available for most drug intoxications. Therefore, therapy has to be directed toward symptomatic normalization of organ functions. Respiratory depression has to be treated with mechanical ventilation and epileptic seizures with NIPEs. Agitation is mitigated with benzodiazepines, hypertensive emergency is treated with antihypertensive drugs and tachycardia with β_1AR antagonists or the CCBs diltiazem or verapamil, life-threatening hypotension is treated with EPI and water and electrolyte substitution, and nausea is alleviated with antiemetics.

In the therapy of drug intoxications, careful balancing of water and electrolyte metabolism is important. Both dehydration (risk of thrombosis) and hyperhydration (risk of hypertension, kidney failure, lung edema, and brain edema) have to be avoided. Hyperkalemia favors occurrence of bradycardia; hypokalemia triggers tachycardia (see ▶ Chap. 17). Effective balancing of water and electrolyte metabolism facilitates "natural" elimination of toxic drugs via the liver and kidney.

4.5 Question and Answers

Questions

Which assignment of a drug to an antidote is correct?

A. Atropine – scopolamine
B. Diazepam – naloxone
C. Morphine – propranolol
D. Paracetamol – acetylcysteine
E. SNP – vitamin K

Answers

A. Scopolamine, like atropine, is an M_xR antagonist and enhances the effects of atropine. Physostigmine is the antidote for M_xR antagonists.
B. Naloxone is a MOR antagonist and reverses the effects of morphine. Flumazenil is the antidote for diazepam.
C. Propranolol is a β_xAR antagonist that antagonizes effects of EPI and NE. Naloxone is the antidote for morphine.
D. Paracetamol intoxication is characterized by glutathione depletion in the liver, resulting in conversion of paracetamol into a toxic metabolite. Acetylcysteine is a substitute for glutathione and prevents formation of the toxic metabolite.
E. Vitamin K is an antidote for the VKA phenprocoumon. During long-term therapy with SNP, cyanide can be generated. In the presence of its antidote sodium thiosulfate, rhodanide is formed.

Answer **D** is correct.

4.6 Exercises

During the course of eye surgery for strabismus under general anesthesia, the 23-year-old female patient suddenly develops bradycardia. The junior resident physician conducting the anesthesia injects atropine (20 mg) i.v. A commonly applied dose of atropine is 1 mg.

Questions

1. Which ADRs can be expected with such a high atropine dose?
2. Does an antidote for atropine exist?

Answers

1. Atropine is an M_xR antagonist, causing an antimuscarinic syndrome. This syndrome is characterized by inhibition of saliva and sweat secretion, impaired eye accommodation, and paralysis of the smooth muscle cells in the GI tract and bladder. Clinically, the patient presents with hot and dry skin, dry mouth, impaired near vision, increased sensitivity to bright light, obstipation, and urinary retention. In addition, CNS can occur.
2. In order to displace atropine from M_xRs, the concentration of the endogenous agonist ACh must be increased. This can be accomplished with the AChEI physostigmine. This drug penetrates the BBB so that even the CNS symptoms of atropine intoxication can be alleviated.

Further Reading

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Pharmacology of Integrative Systems

Contents

Cholinergic and Adrenergic System

R. Seifert, *Basic Knowledge of Pharmacology*, https://doi.org/10.1007/978-3-030-18899-3_5

The NTs ACh and NE and the hormone EPI regulate numerous organ functions via the autonomic nervous system. In addition, ACh plays an important role as NT at the neuromuscular end plate. ACh acts either via ligand-gated ion channels or GPCRs; NE and EPI act via GPCRs. Agonists and antagonists at these receptors can be used for the treatment of different diseases. Moreover, inhibition of ACh release by botulinum neurotoxin is therapeutically relevant. Inhibition of NT degradation, inhibition of NT reuptake, and stimulation of NT release constitute further options for pharmacological intervention.

Key Points

1. Botulinum neurotoxin inhibits ACh release and is used for therapy of dystonias.
2. AChIs are used for therapy of myasthenia gravis and AD.
3. M_xR antagonists are used for therapy of bradycardia, colic pain, AChEI intoxication, asthma, kinetosis, and pupil dilation.
4. M_xR antagonists cause an antimuscarinic syndrome.
5. Many commonly prescribed drug classes, particularly NSMRIs and mGPCR antagonists, antagonize, among other targets, M_xRs and cause an antimuscarinic syndrome.
6. EPI is used in anaphylactic shock, local anesthesia, and cardiac arrest; NE is used in septic shock.
7. Tachyphylaxis limits the therapeutic use of indirect sympathomimetics.
8. α_1AR agonists are used in rhinitis and conjunctivitis.
9. α_1AR antagonists are used in hypertension and BPH.
10. α_2AR agonists are used in hypertension and pain therapy.
11. α_2AR antagonists and inhibitors of neuronal NE uptake and NE degradation are used in depression.
12. β_1AR antagonists are used for treatment of hypertension, CHD, and CHF.
13. β_2AR agonists are used for asthma, COPD, and premature labor.

5.1 Physiological Background

The autonomic nervous system regulates the function of all peripheral organs. The sympathetic nervous system mediates *flight and fight* reactions and increases the physical capability of the body. In contrast, the parasympathetic nervous system mediates *rest and digest* reactions and serves to regenerate the body. The sympathetic and parasympathetic nervous systems are functionally antagonistic, but the two parts of the autonomic nervous system are not of equal relevance for all body functions. Some body functions are also regulated antagonistically within the sympathetic nervous system. The intercellular signaling molecules (first messengers) within the autonomic nervous system are the NTs ACh and NE and the hormone EPI.

The autonomic nervous system consists of two neurons. The first (preganglionic) neuron originates from the spinal cord and interacts with the postganglionic neuron via the ganglionic synapse. The postganglionic neuron forms a synapse with the effector cell. ACh is the NT in the ganglionic synapse, both in the sympathetic and parasympathetic nervous system. ACh also mediates innervation of effector cells in the parasympathetic nervous system. In the sympathetic nervous system, NE and EPI mediate effector cell innervation. Sweat glands are functionally part of the sympathetic nervous system and are activated by ACh. The adrenal medulla constitutes a modified postganglionic neuron and secretes EPI.

5.2 Acetylcholine Receptors and Adrenergic Receptors

ACh is the endogenous agonist at AChR. ACh does not possess any therapeutic relevance because it is degraded very rapidly. Figure 5.1 provides an overview of AChRs, divided into M_xRs (mAChRs) and nAChRs. nAChRs belong to the class of ligand-gated ion channels (see ▶ Chap. 1). They are comprised of five subunits and mediate sodium entry into cells, resulting in depolarization. Depending on the subunit composition, nAchRs possess different pharmacological properties. The nAChR at the neuromuscular end plate consists of two α1 subunits and a β, δ, and ε subunit.

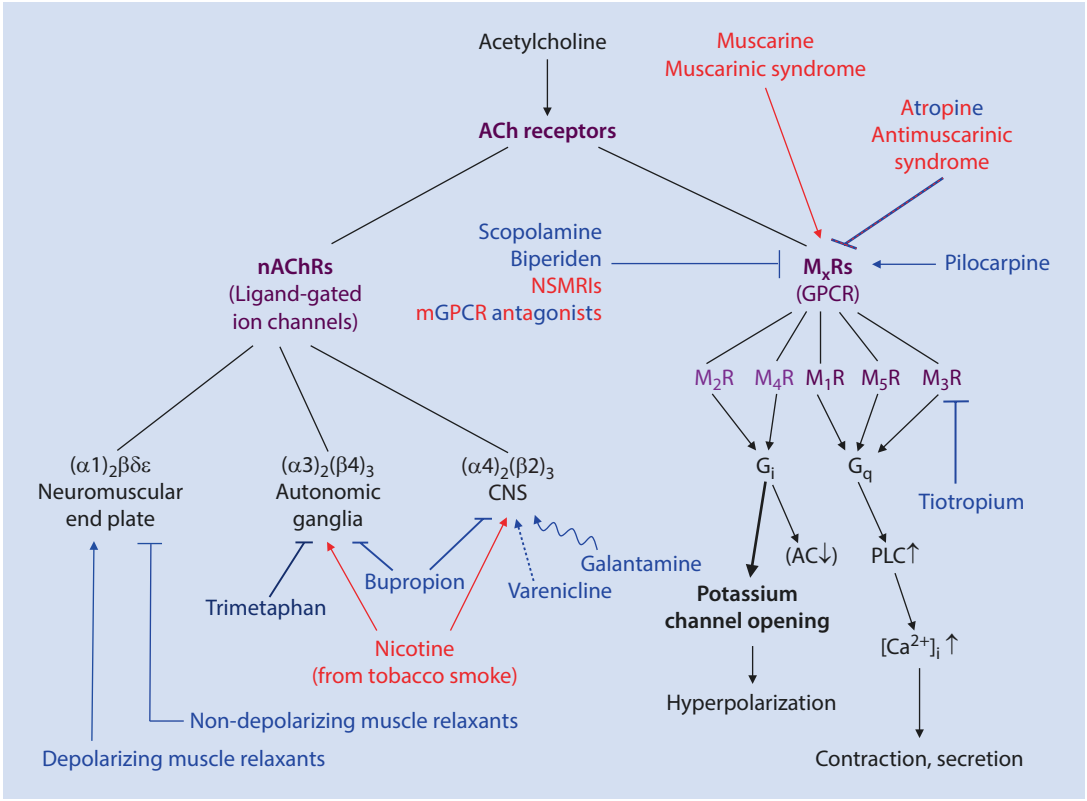


Fig. 5.1 Overview of acetylcholine receptors and selected agonists and antagonists. Additional drugs are shown in Fig. 5.3 and Table 5.1. Many drugs cause an antimuscarinic syndrome! Think of NSMRIs and mGPCR antagonists as cause of an antimuscarinic syndrome in the emergency room

At this nAChR, alcuronium and vecuronium are antagonists. These two drugs are used as non-depolarizing muscle relaxants in anesthesia (see ▶ Chap. 27). Skeletal muscle relaxation facilitates surgery in the abdomen, thorax, arms, and legs. Patients who receive non-depolarizing muscle relaxants have to be mechanically ventilated because of the respiratory paralysis. The classic non-depolarizing muscle relaxant tubocurarine is a CAD and is not used anymore because of its profound effects on mast cell degranulation (see ▶ Chap. 3). For alcuronium and vecuronium, mast cell degranulation is much less pronounced. In case of intoxication with non-depolarizing muscle relaxants, AChEIs are used (see ▶ Chap. 4). As a result, the ACh concentration increases, and ACh displaces the muscle relaxant from the receptor. Suxamethonium (succinylcholine) is a nAChR agonist and is used as depolarizing muscle relaxant (see ▶ Chap. 27). Following short-lasting nAChR activation, clinically presenting as uncoordinated muscle fasciculations, receptor deactivation occurs. Suxamethonium is rapidly inactivated by esterases. Therefore, its duration of action is also very short. Malignant hyperthermia is a serious problem in the clinical use of suxamethonium (see ▶ Chaps. 3 and 27). Additionally, suxamethonium can lead to mast cell degranulation (see ▶ Chaps. 3 and 7).

In ganglionic synapses of the sympathetic and parasympathetic nervous system, nAChRs consist of two α3 and three β4 subunits. Nicotine is an agonist at this receptor and induces a mixture of sympathetic and parasympathetic activation. Trimetaphan is an agonist at ganglionic nAChRs and possesses BP-decreasing properties. However, because of the global paralysis of the autonomic nervous system and the resulting serious ADRs (obstipation, urinary retention, dry and hot skin, mydriasis, increased glare sensitivity), trimetaphan is obsolete.

In the CNS, nAChRs composed of two α4 and three β2 subunits are expressed. Via these receptors, nicotine mediates its stimulatory effects,

Table 5.1 Overview of selected drugs acting on the cholinergic/adrenergic system

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Alcuronium	nAChR antagonist acting on the neuromuscular end plate	Hyperpolarizing muscle relaxant	Used in endotracheal anesthesia	Mast cell degranulation, anaphylaxis	3
Atropine	M_xR antagonist	Blockade of all parasympathetic effects and of sweat secretion	Intraoperative bradycardia, iritis, certain types of myopia (low dose, local application)	Antimuscarinic syndrome: Tachycardia, dry mouth, constipation, urinary retention, mydriasis, hot and dry skin	4, 17, 31
Biperiden	M_xR antagonist	Good penetration of the BBB; thus predominant M_xR antagonism in the CNS	Rigor and tremor therapy in PD; therapy of acute EPSs, caused by D_2R agonists	See atropine	4, 6, 8, 29
Botulinum neurotoxin	Selective inhibition of ACh release at the neuromuscular end plate	Relaxation of skeletal muscles	Dystonias (e.g., spasmodic torticollis)	Excessive skeletal muscle paralysis, allergies, general muscle paralysis in systemic intoxication	1, 10
Butylscopolamine	M_xR antagonist	Relaxation of smooth muscle cells	Colic pain (bile ducts, intestine, uterus, bladder)	In principle as atropine, but no effects on the CNS due to positive charge	10, 13, 23
Clonidine	α_2AR agonist	Reduction of the sympathetic tone	Hypertension, analgesia	Sedation	10, 15
Doxazosin	α_1AR antagonist	Relaxation of smooth muscle cells (blood vessels, prostate)	Hypertension, BPH	Orthostatic hypotension, BP drop	15
EPI	α_xAR- and β_xAR agonist	α_1AR: vasoconstriction β_1AR: positive inotropy β_2AR: bronchodilation	Anaphylaxis (β_1AR, β_2AR, α_1AR), cardiac arrest (β_1AR), local anesthesia (α_1AR, β_2AR)	Excessive EPI effects	1, 3, 17, 26
Metoprolol	β_1AR antagonist	Negative chronotropy, dromotropy, and inotropy	Hypertension, CHD, CHF	In therapeutic doses, bradycardia (β_1AR antagonism), hypoglycemia, and asthma (β_2AR antagonism) are not relevant	15, 16, 17
Mirabegron	β_3AR agonist	Relaxation of smooth muscle cells	Overactive bladder	Desensitization (loss of response) after long-term administration	1

Mirtazapine	α_2AR antagonist	Increased NE release	Depression, various other psychiatric disorders	Tachycardia, hypertension	1, 28
Neostigmine	Reversible AChE inhibition	Increased ACh effects	Myasthenia gravis, overdosed non-depolarizing muscle relaxants	As physostigmine, but no effects on the CNS (tremor, vomiting)	2
Physostigmine	Reversible AChE inhibition	Increased ACh effects	Atropine intoxication	Muscarinic syndrome: bradycardia, salivation, secretion of tears and sweat, bronchoconstriction, urinary urgency, diarrhea, tremor, vomiting	2, 4
Pilocarpine	M_xR agonist	Stimulation of salivation and sweating, miosis	Dry mouth, narrow angle glaucoma, mucoviscidosis diagnosis	Few ADRs after local application	14, 31
Propranolol	β_xAR antagonist	β_1AR: negative chronotropy, dromotropy, and inotropy β_2AR: diverse effects	Infantile hemangioma (vasoconstriction, growth factors↓, β_2AR) essential tremor, migraine prophylaxis	Bradycardia, hypoglycemia, and asthma (β_2AR antagonism at high doses)	1
Salbutamol (albuterol)	Partial β_2AR agonist	Bronchodilation	Acute asthma attack, NOT long-term therapy of asthma	Desensitization (loss of response) after long-term treatment, β_1AR activation at higher doses	1, 14
Scopolamine	M_xR antagonist	Blockade of the vestibular nucleus in the CNS	Kinetosis	In principle as atropine	2, 6
Suxamethonium	nAChR agonist at the neuromuscular end plate	Depolarizing muscle relaxant, initial muscle fasciculations	Constituent of short-term general anesthesia procedures	Mast cell degranulation, malignant hyperthermia	3, 4, 7, 27
Tiotropium	M_3R antagonist; no systemic absorption	Bronchodilation	COPD	Few ADRs after local application, except dry mouth	2, 14
Xylometazoline	α_1AR agonist	Contraction of smooth muscle cells (blood vessels)	Conjunctivitis and rhinitis	Desensitization (loss of response) after long-term treatment	1

MAOIs, NSMRIs, and SSNRIs are discussed in ► Chaps. 6 and 28

activation of the dopaminergic reward system (see ▶ Chap. 8), and addiction. Varenicline is a partial agonist at this receptor and is used for mitigation of nicotine withdrawal symptoms. However, its efficacy is discussed controversially, and the drug possesses serious ADRs including depression and aggression. Bupropion, an antagonist at neuronal and ganglionic nAChR, is used for treatment of nicotine addiction as well. Bupropion prevents activation of nAChR by nicotine. Galantamine is a positive allosteric modulator at neuronal nAChRs and is used in AD treatment (see ▶ Chap. 30).

M_xRs (mAChRs) belong to the class of GPCRs (see ▶ Chap. 1) and are expressed in the CNS and on effector cells. The mushroom poison muscarine is an M_xR agonist and induces a muscarinic syndrome characterized by bradycardia, hypotension, miosis, lacrimation, salivation, sweating, bronchospasm, intestinal spasms, diarrhea, and urinary urgency. In the CNS, muscarine causes vomiting (see ▶ Chap. 6) and tremor (see ▶ Chap. 9). Accordingly, the M_xR antagonist biperiden is used against tremor in PD (see ▶ Chap. 9) and EPSs as ADR under therapy with D_2R-mGPCR antagonists (see ▶ Chaps. 4 and 29). The M_xR antagonist scopolamine is applied against nausea and vomiting in kinetosis (see ▶ Chap. 6).

M_xRs are divided into five subtypes: M_1R, M_3R, and M_5R couple to PLC via G_q proteins. Via these receptors, secretion from glands and contraction of smooth muscle cells is stimulated. The M_3R in smooth muscle cells of the airways is of particular pharmacological importance (see ▶ Chap. 14). Tiotropium is a M_3R antagonist that is widely used for treatment of COPD. Tiotropium is a quaternary amine that only poorly penetrates through membranes and must be therefore applied locally as inhalation spray. M_2R and M_4R couple to G_i proteins and mediate, in addition to AC inhibition, a functionally more important activation of potassium channels in the heart, resulting in hyperpolarization.

Pilocarpine is an M_xR agonist and is used topically for treatment of narrow angle glaucoma (see ▶ Chap. 31). In addition, pilocarpine serves for treatment of xerostomia following irradiation or in autoimmune diseases of the salivary glands (Sjögren syndrome). Atropine, the pharmacologically active substance from the berries of the deadly nightshade, is an M_xR antagonist. Atropine moderately penetrates the BBB and can cause, particularly in children following accidental ingestion of these berries, serious intoxication characterized by CNS and an antimuscarinic syndrome (tachycardia, obstipation, urinary retention, hot and dry skin, dry mouth, mydriasis, and glare sensitivity) (see ▶ Chap. 4). Intrasurgical bradycardia constitutes the most important indication for systemic application of atropine (see ▶ Chap. 17). Atropine is also used topically for induction of mydriasis (see ▶ Chap. 31 and drug list in appendix).

Many commonly prescribed drugs, among other targets, antagonize M_xRs. Among these drugs are NSMRIs (see ▶ Chap. 28) and mGPCR antagonists (see ▶ Chap. 29). Accordingly, such drugs can cause an antimuscarinic syndrome. This is a very common and important ADR of these drugs. However, in case of mGPCR antagonists, the M_xR antagonism can mitigate EPSs (see ▶ Chap. 29).

Figure 5.2 provides an overview of adrenergic receptors. The biogenic amines NE and EPI are the endogenous agonists at adrenergic receptors. These receptors belong to the class of GPCRs (see ▶ Chap. 1) and are divided into α_xARs and β_xARs. The therapeutically obsolete phentolamine antagonizes α_xAR-mediated effects, whereas propranolol antagonizes β_xAR-mediated effects.

α_xARs are divided into α_1ARs (subtypes α_{1A}, α_{1B}, and α_{1D}) and α_2ARs (subtypes α_{2A}, α_{2B}, and α_{2C}). α_1ARs couple to PLC via G_q proteins and mediate contraction of smooth muscle cells. Doxazosin is a prototypical α_1AR antagonist, inducing relaxation of smooth muscle cells. The α_2AR is predominantly localized presynaptically and mediates, via G_i/G_o proteins, inhibition of calcium channels and activation of potassium channels. This results in neuronal hyperpolarization and inhibition of the sympathetic nervous system. Mirtazapine antagonizes the α_2AR and, through blockade of presynaptic inhibition, activates the sympathetic nervous system.

β_xARs are divided into three subtypes (β_1AR, β_2AR, and β_3AR). β_xARs couple to G_s proteins, resulting in AC activation and subsequent cAMP increase (see ▶ Chap. 1). The β_1AR is expressed in the heart and the kidneys, the β_2AR ubiquitously, and the β_3AR in adipose tissue and smooth muscle cells. Although cAMP acts as common second messenger for β_xAR, the biological effects of cAMP are cell type-specific. In the heart, cAMP induces

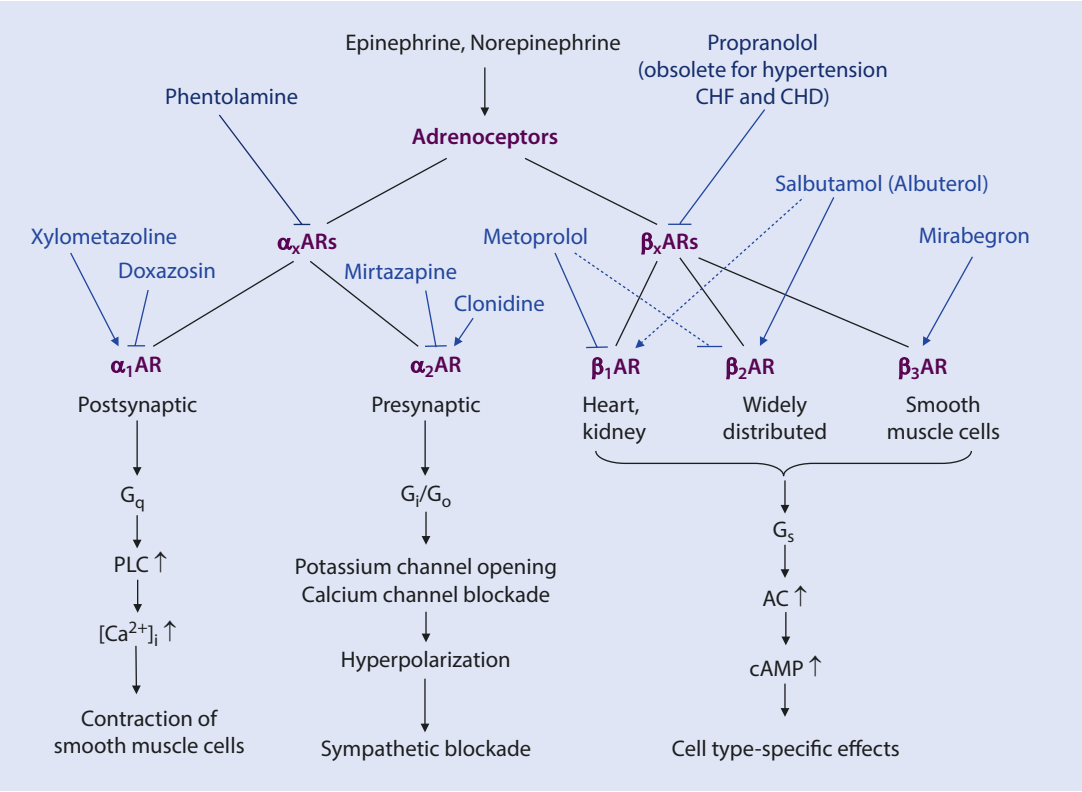


Fig. 5.2 Overview of adrenergic receptors and selected agonists and antagonists. Additional drugs are shown in Fig. 5.4 and Table 5.1. The use of propranolol for hypertension, CHF, and CHD is obsolete

contraction (positive inotropy), but in smooth muscle cells of the respiratory tract and the bladder, cAMP triggers relaxation (see ▶ Chap. 14). An increase in cAMP also inhibits the immune system. β_1AR antagonists like metoprolol that antagonizes the β_1AR with considerably higher potency than the β_2AR (see ▶ Chap. 1) are of great importance for the treatment of cardiovascular diseases. β_2AR agonists such as salbutamol are predominantly used in the treatment of asthma and COPD (see ▶ Chaps. 1 and 14). β_3AR agonists are applied in the treatment of overactive bladder.

The antagonist propranolol exhibits no selectivity among β_xARs. In infantile hemangioma, propranolol induces regression of the vascular tumor via inhibition of growth factors. This effect is mediated via β_2AR antagonism. The effects of the β_xAR antagonist timolol on glaucoma (see ▶ Chap. 31) are consequence of β_2AR antagonism as well. Because of its lack of β_1AR selectivity, propranolol is obsolete for the therapy of hypertension, CHD, and CHF, but it is used for essential tremor and migraine prophylaxis.

5.3 Pharmacological Modulation of Selected Organ Functions by Acetylcholine Receptors and Adrenergic Receptors

In the heart, the β_1AR possesses stimulatory functions. In the sinus node, β_1AR activation mediates positive chronotropic effects, in the atrium and ventricle positive inotropic effects, and in the AV node positive dromotropic effects. These effects, belonging to the sympathetic nervous system, are functionally antagonized by the M_2R, belonging to the parasympathetic nervous system (negative chronotropic, inotropic, and dromotropic effects). In the ventricle, the M_2R is not expressed. This is therapeutically relevant because with atropine, positive chronotropic and dromotropic effects can be induced during intrasurgical bradycardia and AV block without the risk of positive inotropic effects in the ventricle. As a result, the risk of dangerous VT due to alternative β_1AR stimulation, specifically in CHD and CHF, can be avoided (see ▶ Chaps. 16 and 17).

The stimulatory effects of the β_1AR on the heart are used in the therapy of anaphylactic shock and in cardiac arrest. EPI is the drug of choice (see ▶ Chap. 3). The β_1AR is of particularly great importance for the long-term therapy of chronic cardiovascular diseases. β_1AR antagonism results in negative chronotropic, dromotropic, and inotropic effects. Via these mechanisms, the relation between oxygen supply and oxygen consumption in CHD is improved, reducing the probability of AP attacks (see ▶ Chap. 16). In CHF, β_1AR antagonists inhibit the pathophysiologically detrimental activation of the sympathetic nervous system (see ▶ Chap. 16). In hypertension, β_1AR antagonists decrease BP via reduction of CO (see ▶ Chap. 15).

In smooth muscle cells, α_1AR-mediated contraction is of particular importance. α_1AR antagonists such as doxazosin mediate vasodilation. This effect is exploited in hypertension and in CHF. The muscle-relaxing effects of α_1AR antagonists are also used in BPH to facilitate micturition. Local administration of α_1AR agonists like xylometazoline improves impaired nasal inhalation in rhinitis and reduces erythema and itch in conjunctivitis. Both indications exploit vasoconstriction. The β_2AR mediates vasodilation, particularly in the skin. In case of therapy with β_1AR antagonists in high doses, β_2AR antagonism can result, leading to the patient complaining of cold toes and fingers. This ADR actually constitutes a measure to adjust the dose of β_1AR antagonists. M_xR mediates NO-dependent vasodilation (see ▶ Chaps. 12 and 15).

In the GI tract, M_xRs are clinically relevant. The most important function of M_xRs is to induce contraction of smooth muscle cells. In diseases associated with increased contractility of the smooth muscle cells in the GI tract, e.g., in viral infections, M_xR antagonists such as butylscopolamine can be applied p.o. as spasmolytics to alleviate pain (see ▶ Chaps. 10, 13, and 23). In severe colic pain of the gall bladder, biliary tract, or ureter, butylscopolamine has to be applied i.v. to achieve a sufficient pain reduction (see ▶ Chap. 2). M_xR antagonism for colic pain is an example of functional pain therapy (see ▶ Chap. 10).

In the liver, β_2AR activation stimulates gluconeogenesis and glycogenolysis resulting in an increase in blood glucose concentration. The β_2AR in the liver functions as an important rescue mechanism to avoid life-threatening hypoglycemia. Accordingly, upon systemic application of EPI, hyperglycemia develops. During high-dose therapy with β_1AR antagonists, via antagonism at the hepatic β_2AR, hypoglycemia can occur, particularly in diabetics treated with insulin (see ▶ Chap. 19).

In the eye, the sympathetic and parasympathetic systems regulate the wideness of the pupil in an antagonistic fashion. The α_1AR mediates pupil dilation (mydriasis), and M_xR mediates pupil constriction (miosis). The local administration of pilocarpine is of clinical relevance in narrow angle glaucoma in which an IOD increase induces destruction of the retina with subsequent blindness (see ▶ Chap. 31). As a result of miosis, the canal of Schlemm widens, facilitating efflux of fluid from the anterior chamber of the eye and reducing IOD. Short-acting M_xR antagonists such as tropicamide are used for pupil dilation during fundoscopy. Long-acting M_xR antagonists such as atropine are used to avoid synechia between the iris and the lens in iritis.

In bronchi, smooth muscle cells are regulated in an antagonistic fashion by the sympathetic and parasympathetic nervous system. The β_2AR mediates relaxation of smooth muscle cells, whereas the M_3R mediates contraction. These effects are exploited in asthma and COPD (see ▶ Chap. 14). β_2AR agonists and M_3R antagonists reduce respiratory tract resistance. Both drug classes can be combined. Mast cells occur ubiquitously and express the β_2AR. β_2AR activation in mast cells results in inhibition of mediator release, clinically manifesting as an anti-inflammatory effect (see ▶ Chaps. 3 and 7).

The uterus is relaxed via the β_2AR and contracted via M_xR. β_2AR agonists like fenoterol are used i.v. in premature labor (tocolysis) to avoid premature birth. However, for fear of the well-being of the unborn, the β_2AR agonist is often applied in such high doses that the mother suffers from unpleasant β_1AR-mediated tachycardia and β_2AR-mediated hyperglycemia. The hyperglycemia is often misdiagnosed as gestational DM, resulting in inappropriate therapy with insulin (see ▶ Chap. 19). M_xR antagonists like butylscopolamine can be applied p.o. or rectally as suppository to induce relaxation of the uterus.

In the bladder, smooth muscle cells relax as result of β_3AR activation and contract as result of

M_xR activation. Consequently, β_3AR agonists and M_xR antagonists are used for the treatment of functional bladder problems such as overactive bladder.

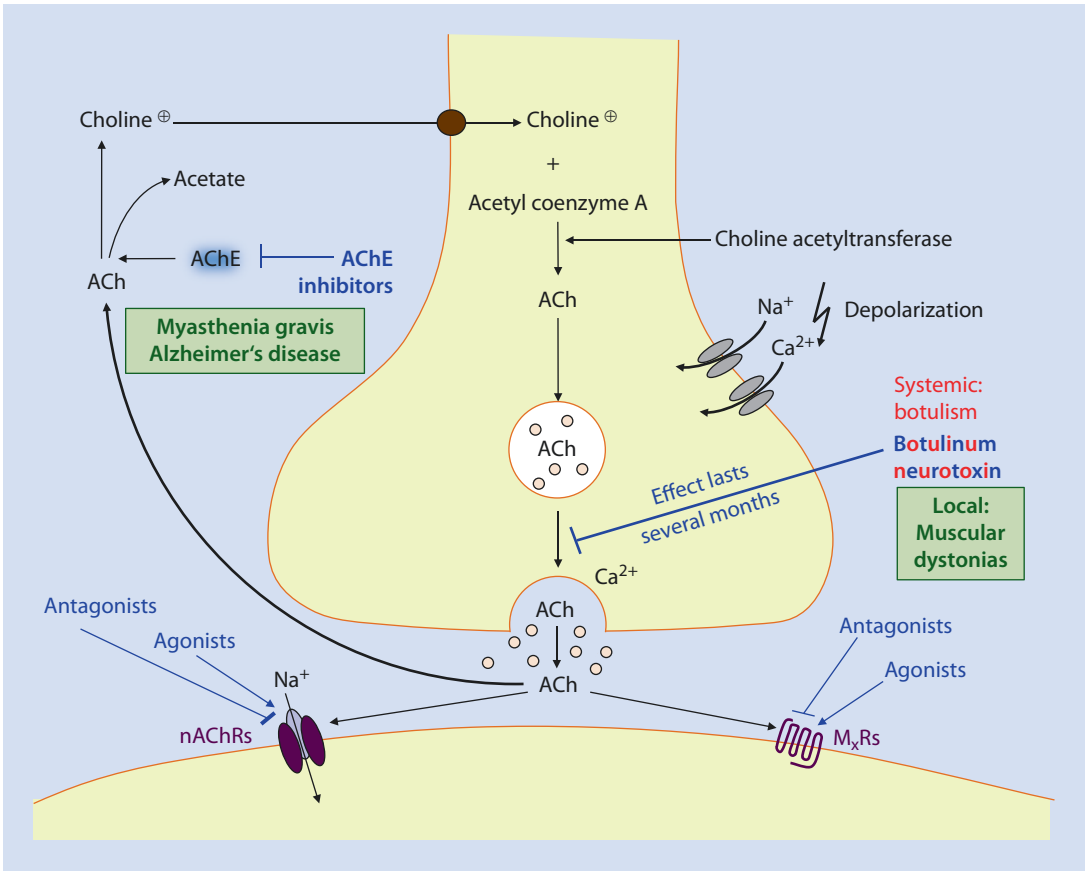
EPI and NE activate α_xARs and β_xARs. The major pharmacological difference between EPI and NE is that EPI activates the β_2AR more potently than NE. As a consequence, NE induces a more potent vasoconstriction than EPI. This effect is exploited in septic shock that is often characterized by strong vasodilation.

Because of its pleiotropic effects mediated via α_xAR and β_xAR, EPI is the drug of choice for the treatment of anaphylactic shock. α_1AR agonism mediates vasoconstriction that is life-saving in case of edema in the face, mouth, and larynx. β_2AR agonism prevents excessive vasoconstriction that could result in tissue necrosis. The agonism of EPI at the β_2AR is also desired for treatment of asthma as a symptom of anaphylactic shock. β_1AR agonism of EPI is useful for normalization of impaired CO (see ▶ Chap. 3). Local anesthesia is another important indication for EPI application (see ▶ Chap. 26).

5.4 Pharmacological Modulation of the Cholinergic Synapse

Synapses are junctions between two neurons or between a neuron and an effector cell. In principle, all synapses function similarly (see ▶ Chaps. 6, 7, 8 and 28, 29, 30), but there are differences regarding details. This is well illustrated by the comparison of the cholinergic synapse (◘ Fig. 5.3) and the noradrenergic synapse (◘ Fig. 5.4).

Excitation of a presynaptic neuron in the cholinergic system (◘ Fig. 5.3) results in influx of



◘ **Fig. 5.3** Pharmacological modulation of the cholinergic synapse. Keep in mind that unprofessional use of botulinum neurotoxin for cosmetic applications has become a serious problem and causes long-lasting hypomimia! This is a very bad ADR causing avoidable misunderstandings in face-to-face communication

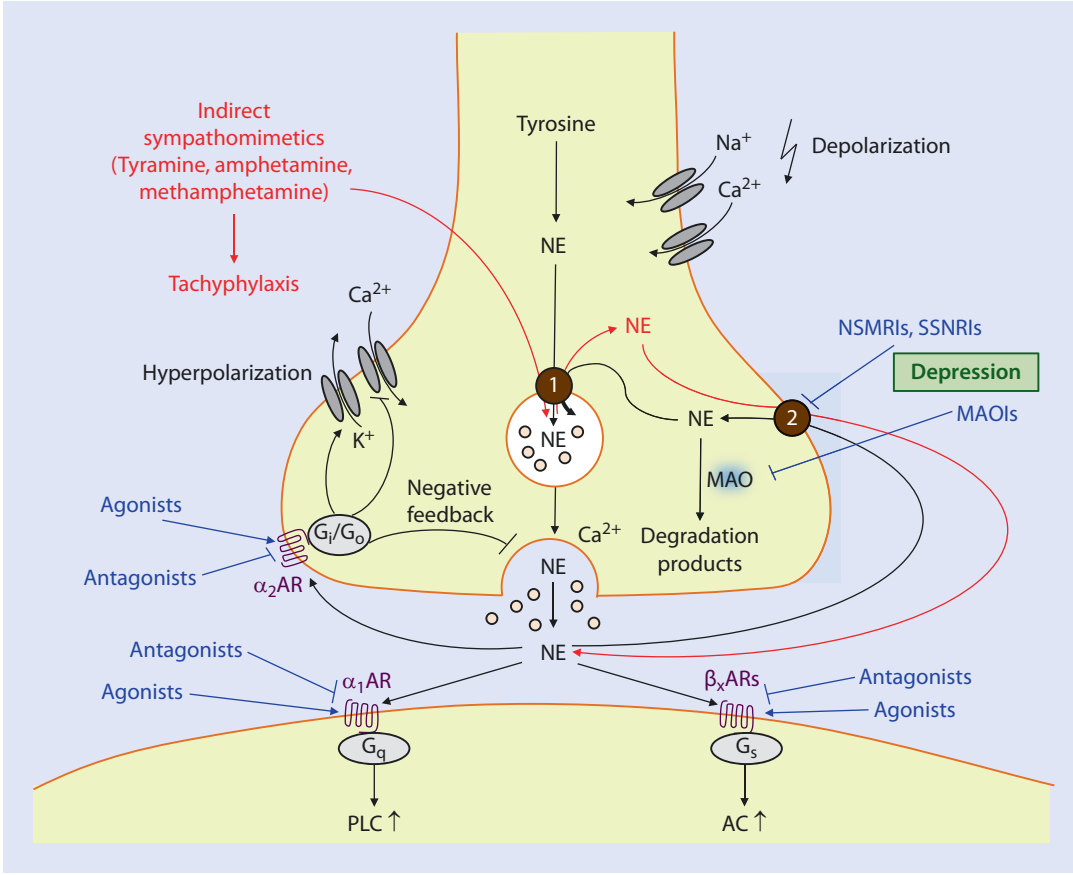


Fig. 5.4 Pharmacological modulation of the noradrenergic synapse. (1) vesicular transporter; (2) NET. See also Figs. 6.1 and 28.2. The abuse of indirectly acting sympathomimetics is a huge global problem! These drugs have a high addiction potential

sodium and calcium. Influx of calcium is important for fusion of NT-containing vesicles with the presynaptic membrane. This process is complex and requires the interaction with specific adapter proteins. Following the release of ACh into the synaptic cleft, ACh activates postsynaptic nAChRs and M_xRs (mAChRs). Inactivation of ACh occurs extracellularly by the highly active AChE cleaving ACh into acetate and choline. Choline as quaternary amine is taken up into the neuron via a transporter. In the neuron, synthesis of ACh occurs via condensation of choline with acetyl coenzyme A catalyzed by choline acetyl transferase. ACh is then packaged into vesicles. As already mentioned in ▶ Sects. 5.2 and 5.3, the cholinergic synapse can be manipulated pharmacologically with agonists and antagonists for nAChRs and M_xRs.

In addition, AChE inhibition is clinically important. AChE inhibition causes an increase in ACh concentration in the synaptic cleft, thereby enhancing the effects of ACh. AChEIs are classified into reversibly and irreversibly acting compounds. Irreversible AChEIs phosphorylate the catalytic center of the enzyme. This leads to a long-lasting flooding of the synapse with ACh (muscarinic syndrome). Irreversible AChEIs are only of toxicological relevance. The cytostatic irinotecan can cause a muscarinic syndrome as a result of reversible nAChE inhibition (see ▶ Chap. 32).

Reversible AChEIs are therapeutically relevant. These drugs are classified into two groups. AChEIs with a tertiary nitrogen are partially uncharged under physiological conditions and can penetrate membranes well; physostigmine and donepezil are representatives. AChEIs with a quaternary nitrogen are largely charged under physiological conditions and penetrate membranes only poorly (see ▶ Chap. 2). Representatives

of this group are pyridostigmine and neostigmine. Donepezil is used for AD therapy because in this disease, degeneration of cholinergic neurons, among other neurons, occurs (see ▶ Chap. 30).

Neostigmine and pyridostigmine are used in the therapy of myasthenia gravis. This is an autoimmune disease in which nAChRs at the neuromuscular end plate are destroyed. As a consequence, neurotransmission is impaired, clinically presenting as pathological fatigability and weakness of skeletal muscles. This fatigability is most prominent in densely innervated muscles such as the outer eye muscles. Through AChE inhibition and increase in the ACh concentration in the synapse, the function of the remaining nAChR can be improved. Because of their positive charge, neostigmine and pyridostigmine do not possess ADRs in the CNS. For diagnosis of myasthenia gravis, the ultrashort-acting AChEI edrophonium is used. During injection of the drug, an immediate improvement of the symptoms is observed in case of myasthenia gravis.

Botulinum neurotoxin selectively inhibits the function of cholinergic synapses. It is taken up into cholinergic neurons and induces degradation of adapter proteins that are important for fusion of ACh-containing vesicles with the plasma membrane. Botulinum neurotoxin inhibits ACh release for several months. These long-lasting and NT-specific effects can be used in neurological diseases that are characterized by local increase of the muscular tone. Examples are torticollis, blepharospasm, and focal dystonias of the hand and the glottis. However, botulinum neurotoxin is best known for its cosmetic use to smoothen wrinkles in the face. If applied unprofessionally and in toxic doses, it can induce long-lasting paralysis of the facial muscles and subsequent hypomimia. Systemic intoxication with botulinum neurotoxin, e.g., as a result of ingestion of canned meat contaminated with *Clostridium botulinum*, results in botulism. This disease is characterized by generalized paralysis of the skeletal muscles including respiratory paralysis, requiring long-term mechanical ventilation of the patient.

5.5 Pharmacological Modulation of the Noradrenergic Synapse

NE synthesis in the noradrenergic synapse starts from the amino acid tyrosine (◘ Fig. 5.4). Following hydroxylation to levodopa, decarboxylation to DA occurs, representing a NT of its own (▶ Chap. 8). DA is the precursor of NE. EPI is formed by N-methylation of NE in the adrenal medulla. Via a vesicular transporter, NE is packaged into vesicles and released into the synaptic cleft following depolarization. NE activates postsynaptic α_1ARs and β_xARs and regulates many cell functions (see ▶ Sects. 5.2 and 5.3).

The rate-limiting step in the termination of the biological effects of NE is neuronal re-uptake via a specific NET. In the neuron, NE (like EPI and DA) is converted to inactive metabolites via COMT and MAO.

Presynaptic α_2ARs are of great functional importance. These receptors are activated by NE in parallel to the postsynaptic α_1ARs and β_xARs. Via G_i/G_o proteins the α_2AR activates potassium channels and inhibits calcium channels. As a result, further release of NE is prevented. Presynaptic α_2AR activation protects the body from excessive sympathetic activation that can be life-threatening. α_2AR agonists like clonidine inhibit the sympathetic tone via reduced NE release and induce sedation. In addition, α_2AR agonists reduce the BP (see ▶ Chap. 15) and inhibit the function of pain-transmitting neurons (see ▶ Chap. 10). Conversely, antagonism of presynaptic α_2ARs enhances NE release. This effect is exploited in depression coming along with a functional NE deficit (see ▶ Chap. 28).

An increase in the synaptic NE concentration can also be achieved by blockade of neuronal NE re-uptake. The NSMRIs and SSNRIs are therapeutically relevant (see ▶ Chap. 28). In severe cases of depression, MAOIs like tranylcypromine are used (◘ Fig. 5.5a).

A number of biogenic amines with structural similarity to NE and EPI activate adrenergic receptors with lower potency and intrinsic activity than NE. However, due to their physicochemical properties, they can penetrate into noradrenergic neurons and are concentrated in NE-containing vesicles via the vesicular transporter. These drugs are designated as indirect sympathomimetics. NE stored in these vesicles is exchanged into the cytosol and retrogradely transported into the synaptic cleft via NET. Indirect sympathomimetics induce a rapid NE release which is accompanied by a transient increase in physical and mental power, alertness, BP, HR, and feeling of well-being.

These are the reasons why certain indirect sympathomimetics such as amphetamine and meth-

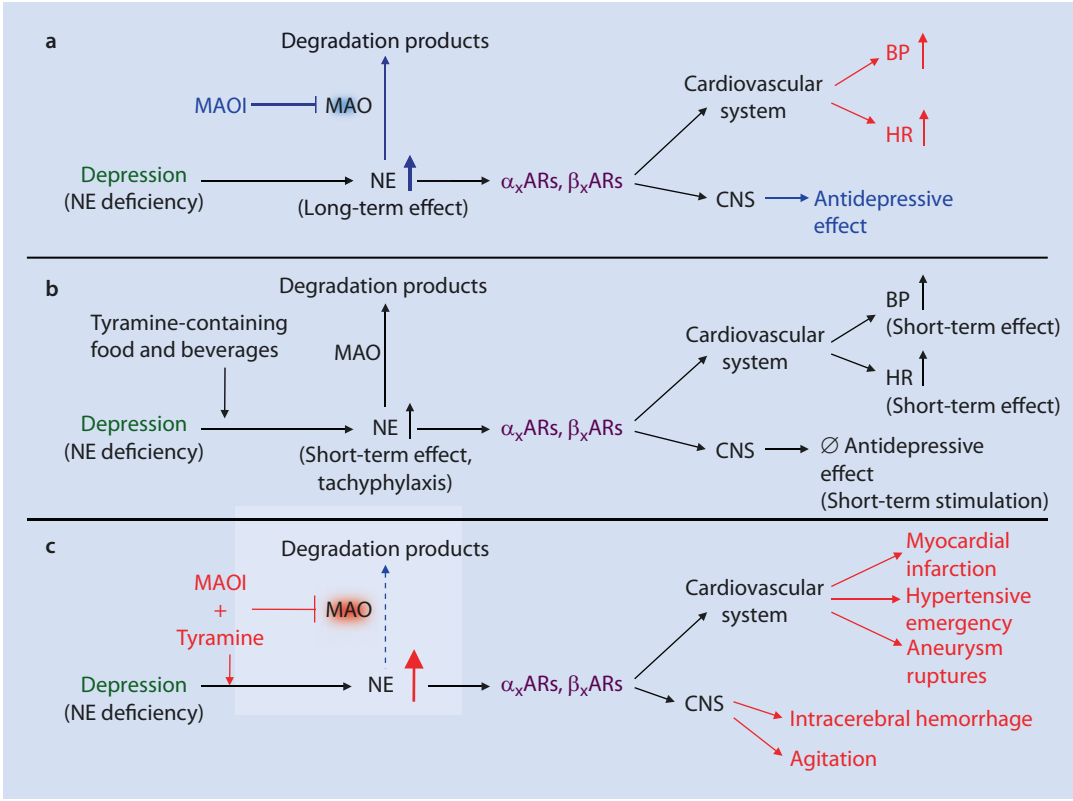


Fig. 5.5 Effects of MAOIs and tyramine on the cardiovascular system and CNS. **a** Effects of MAOIs alone. **b** Effect of tyramine alone. **c** Interaction of MAOIs with tyramine. See also Fig. 6.2. Despite the interactions of MAOIs with tyramine, MAOIs are valuable drugs for refractory depression! MAOIs are prescribed too rarely because of fear of their ADRs and interactions with tyramine

amphetamine are abused as illicit drugs. However, these drugs also exhibit a great potential for addiction. Due to the massive NE release following consumption of amphetamine and methamphetamine, the presynaptic α_2AR protection mechanism is abrogated so that excessive sympathetic activation results which can lead to hypertensive emergency, serious arrhythmias, MI, heart failure, and ultimately death (see ▶ Chaps. 15, 16, and 17).

Another problem of indirect sympathomimetics is that following release of all stored NE, the NT has first to be resynthesized before the normal sympathetic tone is restored. During this time, users of indirectly acting sympathomimetics feel sick and complain about sleepiness and decreased physical and mental power. Because of these withdrawal symptoms and the addiction potential, consumers crave for immediate readministration of the drugs. However, because of the emptied vesicles, indirect sympathomimetics are now without the desired effect. The lack of effect of indirect sympathomimetics following vesicle depletion is referred to as tachyphylaxis and must not to be confused with lack of effect of GPCR agonists following repeated administration. The latter process is referred to as desensitization (see ▶ Chap. 1). Because of tachyphylaxis and addiction potential, the therapeutic relevance of indirect sympathomimetics is very small.

Tyramine is a sympathomimetic contained in many food items such as cheese, nuts, and chocolate and in red wine. Tyramine possesses a much smaller maximum effect than amphetamine and is not of concern if consumed in reasonable amounts (Fig. 5.5b). However, dangerous interactions between tyramine-containing food or beverages and MAOIs can occur. If a patient treated with a MAOI because of a severe depression (prototype tranylcypromine) (Fig. 5.5b) consumes tyramine-containing food or beverages, NE release is increased. Since the additionally released NE cannot be effectively degraded anymore, life-threat-

ening hypertensive emergency, MI, aneurysm ruptures, and intracerebral hemorrhage can occur (Fig. 5.5c). Therefore, all patients treated with a MAOI have to be informed about the fact that they are not allowed to consume tyramine-containing food and beverages.

5.6 Questions and Answers

Questions

Which assignment of a drug class to indication is correct?

A. β_1AR agonists – CHF
B. β_1AR antagonists – AP attack
C. β_2AR agonists – acute hypoglycemia
D. β_2AR antagonists – asthma attack
E. β_3AR agonists – overactive bladder

Answers

A. In CHF, β_1AR antagonists are indicated. β_1AR agonists increase mortality in CHF.
B. β_1AR antagonists act prophylactically in CHD by improving the relation between oxygen supply and oxygen consumption. However, these drugs are not effective in AP attacks.
C. In principle, β_2AR agonists increase blood glucose concentration, but the therapy of choice for acute hypoglycemia is the administration of glucose (p.o. or i.v.).
D. In an asthma attack, β_2AR agonists are indicated. β_2AR antagonism is used in infantile hemangioma and glaucoma.
E. In overactive bladder, β_3AR agonists can be used. M_xR antagonists constitute an alternative.

Answer **E** is correct.

5.7 Exercises

A 27-year-old man has been complaining about tiredness and muscle weakness for several weeks. The major problem is that already in the early morning, his eyes close, and double vision occurs although he sleeps for sufficiently long time periods. Upon inspection you recognize hypomimia and a faint hand shake. You suspect that the patient suffers from myasthenia gravis.

Questions

1. Which pharmacological test do you perform to corroborate the diagnosis?
2. Why do you use pyridostigmine or neostigmine in the long-term therapy of myasthenia gravis, but not physostigmine?

Answers

1. You inject the ultrashort-acting AChEI edrophonium. This test is referred to as Tensilon test because edrophonium is marketed under the trade name Tensilon®. Already during injection you can observe a prominent improvement of muscle strength. As ADR a muscarinic syndrome including increased sweat secretion, intestinal spasms, and increased urinary urgency occurs.
2. Pyridostigmine and neostigmine are quaternary amines that are largely charged at physiological pH. Physostigmine is a tertiary amine that is predominantly uncharged at physiological pH. In contrast to physostigmine, pyridostigmine and neostigmine do not penetrate the BBB. Therefore, the latter two drugs have no effects in the CNS and exhibit better tolerability.

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Serotonergic System

R. Seifert, *Basic Knowledge of Pharmacology*, https://doi.org/10.1007/978-3-030-18899-3_6

5-HT is an NT and local mediator that regulates many cell functions. 5-HT mediates its effects via 5-HT_{1-7}Rs. 5-HT_{1D}R agonists are used in acute migraine attack; 5-HT_{2A}R antagonists act antipsychotically. 5-HT_3R antagonists are antiemetic and have substantially increased the tolerability of chemotherapy. SSRIs, NSMRIs, and MAOIs are used in the treatment of depression. Overdose of SSRIs or MAOIs or a combination of both drug classes can cause a serotonin syndrome. This chapter also discusses the pharmacotherapy of migraine and vomiting based on multiple targets besides the serotonergic system, thus allowing cause-specific therapeutic concepts.

Key Points

1. In carcinoid syndrome, large amounts of 5-HT are secreted; this can be inhibited by somatostatin analogs.
2. 5-HT_{1D}R agonists are used in acute migraine attack.
3. 5-HT_{2A}R antagonists are used as antipsychotics.
4. 5-HT_3R antagonists are effective in chemotherapy-induced vomiting.
5. SSRIs, NSMRIs, and MAOIs are used in depression. The indications for these drugs have expanded during the past 10 years.
6. The serotonin syndrome is a life-threatening ADR of overdosing MAOIs or SSRIs.
7. Therapeutic concepts in migraine are also based on inhibition of the effects of CGRP and PGE_2.
8. Pharmacotherapy of vomiting depends on the specific cause and comprises, besides 5-HT_3R antagonists, antagonism at NK_1R, M_xRs, D_2R, and H_1R.

6.1 (Patho)physiological Background

5-HT is a biogenic amine that functions as NT and local mediator. 5-HT regulates many organ functions which becomes particularly evident when 5-HT metabolism is disturbed. 5-HT is produced from tryptophan via hydroxylation and decarboxylation. Via MAO-A 5-HT is metabolized to 5-hydroxyindole acetic acid. ECL cells in the GI tract contain 90% of the body content of 5-HT. Chemotherapy and irradiation trigger the release of 5-HT from ECL cells, inducing nausea and vomiting. Malignant transformation of ECL cells results in carcinoid syndrome, leading to the release of large amounts of 5-HT and other mediators including HA, bradykinin, and substance P. Clinically, the carcinoid syndrome is characterized by diarrhea, flush, and hypotension. The syndrome is diagnosed by increased urinary excretion of 5-hydroxyindole acetic acid. Secretion of 5-HT and other mediators from carcinoid cells can be inhibited by metabolically stable somatostatin analogs. Somatostatin receptors couple to G_i/G_o proteins and inhibit mediator secretion via calcium channel blockade. This is an example of a targeted therapeutic (see ▶ Chap. 32).

5-HT is a precursor for the NT melatonin. Melatonin production in the pineal gland is regulated by the circadian rhythm and shows a peak during the night. Therefore, melatonin is also classified as "natural sleeping molecule" and is a widely used OTC for jetlag and shift work. However, the efficacy of melatonin is questionable because it shows a large first-pass effect (see ▶ Chap. 2). Synthetic agonists at melatonin receptors, belonging to the GPCR class, constitute a new principle for the therapy of depression. The significance of this approach is still unclear. ◘ Table 6.1 summarizes selected drugs that act in the serotonergic system.

6.2 Pharmacological Modulation of Serotonin Receptors

5-HT mediates its effects via 14 different receptors (5-HT_{1-7}Rs with multiple subtypes). The therapeutically very important 5-HT_3R belongs to the class of ligand-gated ion channels (see ▶ Chap. 1). All other 5-HT_xRs are GPCRs (see ▶ Chap. 1). Currently, just some of the many 5-HT_xRs are clinically relevant. The 5-HT_{1D}R is localized presynaptically and leads to the activation of potassium channels and inhibition of calcium channels via G_i/G_o proteins. This mechanism results in the inhibition of NT release. The 5-HT_{1D}R is expressed in high density in neurons that regulate the tone of meningeal arteries. 5-HT_{1D}R agonists (triptans) indirectly mediate arterial constriction and are used in migraine attack

Table 6.1 Overview of drugs acting on the serotonergic system

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Amitriptyline	NSMRI	Pleiotropic effects in the CNS, antidepressant, pain modulatory	Depression, chronic neuropathic pain, tumor pain, migraine prophylaxis	Serotonin syndrome due to overdose or combination with MAOIs; ADRs caused by antagonism at α_1AR, M_xRs and H_1R (hence the designation NSMRIs)	4, 5, 10, 28
Ondansetron	5-HT_3R antagonist	Antiemetic	Acute cytostatic-induced emesis	Constipation, headache, warmth sensation, flush, oculomotor disorders, TdP, but overall the drug is well tolerated. By using 5-HT_3R antagonists, significant improvements in the prevention of chemotherapy-induced emesis have been achieved	13, 17, 32
Risperidone	p-mGPCR antagonist including 5-HT_{2A}R antagonist	Pleiotropic effects in the CNS, antipsychotic, pain modulatory	Schizophrenia, co-analgesic for chronic pain therapy, bipolar disorder, autism, obsessive-compulsive disorder	Compared to D_2R-mGPCR antagonists, p-mGPCR antagonists have less EPSs but are associated with metabolic syndrome	1, 10, 29
Sertraline	SSRI	Pleiotropic effects in the CNS, antidepressant	Depression, anxiety disorders, obsessive-compulsive disorder, panic disorder, premenstrual dysphoric disorder	Serotonin syndrome due to overdose or combination with MAOIs, sexual dysfunction, nausea, vomiting	1, 28
Sumatriptan	5-HT_{1D}R agonist	Contraction of meningeal arteries	Acute migraine attack	Chest tightness; not to be confused with AP!	
Tranylcypromine	Irreversible inhibition of MAO-A and MAO-B	Pleiotropic effects in the CNS, antidepressant	Depression which cannot be treated with NSMRIs or SSRIs, anxiety and panic disorders	Serotonin syndrome due to overdose or combination with SSRIs, risk of NE intoxication following administration of indirect sympathomimetics	5, 28

treatment (see ▶ Sect. 6.4). Sumatriptan and naratriptan are prototypes of this drug class.

The 5-HT_{2A}R is widely expressed in the CNS and couples to PLC via G_q proteins. The 5-HT_{2A}R is important for correct perception of our environment. Excessive 5-HT_{2A}R activity, e.g., as observed in schizophrenia, can result in hallucinations (see ▶ Chap. 29). 5-HT_{2A}R agonists like LSD are hallucinogenic. As result, deadly accidents can occur, but creativity and associative capabilities may increase. LSD can be effective in cluster headache, an extremely painful condition. Psilocybin, constituent of magic mushrooms (e.g., *Psilocybe semilanceata*), could be used in the treatment of anxiety in tumor patients and in depression. This is currently being explored in clinical studies. Drugs that act antagonistically at 5-HT_{2A}R are of great clinical importance. Many p-mGPCR antagonists including clozapine and risperidone antagonize, among other GPCRs, the 5-HT_{2A}R, thereby inducing at least part of their antipsychotic effects. These effects are exploited in schizophrenia and bipolar disorder (see ▶ Chaps. 28 and 29).

The 5-HT_3R is localized postsynaptically and constitutes a ligand-gated sodium channel. The 5-HT_3R is predominantly localized in the area postrema and in the vagus nerve; its activation causes vomiting. Accordingly, 5-HT_3R antagonists (setrons) are potent antiemetics, particularly for the early phase of chemotherapy-associated vomiting. Ondansetron is a prototype of this drug class.

The 5-HT_4R couples to G_s proteins to mediate AC activation. It is predominantly localized in the GI tract and stimulates intestinal secretion and mobility. The 5-HT_4R agonist prucalopride can be used for resistant obstipation (see ▶ Chap. 13).

There are also mixed 5-HT_xR agonists/antagonists. An example is the 5-HT_{1A}R agonist/5-HT_{2A}R antagonist flibanserin. Flibanserin stimulates the release of DA and NE in neuronal circuits that are important for sexual desire. In certain countries, flibanserin has been approved for treatment of female hypoactive sexual desire disorder (HSDD).

6.3 Pharmacological Modulation of the Serotonergic Synapse

The regulation of the serotonergic synapse (◘ Fig. 6.1) and the noradrenergic synapse (see ▶ Chap. 5) is similar. Following its synthesis, 5-HT is concentrated into vesicles via a vesicular transporter. Neuronal depolarization leads to 5-HT release into the synaptic cleft. 5-HT activates postsynaptic receptors whose function can be manipulated with agonists and antagonists. The 5-HT_{1D}R is localized presynaptically and, as an autoreceptor, inhibits 5-HT release via calcium channel blockade and potassium channel activation. Neuronal uptake of 5-HT constitutes the rate-limiting step for termination of 5-HT effects. In the neuron, 5-HT is inactivated via MAO. In depression (see ▶ Chap. 28), there is a functional 5-HT (and NE) deficit. The 5-HT deficit can be corrected by preventing neuronal NT reuptake with SSRIs or NSMRIs. A major difference between SSRIs and NSMRIs is that the latter drugs are also antagonists at several GPCRs, resulting in serious ADRs (see ▶ Chap. 28). In resistant cases of depression, MAOIs can be used. Tranylcypromine is a prototype of this drug class and inhibits MAO irreversibly.

Because of their use in depression, SSRIs, NSMRIs, and MAOIs have been historically designated as "antidepressants" (see ▶ Chap. 1). However, these drugs have witnessed a dramatic expansion of their clinical use during the past decade, encompassing anxiety, personality, and obsessive-compulsive disorders and various types of pain, to name few examples (see ▶ Chaps. 1 and 10). Accordingly, the designation "antidepressant" is misleading. Rather, the neutral umbrella term NE/5-HT-enhancer should be used.

On the one hand, correction of the 5-HT deficit in depression by SSRIs or MAOIs can induce therapeutic effects (◘ Fig. 6.2a). On the other hand, an excess of 5-HT can result in a serotonin syndrome (◘ Fig. 6.2b). A major problem in depression therapy is that initially drugs improve motivation, but the mood-improving effect only starts after a latency of several weeks (see ▶ Chap. 28). In the time window between the increase of motivation and mood improvement, the suicide risk is increased. If a patient takes many SSRI tablets with a suicidal intent, the body is flooded with 5-HT. Virtually every organ is affected. In the CNS, tremor, epileptic seizures, and hallucinations occur. In the cardiovascular system, tachycardia and hypertension develop. In the GI tract, nausea, vomiting, and diarrhea become apparent. Unfortunately, there is no universal 5-HT_xR antagonist that could be used as antidote. Therefore, the serotonin syndrome must be treated symptomatically. Tachycardia and hypertension are treated

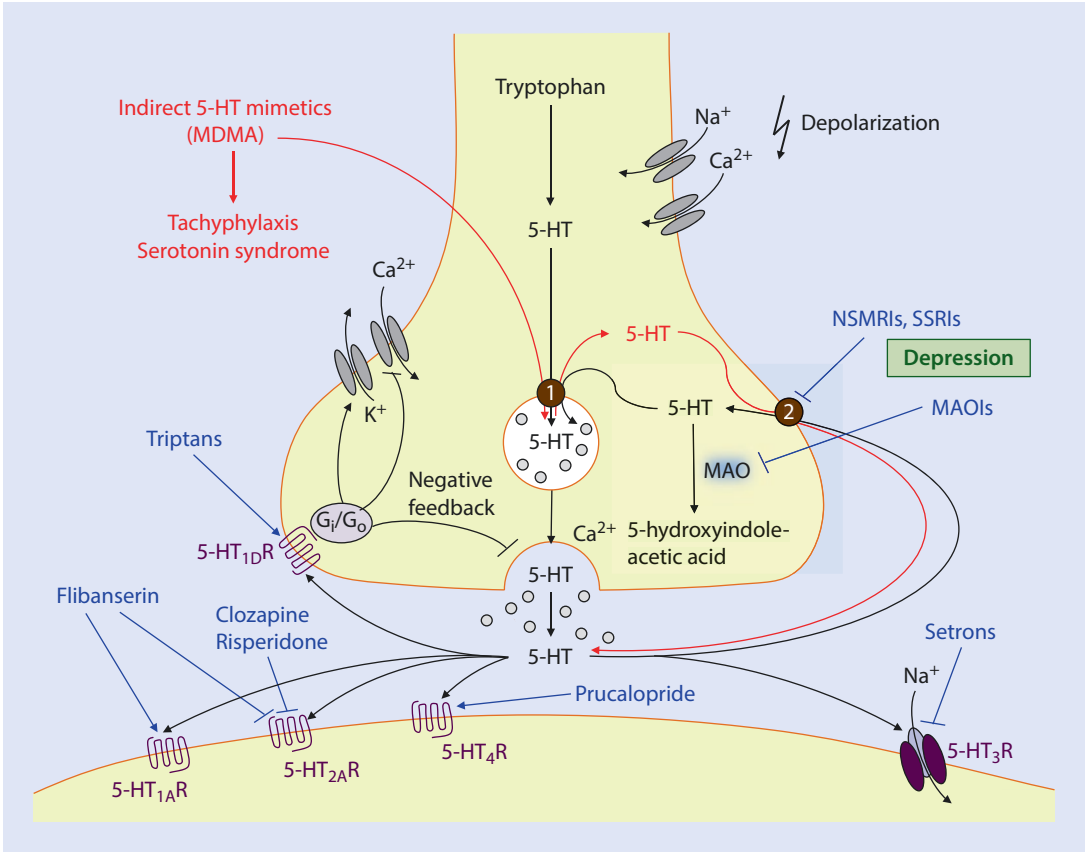

Fig. 6.1 Pharmacological modulation of the serotonergic synapse. MDMA, methylenedioxymethamphetamine (ecstasy). See also Figs. 5.4, 6.2, and 28.2. (1) vesicular transporter; (2) SERT. The abuse of ecstasy is a huge global problem! Beware of the serotonin syndrome (see Fig. 6.2)

with β_1AR antagonists, seizures with NIPEs, and vomiting with 5-HT$_3$R antagonists.

The serotonin syndrome can also occur after overdosing MAOIs or following combined ingestion of SSRIs + MAOIs. Therefore, combination of both drug classes is contraindicated. Because depression is a chronic disease, the physician could tend to prescribe large packages of NE/5-HT enhancers with the intention to render drug therapy less expensive (in general, the costs per tablet are lower in larger packages than in small packages). However, specifically in cases of suicidality, it is important to provide the patient only with a small number of tablets to reduce the suicide risk. Prescription of small packages of NE/5-HT enhancers also has the advantage that the physician can check the suicide risk regularly.

Methylenedioxymethamphetamine (MDMA, ecstasy) is widely used as illicit party drug to lift the mood. MDMA is transported into 5-HT-containing vesicles via the vesicular transporter, ultimately resulting in massive 5-HT release. This mechanism including tachyphylaxis is similar to the mechanism of indirect sympathomimetics (see ▶ Chap. 5). In the time interval between 5-HT depletion and refilling of the vesicles, the MDMA consumer feels sick. However, repeated administration of MDMA has no effect. The addiction potential of MDMA is substantial.

6.4 Pharmacological Treatment of Migraine

Migraine is characterized by hemicranial, throbbing headache accompanied with nausea and vomiting. Often, the patients recognize the beginning of a migraine attack (aura). The pathophysiology of migraine is still incompletely understood. However, over the last years, 5-HT

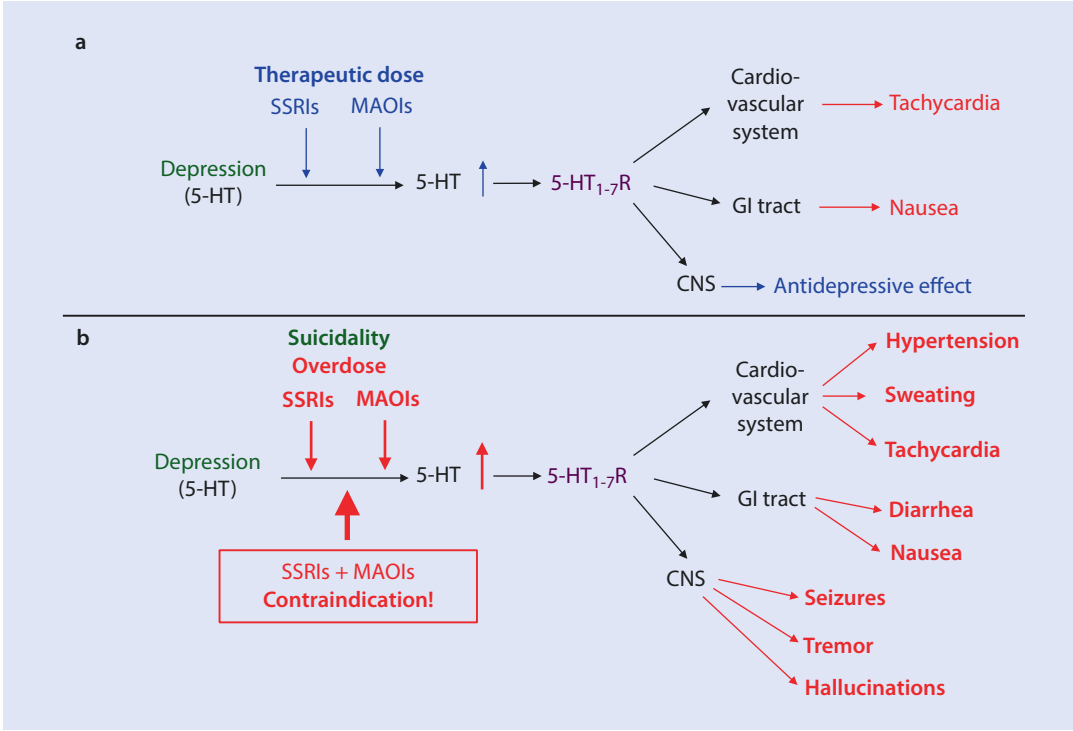

Fig. 6.2 **a**, **b** Pathogenesis and clinical symptoms of the serotonin syndrome. **a** Therapeutic dose of SSRIs or MAOIs. **b** Serotonin syndrome upon overdosing SSRIs or MAOIs or when SSRIs + MAOIs are combined in therapeutic dose. See also Fig. 5.5. Never hand out economy-sized drug packs to suicidal patients

and CGRP have emerged as central NTs for migraine (Fig. 6.3). The synapses between neurons and smooth muscle cells release increased amounts of CGRP which binds to the CGRPR in smooth muscle cells. CGRPRs couple to G_s proteins to stimulate AC with subsequent increase in cAMP mediating vasodilation. As consequence, pain-sensing neurons in the dilated arteries are activated. CGRP-releasing neurons form synapses with 5-HT-releasing neurons and express presynaptic 5-HT_{1D}Rs. These heteroreceptors, via inhibition of calcium channels and activation of potassium channels, inhibit CGRP release and, thereby, vasodilation and pain.

Because the expression density of 5-HT_{1D}Rs in the meningeal arteries is high, 5-HT_{1D}R agonists also possess selective effects, i.e., vasoconstriction in other blood vessels is small. Migraine patients taking 5-HT_{1D}R agonists may complain of chest tightness that must not be confused with AP as symptom of CHD (see ▶ Chap. 16). The safety of 5-HT_{1D}R agonists is also reflected by the fact that some medicines containing these drugs are available OTC in certain countries. Ergotamine, which induces a profound generalized vasoconstriction, is still being used for migraine in several countries, but because of its serious ADRs (necrosis of fingers, toes, and organs), it should not be used anymore and substituted by 5-HT_{1D}R agonists.

The current development of new medicines for migraine focuses on CGRP inhibitors, i.e., either antibodies that bind and neutralize CGRP or antibodies against CGPRR. These drugs are biologicals that are much more expensive than established anti-migraine drugs. Thus, patients, physicians, and insurance companies have to expect that CGRP inhibitors exhibit superior efficacy compared to standard therapies. Recently, the first CGRPR antibody (erenumab) has been approved for clinical use in some countries for migraine prevention. Overall, erenumab is tolerated well, but its efficacy compared to standard prophylactic therapy has still to be evaluated.

Migraine attacks cannot only be treated with 5-HT_{1D}R agonists but also with COX inhibitors such as ibuprofen (see ▶ Chap. 10). Since migraine is often characterized by nausea and vomiting, it is recommended that 20–30 minutes prior to ibu-

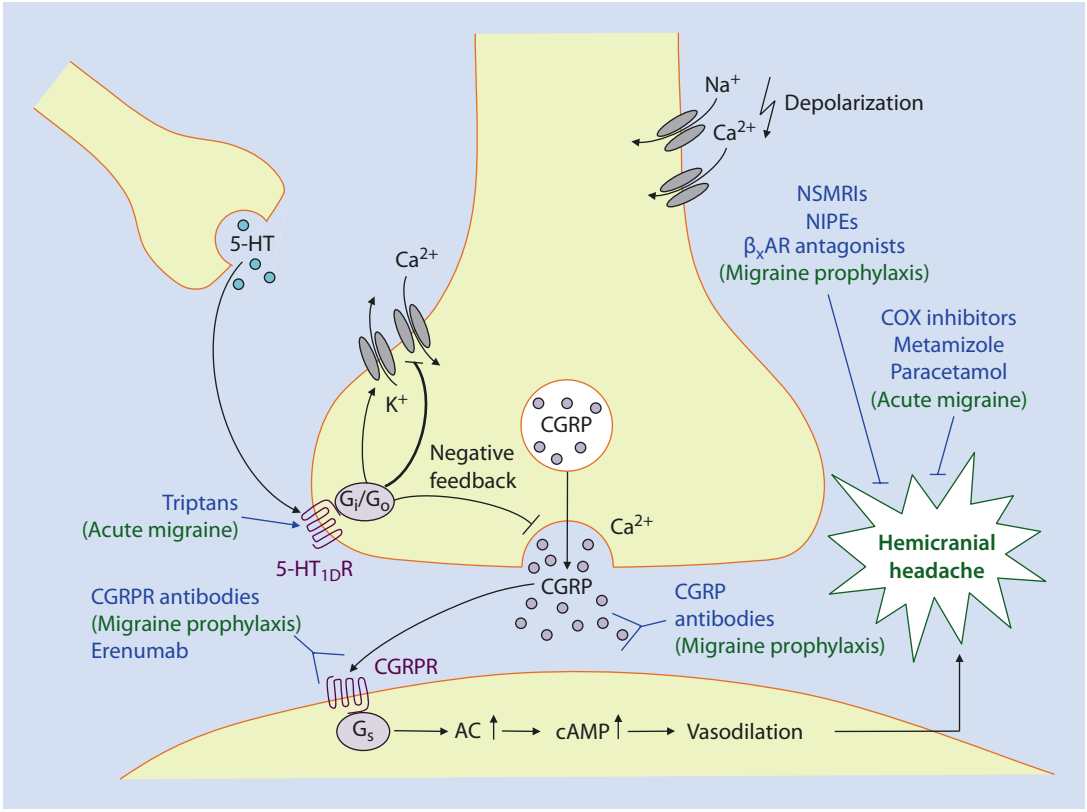

Fig. 6.3 Pharmacological modulation of smooth muscle cells in meningeal arteries by 5-HT and CGRP: Pharmacotherapy of migraine. The new CGRPR antibodies are expensive and should be reserved to refractory patients

profen, the D_2R antagonist MCP is given p.o. to normalize GI tract kinetics and alleviate nausea and vomiting (see ▶ Chap. 8). MCP also improves subsequent absorption of ibuprofen. The efficacy of 5-$HT_{1D}R$ agonists versus ibuprofen + MCP varies interindividually and has to be tested empirically for each patient. In addition, paracetamol and metamizole (the latter drug is not available in all countries) can be applied. In treatment of acute migraine, it is critical to identify triggers and avoid them as far as possible. Among migraine triggers are nicotine, chocolate, and certain types of wine. Stress, menstruation, and chinook winds can cause migraine as well.

If migraine attacks are very frequent and debilitating, prophylactic pharmacotherapy can be considered. NSMRIs (see ▶ Chap. 28), NIPEs (▶ Chap. 25), and β_xAR antagonists (see ▶ Chap. 5) are used, but their efficacy is limited. Possibly, these drugs suppress pathological neuronal excitability.

6.5 Pharmacological Treatment of Vomiting

The vomiting reflex has the function to eliminate ingested toxic substances from the body. Because of its vital importance, the vomiting reflex is secured by several mechanisms. The serotonergic system plays a central role in the control of the vomiting reflex (Fig. 6.4). The vagus nerve and the CTZ in the area postrema (localized outside the BBB) express the 5-HT_3R that is activated by 5-HT released from ECL cells. ECL cells release large amounts of 5-HT following chemotherapy or irradiation. The stimulatory effects of 5-HT on the area postrema and the vagus nerve are integrated in the vomiting center that coordinates the vomiting reflex. In addition, input from the vestibular organ and the vestibular nucleus in the CNS is integrated in the vomiting center. The vestibular nucleus expresses the H_1R and M_xRs. In addition to the 5-HT_3R, the CTZ and the vagus nerve also

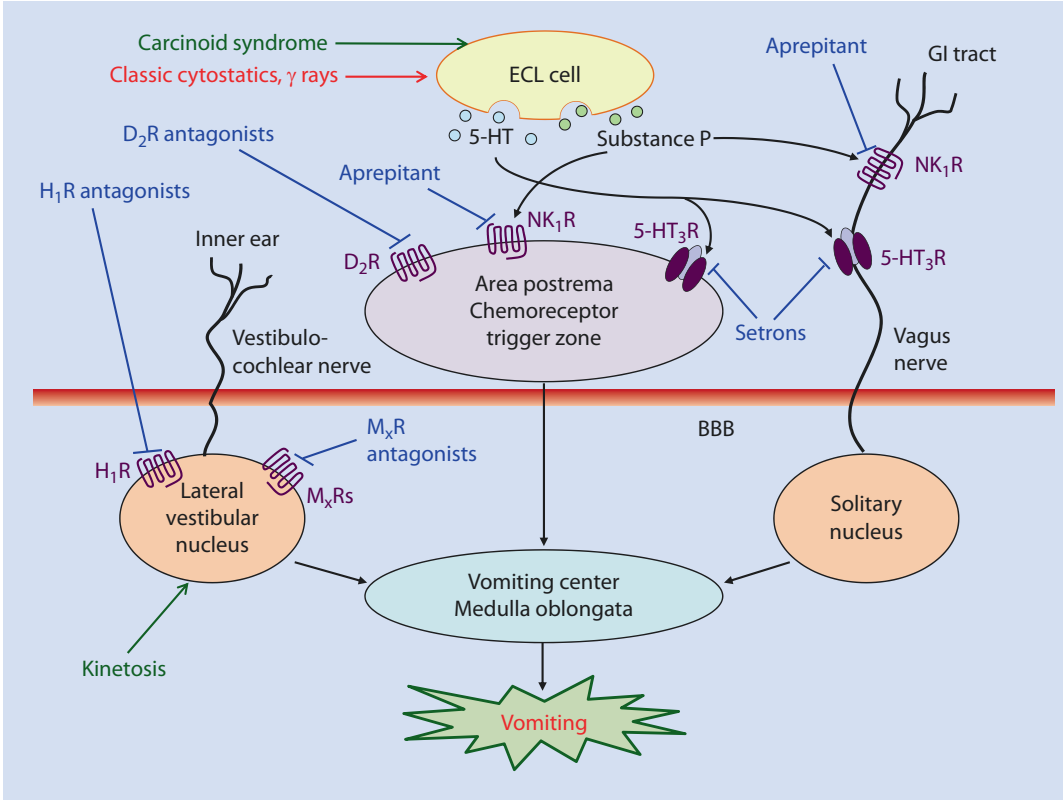

Fig. 6.4 Pathophysiology and pharmacotherapy of vomiting. Depending on the cause of vomiting, you have to use different drugs! Therefore, first find out the reason for vomiting

express receptors for the neurokinin substance P (NK_1R) that also triggers vomiting. Moreover, the CTZ expresses the D_2R, inducing vomiting as well. In principle, antagonism of all the aforementioned receptors results in an antiemetic effect, but there are relevant differences which type of drug is effective in a particular type of vomiting.

The early chemotherapy-induced vomiting is effectively inhibited by 5-HT_3R antagonists, whereas the late chemotherapy-induced vomiting can be effectively suppressed by NK_1R antagonists. Aprepitant is a prototype of the latter drug class. With the combination of 5-HT_3R antagonist + NK_1R antagonist, chemotherapy-induced vomiting can be effectively controlled in many tumor patients. This constitutes a major progress in tumor therapy because previously, vomiting, also associated with severe water and electrolyte loss, was a limiting factor. Nowadays, many cancer patients can be treated as outpatients. This is an example of how symptomatic therapy can result in a substantial increase in life quality.

Vomiting associated with viral GI tract infections can be effectively treated with D_2R antagonists such as MCP or domperidone (see ▶ Chap. 8). In hyperemesis gravidarum, first-generation H_1R antagonists are effective and safe (see ▶ Chap. 7). For kinetosis, the M_xR antagonist scopolamine is applied successfully (see ▶ Chap. 5). First-generation H_1R antagonists are an alternative approach for treatment of kinetosis.

6.6 Questions and Answers

Questions

Which statement on the serotonergic system is *NOT* correct?

A. An overdose of SSRIs can cause a serotonin syndrome.
B. 5-HT_3R antagonists are particularly effective in kinetosis.
C. Psilocybin has therapeutic potential in anxiety and depression.

D. 5-HT_{1D}R agonists are well suited for the therapy of acute migraine attacks.
E. 5-HT release in carcinoid syndrome can be inhibited with somatostatin analogs.

Answers

A. To avoid a serotonin syndrome in suicidal patients, only small packages or parts of larger packages containing few tablets should be handed out to the patient. In addition, regular consultations with the physician are required.
B. 5-HT_3R antagonists work particularly well in chemotherapy-induced vomiting. For kinetosis, the M_xR antagonist scopolamine or first-generation H_1R antagonists are indicated.
C. Psilocybin, like LSD, is a 5-HT_{2A}R agonist. So far, only little is known about the potential clinical usefulness of this drug class. However, current clinical studies point to therapeutic potential in certain psychiatric conditions.
D. 5-HT_{1D}R agonists are effective only in acute migraine attacks. For prophylaxis they are not feasible because of desensitization. For prophylaxis, β_xAR antagonists, NSMRIs, NIPEs, and CGRP inhibitors can be used.
E. Somatostatin receptors couple to G_i/G_o proteins to inhibit calcium channels and, thereby, inhibit secretion of 5-HT and other mediators from carcinoid cells.

Statement **B** is not correct.

6.7 Exercises

A 30-year-old man living in the high mountains suffers from migraine attacks that are triggered by strong chinook winds. The patient has 5–8 migraine attacks per year.

Questions

1. Which drugs are well suited for treatment of the acute migraine?
2. Which drugs are not indicated for the migraine?

Answers

1. First-choice treatment is a 5-HT_1DR agonist like sumatriptan. Alternatively, a COX inhibitor like ibuprofen can be given. In case of severe nausea, the COX inhibitor can be combined with the D_2R antagonist MCP. For the combination, it is important to apply MCP 20–30 minutes prior to ibuprofen to facilitate absorption of the latter drug. Drug therapy should be initiated as soon as the first signs of migraine (aura) are recognized by the patient. The effectiveness of drugs in migraine patients differs interindividually and has to be tested empirically.
2. Previously, the ergot alkaloid ergotamine was frequently used for acute migraine attacks. Like 5-HT_{1D}R agonists, ergotamine induces contraction of the meningeal arteries, but the latter drug induces a general vasoconstriction. This can result, specifically when ergotamine is used regularly, in necrosis of fingers, toes, and internal organs. Anal necrosis can occur when suppositories containing ergotamine are used. For migraine prophylaxis with β_xAR antagonists, NSMRIs, NIPEs, or CGRP inhibitors, the migraine attacks are too infrequent.

Further Reading

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Histaminergic System

R. Seifert, *Basic Knowledge of Pharmacology*, https://doi.org/10.1007/978-3-030-18899-3_7

HA is an NT and local mediator that exerts its effects via H_{1-4}Rs. HA is released from mast cells. Via the H_1R, HA induces edema, urticaria, erythema, and itch. β_2AR agonists effectively inhibit mast cell degranulation. In parietal cells, the H_2R activates proton secretion. The H_2R possesses inhibitory effects on myeloid cells. In the CNS, the H_1R and H_3R regulate alertness. The H_4R mediates activation of eosinophils and itch. CNS-permeable first-generation H_1R antagonists are used as hypnotics, in premedication, in severe type I allergies with itch, in kinetosis, and in hyperemesis gravidarum. Their most important ADR is sedation. Second-generation H_1R antagonists penetrate the BBB less efficiently and are used against urticaria, conjunctivitis, and rhinitis in type I allergies. H_2R antagonists are applied in the (OTC) treatment of GERD and PUD, but have been largely superseded by the PPIs. In acute myelogenous leukemia, HA is used as immune modulator. H_3R antagonists are used in narcolepsy.

Key Points

1. Putrid fish, wine, and cheese can cause HA intoxication that is treated with H_1R and H_2R antagonists.
2. In the parietal cell, the H_2R stimulates proton secretion. PGE_2 possesses protective effects in the stomach, whereas COX inhibitors and GCR agonists are ulcerogenic.
3. Following immunological (type I allergy) and non-immunological stimulation (CADs), mast cells release HA and other mediators.
4. β_2AR activation inhibits mast cell degranulation.
5. First-generation H_1R antagonists are used as hypnotics, in premedication and severe type I allergies with itch, in kinetosis, and in hyperemesis gravidarum.
6. First-generation H_1R antagonists cause sedation and, particularly when taken together with ethanol, reduce the fitness to drive and operate machines.
7. Intoxication with first-generation H_1R antagonists causes an antimuscarinic syndrome.
8. Second-generation H_1R antagonists cause less sedation than first-generation H_1R antagonists and are used against urticaria, rhinitis, and conjunctivitis in type I allergies.
9. H_1R antagonists are ineffective in asthma.
10. PPIs inhibit proton secretion more effectively than H_2R antagonists.

7.1 (Patho)physiological Background and Histamine Receptors

HA is a biogenic amine with the function of an NT and local mediator. HA is generated from histidine by histidine decarboxylase and inactivated by oxidases and N-methyltransferase. HA is stored in high concentrations in mast cells from which it is released under certain conditions and induces important pathophysiological effects (see ▶ Sect. 7.4). Basophils store and release HA as well. Furthermore, HA is stored in the ECL cells of the GI tract. In malignant tumors of ECL cells (carcinoid syndrome; see ▶ Chap. 6), HA is released in large quantities among other mediators and causes symptoms of systemic HA intoxication.

HA possesses important homeostatic functions. ◘ Table 7.1 summarizes selected drugs targeting the histaminergic system. HA mediates its effects via GPCRs that are divided into four subtypes (H_{1-4}Rs). H_1Rs couple to G_q-proteins to mediate PLC activation. In the CNS, the H_1R increases alertness and inhibits appetite; in endothelial cells, it stimulates NO formation (see ▶ Chap. 9). As consequence of the resulting vasodilation, edema, urticaria, and erythema develop. Furthermore, the H_1R mediates itch sensation involving both peripheral and CNS mechanisms.

H_2Rs couple to G_s proteins to activate AC, stimulating proton secretion in parietal cells (see ▶ Sect. 7.3). The H_2R also exerts inhibitory effects on immune cell function. HA is used in the therapy of acute myelogenous leukemia. Via the H_2R, HA inhibits ROS production, thereby preventing destruction of immune cells in the vicinity of the tumor cells. As consequence, immune cells can destroy tumor cells more effectively. Since the H_2R is not exclusively expressed on leukemia cells, systemic HA effects can occur, resulting in ADRs.

Table 7.1 Overview of selected drugs acting on the histaminergic system

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Cromoglicic acid	Plasma membrane stabilization	Inhibition of secretion of HA and other mediators from mast cells	Prevention of type I allergies (conjunctivitis, rhinitis, and asthma)	Local tissue irritation, symptoms similar to type I allergy; prophylaxis is often not feasible due to poor adherence	14
Diphenhydramine	First-generation H_1R antagonist	Sedation, itching relief, antiallergic effects	Type I allergies; itching associated with atopic dermatitis, sunburn, and insect bites; anesthetic premedication, sleeping disorders, kinetosis, hyperemesis gravidarum	Sedation, particularly in combination with ethanol, antimuscarinic syndrome caused by overdose (OTC drug). Increased appetite and weight gain with long-term therapy. This effect is relevant in the long-term treatment of neuropsychiatric diseases with NSMRIs and mGPCR antagonists with H_1R-antagonistic component	4, 6, 28, 29
EPI	Endogenous α_xAR- and β_xAR agonist	Activation of the β_2AR in mast cells acutely inhibits secretion of HA and other mediators	Life-saving treatment of anaphylactic shock! EPI also functionally antagonizes the vasodilatory and prurigenous effects of HA	Tachycardia, arrhythmia (β_1AR agonism)	3, 5
Fexofenadine	Second-generation H_1R antagonist	Itching relief, antiallergic effects	Type I allergies (urticaria, conjunctivitis, rhinitis; not effective in asthma)	Less sedation than first-generation H_1R antagonists	
HA	Endogenous H_xR agonist	Inhibition of ROS production in leukemia cells (H_2R-mediated)	Acute myeloid leukemia (FAB types M4, M5)	As HA does not selectively antagonize the H_2R on leukemia cells, systemic HA effects occur	32
Ranitidine	H_2R antagonist	Inhibition of H_2R-mediated proton secretion in the parietal cell	PUD, GERD (self-medication)	Self-medication with OTC drugs increases the risk that GERD and PUD are diagnosed too late	13
Pantoprazole	Irreversible PP inhibitor (H^+/K^+-ATPase)	Complete inhibition of proton secretion in parietal cells	GERD, PUD	Long-term PPI therapy should be avoided because it may impair various absorption processes	13, 20
Pitolisant	H_3R antagonist	Blockade of the inhibitory effects of the presynaptic H_3R in the CNS	Narcolepsy, sleep apnea	Headache, insomnia, nausea	
Salbutamol	Partial β_2AR agonist	See EPI	Acute asthma attack	Tachycardia (β_1AR activation)	1, 5, 14

H_3Rs are localized presynaptically in the CNS. Like the α_2AR and MOR, the H_3R couples to G_i/G_o proteins leading to inhibition of calcium channels and activation of potassium channels. As a consequence, the H_3R inhibits the release of several NTs including HA and modulates appetite and alertness. Pitolisant is a prototypical H_3R antagonist used for therapy of narcolepsy and sleep apnea.

H_4Rs are expressed in immune cells, most notably eosinophils, and couple to G_i proteins. The released Gβγ subunits mediate activation of PLC and the Gα subunit inhibition of AC. The H_4R possesses proinflammatory effects in asthma and mediates itch. H_4R antagonists may be useful for the treatment of asthma and atopic dermatitis.

In food, histidine can be converted to HA by decarboxylases. Tuna, mackerels, sardines, and seafood are rich sources of histidine. If the cooling chain is interrupted, decarboxylases in fish and seafood can be activated and lead to massive HA accumulation and HA intoxication upon ingestion of rotten food. HA intoxication presents with headache, hypotension, reflex tachycardia, diarrhea, nausea, and vomiting. In most cases, HA intoxication is self-limiting and treated symptomatically with H_1R and H_2R antagonists as well as water and electrolyte substitution. A warning sign for HA intoxication is metallic taste of fish. HA can also be produced via microbial fermentation. Hence, consumption of strongly fermented cheese and wine can cause symptoms of (mild) HA intoxication as well.

7.2 H_1R Antagonists

H_1R antagonists are the most often used prescription and OTC drugs acting in the histaminergic system. They are divided into first-generation H_1R antagonists (prototypes are diphenhydramine, clemastine, and dimetindene) and second-generation H_1R antagonists (prototypes are cetirizine, fexofenadine, and loratadine). First-generation H_1R antagonists are more lipophilic than second-generation H_1R antagonists and, therefore, penetrate the BBB better, leading to more profound CNS effects. But even second-generation H_1R antagonists, particularly in high doses and in combination with ethanol, can compromise CNS function. H_1R antagonists reduce itch, edema, and erythema. Additionally, first-generation H_1R antagonists are strongly sedative.

From these effects the clinical applications can be deduced. First-generation H_1R antagonists are used when sedation is desired, i.e., in sleep disorders and premedication before surgery. In severe itch, e.g., after sun burn or in atopic dermatitis, H_1R antagonists can alleviate itch via peripheral and CNS mechanisms, but this occurs at the expense of sleepiness. In premedication, the M_xR antagonism of first-generation H_1R antagonists is used as well, resulting in reduced secretion in the mouth and airways and increased relaxation of smooth muscles in the airways (see ▶ Chap. 5). Furthermore, first-generation H_1R antagonists are effective in kinetosis and hyperemesis gravidarum. The drugs are very often used systemically in anaphylactic shock (see ▶ Chap. 3). However, they do not inhibit the effects of mediators other than HA. In anaphylactic shock, H_1R antagonists are just supportive but not life-saving; EPI is the drug of choice. First-generation H_1R antagonists can also be applied locally on the skin as gels to reduce erythema, urticaria, and itch, e.g., after insect stings.

Type I allergies are the major indication for second-generation H_1R antagonists. They are applied either locally or systemically. Particularly when urticaria and itch are present in large areas of the skin, systemic administration is required. For rhinitis and conjunctivitis, H_1R antagonists can be applied locally. H_1R antagonists have no effect in asthma.

The most important ADR of H_1R antagonists is sedation unless sedation is specifically desired. Sedation is most pronounced for first-generation H_1R antagonists and can result in decreased fitness to drive or operate machines. This ADR is potentiated upon simultaneous consumption of ethanol. This problem is of great importance because in many countries several first-generation H_1R antagonists are available OTC. Accordingly, pharmacists have high responsibility to control sales and consumption of these drugs. Because of the OTC nature of many medicines containing H_1R antagonists, intoxications are not uncommon coming along with sedation or paradoxical excitation and an antimuscarinic syndrome (see ▶ Chaps. 4 and 5).

If prescribed and administered properly, second-generation H_1R antagonists are well tolerated. For this reason and their effectiveness in type I allergies, they belong to the most widely used drugs worldwide. Upon systemic admin-

istration, sedation can occur, calling for dose reduction or local administration or switch to another drug from the same class. Application of terfenadine, the prodrug of fexofenadine, can cause life-threatening arrhythmias of the TdP type (see ▶ Chap. 17). Therefore, terfenadine was withdrawn from the drug market.

7.3 Pharmacological Modulation of Gastric Proton Secretion

Figure 7.1 shows the regulation of gastric proton secretion. In parietal cells, the H_2R activates the PP via the G_s-AC pathway. H_2R antagonists represented the first effective pharmacological treatment for PUD and GERD and resulted in a strong decline in debilitating partial gastrectomies and vagotomies. However, H_2R antagonists cannot completely prevent proton secretion, because other stimulatory pathways exist. Both M_xRs and CCK_2R, the latter being activated by gastrin and cholecystokinin, stimulate proton secretion via the G_q-PLC pathway. Theoretically, proton secretion could also be partially inhibited by M_xR antagonists and CCK_2R antagonists, but this is clinically not relevant.

The most effective way of inhibiting proton secretion is to block the PP with irreversibly acting drugs, the PPIs. Pantoprazole is a prototype of this drug class (see ▶ Chap. 13). Based on the fact that H_2R antagonists inhibit proton secretion only partially and that PPIs are more effective, the importance of the H_2R as target has declined substantially. Several H_2R antagonists are available OTC in many countries. These medicines are predominantly used in self-medication of GERD and PUD. This constitutes a certain risk because the precise endoscopic diagnosis of the underlying disease may be delayed. Therefore, it is critical

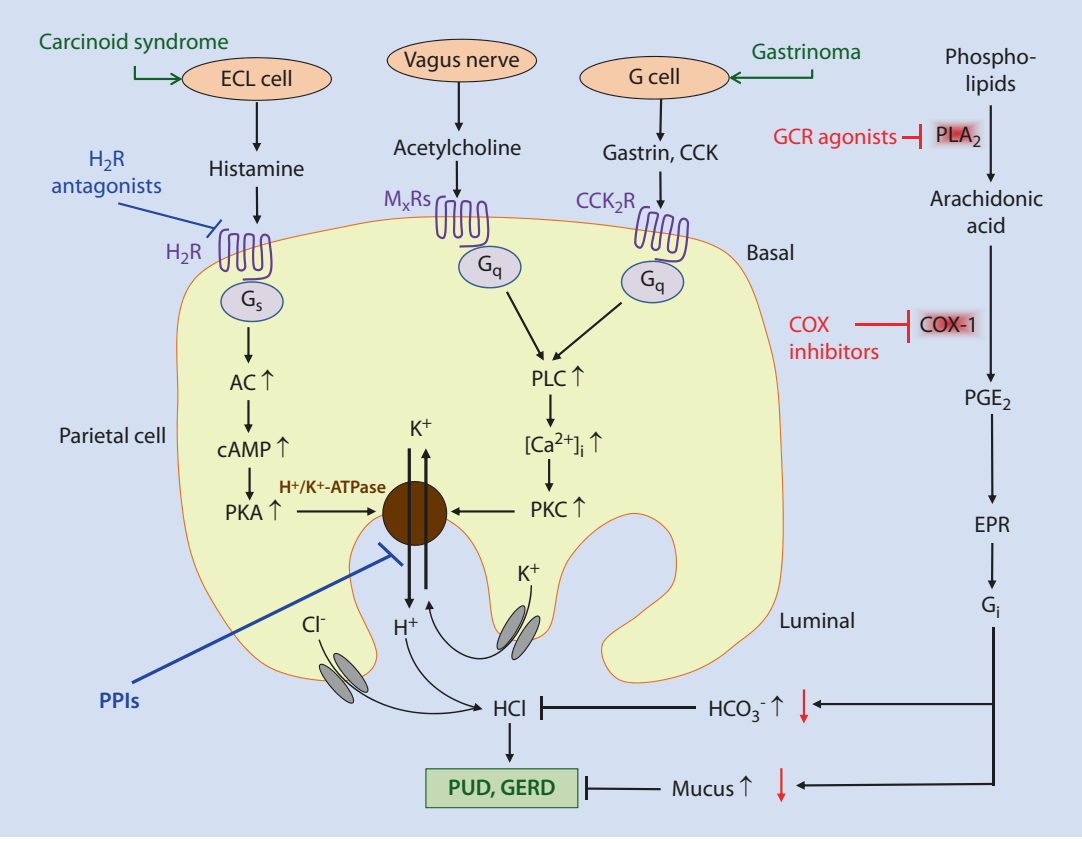

Fig. 7.1 Pharmacological modulation of gastric proton secretion. See also Figs. 13.1 and 13.2. Beware of the long-term use of PPIs + COX inhibitors! The PPIs are clinically much more important and effective for inhibition of proton secretion than the H_2R antagonists. The latter drugs are mostly relegated to self-medication which often delays professional diagnostics (see ▶ Chap. 13)

that pharmacists provide proper information about the benefits and risks of H_2R antagonists in OTC therapy.

Ranitidine is a commonly used H_2R antagonist. At a dose of 150 mg, it inhibits proton secretion by about 70%. Famotidine is more potent than ranitidine, i.e., it exhibits the same effect as ranitidine at a dose of 20 mg. However, the maximum inhibitory effect of both drugs on proton secretion is comparable (see ▶ Chap. 1).

PGE_2 is of great homeostatic importance in the stomach. Via a specific GPCR, PGE_2 activates G_i proteins and a signaling pathway that stimulates mucus and bicarbonate secretion. This pathway counteracts the pathogenesis of PUD (see ▶ Chap. 13). Thus, PGE_2 exerts cytoprotective effects on the stomach. If COX-1 is inhibited upon application of nonselective COX inhibitors, the protective effect of PGE_2 on the stomach is abrogated, and pathogenesis of PUD is facilitated. In addition, inhibition of PLA_2 by GCR agonists resulting in reduced AA release and subsequent PGE_2 formation, can be ulcerogenic. To prevent PUD during long-term therapy with COX inhibitors and GCR agonists, H_2R antagonists and PPIs can be used. However, the long-term use of PPIs is not unproblematic (see ▶ Chaps. 13 and 20).

7.4 Pharmacological Modulation of the Mast Cell

Figure 7.2 shows pharmacological modulation of mast cells. They play a critical role in the pathogenesis of type I allergies (see ▶ Chap. 3). Upon stimulation, they release HA and other mediators, most notably LTD_4. Mast cells express receptors for the Fc portion of IgE. The IgE-Fcε receptor is activated by binding of antigen-IgE complexes. Drugs (see ▶ Chap. 3), pollen, and food constituents can act as allergens. Receptor activation results in stimulation of PLC-γ with subsequent increase in intracellular

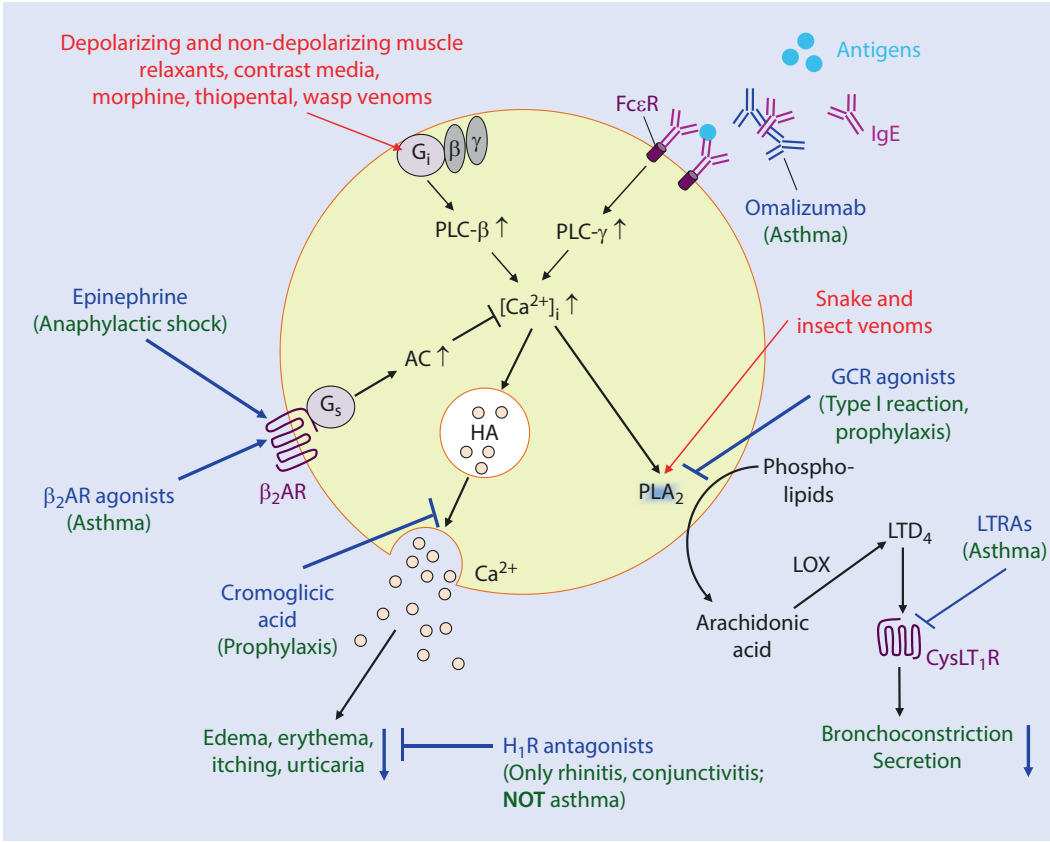

Fig. 7.2 Pharmacological modulation of the mast cell. See also Fig. 3.1. Activation of the β_2AR is the most effective and fastest way to inhibit mast cell activation in a type I allergic reaction! GCR agonists have a delayed onset of action! They are effective in prophylaxis

calcium concentration. Calcium mediates fusion of HA-containing vesicles with the plasma membrane. The release of HA induces typical symptoms of type I allergies (edema, erythema, urticaria, itch). Calcium also mediates activation of PLA_2, releasing AA from phospholipids. LOX converts AA to LTD_4, inducing bronchoconstriction. Many snake and insect venoms contain PLA_2. HA can be released from mast cells also non-immunologically. CADs, i.e., drugs that possess both lipophilic and cationic (positively charged) partial structures, can directly activate G_i proteins without GPCR involvement. The released Gβγ subunits then activate PLC-β with subsequent calcium increase and HA release. Typical CADs are the MOR agonist morphine, depolarizing and non-depolarizing muscle relaxants (see ▶ Chap. 5), contrast media (see ▶ Chap. 12), the injection narcotics propofol and thiopental (see ▶ Chap. 27), and the solubilizer Cremophor EL (see ▶ Chap. 32). Upon i.v. injection, these drugs can cause the symptoms of a type I allergy (see ▶ Chap. 3). Wasp venoms such as mastoparan activate G_i proteins also directly.

These proinflammatory pathways are inhibited by the β_2AR. The β_2AR functionally antagonizes the stimulatory effects of calcium via the G_s-AC pathway. These anti-inflammatory effects of the β_2AR are exploited clinically. In anaphylactic shock, the β_2AR is activated with EPI, because in this situation the α_1AR-mediated vasoconstriction is also important (see ▶ Chaps. 3 and 5). In asthma, selective β_2AR agonists (SABAs and LABAs) are used (see ▶ Chap. 14). H_1R antagonists mitigate urticaria, edema, erythema, and itch, but because of the contribution of the H_4R to itch pathogenesis, the effect of H_1R antagonists on pruritus is only moderate.

The stimulatory effects of LTD_4 on bronchoconstriction are prevented by LTRAs. GCR agonists inhibit PLA_2 and, thereby, reduce LTD_4 formation. Another strategy to mitigate asthma symptoms is to apply IgE inhibitors. The prototype of this class is omalizumab which binds IgE. However, omalizumab is an expensive biological and can for cost reasons only be prescribed to selected patients with refractory type I allergies. It can also be attempted to desensitize the patient against the causative allergen by applying increasing doses of the antigen over a long period of time. The rationale for this therapy is to shift the balance between IgE and IgG toward IgG. The latter immunoglobulins do not activate mast cells.

Cromoglicic acid stabilizes the mast cell membrane via an unknown mechanism and prevents HA release. However, in contrast to EPI, β_2AR agonists and H_1R antagonists, cromoglicic acid does not exhibit acute effects but must be given prophylactically for several weeks. Hence, adherence under cromoglicic acid therapy is a problem. Ketotifen stabilizes mast cells membranes and antagonizes the H_1R.

7.5 Questions and Answers

Questions

Which assignment of a drug to a pharmacological effect is *NOT* correct?

A. Pantoprazole – Inhibition of mast cell degranulation
B. HA – Indirect improvement of tumor cell destruction in acute myelogenous leukemia
C. Ranitidine – Inhibition of proton secretion in parietal cells
D. Pitolisant – Prevention of sleep attacks in narcolepsy
E. Diphenhydramine – Alleviation of itch

Answers

A. Pantoprazole inhibits the H^+/K^+-ATPase in parietal cells and, thereby, inhibits proton secretion very effectively. Cromoglicic acid inhibits mast cell degranulation.
B. HA, via the H_2R, inhibits ROS production in tumor cells and, as consequence, indirectly enhances the function of cytotoxic T cells. As net result, tumor cell destruction is enhanced by HA.
C. Ranitidine is an H_2R antagonist and inhibits the stimulatory effects of HA on proton secretion.
D. Pitolisant is an H_3R antagonist and abrogates the inhibitory effects of the H_3R on neurotransmission, ultimately increasing alertness.
E. Diphenhydramine is a first-generation H_1R antagonist and, via peripheral and CNS mechanisms, alleviates itch in type I allergies, sun burn, atopic dermatitis, and insect stings.

Assignment **A** is not correct.

7.6 Exercises

A 23-year-old female medical student suffers from a type I allergy due to grass pollen. The main symptoms are strongly itching conjunctivitis and rhinitis. The student visits you in your family practice and asks for a medication that quickly alleviates her complaints without interfering with her learning for the upcoming pharmacology exam.

Questions

1. Which drugs are well suited for rapid improvement of the patient's symptoms?
2. Which drugs should be avoided in any case?

Answers

1. You prescribe a second-generation H_1R antagonist such as cetirizine, fexofenadine, or loratadine. To avoid ADRs in the CNS (sedation and impaired learning), drugs should be initially applied topically, i.e., nasal spray for rhinitis and eye drops for conjunctivitis, as soon as the symptoms start. The onset of action of the local therapy is rapid. If local therapy is not sufficient, drugs can be administered orally. This is an option particularly in cases with generalized urticaria. However, systemic therapy with second-generation H_1R antagonists should begin with low doses because even this drug class is not completely devoid of ADRs in the CNS.
2. First-generation H_1R antagonists such as diphenhydramine, clemastine, and dimetindene must be avoided because these drugs cause substantial sedation and, thereby, impair learning. Since several of these drugs are available in numerous countries as OTC medicines, the student may be inclined to assume that the drugs are devoid of ADRs. However, this is not the case. The risk of sedation under therapy with first-generation H_1R antagonists is particularly high when ethanol is consumed simultaneously.

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Dopaminergic System

R. Seifert, *Basic Knowledge of Pharmacology*, https://doi.org/10.1007/978-3-030-18899-3_8

DA is an NT that regulates many body functions in the periphery and CNS. DA mediates its effects via $D_{1\text{-}5}R$ and is used in the ICU to enhance kidney perfusion and cardiac function and to induce vasoconstriction. In PD, there is a loss of function of dopaminergic nigrostriatal neurons with consequent dominance of cholinergic neurons. This results in rigor, tremor, and akinesia. PD symptoms can be alleviated via stimulation of the dopaminergic system with the prodrug levodopa that is converted to DA and the peripherally acting dopa decarboxylase inhibitor carbidopa. D_xR agonists, MAO-B and COMT inhibitors, and M_xR antagonists can be used as well. Hallucinations, confusion, compulsive gambling, hypersexuality, and shopping fever are important ADRs of dopaminergic drugs. Peripherally acting D_2R antagonists are used as antiemetics. The centrally acting D_2R-mGPCR antagonist haloperidol and the p-mGPCR antagonist clozapine (it is also a D_4R antagonist) possess antipsychotic effects. In ADHD, there is a hypofunction of the frontostriatal dopaminergic system that can be improved with the indirect dopamimetic MPH. Before MPH is prescribed, the diagnosis of ADHD must be made by a qualified child and youth psychiatrist. MPH possesses substantial potential for abuse to boost cognitive performance (brain doping, neuroenhancement).

Key Points

1. PD is characterized by hypofunction of dopaminergic nigrostriatal neurons.
2. Strengthening of the dopaminergic system in PD with levodopa + the peripherally acting dopa decarboxylase inhibitor carbidopa, D_xR agonists, and inhibitors of MAO-B and COMT alleviates predominantly the negative symptom akinesia.
3. Dopaminergic drugs can cause hallucinations, hypersexuality, compulsive gambling, and shopping fever.
4. M_xR antagonists like biperiden predominantly improve the positive PD symptoms rigor and tremor.
5. D_2R antagonists acting in the area postrema act as antiemetics.
6. D_2R-mGPCR antagonists acting in the CNS such as haloperidol are antipsychotic and possess a high EPS risk.
7. p-mGPCR antagonists (also blocking theD_4R) like clozapine are antipsychotic as well and possess a low EPS risk but a high risk of metabolic syndrome.
8. ADHD is characterized by hypofunction of the dopaminergic frontostriatal system.
9. MPH is an indirect dopamimetic and effective in ADHD. MPH inhibits neuronal DA re-uptake and promotes DA release from vesicles.
10. MPH has substantial ADRs and can cause tachyphylaxis and addiction.
11. MPH possesses high potential for abuse.

8.1 (Patho)physiological Background and Pharmacological Interventions in the Dopaminergic System

Numerous pharmacological interventions in the dopaminergic system exist (◘ Fig. 8.1). ◘ Table 8.1 provides a summary of selected drugs. DA is a NT that is produced from the precursors tyrosine and levodopa. Dopa decarboxylase converts levodopa to DA. Levodopa is used pharmacologically as prodrug for DA that belongs to the biogenic amines and mediates its effects via the GPCRs $D_{1\text{-}5}R$. DA itself is a precursor for the synthesis of NE and EPI (see ► Chap. 5). DA degradation predominantly occurs via MAO-B and COMT. For both enzymes, selective inhibitors are available. D_xRs can be activated by agonists and inactivated by antagonists.

In the periphery, the D_1R mediates vasodilation, predominantly in the kidney. This effect is exploited in the ICU. Specifically, i.v. infusion of DA in low concentrations can improve kidney perfusion in acute kidney failure (see ► Chap. 12). In higher concentrations, DA additionally activates the β_1AR and improves cardiac function (see ► Chap. 5). This effect is used in the ICU as well. Further increased concentrations of DA induce vasoconstriction via the α_1AR, an effect that can be utilized in septic shock associated with vasodilation.

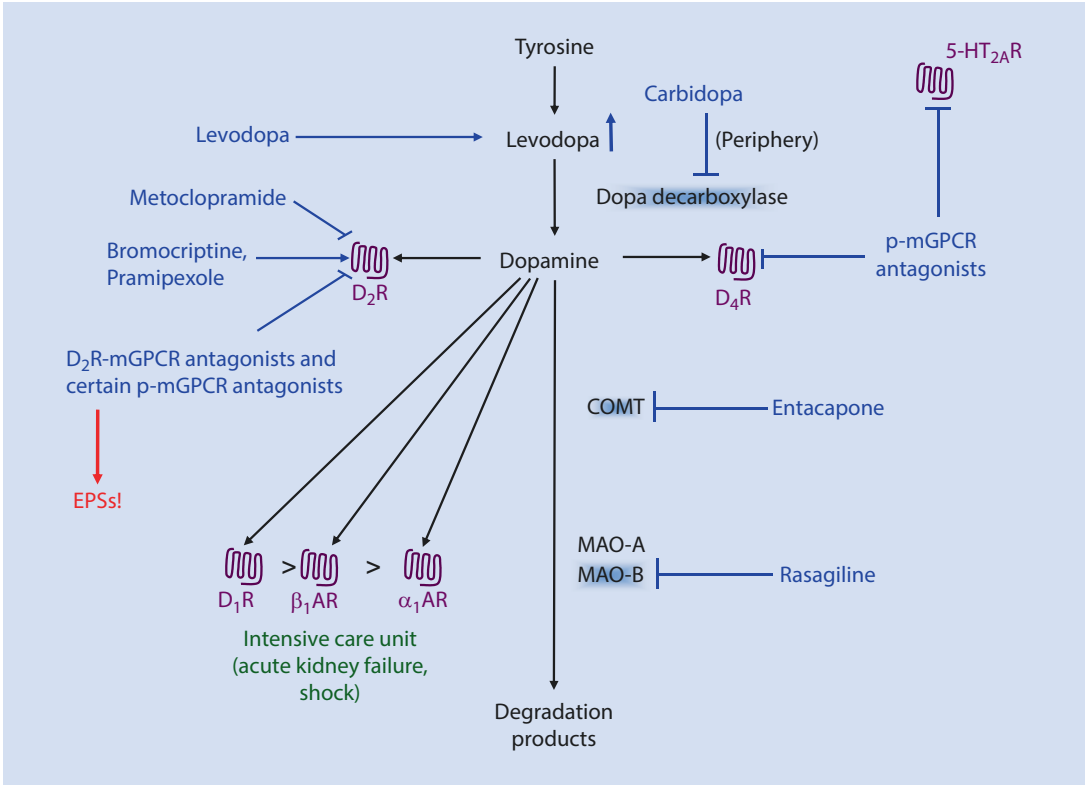

Fig. 8.1 Dopamine metabolism, D_xRs, and pharmacological interventions

Table 8.1 Overview of selected drugs acting in the dopaminergic system

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Bromocriptine	Partial D_xR agonist	Direct partial D_xR activation in the periphery and in the CNS	PD, if the effect of levodopa + carbidopa wears off; all in all less effective than the aforementioned combination	Like levodopa + carbidopa; but all in all weaker because of partial agonism; pulmonary and retroperitoneal fibrosis, ADRs due to activation of α_xARs, β_xARs, and 5-HT_xRs	1
Carbidopa	Inhibition of dopa decarboxylase in the periphery	Enhances the effects of levodopa in the CNS	PD	Deteriorates ADRs of levodopa in the CNS	2

(continued)

Table 8.1 (continued)

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Clozapine	p-mGPCR antagonist including D_4R and 5-$HT_{2A}R$ antagonist	Pleiotropic effects in the CNS, antipsychotic effect (particularly on negative symptoms), reduction in suicidality	Schizophrenia, if D_2R-mGPCR antagonists fail or have severe ADRs and if negative symptoms prevail	Metabolic syndrome, agranulocytosis (white blood cell count is mandatory), fewer EPSs than D_2R-mGPCR antagonists	6, 29
DA	Agonist at D_xRs, β_1AR (with higher doses) and α_1AR (with even higher doses)	Vasodilation and increased renal blood flow (D_1R), enhanced cardiac function (β_1AR), systemic vasoconstriction (α_1AR)	Renal failure or shock. Depending on the cardiovascular situation, DA at different doses can symptomatically improve the situation	The administration of DA requires continuous monitoring of the patient and dose adjustment	5, 12
Entacapone	COMT inhibition	Potentiates DA effect in the periphery and in the CNS	Adjunctive therapy in PD; potentiates effect of levodopa, but has no intrinsic effect	Deteriorates ADRs of levodopa	
Haloperidol	D_2R-mGPCR antagonist	Antipsychotic effect (particularly on positive symptoms) and co-analgesic effect	Schizophrenia and co-analgesia in tumor diseases, bipolar disorder, personality and anxiety disorders, obsessive-compulsive disorders	EPSs, hyperprolactinemia, galactorrhea	10, 29
Levodopa	DA prodrug, delivery to the CNS via amino acid transporters	Is converted to DA which activates D_xRs in the CNS and in the periphery	Initial treatment of PD; almost always combined with carbidopa in order to reduce peripheral ADRs and to enhance effects on the CNS; good effects on minus symptoms, less pronounced effects on plus symptoms	Nausea, vomiting, BP drop, hallucinations, confusion, gambling and sex addiction, compulsive buying disorder, risk for abuse is substantial but underestimated!	2
MCP	Peripherally acting D_2R antagonist	Antiemetic and prokinetic effect in the GI tract	Nausea and vomiting, e.g., in migraine and GI infections	EPSs with high doses and in toddlers (BBB still incomplete!) (acute dystonias)	2, 6, 13

Table 8.1 (continued)

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Methylphenidate	Indirect dopamimetic: Inhibition of DA re-uptake and stimulation of DA release from vesicles	Enhanced dopaminergic neurotransmission in the frontostriatal system improves concentration ability	Attention deficit hyperactivity disorder (ADHD) in children, adolescents, and adults	Abused by healthy people to increase their mental capacity (brain doping); appetite disturbances, BP rise, insomnia, priapism, risk of addiction, and tachyphylaxis especially after i.v. administration	5
Rasagiline	MAO-B inhibition	Potentiates the effect of DA in the periphery and in the CNS	Adjunctive therapy in PD; less effective than bromocriptine	Deteriorates ADRs of levodopa	

Keep in mind that both levodopa and MPH can be abused! Be alarmed when patients request these drugs without proper diagnosis!

In the CTZ of the area postrema, the D_2R triggers vomiting. D_2R antagonists like MCP have an antiemetic effect. MCP predominantly acts in the area postrema only in adults. In high doses or in cases of an incomplete BBB, MCP penetrates into the CNS and can cause acute dyskinesia (see ▶ Chap. 2). Therefore, MCP must not be given in excessive doses and invasion into the CNS must be slow. In babies and toddlers, MCP is contraindicated.

In the CNS, DA has many functions. It activates the reward system and plays a major role in the pathogenesis of drug addiction (e.g., ethanol, nicotine, THC, indirect sympathomimetics, heroin; see ▶ Chaps. 5 and 10). In the mesolimbic and mesocortical system, DA regulates behavior, cognition, and emotions. In schizophrenia, the mesocortical dopaminergic system is hyperactive, resulting in emotional problems, impaired social behavior, cognitive problems, and hallucinations (▶ Chap. 29). Many antipsychotic drugs are D_xR antagonists. D_2R-mGPCR antagonists predominantly antagonize the D_2R; certain p-mGPCR antagonists like clozapine predominantly antagonize the D_4R. D_2R-mGPCR antagonists and p-mGPCR antagonists differ from each other in their therapeutic effects and ADRs (see ▶ Chaps. 1 and 29).

DA plays an important role in the regulation of the extrapyramidal motor system (see ▶ Sect. 8.2), motor behavior and attention (see ▶ Sect. 8.3), and the neuroendocrine system. DA is released in the hypothalamus and inhibits the secretion of prolactin in the adenohypophysis. Prolactin stimulates milk production and inhibits secretion of FSH and LH, preventing ovulation (see ▶ Chap. 24). Hyperprolactinemia is a cause of infertility and amenorrhea. The inhibition of prolactin secretion by D_xR agonists like bromocriptine facilitates re-establishment of a normal menstrual cycle. Conversely, long-term therapy D_2R-mGPCR antagonists can cause hyperprolactinemia and galactorrhea. These ADRs of D_2R-mGPCR antagonists can also occur in men and cause adherence problems (see ▶ Chap. 29).

8.2 Pathophysiology and Pharmacotherapy of Parkinson's Disease (PD)

DA plays an important role in the regulation of the extrapyramidal motor system (Fig. 8.2a). Dopaminergic neurons project from the substantia nigra into the neostriatum and inhibit cholin-

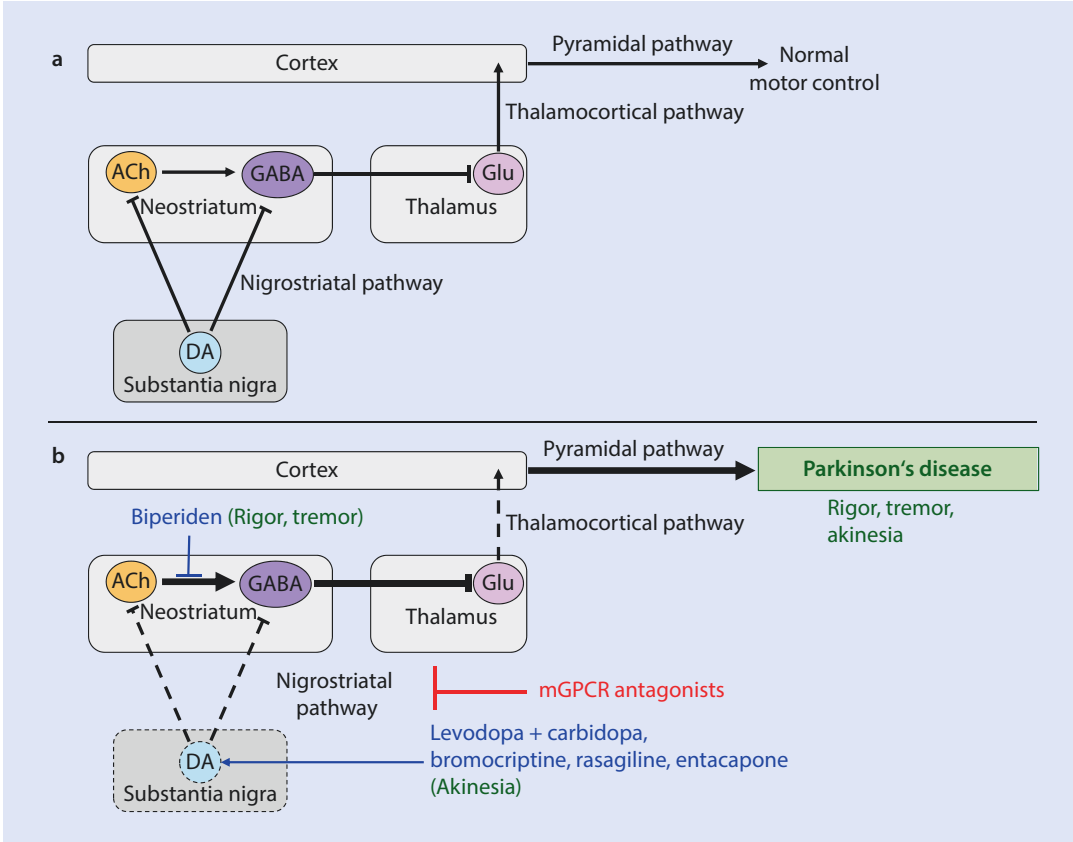

Fig. 8.2 Physiological function of the extrapyramidal system **a** and disturbed function of the extrapyramidal system in PD **b**: pharmacological interventions. The available drugs are just symptomatic. You cannot cure PD! Keep in mind that long-term treatment with mGPCR antagonists for various neuropsychiatric diseases can cause Parkinsonian symptoms! This is a serious ADR often causing dose reduction or change to a different mGPCR antagonist. In contrast to common belief, both D_2R-mGPCR antagonists and p-mGPCR antagonists can cause Parkinsonian symptoms (see ▶ Chap. 29)

ergic and GABAergic neurons. The latter neurons inhibit glutamatergic neurons in the thalamus that project into the cortex. If the activity of these NT systems is balanced, physiological motor behavior with rapid and precisely controlled movements is possible.

PD, like AD (see ▶ Chap. 30), belongs to the group of neurodegenerative diseases. In PD, a progressive degeneration of dopaminergic nigrostriatal neurons occurs (Fig. 8.2b). The cause for degeneration can be illicit drugs, trauma (boxer), and mutations in genes encoding specific neuronal proteins. Long-term therapy with mGPCR antagonists can cause Parkinsonian symptoms as well (see ▶ Chap. 29). Therapy of drug-induced Parkinsonian symptoms is to withdraw the ADR-causing mGPCR antagonist or at least to reduce its dose. Additionally, M_xR antagonists can be applied.

A major problem in the therapy of PD is the fact that the nigrostriatal system possesses a large capacity for functional compensation. This implies that only after the major fraction of the nigrostriatal neurons has lost its function, clinical symptoms occur, rendering drug therapy more difficult. The loss of function of the nigrostriatal neurons abrogates their inhibitory effect on cholinergic and GABAergic neurons. Excessive activity of the latter neurons inhibits the impact of glutamatergic neurons on the cortex. As a consequence of this neuronal imbalance, the clinical symptoms of PD occur. Akinesia is a minus symptom, whereas rigor and tremor constitute plus symptoms.

Pharmacotherapy of PD aims at correcting the NT imbalance. However, the natural course of the disease cannot be influenced by the drugs.

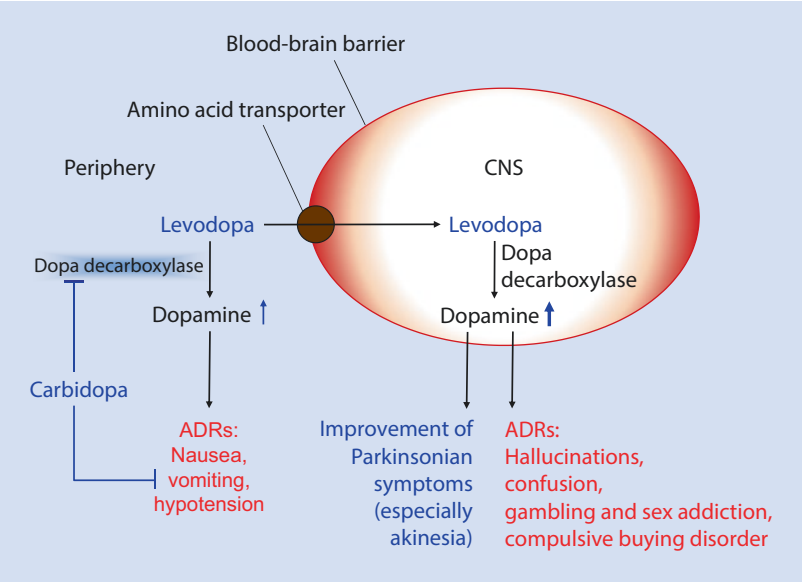

Fig. 8.3 Interaction of carbidopa and levodopa: Therapeutic effects and dopaminergic ADRs in the periphery and CNS. Beware that all dopaminergic drugs used in PD can use the ADRs shown here! Levodopa is abused! Therefore, make sure that you confirmed the diagnosis "PD" when prescribing levodopa + carbidopa

The most important strategy in the therapy of PD is to support the dopaminergic system. The DA prodrug levodopa passes the BBB via an amino acid carrier (see ▶ Chap. 2) and is converted to DA in the CNS (Fig. 8.3). The increased DA release in nigrostriatal neurons predominantly improves akinesia and, to a lesser extent, rigor and tremor. The major problem in the use of levodopa is that it is largely converted to DA already in the periphery. As a result, ADRs including nausea, vomiting and hypotension occur. Due to the peripheral conversion of levodopa to DA, less levodopa is available in the CNS, and therapeutic efficacy is reduced. An increase in the dose of levodopa would predominantly augment peripheral ADRs and is therefore not feasible.

The most important strategy to solve this problem is the co-administration of levodopa with the dopa decarboxylase inhibitor carbidopa which only acts in the periphery but is not taken up into the CNS via the amino acid carrier. Thereby, the peripheral ADRs of levodopa are substantially reduced, and more levodopa is available for conversion in the CNS. This results in better responsiveness of the symptoms. However, conversion of levodopa to DA occurs in all dopaminergic neurons in the CNS. As a result, the overall activity of the dopaminergic system is increased. Typical ADRs of a combination therapy of levodopa + carbidopa are confusions and hallucinations. In addition, the activity of the dopaminergic reward system is increased. Clinically, this manifests in compulsive gambling, hypersexuality (predominantly men), and shopping fever (predominantly women). These effects of DA on the reward system can also lead to abuse of levodopa + carbidopa.

With progressive degeneration of nigrostriatal neurons in PD, the efficacy of levodopa + carbidopa decreases. This can be addressed by application of additional drugs that inhibit DA degradation. Options are MAO-B inhibitors such as rasagiline and COMT inhibitors such as entacapone (Fig. 8.1). MAO-B inhibitors themselves possess a much smaller effect than levodopa + carbidopa. COMT inhibitors themselves have no effect but just potentiate the effects of levodopa + carbidopa. The M_xR antagonist biperiden predominantly improves rigor and tremor but much less effectively akinesia. Biperiden can cause an antimuscarinic syndrome (see ▶ Chap. 5).

In advanced nigrostriatal degeneration, dopa decarboxylase activity is not sufficient anymore to convert levodopa to DA. In this situation, therapy with D_xR agonists can be implemented because then metabolic activation is unnecessary. Bromocriptine

is a prototypical D_xR agonist but less effective than levodopa + carbidopa. On the one hand, this is due to the advanced disease, and on the other hand, bromocriptine is only a partial agonist with a lower efficacy than DA (see ▶ Chap. 1). However, the 5-HT_xR agonism of bromocriptine (see ▶ Chap. 6) gives rise to several ADRs. Bromocriptine is an ergot alkaloid that can cause pulmonary and retroperitoneal fibrosis. Pramipexole is a D_xR agonist without ergoline structure and does not possess the risk of fibrosis but can cause sleep attacks. A problem in the long-term therapy with all D_xR-agonistic drugs is the fact that receptor desensitization can occur (see ▶ Chap. 1). In these cases, therapy must be interrupted. However, this can often only be accomplished with inpatient treatment because the patient is feeling very sick during the withdrawal period. As a general rule, all dopaminergic drugs for PD can also cause ADRs in other dopaminergic systems.

Therapy of PD belongs into the hands of a neurologist. In the end, one has to find a reasonable compromise between sufficient therapeutic effects and acceptable ADRs involving flexible adaption to the progredient disease course. Non-pharmacological treatments such as physiotherapy and specific training of remaining motor capabilities support PD therapy substantially. In severe PD cases, deep brain stimulation is a therapeutic option.

8.3 Pathophysiology and Pharmacotherapy of Attention Deficit Hyperactivity Disorder (ADHD)

The frontostriatal dopaminergic system regulates motor activity and attention. Hypofunction of this system results in ADHD. This disease is characterized by attention deficit, impulsive behavior, and excessive motor activity. Reduced frustration tolerance and self-confidence, forgetfulness, mood swings, and unharmonious relationships can be present as well. It is estimated that the prevalence of ADHD is worldwide around 5%. ADHD is diagnosed more often in boys than in girls. In about 60% of all cases, ADHD persists into adulthood.

In ADHD, the function of dopaminergic synapses in the frontostriatal system is impaired. Figure 8.4 shows a dopaminergic synapse that in principle functions like a noradrenergic synapse (see ▶ Chap. 5). The ultimate cause of ADHD is not yet known, but an important alteration is increased DAT activity in the frontostriatal system (Fig. 8.4b). DA is taken up into the synapse more rapidly so that less DA is available for activation of postsynaptic D_xRs. This functional abnormality does not affect the entire CNS. This is the reason why there are no signs of a global DA deficit in ADHD.

Based on the pathophysiology of ADHD, the most important approach for pharmacotherapy is the inhibition of DA re-uptake (Fig. 8.4c). MPH is the prototypical DAT inhibitor used for ADHD treatment. As a result of DAT inhibition, the DA concentration in the synaptic cleft increases, and dopaminergic signaling in the frontostriatal system is improved. MPH acts symptomatically. The consequences of long-term treatment with MPH are as yet incompletely known.

In addition to DAT inhibition, MPH acts as an indirect dopamimetic (and sympathomimetic) (see ▶ Chap. 5). MPH enters the dopaminergic neuron and is taken up into DA-containing vesicles. In exchange, DA is released in high concentrations into the cytosol and then, via non-specific biogenic amine transporters, transferred into the synaptic cleft. This mechanism contributes substantially to the elevation of the DA concentration. However, because of this additional mechanism of action of MPH, there is also the risk of tachyphylaxis, i.e., when the drug is applied at excessive doses, depletion of DA-containing vesicles can occur, and ADHD symptoms deteriorate.

After p.o. administration MPH shows positive effects on cognition and calming of motor activity within 30–45 minutes. The effect of MPH lasts for 3–6 hours. There are also sustained-release formulations of MPH. The number of children and adolescents treated against ADHD is increasing worldwide. In some countries, MPH can also be prescribed for adults. Non-pharmacological treatment of ADHD includes sport activities, playing music instruments, and reasonably regulated access to the Internet and smartphones.

The diagnosis ADHD must be made by a qualified child and youth psychiatrist. MPH does not only enhance cognition in ADHD patients but also in subjects without ADHD. This is the reason

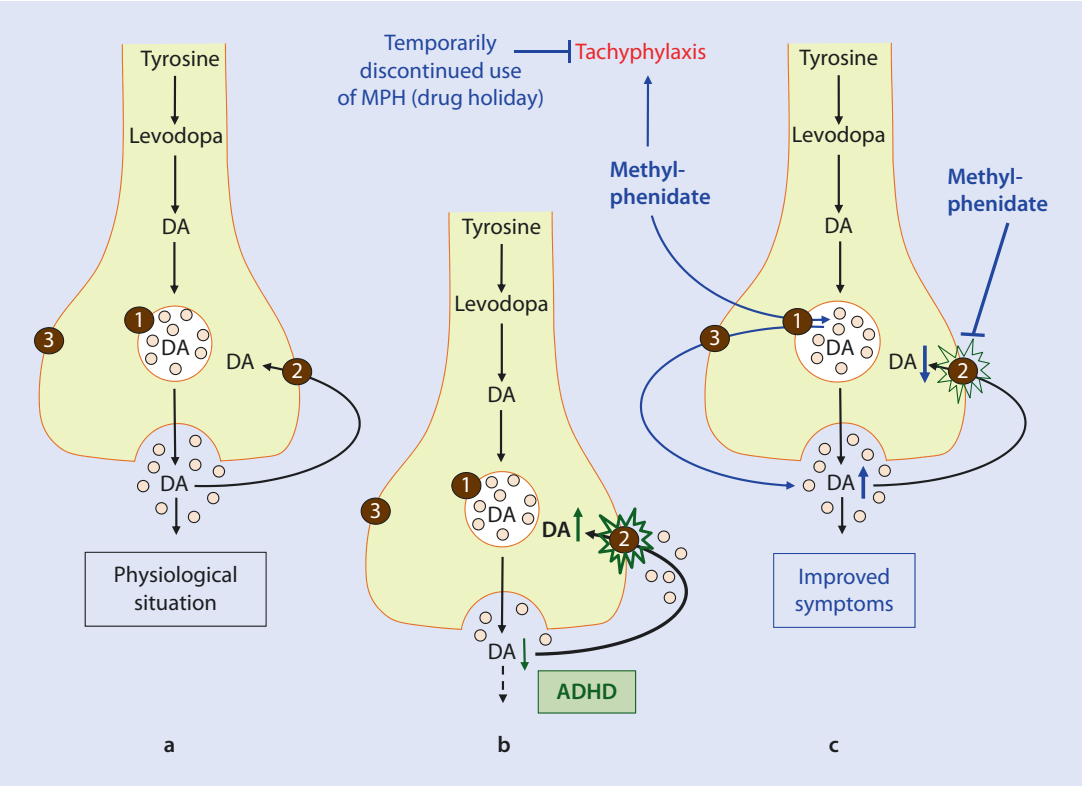

Fig. 8.4 **a–c** Dopaminergic synapse and functional changes in ADHD: Mechanism of action of methylphenidate. **a** Physiological situation. **b** ADHD. **c** ADHD with MPH therapy. 1, vesicular DA transporter; 2, DAT; 3, unspecific transporter for biogenic amines. The key for successful therapy of ADHD with MPH are regular drug holidays to avoid tachyphylaxis. MPH is increasingly abused for "brain doping" in humans without ADHD. Ensure restricted access to MPH medications!

for MPH being increasingly abused for "brain doping." Therefore, precise diagnosis of ADHD is important to avoid MPH abuse. The abuse and addiction potential of MPH is particularly large upon i.v. injection. Rapid invasion of MPH into the CNS induces a "high" feeling, like after the i.v. injection of heroin (see ▶ Chaps. 2 and 10). The risk of tachyphylaxis under MPH therapy requires regular drug holidays, e.g., during the weekends. During the drug holidays, the DA vesicles can refill. Because of its indirect sympathomimetic effects, MPH can cause loss of appetite, increase in HR and BP, and insomnia. In boys priapism can occur (see ▶ Chap. 9). The appetite-reducing effects of MPH can also be abused to induce weight reduction, e.g., in female dancers and models. Taken together, the pharmacological profile of MPH with regard to therapeutic effects and ADRs requires that the drug is prescribed very critically and cautiously to avoid abuse.

8.4 Questions and Answers

Questions

Which statement on the therapy of ADHD with MPH is *not* correct?

A. MPH can cause insomnia.
B. MPH can reduce appetite.
C. MPH can cure ADHD.
D. MPH acts as indirect dopamimetic in the frontostriatal system.
E. MPH can enhance cognitive performance in healthy subjects.

Answers

A. This is a typical ADR due to activation of the sympathetic nervous system.
B. This is another typical ADR due to activation of the sympathetic nervous system. This ADR is often abused by

young women to induce weight loss (models, dancers).

C. Methylphenidate acts symptomatically in ADHD. The increased DAT activity is just one known biochemical abnormality in ADHD. The cause of ADHD is unknown. Upon termination of therapy with MPH, the symptoms can reoccur.

D. This mechanism of action is true. In proper doses MPH does not lead to a general activation of the dopaminergic system with ADRs such as hallucinations or vomiting.

E. This statement is true and constitutes a substantial problem. Since nowadays MPH is widely prescribed, the potential for abuse has increased in parallel. A particular problem is the abuse of MPH to boost intellectual performance in academic exams.

Statement **C** is not correct.

8.5 Exercises

A 72-year-old female patient with PD runs into big financial problems. Her husband reports that with her credit card, she has purchased online 150 designer handbags.

Questions

1. Which drugs could have caused the symptoms?
2. How can the problem be solved?

Answers

1. In principle, all drugs stimulating the dopaminergic system cause the pathological shopping behavior. Most important causes are levodopa + carbidopa, followed by D_2R agonists such as bromocriptine, MAO-B inhibitors such as rasagiline, and the COMT inhibitor entacapone.
2. The patient and her husband have to be informed about the link between the pathological shopping behavior and the medication. In the next step, a dose reduction has to be considered. Addition of M_xR antagonists such as biperiden is an option, too. Disconnection from the Internet has to be considered as well, but practically, this is difficult to accomplish. Moreover, such measure may result into a shift toward traditional shopping behavior. In the end, one has to find a good compromise between therapeutic effects and ADRs that needs to be negotiated between the neurologist, the patient, and her husband.

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NO-cGMP System

R. Seifert, *Basic Knowledge of Pharmacology*, https://doi.org/10.1007/978-3-030-18899-3_9

NO is synthesized in endothelial cells and activates sGC in smooth muscle cells. sGC produces the second messenger cGMP. Relaxation of smooth muscle cells is the most important function of cGMP. cGMP is degraded by PDE5. The NO donor GTN activates sGC and relaxes smooth muscle cells. This effect is used for the treatment of AP, hypertensive emergency, and visceral pain. The NO donor SNP is used for otherwise resistant hypertensive emergency. Long-term therapy with NO donors is problematic due to tolerance. In contrast, allosteric sGC stimulators can be used for long-term treatment. Their muscle-relaxing properties are used for therapy of PAH. ED is caused by reduced NO production in the corpus cavernosum as consequence of cardiovascular, urological, or neurological diseases. ED can be improved by PDE5 inhibitors. In toxic doses, PDE5 inhibitors can cause blue vision. The combination of NO donors + PDE5 inhibitors can lead to life-threatening hypotension.

Key Points

1. Relaxation of smooth muscle cells is the most important function of the NO-cGMP system.
2. sGC is activated by NO donors and allosteric modulators.
3. GTN is an emergency drug for AP, hypertensive emergency, and visceral pain.
4. SNP is the last resort for treatment of hypertensive emergency.
5. ADRs of NO donors are the consequence of vasodilation.
6. PDE5 inhibitors are used for treatment of ED.
7. sGC stimulators are used for treatment of PAH.

9.1 (Patho)physiological Background

NO is a membrane-permeable gas that functions as local mediator and neurotransmitter and regulates numerous body functions. From the pharmacological perspective, the most important function of NO is the relaxation of smooth muscle cells in blood vessels and internal organs such as bile duct and ureter.

Figure 9.1 shows the regulation of the NO-cGMP system and pharmacological interventions. Endothelial cells express a number of GPCRs including the H_1R, M_xRs, and BK_2R. These receptors activate the G_q-PLC pathway and induce a rise in intracellular calcium concentration. Calcium binds to the calcium sensor calmodulin that activates the endothelial NO synthase. This enzyme releases NO from arginine. Because of its low size, NO diffuses into smooth muscle cells beneath the endothelial cells.

Several GPCRs induce contraction of smooth muscle cells via the G_q-PLC pathway (see ▶ Chap. 15). NO functionally antagonizes the G_q-PLC pathway by activation of sGC. NO-stimulated sGC generates the second messenger cGMP. cGMP stimulates PKG which phosphorylates several target proteins, thereby altering their function. One of the target proteins of PKG is IRAG (inositol 1,4,5-trisphosphate receptor-activated cGMP kinase substrate) that, in its phosphorylated form, blocks calcium release from the endoplasmic reticulum. As a result, smooth muscle cells relax. Thus, the function of smooth muscle cells is modulated by an antagonism between calcium (inducing contraction) and cGMP (inducing relaxation). The biological effects of cGMP are terminated by PDE5. This enzyme hydrolyzes cGMP to the biologically inactive GMP. In conditions associated with blood vessel damage such as hypertension, diabetic micro- and macroangiopathy, hypercholesterolemia, and nicotine addiction, endothelial cell functions are impaired, thereby blunting cGMP-mediated vasodilation (see ▶ Chaps. 5, 15, 16, 19, and 22).

NO-liberating drugs (NO donors) constitute the classic pharmacological intervention in this system. However, development of tolerance is a serious problem in the long-term therapy with NO donors. Therefore, only short-term therapy is feasible. The tolerance with NO donors can be circumvented by application of NO-dependent sGC stimulators (see ▶ Sect. 9.4). The latter drugs bind allosterically to sGC and potentiate the effects of endogenous NO. In case of severe damage of endothelial cells, resulting in loss of NO production, the efficacy of sGC stimulators is strongly decreased. In this case, NO-independent sGC activators can be used. Table 9.1 provides a summary of selected drugs acting on the NO-cGMP system.

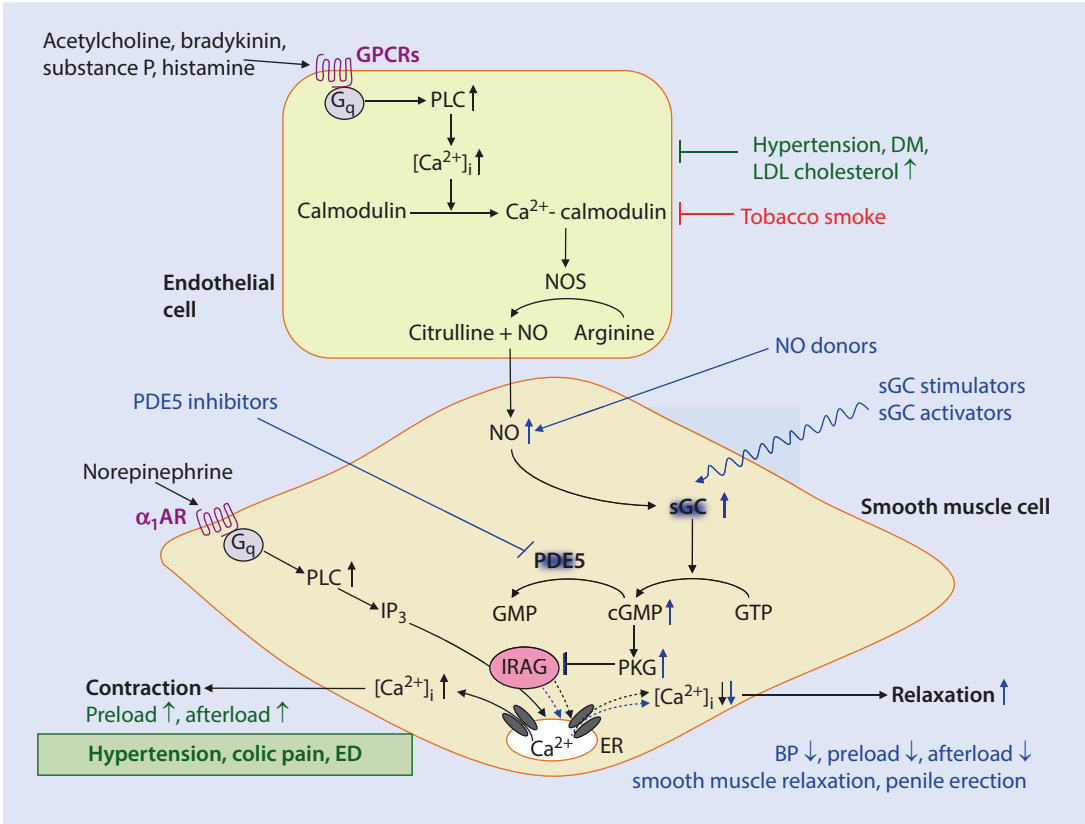

Fig. 9.1 Regulation of the NO-cGMP system and pharmacological interventions. Healthy endothelial cells are key to a healthy cardiovascular system! Don't smoke and treat hypertension, dyslipidemia, and DM

Table 9.1 Overview of selected drugs acting in the NO-cGMP system

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
GTN	Enzymatic liberation of NO and sGC activation	Relaxation of smooth muscle cells	AP, hypertensive emergency, visceral pain	Orthostasis, flush, tachycardia	2, 13, 15
Riociguat	NO-dependent sGC stimulation (allosteric amplification of the effect of NO at sGC)	Relaxation of smooth muscle cells	PAH	Hypotension	15
Sildenafil	PDE5 inhibition and thus cGMP increase	Relaxation of smooth muscle cells	ED, PAH, BPH	Flush, congested nose, blue vision in case of overdose (PDE6 inhibition), dangerous interaction with GTN	13
SNP	Nonenzymatic liberation of NO and sGC activation	Relaxation of smooth muscle cells	Hypertensive emergency	Hypotension, cyanide intoxication	4, 15

9.2 NO Donors

GTN is a prodrug from which NO is enzymatically liberated. GTN possesses a large first-pass effect (see ▶ Chap. 2). Therefore, the liver must be circumvented. GTN is applied either as sublingual capsule or buccal spray. Already 1 minute after application, relaxation of smooth muscle cells begins due to the excellent absorption. However, the effect of GTN lasts for only about 30 minutes because of its rapid inactivation by esterases. GTN relaxes smooth muscle cells in the veins (preload reduction) and arteries (afterload reduction). Additionally, GTN relaxes smooth muscle cells in internal organs.

The muscle-relaxing properties of GTN give rise to its clinical applications. In AP and acute heart failure, GTN works via preload reduction (see ▶ Chap. 16). In hypertensive emergency, afterload reduction is relevant (see ▶ Chap. 15). Because of tolerance, GTN is not suitable for long-term treatment of CHD. Relaxation of smooth muscle cells in the internal organs by GTN is exploited for the treatment of biliary and reno-utereral colic pain. The latter clinical applications are good examples for the important concept that certain types of pain can be effectively treated by other drugs than classic analgesics (see ▶ Chaps. 10 and 23).

Because of its smooth muscle-relaxing properties, GTN is also used off-label for other purposes. Absorption of snake venoms can be delayed when GTN is applied proximally to the bite. In this case, relaxation of lymphatic vessels is relevant. In Raynaud syndrome, local administration of GTN can alleviate the severe pain associated with the impaired perfusion of distal regions of the fingers. Local application of GTN may also facilitate vein puncture for drawing blood or inserting a catheter.

SNP liberates NO nonenzymatically. SNP is applied i.v. as infusion and constitutes the last resort for treatment of hypertensive emergency resistant to other drugs (see ▶ Chap. 15). SNP reduces BP effectively. In toxic doses, shock or heart failure can result. Long-term treatment with SNP can lead to cyanide intoxication (see ▶ Chap. 4). SNP is light-sensitive and must be dissolved freshly before application. For these reasons, the use of SNP is restricted to ICU.

9.3 PDE5 Inhibitors

During sexual arousal, NO is released from endothelial cells and neurons in the corpus cavernosum of the penis where it activates sGC in smooth muscle cells, resulting in cGMP formation. cGMP mediates arterial dilation in the corpus cavernosum, leading to increased blood flow into the penis. In parallel, venous blood efflux from the penis is reduced. The physiological result of these processes is penile erection (◘ Fig. 9.2a). In ED, NO and cGMP production are impaired because of hypertension (see ▶ Chap. 15), DM (see ▶ Chap. 19), or neurological and urological diseases (◘ Fig. 9.2b). Cigarette smoking, ethanol, cocaine, β_xAR antagonists (see ▶ Chap. 5), AR antagonists and 5α-steroid reductase inhibitors (see ▶ Chaps. 24 and 32), NE/5-HT enhancers (see ▶ Chap. 28), diuretics (see ▶ Chaps. 12, 15, and 16), and NIPEs (see ▶ Chap. 25) can aggravate ED as well. In addition, priapism caused by methylphenidate (see ▶ Chap. 8) or p-mGPCR antagonists (see ▶ Chap. 29) can ultimately result in ED. The principles of ED therapy are to treat the cause, avoid ED-promoting drugs, and increase cGMP in the corpus cavernosum.

GTN is not suitable for ED treatment because sGC is expressed ubiquitously. The doses of GTN needed to be effective in ED would be associated with severe ADRs. In contrast, PDE5 is predominantly expressed in the urogenital system and in the lung. Therefore, PDE5 inhibitors show greater organ selectivity in their effects than NO donors. PDE5 inhibitors inhibit cGMP degradation. This effect can be exploited in ED because of the decreased cGMP production. In ED, PDE5 inhibitors promote vasodilation in the corpus cavernosum and enhance erection (◘ Fig. 9.2c). The clinical effects of PDE5 inhibitors on erection are dependent on sexual stimulation, i.e., spontaneous erection or priapism does not usually occur.

Sildenafil is the prototypical PDE5 inhibitor. Following p.o. administration of sildenafil, its effects start after 30 minutes. The maximal duration of action is 4 hours. Other PDE5 inhibitors such as tadalafil possess a longer duration of action.

PDE5 is structurally related with the retinal PDE6 which is involved in vision. In toxic doses,

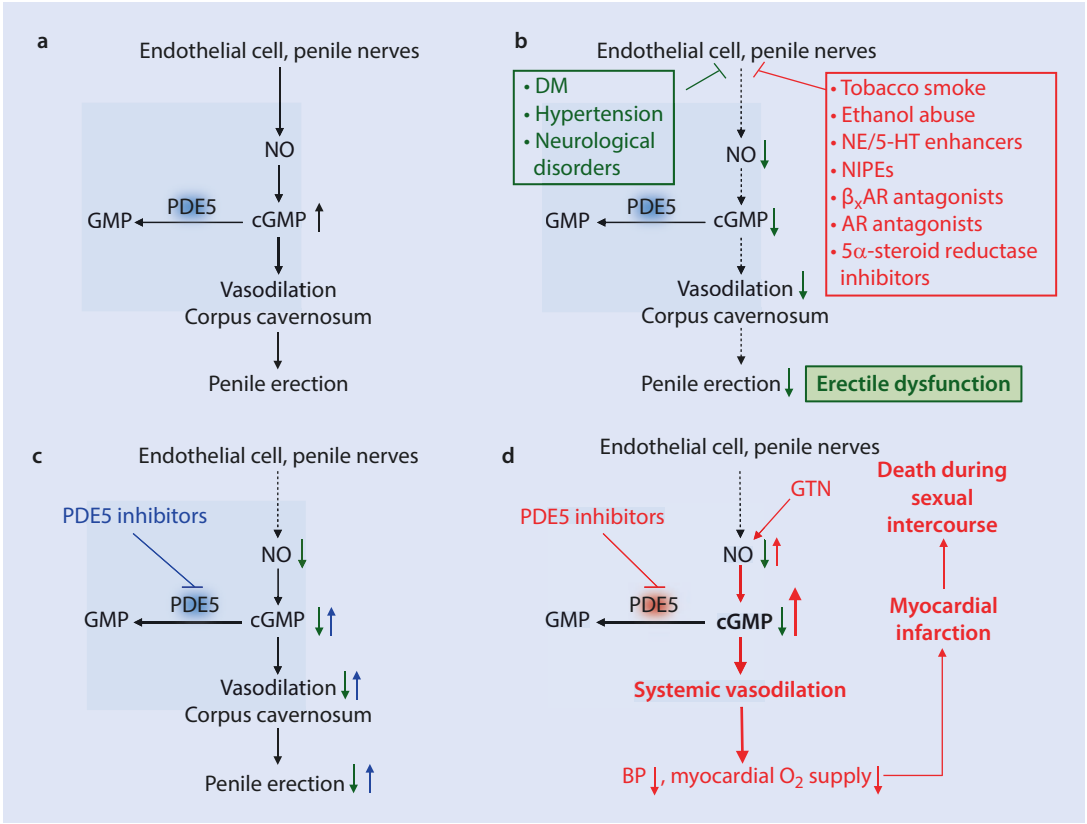

Fig. 9.2 Physiology of erection and pathophysiology of ED: Pharmacological interventions. **a** Physiological situation. **b** ED. **c** ED under therapy with PDE5 inhibitor. **d** Interaction of PDE5 inhibitor + GTN in ED. Always ask a patient whether he has AP before you prescribe a PDE5 inhibitor! Consider that drugs and diseases may aggravate ED! Actively ask men about ED when recording the medical history! Men often do not talk about ED voluntarily

sildenafil inhibits PDE6 and can cause blue vision. This ADR is less prominent with tadalafil which possesses a higher PDE5 selectivity.

The combination of PDE5 inhibitors with GTN is dangerous. Many ED patients suffer from CHD (see ▶ Chap. 16). Insufficiently treated CHD causes AP during sexual intercourse because of the increased oxygen demand. If the patient takes GTN to mitigate AP, NO is liberated in large quantities to activate sGC and cGMP formation. However, the newly formed cGMP cannot be sufficiently degraded by inhibited PDE5, resulting in massive vasodilation (Fig. 9.2d). As a consequence, shock and MI due to impaired coronary blood flow can result, ultimately leading to death during sex. This dangerous drug interaction is clinically very important, also in view of the fact that large illegal black market and internet trade exist for PDE5 inhibitors. These illegal activities circumvent legal prescriptions and prevent doctors and pharmacists from making PDE5 users aware of the drug interaction. CHD in ED patients is treated with the drugs discussed in ▶ Chap. 16.

PDE5 inhibitors also increase blood flow in female genitals and increase lubrication, but the drug class is ineffective in female sexual dysfunction, specifically anorgasmia and decreased sexual desire. Due to its smooth muscle-relaxing effects, PDE5 inhibitors possess the potential to be used in other indications. Clinical studies are ongoing to assess the effects of PDE5 inhibitors in BPH, overactive bladder, urinary incontinence, kidney stone disease, and asthma. PAH is treated with PDE5 inhibitors and sGC stimulators.

9.4 sGC Stimulators and Activators

The problems associated with the long-term use of NO donors (see ▶ Sect. 1.2) stimulated the development of drugs that increase sGC activity without tolerance. sGC stimulators, riociguat being a prototype, bind to sGC allosterically and potentiate the effects of NO. Riociguat is approved for treatment of PAH. In situations with completely missing endothelial and neuronal NO production, NO-independent sGC activators (prototype cinaciguat) could be useful. Potential indications of sGC stimulators and activators include hypertension, PAD, CHF, diabetic micro- and macroangiopathy, Raynaud syndrome, and PDE5 inhibitor-resistant ED. ADRs of sGC stimulators and activators are similar to those of NO donors and PDE5 inhibitors.

9.5 Question and Answers

Questions

Which link between drug and indication is correct?

A. GTN – long-term therapy of CHD
B. SNP – long-term treatment of hypertension
C. Sildenafil – emergency treatment of AP
D. Riociguat – long-term treatment of PAH
E. Tadalafil – short-term treatment of female sexual dysfunction

Answers

A. GTN is only suitable for treatment of AP.
B. SNP is only suitable for acute treatment of hypertensive emergency.
C. PDE5 inhibitors do not possess a sufficiently large preload-reducing effect in AP.
D. In contrast to GTN, the effect of riociguat on sGC shows no tolerance. Therefore, riociguat is suitable for long-term therapy of PAH.
E. Currently, there is no approved and effective short-term therapy for female sexual dysfunction.

Answer **D** is correct.

9.6 Exercises

A 59-year-old man with CHD and type 2 DM comes to your urology practice. The patient tells you that his wife sent him to obtain a prescription for sildenafil. The reason for this request is that he has difficulties to achieve penile erection prior to sexual intercourse. In addition, he regularly suffers from AP during sexual intercourse.

Questions

1. Which pharmacotherapeutic measures are suitable for treatment of CHD and DM in this patient?
2. Which advice do you give the patient if you prescribe sildenafil?

Answers

1. For long-term treatment of CHD, β_1AR antagonists, ACEIs (or AT_1R antagonists), and PAIs (ASA low-dose or $P2Y_{12}$R antagonists) are suitable. A localized coronary stenosis is treated with a stent that can be coated with an immunosuppressant drug to avoid intima hyperplasia. The type 2 DM can be effectively treated with metformin.
2. You inform the patient about onset and duration of action of sildenafil as well as the symptoms of toxic doses on vision. You also have to tell the patient that in case of AP during intercourse, GTN must never be used because of the risk of cardiovascular complications. The patient could also adopt a more passive role during sexual activities, whereas his spouse could adopt a more active role.

Further Reading

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Pain Pharmacology

R. Seifert, *Basic Knowledge of Pharmacology*, https://doi.org/10.1007/978-3-030-18899-3_10

Pain is an unpleasant sensation that possesses highest therapeutic priority. Analgesia can be accomplished by analgesics and co-analgesics and depends on the specific cause of pain. Analgesics are divided into MOR agonists and non-MOR agonists. The COX inhibitors ibuprofen and diclofenac, also possessing anti-inflammatory effects, belong to the non-MOR agonists. Paracetamol and metamizole lack the anti-inflammatory component of COX inhibitors. According to their maximum effect, MOR agonists are divided into weakly effective (e.g., tramadol), intermediately effective (e.g., buprenorphine), and strongly effective MOR agonists (e.g., morphine and fentanyl). Pain therapy is performed according to the WHO pain management plan. In each level co-analgesics can be administered. NIPEs, ketamine, α_2AR agonists, benzodiazepines, NSMRIs, SSNRIs, mGPCR antagonists, muscle relaxants, and anti-osteoporotic drugs belong to this class. Analgesics and co-analgesics possess different ADR profiles, facilitating combination of various drug classes in patients with severe pain.

Key Points

1. NIPEs (traditionally designated as antiepileptics), NE/5-HT enhancers (traditionally designated as antidepressants), and mGPCR antagonists (traditionally designated as antipsychotics) become increasingly important in the treatment of chronic pain.
2. In order to avoid irritation of pain patients by traditional names of drug classes describing completely different indications, mechanistically oriented names of drug classes should be used.
3. Ibuprofen and diclofenac are COX inhibitors.
4. Ibuprofen and diclofenac have analgesic, antipyretic, and anti-inflammatory effects.
5. COX inhibitors can cause PUD, CKD, analgesics asthma, hypertension, and delayed labor.
6. Paracetamol possesses a CNS-mediated analgesic and antipyretic effect and is hepatotoxic in high doses.
7. Metamizole has a larger maximum analgesic and antipyretic effect than paracetamol and is additionally spasmolytic.
8. Metamizole can cause agranulocytosis and, following i.v. injection, anaphylactic shock.
9. Traditionally, MOR agonists are classified according to their potency, but for their clinical use, efficacy (maximum effect) is more important.
10. Via peripheral mechanisms, MOR agonists cause constipation, requiring administration of laxatives.
11. Nausea and vomiting caused by MOR agonists can be treated with MCP.
12. MOR agonists cause hypotension and muscular hypotonia. In conjunction with benzodiazepines, this can result in heavy falls.
13. The most dangerous ADR of MOR agonists is respiratory depression.
14. MOR agonist-caused respiratory depression can be antagonized by naloxone that has only a short duration of action.
15. MOR agonists are not indicated for therapy of trivial headache.
16. Unclear diagnoses, abuse of other drugs, and psychiatric diseases are risk factors for abuse of MOR agonists.

10.1 Pain Pathophysiology

Pain is an unpleasant sensory and emotional experience that is associated with tissue or nerve injury (neuropathy). Pain always possesses highest therapeutic priority. ◘ Figure 10.1 provides an overview of pain causes, pain transmission, and pharmacological interventions. The figure also shows some important ADRs of analgesics and measures to avoid problems in the use of these drugs.

Many stimuli including heat, cold, poisons, and mediators of inflammation can activate specific receptors in pain-sensing neurons. PGE_2 is of particular pharmacological importance. Via the EPR-G_s-AC pathway, PGE_2 increases the activity of voltage-gated sodium channels, resulting in neuronal depolarization and subsequent potentiation of pain perception. One important signaling

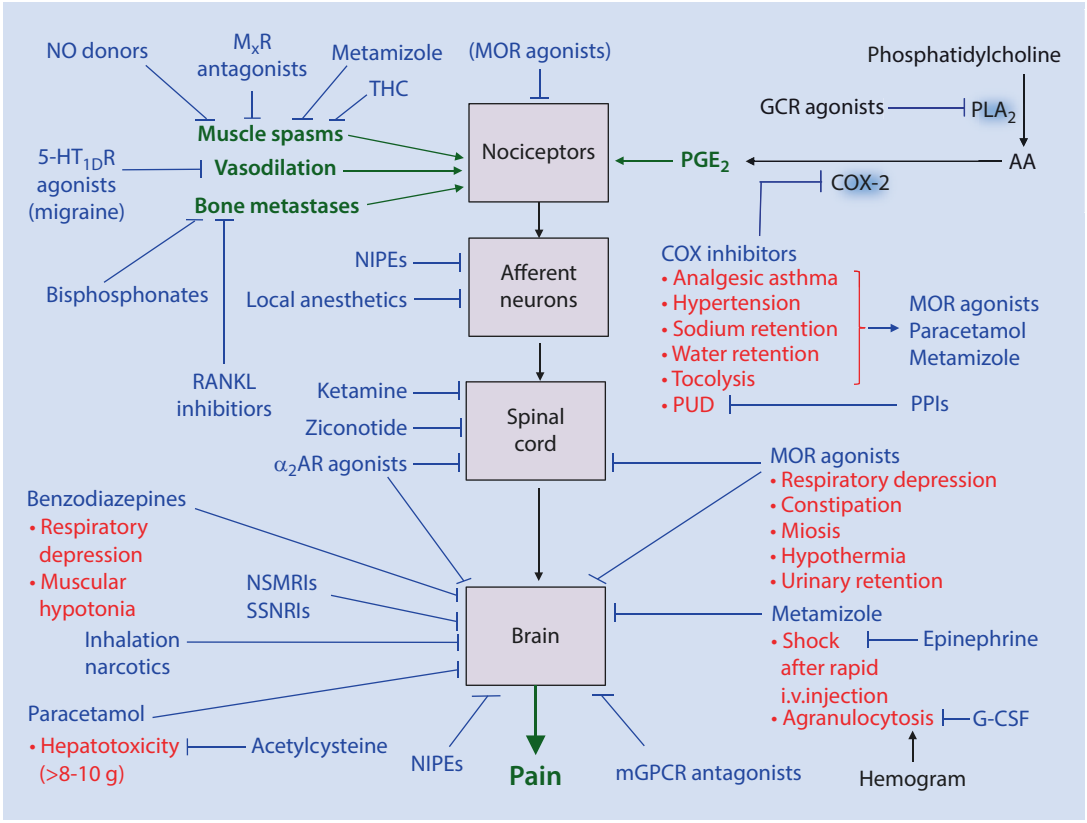

Fig. 10.1 Pain generation and transmission: pharmacological interventions and ADRs of selected drugs/drug classes. Nowadays, pain therapy has become multidimensional. The days of just "opioid analgesics" and "NSAIDs" are over! Use multiple drug classes according to the specific type of pain

pathway functionally antagonizes the many pathways leading to pain perception. Namely, the ORs, via G_i/G_o proteins, mediate activation of potassium channels and inhibition of calcium channels and cause hyperpolarization of pain-transmitting neurons. Table 10.1 gives an overview of the function and pharmacology of ORs. For pain therapy, the MOR is most important. The major reason is the higher potency of agonists at MOR compared to DOR and KOR (see ▶ Chap. 1).

Pain transmission occurs via afferent neurons. Thickly myelinated Aδ fibers mediate rapid and sharp pain sensation. Thinly myelinated C fibers mediate slow and dull pain (see ▶ Chap. 26). The first afferent neuron forms a synapse with the second neuron in the dorsal horn of the spinal cord. On the contralateral side, the second neuron projects into the thalamus where a synapse with a third neuron is formed which projects to the sensory cortex, allowing precise localization and perception of the pain. In addition, there are collateral neurons that project from the spinal cord into the rostroventral medulla, the limbic system, and the periaqueductal gray. In these CNS regions, the subjective evaluation of pain takes place, and emotional and autonomic reactions are initiated (see ▶ Chaps. 5 and 25). These reactions can be addressed pharmacologically.

Important NTs for pain transmission are substance P, activating the NK_1R-G_q-PLC pathway, and glutamate, activating NMDARs with subsequent sodium entry and neuronal depolarization (see ▶ Chaps. 27 and 30). ORs modulate pain perception by presynaptic inhibition of excitatory NT release, a mechanism analogous to α_2ARs in the sympathetic nervous system (see ▶ Chap. 5).

Pain can also be caused by oxygen depletion (excruciating pain in MI, see ▶ Chap. 16), dilatation of meningeal arteries in migraine (see ▶ Chap. 6), contraction of smooth muscle cells in colic pain (see ▶ Chaps. 5, 9, and 23), and bone metastases (see ▶ Chap. 20). As yet poorly under-

Table 10.1 Function and pharmacology of opioid receptors

Parameter	μ (MOR)	δ (DOR)	κ (KOR)
Receptor class	GPCR	GPCR	GPCR
Endogenous ligands	Enkephalin, β-endorphin	Enkephalin	Dynorphin
G protein coupling	G_i/G_o	G_i/G_o	G_i/G_o
Effector coupling	AC↓; calcium channels ↓; potassium channels ↑	AC↓; calcium channels ↓; potassium channels ↑	AC↓; calcium channels ↓; potassium channels ↑
Functional consequence in the neurons	Hyperpolarization and reduced release of excitatory (pain-transmitting) NTs	Hyperpolarization and reduced release of excitatory (pain-transmitting) NTs	Hyperpolarization and reduced release of excitatory (pain-transmitting) NTs
Important receptor localizations	Peripheral sensory neurons, spinal cord (substantia gelatinosa), CNS (brain stem, thalamus, cortex)	Peripheral sensory neurons, CNS (pons, amygdala, cortex)	Peripheral sensory neurons, spinal cord (substantia gelatinosa), CNS (hypothalamus, claustrum)
Most important clinical functions	Peripheral, spinal, and supraspinal analgesia; addiction, respiratory depression, miosis, euphoria, constipation	Supraspinal analgesia, physical addiction	Peripheral, spinal and supraspinal analgesia, dysphoria, miosis, sedation
Full agonists	Morphine, levomethadone, fentanyl, remifentanil	Morphine, levomethadone, fentanyl, and remifentanil (markedly less potent than at the MOR)	Morphine, levomethadone, fentanyl, and remifentanil (markedly less potent than at the MOR)
Moderate partial agonists	Buprenorphine		
Weak partial agonists	Tramadol		
Antagonists	Naloxone, naltrexone	Naloxone, naltrexone	Naloxone, naltrexone, buprenorphine
Clinical relevance	High	Low	Low

Keep in mind that although we have three ORs, the MOR is the most important one for pain therapy

stood, functional abnormalities in the CNS can cause extremely heavy paroxysmal pain, presenting as trigeminal neuralgia or cluster headache.

10.2 Pharmacological Interventions for Pain Therapy

Multiple interventions for pain therapy exist. The specific therapy is based on the particular pain cause and manifestation. In order to estimate the severity of the pain, a linear pain scale ranging from 0 (no pain) to 10 (most severe pain) was developed. Trigeminal neuralgia, cluster headache, and excruciating pain in MI (see ▶ Chap. 16) are among the most severe pain types imaginable. Figure 10.1 shows pharmacological interventions for pain therapy. Pain therapeutics comprise non-MOR agonists (▶ Sect. 10.3), MOR agonists (▶ Sect. 10.4), and co-analgesics. Table 10.2 gives an overview of selected non-MOR agonists and MOR agonists.

Acute pain (e.g., toothache, headache, postsurgical pain, back pain) is generally well accessible to

analgesics. In contrast, chronic pain requires interdisciplinary collaboration in many cases. In addition to pharmacotherapeutic interventions, chronic pain treatment often entails physiotherapeutic, psychotherapeutic, and surgical measures that complement each other. Neuropathic pain and cancer pain are important chronic types of pain. Cancer pain is generally well accessible to analgesics and is often treated by a combination of analgesics and co-analgesics. Neuropathic pain is only poorly responsive to analgesics and therefore primarily treated with co-analgesics.

According to the WHO pain management plan in level 1, non-MOR agonists + co-analgesics are given. In level 2, weak MOR agonists are added to the regime. In level 3, partial MOR agonists are replaced by full MOR agonists. ◘ Figure 10.2 illustrates the differences between various MOR agonists with respect to potency and maximum effect (efficacy) (see ► Chap. 1).

◘ **Table 10.2** Overview of selected analgesics

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Buprenorphine	Partial MOR agonist and KOR antagonist	Analgesia for approx. 6–8 hours, higher maximum effect than tramadol but lower maximum effect than morphine (ceiling effect)	Severe pain that cannot be sufficiently controlled by tramadol, but does not yet require the use of full MOR agonists such as morphine or fentanyl	Mild constipation and respiratory depression if used in transdermal systems	1, 4, 32
Diclofenac	Inhibition of COX-1 and COX-2	Analgesic, antipyretic, anti-inflammatory	Similar to ibuprofen; interindividual differences in effects and tolerability	Similar to ibuprofen; interindividual differences in effects and tolerability	2, 3, 6, 7, 11, 12, 13, 14, 15, 16, 18, 23, 32
Fentanyl	MOR agonist that is 120 times more potent than morphine but has a comparable maximum effect	Strong analgesia and sedation. Due to its high lipophilicity, fentanyl rapidly crosses the BBB, thus rapid onset of action	Anesthesia (in combination with midazolam), transdermal systems with slow drug release to treat severe chronic pain; lollipops or sublingual tablets for rapid relief of severe pain	Less nausea than morphine, no HA release; apart from that typical morphine ADRs; increased respiratory depression (wooden chest caused by redistribution); fentanyl patches are often abused by MOR agonist addicts	1, 27, 32
Ibuprofen	Inhibition of COX-1 and COX-2	Analgesic, antipyretic, anti-inflammatory; well controllable	Pain associated with inflammation (e.g., dental pain, sport injuries, acute exacerbations in degenerative joint or rheumatic diseases, gout arthritis, migraine, acute lower back pain)	PUD, analgesic asthma, sodium and water retention, hypertension, tocolysis	2, 3, 6, 7, 11, 12, 13, 14, 15, 16, 18, 23, 32

(continued)

Table 10.2 (continued)

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Metamizole (dipyrone)	Unknown; hypotheses: predominant CNS effects, blockade of TRPA1 channels (central chemical nociceptor), potassium channel blockade, modulation of serotonergic and opioid synapses; most likely no COX-inhibition (no typical ADRs of COX inhibitors)	Higher analgesic and antipyretic maximum effect than paracetamol; also spasmolytic effect; but no anti-inflammatory effect	Severe pain after surgery and severe colic pain; pain that cannot be treated with paracetamol; tumor pain. Because of its distinct mechanism of action, metamizole can be combined with COX inhibitors	None of the typical ADRs of COX inhibitors; very low risk of PUD and hypertension, no pronounced hepatotoxicity but risk of agranulocytosis (approx. 1:1,000,000); thus regular blood monitoring in case of long-term therapy is required. I.v. infusion might cause an anaphylactic shock (<0.1%), weariness, anxiety, depression	3, 4, 6, 23, 32
Morphine	Potent full MOR agonist; low potency at DOR and KOR	Strong analgesia for 4 hours after p.o. administration (8–12 hours for extended-release formulations); reference drug for the classification of all MOR agonists; sedation, hypnotic-anxiolytic, and antitussive effects	Severest pain (e.g., in MI, cancer), which cannot be controlled by partial agonists like buprenorphine anymore; buprenorphine partially antagonizes/reduces the effect of morphine	At first, emetic effect. Later, antiemetic effect. Dysphoria or euphoria (mostly after fast i.v. injection), respiratory depression, miosis, hypotension, bradycardia, spastic constipation, urinary retention, HA release with anaphylactic shock symptoms after i.v. injection	1, 2, 3, 4, 7, 12, 13, 16, 32
Paracetamol (acetaminophen)	Unknown; hypotheses: predominant CNS effect; modulation of vanilloid receptors, CB_1Rs, and serotonergic synapses. Most likely no COX-inhibition (no typical ADRs of COX inhibitors)	Analgesic and antipyretic; not anti-inflammatory	Mild-moderate pain if inflammation does not play a predominant role (headache, migraine, menstruation pain); often combined with weakly acting MOR agonists and COX inhibitors	Good tolerability of therapeutic doses; none of the typical ADRs of COX inhibitors. The major problem is hepatotoxicity after daily doses of >8–10 g/day in adults (the maximal therapeutic dose in adults is 4 g/day)	4, 6

Table 10.2 (continued)

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Remifentanil	MOR agonist that is 100–200 times more potent than morphine with a comparable maximum effect	Strong analgesia and sedation, very short duration of action	Anesthesia in combination with other injection narcotics in TIVA; can be well controlled due to its extremely short half- life (continuous infusion)	Respiratory depression, hypotension, bradycardia, dizziness, nausea, HA release; ADRs disappear within a short time due to the ultrashort half-life	1, 27
Tramadol	Unknown; hypotheses: weak partial agonism at the MOR, blockade of 5-HT reuptake, antagonism at various NT receptors	Analgesic; not antipyretic and not anti-inflammatory	Mild-moderate pain; often combined with paracetamol	Risk of serotonin syndrome; metabolism via CYP3A4 and CYP2D6, hence, drug interactions may occur: hallucinations, epileptic seizures, weariness, nausea, constipation, itching, respiratory distress, dysphagia	2, 6, 32
Ziconotide	N-type CCB	Strong analgesia after intrathecal injection	Severest pain that does not respond anymore to full MOR agonists	Respiratory depression when ziconotide reaches the respiratory center, confusion, blurred vision, nausea, vomiting, fatigue	1, 32

In certain pain types, other drug classes exhibit analgesic or co-analgesic effects. M_xR antagonists and α_2AR agonists are discussed in ► Chap. 5, 5-HT_{1D}R agonists in ► Chap. 6, NO donors in ► Chap. 9, bisphosphonates and denosumab in ► Chap. 20, NIPEs and benzodiazepines in ► Chap. 25, local anesthetics in ► Chap. 26, injection and inhalation narcotics in ► Chap. 27, NE/5-HT enhancers and alkali metal ions in ► Chap. 28, and mGPCR antagonists in ► Chap. 29

Synthesis of PGE_2 in inflamed tissue occurs via COX-2. Selective COX-2 inhibitors (coxibs) play only a minor role in pain therapy since they can cause serious thromboembolic complications (see ► Chap. 18). Pain therapy is dominated by nonselective COX inhibitors, inhibiting both COX-1 and COX-2. COX inhibitors belong to the non-MOR agonists (► Sect. 10.3). The non-MOR agonists paracetamol and metamizole have a more complex mechanism of action and exert their effects predominantly in the CNS. GCR agonists act anti-inflammatorily by reducing the generation of AA, the precursor for PGE_2. This effect can be used, e.g., in nerve decompression.

MOR agonists act predominantly via inhibition of the release of excitatory NTs involved in pain transmission. Among all ORs (see Table 10.1), the MOR is the most important receptor. It mediates peripheral, spinal, and supraspinal analgesia and the ADRs. In many countries, MOR agonists are used reluctantly because of the perceived risk of addiction. This risk is particularly high when MOR agonists are injected i.v. and rapidly penetrate the BBB as is the case for heroin injection (see ► Chap. 2). In cancer ther-

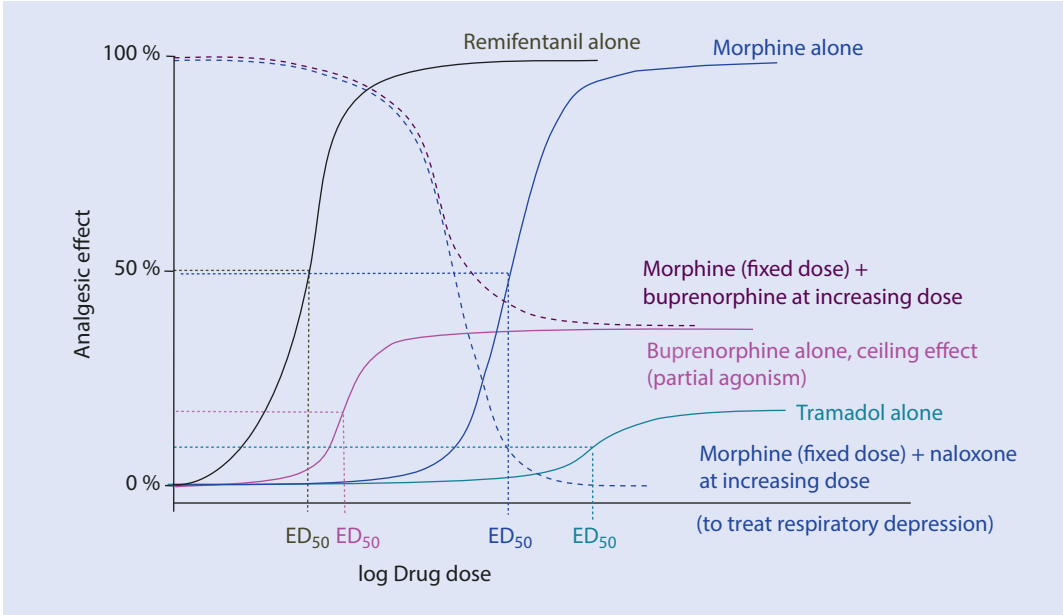

Fig. 10.2 Comparison of the analgesic effects of MOR agonists at MOR. Partial and full agonists. See also Figs. 1.4 and 1.5. It is the efficacy (intrinsic activity), NOT the potency of MOR agonists, that determines the maximum analgesic effects of MOR agonists! Potency is only important for the dose of drug that you have to apply! Therefore, application of a high-potency MOR agonist does not automatically imply a large analgesic effect! It depends on the type of MOR agonists and its dose. This is an important issue where much confusion occurs. The term "high-potency opioid analgesic" is deeply rooted in medical language but does not inform you about maximum analgesic efficacy. Buprenorphine is the classic case for this misconception. Buprenorphine is more potent but less efficacious than morphine

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apy, MOR agonists are mostly given p.o. or continuously via transdermal systems or s.c. injections. With these application forms, the risk of MOR agonist addiction is small. The most dangerous ADR in therapy with MOR agonists is respiratory depression.

Should therapy of extremely severe pain with full MOR agonists become ineffective, ziconotide can be applied. This drug blocks N-type calcium channels in neurons and directly inhibits the release of excitatory NTs. Ziconotide must be applied intrathecally and can cause respiratory depression if the drug reaches the breathing center in the medulla oblongata.

NIPEs have gained increasing importance as co-analgesics (▶ Chap. 25). They are successfully used in the treatment of various types of neuropathic pain (e.g., trigeminal neuralgia, phantom pain) and in cancer pain. In these pain types, NSMRIs, SSNRIs, the alkali metal ion lithium (see ▶ Chap. 28), and mGPCR antagonists (see ▶ Chap. 29) can be applied as well. The precise analgesic mechanism of action of these drugs is not known, but the drugs modify pain perception, i.e., the pain is perceived as less tortuous. Thus, a distancing of patient's psyche from the objective pain perception takes place. The various classes of co-analgesics can be combined.

Bisphosphonates and denosumab are predominantly used in the therapy of pain caused by bone metastases (see ▶ Chaps. 20 and 32). 5-HT_{1D}R agonists are applied in migraine (see ▶ Chap. 6), and M_xR antagonists (see ▶ Chap. 5), NO donors (see ▶ Chap. 9), and metamizole are predominantly used for colic pain. Botulinum neurotoxin, preventing the release of ACh from the neuromuscular endplate (see ▶ Chap. 5), can be applied in painful dystonia and spasticity (e.g., following stroke). The CB_1R agonist THC has beneficial effects on painful muscle spasms in multiple sclerosis. However, the quality of many clinical studies investigating THC is low. Ketamine is an NMDAR antagonist (see ▶ Chap. 25) and is used in acute pain and in cancer pain management. α_2AR agonists inhibit the release of excitatory NTs in pain-transmitting neurons like MOR agonists and,

additionally, the sympathetic nervous system (see ▶ Chap. 5). These effects can be exploited in the therapy of postsurgical pain and cancer pain. Sedation by α_2AR agonists supports pain therapy.

The sedating, muscle-relaxing, and anxiolytic effects of benzodiazepines can be used in the treatment of the excruciating pain in MI (see ▶ Chap. 16) and in cancer pain therapy. However, the increased risk of respiratory depression of the combination of benzodiazepines + MOR agonists has to be taken into consideration. Localized pain can also be treated with long-acting local anesthetics (see ▶ Chap. 26). Oxygen and the class IV antiarrhythmic drug verapamil (see ▶ Chap. 17) can be beneficial in certain types of pain as well.

Each analgesic possesses specific ADRs accounting for contraindications. As a result of the different ADRs and contraindications of the various classes of analgesics and co-analgesics, it is possible in most cases to establish an effective pain management regimen for each patient.

An effective pain therapy requires close cooperation with the patient and good adherence. In order to ensure effective pain management, the physician has to explain to the patient which drug he takes, why he takes it, when he takes it, how he administers the drug, how long he takes it, and which ADRs can be expected. It is also very important that the physician avoids using traditional drug class names such as "antiepileptics," "antidepressants," and "antipsychotics" in patient communication because the patient may incorrectly assume that she/he is suffering from a serious neuropsychiatric disease and is getting mad or addicted. The use of mechanistically oriented names of drug classes reduces patient anxiety, increases adherence to the therapy, and reduces ADRs.

10.3 Non-MOR Agonists: COX Inhibitors, Paracetamol, and Metamizole

In contrast to MOR agonists, non-MOR agonists do not possess a common mechanism of action. These drugs are suitable for mild to intermediate pain. They are divided into two subgroups. The first group comprises the nonselective COX inhibitors with the prototypes ibuprofen and diclofenac and the selective COX-2 inhibitors with the prototype celecoxib. COX inhibitors do not only possess analgesic but also anti-inflammatory and antipyretic properties. The second group comprises paracetamol (acetaminophen) and metamizole (dipyrone). Both drugs have analgesic and antipyretic, but no anti-inflammatory effects. Metamizole has a higher efficacy than paracetamol.

The anti-inflammatory effects of COX inhibitors can be used in pain with an inflammatory component (e.g., sport injuries, arthrosis, and rheumatic diseases). COX inhibitors are suitable for the therapy of acute and transient pain such as tension headache, lower back pain, migraine (see ▶ Chap. 6), acute gout (see ▶ Chap. 23), toothache, menstrual, and postsurgical pain. COX inhibitors can also be used for short-term treatment of chronic pain in arthrosis and rheumatic disease, carefully observing ADRs.

The ADRs of nonselective COX inhibitors result from the fact that they inhibit PG synthesis in the entire body, reducing important homeostatic functions of PGs. Long-term therapy with COX inhibitors can cause CKD (see ▶ Chap. 12) and hypertension (see ▶ Chap. 15). In addition, PUD and GI tract hemorrhage may occur (see ▶ Chap. 7) that can be prevented by simultaneous application of PPIs (see ▶ Chap. 13). In about 15% of all patients with type I allergy, analgesics asthma can arise as a result of increased LT biosynthesis (see ▶ Chaps. 3, 7, and 14). Since COX inhibitors also inhibit synthesis of $PGF_{2\alpha}$ that is important for uterus contraction, labor in pregnant women may be delayed. This ADR spectrum implies that COX inhibitors should not be used in patients with CKD, hypertension, CHF, PUD and asthma, and shortly before birth. In these situations other analgesics, e.g., paracetamol and metamizole (see below), and MOR agonists (see ▶ Sect. 10.4) should be given.

Long-term therapy with COX inhibitors (>2 weeks) should be avoided since they act only symptomatically and the ADR risk increases. Instead, a causal therapy should be conducted. Such therapy can be quite different, depending on the specific cause of pain. In arthrosis, joint replacement is a long-term option. In autoimmune diseases associated with arthritis such as rheumatoid arthritis, psoriasis, or CD, a specific immune therapy with anti-inflammatory and hence indirect analgesic effects is indicated (see ▶ Chap. 11). In general, pharmacotherapy and physiotherapy complement each other. On the one hand, pharmacotherapy improves mobility

via analgesic and anti-inflammatory effects, thereby facilitating physiotherapy which, on the other hand, avoids malposition of joints and restrictions of motion, in the long run reducing consumption of analgesics.

Ibuprofen is a reversible COX inhibitor. The drug is available in various administration forms (e.g., tablets, syrup, suppositories). Ibuprofen is administered in doses of 400–600 mg every 6–8 hours. Its effects are well controllable. In contrast to ASA (see below and ▶ Chap. 18), ibuprofen has no long-term effects on platelet aggregation. Following p.o. administration, ibuprofen is completely absorbed. It is inactivated in the liver, and 90% of the inactive metabolites are eliminated renally. In liver failure and CKD, the dose of ibuprofen must be reduced. Ibuprofen is a chiral drug; only the (S)-enantiomer acts analgesically. The elimination half-life of ibuprofen is just 2 hours. The short duration of action entails that pain therapy with ibuprofen can be well controlled and adjusted to the pain intensity, a particular advantage for acute pain that often changes.

Diclofenac has a similar mechanism of action as ibuprofen and the typical indications of COX inhibitors. Diclofenac can be applied p.o., as suppository and in the form of gels and sprays for local administration in cases of superficially located pain with inflammatory component. Small finger joints and ankles are typical locations for such applications. When applied on small skin areas, systemic ADRs can be largely avoided. Following p.o. administration, diclofenac is completely absorbed and inactivated in the liver. Seventy percent of the inactive metabolites are eliminated renally. The elimination half-life is 2 hours, ensuring good controllability of a therapy with diclofenac. The increased risk of thromboembolic complications (see ▶ Chap. 18) is the consequence of a certain selectivity of diclofenac for COX-2 in contrast to ibuprofen.

ASA acetylates a serine residue in COX and, thereby, irreversibly inhibits PG synthesis until de novo synthesis of COX occurs. Since platelets do not possess a functioning protein synthesis, inhibition of TXA_2 synthesis is predominant at low doses of ASA (about 100 mg per day). This effect is exploited in the therapy of cardiovascular disease (see ▶ Chap. 18). For an analgesic effect, ASA has to be administered in higher doses (about 500–1000 mg), and for an anti-inflammatory effect, daily doses of about 5 g are required. In doses >10 g per day, ASA can result in serious intoxications (salicylism) characterized by nausea, vomiting, agitation, tinnitus, hyperthermia, epileptic seizures, coma, and kidney failure. There is no antidote for ASA intoxication which therefore must be treated symptomatically with activated charcoal and forced alkaline diuresis (see ▶ Chap. 3). Under therapy with ASA, the hemorrhage time following injuries and during surgery is prolonged. The combination of ASA with VKAs can cause life-threatening hemorrhage and is contraindicated (see ▶ Chaps. 2 and 18). Because of its ADR and toxicity, ASA should be avoided as analgesic. It can be readily substituted by reversible COX inhibitors such as ibuprofen.

COX-2 inhibitors were developed to reduce the risk of ADRs of nonselective COX inhibitors in the GI tract mediated via COX-1 inhibition (see ▶ Chap. 7). Celecoxib is a prototypical COX-2 inhibitor. In endothelial cells COX-2 is responsible for the biosynthesis of prostacyclin that is important for vasodilation and inhibition of platelet aggregation (see ▶ Chap. 18). Therefore, COX-2 inhibitors are associated with a high risk of thromboembolic complications (MI, stroke). As a result, various COX-2 inhibitors were withdrawn from the drug market, and many lawsuits were filed because of the thromboembolic incidents. The case of COX-2 is an example for the case that selectivity of a drug for a certain target does not automatically imply a large therapeutic index. Because of the serious ADRs, the clinical use of COX-2 inhibitors is strongly restricted. They should only be used in case of lacking therapeutic alternatives in severe acute pain such as acute gout or exacerbation of arthrosis if the patient does not have a cardiovascular risk.

Paracetamol is a very broadly administered analgesic. COX inhibition cannot explain the pharmacological effects because paracetamol lacks the typical ADR of COX inhibitors. This is of clinical importance since paracetamol can be used in patients with contraindications for COX inhibitors. Paracetamol predominantly acts in the CNS. Its precise mechanism of action is not known. It is discussed that modulation of CB_1R, vanilloid receptors, and serotonergic mechanisms play a role. Paracetamol is available in many administration forms (tablets, syrup,

drops, suppositories, i.v. injection solutions) and given in doses of 0.5–1 g every 4–6 hours in adults. Paracetamol is suitable for mild to intermediate pain of visceral origin and for reduction of mild to intermediate fever. Because of its lacking anti-inflammatory effect, the effect of paracetamol on pain with strong inflammatory component is low.

Paracetamol is the analgesic of choice in pregnancy, lactation, and in children where the dose must be adjusted to body weight. Following p.o. administration, paracetamol is completely absorbed. About 55% of the drug is coupled to glucuronic acid, 30% to sulfuric acid, and about 15% converted to the hepatotoxic N-acetyl-p-benzoquinone imine via CYP2E1. In regular doses this minor metabolic pathway is no problem because the benzoquinone imine is immediately coupled to glutathione and eliminated as mercapturate. The elimination half-life of paracetamol is 2–3 hours. Therefore, therapy with paracetamol exhibits excellent controllability. If paracetamol is administered in therapeutic doses, it is well tolerated and has only few ADRs. Because of its different mechanism of action, paracetamol can be combined with COX inhibitors. The major problem in the therapy with paracetamol is its hepatotoxicity in accidental or suicidal intoxication (see ▶ Chap. 4). In adults, paracetamol in doses of 8–10 g can lead to liver intoxication, and single doses of 10–15 g can be lethal.

In patients with liver failure (e.g., hepatitis C, see ▶ Chap. 34) or alcoholism, the doses of paracetamol inducing liver failure are lower. Hepatotoxicity of paracetamol is due to depletion of glutathione in the liver so that detoxification to the nontoxic mercapturate cannot occur anymore. *N*-acetyl-*p*-benzoquinone imine is a reactive metabolite that covalently modifies liver proteins and thereby impairs organ function. In principle, a paracetamol intoxication can be treated with i.v. injection of the antidote acetylcysteine. The antidote acts by providing SH groups for the inactivation of *N*-acetyl-*p*-benzoquinone imine. However, a major problem in paracetamol intoxication is that often it is not diagnosed early enough. Specifically, there is a latency period of about 24 hours between damage of the liver and onset of clinical symptoms. In case of an irreversible liver damage due to paracetamol intoxication, liver transplantation is the last resort.

Metamizole also acts via COX-independent mechanisms. The drug does not possess the typical ADRs of COX inhibitors. It is discussed that metamizole acts via blockade of central nociceptors and potassium channels and via modulation of opioidergic and serotonergic synapses. It possesses a larger analgesic effect than paracetamol. Therefore, metamizole is predominantly used for pain that does not respond to paracetamol anymore. Metamizole is also spasmolytic, probably due to inhibition of intracellular calcium release. This effect is often used in colic pain (see ▶ Chaps. 13 and 23). Because of its different mechanism of action, metamizole can be combined with COX inhibitors.

It is applied as tablets, drops, suppositories, and i.v. injection solutions. In adults, metamizole is administered every 4–6 hours in doses of 0.5–1.0 g. Like paracetamol, metamizole is well suited for treatment of visceral pain but not for pain with strong inflammatory component. Metamizole is often used for therapy of cancer pain in combination with MOR agonists and to reduce high fever. In the gut, metamizole is converted to the active metabolite 4-methylaminopyrine. This metabolite is completely absorbed and eliminated with a half-life of 2–5 hours. The short half-life enables good controllability of the pain therapy.

Metamizole can cause allergic reactions. Especially upon i.v. injection against colic pain, anaphylactic shock is possible (see ▶ Chap. 3). Therefore, metamizole must be injected slowly and under careful control for anaphylactic symptoms, and prerequisites for therapy of anaphylactic shock with EPI have to be ensured (see ▶ Chaps. 3 and 5). In high doses, a nontoxic metabolite of metamizole can lead to red discoloration of the urine. With an incidence of about 1:1 million patients, metamizole can cause agranulocytosis. Therefore, during long-term therapy, hemogram controls have to be performed. In case of agranulocytosis, metamizole must be immediately withdrawn and replaced by other analgesics. Granulocyte concentration in the blood can be normalized with G-CSF (see ▶ Chap. 4). The agranulocytosis risk is evaluated very differently in various countries. In some countries metamizole is used very broadly as prescription drug, in others available as OTC drug, and in yet others not available at all.

10.4 MOR Agonists

Morphine is the gold standard of MOR agonists. It is predominantly used for treatment of cancer pain. Morphine application in cancer follows the basic rule by ladder, by mouth, and by clock. This implies that the morphine dose is adjusted according to the severity of pain, that morphine is administered preferentially p.o. and not i.v. (see ▶ Chap. 2), and that it is given in regular intervals, not just when pain breaks through. The most important therapeutic effects and ADRs of morphine are mediated via the MOR (see ◘ Table 10.1). Morphine is a full MOR agonist (see ◘ Fig. 10.2 and ▶ Chap. 1). It is a historical convention to differentiate MOR agonists into high-potency and low-potency agonists (see ▶ Chap. 1).

Tramadol belongs to the low-potency MOR agonists; buprenorphine and remifentanil are among high-potency MOR agonists. However, for the practical therapy with MOR agonists, their intrinsic activity (maximum analgesic effect) is more important. Hence, remifentanil, fentanyl, and morphine are full MOR agonists, whereas buprenorphine, despite its high potency, is just a medium-efficacy partial agonist. Accordingly, the maximum analgesic effects of morphine, fentanyl, and remifentanil are comparable.

In contrast, the maximum analgesic effect of buprenorphine is considerably smaller (ceiling effect) and that of tramadol yet smaller. The partial agonist activity of buprenorphine implies that its addition to a fixed dose of morphine reduces the analgesic effect of morphine, i.e., buprenorphine then becomes a partial antagonist (see ◘ Fig. 10.2). As a result, pain intensity is increased instead of decreased. Thus, it is contraindicated to combine the "high-potency" buprenorphine with morphine if the analgesic effects of morphine are insufficient. In such a case, the physician should ensure that the maximum allowable dose of morphine has already been prescribed (saturation of the dose/response curve). In this case, an explanation for insufficient analgesia could be MOR desensitization, i.e., the maximally achievable analgesic effect declined. Hence, the morphine dose should be first increased to test this possibility. The narcotics regulations in many countries allow for sufficient increase of the morphine dose to ensure proper analgesia of terminally ill patients. In case that this strategy is not successful, alternative drugs can be used, e.g., the N-type CCB ziconotide and co-analgesics (see ◘ Fig. 10.1).

Morphine exerts a peripherally and centrally mediated analgesia, sedation, initial dysphoria (later possibly euphoria), hypotension, bradycardia, hypotonia of the skeletal muscles, nausea, vomiting, antitussive effects, respiratory depression, and miosis. Sedation and muscular hypotonia can lead to heavy falls with serious fractures, particularly in elderly patients and in combination with benzodiazepines (see ▶ Chap. 25).

Morphine can also cause spastic constipation, biliary colics, reno-ureteral colics, and urinary retention. When injected i.v., e.g., in excruciating pain in MI (see ▶ Chap. 16), morphine may cause mast cell degranulation mediated by receptor-independent G protein activation (see ▶ Chaps. 3 and 7). This can amplify hypotension and bradycardia and cause bronchoconstriction and urticaria. Therefore, i.v. injection of morphine should be performed slowly.

The risk of addiction and tolerance is overestimated in many countries and results in insufficient pain therapy of seriously ill patients. This unsatisfying situation has fortunately changed in recent years. In contrast, aggressive marketing in the USA has led to prescription of MOR agonists without proper indication (opioid crisis). Specifically, MOR agonists are not indicated in patients with tension headache, arthrosis, fibromyalgia, dementia, and undefined psychological problems. These improper uses add to the development of addiction and tolerance.

Risk factors for the abuse of MOR agonists are known addictions for benzodiazepines and propofol (see ▶ Chap. 25), abuse of cocaine, methamphetamine and ethanol, and the presence of a psychiatric disease. The physician can also suspect the presence of MOR agonist addiction when a patient actively requests the prescription of such drugs.

Respiratory depression is the most dangerous ADR of MOR agonists, specifically when these drugs are administered in high doses and in combination with other centrally depressant drugs such as benzodiazepines and NIPEs (see ▶ Chap. 25). Respiratory arrest requires immediate mechanical ventilation. The depressive but also the analgesic effect of morphine is rapidly reversed by i.v. injection of the MOR antagonist naloxone (see ▶ Chap. 4). However, naloxone has a much shorter

half-life (30–45 minutes) than morphine (about 3 hours) so that respiratory depression can reoccur. Accordingly, it may become necessary to inject naloxone repeatedly. Should a patient with chronic pain, in contrast to the rule, become addicted to morphine, withdrawal of morphine or injection of naloxone results in the occurrence of withdrawal symptoms (cold turkey) which are partially due to activation of the sympathetic nervous system. These effects can be alleviated with the α_2AR agonist clonidine (see ▶ Chap. 5). In heroin addicts, orally applied levomethadone can be used as substitution therapy to prevent withdrawal symptoms and euphoria. Levomethadone possesses a long half-life (16–26 hours) and a continuous effect.

Constipation under MOR agonist therapy is serious and shows only little or no tolerance. Most cancer patients medicated with a MOR agonist need to be treated with a laxative, e.g., macrogol (see ▶ Chap. 13). In addition, methylnaltrexone can be injected s.c. This drug displaces morphine from the MOR in the gut and alleviates the spastic constipation. Since methylnaltrexone is a quaternary amine, it does not penetrate the BBB and, therefore, does not abrogate the centrally mediated analgesia of morphine (see ▶ Chap. 2). In case of nausea or vomiting, MCP (see ▶ Chap. 8) or co-analgesics from the class of D_2R-mGPCR antagonists (see ▶ Chap. 29) can be used. In the aggregate, the ADRs of morphine can be handled well, particularly if the indication and dose are correct and if co-analgesics and drugs for the prevention of morphine-induced ADR are used rigorously.

Morphine possesses a bioavailability of 30% and a duration of action of 4 hours. It is metabolized in the liver (morphine 6-glucuronide is an active metabolite), and elimination predominantly occurs renally. In liver damage and CKD, the morphine dose must be reduced (see ▶ Chap. 12). The goal of cancer pain therapy is to prevent the occurrence of pain. For this purpose, the short half-life of morphine is not ideal. In order to compensate for this disadvantage, extended-release formulations of morphine and morphine derivatives with prolonged half-life (hydromorphone, duration of action 8–13 hours) were developed.

Heroin (also referred to as diamorphine) is the diacetylated form of morphine. Heroin rapidly passes the BBB after i.v. injection (see ▶ Chap. 2). In the CNS, it is rapidly deacetylated to morphine. The rapid penetration into the CNS causes euphoria and a positively perceived dreaming state. The risk of addiction and tolerance after i.v. injection of heroin is very large. Therefore, heroin is not available for pain therapy in many countries.

Fentanyl is more potent at the MOR than morphine, but the efficacy of both agonists is similar. Fentanyl is lipophilic and penetrates the BBB rapidly. This can be used to administer the drug on demand or as rescue in the form of lollipops or nasal sprays to alleviate acute severe or breakthrough pain. For long-term therapy often transdermal systems are used. Such systems are, however, not unproblematic because they can be easily removed from the skin of patients and abused by persons addicted to MOR agonists. Accordingly, the patient suffers from more severe pain. In addition, fentanyl reservoirs can be cut open by MOR agonist addicts, and the content is administered orally as bolus. This administration way entails a high risk of respiratory depression. As full MOR agonist, fentanyl is suited for the therapy of severe pain. According to the WHO pain management plan, first non-MOR agonists and MOR agonists with lower efficacy such as tramadol and later buprenorphine have to be used. Redistribution of fentanyl in the body can cause breathing difficulties (wooden chest).

Tramadolol possesses just 10% of the analgesic efficacy of morphine. In addition to the small MOR activation, other mechanisms are involved in the analgesic effects of tramadol. Because of its short duration of action, therapy with tramadol can be controlled well. However, tramadol is not suited for the treatment of severe pain. Nonetheless, very often the clinical efficacy of tramadolol is overestimated so that patients with severe pain are not sufficiently treated with analgesics.

Buprenorphine is an intermediate partial MOR agonist (and KOR antagonist). It possesses a small bioavailability (5%) so that it has to be applied sublingually or as transdermal system (see ▶ Chap. 2). It is metabolized via CYP3A4. Because of its partial agonism, buprenorphine possesses a smaller risk of respiratory depression and obstipation than morphine and fentanyl. However, buprenorphine dissociates only slowly from the MOR. Therefore, respiratory depression caused by buprenorphine cannot be easily antagonized by naloxone.

Remifentanil is a highly potent full MOR agonist. It is rapidly inactivated and, accordingly, has only a very short duration of action with excellent controllability. Remifentanil is predominantly used for anesthesia (TIVA) (see ▶ Chap. 27).

10.5 Questions and Answers

Questions

Which assignment of a drug to contraindication is correct?

A. Ibuprofen – imminent birth
B. Paracetamol – active PUD
C. Metamizole – biliary duct colic
D. Morphine – Impaired hematopoiesis
E. Buprenorphine – pain that cannot be alleviated with tramadol

Answers

A. Shortly before birth ibuprofen is contraindicated because the drug inhibits synthesis of $PGF_{2\alpha}$. However, this prostaglandin is important for initiation of labor. Thus, under ibuprofen therapy, onset of labor may be delayed. This could have detrimental effects on the newborn because of the risk of peripartal oxygen depletion.
B. In PUD patients, paracetamol can be applied. In contrast, ibuprofen and diclofenac are contraindicated.
C. Metamizole possesses relaxing effects on smooth muscle cells of hollow organs. This effect can be therapeutically used in colic pain, i.e., in biliary tract colic and reno-ureteral colic, to alleviate pain.
D. Morphine does not possess negative effects of hematopoiesis. Therefore, morphine can be used for pain therapy in patients with impaired erythropoiesis, granulocytopoiesis, and thrombopoiesis, e.g., in cancer patients.
E. Tramadol possesses a smaller maximum analgesic effect than buprenorphine. Therefore, buprenorphine can be used in pain that cannot be controlled anymore sufficiently by tramadol.

Answer **A** is correct.

10.6 Exercises

A 26-year-old male soccer player sprained his ankle during a training session and visits you in your sport medicine practice. The physical exam and X-ray show that there is no fracture or ligament rupture. For stabilization of the ankle, you prescribe a cast. The medical history shows that the patient, except for seasonal allergic rhinitis, is healthy. To alleviate the pain and edema associated with the ankle sprain, you prescribe ibuprofen (600 mg four times daily) for a week. After 3 days the patient is brought to the emergency room because of an asthma attack.

Questions

1. What happened and how do you treat the patient initially?
2. How do you treat the patient in the long run?

Answers

1. It appears that the patient suffers from analgesics asthma. This ADR can occur in up to 15% of patients with allergic rhinitis when they are treated with a COX inhibitor like ibuprofen. In the airways, ibuprofen inhibits COX-2 so that the precursor AA is converted more efficiently to LTD_4 that can cause asthma attacks. You confirm the diagnosis by determining the respiratory tract resistance with a peak flow meter. You stop the ibuprofen medication immediately and let the patient inhale, after proper instruction and under supervision, salbutamol (100–200 µg; one to two puffs). With this SABA, the asthma should be relieved within 3–10 minutes.
2. It is critical that the patient is informed about the connection between ibuprofen therapy and the asthma attack because this affects future pain therapy. COX inhibitors as a class (including diclofenac and ASA) have to be avoided. If this drug class should be administered, prior desensitization against the allergens has to be performed. Other analgesics such as paracetamol or metamizole (not available in all countries)

can be applied. However, these drugs do not possess the anti-inflammatory component of COX inhibitors that, in principle, is desired in patients with sport injuries. Alternatively, weak partial MOR agonists such as tramadol can be prescribed. Detumescence of the ankle can also be facilitated by regularly applying cold packs and elevating the injured foot. As emergency medication, the patient should be given a salbutamol inhalation aerosol.

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Immunopharmacology

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Autoimmune diseases are characterized by the loss of immunological tolerance towards the own cells. In transplant rejection, an immune reaction against the transplant is raised, impairing organ function. It is the therapeutic goal to suppress symptoms of the immune process as far as possible without compromising the function of the immune system in host defense against infections and tumor cells too seriously. In many patients, these goals can be reached satisfactorily. An important strategy to optimize therapeutic effects and reduce ADRs is to combine drugs with different mechanisms of action. The most important drugs are still the GCR agonists that suppress immune functions via multiple mechanisms. Immunophilin ligands predominantly inhibit cell proliferation. Classic cytostatics in low doses suppress immune reactions as well. The last years have witnessed an explosion-like development of therapeutic antibodies and fusion proteins being genetically engineered drugs, inhibiting the function of cytokines, cytokine receptors, integrins, and lymphocyte antigens. However, the high costs of biologicals constitute a pharmacoeconomic problem.

Key Points

1. Drugs that affect the immune system increase susceptibility for infections.
2. GCR agonists suppress the immune system via multiple mechanisms.
3. During long-term therapy, GCR agonists can cause a Cushing's syndrome and suppress the adrenal cortex.
4. MTX (low dose) inhibits immune processes indirectly via adenosine receptor activation.
5. Leflunomide inhibits the immune system via inhibition of pyrimidine synthesis.
6. Mycophenolate inhibits the immune system via inhibition of purine synthesis.
7. Ciclosporin and tacrolimus inhibit calcineurin and, thereby, IL-2 production that is important for T-cell proliferation.
8. Sirolimus inhibits T-cell proliferation via mTOR inhibition.
9. Infliximab, adalimumab, and etanercept suppress immune cell function via TNF inhibition.
10. IFN-β inhibits activation and migration of T cells.
11. Anakinra blocks the IL-1R; basiliximab the IL-2R.
12. Natalizumab inhibits integrin-dependent migration of T cells across the BBB.
13. Rituximab binds to CD20 and induces B-cell apoptosis.
14. Alemtuzumab binds to CD52 and causes B-cell and T-cell apoptosis.
15. Muromonab binds to CD3 and causes T-cell apoptosis.
16. Abatacept blocks the interaction of CD80/86 with CD28.

11.1 Pathophysiology of Autoimmune Diseases and Transplant Rejection: Pharmacological Interventions

Physiologically, the immune system is tolerant towards the cells of the body. In autoimmune diseases, the self-tolerance is broken down for as yet poorly understood reasons. As a consequence, an autoimmunological process with the cardinal symptoms of inflammation, i.e., pain (dolor), swelling (tumor), and redness (rubor), develop. Ultimately, this process can lead to a loss of organ function. Every organ can be affected by an autoimmune disease. In transplant rejection, an immune response against the immunologically foreign transplant is generated (exceptions are transplants from genetically identical twins). There are similarities in the immune responses in autoimmune diseases and transplant rejection. Accordingly, pharmacotherapeutic strategies are similar, too. The aim of pharmacotherapy is to suppress pathological immune reactions so that the patient suffers from as few symptoms as possible and that the organ function remains intact or the organ transplant is not rejected.

Figure 11.1 provides an overview of pathophysiological processes in autoimmune diseases and transplant rejection and the resulting pharmacological interventions. In these situations,

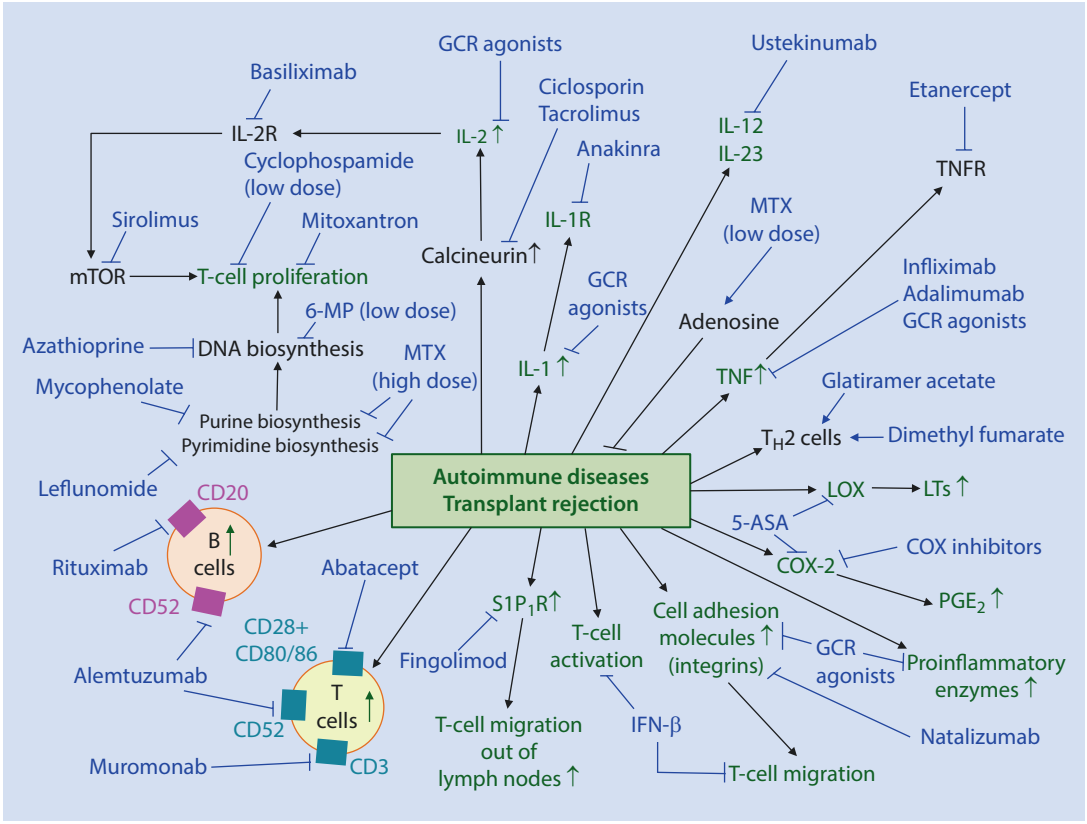

Fig. 11.1 Pathophysiology of autoimmune diseases and transplant rejection: pharmacological interventions. Despite the many new drug targets, GCR agonists remain the basis of the pharmacotherapy of many autoimmune diseases! The new drugs for treatment of autoimmune diseases can cause unexpected and unusual ADRs! These drugs belong into the hands of a specialist for a specific disease

proinflammatory cytokines such as IL-1, IL-12, IL-23, and TNF are released. Inhibition of IL-2 release, resulting in inhibition of T-cell proliferation, is of great pharmacological importance. T cells play a key role in autoimmune processes and transplant rejection and are therefore a key target for many drugs. Table 11.1 provides an overview of selected drugs. The $S1P_1R$ plays a critical role for migration of T cells from the lymph nodes. In addition, the expression of proinflammatory enzymes such as collagenases, COX-2, PLA_2, and NO synthases is increased, and proinflammatory PGs and LTs are released. Moreover, macrophages producing tissue-damaging ROS are activated.

The processes shown in Fig. 11.1 are of varying importance in different diseases. Accordingly, interventions in the immune system are differentially exploited depending on the specific disease. Table 11.2 provides an overview of three common autoimmune diseases, i.e., rheumatoid arthritis, multiple sclerosis, and psoriasis. Other immune diseases affect the thyroid gland (see ▶ Chap. 23), the neuromuscular endplate (see ▶ Chap. 5), the GI tract (see ▶ Chap. 13), and the B cells of the pancreas (see ▶ Chap. 19). Certain processes such as T-cell proliferation (inhibition by inhibitors of purine, pyrimidine and DNA synthesis, monoclonal antibodies, immunophilin ligands, GCR agonists), TNF release (inhibition with monoclonal antibodies and fusion proteins), and the expression of proinflammatory enzymes (inhibition by GCR agonists) are pharmacologically targeted in many diseases. In contrast, other processes such as T-cell migration across the BBB (inhibition by natalizumab) or out of the lymph nodes (inhibition by fingolimod) are only exploited in multiple sclerosis. Certain drugs, most notably monoclonal antibodies and fusion proteins, influence only one defined process, whereas other drugs (GCR agonists, IFN-β, fingolimod, glatiramer acetate, dimethyl fumarate, and 5-ASA (see ▶ Chap. 13) have pleiotropic effects.

Table 11.1 Overview of selected drugs for the treatment of autoimmune diseases and prevention of transplant rejection

Drug	Mechanism of effects	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Abatacept	Fusion protein composed of the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and the Fc portion of human IgG	Immunosuppression; blocks the interaction of CD80/86 with CD28; inhibits T-cell costimulation	Rheumatoid arthritis (in combination with MTX if a TNF inhibitor fails)	Headache, nausea, increased susceptibility to infections (infections of the urinary and bronchial tract), and increased immunosuppression if combined with TNF inhibitors	33
Adalimumab	Human monoclonal antibody against TNF (cytokine inhibitor)	Immunosuppression; blocks the effects of TNF on immune cell functions (phagocytosis, migration, cytokine release)	Autoimmune diseases (rheumatoid arthritis, CD (fistula formation), UC, ankylosing spondylitis, psoriatic arthritis)	As infliximab, but significantly less allergic reactions, as adalimumab contains no protein from other species	13, 16, 32, 33, 34, 35
Alemtuzumab	Humanized monoclonal antibody against the leukocyte glycoprotein CD52	Immunosuppression; depletes B and T cells (reset of the immune system)	Severe relapsing-remitting MS	Infusion reactions (cytokine storm) (prophylaxis with GCR agonists, H_1R and H_2R antagonists and COX inhibitors), herpes infections; autoimmune hypothyroidism (in 20–25% of the patients), thrombocytopenia, pancytopenia	3, 6, 21, 34
Anakinra	Genetically engineered and physiologically occurring IL-1R antagonist (cytokine inhibitor)	Anti-inflammatory effect; inhibits the proinflammatory effects of IL-1 on various effector cells (e.g., in synovial fluid and cartilage)	Rheumatoid arthritis, e.g., in case of non-response to MTX	Local reactions at injection site, headache, neutropenia, severe infections; risk of even more severe infections if combined with TNF inhibitors	33, 34, 35
Azathioprine (AZA)	Prodrug of 6-MP which is ultimately incorporated into DNA and RNA	Immunosuppression; inhibits T-cell proliferation	Low-cost standard drug for many autoimmune diseases	Leukopenia, thrombocytopenia, anemia, increased risk of infections, teratogenicity	2, 32
Basiliximab	Chimeric antibody blocking IL-2R (cytokine inhibitor)	Immunosuppression; inhibits T-cell proliferation	Rejection prophylaxis after organ transplantation (in combination with ciclosporin and GCR agonists)	Hypersensitivity reactions, no increased rate of infections	3

Ciclosporin	Binds to the immunophilin cyclophilin. This complex inhibits the phosphatase calcineurin, thereby inhibiting IL-2 gene transcription	Immunosuppression; inhibits T-cell proliferation by reduced IL-2 synthesis	Standard drug for many autoimmune diseases as well as prevention and treatment of transplant rejection	Renal and liver dysfunctions, hypertrichosis, gingival hyperplasia, increased risk of infections and cancer, hypertension during long-term treatment, dyslipidemia, and DM; metabolization via CYP3A4; hence, many risks of interactions; TDM	2, 12, 15, 19, 22
Dimethyl fumarate	Pleiotropic immune-modulating effects	Immune modulation; differentiation of T cells towards anti-inflammatory T_H2 cells, increased expression of anti-oxidative acting genes	Mild-moderate relapsing-remitting MS; psoriasis	GI disturbances, liver damage, lymphopenia, progressive multifocal, leukoencephalopathy (PML)	34
Etanercept	Fusion protein composed of the extracellular domain of the human TNFR and the Fc fragment of human IgG (cytokine inhibitor); binds TNF	Immunosuppression; blocks the effects of TNF on immune cell functions (phagocytosis, migration, cytokine release)	Autoimmune diseases (rheumatoid arthritis, ankylosing spondylitis, psoriasis). Neither used in treatment of Crohn's disease nor in ulcerative colitis	Similar to adalimumab, as etanercept contains no protein component from other species	13, 16, 32, 33, 34, 35
Fingolimod	Phosphorylation by sphingosine kinase 2 after absorption; binds to $S1P_1R$ before $S1P_1R$ internalization which finally blocks signal transduction	Immunosuppression, prevents lymphocytes from migrating out of lymph nodes	Severe (active) relapsing-remitting MS	Headache, back pain, common cold, cough, diarrhea, lymphopenia, susceptibility to infections (herpes infections, PML), teratogenicity; bradycardia and AV block after first doses (ECG monitoring!), hypertension, macrophage activation syndrome	17, 34
Glatiramer acetate	Synthetic amino acid polymer, chemically similar to the myelin basic protein, with pleiotropic immune modulating effect	Immune modulation: differentiation of T cells towards anti-inflammatory T_H2 cells and inhibition of macrophages attacking the myelin sheath	Mild-moderate relapsing-remitting MS	Skin reactions and lipoatrophy at injection sites, postinjection syndrome with urticaria, tachycardia, respiratory distress, anxiety 5–15 minutes after injection	3
IFN-β	IFN with pleiotropic immune modulating effects	Immune modulation, inhibition of T-cell, activation and T-cell migration	Mild-moderate relapsing-remitting MS	Local reactions at the injection site, flu-like symptoms with fever, chills and fatigue, anemia, lymphopenia, neutropenia, liver damage, autoimmune hypothyroidism	10, 21

(continued)

Table 11.1 (continued)

Drug	Mechanism of effects	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Infliximab	Chimeric monoclonal antibody against TNF (cytokine inhibitor)	Immunosuppression; blocks the effects of TNF on immune cell functions (phagocytosis, migration, cytokine release)	Autoimmune diseases (rheumatoid arthritis, CD (fistula formation), UC, ankylosing spondylitis, psoriatic arthritis)	Reactions at the injection site, flu-like symptoms, GI disturbances, liver damage, anemia, leukopenia, infections (e.g. sepsis, TB, hepatitis B, opportunistic pathogens, reactivation of infections), CHF, tumor formation is facilitated; allergies very often occur; highly increased risk of infections if combined with anakinra	3, 13, 16, 32, 33, 34, 35
Leflunomide	Prodrug of teriflunomide, inhibits dihydroorotate dehydrogenase and, hence, pyrimidine synthesis	Immunosuppression; inhibits T-cell proliferation	Standard drug for autoimmune diseases such as rheumatoid arthritis and psoriasis	GI disturbances, liver damages, hair loss, leukopenia with susceptibility for bronchial infections, allergic reactions, teratogenicity	2
MTX (low dose)	Inhibition of AICAR transformylase results in increased extracellular adenosine concentration and enhanced activation of adenosine receptors	Immunosuppression; inhibits T-cell, endothelial cell and fibroblast proliferation	Standard drug for many autoimmune diseases	Loss of appetite, vertigo, vomiting, diarrhea, stomatitis, increase of liver enzymes, leukopenia, thrombocytopenia, susceptibility to infections, increased risk of lymphoma, teratogenicity	12, 32
Muromonab	Murine antibody against the leukocyte antigen CD3	Immunosuppression; induces T-cell apoptosis	Treatment of acute GCR agonist-resistant organ rejection (liver, heart)	Infusion reactions (cytokine release syndrome), infections, increased risk for malignancies, neuropsychiatric reactions (epilepsy, aseptic meningitis, encephalopathy)	3, 6, 25, 32
Mycophenolate	Inhibition of inosine monophosphate dehydrogenase and, hence, GMP synthesis	Immunosuppression; inhibits T- (and B-) cell proliferation	Kidney, heart, and liver transplantation (in combination with GCR agonists and ciclosporin)	Numerous and serious (>10% of patients) ADRs: vomiting, diarrhea, anemia, thrombocytopenia, leukopenia with susceptibility to infections (sepsis, candidiasis, herpes simplex and herpes zoster infections), PML, teratogenicity	2

Natalizumab	Humanized monoclonal antibody against α4-integrin VLA4 in leukocytes (integrin inhibitor)	Immunosuppression by inhibiting the migration of T cells across the BBB	Severe relapsing-remitting MS	Usually good tolerability, development of neutralizing antibodies (loss of efficacy), allergies, PML (high risk after previous therapy with immunosuppressants and after JC virus infection)	2, 3, 34
Prednisolone	Synthetic GCR agonist. Pleiotropic effects: Inhibits synthesis of cytokines, proinflammatory enzymes, adhesion molecules	Anti-inflammatory and immunosuppressive effects on many cells and parameters of the immune system	Low-cost standard drug for many autoimmune diseases and for prevention of transplant rejection	Cushing's syndrome with edema after systemic administration above the Cushing threshold, hypokalemia, osteoporosis, striae, DM, cataract, glaucoma, CNS modifications, adrenal insufficiency, susceptibility to infections	13, 15, 19, 20, 23, 28, 31, 32
Rituximab	Chimeric antibody against the leukocyte antigen CD20	Immunosuppression; induces B-cell apoptosis	Rheumatoid arthritis (in combination with MTX if TNF inhibitors fail), CD20-positive non-Hodgkin lymphoma	Infusion reactions (cytokine release syndrome), heart failure, and activation of infections (e.g., hepatitis B, TB), PML	3, 6
Sirolimus (Rapamycin)	Binds to the immunophilin FKBP-12. This complex inhibits the serine/threonine kinase mTOR, thereby inhibiting cell cycle progression at the G1/S1 phase transition	Immunosuppression; inhibits T-cell proliferation; antiproliferative effect on endothelial cells and smooth muscle cells in vessels	Prevention of organ rejection (in combination with GCR agonists and ciclosporin), prevention of stent restenosis, lymphangioleiomyomatosis	No nephrotoxicity, but wound healing disorders and anemia, hyperlipidemia, DM, pneumonitis, edema, hypertension, bronchial and urinary tract infections, development of skin cancer and lymphoma, metabolization via CYP3A4; hence many interactions risks; TDM	2, 16, 19, 22, 33
Tacrolimus	Binds to the immunophilin FKBP-12 and, hence, inhibits the phosphatase calcineurin, resulting in inhibition of IL-2 gene transcription (similar to ciclosporin)	Immunosuppression; inhibits T-cell proliferation by reduced IL-2 synthesis (similar to ciclosporin)	Prophylaxis and prevention of transplant rejections; refractory autoimmune diseases, topical application on the skin in atopic dermatitis	Comparison with ciclosporin: nephrotoxicity is similar, no gingival hyperplasia, no hirsutism, less hyperlipidemias, higher diabetogenic effect; neurotoxicity, risk of skin cancer, metabolization via CYP3A4; hence, numerous interaction risks; TDM	2, 12, 19, 32
Ustekinumab	Human monoclonal antibody which binds IL-12 and IL-23 (cytokine inhibitor)	Immunosuppressive effect; inhibits T_H1 response and T-cell proliferation	Autoimmune diseases (psoriasis, CD)	Local reactions at the injection site, infections of the upper bronchial tract, depression, dizziness, headache, diarrhea, weariness, muscle pain	3, 33, 34, 35

Specific drugs for the treatment of UC and CD are discussed in ► Chap. 13; drugs for the treatment of asthma in ► Chap. 14. Some classic cytostatics like cyclophosphamide, 6-MP, and MTX are used in low doses for the treatment of diseases of the immune system. Because of their clinical relevance, in this table, MTX (low dose) and azathioprine (6-MP prodrug) are discussed. Cyclophosphamide and 6-MP are discussed in ► Chap. 32

Table 11.2 Overview of the pathophysiology, clinic, and pharmacotherapy of multiple sclerosis, rheumatoid arthritis, and psoriasis

Parameter	Multiple sclerosis	Rheumatoid arthritis	Psoriasis
Epidemiology	Prevalence ~150 per 100,000 inhabitants. Women:Men = 2:1, disease onset mostly between 15 and 40 years of age	Prevalence approx. 0.5–1% of the population. Women:Men = 3:1; all age groups can be affected; in women, the disease peaks at 55–65 years	Prevalence approx. 2.5% of the population; psoriasis vulgaris is the most common form (60–70% of the cases); manifestation before 40 years of age (peak at 15–25 years of age); men and women are affected with equal frequency
Pathophysiology	Autoimmune disease damaging the myelin sheaths of neurons	Autoimmune disease primarily affecting the joints	Autoimmune disease primarily affecting the skin; associated with certain HLA polymorphisms; caused by triggers (drugs, streptococcal infections)
Pathology	Multiple inflammatory demyelinating lesions in the CNS; typical lesions in MRI	Inflammation of the joints with typical localization and formation of pannus, ultimately leading to joint destruction and loss of function	Hyper- and parakeratosis of the epidermis with functional dysfunction of the skin (punctiform hemorrhages, microabscesses)
Clinical symptoms	Relapsing-remitting MS or progressive MS; broad-spectrum of neurological symptoms (e.g., retrobulbar neuritis, double vision, ataxia, paresthesias, pain, paralyses, muscle spasms)	Insidious or sudden onset with swellings or pain in the small joints of fingers and toes, weariness, fever, loss of appetite, morning stiffness, typical erosions and subchondral osteoporosis, and deformities of joints	Plaques covered with silvery scales (typically on the knees, elbows, and scalp), ranging from punctate to palm size; changes in the nails
Complications	Quality of life massively restricted (mobility problems, urinary dysfunction, sexual dysfunction, chronic pain, depression)	Quality of life massively restricted due to mobility problems, systemic complications (lung fibrosis, peri- and endocarditis, anemia, neuropathy, inflammations of the eyes)	General symptoms (fever, fatigue) and formation of pustules (migration of neutrophil granulocytes). Systemic complications: arthritis, uveitis
Pharmacotherapy	In mild-moderate forms, first-line therapy with IFN-β, glatiramer acetate, dimethyl fumarate or teriflunomide; second-line therapy: azathioprine. In severe forms, first-line therapy with fingolimod, natalizumab, or alemtuzumab; second-line therapy with mitoxantrone or cyclophosphamide; in addition, symptomatic therapy of spasms (THC), pain (NIPEs), and depression (NE/5-HT enhancers)	Basic therapy with MTX (low dose). Initially, MTX is combined with GCR agonists whose dose should be reduced as soon as possible. For patients not responding satisfactorily to this combination, MTX is combined with leflunomide and sulfasalazine. If a patient still does not respond, MTX is combined with TNF inhibitors and/or IL-1 inhibitors. As an alternative, TNF inhibitors and/or IL-1 inhibitors can be initially administered. In refractory cases, patients are treated with rituximab or abatacept. In addition, symptomatic short-term treatment of pain and inflammation with COX inhibitors (no long-term therapy)	Initially, topical therapy with GCR agonists and vitamin D derivatives (calcipotriol). Later, PUVA therapy (Psoralen + UVA). In severe cases, systemic administration of GCR agonists, ciclosporin, MTX (low dose), leflunomide, or dimethyl fumarate; In case of non-response, administration of TNF inhibitors, ustekinumab (IL-12 and IL-23 inhibitor), secukinumab (IL-17 inhibitor), or apremilast (PDE4 inhibitor)

All drugs discussed in this chapter act more or less immunosuppressively on pathological processes and have more or less ADRs without directly addressing the cause of the disease. This implies that the immune disease reoccurs as soon as drug therapy is terminated. Therefore, most autoimmune diseases have to be treated lifelong.

Since many autoimmune diseases already start in early to intermediate adulthood, treatment has to be performed over many decades, entailing great challenges in terms of effectiveness, ADRs, and costs. In principle, effective and affordable treatment of immune diseases is possible in many cases if established and inexpensive drugs such as GCR agonists, MTX, and azathioprine are used as first-line therapy.

In contrast, with therapeutic antibodies and fusion proteins, annual treatment costs in the high 5-digit dollar range can accrue depending on the specific drug, drug dose, and country. Thus, a careful and critical analysis of the costs and benefits of a pharmacotherapy (life quality, ability to work, ADRs, mortality) has to be made for every patient beforehand.

In Western countries, biologicals such as TNF inhibitors belong to the top-selling drugs. Since the pharmaceutical industry can reap large profits from biologicals, the development of such drugs is financially very attractive and has resulted in an explosion-like emergence of new entities. In this context, the reader should be reminded that every new drug must be of therapeutic advance compared to available drug therapies in terms of efficacy and ADRs, particularly if the costs for the newly approved drug are very high.

Although the immune system causes disease symptoms in autoimmune diseases and transplant rejection, it is nevertheless required to protect the body against infections and tumors. Since all available drugs do not discriminate between pathological and physiological immune processes, it is not surprising that many drugs increase susceptibility to infections and tumor incidence. Therefore, it is the goal to keep the drug dose as low as possible to control the disease on the one hand and to avoid life-threatening immune suppression on the other hand. Another strategy to maximize therapeutic effects and minimize ADRs is to combine drugs with different mechanisms of action.

The choice of drugs is adapted to the specific disease situation. Particularly with regard to immunophilin ligands that are CYP3A4 substrates, drug interactions leading to enhanced or reduced drug effects have to be considered (see ▶ Chap. 2). In these cases, TDM has to be performed to achieve optimal therapeutic results. Since donor organs are at a premium worldwide, precise dosing of the patient with immunosuppressants and high adherence are mandatory to avoid transplant rejections.

Certain drugs possess a very strong immunosuppressive effect and are therefore used only in serious clinical situations. For example, the CD3 antibody muromonab and mycophenolate, an inhibitor of purine metabolism, are used in severe transplant rejection reactions. The CD52 antibody alemtuzumab is applied in severe multiple sclerosis. However, all these drugs also cause serious, potentially life-threatening ADRs. Therefore, the drugs discussed in this chapter belong into the hands of a specialist. The role of the general practitioner is to ensure adherence and keep an overview of all prescribed drugs to avoid interactions and ADRs (see ▶ Chap. 2).

Fatigue, fever, and shivering are indicative for an infection. Indications for imminent kidney rejections are decreased urine production and edema. Icterus and light stool color are indicative for imminent liver failure. Hyperglycemia points to pancreas rejection, and fatigue, respiratory distress, edema, and arrhythmia indicate cardiac failure. In such cases, the medication must be checked immediately by TDM and adjusted accordingly.

Since many patients with autoimmune diseases are in their reproductive years, safety of drugs during pregnancy plays an important role. MTX, leflunomide, mycophenolate, azathioprine, 6-MP, and cyclophosphamide have a cytostatic-like mechanism in immune diseases and are potentially teratogenic. Therefore, these drugs are contraindicated in pregnancy. Should these drugs be used in fertile women, safe contraception has to be ensured (see ▶ Chap. 24).

In some autoimmune diseases, particularly psoriasis, atopic dermatitis, and UC (see ▶ Chap. 13), local administration of drugs is feasible, thereby focusing therapeutic effects and ADRs on a specific body region and avoiding systemic ADRs. However, in most cases, pathological immune reactions occur in many places in the organism, rendering systemic therapy unavoidable. Accordingly, systemic ADRs have to be

accepted. Certain autoimmune diseases such as myasthenia gravis (see ▶ Chap. 5), autoimmune hypothyroidism (see ▶ Chap. 21), and type 1 DM (see ▶ Chap. 19) can be primarily treated functionally by correcting the impaired organ function.

11.2 Glucocorticoids (GCR Agonists)

Since decades, GCR agonists belong to the most effective immunosuppressants with well-known ADRs. GCR agonists exhibit anti-inflammatory and immunosuppressive effects. They exert these effects via NRs that regulate the expression of many genes of importance for immune processes (see ▶ Chap. 1). GCR agonists inhibit expression of proinflammatory cytokines such as IL-1, IL-2, IL-6, IL-8, and TNF. Moreover, they reduce the expression of collagenases (protection against connective tissue degradation), PLA_2 (reduced synthesis of PGs and LTs), COX-2 (reduced PG synthesis), and NO synthase (reduced NO production). GCR agonists also reduce expression of integrins and lectins that are important for immune cell adhesion and expression of major histocompatibility complex proteins that are critical for immune recognition self versus foreign. Because of these global effects, GCR agonists can be successfully used in many autoimmune diseases and organ transplants. GCR agonists are also applied for prophylaxis of anaphylactic shock, prevention of cerebral edema, and asthma therapy.

Prednisolone is a prototypical GCR agonist that is often used for treatment of immune diseases. It activates the GCR with fourfold higher potency than the endogenous GCR agonist cortisol and is a full agonist (see ▶ Chaps. 1 and 10). At the MCR, prednisolone possesses a 20% lower potency than cortisol. The plasma half-life of prednisolone is just 3 hours, but because of the impacts on gene transcription, the effects of prednisolone last for 18–36 hours (see ▶ Chap. 2). Accordingly, there is a latency period of 12–18 hours before effects on gene expression become clinically apparent. In the clinical use of prednisolone (and other synthetic GCR agonists), there are four major problems:

1. The desired immunosuppressive and anti-inflammatory effects cannot be dissociated from the metabolic effects.
2. In contrast to SERMs (see ▶ Chaps. 20, 24, and 32), no organ-specific GCR agonists exist.
3. To achieve a sufficient therapeutic effect, doses above the Cushing threshold have to be applied, i.e., the dose above which prednisolone induces a Cushing's syndrome during long-term therapy. This is the case when the GCRs in the body are activated to a greater extent than by the endogenously produced cortisol. The daily production of cortisol in women amounts to about 15–30 mg and in men to 30–40 mg. Since prednisolone is fourfold more potent than cortisol, daily prednisolone doses >3.75–7.5 mg in women and >7.5–10 mg in men may lead to Cushing's syndrome.
4. During a therapy >7 days prednisolone inhibits ACTH secretion from the hypophysis. Consequently, cortisol production in the zona fasciculata is inhibited. After therapy of several weeks, atrophy develops so that endogenous cortisol production cannot start after abrupt cessation of prednisolone therapy, ultimately leading to a cortisol deficit situation (Addison syndrome). A lack of cortisol is life-threatening and is characterized by weakness, weight loss, anorexia, hypoglycemia, and hypotension.

In order to keep these problems under control, prednisolone is initially administered in high doses (30–70 mg/day). This regimen ensures a rapid anti-inflammatory and immunosuppressive effect. Thereafter, the dose is rapidly reduced to 3.75–7.5 mg/day (women) and 7.5–10 mg/day (men). These doses correspond to the Cushing threshold doses. In addition, prednisolone should be administered in the morning (between 6 and 8 a.m.) because the hypophysis is then relatively resistant to the inhibitory effect of prednisolone on ACTH secretion. Alternatively, the double prednisolone dose can be given every other day. Whenever possible, GCR agonists should be applied locally to avoid systemic ADRs. This is feasible in many dermatological diseases, UC (see ▶ Chap. 15), and respiratory tract diseases (see ▶ Chap. 14). To minimize ADRs even further, in local therapy, GCR agonists with high first-pass effect are administered (see ▶ Chap. 2). In serious autoimmune diseases and after transplantation, the Cushing threshold dose has to be exceeded in

many cases, and a Cushing's syndrome has to be accepted as ADR. In such cases, dose reduction and termination of prednisolone therapy must be conducted slowly and stepwise to avoid the development of adrenal gland insufficiency.

Above the Cushing threshold, prednisolone induces sodium and water retention with hypertension as a result of MCR activation (see ▶ Chaps. 15 and 16). GCR activation leads to stimulation of gluconeogenesis and glucagon release as well as reduced insulin secretion. As a consequence of these changes, hyperglycemia and deterioration of DM develop. In insulin-dependent diabetics, the insulin dose has to be increased to avoid hyperglycemia (see ▶ Chap. 19). Augmented gluconeogenesis occurs at the expense of protein degradation, manifested as skeletal muscle wasting, osteoporosis (see ▶ Chap. 20), and skin atrophy (striae and parchment-like skin). Lipolysis is stimulated, and adipose tissue is redistributed. As a result of these metabolic changes, patients treated with prednisolone have a puffy face (moon face), buffalo neck, a bloated abdomen, and atrophic arms and legs. Moreover, anxiety and depression can occur. The psychiatric problems can adversely affect the adherence of the patients. These changes are significant and must be addressed by dose reduction, psychotherapy, and/or NE/5-HT enhancers (see ▶ Chap. 28). In the eye, GCR agonists can increase IOP (see ▶ Chap. 31). A consequence of immunosuppression is increased susceptibility to infections, e.g., candidiasis (see ▶ Chap. 35). Lastly, wound healing is impaired. This is relevant when injuries occur or surgery has to be performed because these changes also increase the risk of wound infections.

11.3 Inhibitors of Purine and Pyrimidine Metabolism and DNA Synthesis

In many autoimmune diseases and in transplant rejection, T cells proliferate massively, sustaining a pathological immune reaction. Therefore, the inhibition of T-cell proliferation is an important strategy to treat immune diseases. This strategy arose from the observation that classic cytostatics cause immunosuppression as important ADRs (see ▶ Chap. 32). In order to use this effect for immune diseases, it was necessary to achieve long-term inhibition of pathological T-cell proliferation without other typical ADR of classic cytostatics, i.e., hair loss, stomatitis, nausea, vomiting, and bone marrow depression. In many autoimmune diseases, effective inhibition of T-cell proliferation without serious impairment of the functions of other rapidly proliferating cell types can be accomplished by applying classic cytostatics in low doses.

The most important drug of this class is MTX. In high (cytostatic) doses, MTX inhibits DHFR, leading to depletion of thymidine and purine bases (see ▶ Chap. 32). MTX is used with substantial success in the treatment of many autoimmune diseases including rheumatoid arthritis and psoriasis (see ◘ Table 11.2), myasthenia gravis (see ▶ Chap. 5), CD (see ▶ Chap. 13), dermatomyositis, scleroderma, sarcoidosis, lupus erythematosus, and ankylosing spondylitis. For immunosuppression, weekly doses of 5–25 mg of MTX are required, i.e., doses that are 70–300-fold lower than for cytostatic therapy. Accordingly, the immunosuppressive therapy with MTX is tolerated much better than the cytostatic one. From the beginning of therapy until the onset of therapeutic effects, a lag phase of 4–8 weeks has to be considered. It is important to inform the patient about the delayed onset of action so that adherence is ensured, and the patient does not terminate the therapy because of perceived lack of effect. Inexpensiveness is another advantage of the low-dose MTX therapy.

The mechanism of action of MTX in low-dose immunosuppressive therapy is different from the high-dose cytostatic therapy. Specifically, MTX in low doses inhibits AICAR transformylase. The accumulating AICAR in turn inhibits both AMP deaminase and adenosine deaminase. This results in an increase in the intracellular adenosine concentration. Adenosine is then released in larger amounts from immune cells and mediates immunosuppressive effects. Consequently, the release of IL-1, IL-6, and TNF is lowered. Additionally, LT release is diminished, and proliferation of T cells, endothelial cells, and fibroblasts are reduced. Lastly, the release of metalloproteases is inhibited. All these changes result in reduced pannus formation in synovia in rheumatoid arthritis.

On therapy with MTX, one important drug interaction has to be observed. Before the MTX therapy begins to show an effect, the patients are often treated with COX inhibitors to mitigate inflammation. COX inhibitors and MTX compete

for tubular secretion. As a result, MTX elimination may decrease, possibly leading to toxic MTX concentrations (see ▶ Chap. 12).

Leflunomide inhibits dihydroorotate dehydrogenase. Orotate is an important building block of pyrimidine bases. Consequently, pyrimidine and DNA synthesis are decreased. This inhibition primarily concerns the T cells that are rapidly proliferating in autoimmune diseases and transplant rejection. Leflunomide is often used in rheumatoid arthritis and psoriasis. The effects of leflunomide appear about 2–3 weeks after initiation of therapy. Following p.o. administration, leflunomide is converted to the active metabolite teriflunomide, i.e., leflunomide is a prodrug. Teriflunomide shows an extensive enterohepatic circulation and a half-life of 14 days (see ▶ Chap. 2). In case of serious ADRs (see ◘ Table 11.1), the enterohepatic circulation can be interrupted with activated charcoal (see ▶ Chap. 4) or cholestyramine (see ▶ Chap. 22) to accelerate elimination and ceasing of ADRs.

Mycophenolate inhibits inosine monophosphate dehydrogenase and thereby GMP synthesis. Consequently, purine bases for DNA synthesis are depleted, ultimately resulting in inhibition of B-cell and T-cell proliferation. This mechanism of action is used to prevent acute transplant rejection in combination with ciclosporin and GCR agonists. Mycophenolate is the active metabolite of the prodrug mycophenolate mofetil. During the first liver passage, mycophenolate is released from the prodrug (see ▶ Chap. 2). Bioavailability is very high and plasma half-life rather long (8–16 hours) due to the enterohepatic circulation. Mycophenolate is glucuronidated in the liver, leading to drug inactivation. Because of its serious ADRs, mycophenolate is not used routinely but only in patients with severe transplant rejection.

Azathioprine is a prodrug of 6-MP. Fallowing p.o. administration, 6-MP is released in the liver by action of glutathione S transferase. The pharmacological properties of 6-MP are discussed in ▶ Chap. 32. In the low doses used for the treatment of immune diseases, azathioprine predominantly inhibits T-cell and B-cell proliferation via integration into the DNA as wrong base. The ADRs of azathioprine are much less pronounced in low than in high doses. But also in low-dose therapy, it has to be considered that patients with low thiomethyltransferase activity inactivate the drug only slowly. If not observed, this gene polymorphism can aggravate the myelotoxicity of the drug. Moreover, the myelotoxicity of azathioprine is increased upon co-medication with XO inhibitors (see ▶ Chap. 23). Azathioprine is a very inexpensive drug and can be used for the therapy of several autoimmune diseases.

The alkylating classic cytostatic cyclophosphamide is used for treatment of severe forms of autoimmune disease as well (rheumatoid arthritis, lupus erythematosus, scleroderma, and vasculitis (see ▶ Chap. 32)). The anthracycline mitoxantrone (see ▶ Chap. 32) is used for severe multiple sclerosis.

11.4 Immunophilin Ligands

Ciclosporin binds to the immunophilin cyclophilin, thereby inhibiting activation of the phosphatase calcineurin which is then unable to activate a transcription factor that regulates IL-2 expression. IL-2 is essential for T-cell proliferation. Thus, ciclosporin inhibits T-cell proliferation and exerts its immunosuppressive effect via reduced IL-2 production. Tacrolimus binds to the immunophilin FKBP-12 and inhibits calcineurin activation as well. Sirolimus (rapamycin) also binds to FKBP-12, but instead of calcineurin, it rather inhibits the protein kinase mTOR that acts as checkpoint enzyme between the G1 and S phase of the cell cycle and controls T-cell proliferation (see ▶ Chap. 32).

Immunophilin ligands have a problematic bioavailability and a small therapeutic index. Therefore, in transplantation, TDM is conducted (see ▶ Chap. 2). This is also of importance because all of the abovementioned drugs are CYP3A4 substrates, possessing a high interaction potential for CYP3A4 inducers or inhibitors (reduced and enhanced effects of the immunophilin ligands, respectively) (see ▶ Chap. 2).

Ciclosporin is used to prevent transplant rejection and for therapy of several autoimmune diseases including rheumatoid arthritis, psoriasis, alopecia areata, and Sjögren syndrome.

Because of its higher efficacy, tacrolimus is predominantly applied in imminent transplant rejection and resistant autoimmune diseases such as CU, CD, and myasthenia gravis. An important indication for tacrolimus is topical administration in atopic dermatitis. In contrast to GCR agonists, tacrolimus does not induce skin atrophy.

Sirolimus is predominantly used for prevention of transplant rejection and of restenosis of coronary stents after MI (see ▶ Chap. 16). Sirolimus is slowly released from coated stents and inhibits excessive proliferation of endothelial and smooth muscle cells. Sirolimus is also used for treatment of the rare lymphangioleiomyomatosis in which smooth muscle cells in the lung proliferate abnormally.

Immunophilin ligands increase susceptibility to infection and tumor incidence. Important clinical aspects have to be considered when choosing the best drug for each patient. Ciclosporin can cause liver and kidney malfunction, hypertrichosis, and gingival hyperplasia. During long-term therapy, hypertension, dyslipidemia, obesity, and DM can be aggravated (see ▶ Chaps. 15, 19, and 22). Tacrolimus possesses a similar nephrotoxicity as ciclosporin but no risk for gingival hyperplasia and hirsutism. The risk for dyslipidemia is reduced, but the DM risk is increased. In contrast to ciclosporin, tacrolimus is neurotoxic. Unlike ciclosporin and tacrolimus, sirolimus is not nephrotoxic (see ▶ Chap. 11) but can impair wound healing.

11.5 Biologicals

Biologicals are proteins produced in genetically engineered cells. Typical biologicals are insulin analogs (see ▶ Chap. 19), coagulation factors and fibrinolytics (see ▶ Chap. 18), hematopoietic growth factors (see ▶ Chaps. 12 and 32), IFNs, monoclonal antibodies, and fusion proteins. In addition to autoimmune diseases, IFNs are used in the treatment of hepatitis C (see ▶ Chap. 34). Monoclonal antibodies are also applied in cancer therapy (see ▶ Chap. 32).

The scientific rationale for the exponentially increasing use of biologicals is to interfere with immune processes as specifically as possible and with as few ADRs as possible. However, this goal is reached only partially. In general, it must be taken into consideration that biologicals that block the function of certain molecules in the immune system do not only act immunosuppressively in the target indication but also increase susceptibility for infections and tumor incidence. Two examples are natalizumab, which favors PML, and infliximab, which can cause lymphoma, particularly in combination with other biologicals. The PML risk can be reduced by exclusion of those patients from therapy who were identified as carrier of the causative human polyoma virus or who were previously treated with immunosuppressive drugs. Under therapy with certain biologicals (e.g., IFN-β and alemtuzumab), the incidence of autoimmune diseases of the thyroid gland is increased (see ▶ Chap. 21).

In general, biologicals that are marketed under a brand name are expensive drugs. In industrialized countries, 15–30% of the annual drug costs are already attributable to biologicals, and the trend is increasing. Moreover, a large fraction of the drugs that are under current clinical development are biologicals. Thus, it is conceivable that health-care systems will be subject to huge financial challenges unless biologicals are prudently and conservatively used. After patent expiration, biosimilars enter the drug market which are generally much less expensive than the original brands. Biosimilars and biologicals exhibit comparable clinical efficacy although for commercial reason, this equivalence is sometimes challenged.

In the therapy of autoimmune diseases, monoclonal antibodies and therapeutic fusion proteins are used that target a defined molecule playing a distinct role in a pathological immune process. The first antibodies introduced into the clinic were mouse proteins. Accordingly, these proteins have a high allergenic potential (see ▶ Chap. 3). In chimeric antibodies (drug ending **_xi**mab), the portion of mouse protein was reduced to 25%, thereby lowering the risk of allergic reactions. In humanized monoclonal antibodies, the portion of mouse protein is only 10% (drug ending **_zu**mab), and in human monoclonal antibodies, there is no more mouse protein present at all (drug ending **_u**mab). Accordingly, the allergy risk with human monoclonal antibodies is very small. In therapeutic fusion proteins (drug ending **_cept**), the extracellular domain of a cytokine receptor is fused with the Fc portion of human IgG. The allergenic potential of fusion proteins is small. In principle, neutralizing antibodies against therapeutic antibodies and fusion proteins can be generated by the organism, annihilating their pharmacological effects.

T cells are of eminent importance in the therapy of autoimmune diseases and prevention of transplant rejection. In certain autoimmune processes, also B cells play a role. Basiliximab is a monoclonal antibody against the IL-2R that is important for T-cell proliferation. Antibodies against the CD3 antigen cause T- cell apoptosis.

Abatacept inhibits the costimulation of T cells by antigen-presenting cells. Alemtuzumab causes apoptosis of T cells and B cells via binding to CD52. Rituximab binds to CD20, leading to B-cell apoptosis. Because of the high costs, therapy with these drugs must be restricted to refractory situations. An additional reason for conservative use of these drugs is that they interfere with fundamental processes in the immune system that are important for host defense against infections.

Another strategy for immunosuppression is to block the function of proinflammatory cytokines. However, susceptibility to infection is increased, particularly when IL-1 inhibitors are combined with TNF inhibitors. Anakinra binds to the IL-1R as antagonist and prevents receptor activation by IL-1. As a result, inflammatory processes are reduced. This approach is exploited in the therapy of rheumatoid arthritis. In the meantime, various antibodies and fusion proteins have been developed that neutralize TNF, thereby preventing TNFR activation. This principle is used in the treatment of many autoimmune diseases including rheumatoid arthritis, ankylosing spondylitis, psoriasis, CD, and UC.

It is uncontested that biologicals exhibit therapeutic effects in certain autoimmune diseases, but marketing aspects play a large role in this area. One example is alemtuzumab. Originally, this antibody was approved for the therapy of chronic lymphatic leukemia. The drug was used off-label, with good success for the treatment of severe cases of multiple sclerosis but then withdrawn from the drug market to stop the off-label use. After a short period of time, alemtuzumab was reapproved for the treatment of multiple sclerosis, but the therapy costs were increased manifoldly. This is a negative example of indication hopping based on commercial reasons.

11.6 Questions and Answers

Questions

Which assignment of a drug to mechanism of action is correct?

A. Infliximab – IL-1R blockade
B. Mycophenolate – Inhibition of pyrimidine synthesis
C. Sirolimus – inhibition of calcineurin
D. Ustekinumab – Neutralization of TNF
E. Fingolimod – Internalization of $S1P_1R$

Answers

A. Infliximab neutralizes TNF; anakinra blocks the IL-1R.
B. Mycophenolate inhibits inosine monophosphate dehydrogenase and, thereby, synthesis of the purine nucleotide GMP.
C. Sirolimus inhibits mTOR; ciclosporin and tacrolimus inhibit calcineurin.
D. Ustekinumab neutralizes IL-12 and IL-23; TNF is neutralized by infliximab, adalimumab, and etanercept.
E. The $S1P_1R$ is important for emigration of T cells from the lymph node. Internalization of the $S1P_1R$ prevents T cell emigration.

Answer **E** is correct.

11.7 Exercises

A family physician refers a 40-year-old woman with joint pain to your rheumatology practice. The patient reports that for several years, she has been suffering from increasing pain in her finger joints. She also suffers from joint swelling, and in the morning, she has warm-up problems. Initially, she could handle the problem with diclofenac sports gel. Later, the family physician had prescribed diclofenac sugar-coated pills (25 mg) as on-demand medication. Once this therapy was not sufficient anymore, the family physician prescribed diclofenac sustained-release sugar-coated pills (50 mg) and finally the 100 mg pills. However, the last dose increase caused stomach pain. In addition, her lower legs have swollen, and recently, her family physician has diagnosed hypertension (140–165/90–95 mm Hg). The physical exam reveals that the interphalangeal joints of both hands are swollen. The hands show erythema, and movements are severely restricted. An X-ray reveals erosions and subchondral osteoporosis at the interphalangeal joints. You can confirm the presence of lower leg edema. The clinical chemistry analysis reveals increased values of the C-reactive protein and anti-citrullinated protein antibodies. Gastroduodenoscopy reveals a small ulcer.

Questions

1. What is your diagnosis and what is your initial therapeutic procedure?
2. Which ADRs can occur under therapy with MTX + prednisolone?

Answers

1. The clinical picture, the X-ray, and the laboratory investigations indicate that the patient suffers from rheumatoid arthritis. The disease process has been ongoing for quite a long time. The symptomatic therapy with a COX inhibitor contributed to the delayed diagnosis. It is also apparent that the patient suffers from serious ADRs as a result of the long-term therapy with diclofenac (CKD with water and sodium retention) with subsequent increase in BP and occurrence of PUD. You tell the patient the diagnosis "rheumatoid arthritis" and inform her about the likely connection between the long-term therapy with diclofenac and the occurrence of CKD, hypertension, and PUD. You terminate the diclofenac therapy with the aim to improve CKD, lower the BP, and cure PUD. In addition, you prescribe a PPI in standard dose (e.g., 40 mg pantoprazole) for 4–6 weeks. In order to improve the arthritis symptoms, you initiate a therapy with low-dose MTX (about 10–20 mg per week) and a systemic high-dose GCR agonist (e.g., prednisolone 30–70 mg/day, then rapid dose reduction to 3.75–7.5 mg per day). Alternatively, you can initiate a therapy with a TNF inhibitor (e.g., infliximab or adalimumab) or an IL-1 inhibitor (anakinra). However, therapy with MTX + GCR agonist is much less expensive. After 8–12 weeks, you can judge the therapeutic effect and adjust the drug dose depending on the clinical symptoms and ADRs.
2. MTX can induce loss of appetite, dizziness, nausea, vomiting, diarrhea, and stomatitis. In addition, liver enzymes may increase. Therefore, liver enzymes have to be controlled. Furthermore, MTX can cause leukopenia and thrombocytopenia, requiring regular hemograms. As a result of immunosuppression, infections may occur more frequently or may be reactivated. Lymphoma may occur as well. GCR agonists can cause a Cushing's syndrome. Therefore, the GCR agonist dose should be decreased as rapidly as possible. In addition, GCR agonists should be administered in the morning to reduce the risk of adrenal cortex insufficiency.

Further Reading

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Pharmacology of the Kidney

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CKD is very common and caused by DM, hypertension, autoimmune diseases, and hereditary diseases. Treatment of the cause is the basis of CKD therapy. CKD leads to several complications that, if untreated, result in uremia and death. The active vitamin D_3 calcitriol is substituted. For hyperphosphatemia, phosphate binders are given, for treatment of secondary hyperparathyroidism calcimimetics, for renal anemia epoetin or darbepoetin, and for ADPKD (autosomal-dominant polycystic kidney disease) the V_2R antagonist tolvaptan. Many drugs including lithium, MTX, aciclovir, gentamicin, vancomycin, metformin, and atenolol are predominantly renally eliminated. In CKD, the doses of these drugs have to be diminished according to the reduced creatinine clearance to avoid ADRs. If available, an alternative is to use drugs with predominant extrarenal elimination. Several drugs including cisplatin, amphotericin B, iodine-containing contrast media, COX inhibitors, and calcineurin inhibitors are nephrotoxic and should be avoided in CKD if possible. Potassium-sparing diuretics and RAAS inhibitors can deteriorate hyperkalemia in CKD. Thiazide and loop diuretics can cause hypokalemia and hypovolemia.

12

Key Points

1. Patients with CKD are multimorbid and are often treated with many drugs, resulting in multiple possibilities for interactions.
2. In CKD, the number of drugs should be limited to the minimum.
3. Epoetin and darbepoetin stimulate erythropoiesis and improve renal anemia.
4. Epoetin and darbepoetin can cause hypertension and thrombosis.
5. Cinacalcet belongs to the group of calcimimetics and increases CaSR sensitivity.
6. Calcimimetics mitigate secondary hyperparathyroidism.
7. Tolvaptan reduces cyst proliferation in ADPKD.
8. The lower the Q_0 value of a drug, the larger its renal elimination and the more its dose must be reduced in CKD.
9. If possible, drugs with a low Q_0 value should be avoided in CKD.

12.1 Pathophysiology of Chronic Kidney Disease (CKD)

The kidney plays a central role in water, electrolyte, and acid/base homeostasis and regulates blood pressure via renin secretion (see ▶ Chap. 15), bone metabolism via calcitriol synthesis (see ▶ Chap. 20), and erythropoiesis via EPO secretion. In addition, the kidney is important for elimination of drugs via glomerular filtration and tubular secretion. These functions are all compromised in CKD. ◘ Figure 12.1 provides an overview of CKD pathophysiology and pharmacological interventions. ◘ Table 12.1 summarizes selected drugs for CKD treatment. ◘ Table 12.2 presents important drugs that are predominantly eliminated renally and whose dose must be adjusted in CKD. ◘ Table 12.3 lists drugs that can deteriorate CKD or induce acute kidney failure.

CKD cannot be cured. The only causative therapy is kidney transplantation, but the number of available donor organs is insufficient. Therefore, most CKD patients are dialyzed to maintain homeostasis. In addition, CKD symptoms are treated pharmacologically.

Many diseases can lead to CKD including DM (see ▶ Chap. 19), hypertension (see ▶ Chap. 15), chronic gout (see ▶ Chap. 23), autoimmune diseases (see ▶ Chap. 11), and cystic kidney disease. Important risk factors for CKD are dyslipidemia (see ▶ Chap. 22), tobacco smoking, nephrotoxic drugs (◘ Tables 12.2 and 12.3), high age, and a sedentary lifestyle. Because of the demographic change in many countries, CKD prevalence increases. Depending on the specific country, annual costs for dialysis and drugs for a single CKD patient can easily reach $ 50,000. Therefore, CKD prevention has high priority.

According to the GFR, CKD is classified into five different stages. The GFR is determined as creatinine clearance. In young adults, the GFR amounts to 120–130 ml/min. In the asymptomatic stage 1 CKD, GFR is reduced to 90–120 ml/min. However, particularly, in this early stage, CKD can be treated effectively. Therefore, if CKD is suspected, the creatinine clearance should be determined early. In stage 2 CKD, the GFR is reduced to 60–89 ml/min, in stage 3 to 30–59 ml/min, and in stage 4 to 15–29 ml/min. Stage 5 CKD is characterized by preterminal renal failure, requiring the patient to be dialyzed or provided with a kidney transplant. Often, stage 1–3 CKD is symptomless. In stage 4, unspecific symptoms such as reduced

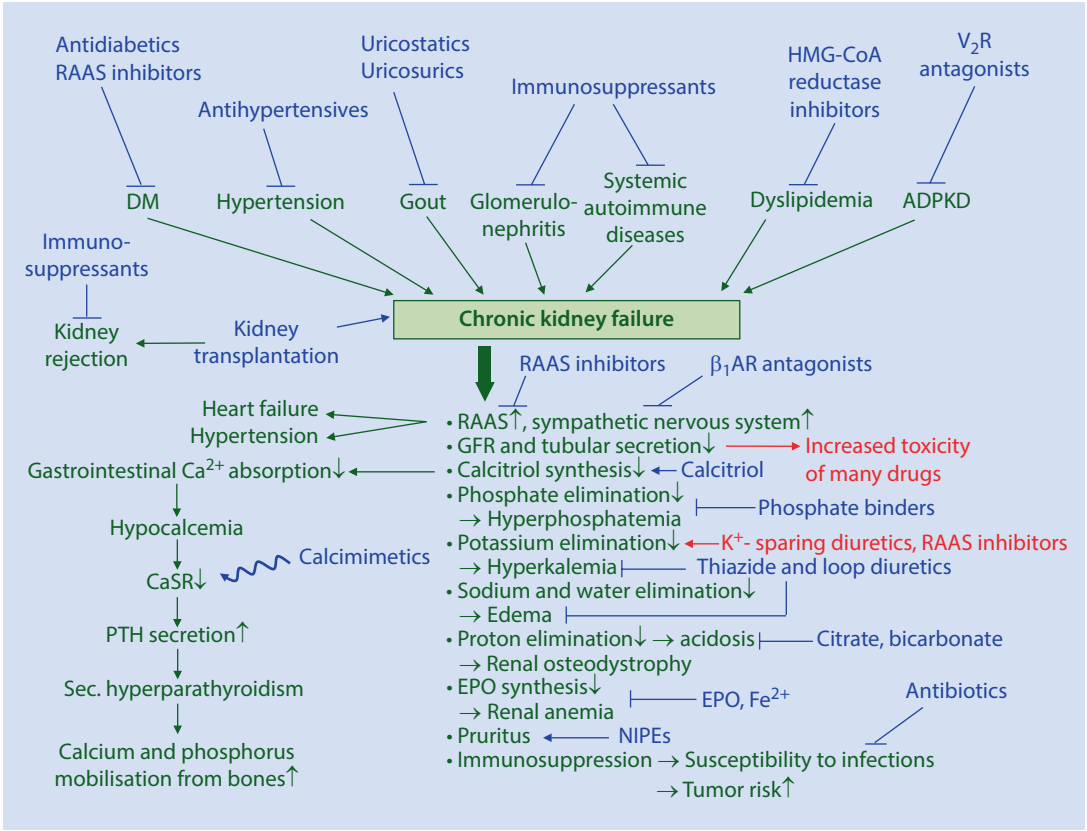

Fig. 12.1 Pathophysiology of CKD: pharmacological interventions. There is no single drug for CKD. CKD therapy requires the combination of many drugs. Beware of drug interactions and do not use of nephrotoxic drugs! Treat the diseases underlying CKD!

physical fitness, fatigue, loss of appetite, nausea, and vomiting occur. Later, edema, dyspnea, and skin alterations appear. Proteinuria and otherwise unexplained itch are important indications for CKD. In stage 5 CKD, additional symptoms including increased hemorrhage tendency, depression, polyneuropathy, susceptibility for infections, and uremic fetor develop.

CKD has serious consequences: initially, as a result of the reduced GFR, the sympathetic nervous system and RAAS are activated as unsuccessful attempts to increase the GFR. Activation of these two systems constitutes an important pathogenic factor for hypertension and CHF (see ▶ Chaps. 15 and 16) that further deteriorate CKD. Due to the reduced GFR and tubular secretion, toxicity of many drugs increases. The reduced GFR and tubular secretion are important problems because most CKD patients are treated with numerous drugs. Therefore, the risk for ADRs is particularly high in these cases.

CKD leads to reduced renal calcitriol synthesis, resulting in impaired GI calcium absorption and hypocalcemia. Further symptoms are muscular spasms and paresthesia (see ▶ Chap. 20). As a consequence of these disorders, the CaSR in the parathyroid glands is activated to a lesser extent, and PTH secretion is increased. This results in higher plasma PTH concentration (secondary hyperparathyroidism). PTH increases calcium and phosphate mobilization from the bone and, in the healthy kidney, additionally enhances elimination of phosphate and reabsorption of calcium. However, the CKD kidney cannot respond anymore properly to PTH. Therefore, normalization of the plasma calcium concentration does not take place, and hyperphosphatemia develops. Hypocalcemia is potentiated by the fact that calcium and phosphate precipitate in blood vessels and organs. Calcification of blood vessels then aggravates hypertension, and calcification of cardiac valves deteriorates CHF. The general organ calcification leads to global organ

Table 12.1 Overview of selected drugs for treatment of CKD

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Calcitriol	Biologically active form of vitamin D_3	Promotes intestinal absorption of calcium and inhibits renal calcium elimination and stimulates osteoblast activity	CKD with impaired calcitriol synthesis	Hypercalcemia, hypercalciuria, urolithiasis	20, 23
Cinacalcet	Calcimimetic; allosteric CaSR modulator	Increases CaSR sensitivity to calcium, thereby more effectively reducing PTH secretion. Hence, calcium and phosphate mobilization from bone is inhibited	CKD with secondary hyperparathyroidism, frequently administered to dialysis patients	Hypocalcemia, hypophosphatemia, hyperkalemia, muscle spasms, nausea, vomiting, diarrhea, headache, paresthesia, myalgia, hypotension, and QT prolongation	1, 13, 17, 20
Darbepoetin	Recombinantly produced EPO in which five amino acids have been exchanged; EPOR agonist	The exchange of amino acids results in a modified glycosylation and, hence, in a threefold longer plasma half-life than that of EPO	Renal anemia. The simultaneous substitution of iron is essential in order to promote hemoglobin formation	See epoetin	15, 18
Epoetin	Recombinantly produced EPO; EPOR agonist	EPOR stimulation on erythrocyte precursor cells stimulates erythropoiesis. Effects after 2–6 weeks of treatment	Renal anemia. The simultaneous substitution of iron is essential in order to promote hemoglobin synthesis	Hypertension, thrombosis, flu-like complaints, CNS disorders; elevated risk of thrombosis with high-dose diuretic therapy (hypovolemia and exsiccosis)	15, 18
Lanthanum carbonate	Phosphate binder. After p.o. administration, lanthanum carbonate forms complexes with phosphates contained in food and, hence, inhibits phosphate absorption	Counteracts hyperphosphatemia in CKD	Hyperphosphatemia in CKD dialysis patients	Lanthanum carbonate is absorbed in small quantities and accumulates in the bone and liver; its toxicity is not yet definitely determined	
Tolvaptan	V_2R antagonist	Inhibits cAMP-dependent cyst growth mediated via V_2R	ADPKD, hyponatremia resulting from inappropriate antidiuretic hormone secretion	Sensation of thirst, dry mouth, high consumption of water, polyuria, nycturia, weariness, vertigo, hypotension, hypernatremia, hyperkalemia, hyperuricemia, creatinine rise, and liver damage	15, 23

Thiazide diuretics, loop diuretics, potassium-sparing diuretics, and RAAS inhibitors are presented in Chap. ► 15 and ◘ Table 12.3

Table 12.2 Selected drugs with very high renal elimination: problems in CKD patients and strategies for problem-solving

Drug	Drug class	Q_0	Possible indication in CKD patients	Consequences of accumulation in CKD	Solution to the problem	Further contexts in Chaps.
Aciclovir	Virustatic, antimetabolite	0.15	Reactivation of an HZV infection as a consequence of immunosuppression	Crystal precipitation in the kidney and urinary tract, hence, impairment of urinary flow, reno-ureteral colics, and deterioration of CKD	Slow i.v. administration and sufficient hydration in order to prevent crystal precipitation. Other virustatics (e.g., ganciclovir, valaciclovir) should only be administered in case of viral resistance, as these virustatics are also predominantly eliminated via the kidney	23, 35
Atenolol	β_1AR antagonist	0.06	Hypertension as a cause/consequence of CKD	Bradycardia, AV block, heart failure, and asthma may conceal signs of hypoglycemia in DM patients	Switch to another drug of the same class with low renal elimination, e.g., metoprolol (Q_0, 0.95)	5, 14, 15, 16, 17
Gentamicin	Aminoglycoside	0.02	Infection with gram-negative bacteria as a consequence of immunosuppression	Nephro- and ototoxicity	Switch to another antibiotic of a different class to which the pathogen of the infection is susceptible (e.g., β-lactam antibiotic, quinolone)	33
Lithium	Alkali metal ions	0.02	Bipolar disorder that deteriorated as a result of CKD	Multi-organ toxicity (kidney, cardiovascular system, thyroid gland, CNS)	Dialysis in case of intoxication. Alternatively, switch to a drug with lower renal elimination (e.g., valproic acid; Q_0, 0.95). Avoid co-administration with thiazide and loop diuretics, COX inhibitors, and RAAS inhibitors (lithium clearance ↓)	4, 15, 16, 28
Metformin	Biguanides	0.10	Type 2 DM as a cause of CKD (diabetic nephropathy)	Lactate acidosis with subsequent electrolyte disorders which cannot be compensated because of CKD	Switch to a drug of another class, e.g., GLP-1R agonists, DPP4 inhibitors, and SGLT-2 inhibitors	19
MTX	Antimetabolite, classic cytostatic, and immunosuppressant	0.06	Long-term therapy with low-dose MTX as immunosuppressant for management of an autoimmune disease (e.g. lupus erythematosus, vasculitis)	Increased toxicity, e.g., liver damage, stomatitis, leukopenia, and nephrotoxicity caused by crystal precipitation in the kidney and urinary tract, reno-ureteral colics, in addition, tumor lysis syndrome	Slow i.v. administration. Ensure sufficient hydration and raise. pH in order to prevent crystal precipitation. Avoid co-administration of penicillins or uricosurics, which inhibit renal elimination of MTX Switch to another cytostatic or immunosuppressant with similar mechanism of action but lower renal elimination (e.g., leflunomide)	23, 32

(continued)

Table 12.2 (continued)

Drug	Drug class	Q_0	Possible indication in CKD patients	Consequences of accumulation in CKD	Solution to the problem	Further contexts in Chaps.
Vancomycin	Glycopeptide antibiotic	0.03	Infection with *Clostridium difficile* (pseudomembranous enterocolitis) following hospitalization in a CKD patient	Nephro- and ototoxicity, red man syndrome	Switch to another antibiotic of a different class to which the pathogen of the infection is susceptible (e.g., metronidazole or teicoplanin in *Clostridium difficile* infections, daptomycin or tigecycline in MRSA infections)	33

For all drugs listed in the table, dose reduction according to the creatinine clearance has to be performed

Table 12.3 ADRs of various drug classes on renal function: problem-solving strategies

Drug class	Typical drug	Typical indication	Drug effect, mechanism of renal damage	Effect on renal function and function of other organs	Solution to the problem	Further contexts in Chaps.
Calcineurin inhibitors	Ciclosporin, tacrolimus	Immunosuppression after organ transplantation and in autoimmune diseases	Increased ROS formation, activation of RAAS and the sympathetic nervous system	Deterioration of renal function (also of a transplanted kidney), hypertension	TDM, combination of different immunosuppressants, administration of non-nephrotoxic immunosuppressants (e.g., sirolimus)	11
Classic cytostatics	6-MP, vinblastine, paclitaxel, MTX, cisplatin	Various tumor diseases, may develop in CKD patients due to immunosuppression	Tumor lysis syndrome: large quantities of uric acid as final product of purine metabolism	Precipitation of uric acid crystals in the kidney and urinary tract → deterioration of renal function and reno-ureteral colics	Dose reduction, the use of targeted antineoplastic drugs, sufficient hydration, urinary alkalization, avoid uricostatics	11, 23, 32
COX inhibitors	Ibuprofen	Acute pain following injuries and surgeries and in rheumatic diseases	Reduced synthesis of PGE_2 and, hence, reduced renal blood flow	Impairment of renal function with sodium and water retention as well as hypertension especially during long-term treatment; reduced effects of thiazide and loop diuretics, RAAS inhibitors, and β_1AR antagonists	Avoid combination with other potentially nephrotoxic drugs; the use of COX inhibitors in CKD patients should generally be avoided; use other analgesics (metamizole, paracetamol, weakly and moderately effective MOR agonists) and co-analgesics; treat the disease causing the pain	10, 15, 16, 17
Drugs for dyslipidemia	HMG-CoA reductase inhibitors (e.g., simvastatin), fibrates (e.g., fenofibrate)	Dyslipidemia, often in CKD	If combined with CYP3A4 inhibitors and/or OATB1 inhibitors, ubiquinone synthesis in skeletal muscle is inhibited → rhabdomyolysis and myoglobin release	Acute renal failure (1) Obstruction of tubules with hemoglobin casts; (2) tubules damaged by iron; (3) reduced renal blood flow	Dose reduction, avoid administration of drugs inhibiting CYP3A4 or OATB1; treat acute liver failure with forced diuresis (loop diuretics and increased hydration) and urinary alkalization; dialysis, if required	2, 22

(continued)

Table 12.3 (continued)

Drug class	Typical drug	Typical indication	Drug effect, mechanism of renal damage	Effect on renal function and function of other organs	Solution to the problem	Further contexts in Chaps.
Iodine-containing contrast media	Iohexol, Iodixanol	Visualization of vessels (angiography of cardiac structures and of renal artery stenosis), visualization of urinary tract	Direct damage of the tubule epithelium, vasoconstriction, and reduced oxygen supply	Deterioration of renal function in already diagnosed CKD (contrast-induced nephropathy, CIN), highly varying frequency, 1–45%; rare in people with intact renal function	Preferably use contrast media with low viscosity and osmolarity; small volumes, if possible; avoid potentially nephrotoxic drugs, ensure sufficient hydration (infusion of NaCl-containing solutions), exclude high-risk patients (very low creatinine clearance, age >75 years, DM, very low BP, CHF, low hematocrit), and use other diagnostic methods	15, 16, 19
Loop diuretics	Furosemide	Hypertension, CHF, hepatic and nephrogenic edema, forced diuresis to treat intoxications	Inhibition of the $Na^+/K^+/2Cl^-$ cotransporter in the ascending limb of the loop of Henle (high-ceiling diuretic); high efficacy, even with very low GFR; in this case, use high dose, if required	Hypokalemia, hypomagnesemia, hypocalcemia (deterioration of osteoporosis), hypovolemia, rarely diuretic-induced hyponatremia because of postdiuretic sodium retention, hyperuricemia, reduced glucose tolerance, dyslipidemia, ototoxicity, and nephrotoxicity if combined with other drugs	See ADRs of thiazide diuretics which are principally similar. Avoid combination with other nephrotoxic drugs such as COX inhibitors, aminoglycosides, iodine-containing contrast media, and cisplatin. Use calcium supplements and vitamin D in case of hypocalcemia	15, 20, 22, 23
MOR agonists (special case of CNS toxicity)	Morphine	Tumor pain	Accumulation of the active metabolite morphine-6-glucuronide, which is only eliminated with delay in CKD patients	Increased morphine effects, particularly respiratory depression and risk of falling	Dose reduction or extended-interval dosing, switch to other MOR agonists without risk of accumulation in CKD. The most suitable drug is fentanyl with a Q_0 value of 0.95	10

Platinum agents	Cisplatin	Seminoma, ovarial carcinoma, mammary carcinoma, bladder carcinoma, tumors of head and neck, and esophageal carcinoma	ROS formation and, hence, damage of the tubule epithelium; breakdown of electrolyte gradients; ototoxicity	Renal failure with hypokalemia, hypomagnesemia, and hypocalcemia; in addition, tumor lysis syndrome	Sufficient hydration (infusion of NaCl-containing solutions), avoid administration of loop diuretics as they potentiate the nephrotoxicity of cisplatin, use radical scavengers (amifostin), and switch to non-nephrotoxic platinum complexes (carboplatin)	32
Polyene antimycotics	Amphotericin B	Systemic mycosis with *Aspergillus fumigatus*, also as a result of immunosuppression in CKD patients	Insertion into the plasma membrane (binding to cholesterol) and, hence, unspecific damage to renal tubule cells; breakdown of electrolyte gradients	Renal failure with hypokalemia	Infusion of liposomal preparations with lower nephrotoxicity, infusion of NaCl-containing solutions, switch to other antimycotics to which the pathogen is susceptible (e.g., azole antimycotics, echinocandins)	35
Potassium-sparing diuretics	Triamterene, spironolactone (MCRAs)	In combination with thiazide and loop diuretics to counteract hyperkalemia; MCRAs in CHF and hyperaldosteronism (e.g., liver cirrhosis and ascites)	Triamterene: inhibition of the sodium transporter in the late distal tubule and collecting duct → very small inhibition of sodium secretion and reduced potassium secretion; MCRAs: reduced expression of the sodium channel in the late distal tubule and collecting duct	Hyperkalemia, GI disturbances, vertigo, paresthesia; co-administration of RAAS inhibitors may deteriorate hyperkalemia, co-administration of β_1AR antagonists may aggravate bradycardia	Regular ECG and plasma electrolyte monitoring, avoid co-administration with β_1AR antagonists and RAAS inhibitors; use in combination with loop and thiazide diuretics	15, 16, 17
RAAS inhibitors	Ramipril, candesartan	Hypertension, CHF	ACE inhibition and AT_1R antagonism reduce aldosterone secretion and expression of sodium channels in the late distal tubule and collecting duct	Hyperkalemia, GI disturbances, vertigo, paresthesias; potassium-sparing diuretics may deteriorate hyperkalemia; co-administration of β_1AR antagonists may deteriorate bradycardia caused by β_1AR antagonists; hypotension and reduction of renal blood flow	Regular ECG and plasma electrolyte monitoring; co-administration with loop and thiazide diuretics, avoid co-administration of potassium-sparing diuretics	15, 16, 17

(continued)

Table 12.3 (continued)

Drug class	Typical drug	Typical indication	Drug effect, mechanism of renal damage	Effect on renal function and function of other organs	Solution to the problem	Further contexts in Chaps.
Thiazide diuretics	Chlorthalidone	Hypertension, CHF, hepatic and nephrogenic edema, diabetes insipidus	Inhibition of the Na^+/Cl^- cotransporter in the early distal tubule, low-ceiling diuretics (low efficacy)	No diuretic effect in severe CKD (GFR <30 ml/min), hypokalemia, hyponatremia, hypovolemia, hypercalcemia, hypomagnesemia, hyperuricemia, reduced glucose tolerance, dyslipidemia; ceiling effect (lower maximum effect than loop diuretics)	Regular ECG and plasma electrolyte monitoring; avoid use of GCR agonists, laxatives, and loop diuretics in hypokalemia; do not use uricosurics in gout; adjust lithium doses; avoid COX inhibitors, which reduce the effects of thiazide diuretics; avoid calcium supplements and vitamin D_3 in hypercalcemia; supplement magnesium in hypomagnesemia; ensure sufficient hydration in hypovolemia, ensure adequate diet and administer antidiabetics in hyperglycemia; treat dyslipidemia with HMG-CoA reductase inhibitors or PPAR-α agonists	15, 16, 17, 18, 19, 20, 22, 23, 28
Uricosurics	Benzbromarone, Lesinurad	Chronic gout; may cause CKD	Inhibition of uric acid reabsorption in the proximal tubule	Precipitation of uric acid crystals in kidney and urinary tract → deterioration of renal function and reno-ureteral colics	Dose reduction, combination with XO inhibitors; do not combine with classic cytostatics, ensure sufficient hydration, perform urine alkalinization	23

dysfunction including impaired function of the CNS and the reproductive system. The bone loss leads to renal osteodystrophy and increased risk of bone fractures.

CKD also reduces potassium elimination, leading to hyperkalemia. This can result in bradycardia (see ▶ Chap. 17). Disturbed sodium and water elimination leads to edema. Often, it is difficult to discriminate whether edema is of nephrogenic or cardiac origin (see ▶ Chap. 16), but pharmacotherapy is comparable anyway. Another consequence of CKD is disturbed proton elimination resulting in acidosis which, in turn, can aggravate renal osteodystrophy.

Biosynthesis of the hematopoietic factor EPO in the peritubular interstitial cells of the renal cortex is impaired in CKD. Furthermore, iron losses develop. In the end, renal anemia occurs, substantially contributing to the reduced physical and mental capacity of CKD patients. In late CKD stages, the immune system is compromised so that the incidence of tumors and the susceptibility for infections (pneumonia, hepatitis, influenza) increase.

12.2 Pharmacotherapeutic Principles and Specific Drugs for CKD Treatment

Recognition and therapy of the cause constitute the basis of CKD treatment. Since CKD is a chronic disease, treatment has to be performed lifelong. Therefore, it is important to obtain high patient adherence and to use drugs with as few ADRs as possible.

Insufficient treatment of a type 2 DM results in diabetic nephropathy. This accounts for about a third of all cases of kidney transplantation. Accordingly, a type 2 DM must be rigorously treated with diet and oral antidiabetics, specifically metformin (see ▶ Chap. 19). AT_1R antagonists and ACEI delay development of diabetic nephropathy. For treatment of hypertension, numerous drug classes are available (see ▶ Chap. 15). Based on pathophysiological considerations, in CKD patients with hypertension, the drug classes A, B, and D should be used. For treatment of autoimmunologically caused CKD, numerous immunosuppressive drugs are available. However, because of their nephrotoxicity and BD-increasing properties, the calcineurin inhibitors ciclosporin and tacrolimus should only be used cautiously (see ▶ Chap. 11 and ◘ Table 12.3).

For treatment of ADPKD, the V_2R antagonist tolvaptan is available. This drug inhibits V_2R-mediated cyst growth but possesses substantial ADRs resulting from the blockade of the physiological effects of the antidiuretic hormone vasopressin.

The impaired calcitriol synthesis can be compensated by administration of the biologically active calcitriol, but hypocalcemia should not switch into hypercalcemia (see ▶ Chap. 20). Allosteric activation of the CaSR with calcimimetics is a novel approach to treat secondary hyperparathyroidism. Calcimimetics increase sensitivity of the CaSR for the endogenous ligand calcium (see ▶ Chap. 1). Cinacalcet is the prototypical calcimimetic. Since it has to be administered lifelong, adherence problems can occur. Etelcalcetide is a newly developed calcimimetic that can be administered i.v. during the course of dialysis. Based on their mechanism of action, calcimimetics can aggravate hypocalcemia. To this end, conclusive clinical data about the effects of calcimimetics on blood vessel calcification and organ calcification, renal osteodystrophy, and mortality are not yet available so that a definitive assessment of the value of this therapeutic principle is currently impossible.

For treatment of hyperphosphatemia, GI phosphate absorption can be reduced by phosphate binders. Lanthanum carbonate is frequently used, but it is not yet clear whether lanthanum exhibits long-term toxic effects. Aluminum-containing phosphate binders should be avoided because aluminum can be absorbed and cause dementia (see ▶ Chap. 30). In case of calcium-containing phosphate binders, increased calcium absorption constitutes a problem, resulting in a switch of hypocalcemia into hypercalcemia which is problematic as well.

In CKD, elimination of sodium, potassium, and water is impaired, resulting in edema and hyperkalemia. If the GFR amounts to >30 ml/min, thiazide diuretics possess a diuretic effect. Via this mechanism, edema can be eliminated but at the expense of the risk that hyperkalemia converts into hypokalemia, leading to tachycardia, constipation, and muscle paralysis. It is advantageous that thiazide diuretics inhibit calcium elimination, counteracting the hypocalcemia in CKD. However, this effect can change into hypercalcemia. At a GFR <30 ml/min, thiazide diuretics lose their effectiveness, but loop

diuretics are still effective. They also induce hypokalemia. In order to mitigate hypokalemia induced by thiazide and loop diuretics, these drug groups are often combined with potassium-sparing diuretics which possess only a small natriuretic effect. Triamterene and the MCRA spironolactone are typical representatives of this group. In addition, ACEIs and AT_1R antagonists counteract hypokalemia for which reason these drugs are often combined with thiazide and loop diuretics. If used alone, potassium-sparing diuretics, ACEIs, and AT_1R antagonists can cause hyperkalemia in CKD. Therefore, these drugs must only be used in combination with thiazide and/or loop diuretics.

In contrast to thiazide diuretics, loop diuretics enhance calcium elimination, aggravating the hypocalcemia in CKD. Both thiazide and loop diuretics can promote hypomagnesemia, resulting in muscle cramps, nervousness, and tachycardia. A magnesium deficit must be corrected. Because of possible electrolyte disturbances during therapy with diuretics, plasma concentrations of sodium, potassium, calcium, and magnesium must be checked regularly. Particularly with high doses of diuretics, dehydration, leading to hypovolemia and exsiccosis, thrombosis, and orthostatic dysregulation with risk of heavy falls, may develop. When loop diuretics are used, it has to be kept in mind that nephrotoxicity of other drugs, particularly lithium and iodine-containing contrast media, can be increased. In addition, loop diuretics may enhance ototoxicity of drugs, particularly of aminoglycoside antibiotics and cisplatin.

Another problem in CKD is the development of acidosis. This problem can be corrected during regular dialysis sessions by applying alkalizing drugs such as citrate and bicarbonate. Such measures also counteract the development of renal osteodystrophy.

The kidney produces the hematopoietic growth factor EPO. EPO biosynthesis is stimulated by hypoxia, e.g., caused by anemia or long-term stay in altitudes >2.000 m. In CKD, EPO biosynthesis is reduced, and iron reabsorption is impaired. However, iron is essential for function of heme groups and oxygen binding in hemoglobin. Therefore, in CKD, renal anemia develops. It is treated with recombinant EPO in combination with iron salts (i.v.), e.g., in context with dialysis. The therapeutic goal is to increase hemoglobin concentration to 11.0–12.0 g/dl, i.e., somewhat below physiological levels. A further increase in hemoglobin concentration promotes hypertension, stroke, and thrombosis of dialysis shunts because the patients are also often treated with diuretics. Thus, a subnormal hemoglobin concentration in CKD patients is a compromise between improved physical and mental fitness on the one hand and prevention of thrombosis on the other hand.

For therapy of renal anemia, several recombinant EPO proteins are available. The amino acid sequence of epoetin corresponds to that of the natural EPO. In darbepoetin, five amino acids are exchanged. This results in altered protein glycosylation and delayed elimination from the circulation. Therefore, darbepoetin can be applied less frequently than epoetin, but in principle, both proteins exhibit comparable effects on renal anemia.

CKD leads to immunosuppression, resulting in increased susceptibility to infections. Therefore, CKD patients have to be treated more often with antibiotics (see ▶ Chap. 33), virustatics (see ▶ Chap. 34), and antimycotics (see ▶ Chap. 35). Depending on the specific drug, the risk of ADRs or drug interactions rises. Lastly, the tumor risk is increased in CKD patients.

Many patients with advanced CKD suffer from itch with as yet poorly understood pathogenesis, so that causal therapy is difficult. Key for itch prevention is a good symptomatic therapy of CKD with the above-discussed drug groups. Itch can be alleviated with NIPEs (see ▶ Chap. 25) or inhibitors of mast cell degranulation (see ▶ Chap. 7).

Kidney transplantation is the last resort in CKD treatment if a donor organ is available. To prevent transplant rejection, recipients have to be treated lifelong with immunosuppressants which also possess serious ADRs (see ▶ Chap. 11). In context with renal transplantation, the ADRs of the calcineurin inhibitors ciclosporin and tacrolimus are particularly relevant. Both drugs are nephrotoxic and increase BP. Therefore, in kidney transplantation, ciclosporin and tacrolimus should only be used cautiously and in combination with other immunosuppressants.

12.3 Dose Adjustment in CKD

Many drugs are eliminated to a significant extent via glomerular filtration (and tubular secretion). If creatinine clearance decreases in CKD, drug elimi-

nation is reduced correspondingly. Consequently, the plasma half-life of drugs is increased, and drugs accumulate, causing more serious ADRs. The more relevant renal elimination of a drug, the more relevant is the problem of accumulation and toxicity. For dose adjustment, not only creatine clearance is required but also the extrarenal dose fraction Q_0. This fraction defines the portion of the drug that is eliminated extrarenally. At $Q_0 = 1$, the kidney does not play a role for elimination; at Q_0 values <0.20, renal elimination dominates with a high risk for accumulation and toxicity.

Several dugs with high renal elimination such as gentamicin and vancomycin are predominantly used in the clinic and can be reasonably well controlled. However, many critical drugs such as metformin, lithium, and aciclovir are also applied in outpatients. Controlling these drugs is much more problematic in terms of adherence, and application of additional prescription and OTC drugs may interfere with their elimination. Accordingly, the ADR risk is much greater. To ensure good drug effects without toxicity in CKD patients, it is very important that the necessity and dose of each drug are critically assessed in regular intervals and that deprescription of drugs is considered all the time.

The dose of a problematic drug can be decreased or the dose interval can be prolonged. For particularly critical drugs such as lithium, gentamicin, vancomycin, aciclovir, and MTX, TDM should be implemented for therapy adjustment. If possible, a predominantly renally eliminated drug should be substituted by a predominantly hepatically eliminated one. For example, the β_1AR antagonist atenolol can be substituted by metoprolol (see ▶ Chap. 5), lithium by valproic acid (see ▶ Chaps. 25 and 28), and MTX by leflunomide (see ▶ Chap. 11). In CKD, the use of nephrotoxic aminoglycoside antibiotics in bacterial infections should be avoided if the antibiogram provides other therapeutic options (see ▶ Chap. 33). Certain drugs, e.g., aciclovir and MTX, can crystallize in the kidney and ureter, deteriorating renal function and causing reno-ureteral colics. Therefore, in case of therapy with these drugs, sufficient hydration (i.v.) and urine alkalization are important to avoid drug precipitations. Additional measures are slow and low-dose infusions of the critical drug.

In principle, if CKD patients are treated with necessary but predominantly renally eliminated drugs, additional application of nephrotoxic drugs should be avoided (◘ Table 12.3). COX inhibitors, reducing kidney perfusion via diminished PGE_2 production, can aggravate CKD. However, for pain therapy, several non-nephrotoxic alternatives such a paracetamol and metamizole (see ▶ Chap. 10) are available. Thiazide and loop diuretics reduce lithium clearance and increase its toxicity (see ▶ Chap. 28). Therefore, therapy of patients with bipolar disorder and CKD constitutes a big challenge, particularly if one considers the problematic adherence of these patients. Uricosuric drugs reduce the elimination of MTX and increase its toxicity. Therefore, patients with chronic gout should be preferentially treated with uricostatic drugs if simultaneous therapy with MTX is required (see ▶ Chap. 23).

12.4 ADRs of Drugs on Kidney Function

Drugs can deteriorate kidney functions via different mechanisms (◘ Tables 12.2 and 12.3). COX inhibitors reduce kidney perfusion (see ▶ Chap. 15), aminoglycoside antibiotics and polyene antibiotics are tubulotoxic due to insertion into membranes (see ▶ Chaps. 33 and 35), and cisplatin impairs tubuli via ROS generation (see ▶ Chap. 32). Calcineurin inhibitors increase ROS production and activate both RAAS and the sympathetic nervous system (see ▶ Chap. 11). Classic cytostatic drugs impair tubuli via increased accumulation of purines with subsequent crystallization of urate (see ▶ Chap. 23). In addition, monotherapy with uricosuric drugs may cause urate precipitation via increased renal elimination (see ▶ Chap. 23). Other drugs such as aciclovir (see ▶ Chap. 34) and MTX (see ▶ Chaps. 11 and 32) can precipitate themselves. HMG-CoA-reductase inhibitors and PPARα agonists (see ▶ Chap. 22) may impair kidney function via myoglobin release and subsequent precipitation of heme and tubule impairment via iron release and reduced perfusion. Iodine-containing contrast media can reduce kidney perfusion particularly if they are very viscous and possess a high molecular mass. Lastly, drugs that are regularly used in CKD treatment can

adversely affect kidney function. Among these drugs are ACEIs and AT_1R antagonists and potassium-sparing diuretics that may cause hyperkalemia and thiazide and loop diuretics that can lead to hypovolemia, hypokalemia, and exsiccosis.

In order to reduce ADRs in CKD, the dose of these drugs should be reduced, the dose interval should be increased, and TDM should be performed. In general, combination of nephrotoxic drugs should be avoided. Moreover, it has to be considered whether drugs with reduced nephrotoxicity can be used. In many cases, aminoglycoside antibiotics may be replaced by β-lactam antibiotics (see ▶ Chap. 33).

In case of amphotericin B, nephrotoxicity has been reduced by development of improved galenics, i.e., packaging of the drug into liposomes (see ▶ Chap. 35). In case of cisplatin, platinum agents without nephrotoxicity have been developed or cisplatin is combined with radical scavengers (see ▶ Chap. 32). Toxicity of iodine-containing contrast media has been reduced by diminishing viscosity and osmolarity. For calcineurin inhibitors (see ▶ Chap. 11), sirolimus is an alternative without nephrotoxicity. In case of drugs that directly (aciclovir, MTX) or indirectly (classic cytostatic drugs, uricosuric drugs) result in crystal precipitations in the kidney or ureter, sufficient hydration and alkalization are important. This strategy can also be used in combination with forced diuresis in acute kidney failure due to myoglobin release as a result of treatment with lipid-lowering drugs. During treatment with RAAS inhibitors and diuretics, regular electrolyte and ECG controls are important to early identify clinically relevant hypokalemia or hyperkalemia. The combination of an ACEI + AT_1R antagonist must be avoided in CKD because life-threatening hyperkalemia can develop.

The pharmacokinetics of morphine metabolites are a special case in the context of CKD because here, the problem is not kidney impairment but rather life-threatening ADRs in the CNS. Many terminally ill tumor patients are treated with morphine (see ▶ Chap. 10) and suffer from reduced kidney function. In this situation, the renally eliminated and pharmacologically active metabolite morphine-6-glucuronide can accumulate. This can lead to respiratory depression, sedation, and heavy falls, particularly in case of combination of morphine with other centrally active drugs. In order to avoid ADRs of morphine metabolites in the CNS, the dose of morphine has to be reduced. Alternatively, fentanyl can be prescribed because this drug possesses a high Q_0 value and is predominantly eliminated extrarenally.

12.5 Questions and Answers

Questions

Which assignment of a drug to an effect in CKD is **NOT** correct?

A. Cincalcet – Inhibition of PTH secretion
B. Bicarbonate – Correction of acidosis
C. Calcitriol – Improved calcium absorption in the GI tract
D. Epoetin – Improvement of renal anemia
E. Ciclosporin – BP decrease

Answers

A. Cinacalcet is a calcimimetic drug that allosterically increases the sensitivity of the CaSR for calcium and, thereby, reduces PTH secretion. As a consequence, calcification of organs and blood vessels and bone demineralization are diminished.
B. Blood alkalinization counteracts bone demineralization and supports the effects of calcimimetics and calcitriol.
C. In CKD, calcitriol formation is impaired, and renal calcium elimination is increased. Therefore, calcitriol must be substituted to ensure sufficient calcium absorption in the GI tract.
D. In CKD, EPO biosynthesis is impaired. EPO must be substituted to counteract renal anemia.
E. Via activation of RAAS and the sympathetic nervous system, ciclosporin increases BD. Via ROS formation, ciclosporin is nephrotoxic.

Assignment **E** is not correct.

12.6 Exercises

A 64-year-old patient with stage 4 CKD (GFR, 25 ml/min) is treated with ASA (low dose), atenolol, simvastatin, $NaHCO_3$, epoetin, iron gluconate, cinacalcet, ramipril, furosemide, and pantoprazole. Because of a heavy fall that resulted in distortion of the left wrist, the patient is now additionally treated with ibuprofen (3 × 600 mg/day). After a few days, the patient develops second-grade AV block resulting in anxiety and lightheadedness.

Questions

1. What is the most likely cause of the AV block?
2. What do you do to improve the condition of the patient?

Answers

1. Most CKD patients receive many drugs. Currently, the patient receives ten different drugs. As a result, the risk of drug interactions increases. Most likely, the heart problems are related to the therapy with ibuprofen. It inhibits renal PGE_2 production and renal perfusion. This results in a decrease in GFR and accumulation of renally eliminated drugs. Since atenolol is predominantly eliminated renally (Q_0, 0.06), one can assume that this drug accumulated and caused the AV block.
2. You determine the creatinine clearance in order to assess the current kidney function. You also determine the plasma potassium concentration because a potential hyperkalemia as consequence of impaired kidney function can further aggravate the AV block. You stop the ibuprofen therapy and try to alleviate the pain in the wrist with local measures (immobilization, local application of small amounts of locally acting diclofenac gel). Moreover, based on the creatinine clearance, you adjust the atenolol dose. Alternatively, you switch the patient to another β_1AR antagonist that is not predominantly renally eliminated, e.g., metoprolol (Q_0, 0.95). In case of hyperkalemia, you increase the furosemide dose and/or reduce the ramipril dose.

Further Reading

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Pharmacotherapy

Contents

Drugs for Treatment of Gastrointestinal Diseases

R. Seifert, *Basic Knowledge of Pharmacology*, https://doi.org/10.1007/978-3-030-18899-3_13

In GERD, acidic stomach content flows back into the lower esophagus to cause erosions that can convert into malignancies. In GERD therapy, elimination of causative factors and elevation of pH by PPI are critical. In PUD, eradication of *Helicobacter pylori* with triple therapy (PPI + clarithromycin + amoxicillin or metronidazole) is effective. PAIs, VKAs, DOACs, COX inhibitors, and GCR agonists can promote PUD development. Diarrheas have different causes including antibiotic therapy. Water and electrolyte substitution are the most important therapeutic measures. In severe cases, loperamide can be used. Chronic constipation is a common health problem, particularly in women. Constipation is promoted by abuse of laxatives and a sedentary lifestyle. Lifestyle change is the key measure to abolish constipation. For short-term therapy, the antiresorptive and prosecretory bisacodyl or the osmotic laxative macrogol can be used. MOR agonist-induced constipation can be treated with macrogol or the peripherally acting MOR antagonist methylnaltrexone. UC and CD are chronic inflammatory bowel diseases with as yet incompletely understood pathophysiology. In UC, local application of 5-ASA and GCR agonists is the main therapy. In severe cases, GCR agonists and immunosuppressants are given systemically. CD is treated with GCR agonists, sulfasalazine, antibiotics, immunosuppressants, and TNF inhibitors.

13

Key Points

1. M_xR antagonists, benzodiazepines, CCBs, NO donors, ER agonists, and PDE inhibitors promote GERD.
2. GERD is treated with PPIs and by elimination of causative factors.
3. ADRs of long-term PPI use are anemia, polyneuropathy, osteoporosis, and increased susceptibility to infections.
4. *Helicobacter pylori* is an important factor in PUD pathogenesis and is eradicated by a triple therapy with PPIs and antibiotics.
5. PPIs are given as comedication to patients treated with COX inhibitors or PAIs.
6. Antibiotics, abuse of laxatives, magnesium-containing antacids, prokinetic drugs, and AChEIs can cause diarrhea.
7. Dehydration is treated with a rehydration solution consisting of water, glucose, sodium citrate, NaCl, and KCl.
8. Long-term use of laxatives causes water, sodium, and potassium losses that can aggravate constipation.
9. Diuretics, M_xR antagonists, aluminum-containing antacids, and MOR agonists can cause constipation.
10. The basis of constipation therapy is a diet high in fibers and potassium, sufficient hydration, active lifestyle, and abstinence from laxatives.
11. Laxatives can be used for short periods of time. Bisacodyl, being antiresorptive and prosecretory, and the water-retaining macrogol are prototypical laxatives.
12. MOR agonist-induced constipation is treated with macrogol or peripherally acting MOR antagonists.
13. 5-ASA is the first-line drug for UC; in case of insufficient efficacy, local (or systemic) GCR agonists are added.
14. Acute CD is predominantly treated with GCR agonists; sulfasalazine, metronidazole, and ciprofloxacin are supportive.
15. In severe CD episodes, TNF inhibitors are used.
16. In CD remission therapy, azathioprine, 6-MP, and MTX are effective.

13.1 Pathophysiology and Pharmacotherapy of Gastroesophageal Reflux Disease (GERD)

GERD is caused by reflux of acidic stomach content into the esophagus. Figure 13.1 shows the pathophysiology of GERD and pharmacological interventions. Table 13.1 summarizes selected drugs for treatment of GI diseases. In Western countries, 10–20% of the population suffer from weekly reflux. Causes for GERD are reduced tone of the cardia and impaired propulsive motion. Hiatus hernias, delayed emptying of the stomach, obesity, and pregnancy promote GERD development. GERD lead symptoms are heartburn,

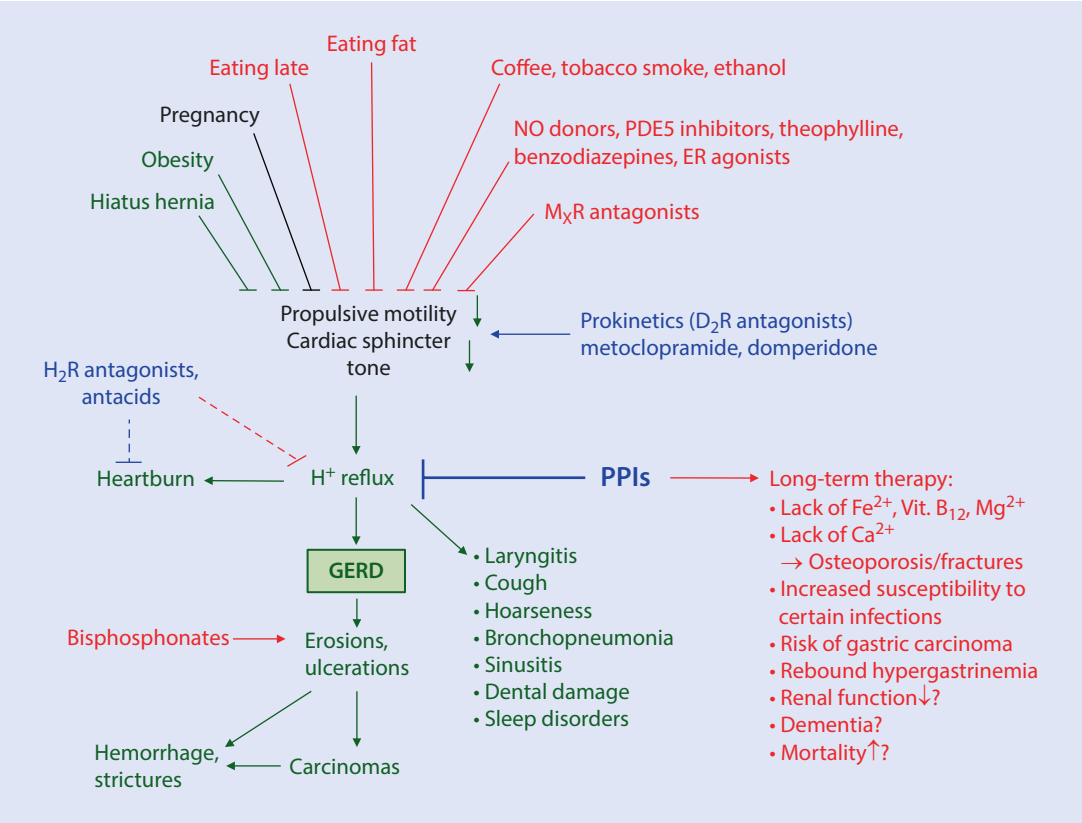

Fig. 13.1 Pathophysiology of GERD: pharmacological interventions. See also Fig. 7.1. The uncritical long-term use of PPIs, prescribed or as self-medication, over years and decades is dangerous! The extent of the problems associated with long-term PPI use is just beginning to emerge. Keep in mind that many drugs can cause GERD!

epigastric pain, regurgitation, and dysphagia. As a consequence, airways can be damaged by acidic stomach content, and asthma, cough, hoarseness, sinusitis, and pneumonia may develop (see ▶ Chap. 14). Teeth damage and sleep disturbances can occur as well. GERD is one of the most common causes for patients visiting a physician. Prior to that, many patients try to control the symptoms themselves by taking OTC antacids or H_2R antagonists (see ▶ Chap. 7). However, OTC therapy with these drug classes is problematic because they have only an insufficient efficacy and they may delay proper diagnosis and therapy.

Fifty percent of the GERD patients develop esophagitis. Via erythema (stage 1), isolated erosions (stage 2), and confluent erosions (stage 3), esophagitis can develop into ulcera, strictures, or Barrett esophagus carcinoma. Because of the long-term risks of GERD, professional therapy is required. The goal is to improve symptoms, to induce healing of lesions, and to avoid complications.

The basis of GERD therapy is the identification and avoidance of factors that favor the disease. First, general measures such as raising the head in the bed by additional pillows, weight reduction, avoidance of greasy food, ethanol, nicotine, coffee, and late meals are implemented. Second, drugs that reduce the cardia tone should be avoided. Among these drugs are NSMRIs (see ▶ Chap. 28), certain mGPCR antagonists (see ▶ Chap. 29), and spasmolytics (see ▶ Chap. 5). In addition, benzodiazepines (see ▶ Chap. 25), CCBs (see ▶ Chap. 15), NO donors and PDE5 inhibitors (see ▶ Chap. 9), nonselective PDE inhibitors such as theophylline (see ▶ Chap. 14), and ER agonists (see ▶ Chap. 24) may reduce cardia tone. For stimulation of esophagus contractility, the prokinetic drug MCP can be administered (see ▶ Chaps. 6 and 8).

Table 13.1 Overview of selected drugs for treatment of GI diseases

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
5-ASA (Mesalazine)	Pleiotropic: inhibition of PG and LT synthesis, leukocyte chemotaxis and T-cell activation, radical scavenger	Anti-inflammatory effect; prevention of carcinoma	Local or systemic administration in ulcerative colitis; in CD, the conjugate of 5-ASA with sulfapyridine (sulfasalazine) is employed	Generally well tolerated. Rarely: GI disturbances, headache, vertigo, and pericarditis	11
Azathioprine	Prodrug of 6-MP; 6-MP is incorporated as wrong base into DNA and RNA	Immunosuppression by inhibition of lymphocyte proliferation	Severe courses of UC and remission of CD	Leukopenia, thrombocytopenia, anemia, and increased risk of infections	11, 32, 33
Bisacodyl	Antiresorptive and prosecretory effect	Enlarges and liquefies intestinal contents by inhibiting the reabsorption of water and NaCl and by stimulating the secretion of water and NaCl. Onset of effect within 1–3 hours (suppositories) or 6–8 hours (p.o. administration)	Short-term treatment of chronic constipation until positive effects of lifestyle changes become apparent	Water and electrolyte losses with chronic use (abuse), stomach, and intestinal spasms	
Budesonide (local)	See prednisolone	See prednisolone	Especially UC	Budesonide is inactivated during the first liver passage (first-pass effect); thus, only few systemic ADRs occur	2, 14
Infliximab	Monoclonal antibody against TNF	Immunosuppressive effect	Especially CD	Infections (e.g., sepsis, TB, hepatitis B, opportunistic pathogens, reactivation of infections), CHF; formation of tumors may be facilitated; allergy	11, 32, 35
Loperamide	Peripheral MOR agonist	Reduction of GI peristalsis/motility	Diarrhea, if the cause cannot be eliminated or if rehydration is not sufficient	In order to avoid constipation, use only until the stool solidifies. No CNS effects. Contraindicated in severe diarrhea, in bloody stools and in immunosuppressed patients (risk that the disease deteriorates)	10, 11

Macrogol	Nontoxic water-binding polyethylene glycol (osmotic laxative)	By enlarging the GI contents (volume expansion) macrogol stretches the intestinal wall and stimulates peristalsis; slow onset of action (1–3 days)	Short-term treatment of chronic constipation until positive effects of lifestyle changes become apparent; proactive treatment of constipation caused by MOR agonists	Water and electrolyte losses with chronic use (abuse), apart from that macrogol is well tolerated, no flatulence	10
Pantoprazole	PPI, irreversible proton pump inhibitor (H^+/K^+-ATPase)	Complete inhibition of proton secretion in parietal cells	GERD (acute therapy, long-term therapy, and on-demand medication), PUD	Headache, sleeping disorders, vertigo, GI disorders, liver damage, allergy, increased risk of infections with certain pathogens, reduced iron and vitamin B_{12} absorption (causing anemia), reduced calcium absorption (causing osteoporosis), and rebound hypergastrinemia after longer periods of treatment	7, 20, 33
Prednisolone (systemic)	Synthetic GCR agonist. Pleiotropic effects: inhibition of synthesis of cytokines, proinflammatory enzymes and adhesive molecules	Anti-inflammatory and immunosuppressive effect	UC, CD	If prednisolone is systemically applied above the Cushing threshold, Cushing's syndrome with edema, hypokalemia, osteoporosis, striae, DM, cataract, glaucoma, CNS symptoms, adrenal insufficiency, and susceptibility to infections may occur	11, 15, 16, 17, 19, 20, 28, 31, 33
WHO oral rehydration solution	The solution contains glucose, sodium citrate, NaCl, and KCl. Glucose and sodium are absorbed via the sodium glucose symporter. As a consequence, water is taken up from the body as a function of the osmotic gradient	Symptomatic correction of water and electrolyte losses	Severe diarrhea due to any cause leading to exsiccosis (for diarrhea in infants and toddlers, an early onset of therapy is life-saving!)	No ADRs in therapeutically indicated volumes (adults up to 3 l per day); hyperhydration should be avoided (risk of edema formation)	1

This table does not contain drugs for pharmacotherapy of vomiting. These drugs are discussed in ► Chaps. 5, 6, 7, and 8. H_2R antagonists are discussed in ► Chap. 7. Antibiotics for eradication of *Helicobacter pylori* are discussed in ► Chap. 33

Bisphosphonates may directly cause gastroesophageal ulcerations (see ▶ Chap. 20).

PPIs are the most effective drugs for GERD therapy. In the intestine, they are released from acid-resistant capsules, absorbed, and transported to parietal cells. From these cells, the drugs are secreted into the lumen and, catalyzed by protons, converted into the pharmacologically active sulfenamides. These metabolites form disulfide bonds with a cysteine residue of the apical H^+/K^+-ATPase, causing irreversible inhibition of the enzyme. As a result, basal and stimulated proton secretion is inhibited. This mechanism of action explains the discrepancy between the short plasma half-life (1–2 hours) and the long duration of action (about 48 hours, see ▶ Chap. 2) of PPIs. The PPI effects are terminated by de novo expression of H^+/K^+-ATPase. PPIs cause long-term pH increase in the stomach.

Numerous PPIs are available; pantoprazole is a prototype. Initially, the PPI is administered for 4–8 weeks in a standard dose (in case of pantoprazole, 40 mg) about 30 minutes before breakfast. Within weeks, PPIs promote symptom relief and healing of lesions. The therapeutic success should be controlled after 4–8 weeks by endoscopy. For long-term therapy, PPIs are given in 50% of the standard dose. Without treatment, the relapse rate of GERD is high. The half PPI standard dose can also be given as on-demand medication. In several countries, PPIs (in low doses and small packages) are available OTC.

Since pantoprazole is a CYP2C19 inhibitor, drug interactions can occur (see ▶ Chap. 2). It is controversially discussed whether PPIs reduce the effectiveness of CYP2C19-activated clopidogrel in CHD therapy (see ▶ Chaps. 2 and 18). PPIs impair vitamin B_{12} and iron absorption. Vitamin B_{12} deficiency can cause pernicious anemia and neurological problems. Absorption of anti-HIV drugs and azole antimycotics (see ▶ Chaps. 34 and 35) can be reduced. PPIs may cause headache, dizziness, sleep disturbances, nausea, vomiting, diarrhea, or constipation. Liver damage and allergies are observed as well. The i.v. application of PPIs should be avoided because reversible hearing, vision, and taste disturbances can occur.

Long-term therapy with PPIs is problematic. Due to the impaired calcium absorption, PPIs can cause osteoporosis and hip fractures (see ▶ Chap. 20). Hypomagnesemia may also occur. Due to the missing acid barrier of the stomach, the risk of infection with *Clostridium difficile*, *Campylobacter jejuni*, and *Salmonella* species is increased. PPI therapy has also been linked to greater incidence of pneumonia, dementia, CKD, and gastric carcinoma. After long-term treatment, PPIs should be gradually discontinued to avoid ulcer-promoting hypergastrinemia and enhanced proton secretion. As consequence of these ADRs, regular control analyses of the hemogram and of the plasma concentrations of vitamin B_{12}, calcium, magnesium, and iron have to be performed during long-term therapy with PPIs to detect deficiencies of these constituents early.

Creatinine controls are necessary to uncover deterioration of kidney function. In manifest vitamin B_{12} deficiency, the vitamin has to be substituted parenterally. The patient should adhere to a diet rich in calcium, magnesium, and iron. If necessary, dietary supplements have to be given. Since the number of patients being treated with PPIs for months, years, or even decades is steadily increasing, the long-term ADRs of PPIs become more and more important. Therefore, a therapy with PPIs should be kept as short as possible, and after long-term therapy, deprescribing should be attempted.

13.2 Pathophysiology and Pharmacotherapy of Peptic Ulcer Disease (PUD)

PUD is characterized by a mucosa defect of a depth of ≥3 mm, reaching beyond the lamina muscularis. PUD is a very common disease with a life incidence of about 10%. In PUD, a dysbalance between aggressive and protective factors occurs. ◘ Figure 13.2 shows PUD pathophysiology and pharmacological interventions. The lead symptom of PUD is epigastric pain 1–3 hours after a meal that is improved by food intake. Secretion of bicarbonate and mucus as well as normal perfusion are protective factors for an intact mucosa. For these functions, PGE_2 is important.

The most important factor for the pathogenesis of PUD is infection with *Helicobacter pylori*. The bacterium is found in >90% of all patients with duodenal ulcer and >70% of all patients with gastriculcer. Pathogen transmission occurs via an oral-fecal pathway. Through pathogenic factors and

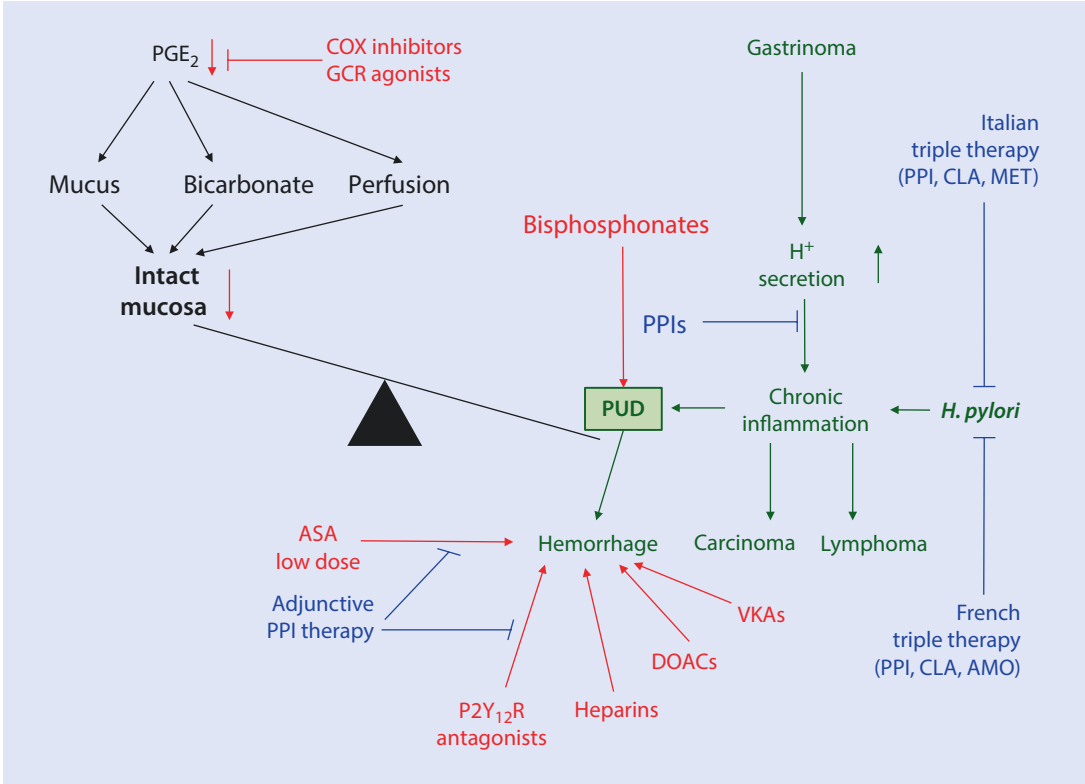

Fig. 13.2 Pathophysiology of PUD: pharmacological interventions. CLA clarithromycin, MET metronidazole, AMO amoxicillin. See also Fig. 7.1. Beware that many drugs can cause or aggravate PUD!

toxins, *Helicobacter pylori* causes a chronic inflammation that can develop into ulcer, carcinoma, or lymphoma. Following biochemical, microscopic, or immunological diagnosis of *Helicobacter pylori*, the therapeutic principle is "treat once successfully." For a period of 7–14 days, a triple therapy is conducted, consisting of the PPI **p**antoprazole, the macrolide antibiotic **c**larithromycin (see ▶ Chap. 33), and the β-lactam antibiotic **a**moxicillin (see ▶ Chap. 33) (**PCA**, French triple therapy). Except for penicillin allergy and diarrhea, this therapy is characterized by good tolerability, efficacy, and high eradication rates. In penicillin allergy, **m**etronidazole (see ▶ Chap. 33) is used instead of amoxicillin. This regimen is designated as Italian triple therapy (**PCM**). There is also an option to conduct a 7-day quadruple therapy (**PCAM**). In case of failure due to bacterial resistance, bismuth salts, tetracyclines, and quinolone antibiotics can be used. However, the tolerability of bismuth salts is only poor.

Treatment with COX inhibitors is the second most important reason for PUD pathogenesis (see ▶ Chaps. 7 and 10). Since COX inhibitors inhibit COX-1-mediated PGE_2 synthesis in the stomach, the protective effects of PGE_2 are diminished. Attempts to reduce gastrotoxicity of COX inhibitors with the PGE_2 analog misoprostol were disappointing since this drug causes GI spasms, diarrhea, headache, and hypotension in up to 40% of the patients. In women, misoprostol can lead to uterus contractions and abortions. The attempt to substitute nonselective COX inhibitors by selective COX-2 inhibitors in pain therapy largely failed because the latter drugs, despite reduced gastrotoxicity, have increased risk for cardiovascular ADRs (see ▶ Chaps. 10 and 18). Therefore, in case of poor tolerability, nonselective COX inhibitors are combined with PPIs in PUD. Alternatively, analgesics without gastrotoxicity such as paracetamol, metamizole, and MOR agonists can be used (see ▶ Chap. 10).

In principle, all anticoagulants can favor hemorrhage in PUD (see ▶ Chap. 18). This risk is particularly high in case of administration of PAIs (ASA low-dose and clopidogrel). Therefore, patients receiving one or both of these drugs are often co-treated with PPIs to reduce the risk of

hemorrhages. However, the long-term ADRs of PPIs have to be considered in case of such a therapy.

Gastrinoma is characterized by increased proton secretion. If the gastrinoma cannot be removed surgically, PPIs are administered.

13.3 Pathophysiology and Pharmacotherapy of Diarrhea

Diarrhea is present if defecation occurs more often than three times daily, if the stool is amorphous and if the stool weight is >250 g. Figure 13.3 provides an overview of the pathophysiology of diarrhea and pharmacological interventions. Most diarrheas are of viral origin (Noro and Rota viruses) for which no specific medication is available. Therefore, therapy focuses on symptomatic measures.

In addition, bacteria can form toxins and induce diarrhea. In developing countries, cholera epidemics occur regularly. Cholera goes along with a persistent activation of the G_s-AC pathway in enterocytes (see ▶ Chap. 1) that leads to massive water and electrolyte secretion. *Clostridium difficile* causes a pseudomembranous enterocolitis that plays an important role in hospitals and is treated with metronidazole (see ▶ Chap. 33). Food intolerance, food allergy, malabsorption, hyperthyroidism (see ▶ Chap. 21), and bile acids (see ▶ Chap. 22) can cause diarrhea as well.

In addition, a number of drugs may lead to diarrhea. The most important cause is therapy with antibiotics that leads to disturbance of the GI microbiome. Diarrhea can also evolve due to abuse of laxatives with the goal to "detoxify" the organism or to reduce weight, e.g., in fashion models or athletes competing in weight classes. Moreover, magnesium-containing antacids, PPIs,

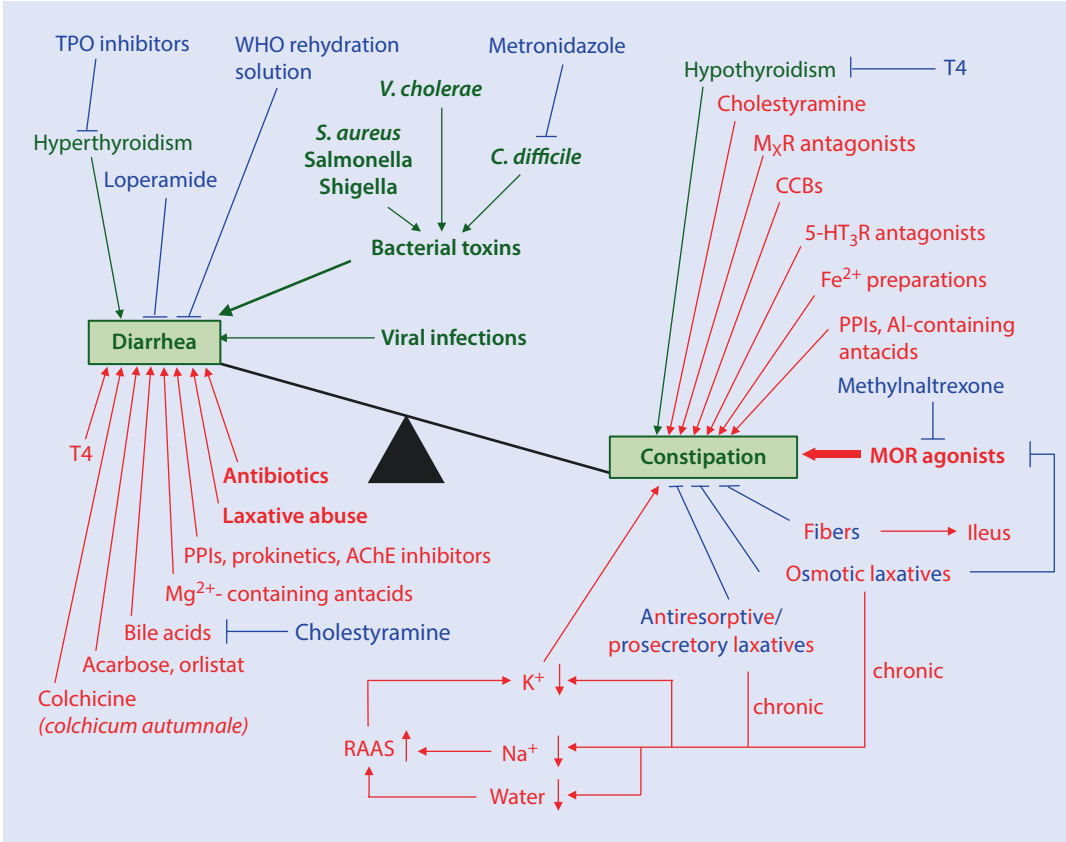

Fig. 13.3 Pathophysiology of diarrhea and constipation: pharmacological interventions. Many drugs can cause either diarrhea or constipation. Abuse of laxatives is a global problem! Laxatives are only for short-term use, with the exception of MOR agonist-induced constipation! Keys to normal bowel movements are an active lifestyle and a diet rich in fibers, NOT the abuse of laxatives. These drugs are often advertised as having a "detox" effect, but this is wrong

prokinetics, acarbose (see ▶ Chap. 19), AChEIs for treatment of myasthenia gravis (see ▶ Chap. 5) and AD (see ▶ Chap. 30), T4 (see ▶ Chap. 21), colchicine (see ▶ Chap. 24), and the classic cytostatic drug irinotecan (see ▶ Chap. 24) can induce diarrhea. Orlistat causes a specific form of diarrhea characterized by steatorrhea. It inhibits intestinal lipases and is used in the treatment of obesity with very moderate success. Non-absorbed lipids are metabolized to short-chain fatty acids in the colon, resulting in flatulence and diarrhea.

Key in the treatment of diarrhea is the recognition and, if possible, elimination of the cause. The indication and dose of diarrhea-inducing drugs must be analyzed critically. The major problem in diarrhea is the loss of water and electrolytes that can lead to exsiccosis and thrombosis (see ▶ Chap. 18). Therefore, regardless of the cause, substitution of water and electrolytes is essential in every diarrhea.

In diarrhea therapy, the intestinal sodium-glucose symporter plays the critical role. Via this transporter, sodium and glucose are coabsorbed; water is following osmotically. In mild cases, consumption of cola beverages and salt sticks may be sufficient. In more serious cases, a WHO rehydration solution has to be administered (up to 3 l per day), containing glucose, citrate, sodium, potassium, and chloride in optimal ratio for reconstitution of balanced water and electrolyte metabolism. The WHO rehydration solution can be prepared easily and inexpensively even for large patient populations. In industrialized countries, expensive ready-to-use drinks are often used for the treatment of diarrhea. If the patient is too weak to drink sufficient fluid quantities, i.v. substitution of water and electrolytes has to be performed.

For therapy of cholera, water and electrolyte substitution is essential, but not the administration of antibiotics such as ciprofloxacin. In case of bloody diarrhea and high fever, severe salmonellosis or shigellosis can be suspected. In these cases, following asservation of samples for microbiological and resistance analysis, i.v. therapy with antibiotics with efficacy against gram-negative bacteria should be initiated. Pseudomembranous enterocolitis is treated with metronidazole or vancomycin.

In severe diarrhea, short-term comedication with loperamide can be performed. Loperamide is a peripherally acting MOR agonist which reduces GI motility. The drug does not penetrate the BBB and does therefore not lead to sedation or respiratory depression. Because the BBB is not yet physiologically complete in infants and toddlers, loperamide must not be given to these patients. Otherwise, severe respiratory depression can occur (see ▶ Chap. 2). In older children, loperamide is dosed according to the body weight to avoid the ADRs. Loperamide must not be administered in case of high fever, bloody stool, or immunosuppression. In these cases, pathogen elimination may be delayed, and the clinical symptoms may deteriorate.

Often, diarrhea is accompanied by severe intestinal spasms which can be symptomatically treated with the M_xR antagonist butylscopolamine (see ▶ Chap. 5). Additional symptoms in diarrhea are nausea and vomiting. For short-term treatment of these symptoms, D_2R antagonists can be applied (see ▶ Chaps. 6 and 8). These drugs act antiemetically and prokinetically. Domperidone only acts in the area postrema and does not penetrate the BBB. It prolongs the QT interval and increases the risk of TdP arrhythmias, particularly if CYP3A4 inhibitors are given concomitantly (see ▶ Chap. 17).

In contrast to domperidone, MCP penetrates the BBB. In case of rapid accumulation of MCP in the CNS, acute dyskinesias can occur, particularly following i.v. application or application of drops with high drug concentration (see ▶ Chap. 8). In order to avoid the ADR, formulations with reduced MCP concentrations were developed, facilitating precise dosing. In children younger than 1 year, MCP is contraindicated; in elder children and adolescents, MCP is dosed according to the body weight. If a diarrhea is accompanied by fever (and headache), paracetamol or metamizole can be used. The latter drug possesses an additional spasmolytic effect (see ▶ Chap. 10). COX inhibitors should not be used in diarrhea because of their gastrotoxicity. If meteorism and flatulence occur during a diarrhea, the surfactant dimethicone can be given. It reduces the surface tension in gas bubbles, thereby causing their collapse and reduction of intraintestinal tension.

13.4 Pathophysiology and Pharmacotherapy of Constipation

For regular defecation, a diet rich in fibers (cereals, fruits, vegetables, legumes), sufficient potassium content (e.g., orange juice, pistachios, apricots, soy, wheat), sufficient fluid ingestion (1.5–2 liter per day,

e.g., mineral water), and sufficient physical activity (e.g., walking, running, bicycling, gymnastics) are important. ◘ Figure 13.2 summarizes causes and pharmacotherapy of constipation. It is present when defecation occurs fewer than three times per week. In Western countries, about 20% of the population suffer from constipation at least temporarily. Women are three times more often affected than men. With increasing age (associated with decreased mobility), constipation becomes more frequent. Dehydration, DM (see ▶ Chap. 19), hypothyroidism (see ▶ Chap. 21), multiple sclerosis, PD, and depression (see ▶ Chap. 28) can cause or aggravate constipation as well. Long transcontinental flights compromise GI motility as do colorectal carcinomas, strictures, rectum prolapse, and hemorrhoids.

Many drugs can cause constipation. Most important in this respect are MOR agonists (see ▶ Chap. 10). In addition, aluminum-containing antacids, 5-HT_3R antagonists, PPIs, iron, CCBs (see ▶ Chap. 15), cholestyramine (see ▶ Chap. 22), M_xR antagonists (see ▶ Chap. 5), NSMRIs (see ▶ Chap. 28), first-generation H_1R antagonists (see ▶ Chap. 7), various mGPCR antagonists (see ▶ Chap. 29), and biperiden, used in PD therapy (see ▶ Chap. 8), can cause constipation.

Potassium deficiency is an important cause for constipation. This deficiency can result from potassium-poor diet and long-term therapy with thiazide and/or loop diuretics without potassium-saving component such as ACEIs or MCRAs (see ▶ Chaps. 15 and 16). Indications and dosing of these drugs have to be critically assessed in case of constipation. One of the most important causes for constipation is the often many year-long use of laxatives (often herbal medicines that are incorrectly assumed to be harmless) without consultation of a physician or pharmacist. In the Internet, such laxatives are often misleadingly advertised as possessing a wellness or detoxification effect. As a result of long-term ingestion of laxatives, water and electrolyte losses develop. Hypokalemia slows GI motility. The water and sodium losses cause compensatory activation of the RAAS with increased aldosterone secretion further amplifying potassium losses. Thus, over the years, a vicious cycle of laxative abuse, hypokalemia, and constipation can develop. Key for breaking the cycle is the discontinuation of the causative drug.

Rigorous adherence to the abovementioned dietary and lifestyle rules is important for normal GI tract motility. If these general measures are not successful, an osmolaxative such as a macrogol can be used. It has a delayed onset of action and is well tolerated. Macrogol is a polyethylene glycol with a molecular mass of 3,300–4,000 Dalton and is neither absorbed nor metabolized by bacteria. Via water retention, the intestinal content liquefies and enlarges. These two factors stimulate GI motility and facilitate defecation. Macrogol is the osmotic laxative of choice. It is very important to communicate to the patient that the "convenient" ingestion of a laxative is no substitute for the "inconvenient" general measures but just a temporary adjunct. Lactulose is another often-used osmotic laxative. It is a disaccharide of galactose and fructose and is converted to short-chain fatty acids by bacteria in the colon. Lactulose is less effective than macrogol and has the disadvantage that bacterial metabolization of the drug in the colon results in nausea, meteorism, and flatulence.

If classic fibers such as wheat bran or flaxseed are used, it is crucial to ensure sufficient intake of fluids because otherwise, extremely hard stool and an ileus can develop. If these measures are not sufficient, antiresorptive and prosecretory laxatives can be used for as short periods of time as possible. Bisacodyl is a prototype of this drug class. It inhibits absorption of water and electrolytes and also stimulates their secretion. Following p.o. administration, bisacodyl acts within 6–8 hours. If applied as suppository, the action lasts for 1–3 hours. Castor oil and saline laxatives such as Glauber's salt have rapid and drastic effects and are not suitable for treatment of chronic constipation. In resistant constipation, the motilin receptor agonist erythromycin (see ▶ Chap. 33), the 5-HT_4R agonist prucalopride (see ▶ Chap. 6), or the guanylyl cyclase C activator linaclotide can be used. Application of these drugs should be restricted to severe cases. Often, constipation is associated with flatulence and meteorism. In these cases, an active lifestyle and wearing of casual clothes are recommended. In addition, surfactants can be given.

Constipation caused by MOR agonists is a special case. They must be administered for severe and most severe pain, e.g., in terminal tumor patients (see ▶ Chap. 10). In these cases, constipation as ADR cannot be avoided. However, one does not wait until constipation develops but treats the patient proactively with water-retaining osmotic laxatives such as macrogol or the peripherally acting MOR antagonist methylnaltrexone.

13.5 Pathophysiology and Pharmacotherapy of Ulcerative Colitis (UC) and Crohn's Disease (CD)

UC and CD belong to the group of inflammatory bowel diseases (IBDs). They share certain similarities in terms of epidemiology, pathophysiology, pathology, clinical symptoms, and complications. As a result, therapeutic principles are also similar (Table 13.2). Since UC and CD mostly affect young patients, effective therapy with as few ADRs as possible is essential to ensure the highest life quality possible.

In both diseases, there is a dysregulation of the immune system. As a result of the autoimmune reaction, lesions in the GI tract develop. In UC, superficial lesions dominate. The most common location of UC is the rectum, from where the inflammation can ascend into the colon. The preference of UC for the rectum enables local therapy with enemas. If the disease further proceeds proximally, systemic

Table 13.2 Overview of pathophysiology, clinical symptoms, and pharmacotherapy of UC and CD

Parameters	UC	CD
Epidemiology	Prevalence is approx. 200 per 100,000 inhabitants in industrialized countries; approx. 3–4 new cases per 100,000 inhabitants; similar frequency in men and women; disease peaks between 20 and 40 years of age	Prevalence is approx. 150 per 100,000 inhabitants in industrialized countries; approx. 7–8 new cases per 100,000 inhabitants; similar frequency in men and women; disease peaks between 15 and 35 years of age and >60 years
Pathophysiology	Pathologic immune reaction to intestinal bacterial flora in genetically predisposed persons	Autoimmune disease of the GI tract triggered by a defect in the innate defense against intestinal bacteria
Pathology	Continuous inflammation of the colorectum, with superficial ulcerations, most frequently located in the rectum and proximal colon	Discontinuous, segmental, and transmural inflammation with barrier disturbance that can affect the whole intestine; most frequently (45%) located in the terminal ileum and proximal colon
Clinical symptoms	Recurring diarrhea, intestinal hemorrhage, colics; the course of the disease is difficult to predict. Often insidious course with acute exacerbations	Abdominal pain, diarrhea (possibly bloody), fever, loss of weight, nausea, vomiting, general weakness, and growth retardation in children
Complications	Incontinence, flatulence, sugar intolerance, psychological problems (fear, depression), multiple extraintestinal manifestations (e.g., arthritis, osteoporosis, uveitis), increased risk of carcinoma, toxic megacolon	Very often fistulas (e.g., enterovaginal, enterovesical, enterocutaneous), abscesses, intestinal hemorrhage, toxic megacolon, increased risk of carcinoma, osteoporosis, gallstones, anemia, extraintestinal manifestations (e.g., arthritis, uveitis, erythema nodosum)
Diet	Exclusion of food that is not tolerated; vitamin and mineral substitution	Exclusion of food that is not tolerated; vitamin and mineral substitution
Pharmacotherapy	Local or systemic administration of 5-ASA as long-term therapy; local or systemic administration of GCR agonists if 5-ASA fails (only short-term therapy, whenever possible); administration of immunosuppressants in severe cases (azathioprine or 6-MP); MTX, ciclosporin, tacrolimus, and TNF inhibitors as second-line therapy	Acute episode: systemic or local application of GCR agonists, sulfasalazine, metronidazole, and ciprofloxacin; TNF inhibitors for treatment of fistulas. Remission: azathioprine, 6-MP, MTX, and TNF inhibitors

therapy becomes necessary. The main manifestation of CD is in the ileum and proximal colon. Based on this localization, in most cases, a systemic therapy is needed. In principle, CD can affect the entire GI tract. In both UC and CD, diarrhea can occur. In UC, often hemorrhage from the rectum and/or colon is observed. In CD, fever, GI spasms, weight loss, nausea, and vomiting are additional symptoms. Both diseases have an unpredictable course with acute exacerbations and chronic phases. Accordingly, there is a need for life-long treatment.

Since the causes of UC and CD are unknown, pharmacotherapy is symptomatic. It is the goal to minimize disease symptoms as far as possible. Therapy depends on the localization and severity of the inflammation and comprises anti-inflammatory and immunosuppressive strategies. An adapted diet, surgical therapy, and psychological counseling support the pharmacotherapy.

5-ASA (mesalazine) is the basic drug for local and systemic treatment of UC, preferably as sustained-release preparation. 5-ASA acts anti-inflammatorily and immunosuppressively; reduces the risk of colorectal carcinoma; inhibits PG and LT synthesis, leukocyte chemotaxis, and T-cell activation; and acts as radical scavenger (see ▶ Chap. 11). For p.o. administration, tablets with acid-resistant coating are applied. These tablets dissolve at a pH >6. Thereby, systemic absorption and ADRs are minimized, and local effects on the colonic and rectal mucosa are maximized. Accordingly, most patients tolerate 5-ASA very well. Unspecific ADRs such as headache and lightheadedness are observed.

If 5-ASA is not sufficient to control UC symptoms, GCR agonists can be administered locally or systemically. GCR agonists act anti-inflammatorily and immunosuppressively. For local therapy, budesonide is suited because after absorption, the drug is inactivated during the first liver passage and, accordingly, has only minimal systemic ADRs (see ▶ Chap. 2). In severe cases, GCR agonists have to be applied p.o. in high doses. In general, symptoms can thereby be well controlled, but there is the risk to develop a Cushing's syndrome, and, because of suppression of hypophyseal ACTH release, adrenal insufficiency may arise after termination of GCR agonist therapy (see ▶ Chap. 11). Therefore, systemic GCR agonists such as prednisolone should be given for as short periods of time as possible and discontinued under slow dose reduction. In order to reduce the risk of adrenal insufficiency, GCR agonists are preferentially administered in the morning because then the sensitivity of the hypophysis towards inhibitory effects of GCR agonists is the lowest.

If additional application of GCR agonists is not sufficient or ADRs are too serious, therapy with azathioprine or 6-mercaptopurine is an option. Azathioprine is a prodrug of 6-MP that is used in high doses as cytostatic and in low doses as immunosuppressive drug (see ▶ Chaps. 11 and 32). Following absorption (bioavailability amounts to 60–90%), the pharmacologically active 6-MP is released from azathioprine. As wrong base, 6-MP is integrated as substitute for guanine into DNA and RNA, preferentially inhibiting T-cell proliferation that is important for sustaining the inflammation in UC. 6-MP has important ADRs on the hematopoietic system, i.e., anemia, thrombocytopenia, and leukopenia. In liver failure, CKD, and pregnancy (teratogenicity), azathioprine is contraindicated. Since 6-MP is metabolized via XO (see ▶ Chap. 23), the effects of azathioprine are enhanced during simultaneous treatment with XO inhibitors. Therefore, the dose of azathioprine or 6-MP must be reduced. 6-MP is also metabolized via thiopurine methyltransferase. In patients with low activity of this enzyme, the effects of azathioprine are increased as well. As an alternative to azathioprine, the active metabolite 6-MP can be applied itself for immunosuppression in UC. As drugs of last resort, ciclosporin, tacrolimus, and TNF inhibitors are used.

While 5-ASA as drug for acute exacerbations and remissions is available in UC, the situation in CD is more complicated. In acute CD, application of GCR agonists is often mandatory. Preferentially, a GCR agonist with high first-pass effect such as budesonide is applied to minimize systemic ADRs. In mild to moderate CD exacerbations, sulfasalazine can be used. This drug is a conjugate of sulfapyridine and 5-ASA. In the colon, sulfasalazine is cleaved in its two components via bacterial enzymes. Most likely, sulfapyridine mediates the therapeutic effects of sulfasalazine, constituting a combination of antibacterial and anti-inflammatory components. Sulfapyridine is a sulfonamide (see ▶ Chap. 32) and can cause anemia and agranulocytosis as a result of folic acid depletion. Moreover, sulfonamides can lead to severe allergic reactions (see ▶ Chap. 3).

Formation of fistulae that can become inflamed or form abscesses constitutes a serious CD compli-

cation. For therapy of infected fistulae, antibiotics such as metronidazole and ciprofloxacin can exert beneficial effects (see ► Chap. 33). In colic pain, M_xR antagonists are used. In CD, severe losses of water and electrolytes can develop which must be compensated. Moreover, a vitamin B_{12} deficiency must be corrected by parenteral application. Therefore, the vitamin B_{12} concentration in the plasma must be monitored, and regular hematological and neurological control exams need to be performed.

Inflammation in CD and fistula formation are sustained by TNF. Therefore, a rational approach in CD therapy is to abrogate the effects of TNF. This goal can be accomplished by administration of monoclonal TNF antibodies. Infliximab was the first approved antibody. In the meantime, additional antibodies such as adalimumab are available. Infliximab can be administered only i.v., whereas adalimumab may be applied more conveniently s.c. TNF antibodies can substantially improve the symptoms of CD patients. Unfortunately, the high therapy costs constitute a significant pharmacoeconomic problem in the therapy with TNF antibodies. Since they act immunosuppressively, the incidence of infections, e.g., sepsis, TB, and infections with opportunistic pathogens or activation of hepatitis B, increases. In addition, TNF antibodies can deteriorate CHF and, particularly during long-term treatment, increase the risk of tumors, e.g., lymphoma. Since infliximab is not a completely humanized antibody (30% mouse, 70% human protein), severe allergic reactions can develop (see ► Chap. 3). This risk is smaller for the completely humanized antibody adalimumab.

The remission therapy of CD is similar to that of UC. Long-term therapy with azathioprine can be performed. Alternatively, 6-MP in lower doses than for tumor chemotherapy can be used. MTX and TNF inhibitors are therapeutic alternatives.

13.6 Questions and Answers

Questions

Which statement on PPIs is *NOT* correct?

A. PPIs inhibit proton secretion in parietal cells.
B. PPIs inhibit proton secretion more effectively than H_2R antagonists.
C. PPIs covalently bind to H^+/K^+-ATPase.
D. PPIs promote survival of *Helicobacter pylori* in the stomach.
E. PPIs are superior to antacids in the therapy of GERD.

Answers

A. Because of the irreversible inhibition of proton secretion, PPIs possess a very long duration of action.
B. PPIs inhibit the most distal step of proton secretion irreversibly. In contrast, H_2R antagonists reversibly inhibit just one out of several signaling pathways that stimulate proton secretion.
C. The covalent binding of PPIs to H^+/K^+-ATPase is responsible for the irreversible inhibition of proton secretion.
D. PPIs are a component of all therapy schedules for eradication of *Helicobacter pylori*.
E. Antacids have only a short-lasting and symptomatic effect. They can mask the development of serious lesions and can delay patients visiting the physician for professional diagnosis and pharmacological therapy. GERD lesions can develop into carcinoma.

Statement **D** is not correct.

13.7 Exercises

A 61-year-old woman visits you in your gastroenterology office because of bowel movement problems. The patient reports that she has defecation only once a week. The patient denies the intake of any prescription or OTC drugs upon your specific questions. Your diagnostic procedures including ultrasound, gastroduodenoscopy, and colonoscopy do not yield any pathological finding. An extensive lab analysis does not yield pathological findings either except for hypokalemia (plasma potassium concentration of 3.1 mmol/l). Upon your specific questions, the patient tells you that for many years, she has been using biologically dynamic detox tea from an internet supplier for purging, but the patient cannot tell you any details. You then ask the patient to bring with her the detox tea during her next visit in your office. It becomes evident that the patient has been consuming tea with leaves from *Senna alexandrina*.

Questions

1. What is your diagnosis and which are your initial therapeutic measures?
2. Which drug classes can aggravate constipation of the patient in case she needs treatment because of another interfering disease?

Answers

1. The patient fulfills the criteria of constipation (fewer than three defecations per week). With your diagnostic procedures, you can exclude a serious organic disease. Hypokalemia is indicative for long-lasting abuse of laxatives. The patient admitted the long-lasting abuse of Senna products purchased on the Internet without consultation of a physician or pharmacist. Senna products contain anthraquinones and promote bowel motion via an antiresorptive action. You explain the patient the connection between the intake of Senna products and the constipation. You also need to explain to the patients the health risks of hypokalemia such as neurological problems and tachycardia. You ask the patient to stop consumption of the Senna product-containing detox tea. Instead, the patient should drink about 2 liter of mineral water per day. Moreover, the patient should eat fiber-containing bread instead of the white bread that she has preferred so far. Moreover, the patient should eat food rich in potassium such as apricots, soy, and tomatoes. Furthermore, the patient who has adhered to a sedentary lifestyle should become more active. Long walks with a dog or daily gymnastics are a good starting point. The patient has a free choice of activities that she enjoys. After some weeks, you should check whether these lifestyle changes have improved the constipation.
2. Thiazide and loop diuretics deteriorate constipation due to potassium losses. MOR agonists cause spastic constipation. Iron-containing drugs and aluminum-containing antacids cause constipation as well. Several drug classes including spasmolytics, NSMRIs, numerous mGPCR antagonists, and antimuscarinic anti-PD drugs cause constipation via M_xR antagonism.

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Drugs for Treatment of Respiratory Tract Diseases

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Asthma is characterized by inflammation of the bronchi and hyperreactivity of the respiratory tract smooth muscle cells. Both factors lead to increased respiratory tract resistance. The therapeutic goal is to normalize these pathophysiological changes. In intermittent asthma, SABAs are administered on demand. In mild asthma, IGCR agonists are added as long-term medication. In moderate asthma, IGCR agonists + LABAs are used. In severe asthma, LTRAs can be applied; status asthmaticus may be treated with theophylline. In very severe asthma, systemic GCR agonists, IgE inhibitors, and IL-5 inhibitors are additional therapy options. COPD is mostly due to chronic tobacco consumption, resulting in irreversible respiratory tract obstruction, emphysema, and inflammation. Initially, LABAs and/or LAMAs are administered. If these drug classes are not sufficient, the nonselective PDE inhibitor theophylline or selective PDE4 inhibitors are added. IGCR agonists should only be given cautiously because these drugs increase the risk of pneumonia. CF is an autosomal-recessive disease in which genetically heterogeneous CFTR defects result in the formation of viscous secretions, ultimately leading to chronic pneumonia with problem pathogens and dysfunction of multiple organs. CFTR potentiators and CFTR correctors constitute the first specific drugs to normalize CFTR function.

14

Key Points

1. SABAs can be used for treatment of intermittent asthma.
2. LABAs + IGCR agonists are applied for long-term asthma therapy.
3. LAMAs are used in COPD therapy either alone or in combination with LABA.
4. IGCR agonists constitute the basic medication for most asthma forms.
5. IGCR agonists are effective in asthma and have no systemic ADRs if applied correctly.
6. In COPD, IGCR agonists can increase the risk of pneumonia.
7. The most important ADRs of IGCR agonists are oral candidiasis and larynx dysfunction.
8. LTRAs and cromoglicic acid are additional treatment options in asthma.
9. In very severe asthma, IgE and IL-5 inhibitors can be used.
10. Theophylline is a nonselective PDE inhibitor and adenosine receptor antagonist.
11. Theophylline has serious ADRs and is therefore only used in severe asthma and COPD.
12. Roflumilast is a selective PDE4 inhibitor with better tolerability than theophylline.
13. Roflumilast is used in severe COPD in combination with LABA and LAMA.
14. Ivacaftor is a CFTR potentiator and increases chloride conductance of the G551D mutant.
15. Lumacaftor is a CFTR corrector and enhances CFTR translocation to the plasma membrane in the common F508 deletion.

14.1 Pathophysiology of Asthma

About 350 million people worldwide suffer from asthma. Its prevalence varies between 1% and 8% in various countries; males are more often affected than females. ◘ Figure 14.1 shows asthma pathophysiology and pharmacological interventions. ◘ Table 14.1 summarizes selected drugs used in asthma therapy. Allergic asthma is a type I allergic reaction (see ▶ Chap. 3). In this asthma form, the immune system is dysregulated, resulting in a predominant T_H2 reaction. Following exposure to allergens, e.g., pollen, acari, or food constituents, enhanced IgE production takes place, ultimately leading to mast cell degranulation (see ▶ Chap. 7). Within the T_H2 response, the production of IL-5 is increased, recruiting and activating eosinophils. These cells release numerous mediators, cytotoxic enzymes, and ROS, causing inflammation of the bronchial mucosa with reduced mucociliary clearance, mucosal thickening, and hypersecretion. As a consequence, hyperreactivity of the respiratory tract smooth muscle cells develops, manifesting itself as hypertrophy and increased contractility of the smooth muscle cells. Ultimately, the respiratory tract resistance is increased, and the lungs become overinflated. Asthma predominantly affects the larger airways.

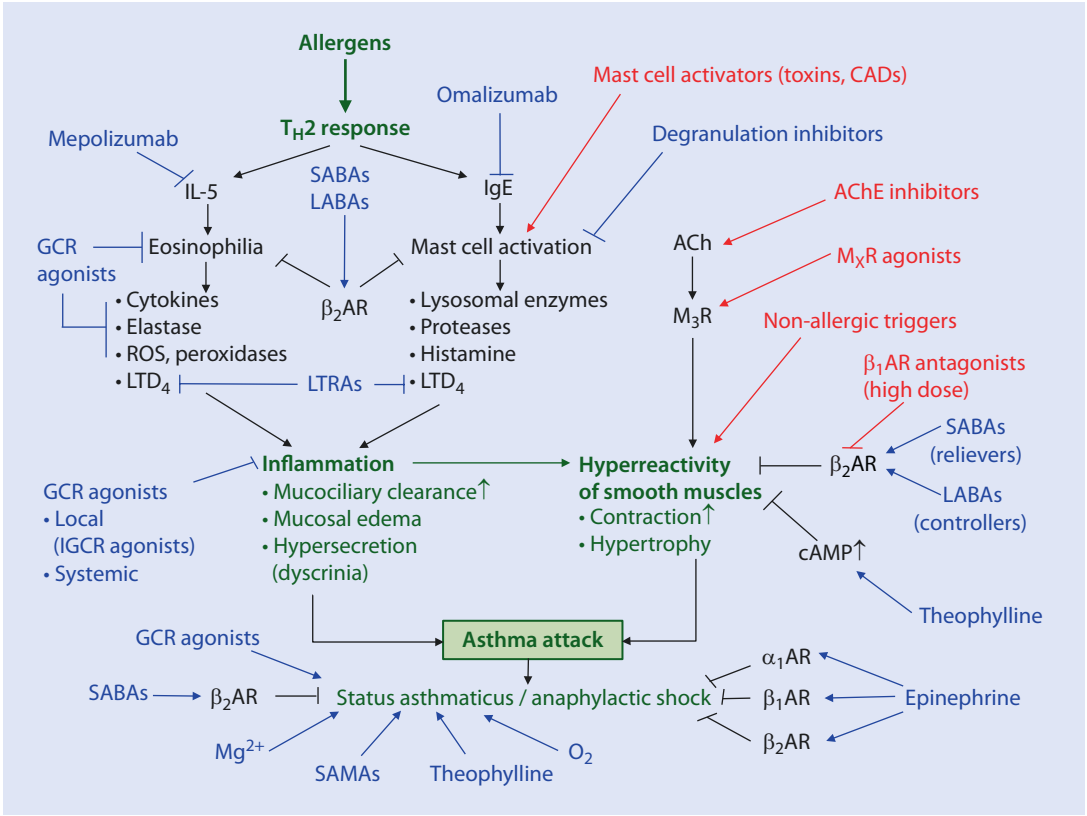


Fig. 14.1 Pathophysiology of asthma: pharmacological interventions. SABAs alone are not suitable for long-term treatment! Early use of IGCR agonists is the key for successful long-term control of asthma. IGCR agonists have no systemic effects on GCRs (NO Cushing's syndrome). Only systemically applied GCR agonists cause Cushing's syndrome

In intermittent asthma bronchoconstriction predominates, while persistent asthma is mainly characterized by bronchial inflammation with hypersecretion and hyperreactivity.

In non-allergic asthma, GERD (see ▶ Chap. 13), cold, toxic gases (e.g., ozone, nitrogen oxides, fine dust), tobacco constituents, physical activity, or direct mast cell activators (e.g., insect venoms or CADs such as morphine) (see ▶ Chaps. 7 and 10) lead to inflammation and hyperreactivity. AChEIs (myasthenia gravis), COX inhibitors (see ▶ Chap. 10), and β_1AR antagonists in high doses (see ▶ Chaps. 15, 16, 17, and 31) can promote asthma as well.

The pathophysiological changes in asthma result in dry cough and intermittent dyspnea that predominantly manifests itself during expiration. In the sputum, some patients show eosinophilia. Severe cases may come along with anxiety and agitation. In principle, the pathophysiological changes in asthma are reversible. Spirometry is important for diagnostics. The vital capacity, the one-second capacity (FEV_1), and the peak expiratory flow (PEF) are determined. PEF determinations can be readily used for self-control of disease activity by the patient. In asthma, FEV_1 and PEF are reduced. Asthma is divided into various degrees of severity. In intermittent asthma (stage 1), there is not more than one attack per week; FEV_1 and PEF are reduced by up to 20%. In mild persistent asthma (stage 2), patients have fewer than one attack per day without substantial further deterioration of FEV_1 and PEF. In moderate persistent asthma (stage 3), daily attacks occur; FEV_1 and PEF range between 60% and 80% of the norm. In severe persistent asthma, attacks occur frequently; FEV_1 and PEF are <60% of the norm. In status asthmaticus, a life-threatening narrowing of the airways develops, jeopardizing oxygen supply of the organism.

The aim of asthma therapy is to avoid acute attacks, to normalize lung function, to ensure

Table 14.1 Overview of selected drugs for treatment of respiratory tract diseases

Drug	Mechanism of action	Important effect	Important indications	Important ADRs	Further contexts in Chaps.
Budesonide	IGCR agonist, controller	Induces altered gene expression and, hence, pleiotropic anti-inflammatory effects in the bronchi, enhanced lung function, and increased β_2AR expression; systemic ADRs are rare due to first-pass metabolism	First-line therapy of asthma; use in COPD patients only in late stages because of bronchopneumonia risk	Dysphonia and hoarseness (10–30%), larynx myopathy, vocal cord papilloma, oropharyngeal candidiasis (5–15%), cough, throat irritation. Increased risk of bronchopneumonia in COPD patients	11, 13
Cromoglicic acid	Plasma membrane stabilization	Inhibits secretion of HA and other mediators from mast cells (inhibition of degranulation)	Prevention of type I allergies (conjunctivitis, rhinitis, and asthma)	Local tissue irritations, symptoms that may be similar to those of an type I allergy; prophylaxis requires high adherence	7
Formoterol	LABA, β_2AR agonist, controller	Relaxation of respiratory tract smooth muscles, prevention of bronchospasm and respiratory tract smooth muscle hypertrophy, release of inflammatory mediators ↓, mucociliary clearance ↑, hypersecretion↓; slow onset of action and long duration of action	Second-line therapy of asthma when patients do not respond to IGCR agonists and SABAs anymore; first-line therapy of COPD, often in combination with LAMAs	Tremor, headache, restlessness, vertigo, tachycardia, hypokalemia, hyperglycemia; especially with high doses and if applied as monotherapy; in the latter case, formoterol becomes less effective and asthma exacerbations (receptor desensitization) may occur	1, 5
Ipratropium	SAMA, M_3R antagonist, reliever	Short-acting bronchodilator	Status asthmaticus	Dry mouth if locally applied; antimuscarinic syndrome if systemically applied	2, 4, 5
Ivacaftor	CFTR potentiator	Improves CFTR chloride transport, especially in patients with CFTR-G551D mutation (gateway mutation)	Administered in CF patients with G551D mutation; applied in combination with lumacaftor in CF patients with F508 deletion	GI disturbances (abdominal pain, diarrhea), weariness, allergy, headache, nasopharyngitis, sinusitis, oropharyngeal irritation. Risk of drug interactions due to CYP3A4 metabolism	2

Lumacaftor	CFTR corrector	Acts as chaperone and improves the transport of truncated CFTR from the endoplasmic reticulum to the plasma membrane	Applied in combination with ivacaftor in CF patients with F508 deletion	Liver function disorders, risk of drug interactions due to CYP3A4 metabolism	2
Mepolizumab	Humanized monoclonal antibody against IL-5	By binding to IL-5, mepolizumab blocks the biological effects of IL-5, especially activation of eosinophilic granulocytes	Severe persistent eosinophilic asthma	Reactions at the injection site, headache, infections of the urinary and bronchial tract	11
Montelukast	LTRA, $CysLT_1R$ antagonist	Long-term inhibition of vasodilation, inflammation and bronchoconstriction caused by LTD_4	Adjunctive therapy to IGCR agonists in asthma with the aim of IGCR agonist reduction; applied as an alternative to IGCR agonists; long-term therapy only, no acute effects	GI disturbances, headache, allergies, Churg-Strauss syndrome (vasculitis, eosinophilia)	3, 7
Omalizumab	Humanized monoclonal antibody against IgE	By binding to IgE, omalizumab prevents the activation of the IgE receptor on mast cells thereby reducing mediator release	Severe persistent asthma, severe urticaria	Reactions at the injection site, fever, sinusitis, nasopharyngitis	7
Roflumilast	PDE4 inhibitor	Inhibits infiltration of neutrophilic granulocytes, release of inflammatory mediators ↓, bronchodilation, respiratory tract smooth muscle hypertrophy ↓	Severe COPD, often in combination with LAMAs + LABAs + IGCR agonists	GI disturbances (nausea, diarrhea, vomiting, loss of appetite, loss of weight), sleep disorders, restlessness, tremor	1, 11
Salbutamol	SABA, partial β_2AR agonist, reliever	See formoterol; but faster onset of action and shorter duration of action	Acute asthma attack	Desensitization (loss of effect) after long-term application, β_1AR activation at higher doses	1, 5
Theophylline	PDE inhibitor and adenosine receptor antagonist	Release of inflammatory mediators ↓, mucociliary clearance ↑, bronchodilation, respiratory tract smooth muscle hypertrophy ↓	Refractory cases of asthma and COPD, status asthmaticus	Due to the low therapeutic index and CYP1A2-induced drug interactions, TDM is required; tachycardia, arrhythmias, GERD, diarrhea, nausea, vomiting, agitation, restlessness, tremor, seizures	1, 2, 13, 17, 25
Tiotropium	LAMA, M_3R antagonist, controller	Bronchodilation; slow onset of action and long duration of action	COPD	Few, except dry mouth, if locally applied	2, 5

high life quality, and to ascertain normal mental, physical, and social development of children. The most important therapeutic measure is avoidance of the asthma cause, if possible. In allergic asthma, via hyposensitization, i.e., reconstitution of the normal balance between T_H1 and T_H2, reactions can be attempted. However, this therapy is long-lasting and cumbersome and requires high adherence, and the outcome is not predictable. In addition, patients must be continuously monitored during allergen exposition to avoid development of an anaphylactic shock that has to be treated immediately (see ▶ Chap. 3). Therefore, this therapy works only for selected patients.

14.2 Pharmacotherapy of Asthma

Drugs are grouped into relievers that cause rapid and short-term symptom reduction and controllers that induce long-term reduction of inflammation and hyperreactivity of respiratory tract smooth muscle cells. In an acute asthma attack, predominantly SABAs are used as reliever. Salbutamol (albuterol) is the prototype of this drug class (see ▶ Chap. 5). Other representatives are fenoterol and terbutaline. In general, SABAs can be used in all asthma stages as on-demand medication if FEV_1 and/or PEF values deteriorate. In status asthmaticus, theophylline, magnesium, and ipratropium (SAMAs) are additionally applied as relievers. However, ipratropium has a slower onset of action (about 30 minutes) upon inhalation than SABAs (about 2–3 minutes). In status asthmaticus, it is often necessary to administer drugs i.v. because the massive respiratory tract constriction impedes drug absorption in case of inhalation.

IGCR agonists, p.o. administered and systemically acting GCR agonists, LABAs, LTRAs, mast cell stabilizers (see ▶ Chap. 7), and sustained-release theophylline are used as controllers. The H_1R plays a major role in the pathogenesis of urticaria, allergic rhinitis, and conjunctivitis, but not in asthma. Therefore, H_1R antagonists are not effective antiasthmatic drugs (see ▶ Chap. 7).

If the on-demand medication with SABAs (stage 1) is insufficient, IGCR agonists are added as controller in stage 2. Alternatively, LTRAs or cromoglicic acid can be given. In stage 3 asthma, the IGCR agonist dose may be increased, and LABAs may be integrated. Theophylline can be added as well. In stage 4 asthma, IGCR agonists are applied in high doses and combined with LABAs and theophylline. GCR agonists administered p.o. (e.g., prednisolone; see ▶ Chap. 11) are an option in resistant cases. If symptoms are not yet controlled by all these measures, IgE inhibitors (omalizumab) and, in cases of strong eosinophilia, IL-5 inhibitors (mepolizumab) can be added.

In asthma, SABAs, LABAs, SAMAs, and IGCR agonists are routinely administered with inhalers containing the drug as powder. In order that the drugs properly reach their site of action, the patient has to be educated how to coordinate drug inhalation with respiration. Specifically, the drug must be delivered during inhalation, and then the patient needs to stop breathing for few seconds. If coordination of drug delivery with respiration is impossible, e.g., in children, inhalation devices are an alternative. With these apparatuses, the drug is delivered in nebulized form via a mask.

In acute asthma attacks and in status asthmaticus, SABAs possess good efficacy. Their effect is elicited via inhibition of mediator release from mast cells, increased mucociliary clearance, reduction of hypersecretion, and relaxation of smooth muscle cells. SABA effects arise within few seconds. For this reason, they are also referred to as rapid-acting β_2AR agonists (RABAs). The duration of action amounts 4–6 hours. As on-demand medication, SABAs are better suited than SAMAs which exhibit their effects only after about 30 minutes. The effects of LABAs, formoterol and salmeterol being prototypes, start after 10–20 minutes and last for 12–24 hours. The reason for the different durations of action of SABAs and LABAs is that the latter possess a lipophilic substituent, resulting in a much longer residence time at the β_2AR. In addition to the mechanisms discussed for SABAs, a reduction of respiratory tract smooth muscle hypertrophy plays a role in the therapeutic effects of LABAs.

Neither SABAs nor LABAs are suitable for monotherapy of asthma of stages 2–4. In fact, mortality may increase with monotherapy. All asthma patients have to be informed about the risks of excessive use of SABAs and LABAs, particularly when applied as the sole drug class:

1. Compared to IGCR agonists, the anti-inflammatory effects of SABAs and LABAs are small.
2. During long-term therapy, β_2AR desensitization and loss of efficacy can result.

3. As a result of the reduced efficacy, often patients increase the dose of SABAs and LABAs without consulting the pharmacist or physician.
4. As a consequence of the increased drug dose, enhanced β_1AR activation occurs, which can be cardiotoxic, cause deterioration of CHF and hypertension, and induce arrhythmias (see ▶ Chaps. 15, 16, and 17). Agitation, tremor, restlessness, heart palpitations, and tachycardia are warning symptoms of excessive β_1AR activation. In addition, patients may become aware of a bitter taste resulting from oral drug deposition.

In order to keep these problems under control, SABAs and LABAs should be co-administered with IGCR agonists in stages 2–4. Fixed combinations of IGCR agonists + LABAs have certain advantages:

1. The combination of two drugs in one inhaler renders application easier and more convenient for the patient. This will increase adherence.
2. IGCR agonists and LABAs fit well to each other in terms of their duration of action.
3. IGCR agonists and LABAs complement each other in terms of their anti-inflammatory effects.
4. IGCR agonists enhance β_2AR expression, thereby counteracting receptor desensitization and loss of efficacy of LABAs.

IGCR agonists constitute a particularly important drug class in asthma therapy. Because of their mechanism of action (regulation of gene expression via NRs; see ▶ Chaps. 1 and 11), it takes several days until IGCR agonists exhibit their full effect. In order to ensure good adherence, the patient has to be educated about the fact that IGCR agonists are well suited for long-term therapy because they, in contrast to LABAs, do not show receptor desensitization and loss of efficacy. IGCR agonists reduce the allergic inflammation, the disease progression, and the severity of asthma. Therefore, they should be administered early on in asthma, beginning from stage 2. In stages 3 and 4, the IGCR agonist dose is doubled stage by stage. Should this procedure not be sufficient, GCR agonists can be given p.o. In anaphylactic shock, GCR agonists are administered i.v. at high doses (see ▶ Chaps. 3 and 11).

In asthma, IGCR agonists and p.o. applied GCR agonists inhibit infiltration of T cells and eosinophils, expression of proinflammatory enzymes, hyperreactivity and secretion, and enhance β_2AR expression (see ▶ Chap. 11). SABAs and LABAs inhibit the release of inflammatory mediators and proinflammatory enzymes from eosinophils as well as mast cells and relax the smooth muscle cells of the airways (see ▶ Chaps. 1 and 5).

The most important ADRs of IGCR agonists are of local nature. Oral candidiasis can develop (see ▶ Chap. 35), pharynx irritations may lead to dry cough, and larynx irritation can cause hoarseness and dysphonia. These ADRs can be avoided if the patient uses the correct drug application technique that prevents deposition of the drug in these anatomical regions. Oral candidiasis can be prevented by rinsing the mouth following IGCR agonist inhalation.

The fact that IGCR agonists exhibit few ADRs even at high doses is related to their pharmacokinetic properties. Only about 30% of the inhaled IGCR agonists arrive in the lung; the remaining 70% reach the GI tract. However, due to the pronounced first-pass effect of IGCR agonists, no systemic ADRs result. The inhaled IGCR agonist reaching the airways is either metabolized in the lung or during the first liver passage following pulmonary absorption. For budesonide, the first-pass effect amounts to 90% and for fluticasone even to 99%.

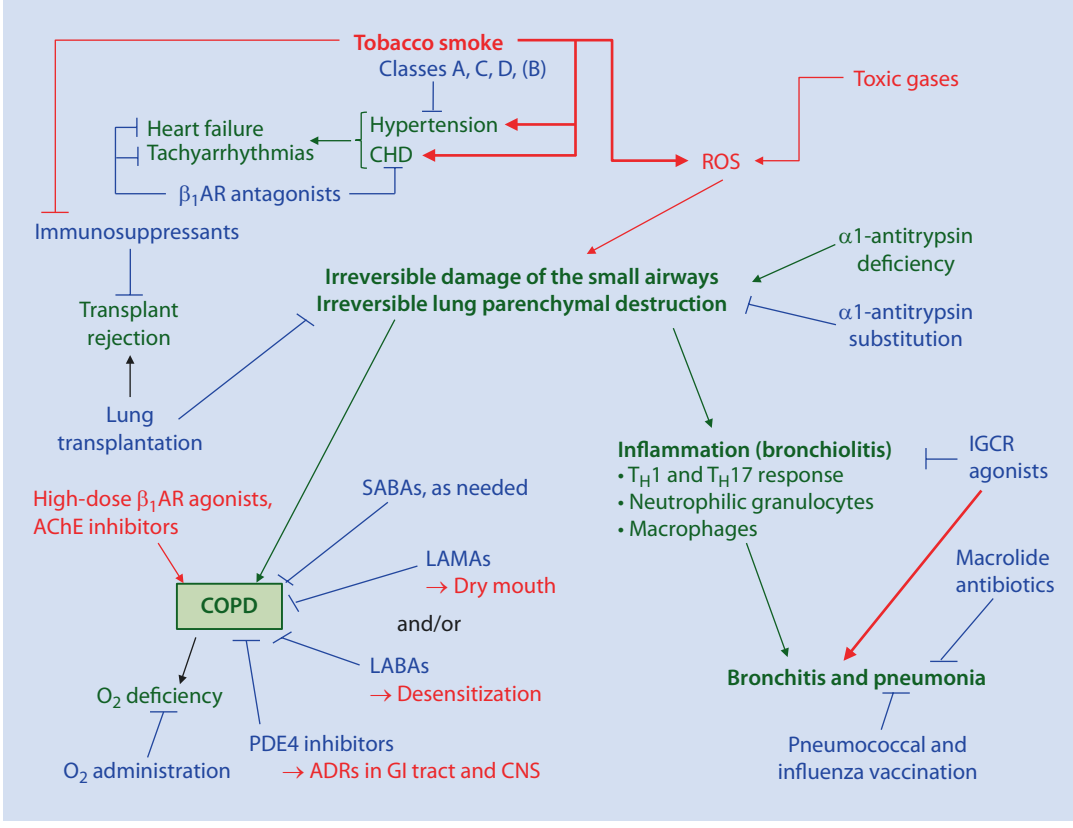
Theophylline inhibits PDEs nonselectively, thereby reducing cAMP degradation. Via this mechanism the drug acts anti-inflammatorily and bronchodilatorily. In addition, antagonism at adenosine receptors contributes to the therapeutic effects of theophylline in asthma. Because both PDEs and adenosine are ubiquitously expressed in the organism, it is not surprising that theophylline possesses serious ADRs in many organs. The drug can cause diarrhea, GERD, arrhythmias, agitation, and epileptic seizures that must be treated symptomatically (see ▶ Chaps. 13, 17, and 25). In status asthmaticus, theophylline can be administered i.v. as reliever. During long-term therapy of asthma, it is administered as controller using a sustained-release formulation.

Since theophylline has only a small therapeutic index, TDM must be performed. The plasma

concentration should be adjusted to 10–20 µg/ml. Therapy with theophylline is further complicated since the drug is inactivated via CYP1A2 (see ▶ Chap. 2). Due to CYP1A2 induction (e.g., in tobacco smokers), the efficacy of theophylline is reduced. In contrast, its effects are enhanced during concomitant application of CYP inhibitors such as macrolide antibiotics (see ▶ Chap. 33). Because of the numerous ADRs and drug interactions, theophylline is only used if the patient is not sufficiently controlled with IGCR agonists, LABAs, LTRAs, and mast cell stabilizers. If a patient suffers from an acute asthma attack because of excessive use of SABAs and subsequent β_2AR desensitization, bronchodilation can be achieved with theophylline because it increases cAMP via a mechanism distally to the β_2AR and resistant to desensitization (see ▶ Chap. 1). Therefore, despite all problems, theophylline is a valuable drug of last resort in asthma therapy.

14.3 Pathophysiology of Chronic-Obstructive Lung Disease (COPD)

Worldwide, more than 175 million people suffer from COPD with more than three million deaths annually. The prevalence of COPD will further rise because of increased tobacco smoking in developing countries and a globally aging population. Men and women are about equally affected by COPD. ◘ Figure 14.2 shows the pathophysiology of COPD and pharmacological interventions. ◘ Table 14.1 summarizes selected drugs for COPD treatment. The main cause for COPD is chronic tobacco consumption. Toxic gases (e.g., industrial smog, nitrogen oxides) can contribute to COPD pathogenesis as well. Tobacco smoking leads to increased ROS production, irreversibly destroying the lung and causing chronic respiratory tract obstruction and inflammation. Since



◘ **Fig. 14.2** Pathophysiology of COPD: pharmacological interventions. The classification of antihypertensive drugs in classes A, B, C, and D is discussed in ▶ Chap. 15. The combination of LAMAs + LABAs is crucial! Be cautious with the use of IGCR agonists

COPD is the result of long-term tissue damage, the disease manifests itself mostly beyond the age of 50 years.

In COPD, bronchoconstriction is mainly mediated by the M_3R (see ▶ Chap. 5) which is of therapeutic relevance (see ▶ Sect. 14.4). The small airways are mostly affected. Bronchiolitis and destruction of alveoli develop. The elasticity of the lung tissue is reduced, promoting development of emphysema. Inflammation in COPD is T_H1 and T_H17-dominated, entailing increased release of IFN-γ and IL-17. The sputum of COPD patients is rich in neutrophils and macrophages. α_1-Antitrypsin deficiency is a rare cause of COPD that can be well treated with α_1-antitrypsin substitution. By this means, lung autodigestion via proteases is inhibited.

Shortness of breath, cough, and sputum are COPD lead symptoms. In the long run, dyspnea can result in immobilization and right-sided heart failure. COPD is deteriorated by acute exacerbations due to cardiovascular diseases and viral or bacterial infections presenting as bronchitis or pneumonia. Like in asthma, predominantly expiration is affected, but in COPD, irreversible structural changes in the lung develop and FEV_1 reduction prevails.

COPD is divided into four stages. In mild COPD (stage 1), FEV_1 is ≥80% with only minor clinical symptoms. In moderate COPD (stage 2), FEV_1 ranges between 50% and 80%, and clinical symptoms become more prominent. In severe COPD (stage 3), FEV_1 ranges between 30% and 50% with pronounced clinical symptoms. In very severe COPD (stage 4), FEV_1 is reduced even further, and symptoms of respiratory insufficiency occur.

The goal of COPD therapy is to reduce symptoms and exacerbations and to improve or preserve physical capability and life quality. Except for α_1-antitrypsin deficiency, COPD progression cannot be prevented by the currently available drugs. Key to prevent COPD progression is tobacco abstinence. Vaccination against influenza and pneumococci can mitigate COPD progression as well.

14.4 Pharmacotherapy of COPD

Pharmacotherapy of COPD is performed according to the results of spirometry and the clinical symptoms. In stage 1, SABAs are used on demand. In stage 2, LAMAs are additionally given as long-term therapy (prototype tiotropium). The drug is applied via inhalation (see ▶ Chap. 5). Tiotropium antagonizes the M_3R with high potency and has to be administered only once daily because the half-life of the drug amounts to about 35 hours. The effect of tiotropium begins only after about 30 minutes following inhalation. Since for GPCR antagonists no receptor desensitization takes place (see ▶ Chap. 1), LAMAs can be readily used for long-term basic COPD therapy. M_3R antagonists cause bronchodilation. The most important ADR of tiotropium is xerostomia as a result of oral deposition of the drug and oral M_xR antagonism (see ▶ Chap. 5). This ADR can be avoided by optimizing the inhalation technique and by rinsing the mouth after drug inhalation. Systemic ADRs (see ▶ Chap. 5) are not prominent since tiotropium is only poorly absorbed systemically because of its positive charge (see ▶ Chap. 2).

Alternatively or in addition to LAMAs, LABAs are administered in COPD. However, LABAs may cause receptor desensitization (see ▶ Chaps. 1 and 5 and ▶ Sect. 14.2). In contrast to asthma, IGCR agonists should only be administered cautiously and in late stages of COPD because these drugs increase the risk of bronchopneumonia. Bacterial lung infections in COPD patients are often treated with macrolide antibiotics (see ▶ Chap. 35). In COPD, IGCR agonists do not improve FEV_1. Due to the limitations of IGCR agonist application in COPD, it is also more difficult to properly apply LABAs because the increased β_2AR expression induced by IGCR agonists cannot be exploited (see ▶ Sect. 14.2).

In principle, PDE inhibitors are well suited for COPD therapy because they do not lead to receptor desensitization (see ▶ Chap. 1). However, the cardiac ADRs of theophylline (tachycardia, arrhythmias) are unfavorable in COPD since the patients often suffer from concomitant right-sided heart failure and other diseases such as CHD and hypertension due to tobacco consumption. Theophylline also inhibits PDE3 expressed in cardiac myocytes. In order to avoid cardiotoxicity of nonselective PDE inhibitors (see ▶ Chap. 16), selective PDE4 inhibitors were developed. Roflumilast is a prototype. PDE4 is highly expressed in small airways and inflammatory cells. PDE4 inhibition results in anti-inflammatory and bronchodilatory effects without substantial cardiac ADRs. Therefore, in several countries roflumilast now largely

substitutes theophylline in COPD patients who cannot be sufficiently treated with a LAMA + LABA + IGCR agonist. However, PDE4 is also expressed in the GI tract and CNS, causing ADRs in these organ systems. In addition, therapy with roflumilast is considerably more expensive than that with theophylline.

In end-stage COPD patients, oxygen is additionally applied to drugs in order to compensate the oxygen deficiency at least partially. Once all these measures are not effective anymore, lung transplantation is the last resort. However, it can only be offered to few selected patients because there is a paucity of donor organs and because the cardiovascular condition of COPD patients is often poor. Another obstacle in COPD therapy is that many patients do not quit smoking. Following a lung transplantation, the patients have to be treated with immunosuppressants that can further deteriorate the cardiovascular situation (e.g., GCR agonists and ciclosporin; see ▶ Chap. 11). Another problem is that nicotine induces several CYPs in the liver and, thereby, accelerates inactivation of certain immunosuppressants. Therefore, the risk of transplant rejection is increased in smokers (see ▶ Chap. 2).

Often, COPD is associated with hypertension and CHD (see ▶ Chaps. 15 and 16) which both can lead to CHF and arrhythmias (see ▶ Chaps. 16 and 17). For the long-term prognosis of COPD, treatment of these concomitant cardiovascular diseases is important. β_1AR antagonists are principally well suited for this purpose. But in high doses, they can also antagonize the β_2AR and thereby annihilate the therapeutic effects of SABAs and LABAs (see ▶ Chaps. 1 and 5). Therefore, many pharmaceutical companies explicitly warn from using β_1AR antagonists in COPD patients. However, one should keep in mind that information on drugs provided by pharmaceutical companies does not only serve to inform physicians, pharmacists, and patients but also to prevent lawsuits because of ADRs. From a therapeutic perspective, it is not appropriate to withhold β_1AR antagonists from COPD patients because the prognosis then deteriorates. Rather, in low doses, β_1AR antagonists possess beneficial effects in COPD patients with cardiovascular complications. In hypertension, one could refrain from β_1AR antagonists (class B antihypertensives) because good alternatives are available with the classes A, C, and D.

14.5 Pathophysiology of Cystic Fibrosis (CF)

CF is an autosomal-recessive disease with a prevalence of 1:2000. In CF, function of the CFTR is impaired. CFTR mediates chloride export into the extracellular space and is expressed in numerous organs. This explains why CF is a multi-organ disease. ◘ Figure 14.3 shows CF pathophysiology and pharmacological interventions. In ◘ Table 14.1, selected drugs for CF treatment are summarized. In CF the organism attempts, in vain, to compensate the impaired CFTR function. Exocrine glands do not anymore produce serous secretions but rather viscous ones with increased NaCl concentration. If CF is suspected (e.g., in newborns with meconium ileus or salty tasting skin), the pilocarpine sweat test is performed. The M_xR agonist pilocarpine is administered intradermally to stimulate sweat production. The sweat is analyzed biochemically. If the NaCl concentration is >60 mmol/l, CF is strongly indicated. This is an example of how drugs can be used for the diagnosis of diseases.

If the pilocarpine sweat test yields a suspicious result, genetic testing is performed. Genetically, CF is very heterogeneous with six different mutation classes. The F508Δ mutant (deletion of the C-terminus of CFTR) is the most common cause of CF (>70% of all cases). In the deletion mutant, CFTR is still functional, but remains in the endoplasmic reticulum and is degraded in the proteasome instead of being transported to the plasma membrane. All other CFTR mutants are much less common. In the G551D mutant, a neutral glycine is exchanged against a negatively charged aspartate at position 551. This mutant is inserted into the plasma membrane but possesses a reduced chloride conductance. The G551D mutant (gateway mutant) is responsible for about 1% of all CF cases.

The viscous secretions in CF impede with mucociliary clearance in the lung. This facilitates infection with problem pathogens such as *Pseudomonas aeruginosa* and *Staphylococcus aureus* (see ▶ Chap. 33) or *Aspergillus fumigatus*

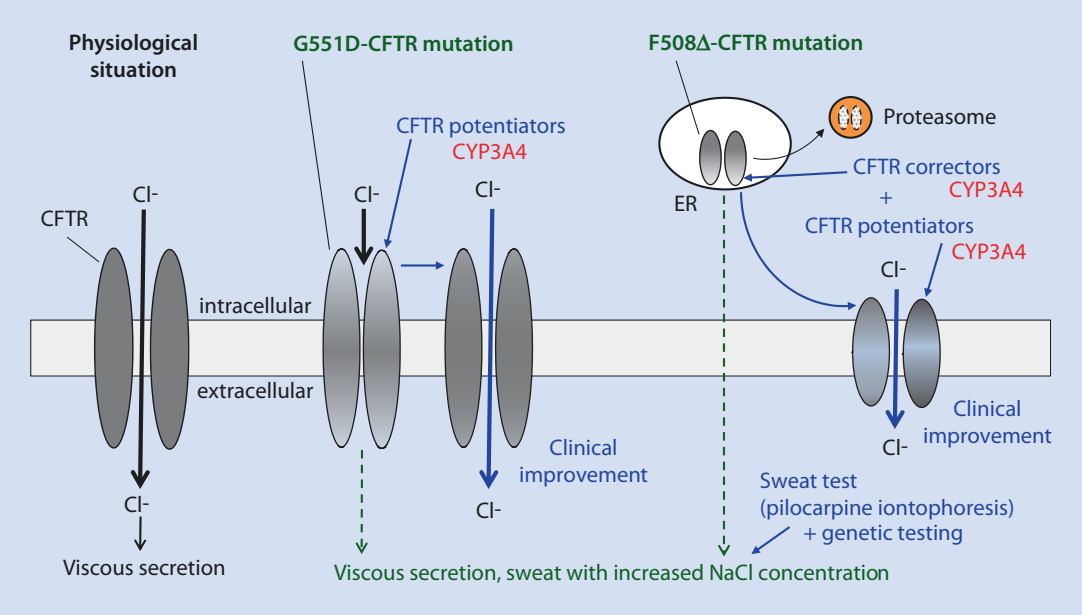


Fig. 14.3 Pathophysiology of CF: pharmacological interventions. This is an example for personalized treatment of rare disease with orphan drugs. For space reasons, in this book orphan drugs cannot be dealt with comprehensively, although this is a topic of increasing pharmacological importance. Other orphan diseases treated in this book are narcolepsy (pitolisant), PAH (riociguat, ▶ Chap. 9), and Lesch-Nyhan disease (allopurinol, ▶ Chap. 23)

(see ▶ Chap. 35). Finally, abscesses, cysts, and fibrosis develop. Viscous pancreas secretions cause exocrine organ failure with maldigestion, growth retardation in children and juveniles, and osteoporosis. In addition, endocrine pancreas failure can develop, resulting in type 1 DM (see ▶ Chap. 19). Infertility is another consequence of increases in viscosity of secretions.

14.6 Pharmacotherapy of CF

Until recently, CF could only be treated symptomatically: infections have been treated with antibiotics or antimycotics (see ▶ Chaps. 33 and 35), exocrine pancreas insufficiency with pancreas enzymes, growth retardation with growth hormone, DM with insulin (see ▶ Chap. 19), osteoporosis with bisphosphonates (see ▶ Chap, 20), and infertility with in vitro fertilization. Organ transplantation is the last resort, but this procedure entails administration of immunosuppressants which is problematic as well (see ▶ Chap. 11). However, the efficiency of symptomatic CF treatment should not be underestimated. Just 20 years ago, most CF patients died before the age of 20 years. Provided proper treatment, newborn CF patients can now readily reach an age of 50 years and beyond.

In collaboration of a foundation with a pharmaceutical company, classic low-molecular mass drugs have been developed for the first time to correct the functional deficits of CFTR mutations. The development of ivacaftor took 25 years and was the result of basic research combined with targeted drug development. Ivacaftor is the prototype of the class of CFTR potentiators that increase the chloride conductance of certain CFTR mutants. The drug has been approved for CF patients with G551D mutation. This is an example for personalized medicine in which a drug is specifically designed to correct the molecular disease defect in a patient. Ivacaftor improves the lung function and reduces hospitalization frequency of patients with the G551D mutation. Ivacaftor is a CYP3A4 substrate so that drug interactions can occur. This constitutes a relevant problem because CF patients often receive several drugs. The high therapy costs, easily exceeding $ 300,000 per year and patient, have been widely criticized.

When applied alone, ivacaftor is without effect in the common F508Δ mutant because the primary defect is the lack of transport of the mutant to the plasma membrane. Lumacaftor is the first representative of the class of CFTR correctors that act as pharmacological chaperones and, via binding to the truncated CFTR, improve its transport to the plasma membrane. The chloride conductance of the translocated truncation mutant is then further enhanced by ivacaftor. Like ivacaftor, lumacaftor is a CYP3A4 substrate. The combination of ivacaftor + lumacaftor improves lung function in the F508Δ patients and reduces hospitalizations. Again, the annual treatment costs of > $250,000 per year and patient are of great concern. The very high market prices for these novel drugs for personalized medicine highlight the economical challenges that many healthcare systems now face. It will be almost impossible to treat all eligible CF patients with the new drugs. Accordingly, transparent and fair criteria have to be developed determining which patients should be treated with CFTR potentiators and CFTR correctors.

14.7 Questions and Answers

Questions

Which assignment of drug to indication is correct?

A. Cromoglicic acid – asthma attack
B. Theophylline – basic therapy of mild asthma
C. Prednisolone – basic therapy of COPD
D. Ivacaftor – CF due to G551D mutation
E. EPI – status asthmaticus

Answers

A. Cromoglicic acid can only be used for prophylaxis of asthma attacks. The drug has to be administered for several weeks until an effect becomes evident and requires high adherence.
B. Theophylline possesses serious ADRs and should only be administered in severe asthma forms.
C. LAMAs and LABAs belong to the basic drug classes for COPD therapy. Systemic GCR agonists such as prednisolone should be avoided because the resulting immunosuppression increases the risk of dangerous bronchopneumonia.
D. Ivacaftor is a paradigm drug for personalized medicine. The drug binds specifically to a rare mutant of CFTR that causes CF, thereby normalizing chloride conductance.
E. In status asthmaticus, SABAs, SAMAs, magnesium, GCR agonists, theophylline, and oxygen are administered. Due to its pleiotropic effects on the β_1AR, β_2AR, and α_1AR, EPI is only administered in anaphylactic shock. In status asthmaticus, the agonism of EPI at the β_1AR and α_1AR causes ADRs.

Answer **D** is correct.

14.8 Exercises

A 26-year-old man visits you in your dental office and complains about soreness at the gums, the oral mucosa, and the tongue. Recently, white plaques and bad mouth odor have become apparent. Upon inspection you see generalized erythema of the mucosa, and you can confirm the white plaques. The plaques can be easily removed and bleed when touched gently. Upon specific questioning the patient tells you that his family doctor has prescribed salbutamol spray because of his asthma. He has taken up to eight puffs a day, but the asthma did not get any better. Therefore, since 4 weeks, he has been additionally inhaling budesonide spray. But despite this additional drug intake, the asthma still did not improve. Lastly, he often has a bitter taste in the mouth.

Questions

1. What is your diagnosis and how do you proceed in collaboration with the family physician?
2. In further interviews the patient tells you that he is afraid of ADRs of budesonide. On the Internet he read some bad things about GCR agonists. What do you do?

Answers

1. It appears that the patient is suffering from oral candidiasis due to incorrect application of the IGCR agonist spray. In collaboration with the family physician, you first exclude that a disease causing

immune system suppression such as leukemia is responsible for the candidiasis. The diagnosis should be confirmed by microscopic examination of the plaque material. Candidiasis is treated with a locally acting antimycotic drug such as clotrimazole. The lack of efficacy of salbutamol (applied much too often) and budesonide (candidiasis) is most likely due to the fact that the drugs do not reach the airways but become deposited in the mouth (bitter taste of salbutamol). Accordingly, the patient must receive proper training for drug administration from his family physician, pulmonologist, or pharmacist. In this context, the patient is also educated about the link between the current health problems and the incorrect drug therapy. Following this education, you start all over again with the pharmacotherapy. As basis, the budesonide spray is being used. The patient has to be informed about the fact that it takes some days until the effect becomes evident. In addition, the patient should be educated to extensively rinse his mouth with water after inhalation. The salbutamol spray should only be used cautiously and in acute asthma attacks with substantial dyspnea. For correct indication of salbutamol application, the patient receives a peak flow meter and is educated about the importance of the PEF value for self-administration of salbutamol.

2. You try to find out which website the patient visited to inform himself. You tell the patient that in many cases, medical information posted on websites has to be viewed very critically because it may not have been written and peer-reviewed by medical experts. You inform the patient about the fact that the efficacy of budesonide has been documented in clinical studies and that the major problem, as evidenced by the ADRs, is improper handling of the spray. Among the local ADRs of budesonide are, in addition to candidiasis, dysphonia, hoarseness, coughing, and pharynx irritation. Fortunately, the patient does not have to be concerned about systemic ADRs because budesonide is rapidly metabolized in the liver (first-pass effect). For this reason, budesonide accidentally swallowed and absorbed in the GI tract cannot act systemically.

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Drugs for Treatment of Hypertension

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Arterial hypertension affects between 15% and 35% of the global population. DM is the most important risk factor. Untreated, hypertension leads to serious complications including CHD, CHF, stroke, and CKD. However, hypertension can be treated very effectively and economically. The key for therapeutic success is the early onset of treatment, encompassing a healthy lifestyle and judicious use of different drug classes. BP can be decreased via reduction of SVR and CO. ACEIs and AT_1R antagonists (class A), β_1AR antagonists (class B), dihydropyridine-type CCBs (class C), and (thiazide) diuretics (class D) represent the basic drug classes for hypertension treatment. The classes can be flexibly combined with each other, and most patients can be very well treated with these drugs. By combination of classes A + D, ADRs on potassium balance can be minimized. In general, antihypertensive drugs of all four classes are well tolerated. In addition, drugs for resistant hypertension and for treatment of hypertensive emergencies are available.

Key Points

1. DM is the most important risk factor for hypertension.
2. A healthy lifestyle is the basis of antihypertensive treatment.
3. COX inhibitors, oral contraceptives, GCR agonists, calcineurin inhibitors, angiogenesis inhibitors, and indirect dopamimetics can increase BP.
4. Early start of antihypertensive treatment effectively prevents complications.
5. Class A, B, C, and D antihypertensive drugs are effective, well tolerated, and inexpensive.
6. Class A drugs comprise the ACEIs and AT_1R antagonists. They decrease SVR and influence vascular remodeling positively.
7. Class B drugs comprise the β_1AR antagonists. They lower SVR via reduced renin secretion and decrease CO.
8. Class C drugs comprise dihydropyridine-type CCBs. They reduce SVR.
9. Class D drugs comprise the thiazide (and loop) diuretics. They predominantly reduce SVR.
10. Potassium channel openers, α_1AR antagonists, α_2AR agonists, and MCRAs are drugs for resistant hypertension.
11. For treatment of hypertensive emergencies, NO donors, α_2AR agonists, short-acting dihydropyridines, and loop diuretics may be used.
12. Even for patients with concomitant diseases and in pregnancy, suitable antihypertensive drugs can be specified.

15.1 Pathophysiology of Hypertension

Blood pressure is the product of CO and SVR. Hypertension is present when the blood pressure is permanently above 140/90 mm Hg. There is a controversy whether lower BP values should be implemented to define "hypertension." It remains to be clarified whether then antihypertensive therapy really decreases mortality and morbidity or whether a redefinition just generates large populations of additional "hypertensive" patients for commercial purposes, ultimately increasing the costs in healthcare systems. Globally, hypertension is the most common disease, but it can be treated very well. The goal is to normalize BP and avoid complications. Pharmacological strategies aim at reducing SVR and/or CO. ◘ Table 15.1 summarizes the properties of commonly used antihypertensive drugs.

Hypertension is divided into primary (essential) hypertension (90% of all cases) with as yet unknown causes and secondary hypertension with very well-defined causes. The most important risk factor for primary hypertension is DM (see ► Chap. 19) which leads to micro- and macroangiopathy, increasing SVR. Additional risk factors for primary hypertension are obesity, increase in LDL cholesterol (see ► Chap. 22), sedentary lifestyle, tobacco abuse, NaCl-rich diet, pregnancy, and high age (men >55 years, women >65 years). Untreated hypertension leads to CHD, CHF, ischemic or hemorrhagic stroke, retinopathy, PAD, and ED (see ► Chaps. 9, 12, 16, 18, and 31).

The basis for any antihypertensive therapy is a healthy lifestyle including body weight reduction, endurance sports, tobacco abstinence, moderate ethanol consumption, as well as a diet rich in fruits and vegetables and poor in NaCl.

Table 15.1 Overview of selected antihypertensive drugs

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Amlodipine	Class C, long-acting dihydropyridine-type CCB	SVR↓	Long-term therapy of hypertension	Well-tolerated, only mild orthostatic hypotension and pretibial edema; favors GERD and gingival hyperplasia	2, 13
Candesartan	Class A, AT_1R antagonist	See ramipril	Long-term therapy of hypertension; contraindicated in pregnancy and in double-sided renal artery stenosis; alternative in ACEI-intolerant patients (cough, angioedema), CHF, DM	Hyperkalemia, no angioedema, no cough	12, 16, 17, 19
Chlorthalidone	Class D, thiazide diuretic	SVR↓	Long-term therapy of hypertension, nephrogenic edema	Hypokalemia, dehydration, thrombosis	12, 16, 17, 19, 20
Clonidine	α_2AR agonist	Central sympathetic tone↓ (CO↓)	Hypertensive emergencies, analgesia (postoperative, tumor diseases), heroin withdrawal	Sedation	5, 10
Doxazosin	α_1AR antagonist	SVR↓	Second-line drug for long-term therapy of hypertension, BPH	Orthostatic hypotension, reflex tachycardia	5
Eplerenone	MCRA	CO↓, cardiac remodeling↓	Second-line drug for long-term therapy of hypertension, CHF, hepatogenic edema	Hyperkalemia (particularly in combination with class A drugs; in CHF only)	12, 16
Furosemide	Loop diuretic	SVR↓	Therapy of hypertensive emergency and long-term therapy of hypertension in CKD and CHF, nephrogenic edema	Hypokalemia, dehydration, thrombosis	12, 16, 17, 19, 20

(continued)

Table 15.1 (continued)

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Metoprolol	Class B, β_1AR antagonist	CO and SVR ↓(via reduced renin release)	Long-term therapy of hypertension, CHD, tachycardia and CHF	Sexual dysfunction, sedation, asthma attacks, impaired perception of hypoglycemia, heart failure, bradycardia	1, 5, 9, 14, 16, 17, 19
Minoxidil	Potassium channel opener	SVR↓	Second-line drug for long-term therapy of hypertension (only in combination with other antihypertensive drugs), local application in alopecia	Massive orthostatic hypotension and reflex tachycardia (has to be administered in combination with an β_1AR antagonist), hypertrichosis	
Nifedipine	Class C, short-acting dihydropyridine-type CCB	SVR↓	Hypertensive emergencies	Orthostatic hypotension, reflex tachycardia, headache, pretibial edema, favors GERD and gingival hyperplasia	2, 13
Ramipril	Class A; ACEI	SVR, cardiovascular remodeling ↓, nephroprotection	Long-term therapy of hypertension; contraindicated in pregnancy, double-sided renal artery stenosis, and angioedema; CHF, DM	Cough, angioedema, hyperkalemia	3, 12, 16, 17, 19

GTN and SNP for treatment of hypertensive emergencies are presented in ► Chap. 9

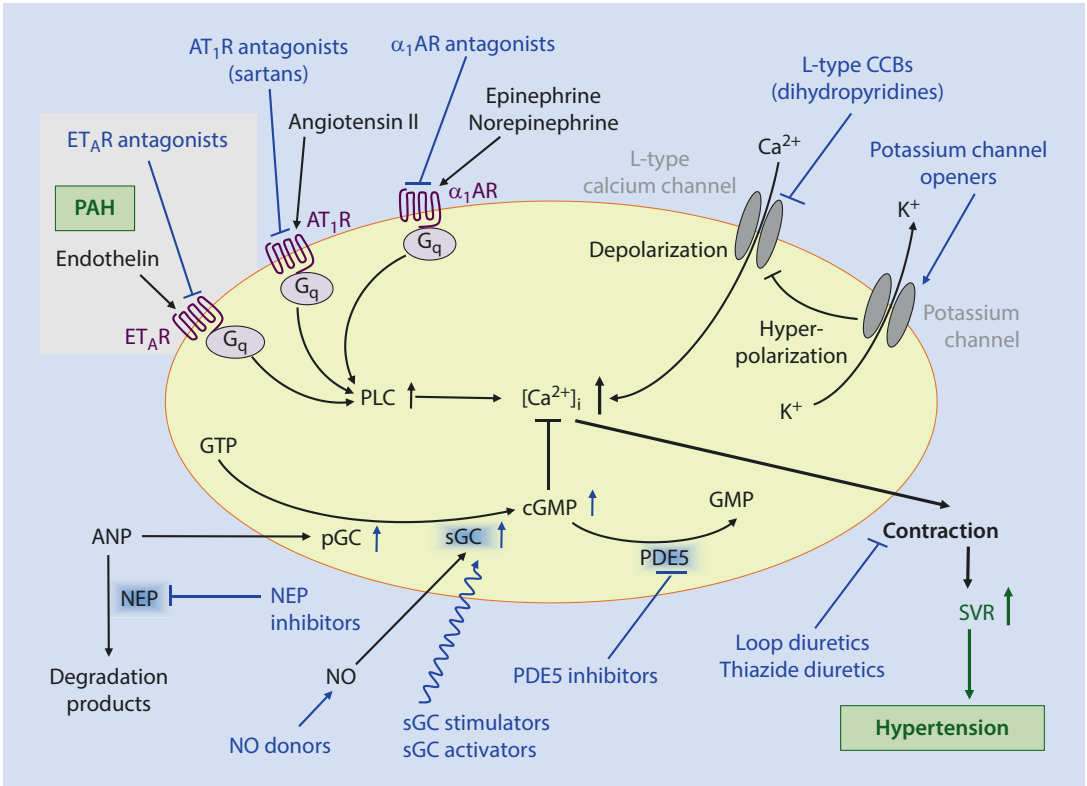
The rarer forms of secondary hypertension have a defined cause such as renal artery stenosis, glomerulonephritis (see ▶ Chaps. 11 and 12), and endocrine diseases such as hyperaldosteronism, Cushing's syndrome (see ▶ Chap. 11), or pheochromocytoma. In addition, various drugs can cause or deteriorate hypertension. Examples are discussed in ▶ Sect. 15.3.

15.2 Vascular Smooth Muscle Cells as Targets for Antihypertensive Drugs

Vascular smooth muscle cells are the most important target for antihypertensive drugs, achieving a decrease in SVR. ◘ Figure 15.1 shows important mechanisms of contraction and relaxation of smooth muscle cells and pharmacological interventions. Via the G_q-PLC pathway, several GPCRs mediate an increase in intracellular calcium concentration with subsequent contraction. The α_1AR, AT_1R, and ET_AR act via this pathway. For treatment of hypertension, the AT_1R is the most important GPCR. AT_1R antagonists (sartans) block the effects of angiotensin II at the AT_1R. α_1AR antagonists inhibit the effects of NE and EPI at the α_1AR (see ▶ Chap. 5). ET_AR antagonists play only a role in the treatment of PAH. The reason for this indication is that the ET_AR is strongly expressed in the pulmonary arteries. Accordingly, the effects of ET_AR antagonists on these vessels are particularly pronounced.

Contraction of smooth muscle cells can also be accomplished via L-type calcium channels. Activation of these channels results in an increase in intracellular calcium concentration. Accordingly, L-type CCBs cause relaxation of smooth muscle cells.

The NO-cGMP pathway functionally antagonizes the G_q-PLC pathway and relaxes smooth muscle cells (see ▶ Chap. 9). Pharmacological



◘ **Fig. 15.1** Vascular smooth muscle cells as target for antihypertensive drugs. β_1AR antagonists are discussed in ▶ Chap. 5, NEP inhibitors in ▶ Chap. 16, and drugs acting on the NO-cGMP system in ▶ Chap. 9. AT_1R antagonists, CCBs, and diuretics relax vascular smooth muscle cells

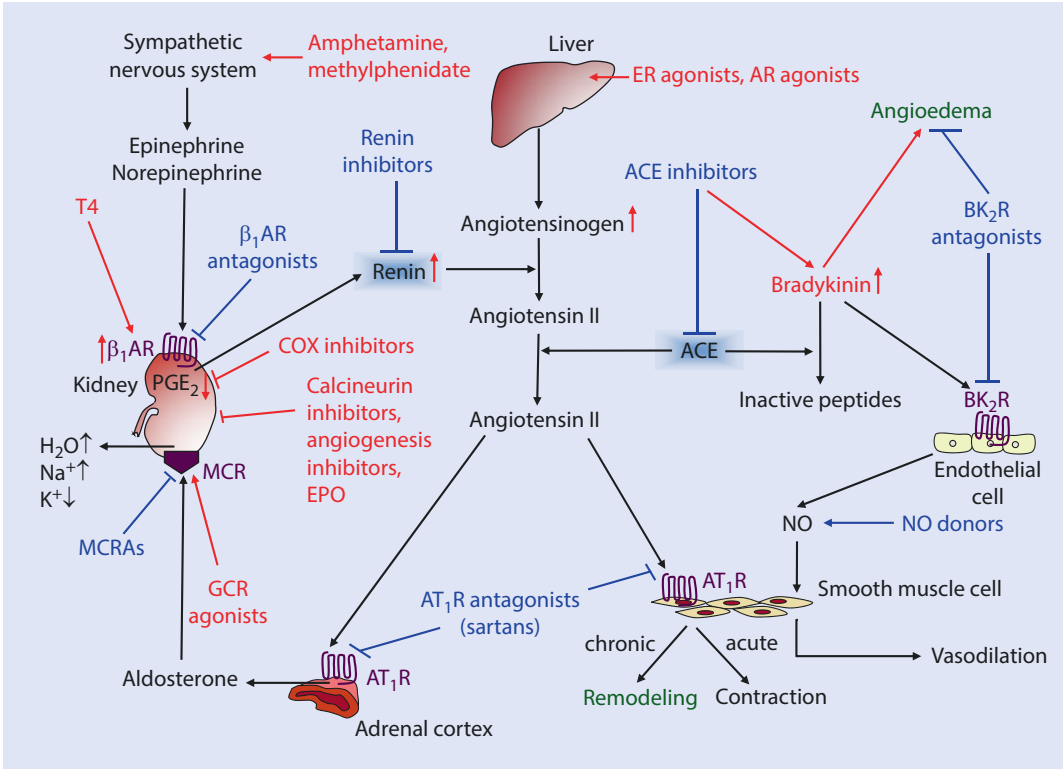


Fig. 15.2 Pharmacological modulation of BP via the RAAS. See also Fig. 16.1. Understanding the RAAS is key to understanding treatment of hypertension and CHF! Beware of drugs that stimulate RAAS! Through RAAS stimulation, many drug classes can cause hypertension

interventions are feasible at the level of sGC with NO donors, sGC activators, and sGC stimulators and at the level of PDE5 with PDE5 inhibitors. In addition to sGC, a particulate GC (pGC) exists. pGC is activated by atrial natriuretic peptide (ANP) and increases cGMP. ANP inactivation is mediated via NEP. Accordingly, NEP inhibition prolongs the effects of ANP. Currently, NEP inhibitors (prototype sacubitril) are predominantly used in CHF (see ▶ Chap. 16).

Diuretics can also directly relax vascular smooth muscle cells. During long-term therapy, thiazide diuretics lead to vasodilation and decrease in BP. Loop diuretics dilate blood vessels immediately after i.v. injection. This effect is exploited in hypertensive emergencies (see ▶ Sect. 15.10). The mechanism of action of diuretics on smooth muscle cells is not definitively known.

Activation of potassium channels leads to hyperpolarization with subsequent relaxation of smooth muscle cells.

15.3 Pharmacological Modulation of Blood Pressure via the RAAS

The RAAS plays a central role in BP regulation and can be modulated at various sites. Figure 15.2 shows regulation of RAAS and pharmacological interventions. The biologically inactive precursor peptide angiotensinogen is synthesized in the liver. Renin, a protease released from the kidney, hydrolyzes the peptide to yield the still biologically inactive angiotensin I. Renin release from the juxtaglomerular apparatus is stimulated by a reduction of the renal perfusion pressure and via β_1AR activation (see ▶ Chap. 5).

ACE converts angiotensin I to the biologically active angiotensin II. Via the AT_1R, angiotensin II acutely leads to contraction of vascular smooth muscle cells (Fig. 15.1). Chronic activation of the AT_1R stimulates proliferation of vascular smooth muscle cells and fibroblasts, leading to hemodynamically unfavorable remodeling, particularly in the kidney and in the heart.

Remodeling promotes atherosclerosis and diabetic nephropathy (see ▶ Chap. 12). In addition, AT_1R activation stimulates secretion of aldosterone from the zona glomerulosa of the adrenal cortex. Via the MCR, aldosterone mediates sodium and water retention in the kidney, culminating in an increase in intravasal volume and in BP. However, the effects of aldosterone on the kidney are not neutral with regard to electrolytes. Especially potassium elimination is enhanced, leading to hypokalemia.

Via RAAS blockade with ACEIs, the acute and chronic effects of angiotensin II on blood vessels and of aldosterone on the kidney can be prevented. However, angiotensin II is not the only ACE substrate. This enzyme also catalyzes the degradation of the local mediator bradykinin that affects vasodilation via BK_2R-mediated NO formation in endothelial cells (see ▶ Chaps. 3 and 9). Most ADRs of ACEIs are due to bradykinin that may cause angioedema in the face, mouth, and larynx as well as dry cough. These ADRs can be largely avoided by switching patients to AT_1R antagonists.

Renin inhibitors (prototype aliskiren) could be a conceptual alternative to ACEIs and AT_1R antagonists. However, the high costs of a therapy with aliskiren and the low bioavailability are of concern. In the treatment of hypertension, renin inhibitors do not have a therapeutic advantage compared to ACEIs and AT_1R antagonists. Renin inhibitors are a good example that an innovative pharmacological strategy does not necessarily result in a therapeutic advance.

Estrogens can stimulate angiotensinogen biosynthesis, increasing BP via enhanced generation of angiotensins I and II. This aspect needs to be considered as ADR during long-term administration of oral contraceptives (see ▶ Chap. 24). Anabolic drugs raise BP as well (see ▶ Chap. 24). Furthermore, calcineurin inhibitors can increase BP via RAAS stimulation (see ▶ Chap. 11).

In the therapy of autoimmune diseases, GCR agonists like prednisolone are used at high doses (see ▶ Chap. 11). Via the MCR, GCR agonists can cause water and sodium retention. Chronic consumption of licorice increases BP via MCR stimulation as well, an example how BP responds to dietary habits. Conversely, MCRAs like eplerenone promote water and sodium elimination, thereby reducing intravasal volume. This effect of MCRAs is predominantly exploited in CHF therapy (see ▶ Chap. 16) but is currently also tested in the treatment of hypertension. Hyperkalemia is the most important ADR of a chronic MCRA therapy (see ▶ Chaps. 12 and 17).

PGE_2 is essential for normal kidney perfusion. If its synthesis is reduced by COX inhibitors, kidney perfusion is reduced, and renin release is stimulated (see ▶ Chap. 12). Particularly during long-term therapy with COX inhibitors, BP can increase. Therefore, long-term therapy of pain with this drug class must be avoided (see ▶ Chap. 10).

Hyperthyroidism or abuse of T4 for body weight reduction can increase BP via enhanced β_1AR expression in the kidney and heart (see ▶ Chap. 21). Abuse of indirect sympathomimetics (see ▶ Chap. 5) and MPH, used in treatment of ADHD (see ▶ Chap. 8), raises BP via enhanced NE release. EPO proteins can increase BP via hypervolemia (see ▶ Chap. 12). Lastly, angiogenesis inhibitors that are used as targeted therapeutics in tumor therapy may also lead to higher BP (see ▶ Chap. 32). Therefore, before starting an antihypertensive treatment, it is essential to answer the question whether the patient has dietary habits or takes drugs that can increase BP.

15.4 Class A Antihypertensive Drugs

ACEIs and AT_1R antagonists constitute the class A antihypertensive drugs. Ramipril is a prototypical ACEI. It is inexpensive and effective (reduction of SVR), has no effects in the CNS, and exhibits cardio-and nephroprotective effects via inhibition of remodeling processes. Class A drugs do not cause sexual dysfunction and have only a small risk for orthostatic hypotension.

Hyperkalemia is the most important ADR of ACEIs. Therefore, the serum potassium concentration has to be controlled regularly. Hyperkalemia can lead to bradycardia, calling for regular ECG controls (see ▶ Chap. 17). Excessive consumption of food rich in potassium such as bananas, dry fruits, and nuts should be avoided.

Particularly in cases of insufficient BP reduction, the combination of class A drugs with class D drugs is advisable. CKD is no contraindication for therapy with ACEIs because the nephroprotective effects are more important than the risk of hyperkalemia (see ▶ Chaps. 12 and 19). Other

important ADRs of ACEIs are the consequence of the inhibited bradykinin degradation. In most cases, the resulting dry cough is not permanent. If a patient develops angioedema under ACEIs therapy, the drug must be discontinued immediately (see ▶ Chap. 3). Patients with known hereditary angioedema and insect sting allergy must not be treated with ACEIs. In case of double-sided renal artery stenosis, ACEIs are contraindicated because in this situation, the RAAS ensures minimal kidney perfusion that is annihilated by ACEIs, ultimately leading to acute kidney failure. Therefore, before treatment with an ACEI is initiated, sonography of both kidneys has to be performed.

The RAAS is also essential for normal kidney development. ACEIs are teratogenic and can cause serious kidney dysfunction in the embryo, fetus, and newborn. Therefore, ACEIs are contraindicated in pregnancy. However, due to the broad therapeutic use of ACEIs, teratogenic effects of this drug group are still observed.

In principle, AT_1R antagonists and ACEIs possess a similar spectrum of pharmacological effects and ADRs. Candesartan is a prototypical AT_1R antagonist. Since AT_1R antagonists have become available as generic drugs, the therapy costs for this effective drug class have decreased substantially. However, the flip side of this development is that drug companies search for less expensive synthesis routes for drugs. Such an effort has recently resulted in contamination of certain valsartan formulations with carcinogens.

The major difference between ACEIs and AT_1R antagonists is that the latter drugs do not interfere with bradykinin degradation. Accordingly, they do not cause dry cough and only rarely angioedema.

15.5 Class B Antihypertensive Drugs

β_1AR antagonists have been successfully used for many years in the treatment of hypertension. They reduce CO (negative inotropic effect in the heart) and SVR (via inhibition of renin release in the kidney) (see ▶ Chap. 5). β_1AR antagonists are inexpensive and available as generic drugs. Metoprolol is a prototype of this class.

To avoid ADRs, the dose of β_1AR antagonists should be increased slowly. In principle, there is a risk of deterioration of asthma or COPD due to blockade of the bronchodilatory β_2AR effects of NE and EPI (see ▶ Chaps. 1 and 14). Accordingly, the respiratory tract resistance should be controlled regularly. In diabetics who are treated with insulin or sulfonylureas (see ▶ Chap. 19), β_1AR antagonists increase the risk of hypoglycemia. This is due to blockade of the hepatic β_2AR that mediates compensatory glucose release (see ▶ Chap. 5). Therefore, regular control of blood glucose concentration is necessary. Neither COPD nor DM is a contraindication for β_1AR antagonists. If the dose of β_1AR antagonists is rapidly increased, CHF can deteriorate. Thus, patients have to be regularly controlled for CHF symptoms. Regular ECG controls serve for detection of an AV block (see ▶ Chap. 17). Via blockade of the vasodilatory function of the β_2AR in the skin, β_1AR antagonists in high doses can cause a painful Raynaud syndrome. β_1AR antagonists may deteriorate ED (see ▶ Chap. 9), reduce libido, and cause fatigue.

15.6 Class C Antihypertensive Drugs

CCBs are a standard drug class for hypertension as well and designated as class C. They reduce SVR. Therapy is dominated by dihydropyridine type CCBs. In therapeutic doses, these drugs inhibit the L-type calcium channels in the vascular smooth muscle cells, but not in the heart. Due to this selectivity for blood vessels, dihydropyridines do not directly interfere with heart function. Nifedipine is a prototypical dihydropyridine. It has a rapid onset and short duration of action (see ▶ Chap. 2). For long-term therapy, these are unfavorable properties because BP fluctuations occur. These fluctuations are unpleasant for the patient. Orthostatic hypotension and reflex tachycardia (potentially accompanied by AP) are other typical ADRs of nifedipine. Headache and pretibial edema can result from vasodilation. Therefore, nifedipine is mostly used for hypertensive emergencies when a rapid effect is needed.

In sustained-release formulations of nifedipine, orthostatic hypotension and reflex tachycardia are less pronounced. However, long-acting dihydropyridines (amlodipine is a prototype) have largely superseded sustained-release nifedipine in the long-term therapy of hypertension. These drugs possess a slower onset and a longer

duration of action than nifedipine. Therefore, tolerability is better. The availability of inexpensive generic long-acting dihydropyridines allows for economic treatment of large patient populations. Effects on the heart do not occur in therapeutic doses. As a consequence of relaxation of smooth muscle cells in the GI tract, dihydropyridines can deteriorate GERD symptoms (see ▶ Chap. 13).

In contrast to dihydropyridines, the CCBs diltiazem and verapamil additionally exhibit inhibitory effects on cardiac L-type calcium channels in therapeutic doses. Via this mechanism, pronounced bradycardia (negative chronotropic effect), AV block (negative dromotropic effect), or heart failure (negative inotropic effect) can result. Therefore, the general practitioner should avoid using verapamil and diltiazem. These drugs belong into the hands of the cardiologist for specialized indications (see ▶ Chap. 17).

15.7 Class D Antihypertensive Drugs

Thiazide diuretics belong to the class D antihypertensive drugs. They are effective, safe, and inexpensive. They have the advantage of no ADRs in the CNS and do not cause orthostatic hypotension. Thiazide diuretics reduce BP predominantly via reduction of the SVR (see ◘ Fig. 15.1) and much less via the diuretic effect that leads to a reduction in intravasal volume and CO. Hydrochlorothiazide and chlorthalidone are the prototypes of this drug class. There are habitual differences in the use of the two drugs in various countries. Recently, reports of increased risk of certain skin tumors developing after long-term therapy with hydrochlorothiazide have been published. However, chlorthalidone represents a similarly effective alternative drug.

Hypokalemia is the most important ADR of thiazide diuretics (see ▶ Chap. 12). It can result in tachyarrhythmias (see ▶ Chap. 17). Therefore, the serum potassium concentration has to be controlled regularly under thiazide diuretic therapy. ECG controls are indicated as well. Hypokalemia can be avoided with a diet rich in potassium. Alternatively, potassium-sparing diuretics such as triamterene or MCRAs can be co-administered. In these drugs, the potassium-sparing effect is much more pronounced than the diuretic effect. The combination of drug classes A + D is highly advisable. With this combination, enhanced blood pressure reduction and neutralization of the opposite drug effects on potassium balance are accomplished.

To avoid exsiccosis and thrombosis, patients treated with thiazide diuretics should drink sufficient volumes of fluids. Additional ADRs are elevations of serum glucose, uric acid, and LDL concentration (see ▶ Chaps. 12, 19, 22, and 23). However, clinically these ADRs are largely irrelevant. Loop diuretics also belong to the class D. They are predominantly used in patients with CKD (see ▶ Chap. 12) and CHF (see ▶ Chap. 16) and in hypertensive emergencies (see ▶ Sect. 15.10).

15.8 Drugs for Resistant Hypertension

It is possible to effectively treat the large majority of all hypertensive patients with drugs of the classes A–D, either alone or in combination. Drugs for resistant hypertension are only rarely needed. Usually, they are added to classes A–D. Potassium channel openers are one therapeutic option, minoxidil being the prototype. It effectively reduces SVR, but possesses a very high risk for orthostatic hypotension and reflex tachycardia. Accordingly, minoxidil is not suitable for monotherapy but exclusively used in combination with β_1AR antagonists that mitigate reflex tachycardia. Hypertrichosis is another important ADR of minoxidil. Its stimulatory effect on hair growth is used in local therapy of alopecia. However, application of minoxidil on large skin areas may cause orthostatic hypotension. α_1AR antagonists such as doxazosin reduce SVR as well. Typical ADRs are hypotension and reflex tachycardia.

The MCRA eplerenone is mostly used in CHF therapy. MCRAs possess beneficial effects on cardiac remodeling. It is currently being evaluated to which extent eplerenone is useful in the therapy of hypertension. Hyperkalemia is the most important ADR of eplerenone, particularly in combination with class A drugs.

α_2AR agonists such as clonidine effectively reduce BP by diminishing the central sympathetic tone (see ▶ Chap. 5), but sedation and sexual dysfunction are unfavorable ADRs during long-term therapy.

15.9 Practical Aspects of Hypertension Therapy

Treatment of hypertension is generally lifelong. Antihypertensive drugs should be effective, convenient to administer, economical, and devoid of serious ADRs. Moreover, the potential for drug interactions should be small because many hypertensive patients are multimorbid and treated with numerous drugs. Class A–D antihypertensive drugs fulfill the above criteria very well. For therapeutic success it is essential that drugs are taken regularly by the patients. Adherence is increased by flashy tablet color, simple once-daily administration, dosing aids, and BP measurements at regular intervals. BP measurements are crucial for therapeutic success since patients often, particularly in early disease stages, do not yet have symptoms or organ complications. Education about the positive consequences of strict adherence to therapy and negative consequences of nonadherence are essential for long-term success.

Initially, a monotherapy with a drug of classes A–D is implemented. The choice of drug is guided by comorbidities and ADRs. The goal is to normalize the BP (<140/90 mm Hg). If the initial therapy is insufficient, an increase in drug dose and switching to another drug class are therapeutic options. This is also required if ADRs are inacceptable. If even an adjusted monotherapy is insufficient, a combination of two drugs is applied. In principle, class A–D drugs can be arbitrarily combined. The combination of classes A + D is particularly well suited because it largely annihilates disturbances of potassium balance. The combination of ACEIs + AT_1R antagonists must be avoided because very serious hyperkalemia may develop (see ▶ Chaps. 12, 15, and 17). With a monotherapy or a combination of two drugs, about 90% of all patients can be effectively treated. Every general practitioner can and should treat hypertensive patients. Another 9% of the patients can be well treated with a combination of three or four drugs. Just 1% of all patients require drugs for resistant hypertension. In general, treatment of hypertension should be started with a low dose and continued with slow dose increase under BP control. Switching of drugs should be performed cautiously as well in order to avoid hypertensive emergencies.

In hypertensive patients with concomitant asthma or COPD, initially class A and C drugs are feasible because they possess no risk of bronchoconstriction. If a patient is coughing a lot, e.g., as consequence of a respiratory tract infection or tobacco smoking, ACEIs should be avoided and substituted by AT_1R antagonists. Class B drugs can be principally used in asthma and COPD patients, too. To avoid asthma attacks, the dose should be increased slowly, and respiratory tract resistance should be monitored with a peak flow meter (see ▶ Chap. 14).

In general, every diabetic patient should be treated with class A drugs because they exert a nephroprotective effect and improve vascular remodeling (see ▶ Chap. 19). To avoid hyperkalemia, a class D drug, i.e., either a thiazide diuretic or, if CKD is already present, a loop diuretic (see ▶ Chap. 12), should be added. Class B drugs must be dosed cautiously to avoid unrecognized development of hypoglycemia.

Because of the beneficial effects on cardiac remodeling, class A drugs should be administered also in CHF, again in combination with class D drugs. The additional treatment with MCRAs has to be considered because these drugs exert a cardioprotective effect additive to that of class A drugs (see ▶ Chap. 16). However, this combination increases the risk of hyperkalemia so that the additional application of loop diuretics is often required. In CHF, class B drugs are principally indicated as well, but they must be dosed cautiously because of the risk of deterioration of heart function.

In case of a higher-degree AV block, dihydropyridines may be used. Verapamil and diltiazem must be avoided because of their negative dromotropic effect and the associated risk of AV block deterioration (see ▶ Chap. 17). Moreover, class D drugs can be used in these patients, possibly in combination with class A drugs. However, the latter alone should be avoided because of the risk of hyperkalemia and bradycardia. Class B drugs are also problematic in this situation due to their negative dromotropic effects.

Pregnancy constitutes a special therapeutic situation since class A and C drugs are contraindicated because of their teratogenic potential. Application of the α_2AR agonist methyldopa is considered to be safe in pregnancy. Hypertension in pregnancy must be treated in any case because eclampsia or hypertensive emergencies may develop. Metoprolol is an alternative to methyldopa.

15.10 Therapy of Hypertensive Emergencies

A hypertensive emergency is an acute and life-threatening increase in diastolic BP >120 mm Hg. Insufficiently treated hypertension, abrupt termination of antihypertensive treatment, non-overlapping switching of antihypertensive drugs, glomerulonephritis, or insufficiently treated hypertension in pregnancy may be causes for emergencies. Cardinal symptoms are severe pulsating, headache, nose and conjunctival hemorrhage, nausea, and vomiting (see ▶ Chaps. 6 and 13). Untreated hypertensive emergencies can lead to intracranial hemorrhage, hypertensive encephalopathy, MI, cardiac failure (see ▶ Chap. 16), and dissection of aortic aneurysm. In order to decrease the intracranial pressure, the patient should sit upright but never lie in a horizontal position.

The therapeutic goal is to reduce BP rapidly and effectively and, in parallel, to initiate an effective long-term treatment of hypertension. GTN (see ▶ Chap. 9) is suitable for treatment of hypertensive emergencies. It can be applied sublingually as capsule or buccally as spray (in case of unconsciousness). GTN rapidly decreases BP by reduction of SVR. The ADRs are the result of vasodilation and include orthostatic hypotension with reflex tachycardia, headache, and flush. Because of desensitization, GTN is not suitable for long-term therapy. Nifedipine capsules are an alternative, reducing SVR via blockade of L-type calcium channels. Upon i.v. injection, the loop diuretic furosemide also rapidly decreases SVR. Another option is the application of clonidine. Via α_2AR agonism, this drug reduces the central sympathetic tone and thus CO (see ▶ Chap. 5).

If none of these drugs effectively reduces BP, it can be titrated to any desired level with SNP (see ▶ Chap. 9). SNP has to be freshly dissolved and infused i.v. from light-protected infusion containers because of its light sensitivity. The BP must be tightly controlled since overdose of SNP may lead to life-threatening hypotension and even death. SNP infusion does not constitute a long-term therapy of hypertension because SNP releases cyanide so that a chronic cyanide intoxication with global impairment of cell respiration can develop (see ▶ Chap. 4). Although being a well-established generic drug, SNP recently has undergone massive and unexplained price increases in some countries. Therefore, it is essential to start very soon with an effective long-term treatment for which it is critical to identify the cause of the hypertensive emergency.

15.11 Questions and Answers

Questions

Which assignment of drug class to indication is correct?

A. AT_1R antagonists – hypertension in pregnancy
B. Thiazide diuretics – initial therapy of hypertension
C. Potassium channel openers – monotherapy of resistant hypertension
D. ACEIs – first-line therapy in hypertensive patients with insect sting allergy
E. Short-acting dihydropyridines – first-line therapy of hypertensive patients with asthma

Answers

A. AT_1R antagonists are contraindicated in pregnancy because they can induce kidney dysfunction in the embryo/fetus/newborn.
B. Thiazide diuretics are well tolerated and inexpensive and can be used in initial therapy of hypertension. Hypokalemia and dehydration are important ADRs.
C. Potassium channel openers are not suited for monotherapy of resistant hypertension. They can induce orthostatic hypotension and reflex tachycardia and must be used only in combination with other drug classes (preferentially class B drugs).
D. In patients with insect sting allergy, ACEIs are contraindicated. As a result of inhibition of bradykinin degradation, life-threatening angioedema in the face, mouth, and larynx can occur.
E. In principle, dihydropyridines are feasible in hypertensive patients with asthma since class C drugs cause relaxation of smooth muscle cells. However, short-acting dihydropyridines cause substantial fluctuations in BP. Therefore, nowadays, only long-acting dihydropyridines are used in long-term therapy of hypertension.

Answer **B** is correct.

15.12 Exercises

A 65-year-old male patient with hypertension known for many years and poorly controlled type 2 DM stops taking his antihypertensive medication because of libido problems without consulting his physician. Suddenly, the patient complains of severe headache and nasal and conjunctival hemorrhage. The patient is admitted to the emergency room. You measure a blood pressure of 250/140 mm Hg, indicative for a hypertensive emergency. You apply two puffs of a GTN buccal spray, but the blood pressure does not decrease. A nifedipine sublingual capsule remains without effect as well.

Questions

1. Which drugs can probably decrease the resistant increase in BP?
2. How do you proceed once the BP has stabilized?

Answers

1. You start an i.v. infusion of SNP. With this drug you can probably normalize the BP. However, SNP infusion is only feasible under ICU conditions because life-threatening hypotension can occur. In addition, SNP infusion is technically difficult because the drug is light-sensitive. During prolonged SNP infusion, cyanide intoxication may develop. Also, in some countries, you need to consider the high costs of SNP therapy.
2. You record the medical history of the patient with particular focus on the previously used antihypertensive drugs. In collaboration with the family physician, you try to find out which drugs could have caused the libido problems. β_1AR antagonists constitute one possibility. You then implement a long-term therapy with drugs of the classes A + C + D. Class A drugs have favorable effects on vascular changes in diabetics, and class D drugs should compensate class A-induced hyperkalemia. Class C drugs additionally decrease the BP. These chosen drug classes have no effect on libido. It will also be critical to implement a healthy diet and therapy with metformin.

Further Reading

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Drugs for Treatment of Chronic Heart Failure and Coronary Heart Disease

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CHF is the inability of the heart to pump a blood volume that is adequate to meet the metabolic demands of the body. Activation of the sympathetic nervous system and RAAS is only a short-term adaptation to this situation. In the long run, remodeling of the blood vessels, the kidney, and the heart takes place, deteriorating CHF. Based on the pathophysiology and clinical studies, β_1AR antagonists, ACEIs, AT_1R antagonists, and MCRAs are the most important drug classes for CHF treatment. Thiazide and loop diuretics support CHF therapy and reduce the risk of hyperkalemia in combination with RAAS inhibitors. HCN channel blockade and NEP inhibition are new therapeutic strategies for CHF. In CHD, β_1AR antagonists, HMG-CoA reductase inhibitors, and PAIs reduce mortality. The risk factors hypertension, DM, and tobacco abuse need to be treated. The MI therapy follows the MONA scheme (**m**orphine, **o**xygen, **n**itroglycerin (GTN), **A**SA) and includes recanalization of occluded coronary arteries with stents or fibrinolysis with plasminogen activators. VT is a MI complication that is difficult to treat; in this situation the classes I–IV antiarrhythmic drug amiodarone may be used.

Key Points

1. In CHF, β_1AR antagonists, ACEIs, AT_1R antagonists, and MCRAs reduce mortality.
2. COX inhibitors, GCR agonists, lithium, positive inotropic drugs, verapamil, and diltiazem can deteriorate CHF.
3. Combination of RAAS inhibitors with diuretics reduces the risk of hyperkalemia.
4. Risk factors for CHD (hypertension, DM, hypercholesterolemia, tobacco abuse) need to be treated rigorously.
5. In CHD, β_1AR antagonists, HMG-CoA reductase inhibitors, and PAIs reduce mortality.
6. MI therapy follows the MONA scheme (**m**orphine, **o**xygen, **n**itroglycerin (GTN), **A**SA).
7. VT is a dangerous CHD complication that can be treated with amiodarone.

16.1 Pathophysiology of Chronic Heart Failure (CHF)

In CHF, the heart is not capable anymore of contracting adequately to supply the organism with oxygen and nutrients due to myocardial dysfunction (systolic failure). The ejection fraction of the left ventricle is reduced. More than 10% of the global population older than 70 years suffer from CHF. CHF is divided into four stages according to the New York Heart Association (NYHA). In stage NYHA I, CHF is detected only by checkup (e.g., cardiac sonography), but clinical dysfunction is not yet apparent. NYHA II is characterized by dyspnea during moderate physical activities. In NYHA III dyspnea is evident during mild physical activities, and NYHA IV is characterized by dyspnea under resting conditions.

Figure 16.1 provides an overview of CHF pathophysiology and drugs that can deteriorate CHF. It can be the consequence of CHD (see ▶ Sect. 16.4), hypertension (see ▶ Chap. 15), cardiomyopathies, myocarditis, or a cardiac valvular defect. In addition, anemia and hyperthyroidism or hypothyroidism (see ▶ Chap. 21) may lead to CHF. Diseases causing CHF have to be treated, and valvular defects have to be corrected surgically.

CHF causes a vicious cycle of maladaptations. Pharmacotherapeutic concepts aim at breaking this cycle. An optimal CHF pharmacotherapy is important because of the extreme paucity of available donor organs. Table 16.1 summarizes the properties of selected drugs for CHF treatment.

As consequences of systolic failure, myocardial hypertrophy and dilation develop. However, this mechanism only partially compensates for the failure because the dilation reduces contractility at a certain threshold, further aggravating oxygen supply for the myocardium. Activation of the sympathetic nervous system (positive inotropic action of the β_1AR, see ▶ Chap. 5) has only short-term ameliorating effects on the situation as well; its long-term activation results in apoptosis of cardiomyocytes and decreases contractility again.

The systolic failure activates the RAAS (see ▶ Chap. 15). Angiotensin II induces vasoconstriction and deteriorates organ perfusion further. The angiotensin II-induced increase in BP deteriorates CHF because of increased cardiac workload. In addition, angiotensin II causes a hemodynamically

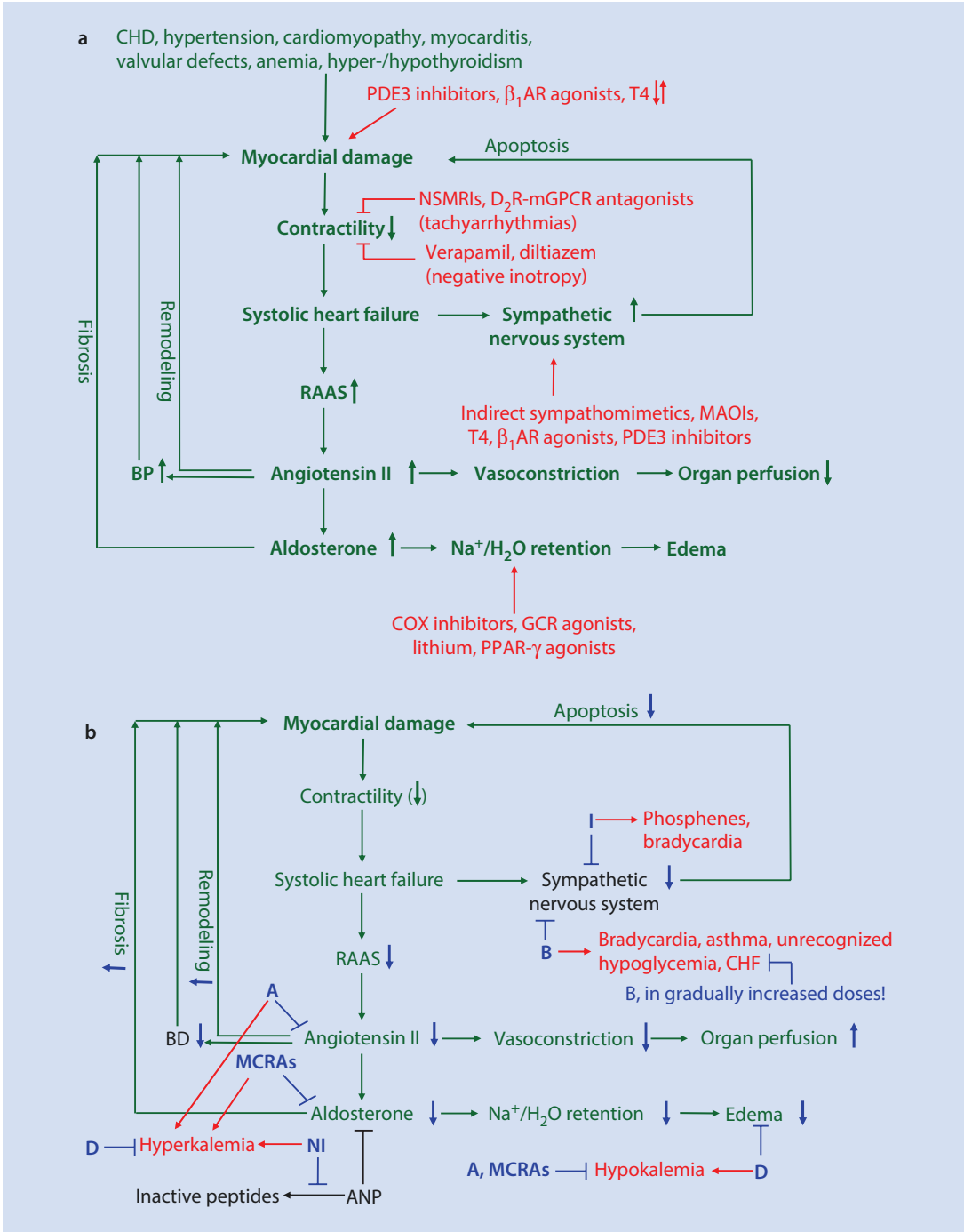

Fig. 16.1 **a**, **b** Pathophysiology of CHF, pharmacological interventions, and drugs that can deteriorate CHF. **a** Pathophysiology without pharmacotherapy and drugs deteriorating CHF. **b** Pathophysiological situation of CHF with pharmacotherapy and important ADRs. The currently available pharmacotherapy is acting just symptomatically. See also Fig. 15.2. Pharmacotherapy of CHF tries to break the vicious cycle of maladaptations! The various drug classes can be combined with each other

Table 16.1 Overview of selected drugs for treatment of CHF

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Candesartan	AT_1R antagonist (class A)	Inhibits effects of angiotensin II on remodeling of the vessels, kidney, and heart. Lowers BP	CHF-NYHA I–IV, status after MI, hypertension, DM (prevention of diabetic nephropathy)	Hyperkalemia, especially in renal failure and in combination with MCRAs; thus, if possible, combine with thiazide and/or loop diuretics. No risk of edema and cough	12, 15, 17
Chlorthalidone	Thiazide diuretic (class D); inhibition of the Na^+ Cl^- cotransporter in the early distal tubule	Moderate renal excretion of water, sodium, potassium, and chloride	CHF-NYHA I with hypertension; NHYA-II with hypertension and edema; NHYA III–IV, often in combination with loop diuretics; prevention of hyperkalemia induced by classes A, MCRA and particularly A + MCRA	Hypokalemia, hypercalcemia, uric acid retention, hearing impairment, exsiccosis. Hypokalemia is no problem if chlorthalidone is combined with classes A, MCRA and A + MCRA	2, 12, 15, 17
Enalapril	ACEI (class A)	See candesartan	See candesartan	See candesartan, but risk of edema and cough. In case these ADRs occur, switch to AT_1R antagonists	3, 13, 15, 17
Eplerenone	Class MCRA	See spironolactone	As spironolactone, but therapy is much more expensive. Hence, mostly employed as second-line therapy in case of ADRs associated with spironolactone	As spironolactone, but no gynecomastia due to missing AR antagonism	12, 15, 17
Furosemide	Loop diuretic (class D); inhibition of the Na^+-K^+-$2Cl^-$ cotransporter in loop of Henle	High renal excretion of water, sodium, potassium, and chloride	CHF-NYHA II with edema; NYHA III–IV, often in combination with thiazide diuretics to increase effects; prevention of hyperkalemia induced by classes A, MCRA and particularly A + MCRA	Hypokalemia, hypocalcemia, uric acid retention, hearing impairment, exsiccosis. Hypokalemia is no problem if furosemide is combined with classes A, MCRA, and A + MCRA	12, 15, 17, 23

Ivabradine	HCN4 channel blocker (class I)	Blocks the sodium inward current in the sinoatrial node and, hence, spontaneous depolarization. As a result, tachycardia is reduced	CHF with sinus rhythm ≥ 70/minute and in patients who are not sufficiently treated with classes A + B + D + MCRA; long-term therapy of CHD in case of contraindications or intolerance of class B	Phosphenes, severe bradycardia	17
Metoprolol	β_1AR antagonist (class B)	Negative chronotropic, dromotropic, and inotropic effect; inhibits the deleterious effects of long-term activation of the sympathetic nervous system on the heart	CHF-NYHA II–IV (slow dose increase in order to avoid acute heart failure). NHYA-I with hypertension; status after MI	Decompensation of CHF if dose is increased too fast, bradycardia, AV block. Cold extremities, risk of asthma attacks, and unrecognized hypoglycemia; particularly at higher doses when the β_2AR is antagonized as well	1, 5, 14, 15, 17, 19
Sacubitril	NEP inhibition (class NI)	BP drop, reduced sympathetic tone, reduced aldosterone secretion, increase of diuresis and natriuresis, inhibition of remodeling and fibrosis	Applied as fixed combination with the AT_1R antagonist valsartan to patients who have been insufficiently treated by classes A + B + D + MCRA	Angioedema with simultaneous administration of ACEIs; hypotension, hyperkalemia, renal dysfunction	3, 12, 15
Spironolactone	Class MCRA	Inhibits profibrotic effects of aldosterone in cardiac remodeling; can be combined with ACEIs and AT_1R antagonists to yield additional effects	CHF-NYHA III–IV; for status after MI also NYHA II. Often combined with ACEIs and AT_1R antagonists; inexpensive standard drug	Hyperkalemia, especially when combined with class A drugs. Additional administration of thiazide and/or loop diuretics to prevent hyperkalemia. Gynecomastia due to AR antagonism	12, 15, 17, 24

unfavorable remodeling of the blood vessels and the heart and stimulates the secretion of aldosterone, augmenting these adverse effects. Aldosterone increases the blood volume via higher water and sodium retention. The result is an increased cardiac workload. Subsequently edema develops, first in the periphery (predominantly legs) and later centrally (lungs). The latter process decreases blood oxygenation. Moreover, aldosterone causes cardiac fibrosis, reducing cardiac contractility.

16.2 Important Clinical Studies on CHF Pharmacotherapy

The goal of CHF therapy is to improve symptoms and to reduce hospitalizations and mortality. ◘ Figure 16.2 summarizes some important clinical studies on CHF pharmacotherapy. Historically, CHF treatment started with Na^+/K^+-ATPase inhibitors such as digoxin and digitoxin. These drugs inhibit the Na^+/K^+-ATPase in every cell of the body. Due to the ubiquitous expression of the enzyme, a very broad ADR spectrum is observed. Via an increase in intracellular calcium concentration in cardiomyocytes, digoxin and digitoxin exhibit positive inotropic effects. In addition, activation of the parasympathetic nervous system causes a negative dromotropic effect. Na^+/K^+-ATPase inhibitors possess only a very small therapeutic index (see ▶ Chap. 4). Greenish-yellowish vision is typical for intoxication with Na^+/K^+-ATPase inhibitors. They can also cause nausea, vomiting, multiple CNS dysfunctions, and any type of arrhythmia. Alterations in electrolyte balance (particularly potassium and calcium) increase the arrhythmia risk considerably. There are numerous contraindications for the administration of Na^+/K^+-ATPase inhibitors such as sick sinus syndrome, AV block, and cardiomyopathy. The DIG study failed to reveal a beneficial effect on mortality in NYHA III–IV patients. The role of Na^+/K^+-ATPase inhibitors in CHF treatment remains controversial.

Based on the assumption that positive inotropy is a valid strategy in CHF, the PDE3 inhibitor milrinone was studied in NYHA III–IV patients in the PROMISE study. PDE3 is strongly expressed in the heart. PDE3 inhibition increases cAMP and exerts a positive inotropic effect (see ▶ Chaps. 1 and 5). However, in contrast to the suggestive name of the study, milrinone increased mortality. Therefore, it has also been called "killrinone." In the XHFS study, positive inotropy was induced by the partial β_1AR agonist xamoterol (see ▶ Chaps. 1 and 5). However, a dramatic increase in mortality was found, resulting in early termination of the study. Although the aforementioned studies were disappointing, they caused revision of pharmacotherapeutic concepts for CHF away from positive inotropy to correction of pathophysiological maladaptations (see ◘ Fig. 16.1).

Study	Drug	NYHA stage	Mortality
MERIT-HF	Metoprolol	II–IV	– 35%
RALES	Spironolactone	III–IV	– 35%
CONSENSUS I	Enalapril	IV	– 40%
ELITE II	Captopril *versus* losartan (equivalent)	II–III	– 30%
SHIFT	Ivabradine (*versus* standard therapy A + MCRA + B + D)	II–IV	– 18% (especially hospitalization)
PARADIGM-HF	Sacubitril + valsartan (*versus* enalapril)	II–IV	– 16%
XHFS	Xamoterol	III–IV	+ 245%
PROMISE	Milrinone	III–IV	+ 28%
DIG	Digoxin	III–IV	± 0%
Current meta-analysis of 16 clinical studies in AF patients	Digoxin	AF in patients with or without CHF in different stages	+ 27%

◘ **Fig. 16.2** Overview of important clinical studies on CHF pharmacotherapy. Beware of the uncritical use of Na^+/K^+-ATPase inhibitors in CHF! All positive inotropic drugs are problematic in this disease! The corresponding clinical studies are marked in light gray

The beneficial effects of long-term inhibition of the sympathetic nervous system were impressively demonstrated in the MERIT-HF study. Via β_1AR antagonism in the heart and in the kidney and consequent inhibition of RAAS, mortality in NYHA II–IV patients was substantially reduced. The CONSENSUS I study convincingly demonstrated that RAAS inhibition with ACEIs lowers mortality in NYHA IV patients. By analogy to hypertension treatment (see ▶ Chap. 15), AT_1R antagonists are similarly effective as ACEIs in CHF. This was shown in the ELITE II study. The RALES study documented that MCR antagonism with spironolactone exhibits beneficial effects on mortality. The PARADIGM-HF study revealed that NEP inhibition in combination with AT_1R antagonism decreases mortality in NYHA II–IV more effectively than ACE inhibition. Ivabradine selectively blocks the HCN4 channel that plays a critical role in spontaneous depolarization of the sinoatrial node. In the SHIFT study, ivabradine exhibited additional benefits to a standard CHF treatment, particularly via reducing hemodynamically unfavorable tachycardia.

16.3 CHF Pharmacotherapy

The clinical studies on CHF pharmacotherapy provide rational starting points for treatment. Prior to pharmacotherapy, general measures have to be implemented. An exercise program commensurate with the physical capabilities of the NYHA I–III patient is essential to keep the cardiovascular system functional and to prevent atrophy of the heart and skeletal muscles as well as osteoporosis (see ▶ Chap. 20). NaCl consumption should be restricted to <3 g/day. Beverages should only be consumed in moderate volumes to avoid edema. Body weight reduction is indicated. Long air travels and journeys into tropical regions should be avoided because they can facilitate edema development. Thrombosis prevention with compression hosiery and ASA (low dose) may be required (see ▶ Chap. 18). Both hypothyroidism and hyperthyroidism must be treated because changes in thyroid gland function adversely affect heart function (see ▶ Chap. 21). Arrhythmias should be corrected, amiodarone and β_1AR antagonists being important drugs (see ▶ Chap. 17).

Before a specific CHF pharmacotherapy is implemented, it has to be checked whether the patient takes drugs that deteriorate CHF. COX inhibitors, PPAR-γ agonists, lithium, and GCR agonists can induce water and sodium retention during long-term treatment (see ▶ Chaps. 10, 11, 12, and 28). The classic cytostatic drug doxorubicin as well as VEGF and TNF inhibitors possesses cardiotoxic effects, too (see ▶ Chaps. 11 and 32). Because of their pronounced negative chronotropic, dromotropic, and inotropic effects, the CCBs verapamil and diltiazem can deteriorate CHF (see ▶ Chap. 17). NSMRIs and mGPCR antagonists exhibit antagonistic properties at α_1AR and M_xRs (see ▶ Chaps. 28 and 29). α_1AR antagonism causes vasodilation with subsequent reflex tachycardia which is enhanced by M_xR antagonism, culminating in tachyarrhythmias. In addition, drugs available on the Internet such as extracts from dried bovine thyroid glands (see ▶ Chap. 21) or the AC stimulator forskolin can deteriorate CHF; this is also the case for indirect sympathomimetics such as ephedrine and amphetamine (see ▶ Chaps. 1 and 5).

After implementation of the aforementioned measures and adjustment of potentially cardiotoxic medication, CHF pharmacotherapy is performed according to the NYHA stage. In NHYA-I, class A drugs, i.e., ACEIs, and in the case of ADRs (angioedema, dry cough), AT_1R antagonists are used (see ▶ Chap. 15). The most important ADR of class A drugs is hyperkalemia, resulting in bradycardia. In the case of concomitant hypertension, class D drugs (thiazide diuretics, see ▶ Chap. 15) are additionally administered, not only to reduce the BP but also to counteract hyperkalemia. In MI patients, MCRAs are used because they can improve the hemodynamically unfavorable fibrosis of the myocardium. In case of hypertension and following MI, class B drugs are additionally applied.

In NYHA II patients, class B drugs (β_1AR antagonists) are included into the therapeutic regime. It is critical to start the therapy with about 1/10 of the finally intended target dose and to slowly increase the dose every 2–4 weeks under close observation of the clinical symptoms. With this procedure, the risk of a CHF impairment by class B drugs can be largely reduced. In case of edema, class D drugs (thiazide or loop diuretics) are added. The main effect of diuretics is that they reduce dyspnea, peripheral edema, and ascites. However, they do not decrease mortality. Therapy with class D drugs entails the risk of exsiccosis

and hypokalemia. The hypokalemia risk can be reduced by concomitant application of class A drugs.

In NYHA III–IV patients, MCRAs are added to classes A + B. The combination of classes A + MRCA substantially increases the risk of severe hyperkalemia that can result in life-threatening bradycardia. Therefore, in case of combination of classes A + MRCA, the inclusion of class D drugs (thiazide and/or loop diuretics) is mandatory. Particularly in cases of reduced kidney function, the combination of thiazide and loop diuretics is important. Furosemide and torasemide are prototypical loop diuretics.

If the combination of drugs of the classes A + B + D + MRCA is still insufficient, further drug classes can be added. In patients with sinus rhythm and a HR ≥ 70/minute, the HCN4 channel blocker ivabradine can be administered. An alternative is the integration of the NEP inhibitor sacubitril into the regime (see ▶ Chap. 15). The drug reduces aldosterone secretion and stimulates sodium elimination. Additionally, BP decreases and remodeling is positively influenced.

In acute HF, the goal is to achieve short-term improvement of heart function until long-term therapy becomes effective. Therapy of acute HF is unsatisfying because in most cases, there is an underlying severe damage of the myocardium, limiting the options. Cardinal symptoms of acute HF are pulmonary edema with resulting hypoxia and dyspnea. Therefore, application of oxygen is important. In acute HF, morphine alleviates dyspnea via respiratory depression (see ▶ Chap. 10). The pulmonary edema can be reduced with loop diuretics which induce dilation of venous capacity vessels and reduce preload (see ▶ Chap. 15). With a delay, the diuretic effect contributes to the reduction of pulmonary edema (see ▶ Chap. 12). Preload reduction can also be achieved with GTN (see ▶ Chap. 9). In resistant cases, preload and afterload may be diminished with SNP (see ▶ Chaps. 9 and 15).

Short-term therapy with positive inotropic drugs can be accomplished using the PDE3 inhibitor enoximone or the synthetic catecholamine dobutamine (not to be confused with dopamine). Dobutamine is an agonist at β_1AR, β_2AR, and α_1AR. Since vasoconstriction via the α_1AR and vasodilation via the β_2AR neutralize each other (see ▶ Chap. 5), the positive inotropic β_1AR effect dominates. The risk of a positive inotropic therapy is that it can trigger tachyarrhythmias (see ▶ Chap. 17). Therefore, as soon as possible, an effective long-term therapy has to be implemented. Temporary cardiac support systems complement pharmacotherapy. Heart transplantation is the last resort but is available only for few selected patients.

16.4 Pathophysiology of Coronary Heart Disease (CHD) and Pharmacotherapeutic Concepts

CHD is mostly caused by atherosclerosis and subsequent narrowing of the coronary arteries, resulting in insufficient supply of the myocardium with oxygen and nutrients. CHD is one of the most common causes of death globally. The annual mortality of CHD patients is about 1–2%. Figure 16.3 provides an overview of CHD pathophysiology and pharmacological interventions. Stress, hypertension, DM, hypercholesterolemia, tobacco abuse, and increased age are important risk factors (see ▶ Chaps. 15, 19, and 22). Atherosclerosis leads to myocardial ischemia that is initially symptomless. Later, AP develops. In stage I, symptoms are present during vigorous physical activities. Stages II and III are characterized by mild complaints and severe symptoms, respectively, during normal physical activities. In stage IV, symptoms are present at rest. AP can develop into an ACS that is due to thrombosis of coronary arteries. ACS typically presents with severe retrosternal pain that projects into the left arm accompanied by anxiety, dyspnea, BP decrease or increase, bradycardia, or tachycardia. ACS can culminate in MI, leading to irreversible destruction of the myocardium. MI mortality amounts to 30–50% within the first month, with about 50% of total mortality occurring within the first 2 hours. MI with ST elevation (STEMI) is particularly dangerous. MI can lead to VT and (sudden) heart death or acute HF. In the chronic phase after MI, a hemodynamically unfavorable remodeling in the heart takes place that is dominated by fibrosis. This process is aggravated by RAAS activation. Extensive heart fibrosis leads to heart dilation and CHF.

Short-term goals of ACS and MI therapy are the reduction of acute symptoms (pain, anxiety, dyspnea) and recanalization of the occluded

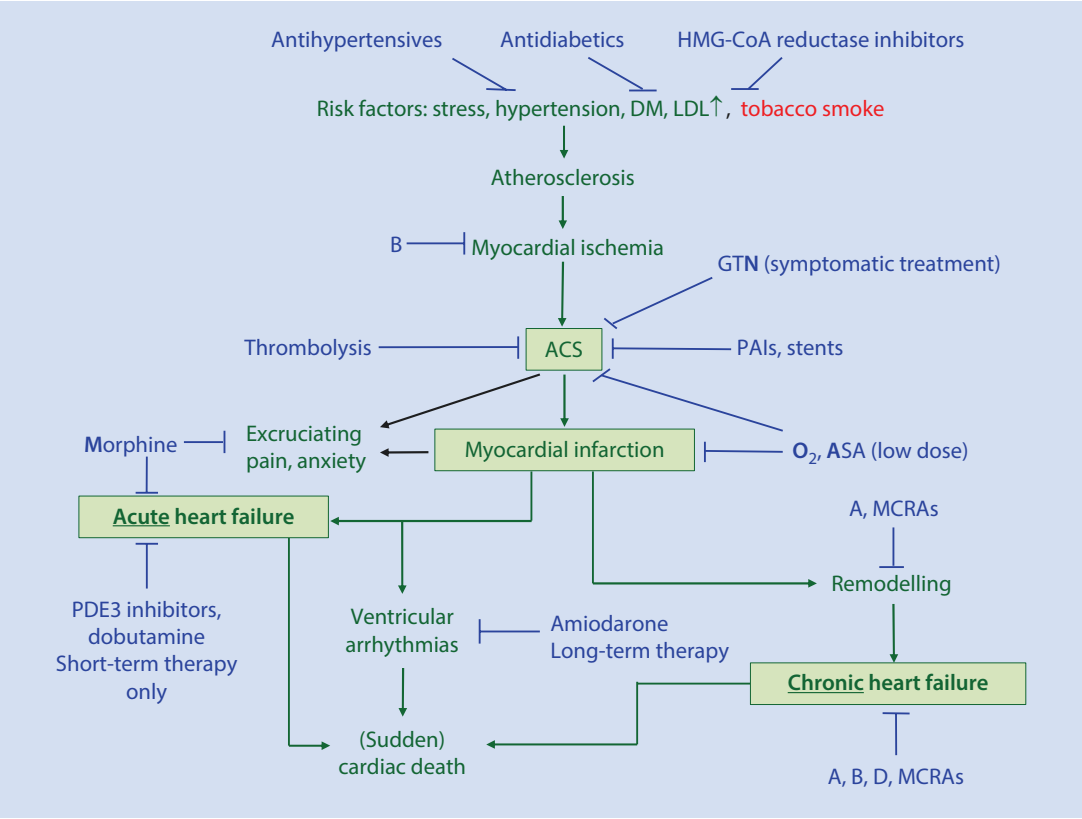

Fig. 16.3 Pathophysiology of CHD and pharmacological interventions. In general, CHD can be divided into a chronic stage and an acute stage (AP → ACS → MI). Depending on the specific symptoms and diseases stage, in CHD a number of different drug classes are used. These drugs are dealt with in various chapters of this book. References to the specific chapters are provided in the main text. The key of CHD therapy is the treatment of causative diseases

coronary arteries. Mortality can reduced below 10% in the first month after the event with rapid reperfusion of coronary arteries applying percutaneous transluminal coronary angioplasty (PTCA) including vessel dilation with or without stent implantation. Long-term goals of CHD treatment are the elimination of causative factors, reduction of cardiac oxygen consumption, and prevention of restenosis, remodeling, VT, and CHF.

GTN is an on-demand medication of AP. The drug reduces oxygen consumption of the heart via preload reduction and can be administered by the patient himself (see ▶ Chap. 9). GTN does not reduce mortality and is not suitable for long-term therapy due to desensitization. Emergency treatment of ACS and MI follows the MONA scheme. The MOR agonist **m**orphine (3–5 mg i.v., see ▶ Chap. 10) is analgesic, reduces pre- and afterload, and mitigates dyspnea via respiratory depression (see ▶ Chap. 10). **O**xygen administration (4–8 l/minute) improves organ oxygenation. **N**itroglycerin (GTN, 0.4–0.8 mg sublingual) reduces oxygen consumption of the heart via preload reduction. **A**SA (165–375 mg i.v.) inhibits TXA_2 formation in platelets, platelet aggregation, and growth of the thrombus (see ▶ Chap. 18). Treatment of VT with the class I antiarrhythmic drug lidocaine is ineffective. During PTCA, coagulation is further inhibited by administration of heparin and glycoprotein IIb/IIIa receptor antagonists (see ▶ Chap. 18). If a stent is inserted into a coronary artery to keep the lumen open, there is a risk of stent thrombosis. To reduce the risk, long-term therapy with ASA (low dose) + $P2Y_{12}R$ antagonists such as clopidogrel is required (see ▶ Chap. 18).

The risk of intima hyperplasia may be lowered by coating of certain stents with immunosuppressants such as sirolimus (see ▶ Chap. 11) or classic cytostatics such as paclitaxel (see ▶ Chap. 32). The

effectiveness of coated stents is still a matter of debate. If PTCA cannot be performed or is contraindicated, fibrinolysis with a plasminogen activator constitutes a therapeutic alternative (see ▶ Chap. 18). The most critical factor in successful treatment of ACS and MI is rapid initiation of therapy in order to keep the tissue damage as small as possible.

In long-term therapy of CHD general measures and pharmacotherapy complement each other. It is crucial to stop tobacco smoking immediately because toxic ingredients of the smoke impair blood vessels, particularly endothelial cells (see ▶ Chaps. 9 and 22). The pharmacological options to support nicotine withdrawal with partial nAChR agonists and nAChR antagonists (see ▶ Chap. 5) are far from satisfying and limited by serious ADRs. It is best if the patient manages tobacco withdrawal without pharmacological aids. The experience of the excruciating pain in ACS and MI may be a great motivation for tobacco abstinence. It increases life quality and decreases mortality. A calory- and cholesterol-restricted diet rich in fruits and vegetables and polyunsaturated fatty acids (Mediterranean diet including moderate consumption of red wine) and an exercise program commensurate with the physical capabilities of the patient enhance capacity of the cardiovascular and musculoskeletal system.

In long-term treatment of CHD, β_1AR antagonists decrease mortality due to the reduction of cardiac oxygen consumption (see ▶ Chap. 5) and RAAS inhibition (see ▶ Chap. 15). HMG-CoA reductase inhibitors decrease mortality via reduction of LDL cholesterol (see ▶ Chap. 22). Further drugs reducing mortality after MI are PAIs (ASA low dose and $P2Y_{12}$R antagonists, see ▶ Chap. 18) as well as ACEIs and AT_1R antagonists which positively influence cardiac remodeling. The secondary prevention of CHD can be performed by the primary care physician. Primary prevention of CHD with β_1AR antagonists, HMG-CoA reductase inhibitors, and PAIs can cause ADRs and adds costs to healthcare systems. Although advertised quite aggressively in some countries, primary prevention of CHD should not be performed with drugs but focus on a healthy and active lifestyle, tobacco abstinence, and treatment of diseases that are CHD risk factors.

DM (mostly type 2) is a major risk factor for atherosclerosis and CHD and must be therefore rigorously treated with diet and metformin (see ▶ Chap. 19). Hypertension must be properly treated as well (see ▶ Chap. 15). Treatment of VT in MI patients is difficult. Amiodarone has been shown to be effective, but its use is compromised by unfavorable pharmacokinetic properties and ADRs (see ▶ Chaps. 2 and 17).

16.5 Questions and Answers

Questions

Which statement on pharmacotherapy of CHD is correct?

A. GTN can be used for long-term therapy of CHD.
B. Clopidogrel and ASA are contraindicated because of increased risk of hemorrhage.
C. β_1AR antagonists are contraindicated because of the risk of CHF.
D. Morphine is suitable for treatment of the excruciating pain in MI.
E. Antihypertensive drugs are contraindicated because of the risk of reduced coronary perfusion.

Answers

A. GTN can only be used for symptomatic therapy of AP and ACS within the MONA scheme. Via reduction of preload, oxygen consumption is reduced. Because of desensitization, GTN is not suitable for long-term therapy of CHD.
B. Clopidogrel and ASA increase the risk of hemorrhage, but the reduced risk of coronary artery thrombosis overrides these ADRs. Mortality-reducing effects of ASA and clopidogrel in CHD have been demonstrated in clinical studies.
C. Because of the negative inotropic effects of the β_1AR antagonists, oxygen consumption and the MI risk are reduced. β_1AR antagonists reduce mortality in CHD.
D. The early application of morphine constitutes an important therapeutic measure within the MONA scheme. Via analgesia and sedation, the stress reaction, accompanied by release of the cardiotoxic catecholamines NE and EPI, is reduced. In addition, morphine can reduce pre- and afterload.

E. Hypertension is an important risk factor for pathogenesis of atherosclerosis and hence, CHD. Therefore, hypertension has to be treated with class A, B, C, and/or D drugs and, if not sufficient, with drugs for resistant hypertension.

Answer **D** is correct.

16.6 Exercises

A 78-year-old female patient is admitted to the emergency room. The patient complains about dyspnea, palpitations, nausea, and altered vision. Everything looks greenish-yellowish. Last week, the patient had a GI tract infection accompanied by diarrhea. The infection weakened her substantially. It has become almost impossible for her to take care of her household alone. The chest X-ray shows a moderate enlargement of the heart and a central opacity. The laboratory analysis reveals a plasma potassium concentration of 3.0 mmol/l and a plasma digoxin concentration of 1.1 ng/ml. The ECG reveals sinus tachycardia (120/minute). The patient tells you that her general practitioner has been treating her for years with heart pills. Apart from these pills, she does not take any other drugs.

Questions

1. What is your diagnosis?
2. How do you proceed therapeutically?

Answers

1. Apparently, the patient has CHF (NYHA III–IV). In addition, the patient is suffering from digoxin intoxication because the therapeutic digoxin concentration of 0.8 ng/ml has been clearly exceeded. The impaired color vision virtually proofs the digoxin intoxication. Nausea is another symptom of digoxin intoxication, but it is not nearly as specific as impaired color vision. It also appears that the GI infection has resulted in substantial potassium losses and hypokalemia (plasma potassium concentration <3.6 mmol/l). In combination with hypokalemia, digoxin intoxication can cause tachycardia.
2. It is the therapeutic goal to ameliorate the NYHA stage of the patient to stage I or at least stage II. You immediately terminate the digoxin therapy. You could apply F_{ab} fragments against digoxin, but the risk of allergic reactions has to be considered. Since the patient does not appear to be massively intoxicated, you can proceed conservatively and wait for spontaneous improvement. You could normalize plasma potassium concentration by substituting potassium by i.v. infusion. However, you need to ensure that you do not infuse too large volumes of fluid because this could deteriorate CHF. So far, the patient has not yet been treated according to modern CHF principles. Therefore, you start a therapy with an ACEI (e.g., enalapril) or an AT_1R antagonist (candesartan) and add a thiazide diuretic such as chlorthalidone, perhaps also a loop diuretic such as furosemide. With this combination, you should observe a rapid improvement of the CHF symptoms and move into a better stage. Due to the potassium neutrality of the therapy, the tachycardia risk is also reduced. You perform regular controls of plasma potassium concentration and ECG. Starting from this regime, you may later add an MCRA, depending on the clinical course. However, if you elect to do so, you have to take into consideration the risk of bradyarrhythmia and hyperkalemia.

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Drug-Induced Arrhythmias and Drugs for the Treatment of Arrhythmias

R. Seifert, *Basic Knowledge of Pharmacology*, https://doi.org/10.1007/978-3-030-18899-3_17

The physiological excitation of the heart is generated in the sinoatrial node and propagated via the atrium and AV node to the ventricles. Alterations in electrolyte balance, drugs, genetic diseases, CHD, and CHF are common causes for arrhythmias. They can lead to sudden heart death or thromboembolic complications. AF leads to blood stasis in the atrium with subsequent thrombus formation and risk of pulmonary embolism or stroke. VT is a common complication of MI. Since pharmacological treatment of arrhythmias is unsatisfying, non-pharmacological measures such as pacemakers, ablation of diseased cardiac tissue, and implanted defibrillators become more important. Amiodarone is the most effective antiarrhythmic drug in AF and VT, but must be used very cautiously because of serious ADRs and unfavorable pharmacokinetics. The prescription of antiarrhythmic drugs belongs into the hands of the cardiologist. Drugs for diverse indications can cause TdP via blockade of repolarizing potassium channels. Rapid i.v. injection, electrolyte imbalances, eating disorders, comedication with CYP inhibitors, as well as liver and kidney diseases are risk factors for TdP.

Key Points

1. Various drugs for very different indications can cause TdP.
2. QT prolongation predisposes for TdP.
3. TdP are often the cause for drug market withdrawal of drugs.
4. The effects of antiarrhythmic drugs on mortality are unsatisfying.
5. Among all antiarrhythmic drugs, amiodarone possesses the highest efficacy.
6. Therapy with amiodarone is burdened by ADRs and unfavorable pharmacokinetics.
7. Compared to amiodarone, the clinical efficacy of dronedarone is unsatisfying.

17.1 Pathophysiology of Arrhythmias and Pharmacological Interventions

Under physiological conditions, the sinoatrial node is the pacemaker that determines HR (chronotropy). HR is regulated to a large extent by HCN4 channels that modulate spontaneous diastolic depolarization of the sinoatrial node. The excitation moves across the atrium to the AV node that mediates transmission of the signal to the ventricles (dromotropy). Efficient and coordinated contraction of the atria and ventricles is dependent on normal depolarization and repolarization of the cardiac conduction system. Electric conduction is mediated via voltage-dependent sodium channels and L-type calcium channels. For repolarization, potassium efflux is critical. This efflux is mainly based on HERG channels. The sympathetic nervous system mediates positive chronotropic and dromotropic effects via the β_1AR (see ► Chap. 5), HCN4 channels, and L-type calcium channels. In contrast, the parasympathetic nervous system triggers negative chronotropic and dromotropic effects via the M_2R, resulting in increased conductance of potassium channels (see ► Chap. 5).

Two major mechanisms cause arrhythmias. First, ectopic areas in the atria or ventricles can gain automaticity and take over the pacemaker function of the sinoatrial node. Second, circle-like reentry of excitation waves can occur so that the normal cycle of depolarization and repolarization is impaired. The hemodynamic consequence of arrhythmia is an irregular and inefficient heart function, resulting in fatigue, reduced physical capacity, sleep disorders, palpitations, thromboembolic complications, VT, and sudden death.

The most common causes of arrhythmias are insufficiently treated hypertension, CHD, and CHF. Many arrhythmias can be prevented by BP control (see ► Chap. 15). Most cases of CHD could be avoided by abstinence from tobacco smoking (see ► Chap. 16) and by treatment of hypertension (see ► Chap. 15) and hypercholesterolemia (see ► Chap. 22). CHF therapy can reduce arrhythmias as well since ACEIs and AT_1R antagonists (class A drugs) as well as MCRAs inhibit unfavorable remodeling processes in the heart (see ► Chap. 16). β_1AR antagonists (class B drugs) alleviate tachyarrhythmias.

Cardiomyopathies, myocarditis, and cardiac valvular defects are additional causes for arrhythmias. Hypercalcemia and hypokalemia favor tachycardia, and hyperkalemia favors bradycardia. Hyperthyroidism or overdosing of T4 (see ► Chap. 21), β_2AR agonists in high doses and indirect sympathomimetics (see ► Chap. 5), NSMRIs (see ► Chap. 28), and D_2R-mGPCR antagonists (see ► Chap. 29) can cause various

types of tachyarrhythmia. Moreover, hereditary diseases with mutations in ion channels may increase the risk of arrhythmias, particularly TdP that are life-threatening and can be evoked by many drug classes. Prevention of TdP has top priority for drug safety and is relevant for every physician, regardless of specialization (see ▶ Sect. 17.4).

From the regulation of normal and pathological heart excitation, strategies for treatment of arrhythmias can be deduced. ◘ Table 17.1 summarizes the properties of selected antiarrhythmic drugs. Traditionally, antiarrhythmics have been classified into four classes (I–IV) according to Vaughan Williams. However, this classification does not include all relevant drug classes. In addition, certain drugs (most notably amiodarone) have properties encompassing several classes. Therefore, the Vaughan Williams classification is predominantly of historic relevance.

Class I antiarrhythmic drugs block voltage-dependent sodium channels, β_1AR antagonists represent class II, and class III and class IV antiarrhythmics block repolarizing potassium channels and cardiac L-type calcium channels, respectively. Amiodarone and dronedarone possess properties of classes I–IV. In addition, M_xR antagonists and HCN4 channel blockers are used for specific arrhythmias. A problem of all antiarrhythmic drugs is that they do not discriminate between diseased and healthy cardiac tissue so that they may also cause arrhythmias themselves. Antiarrhythmics of classes II and IV and HCN4 channel blockers predominantly cause bradycardia.

The demonstration of clinical efficacy of antiarrhythmic drugs is difficult. In the CAST study, the class I antiarrhythmic drugs flecainide and encainide increased mortality in MI patients with VT. The CAST study had to be discontinued and resulted in a large reduction of prescription of class I antiarrhythmics.

In low doses the Na^+/K^+-ATPase inhibitor digoxin is widely used in AF. The therapeutic effect is assumed to be mediated by indirect stimulation of the parasympathetic nervous system and subsequent negative chronotropic and dromotropic effects. However, recent meta-analyses of clinical studies on this topic could not demonstrate convincing clinical efficacy of digoxin in AF. In fact, mortality may actually be increased. Because of the insufficient clinical efficacy and serious ADRs, digoxin should not be routinely used in AF (see ▶ Chap. 16).

Due to the unsatisfying effects of many antiarrhythmic drugs, interventional procedures for treatment of arrhythmias have gained more importance. Pacemakers, implantable defibrillators, and ablation of dysfunctional electric tissue are commonly used and effective procedures.

17.2 Atrial Fibrillation (AF)

AF is a transient or permanent arrhythmia in which the atria contracts with very high frequency (>300/minute). Due to erratic AV transmission, ventricular contractions are irregular, too fast or too slow. AF is the most common arrhythmia and affects about 1–2% of the population. The risk for AF increases with age. Men are affected more often than women. The causes and symptoms of AF have already been described in ▶ Sect. 17.1.

The first goal in AF therapy is the prophylaxis of thromboembolic complications. ASA (low dose), VKAs, and DOACs are used (see ▶ Chap. 18). In addition, the arrhythmia itself is addressed. In frequency control, AF is not interrupted, but HR is adjusted to 60–80/minute with negative chronotropic and dromotropic drugs. β_1AR antagonists or L-type CCBs with cardiac actions can be used (◘ Table 17.1).

Restoration of sinus rhythm can be achieved by ablation of pathologically active tissue or pharmacologically. Amiodarone is an important antiarrhythmic drug with proven effect on rhythm control. The drug is very lipophilic but nonetheless shows a quite variable bioavailability (25–80%). Very high plasma protein binding implies the risk of drug interactions due to competition for protein-binding sites. Furthermore, amiodarone has a long half-life between 14 and 100 days. Therapeutic plasma concentrations range between 0.5 and 2.5 µg/ml. These pharmacokinetic properties hamper effective and safe therapy with amiodarone. Following initial saturation with 200 mg three times a day for 10 days and then 200 mg twice daily for another 10 days, long-term therapy is performed with a dose of 200 mg per day. With this regime, the risk of drug interactions and ADRs is generally acceptable.

Because of the structural similarity of amiodarone with T4 and its two iodine substituents, up to 40% of the patients under long-term treatment

Table 17.1 Overview of selected antiarrhythmic drugs

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Ajmaline	SBC prolonging action potential (class Ia of the Vaughan Williams classification)	Antiarrhythmic, principally also proarrhythmic	VT, SVES, VES	Nausea, headache, cholestasis, arrhythmias	
Amiodarone	Mixed class I–IV antiarrhythmic drug (formerly class III of the Vaughan Williams classification)	Antiarrhythmic, principally also proarrhythmic	AF, VT, VES; has been shown to possess the best effect in various clinical studies	Hypo- and hyperthyroidism, photosensitivity, corneal deposits, pulmonary fibrosis, tremor, polyneuropathy, hepatopathy, TdP	2, 21
Atropine	M_xR antagonist	Antagonizes the negative chronotropic and dromotropic effect of ACh	Sinusoidal bradycardia, AV block (intraoperative and emergency situations; no long-term therapy because of unfavorable ADRs)	Generalized M_xR antagonism with antimuscarinic syndrome	4, 5
Dronedarone	Mixed class I–IV antiarrhythmic drug	Antiarrhythmic, principally also proarrhythmic	AF, but generally less effective than amiodarone	Diarrhea, nausea, exanthemas, renal disorders, vomiting, arrhythmias (bradycardia, TdP)	2
Ivabradine	Blockade of sinoatrial HCN4 channels	Negative chronotropy	Sinus tachycardia in CHF and CHD	Phosphenes, severe bradycardia	16
Metoprolol	β_1AR antagonist (class II of the Vaughan Williams classification)	Negative chronotropy and dromotropy	SVT, AF, VES	Deterioration of CHF if dose is increased too fast; bradycardia, AV block. Cold extremities, risk of asthma attacks, and unrecognized hypoglycemia. The latter ADRs are especially observed with higher doses when also the β_2AR is antagonized	1, 5, 14, 15, 16, 19
Verapamil	Blockade of L-type calcium channels (class IV of the Vaughan Williams classification)	Negative chronotropy and dromotropy	AF, SVES	Bradycardia, AV block, CHF because of negative inotropic effect, and BP drop	15

ST sinus tachycardia, *SVT* supraventricular tachycardia, *SVES* supraventricular extrasystoles, *VES* ventricular extrasystoles. Because of the overall very limited clinical importance of antiarrhythmics, several drug classes are not covered here

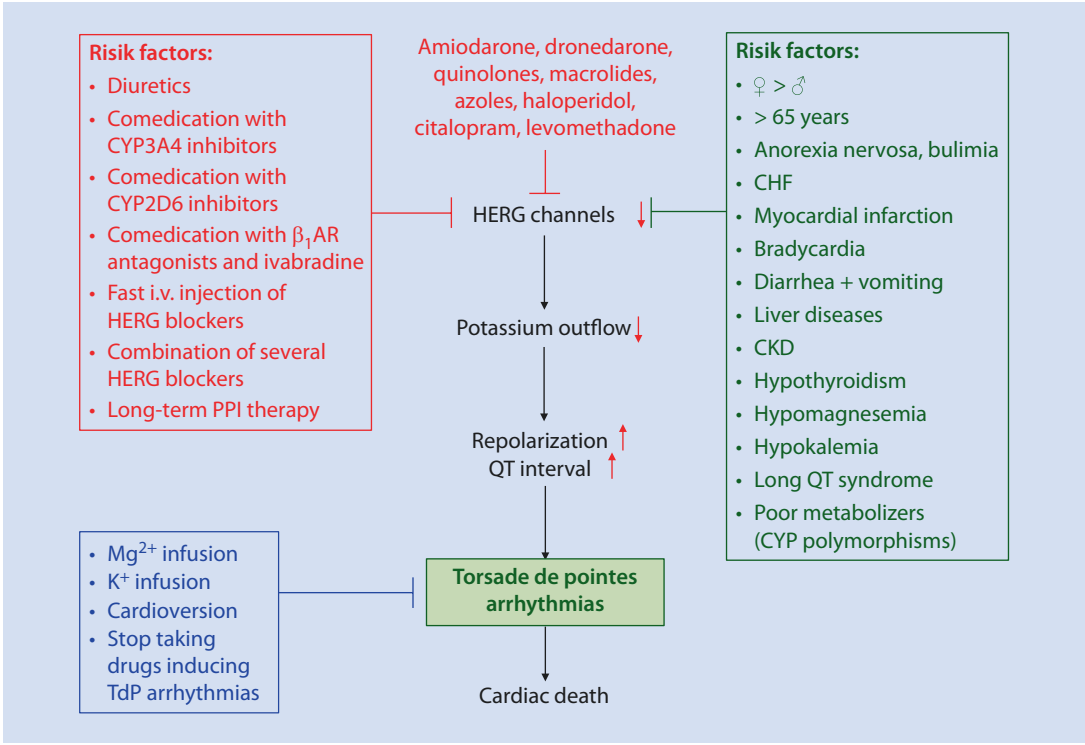

Fig. 17.1 Drug-induced TdP due to inhibition of HERG channels. Because TdP are life-threatening and difficult to treat, prevention and knowledge about problematic drugs and risk factors are essential

develop hypo- or hyperthyroidism (see ▶ Chap. 21). Hypothyroidism is due to inhibition of deiodases that convert the inactive T4 into the active T3. Amiodarone-induced hyperthyroidism is particularly dangerous because tachyarrhythmias may develop. Amiodarone can cause hyperthyroidism via two different mechanisms. In the early form, requiring cessation of amiodarone therapy, synthesis of T4 and T3 is increased. In the late form, requiring no cessation of therapy, T3 and T4 are temporarily released to a greater extent. This ADR is associated with thyroiditis and can be treated with GCR agonists.

In up to 90% of the patients, amiodarone accumulates in the cornea; in 1–10%, mild vision problems may result. In about 1–2%, optic neuropathy and scotomas develop. Therefore, a patient treated with amiodarone needs to have regular eye examinations by the ophthalmologist. Amiodarone also increases the sensitivity of the skin toward UV light exposure. The potentially lethal pulmonary fibrosis can be largely avoided if the daily amiodarone dose is kept <400 mg. If fibrosis is diagnosed in an early stage (pneumonitis), it is reversible. Therefore, patients treated with amiodarone also need to have regular lung examinations by the pulmonologist. Moreover, amiodarone can cause increase in liver enzymes and polyneuropathy with tremor and ataxia. Due to its mechanism of action, amiodarone may lead to bradycardia and TdP (see ◘ Fig. 17.1). If the QT interval is >500 ms, the therapy must be terminated.

Amiodarone can also cause dangerous drug interactions. As a result of CYP3A4 and CYP2C9 inhibition, the risks of statin myopathy (see ▶ Chap. 22) and of severe hemorrhage under VKA therapy (see ▶ Chaps. 2 and 18), respectively, increase.

Amiodarone highlights a dilemma in pharmacotherapy of arrhythmias: on the one hand, it is an effective drug. On the other hand, it possesses unfavorable pharmacokinetic properties and serious ADRs (see ▶ Chap. 2). This situation was the starting point for the development of dronedarone (◘ Table 17.1) that is chemically related to amiodarone but does not contain iodine. Accordingly, dronedarone does not interfere with thyroid gland function. This is a substantial advantage compared to amiodarone.

Dronedarone is absorbed more reliably (70–95%) than amiodarone and possesses a much shorter half- life (12 hours). Like amiodarone, dronedarone inhibits CYP3A4. After approval, it turned out that dronedarone can also cause pulmonary fibrosis and polyneuropathy in contrast to expectations. Additionally, it possesses ADRs on the skin, the liver, and in the GI tract. Clinical studies revealed that altogether dronedarone has fewer and less serious ADRs than amiodarone, but the therapeutic effect in AF is smaller. In the PALLAS and ANDROMEDA studies, dronedarone increased mortality compared to placebo in patients with advanced CHF. Therefore, dronedarone must not be administered in these patients. Like amiodarone, dronedarone can cause bradycardia. Taken together, there is no ideal antiarrhythmic drug for treatment of AF, but amiodarone still remains the gold standard.

17.3 Ventricular Tachycardia (VT)

VT originates in the ventricles and may be life-threatening. Clinically, VT goes along with palpitations, dyspnea, AP, pulmonary edema, and cardiogenic shock. Intoxication with Na^+/K^+-ATPase inhibitors and/or hypokalemia can facilitate the occurrence of VT (see ▶ Chaps. 4 and 12). Especially polymorphic VT can proceed to ventricular fibrillation and result in cardiac arrest. VT is caused by ectopic pacemakers or reentry processes. Electric cardioversion is the therapy of choice. Pharmacologically, the class I antiarrhythmic drug ajmaline (◘ Table 17.1, 50 mg slowly administered i.v. under ECG control) or the class I-IV antiarrhythmic drug amiodarone (500 mg administered slowly i.v. under ECG control) are treatment options.

The long-term therapy of VT is difficult. Meta-analysis of many clinical studies revealed that amiodarone is the antiarrhythmic drug of choice to prevent VT and sudden cardiac arrest in MI patients. Implanted defibrillators are an alternative approach. It is crucial to effectively treat underlying diseases such as hypertension (see ▶ Chap. 15), CHF, and IHD (see ▶ Chap. 16), to avoid arrhythmogenic drugs, particularly Na^+/K^+-ATPase inhibitors, and to prevent hypokalemia.

17.4 *Torsade-de-pointes* Arrhythmia (TdP)

TdP are a special type of VT and characterized by spindle-shaped ECG signatures. TdP are life-threatening and can proceed to ventricular fibrillation, resulting in cardiac arrest and death. Malfunctioning HERG potassium channels are the culprit of TdP (◘ Fig. 17.1). These channels are important for repolarization of the myocardium. Blockade of HERG channels delays repolarization as is evident from prolonged QT intervals in the ECG. This, in turn, promotes pathological afterdepolarizations and excessive spreading of repolarization. QT intervals >500 ms enhance TdP risk.

Numerous drugs for different indications can block HERG channels (◘ Table 17.2). Among these drugs are class I–IV antiarrhythmic drugs, mGPCR antagonists, NE/5-HT enhancers, certain MOR agonists, macrolide antibiotics, quinolone antibiotics, and azole antimycotics. Hydrophobic aromatic ring systems of these drug classes interact with hydrophobic amino acids in the pore of the HERG channel and, thereby, prevent potassium efflux. The TdP risk is particularly high when problematic drugs in high doses are rapidly injected i.v. A classic example for this issue is the i.v. injection of the D_2R-mGPCR antagonist haloperidol that very often, but inappropriately, is used in confused and agitated geriatric patients (see ▶ Chaps. 29 and 30). This dangerous practice resulted in numerous deaths and must be avoided.

Prevention of TdP is more effective than their treatment. It is particularly important to recognize risk factors such as hypokalemia and hypomagnesemia (see ◘ Fig. 17.1). Therapy with thiazide and/or loop diuretics facilitates TdP development unless these drugs are combined with potassium-sparing diuretics, ACEIs, AT_1R antagonists, or MCRAs (see ▶ Chaps. 12, 15, and 16). Eating disorders and GI diseases accompanied by vomiting and diarrhea and long-term therapy with PPIs can promote hypokalemia (see ▶ Chap. 13). Bradycardia, e.g., caused by hypothyroidism (see ▶ Chap. 21), prolongs the QT interval and promotes TdP. β_1AR antagonists and ivabradine may lead to TdP in bradycardia. MI and CHF are risk factors for TdP as are female sex

Table 17.2 Overview of important drugs that can cause TdP

Group of Drugs	Prototypical drug	Further contexts in Chaps.
Class I–IV antiarrhythmic drugs	Amiodarone	17
AChE inhibitors	Donepezil	30
5-HT_3R antagonists	Ondansetron	6
Azole antimycotics	Fluconazole, itraconazole	35
Quinolone antibiotics	Sparfloxacin and grepafloxacin were withdrawn from the drug market, but basically, all quinolone antibiotic drugs bear the risk of developing TdP	33
H_1R antagonists	Astemizole, terfenadine (fexofenadine prodrug; terfenadine was withdrawn from the drug market)	7
5-HT_4R agonists	Cisapride (withdrawn from the drug market); prucalopride has a much lower TdP risk	6
Macrolide antibiotics	Erythromycin, clarithromycin	33
MOR agonists	Levomethadone	10
SSRIs	Citalopram	28
D_2R-mGPCR antagonists	Haloperidol	29

The TdP risk for the drugs listed in this table is proven. Only few of these drugs were actually withdrawn from the drug market. Therefore, prior to administration of problematic drugs, it is essential to assess the TdP risk for each patient

and high age. Liver insufficiency and CKD can cause TdP due to delayed elimination of drugs. Many TdP-causing drugs are substrates for CYP3A4 and CYP2D6. Therefore, comedication with CYP3A4 or CYP2D6 inhibitors may increase TdP risk (see ▶ Chap. 2). Moreover, genetic factors result in higher TdP probability. On the one hand, there are CYP polymorphisms associated with low activity and accordingly reduced drug elimination (poor metabolizer). On the other hand, mutations in various ion channels including HERG channels can result in hereditary long-QT syndrome.

TdP manifest themselves like VT and are diagnosed in the ECG. Intake of the TdP-causing drug has to be terminated immediately. Infusion of magnesium sulfate and correction of hypokalemia may eliminate TdP. Electric cardioversion is the last resort.

The high clinical relevance of TdP is exemplified with terfenadine. In the early 1980s, terfenadine was approved as second-generation H_1R antagonist for the treatment of type I allergies (conjunctivitis and rhinitis) (see ▶ Chap. 7). Terfenadine is a prodrug and converted to the active metabolite fexofenadine by CYP3A4 in the liver (see ▶ Chap. 2). Tragically, terfenadine resulted in sudden deaths of otherwise healthy allergic patients. The reason was blockade of HERG channels. As a consequence of these events, physicians, the pharmaceutical industry, and drug approval authorities have become much more aware of the clinical relevance of drug-induced TdP. Nonetheless, many drugs that cause TdP are still on the drug market. This example highlights that physicians and pharmacists bear great responsibility in choosing drugs for their patients wisely and trying to avoid drugs inducing TdP. The risk factors shown in Fig. 17.1 should be checked in every patient prior to initiating therapy with a problematic drug.

17.5 Questions and Answers

Questions

Which assignment of antiarrhythmic drug to mechanism of action is correct?

A. Metoprolol – antagonism at the β_2AR
B. Atropine – inhibition of AChE
C. Digoxin – inhibition of the parasympathetic system
D. Ivabradine – blockade of voltage-dependent calcium channels
E. Amiodarone – blockade of repolarizing potassium channels

Answers

A. Metoprolol antagonizes the β_1AR and, thereby, exerts negative chronotropic and dromotropic effects. Therefore, metoprolol can be used for the treatment of several tachyarrhythmias.
B. Atropine antagonizes M_xRs and, thereby, alleviates the negative chronotropic and dromotropic effects of the parasympathetic system. Therefore, atropine is used for emergency treatment of sinus bradycardia and AV block.
C. Digoxin therapy actually stimulates the parasympathetic nervous system. Theoretically, this effect could be exploited in the therapy of AF. However, the results of clinical studies on digoxin use in AF are not supportive for its clinical use in this condition.
D. Ivabradine blocks sinoatrial HCN4 channels and, thereby, spontaneous depolarization. Therefore, ivabradine can be used for the treatment of sinus tachycardia, predominantly in CHF and IHD.
E. Due to potassium channel blockade, amiodarone can be used for treatment of AF, VT, and ventricular extrasystoles.

Answer **E** is correct.

17.6 Exercises

An 88-year-old male AD patient is agitated and confused. To improve the symptoms as soon as possible, the attending physician of the geriatric ward rapidly injects 5 mg haloperidol i.v. Within few seconds, the patient turns pale and sweaty and becomes somnolent. The pulse is very irregular and faint. The astonished ward physician does not know what to do and calls the cardiologist. He takes an ECG and diagnoses TdP. An immediately executed cardioversion restores sinus rhythm. The patient's face color normalizes quickly and he becomes responsive. The BP is 110/80 mm Hg, and the HR is 80/minute.

Questions

1. How could these life-threatening TdP have been avoided?
2. Except for elderly patients, which other patients have an increased risk for TdP?

Answers

1. Haloperidol is a drug that blocks HERG channels with high potency and, therefore, has a substantial risk for TdP. The risk is particularly high when haloperidol reaches the heart rapidly and at high concentrations. Evidently, this is the case upon rapid i.v. injection of the drug. Therefore, haloperidol should only be injected i.v. in exceptional cases (e.g., in massive acute psychosis associated with hallucinations and aggression). If the indication for i.v. application is given, the drug should be injected very slowly and under ECG control. Old patients often have disturbances of electrolyte balance, further increasing the TdP risk. Because of serious ADRs and very questionable effects in confused geriatric patients (actually no sedation is caused by the drug!), haloperidol should be used only with the greatest caution in these patients.
2. A QT interval >500 ms, female sex, MI, CHF, hypokalemia, hypomagnesemia, hypocalcemia, eating disorders, bradycardia, CKD, drugs that prolong the QT interval, polypharmacy, and i.v. injection of drugs all constitute risk factors for TdP.

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Drugs for Treatment of Thromboembolic Diseases

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Thromboembolic diseases are caused by reduced blood flow, injury of the endothelium, increase in blood coagulability, and/or contact of the blood with foreign material. COX-2 inhibitors, oral contraceptives, EPO, and certain tumor therapeutics can favor thromboembolism. The therapeutic goal is to prevent thromboembolism and to dissolve thrombi. Drugs for the treatment of thromboembolic diseases can cause hemorrhage and anemia. UFHs inhibit factor Xa and thrombin via complex formation with antithrombin III; LMWHs inhibit only factor Xa. Heparins are used in many acute medical situations such as thrombosis prophylaxis following surgery. VKAs inhibit carboxylation of several clotting factors and are used in long-term therapy, e.g., for stroke prevention in AF. They have several ADRs but are very inexpensive. DOACs comprise factor Xa and thrombin inhibitors and include the indications of heparins and VKAs. They possess fewer ADRs and drug interactions than VKAs but are much more expensive. Plasminogen activators are used in emergency treatment of MI and non-hemorrhagic stroke. ASA in low dose (~100 mg per day) inhibits platelet aggregation via irreversible inhibition of COX-1-catalyzed TXA_2 formation and clopidogrel via irreversible binding to the $P2Y_{12}R$. Both drugs are used for secondary prevention of MI and stroke.

Key Points

1. UFHs and LMWHs possess similar indications, but LMWHs are easier to administer and have a lower HIT risk.
2. Protamine is an antidote for UFHs.
3. Provided that regular INR controls are performed and certain foods and drug interactions are avoided, VKAs are well suited and effective for prevention of thromboembolic diseases.
4. Vitamin K is an antidote for VKAs.
5. In case of contraindications for VKAs or ADRs, DOACs are used.
6. DOACs comprise factor Xa and thrombin inhibitors.
7. If DOACs are used, the currently high treatment costs have to be considered.
8. In case of acute hemorrhage under therapy with VKAs or DOACs, clotting factor concentrates are applied.
9. In order for plasminogen activators to be effective in stroke and MI, a short latency between onset of symptoms and start of therapy is crucial.
10. ASA (low dose) is very inexpensive and well suited for secondary prevention of MI.
11. Clopidogrel can also be used for secondary MI prevention but is more expensive than ASA.
12. The combination of ASA + clopidogrel increases the risk of hemorrhage.

18.1 Hemostasis, Fibrinolysis, and Pharmacological Interventions for Thromboembolic Diseases

Under physiological conditions, an equilibrium between hemostasis and fibrinolysis exists, ensuring blood flow in the vessels and oxygen supply for the organs. ◘ Figure 18.1 provides an overview of hemostasis, fibrinolysis, and pharmacological interventions. ◘ Table 18.1 summarizes representative drugs for thromboembolic diseases. Factor Xa is the key enzyme for fibrin formation. It is activated via the intrinsic and extrinsic system. Factor Xa converts prothrombin into the active protease thrombin. Biosynthesis of prothrombin (and other clotting factors) occurs in the liver and requires vitamin K-dependent carboxylation. Thrombin catalyzes the conversion of fibrinogen to fibrin, thereby mediating thrombus formation and vascular occlusion. Additionally, platelets play an important role in thrombus formation (see ▶ Sect. 18.6).

If hemostasis is increased relative to fibrinolysis, thromboembolic diseases develop. Among these diseases are MI (see ▶ Chap. 16), PAD, and DVT with consecutive PE. Risk factors for thromboembolism are:

1. Reduced blood flow, e.g., due to immobilization after surgery, AF (see ▶ Chap. 17), CHF (see ▶ Chap. 16), venous insufficiency, and tumor diseases (see ▶ Chap. 32)
2. Endothelial cell damage, e.g., after trauma, postsurgically or as consequence of tobacco consumption (see ▶ Chaps. 3, 9, and 22) or rupture of atherosclerotic plaques (see ▶ Chap. 22)

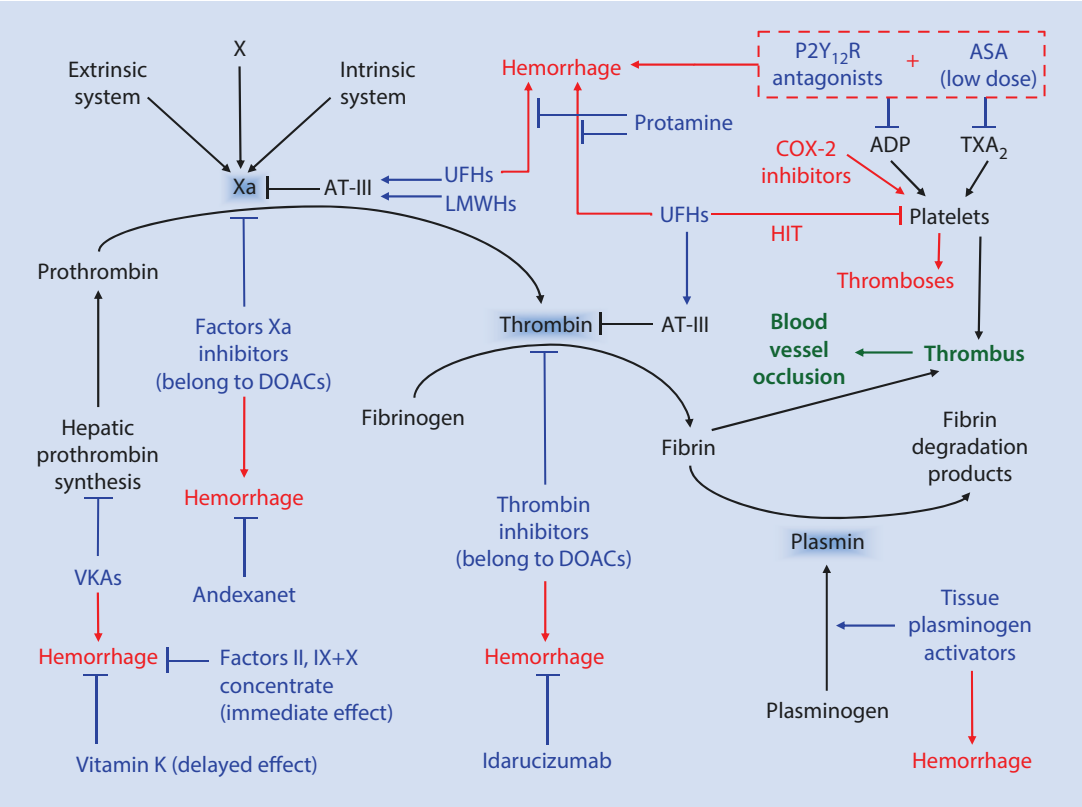

Fig. 18.1 Regulation of hemostasis and fibrinolysis and pharmacological interventions. X inactive factor X precursor, Xa activated factor X, HIT heparin-induced thrombopenia, AT-III antithrombin III. VKAs and ASA are still the most important drugs for long-term treatment of thromboembolic diseases

3. Increased coagulability, e.g., during therapy with EPO (see ▶ Chap. 12)
4. Contact of blood with foreign materials, e.g., dialysis membranes, CPB, and MHVs
5. Drugs can promote thromboembolic diseases. Among these drugs are ER agonists (see ▶ Chap. 24), SERMs (see ▶ Chaps. 20, 24, and 32), COX-2 inhibitors (see ▶ Chap. 10), diuretics (see ▶ Chaps. 11, 15, and 16), SGLT2 inhibitors (see ▶ Chap. 19), and antiangiogenic drugs (see ▶ Chap. 32).

Thromboembolic diseases are very common. Since they are chronic, costs for healthcare systems are very high. Worldwide, sales for one of the leading factor Xa inhibitors approached $ 6 billion in 2017. As an example, the incidence of stroke is about 100 cases per 100,000 people, and the number of fatalities due to stroke approaches 10 million cases per year. Therefore, rational and cost-effective treatment of thromboembolic diseases is of high pharmacoeconomic relevance. For determination of stroke probability in AF, risk scores are calculated, CHF (see ▶ Chap. 16), hypertension (see ▶ Chap. 15), age, sex, previous strokes or TIA, CHD (see ▶ Chap. 16), and atherosclerosis being relevant parameters. On the basis of the risk scores, a decision is made whether an anticoagulant therapy should be initiated.

Various pharmacological interventions influence the equilibrium between hemostasis and fibrinolysis. Generally, every drug for the treatment of thromboembolic diseases can cause hemorrhage, ranging from prolonged hemorrhage time following razor injuries to potentially lethal hemorrhage, and anemia (see ◘ Fig. 18.1). Therefore, it is very important to dose the drugs correctly, to ensure close therapy surveillance, and to consider all contraindications and interactions. Under therapy with SSRIs and SSNRIs (see ▶ Chap. 28) and certain antibiotics (e.g., quinolones, amoxicillin + clavulanic acid, see ▶ Chap. 33), hemorrhage tendency can be increased. This is also the case for liver diseases, CKD, certain tumors, sepsis, and hypothyroidism.

Table 18.1 Overview of selected drugs for thromboembolic diseases

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Alteplase	Activation of plasmin	Dissolution of thrombi/emboli by fibrinolysis	Acute MI if PTCA is not possible, acute non-hemorrhagic stroke	Intracranial hemorrhage (2–8%), extracranial hemorrhage (0.4–1.5%); careful consideration of inclusion and exclusion criteria	
ASA (low dose, approx. 100 mg per day)	Irreversible inhibition of COX-1 in platelets (PAI)	Platelet aggregation is prevented by selective inhibition of TXA_2 synthesis	Secondary prophylaxis of MI and stroke, thrombosis prophylaxis after stent implantation	Prolonged hemorrhage time after minor (e.g., shaving cut) and major injuries, internal hemorrhages, especially in the GI tract, anemia; effect lasts up to 7 days; very low annual therapy costs (approx. $ 5/patient), can also be administered in combination with clopidogrel	10
Clopidogrel	Metabolization by CYP2C19 and hydrolysis to the active metabolite which irreversibly inhibits $P2Y_{12}R$ in platelets	Inhibition of ADP-induced platelet aggregation	Secondary prophylaxis of MI and stroke, thrombosis prophylaxis after stent implantation, PAD	Prolonged hemorrhage time after minor (e.g., shaving cut) and major injuries; anemia; effect lasts up to 7 days; higher annual therapy costs than ASA (approx. $ 200/patient)	2
Dabigatran	DOAC; direct reversible inhibition of thrombin	Inhibition of blood clotting. The antidote is idarucizumab. In emergency situations, factor II, IX + X concentrates are given	Short-term/long-term prophylaxis and therapy of DVT, PE, AF	Hemorrhage; all in all fewer ADRs and interactions than under phenprocoumon/warfarin therapy, but significantly higher therapy costs (approx. 8–10 times)	4
Enoxaparin (LMWH)	Average chain length of 13–22 sugar residues. Forms a complex with antithrombin III, thereby reversibly inactivating factor Xa (but not thrombin)	Inhibition of blood clotting	As UFHs, but easier to administer (1–2 times daily) than UFHs	As UFHs, but a markedly lower risk of HIT (<0.1%)	3, 4, 20

Phenprocoumon (Germany); warfarin (USA)	VKA; inhibits carboxylation and, hence, factor II, VII, IX, and X function	Inhibition of blood clotting. The antidote is vitamin K (delayed onset of effect) or factor II, IX + X concentrates (immediate effect)	Long-term thrombosis prophylaxis in DVT, PE, AF, and MHV	Hemorrhage (especially dangerous if administered in combination with ASA!), anemia, hematomas, skin necrosis, osteoporosis, teratogenicity, hair loss, allergy, thromboses. Phenprocoumon is metabolized via CYP3A4 and CYP2C9; thus, there is a risk of interactions with CYP inducers (thromboses) or CYP inhibitors (hemorrhage); very inexpensive, annual therapy costs of approx. $ 70/patient	2, 4, 20
Rivaroxaban	DOAC; direct reversible inhibition of factor Xa	Inhibition of blood clotting. The antidote is andexanet. In emergency situations, factor II, IX + X concentrates are given	Similar to dabigatran, in addition ACS/MI and PTCA (+PAI)	Hemorrhage, all in all less ADRs and interactions than under VKA therapy, but significantly higher therapy costs (approx. 10–20 times)	4
Unfractionated heparin (UFH)	High-molecular heparin (average chain length of 40–50 sugar residues) that forms a complex with antithrombin III and, hence, reversibly inactivates thrombin (factor IIa) as well as factor Xa	Inhibition of blood clotting. The antidote is protamine	Short-term/long-term prophylaxis and therapy of DVT and PE, ACS, MI, PTCA, CPB; hemodialysis. Suboptimal administration (2–3 times daily)	Allergy, hematomas, hemorrhage risk, anemia, skin necrosis, reversible hair loss, and osteoporosis in long-term therapy, HIT (can lead to thromboembolism or spontaneous hemorrhages) in 2–3% of the patients	3, 4, 20

DVT deep vein thrombosis, *PE* pulmonary embolism, *ACS* acute coronary syndrome, *CPB* cardiopulmonary bypass, *AF* atrial fibrillation (stroke prevention), *MHV* mechanical heart valves, *IS* ischemic stroke, *PAD* peripheral arterial disease, *HIT* heparin-induced thrombopenia

Heparins bind to antithrombin III and form a complex with factor Xa, in case of UFH also a complex with thrombin, leading to functional inactivation of the clotting factors. VKAs inhibit vitamin K epoxide reductase in the liver, thereby preventing carboxylation of factors II (thrombin), VII, IX, and X. DOACs comprise factor Xa inhibitors (xabans) and thrombin inhibitors. The dissolution of fibrin clots is initiated by tissue plasminogen activators. Lastly, thromboembolic diseases can be very effectively influenced at the level of platelets. Low-dose ASA selectively and irreversibly inhibits synthesis of the proaggregatory TXA_2, and $P2Y_{12}R$ antagonists irreversibly inhibit the function of the likewise proaggregatory ADP. The irreversibility implies that the duration of action of both drug classes is long and lasts until new platelets are produced in the bone marrow.

18.2 Heparins

Heparins are polyanionic and a mixture of sulfated glycosaminoglycans. UFHs possess an average length of 40–50 and LMWHs 13–22 sugar residues. Enoxaparin is a LMWH prototype. Heparins form a complex with antithrombin III that binds to and inactivates factor Xa. UFHs additionally inactivate thrombin. Because of their high-molecular mass and their negative charge, both UFHs and LMWHs are not absorbed following oral administration (see ▶ Chap. 2) but must be applied i.v. or s.c.. UFHs have to be administered more frequently (two to three times daily) than LMWHs (once or twice daily). In case of UFHs, therapy is controlled with the partial thromboplastin time; in case of LMWHs, clotting test controls are not required. Heparins are used for the prophylaxis and therapy of a number of thromboembolic diseases, predominantly DVT, PE, ACS, and CPB. In case of overdosing, hemorrhage can occur. Hemorrhages due to UFHs but not LMWHs can be terminated within minutes using the antidote protamine (see ▶ Chap. 4).

UFHs possess a shorter plasma half-life (2 hours) than LMWHs (3–7 hours). Heparins are predominantly eliminated via the kidney. For UFHs, dose adjustment according to the thromboplastin time has to be performed in CKD. In advanced CKD, the dose of LMWHs is adjusted according to the factor Xa activity (see ▶ Chap. 12).

Since heparins do not pass the placental barrier, they are an excellent therapeutic alternative to the teratogenic VKAs in pregnancy. Heparins can cause allergic reactions, hematomas, hemorrhage, anemia, liver damage, skin necrosis, osteoporosis, and alopecia. An important ADR is the heparin-induced thrombopenia (HIT). For UFHs, the incidence of HIT is much higher than for LMWHs (2–3% versus <0.1%). HIT develops after 5–14 days. Antibodies against a complex of heparin and platelet factor 4 are formed. This complex binds to platelets and activates them. The platelet concentration decreases dramatically and remains low if the therapy is continued. The major risk of HIT is that patients incur DVT, PE, or disseminated intravascular coagulation with spontaneous hemorrhage. Multiorgan failure may occur. HIT lethality is high (30%). Since the immune diagnostics of this ADR takes too long to adjust the therapy timely, heparin administration must be terminated immediately when HIT is suspected. Instead the heparinoid danaparoid (mixture of heparan sulfate and dermatan sulfate) can be applied. There is only a small risk of cross-allergy. Alternatively, patients can be switched to VKAs.

18.3 Vitamin K Antagonists (VKAs)

VKAs have been successfully applied as anticoagulants for decades. There are cultural differences in the use of specific VKAs in various countries. For example, warfarin is widely given in the USA, whereas phenprocoumon is broadly used in Germany. Most clinical studies have been performed with warfarin. The major indications of VKAs are the long-term prophylaxis of DVT and PE and the prophylaxis of stroke in patients with AF or MHVs. Since the effects of VKAs depend on prevention of a covalent protein modification, it takes about 5–7 days until maximum efficacy is reached. Conversely, it takes 5–7 days after drug discontinuation until the anticoagulant effect is abrogated. After an initial saturation phase, patients are treated with a fixed daily dose of the VKA. This dose can vary considerably among patients. One reason for this variability is that VKAs are metabolized via CYP2C9. Polymorphisms of CYP2C9 (slow or rapid metabolizer) may influence VKA inactivation (see ▶ Chap. 2). VKA therapy is controlled by determination of the INR. In AF, DVT, and PE, the INR

target values are 2–3, whereas patients with MHVs are adjusted on target values of 2.5–3.5. In these indications, VKAs possess proven clinical efficacy. In addition to regular INR controls, therapeutic success hinges on excellent patient adherence to the medication and avoidance of interferences with other drugs or food ingredients (see below).

VKAs have an excellent bioavailability. Because of their metabolism via CYP3A4 and CYP2C9, VKAs can cause drug interactions with CYP inducers or inhibitors. Carbamazepine, phenobarbital, and phenytoin (see ▶ Chap. 25), RMP (see ▶ Chap. 33), and St. John's wort (see ▶ Chap. 28) are potent CYP inducers and diminish the effects of VKAs. Comedication with these drugs should be avoided or, if necessary, only conducted under tight INR control. Azole antimycotics (see ▶ Chap. 35), certain macrolide antibiotics (see ▶ Chap. 33), and antiviral protease inhibitors (see ▶ Chap. 34) as well as ciclosporin and tacrolimus (see ▶ Chap. 11) are potent CYP3A4 inhibitors and enhance the risk of hemorrhage under VKA therapy. This is also the case for comedication with CYP2C9 inhibitors such as PPIs (see ▶ Chap. 13), sulfonylureas (see ▶ Chap. 19), allopurinol (see ▶ Chap. 23), and PPAR-α agonists (see ▶ Chap. 22).

Moreover, "healthy" food items can modulate the efficacy of VKAs. Specifically, vegetables rich in vitamin K such as spinach, kale, chickpea, chives, fennel, and Brussels sprouts increase the risk of thromboembolism. Conversely, Goji berries and woodruff lead to higher hemorrhage risk under VKA therapy due to CYP inhibition.

VKAs cross the placental barrier and are teratogenic. Accordingly, VKAs must be avoided during pregnancy and substituted by other drugs. LMWHs are a safe and effective alternative. In rare cases (0.1%), VKAs can cause skin necrosis. In addition, VKAs may induce hemorrhages, anemia, liver damage, alopecia, allergies, and osteoporosis (see ▶ Chap. 20).

18.4 Direct-Acting Oral Anticoagulants (DOACs)

VKA therapy cannot always be conducted safely and effectively, specifically in patients taking multiple drugs and patients with problematic adherence. Moreover, VKAs possess serious ADRs. Furthermore, their long duration of action constitutes a problem in emergency situations, specifically injuries with severe hemorrhage or prior to surgery. These problems were the reasons for the development of new drugs devoid of these disadvantages. The results are the DOACs that selectively, directly, and reversibly inhibit factor Xa (prototype rivaroxaban) or thrombin (prototype dabigatran). Generally, like all other anticoagulants, DOACs can cause hemorrhage and anemia, particularly when overdosed. DOACs are used for the same indications as VKAs and additionally for short-term prophylaxis of DVT and PE. Factor Xa inhibitors are also applied for treatment of ACS.

A controversial discussion is ongoing whether for various indications DOACs possess therapeutic advantages and fewer ADRs compared to VKAs. In this discussion, the currently high therapy costs with DOACs vs. the costs of a therapy with VKAs have to be considered in relation to a potential therapeutic advance. If a patient is well treated with a VKA and without serious ADRs, there is no need to switch the patient to a DOAC, but pharmaceutical marketing pressure on physicians is high in some countries. Recent "real-world" studies indicate that some advantages observed for DOACs relative to VKAs in clinical studies with highly selected patient populations do not translate into the general patient population.

DOACs possess a shorter half-life (10–14 hours) than VKAs. Since they, in contrast to VKAs, inhibit their target proteins reversibly, therapy can be adjusted more rapidly. Dabigatran is not a CYP substrate and is eliminated unaltered via the kidney. In mild CKD, the dabigatran dose needs to be adjusted. In severe CKD, dabigatran is contraindicated (see ▶ Chap. 12). Rivaroxaban is a CYP3A4 substrate. Inactive metabolites are eliminated renally. Overall, DOACs possess a smaller interaction potential than VKAs and do not have some typical ADRs of VKAs such as skin necrosis, alopecia, and osteoporosis. However, in case of DOACs, no convenient coagulation test is available for therapy surveillance. Idarucizumab, a monoclonal antibody against dabigatran, and andexanet, a decoy receptor binding rivaroxaban, can be used as antidotes in case of overdosing. Serious acute hemorrhage under DOAC therapy must be treated with clotting factor concentrates (factors, II, VII, IX, and X).

18.5 Fibrinolytics

The drugs discussed in ▶ Sects. 18.2, 18.3, and 18.4 aim at preventing the formation or growth of a thrombus. In contrast, fibrinolytics dissolve thrombi that were formed via cross-linking of fibrin. Fibrinolysis is catalyzed via the protease plasmin. It is generated from plasminogen via proteolytic cleavage by the tissue plasminogen activator. Alteplase is a recombinantly produced tissue plasminogen activator that is used in MI when a PTCA cannot be performed. Further indications for alteplase are PE and non-hemorrhagic stroke. For therapeutic success it is critical to start with the therapy as soon as possible after the thromboembolic event and the onset of clinical symptoms. Alteplase is administered i.v. or preferably intra-arterially in order to focus the drug effect on the affected organ.

In non-hemorrhagic stroke, alteplase should be administered not later than 3 hours after the thromboembolic event. Prior to drug administration, a number of diagnostic measures have to be performed since the risk of hemorrhage is considerable (intracranial hemorrhage 1.7–8.9%, extracranial hemorrhage 0.4–1.5%). In particular, it must be excluded that the patient has an acute intracranial hemorrhage. In addition, the blood pressure must be <185/100 mm Hg (see ▶ Chap. 15). Heparin therapy during the past 48 hours, VKA therapy with an INR value >1.7, and thrombopenia (<100,000 platelets/μl) are contraindications. Hypoglycemia must be corrected as well.

18.6 (Patho)physiological Regulation of Platelet Activation

Figure 18.2 provides an overview of platelet activation and pharmacological interventions. Platelets play a key role in hemostasis and thrombus formation. They express three GPCRs (PAR1, TPR, $P2Y_{12}R$) that promote platelet aggregation and thrombus formation. The IPR is a functional antagonist of these receptors. Thrombin cleaves the N-terminus of PAR1, thereby irreversibly activating the receptor and stimulating the G_q-PLC pathway with subsequent increase of intracellular calcium concentration. Calcium is important for aggregation and activates PLA_2 that hydrolyzes phospholipids to release AA (see ▶ Chap. 10). AA is a substrate for COX-1, catalyzing the formation of prostaglandin H_2, the precursor of TXA_2. Following secretion from platelets, TXA_2 stimulates them in an autocrine fashion via the TPR, thereby enhancing the signaling cascade initiated by PAR1. In addition, TXA_2 induces vasoconstriction, supporting hemostasis. An increase in intracellular calcium concentration causes the release of ADP that stimulates platelets via the $P2Y_{12}R$ in an autocrine manner as well. ADP enhances expression of the fibrinogen receptor (glycoprotein IIb/IIIa), further accelerating thrombus formation.

In intact blood vessels, platelets do not aggregate. An important factor for this physiological situation is the release of PGI_2 from endothelial cells. In platelets, PGI_2 binds to the IPR that, via the G_s-AC pathway, functionally antagonizes the increase in intracellular calcium concentration mediated by PAR1 and TPR. Thus, in platelets, three proaggregatory GPCRs face one antiaggregatory GPCR. In dyslipidemia and in tobacco consumers, endothelial cells are damaged (see ▶ Chaps. 9 and 22), resulting in decreased PGI_2 synthesis. PGI_2 also induces vasodilation. If PGI_2 formation is diminished, platelet aggregation and vasoconstriction are favored, enhancing the risk of thromboembolism.

18.7 Platelet Aggregation Inhibitors (PAIs)

The key point for pharmacological modulation of platelets is that these cells (actually cell fragments devoid of a nucleus) are not capable anymore of performing protein synthesis. The most effective and most economical measure to modulate platelet function is the irreversible inhibition of COX-1-mediated TXA_2 formation with ASA in low doses (about 100 mg/day). ASA acetylates the catalytic center of COX-1 at a serine residue. Accordingly, the antiaggregatory and vasodilatory effect of PGI_2 dominates. This effect can be exploited in the secondary prophylaxis of certain thromboembolic diseases, most notably MI and stroke. In principle, ASA also inhibits the PGI_2-forming COX-2 in endothelial cells. However, this effect is not clinically relevant in low doses because endothelial cells can compensate COX-2 inhibition via de novo enzyme synthesis. At ASA doses above 300 mg/day, an about similar inhibition of TXA_2 and PGI_2 formation becomes evident. Accordingly, the prophylactic effect of ASA on thromboembolic diseases disappears. ASA

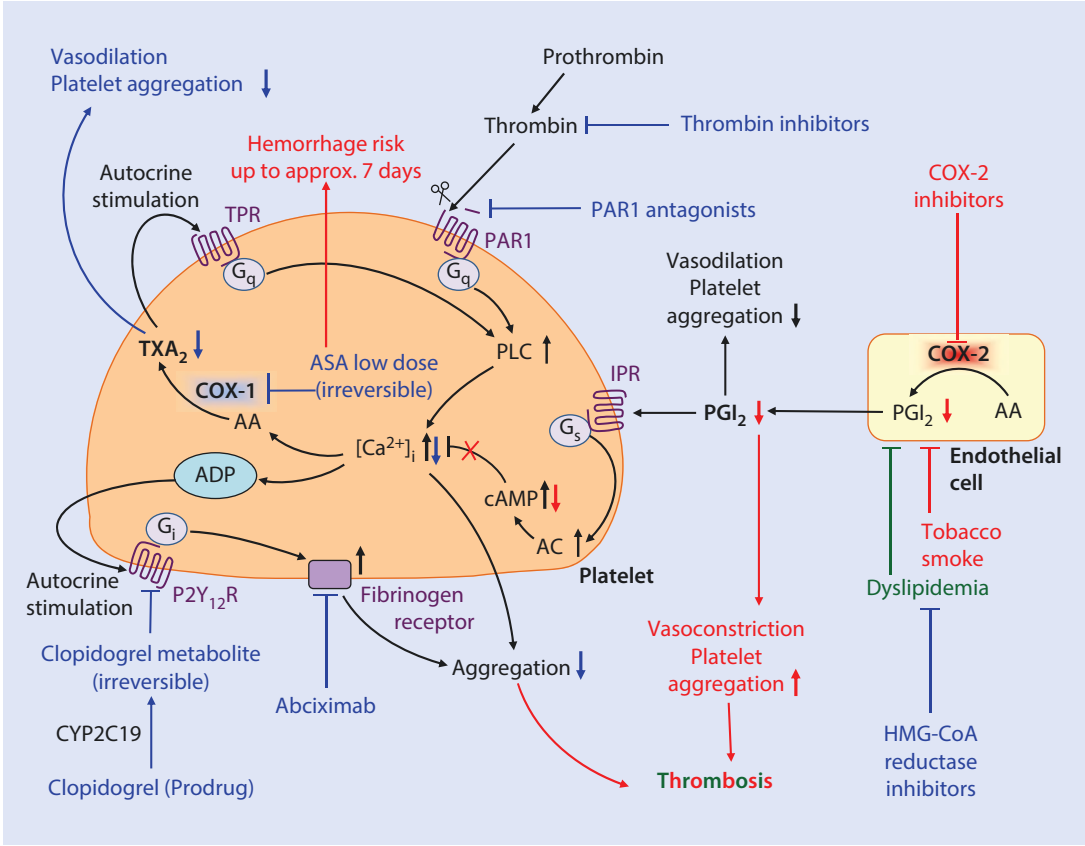

Fig. 18.2 Regulation of platelet activation and pharmacological interventions. Low-dose ASA is very effective at preventing MI and stroke in patients at risk! Use the INN of ASA and NOT the brand name Aspirin® because numerous generic preparations of ASA are available. Medical language should not focus on just one brand

possesses proven clinical efficacy in the secondary prophylaxis of MI and ischemic stroke. There is no evidence for efficacy of ASA in primary prophylaxis of these diseases although practiced and advertised in several countries.

Following discontinuation of ASA therapy, the inhibitory effects on platelet aggregation last for up to 7 days (see ▶ Chap. 2). This can be a problem when patients have to undergo emergency surgery. In such cases, platelet concentrates can be administered.

The most important ADRs of low-dose ASA therapy are prolonged hemorrhage time and unnoticed GI hemorrhage that can lead to anemia. Accordingly, patients taking ASA in low doses and with unexplained anemia should undergo endoscopy and a guaiac fecal occult blood test. The risk of GI hemorrhages can be reduced with PPIs, but long-term therapy with this drug class is problematic (see ▶ Chaps. 13 and 20). The combination of low-dose ASA with the similarly long-acting VKAs (see ▶ Sect. 18.3) is contraindicated because of high hemorrhage risk.

Other COX inhibitors than ASA influence platelet aggregation as well, but their effects cannot be used therapeutically or are even harmful (see ◘ Fig. 18.2). This is particularly evident for the COX-2 inhibitors. In therapeutic doses, they effectively inhibit PGI_2 formation in endothelial cells but not COX-1-mediated TXA_2 formation in platelets. Accordingly, the equilibrium between TXA_2 and PGI_2 is shifted toward TXA_2, and platelet aggregation and vasoconstriction are enhanced. Clinically, this altered equilibrium increases the risk of thromboembolic events. Therefore, COX-2 inhibitors are contraindicated in patients with MI and stroke (see ▶ Chap. 10). The commonly employed nonselective COX inhibitors (prototypes ibuprofen and diclofenac) inhibit both PGI_2 and TXA_2 synthesis. This can

result in inhibition of platelet aggregation with increased hemorrhage risk, but because of the likewise reduced PGI_2 synthesis, no protective effects on thromboembolic diseases result.

Another option to modulate platelet function is to antagonize the proaggregatory $P2Y_{12}R$. Clopidogrel is a prototypical $P2Y_{12}R$ antagonist. It is a prodrug, activated in the liver by CYP2C19 and subsequent hydrolysis (see ▶ Chap. 2). The active metabolite covalently binds to the $P2Y_{12}R$ and inactivates the receptor irreversibly. Because of the absent protein synthesis in platelets, a long-lasting antiaggregatory effect results. Since CYP2C19 polymorphisms with low activity (poor metabolizer) are common in the general population, one has to take into consideration that clopidogrel is ineffective (nonresponder). Prior to clopidogrel therapy, pharmacogenetic screening for such polymorphism should be performed to identify nonresponder a priori.

After coronary stent insertion in MI patients, clopidogrel is often combined with low-dose ASA for several months to prevent stent thrombosis and reinfarction (see ▶ Chap. 16). However, the dual inhibition of platelet aggregation increases the risk of hemorrhage. Therefore, in general, long-term secondary MI prophylaxis is only performed with ASA. Clopidogrel is also effective in PAD. Following discontinuation, clopidogrel effects persist for 4–5 days because of the irreversible $P2Y_{12}R$ inactivation. This can become a problem if emergency surgery has to be performed. In such cases, infusion of platelet concentrates may be necessary. The combination of clopidogrel with VKAs must be avoided due to high hemorrhage risk. The most important ADRs of clopidogrel are hemorrhage and anemia. The GI hemorrhage risk under clopidogrel is smaller than under low-dose ASA, but the therapy costs are higher.

Abciximab is a fragment of a monoclonal antibody that binds to glycoprotein IIb/IIIa on platelets and inhibits the interaction of fibrinogen and other clotting factors with this receptor. Abciximab is used in ACS therapy and stent insertion but not in long-term therapy of CHD.

Recently, the first PAR1 inhibitor (vorapaxar) has been approved in some countries for the treatment of MI and PAD. In these diseases, vorapaxar reduces cardiovascular mortality, but the long half-life and CYP3A4 metabolism are problematic, increasing the risk of drug interactions (see ▶ Chap. 2). In addition, vorapaxar is contraindicated in patients with hemorrhagic and non-hemorrhagic stroke because of an increased risk of intracranial hemorrhage. Thus, the significance of vorapaxar in the therapy of cardiovascular diseases still needs to be determined.

18.8 Questions and Answers

Questions

Which statement on drugs affecting blood clotting is correct?

A. For hemorrhage caused by dabigatran overdose, no antidote is available.
B. Protamine can antagonize the consequences of ASA overdosing.
C. Alteplase can cause intracranial hemorrhage.
D. Enoxaparin possesses a high risk of thrombopenia.
E. The risk of hemorrhage under warfarin is increased by CYP3A4 and CYP2C9 inducers.

Answers

A. The monoclonal antibody idarucizumab is an antidote for dabigatran. As alternative, concentrates of factors II, IX, and X can be used.
B. Protamine can antagonize the effects of protamine but not of ASA overdosing. The negatively charged heparin forms a complex with the positively charged protamine.
C. Prior to administration of alteplase, the presence of intracranial hemorrhage has to be excluded. But even after exclusion of intracranial hemorrhage, this ADR can occur in up to 8% of all treated patients.
D. The risk of thrombopenia under enoxaparin, belonging to the LMWHs, is much lower than under the UFHs. The higher safety of enoxaparin is a major reason for the fact that it is currently used much more frequently than heparin.
E. Inducers of CYP3A4 and CYP2C9 such as carbamazepine, RMP, phenobarbital, and St. John's wort accelerate warfarin inactivation and decrease its anticoagulant efficacy.

Answer **C** is correct.

18.9 Exercises

Because of AF, a 73-year-old female patient has been treated with warfarin for 5 years. The patient visits you regularly into your internal medicine office to have her INR checked. So far, there have been no problems with the warfarin therapy. One evening, the patient's husband calls you very nervously and tells you that his wife has gotten a spontaneous and very profuse epistaxis. You immediately make a home visit and learn that the patient has taken a half ASA 500 mg tablet against a headache 3 days ago, but otherwise she has adhered to her warfarin therapy as usual. In passing you also learn that after reading an article in a women's magazine, she has switched her diet to improve her health and is now drinking about half a liter of Goji berry juice daily.

Questions

1. What is the most likely cause for the epistaxis, and how do you proceed diagnostically and therapeutically?
2. What do you do with respect to the warfarin medication of the patient?

Answers

1. Because there is an emergency situation, first you stop the epistaxis. You ensure that the patient is sitting in an upright position, bends the head forward, and compresses the nasal wings. In addition, you apply cold packs in the neck and insert a nasal tamponade. You have to avoid backward bending of the head, a common treatment error. In this position, the risk of aspiration is increased. The epistaxis probably has two causes. First, the patient took a long-acting PAI (250 mg of ASA) just few days ago. Second, ingredients of Goji berries inhibit VKA metabolism and, thereby, prolong its duration of action. Because it is difficult for you to assess the severity of the situation properly, you admit the patient into the hospital for further treatment by an ENT physician. In addition, the INR value has to be determined as soon as possible. If this value is too high, a concentrate of the factors II, IX, and X must be administered i.v. to stop further (potentially life-threatening) hemorrhage.
2. Once the emergency situation is under control, you can continue with the warfarin therapy under INR control. A prerequisite for this strategy is that you educate the patient which types of presumably "healthy" food items either reduce the effects of VKAs (e.g., spinach, kale, and chickpeas) or increase the effects of VKAs. In addition to the presumed "superfood" Goji berries, woodruff is problematic in this regard. In addition, the patient needs to be informed about the fact that consumption of ASA, particularly in low doses, is dangerous. In case of pain, paracetamol, metamizole, and a low-efficacy MOR agonist such as tramadolol constitute therapeutic options because these drugs do not interfere with platelet aggregation. Moreover, the patient needs to be educated about all other drugs that may interfere with the warfarin therapy. Should you come to the conclusion that the patient does not understand why the epistaxis occurred and which measures have to be implemented to avoid future emergencies, you may need to switch the patient to a DOAC because with these drugs, the interaction potential is smaller. If you make such a decision, you have to inform the patient about the higher costs that are not necessarily covered by health insurance companies.

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Drugs for Treatment of Diabetes Mellitus

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DM is characterized by chronic hyperglycemia and subsequent organ damage. DM is caused by absolute insulin deficiency (type 1 DM) or insulin resistance (type 2 DM). Type 1 DM is treated with insulin substitution commensurate with energy consumption. Short-acting and sustained-release insulins are combined. The basis of type 2 DM therapy is alleviation of insulin resistance with calorie restriction and an active lifestyle. Metformin is the best studied and most effective drug for treatment of type 2 DM. It has pleiotropic metabolic effects and increases insulin sensitivity. Other therapy options for type 2 DM are stimulation of insulin secretion with sulfonylureas, GLP-1R agonists, and DPP4 inhibitors, increase of renal glucose elimination with SGLT2 inhibitors, and delay of intestinal glucose absorption with α-glucosidase inhibitors. Treatment of accompanying diseases including hypertension, CHD, dyslipidemia, nephropathy, and polyneuropathy is important in DM management. Hypoglycemia is treated with glucose or glucagon. Diabetic coma is treated with water, electrolyte, and insulin substitution.

Key Points

1. Type 1 DM is due to absolute insulin deficiency.
1. Type 2 DM is due to insulin resistance.
2. Therapy of diseases accompanying DM is essential.
3. By exchanging particular amino acids, insulins with different pharmacokinetic properties are produced.
4. Metformin is the most effective drug for treatment of type 2 DM and has pleiotropic metabolic effects.
5. Metformin increases insulin sensitivity and has no risk for hypoglycemia and weight gain.
6. PPAR-γ agonists increase insulin sensitivity but have serious ADRs.
7. Sulfonylureas inhibit ATP-dependent potassium channels and increase insulin secretion glucose-independently.
8. Sulfonylureas possess a high risk for hypoglycemia.
9. GLP-1R agonists stimulate insulin secretion via GLP-1R activation.
10. DPP4 inhibitors stimulate insulin secretion via inhibition of GLP-1 degradation.
11. Gliflozins increase renal glucose elimination via SGLT2 inhibition.
12. α-Glucosidase inhibitors reduce intestinal glucose absorption.
13. Hypoglycemia is treated with glucose or glucagon.
14. Diabetic coma is treated with substitution of water, electrolytes, and insulin.

19.1 Pathophysiology of Diabetes Mellitus (DM) and Pharmacotherapeutic Concepts

Insulin is a peptide hormone consisting of an A chain (21 amino acids) and a B chain (30 amino acids) that are connected via two disulfide bonds. The insulin receptor belongs to the class of RTKs (see ▶ Chap. 1). Insulin mediates its effects via phosphorylation cascades. Insulin stimulates glucose uptake into cells, glycogen synthesis, and inhibition of lipolysis. Insulin is anabolic and increases body weight.

Hyperglycemia and glucosuria are the cardinal biochemical symptoms of DM that are due to insufficient insulin effects. DM is present when the fasting blood glucose concentration is >7 mmol/l. Cardinal clinical symptoms are thirst (polydipsia), dry skin, acetone breath, susceptibility to infections, and fatigue.

The most important function of insulin being reduced in DM is cellular glucose uptake. DM is classified into two major forms, i.e., type 1 DM and type 2 DM (◘ Table 19.1). Type 1 DM is characterized by absolute insulin deficiency requiring life-long insulin substitution. The major pathophysiological change in type 2 DM is insulin resistance. This leads to initial hyperinsulinemia and subsequent exhaustion of B cell function. Accordingly, overcoming insulin resistance is the most important therapeutic principle in treatment of type 2 DM. ◘ Table 19.2 summarizes selected insulins and drugs for treatment of type 2 DM.

Patients with type 2 DM often have concomitant obesity and cardiovascular diseases (metabolic syndrome) that need to be treated.

Table 19.1 Overview of pathophysiology and pharmacotherapy of type 1 and type 2 DM

Parameter	Type 1 DM	Type 2 DM
Frequency	Approx. 400 million patients globally	Approx. 40 million patients globally
Age of manifestation	Childhood and youth	Mostly middle and high adulthood, but due to malnutrition increasingly in young people. Widespread disease
Pathophysiology	Autoimmune disease leading to destruction of B cells; thus, absolute insulin deficiency	Initially, insulin resistance of organs with hyperinsulinemia. In later stages, exhausted capacity of B cells to secrete insulin
Association with other diseases	No association with metabolic syndrome	Metabolic syndrome: DM, hypertension, dyslipidemia, CHD and obesity
Acute complications	Ketoacidotic coma, hypoglycemia (particularly with intensive insulin therapy and in physically active patients)	Hyperosmolar coma, more rarely hypoglycemia (especially when sulfonylureas are administered)
Long-term complications	Diabetic micro- and macroangiopathy with organ complications	Diabetic micro- and macroangiopathy with organ complications
Pharmacotherapeutic principles	Calorie intake should be based on the individual demand. The (intensive) insulin therapy should be adapted accordingly. Use an insulin pump to optimize insulin delivery. Reduction in calorie intake is not required. The therapy of late complications is also important (see ▶ Chaps. 12, 15, 16, and 22). To prevent hypoglycemia, patients should always carry glucose and a glucagon syringe. Be careful with ethanol consumption (risk of hypoglycemia). Adapt insulin dose to the individual metabolism condition (infections, surgeries, GC therapy, pregnancy, hypo- and hyperthyroidism; see ▶ Chaps. 11 and 21)	Reduce weight and change your lifestyle (eat healthy food, especially avoid junk food and sweetened soft drinks, practice endurance sports). This is the key to reverse insulin resistance and to correct the metabolic syndrome. Drug of choice for most of the patients is metformin (no risk of hypoglycemia); other oral antidiabetics like GLP-1R agonists and DPP4 inhibitors may be added to support the therapy. In later stages, when the B cells are exhausted, administration of insulin may be required. It is also important to treat hypertension (see ▶ Chap. 15), CHD (see ▶ Chap. 16), dyslipidemia (see ▶ Chap. 22), nephropathy (see ▶ Chap. 12), and neuropathy (see ▶ Chap. 10). Avoid or reduce dose of diabetogenic p-mGPCR antagonists (see ▶ Chap. 29) and of antiviral protease inhibitors (see ▶ Chap. 34)

p-mGPCR antagonists (see ▶ Chap. 29) and antiviral protease inhibitors (see ▶ Chap. 34) can deteriorate type 2 DM. CHD is treated with β_1AR antagonists, low-dose ASA and ACEIs, or AT_1R antagonists (see ▶ Chap. 15), dyslipidemia generally with HMG-CoA reductase inhibitors (see ▶ Chap. 22), and polyneuropathy with co-analgesics of the NSMRI and NIPE classes (see ▶ Chaps. 25 and 28). Diabetic coma is a life-threatening complication, particularly of type 1 DM. Microangiopathy, leading to retinopathy, nephropathy, neuropathy, and diabetic feet ulcer, and macroangiopathy, leading to CHD, MI, stroke, PAD, and hypertension, are long-term complications of both DM forms as a consequence of pathological protein glycosylation. The concentration of glycosylated hemoglobin (HbA_{1C}) is a biomarker for the quality of long-term DM treatment. HbA_{1C} values in diabetic patients should be between 6.5% and 7.5%.

The B cell is in the center of pharmacological interventions and origin of the life-threatening ADR hypoglycemia (Fig. 19.1). Upon an increase in blood glucose concentration, glucose is transported into the B cell via the GLUT2 transporter. In mitochondria, glucose stimulates ATP

Table 19.2 Overview of selected drugs for treatment of type 1 and type 2 DM

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Type 1 DM					
Insulin glargine	Long-acting human insulin analog	Onset of action 4 hours; duration of action 24 hours	Type 1 DM	Hypoglycemia, weight gain, lipodystrophy	
Insulin lispro	Short-acting human insulin analog	Onset of action 5–15 minutes; duration of action 3 hours	Type 1 DM	Hypoglycemia, weight gain, lipodystrophy	
Normal insulin	Short-acting human insulin	Onset of action 30 minutes; duration of effect 5 hours	Type 1 DM	Hypoglycemia, weight gain, lipodystrophy	
NPH insulin	Intermediate-acting insulin	Onset of action 2 hours; duration of effect 12 hours	Type 1 DM	Hypoglycemia, weight gain, lipodystrophy	
Type 2 DM					
Acarbose	Inhibitor of the intestinal α-glucosidase	Inhibits intestinal glucose uptake	Type 2 DM; supportive effect, the same therapeutic aim can be reached by reducing glucose intake	Common (25%): GI disturbances like diarrhea and flatulence ("biofeedback")	13
Empagliflozin	Gliflozin class, SGLT-2 inhibitor	Increases renal glucose excretion	Type 2 DM; more recent and as yet not completely evaluated therapeutic principle	Hypoglycemia, dehydration, BP drop, risk of thrombosis, urogenital infections, increased risk of osteoporosis	15, 18, 20, 33
Glibenclamide	Sulfonylurea class, inhibitor of ATP-sensitive potassium channels	Increases insulin secretion from B cells	Type 2 DM; controversial clinical efficacy with regard to morbidity and mortality	Weight gain, hypoglycemia	
Liraglutide	GLP-1R agonist	Increases insulin secretion from B cells	Type 2 DM and weight reduction; more recent and as yet not completely evaluated therapeutic principle	Hypoglycemia, GI disturbances	13

Metformin	Biguanide class; pleiotropic effects including activation of AMP kinase	Improves the overall metabolism without hypoglycemia and weight gain; inhibits hepatic gluconeogenesis and lipogenesis, increases insulin sensitivity (may be less relevant for clinical efficacy that generally assumed)	Type 2 DM; the best analyzed and validated drug with clinically proven life-extending effects; very inexpensive	Taste disturbances, GI disturbances, lactic acidosis in risk patients (liver insufficiency, alcoholism, CHF, CKD, pancreatitis, infections, tumor diseases)	1, 2, 12, 16, 32, 33, 34, 35
Pioglitazone	PPAR-γ agonists, altered gene expression	Increases insulin sensitivity, increases glucose uptake, differentiation of adipocytes	Type 2 DM; controversial clinical efficacy with regard to morbidity and mortality. Poor clinical efficacy is disappointing in view of the apparently relevant molecular effects	Weight gain, edemas, CHF, increased risk of fractures in women, increased risk of bladder carcinoma	12, 16, 20, 32
Sitagliptin	Gliptin class, incretin amplifier, DPP4 inhibitor	Inhibits GLP-1 degradation and thus increases insulin secretion from B cells	Type 2 DM; more recent and as yet not completely evaluated therapy principle	GI disturbances, respiratory infections. Compared with other diabetic drugs, it bears only a low risk of hypoglycemia, as the effect of sitagliptin is dependent on the presence of GLP-1 which, in turn, is released as a function of the blood glucose concentration	13, 14, 33
Hypoglycemia					
Glucagon	Glucagon receptor agonist	Stimulates hepatic glycogenolysis	Type 1 DM; treatment of life-threatening hypoglycemia	Tachycardia	17

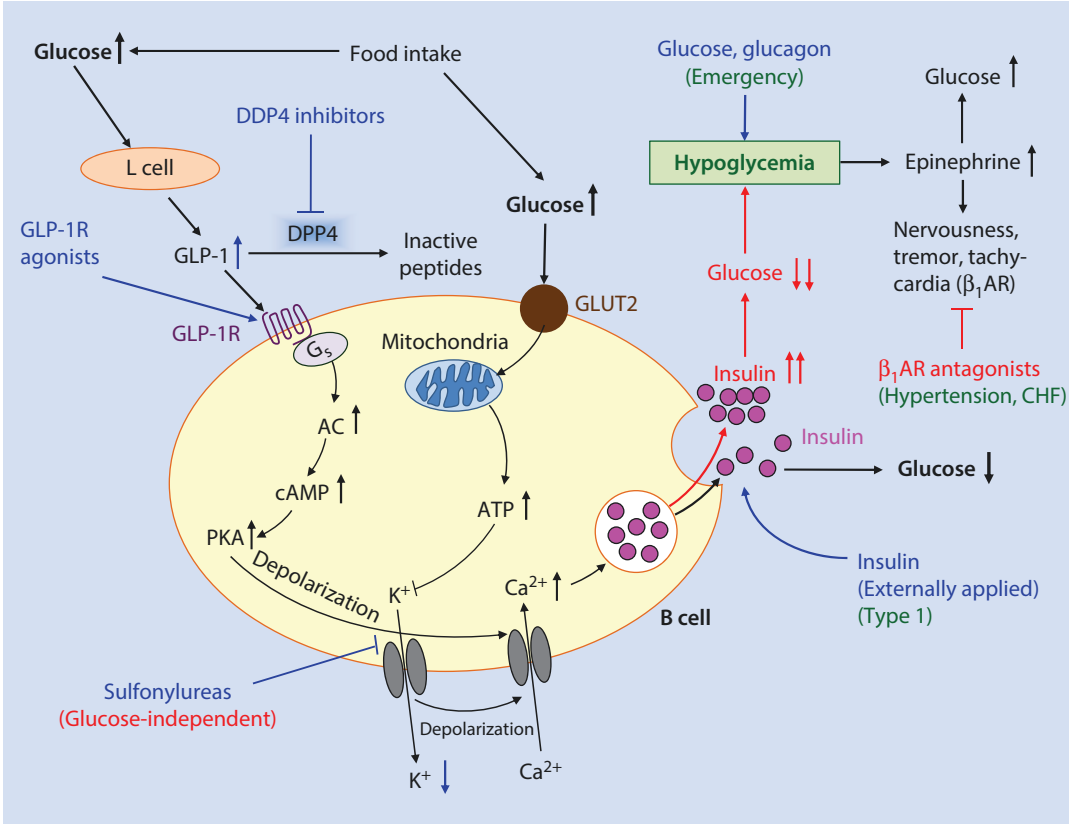

Fig. 19.1 Regulation of insulin secretion from B cells and pharmacological interventions as well as pathogenesis and therapy of hypoglycemia. Note that the clinically most effective drug for treatment of type 2 DM, metformin, is not included in this scheme because its mechanism of action leading to the beneficial effects is not yet clear! Hypoglycemia is a life-threatening emergency that must be recognized and treated immediately

production. An increase in ATP concentration inhibits potassium channels, ultimately leading to depolarization, opening of calcium channels, and an increase in intracellular calcium concentration. Calcium mediates secretion of insulin which reduces blood glucose concentration. If insulin is secreted excessively, hypoglycemia can develop.

Glucose increases insulin secretion also via an indirect pathway. In the small intestine, carbohydrates stimulate GLP-1 secretion from L cells. GLP-1 binds to the GLP-1R in B cells and induces depolarization via the G_s-AC pathway. GLP-1 degradation is mediated via DPP4.

19.2 Insulins

Insulins are used in type 1 DM and in late stages of type 2 DM when B cell capacity is exhausted. In addition, insulin is applied in type 2 DM patients during major surgery, serious infections, and pregnancy in which tight DM control is particularly important because otherwise diabetic fetopathy may result.

Since insulin is a peptide hormone, it cannot be administered orally. In long-term therapy, insulin is administered s.c.; in emergency situations (diabetic coma; see ▶ Sect. 19.10), short-acting insulins are administered i.v. Insulins differ from each other with respect to their pharmacokinetic properties. Two major insulin classes are distinguished: the rapid- and short-acting insulins and the sustained-release and long-acting insulins. Both insulin types complement each other.

The effect of regular, short-acting insulin starts 30 minutes after s.c. injection. This implies that it has to be injected about 20–30 minutes prior to food intake. There are also insulins with a more rapid onset of action. They allow for more flexible meal times and ensure a higher quality of

life. A prototype of this class is insulin lispro with exchanged positions of two amino acids in the C-terminal portion of the B chain, resulting in faster absorption from the injection site. Insulin aspart and insulin glulisine are analogs with similar properties as insulin lispro.

Sustained-release insulins are absorbed more slowly from the injection site and accordingly showing a prolonged duration of action. NPH insulin (neutral protamine Hagedorn insulin) is a prototype of this class. Here, insulin forms a complex with the basic protamine. Replacement of amino acids can also delay the absorption rate from the injection site. In insulin glargine, an amino acid is mutated in the C-terminus of the A chain, and the B chain is extended by two arginine residues. This insulin precipitates at neutral pH and is absorbed slowly from the subcutaneous adipose tissue. Insulin zinc crystal suspensions possess similar pharmacokinetic properties as insulin glargine.

In the basis bolus insulin therapy, a sustained-release insulin ensures basic insulin supply of organs. In addition, a short-acting insulin is injected prior to meals, the dose being commensurate with the amount of carbohydrates consumed. In intensive insulin therapy, the applied amount of insulin is adjusted to the current blood glucose concentration. This concept can be realized with s.c. injection of insulin or, more accurately, with insulin pumps. The advantage of the intensive insulin therapy is that long-term complications are reduced and delayed. A disadvantage is the increased risk of hypoglycemia (see ▶ Sect. 19.9).

Currently, insulins are mostly applied with U100 pens, i.e., the pen contains 100 international units (IU) per ml. Thus, one click on the pen corresponds to a dose of 1 IU. This simplifies insulin dosing in daily life. It is important to avoid arbitrary changes of the injection site because this can alter the absorption rate and, accordingly, the risk of hypoglycemia and hyperglycemia. Within an anatomical region, the injection site should be changed by about 1 cm to reduce the risk of lipodystrophy. These changes are cosmetically disturbing and painful and interfere with the reproducibility of insulin absorption. From the abdominal adipose tissue, insulin is absorbed rapidly. Therefore, this region is well suited for administration of short-acting insulins. From the thighs, insulin is absorbed more slowly, rendering this region suitable for the injection of sustained-release insulins. Injection needles have to be changed daily, since blunt cannulas increase the risk of infection and fibrosis. The supply of insulin vials for the pen has to be refrigerated, but must not freeze. Temperatures above 37 °C have to be avoided as well.

A healthy adult requires about 45 IU of insulin per day, with 40% amounting to basal and 60% to postprandial secretion. In insulin resistance, the daily requirement can increase up to 200 IU.

For initial adjustment of a newly diagnosed type 1 DM patient, a daily requirement of 0.5–1.0 IU/kg/day is assumed. In the morning, the relative insulin requirement is the highest, during lunch the lowest, and in the evening it is intermediate.

Physical activity and hypothyroidism (see ▶ Chap. 21) decrease; a sedentary lifestyle, pregnancy, fever, infections, major surgery, hyperthyroidism (see ▶ Chap. 21), Cushing's syndrome, and administration of high GC doses for therapy of an autoimmune disease (see ▶ Chap. 11) increase insulin requirement.

19.3 Metformin

The biguanide metformin was introduced into DM therapy almost 70 years ago. Accordingly, clinical experience is vast. Since the patent for metformin expired long ago, numerous inexpensive generic drugs are available, allowing the economic treatment of large patient cohorts over long periods of time. This is an important point because type 2 DM has to be treated lifelong in most cases. Overall, metformin is a safe drug if administered properly. In clinical studies, it was convincingly shown to reduce morbidity and mortality. Thus, metformin is the most important and best studied drug for type 2 DM and the drug of first choice.

Metformin is taken up into cells via organic cation transporters and inhibits mitochondrial function. The increase in AMP concentration activates AMP kinase, ultimately inhibiting gluconeogenesis and lipogenesis. Additionally, metformin indirectly increases insulin sensitivity and stimulates the incretin regulatory circuit (see ▶ Sect. 19.6). Given the fact that both biguanides and PPAR-γ agonists increase insulin sensitivity, but that only biguanides are clinically effective, it appears that insulin sensitivity is not critical for the beneficial effects of metformin.

Metformin does not cause an increase in body weight, thereby, supporting insulin sensitivity. In contrast to other drugs for type 2 DM, particularly sulfonylureas, hypoglycemia does not occur.

Metformin can cause loss of appetite, but this effect may actually contribute to weight loss. Nausea, diarrhea, and metallic taste are other typical ADRs that are predominantly evident during the initial phase of therapy. In rare cases, metformin may cause lactic acidosis. This ADR can be avoided if contraindications (CHF, CKD, liver failure, ethanol addiction, pancreatitis, malignant tumors, and infections associated with fever) are observed and the drug dose is increased incrementally.

Metformin is currently "repurposed" for numerous other indications including polycystic ovary syndrome, neurodegenerative diseases, infectious diseases, and even malignant tumors (!). These multiple indications may reflect the pleiotropic mechanism of action of biguanides. Since other mechanisms than AMK kinase activation are probably involved in the pharmacological effects of biguanides, the chemistry-based class designation "biguanides" is more neutral than the incomplete mechanism-based designation "AMP kinase activators" (see ▶ Chap. 1).

19.4 PPAR-γ Agonists

PPRA-γ is an NR that increases insulin sensitivity via altered gene expression. Glitazones (prototype pioglitazone) are PPAR-γ agonists. They reduce HbA_{1C}, but their efficacy in type 2 DM in terms of reduced morbidity and mortality is not proven. PPAR-γ agonists can be administered p.o. but have serious ADRs. Weight gain, edema, CHF (see ▶ Chap. 16), increased MI risk, liver dysfunction, and increased risk of fractures in women (see ▶ Chap. 20) and of urinary bladder carcinoma have been reported. Therefore, PPAR-γ agonists are only of marginal therapeutic relevance. The case of PPAR-γ agonists shows how important it is to avoid the suggestive and misleading term "insulin sensitizer" as umbrella name for drugs encompassing glitazones and biguanides. Whereas biguanides are most valuable drugs for type 2 DM, glitazones are not.

19.5 Sulfonylureas

Sulfonylureas inhibit ATP-dependent potassium channels, depolarize B cells glucose-independently, and increase insulin secretion (◘ Fig. 19.1). Therefore, they (prototype glibenclamide) possess a substantial risk for hypoglycemia. DM complications, but not mortality, can be reduced. Sulfonylureas may increase body weight as a consequence of hyperinsulinemia. They can be administered p.o. The therapeutic value of sulfonylureas in type 2 DM is very limited.

19.6 GLP-1R Agonists and DPP4 Inhibitors

Exenatide, a peptide from the saliva of the Gila monster (a lizard), is a prototypical GLP-1R agonist. It has to be administered s.c. In the meantime, sustained-release formulations of exenatide have become available. Liraglutide is a GLP-1 analog with a long duration of action. GLP-1R agonists reduce HbA_{1C} and body weight, but the effect on cardiovascular mortality is small. Nausea and vomiting are typical ADRs. Compared to metformin, the costs of a therapy with GLP-1R agonists are high.

Incretin enhancers (gliptins) inhibit DPP4 and, thereby, GLP-1 degradation. As a result, the effects of GLP-1 are prolonged. Sitagliptin is a prototypical drug of this class. Since GLP-1 release is glucose-dependent, the risk of hypoglycemia is smaller than with sulfonylureas and insulin. GLP-1 stimulates insulin secretion, inhibits glucagon secretion, enhances the feeling of satiety, and delays stomach emptying. DPP4 inhibitors constitute a promising therapeutic principle for type 2 DM because they support a physiological mechanism. However, long-term studies showing superiority of gliptins relative to metformin have not yet been performed until now. In this context, the extensive costs of a therapy with gliptins need to be considered. Because of the high prevalence of type 2 DM in many countries, this is pharmacoeconomically relevant. Since DPP4 does not only inactivate GLP-1 but also other peptides, DPP4 inhibitors can cause several ADRs. Among these are GI disturbances, pancreatitis, infections of the upper airways, arthrosis, and skin inflammation. Gliptins

can be applied p.o. Sitagliptin is eliminated unaltered via the kidney.

19.7 SGLT-2 Inhibitors

Empagliflozin is a prototype of the SGLT-2 inhibitors (gliflozins). It inhibits SGLT-2 at the luminal side of the tubule and prevents reabsorption of glucose from the glomerular filtrate. This results in glucosuria and weight loss. However, SGLT-2 inhibitors reduce cardiovascular mortality only to a small extent. The ADRs of SGLT2 inhibitors can be explained by their mechanism of action. Polyuria and dehydration with the risk of hypotension and thrombosis (see ▶ Chap. 18) are observed. Glucosuria additionally increases the risk of urogenital infections, e.g., with *Escherichia coli* (see ▶ Chap. 33) and *Candida albicans* (see ▶ Chap. 35). Moreover, hypoglycemia can occur, and increased calcium elimination enhances the risk for osteoporosis and bone fractures (see ▶ Chap. 20).

19.8 α-Glucosidase Inhibitors

Acarbose is a prototypical α-glucosidase inhibitor. It inhibits intestinal disaccharidases. Consequently, disaccharides enter the colon. Since there they cannot be absorbed, they serve as substrates for bacteria, converting disaccharides to carbon dioxide, methane, and short-chain fatty acids. Clinically, this manifests as flatulence (60–70%), diarrhea, and staining of the underwear (spotting). Because of these ADRs, also designated as "biofeedback", consumption of sugar-containing food and beverages should be reduced. However, avoiding consumption of these food items and beverages should rather be the goal in the first place. Acarbose reduces postprandial blood glucose peaks and HbA_{1C}, but neither mortality nor morbidity. Thus, the therapeutic value of acarbose in type 2 DM is low.

19.9 Therapy of Hypoglycemia

Hypoglycemia is defined as a blood glucose concentration <2.8 mmol/l. Cardinal symptoms of hypoglycemia are the consequences of the compensatory activation of the sympathetic nervous system (tachycardia, tremor, nervousness, and voracious appetite; see ▶ Chap. 5) and neuroglycopenic symptoms (confusion, delirium, epileptic seizures, loss of consciousness) since the CNS obligatorily depends on glucose as energy substrate.

Overdosing of insulin, sulfonylureas, and GLP-1R agonists, insufficient or irregular food intake, physical exhaustion, and excessive ethanol consumption can cause hypoglycemia (◘ Fig. 19.1). Causative factors potentiate each other when combined. β_1AR antagonists (see ▶ Chaps. 5 and 15) can mitigate warning symptoms of activation of the sympathetic nervous system and impede with proper recognition of hypoglycemia. The risk of hypoglycemia is particularly high under β_xAR antagonists that are used for treatment of infantile hemangioma (see ▶ Chap. 5). The suspected diagnosis of hypoglycemia bases on clinical symptoms if the patient is a known diabetic and has to be confirmed by measurement of blood glucose concentration.

Hypoglycemia is an emergency and must be treated immediately. If the patient recognizes symptoms of hypoglycemia or diagnoses it biochemically, she/he has to administer p.o. 15–30 g of glucose along with fluids followed by ingestion of slowly absorbed carbohydrates in form of fruits or bread. If the patient is not anymore capable of treating herself/himself, 30 g of glucose are injected i.v.. Particularly physically active type 1 DM patients should always carry a glucagon rescue syringe. Glucagon is injected into the thighs. The hormone stimulates hepatic glycogenolysis and, thereby, increases blood glucose concentration (see ◘ Fig.19.1). In principle, EPI has the same effect as glucagon, but the former hormone is not clinically used for hypoglycemia because it affects many more organ functions, i.e., it has more ADRs in this context (see ▶ Chaps. 5 and 15).

19.10 Therapy of Diabetic Coma

Diabetic coma develops in type 1 DM patients as a result of chronic insulin deficiency and leads to dehydration, hyperglycemia (blood glucose concentration >15–40 mmol/l), and ketoacidosis. Clinical cardinal symptoms are acetone breath, polydipsia, polyuria, and CNS symptoms (e.g., somnolence, confusion, loss of

consciousness). Rehydration is the most important measure in diabetic coma and is achieved by slow (over 12 hours) i.v. infusion of large volumes (4–6 l) of 0.9% NaCl solution. Slow infusion is important to avoid the development of cerebral edema. In addition, a short-acting insulin is infused (about 4 IU/hour), until the blood glucose concentration reaches 11 mmol/l. Since insulin also stimulates potassium uptake into cells, infusion of KCl at a dose of 13–20 mmol/hour is essential to avoid life-threatening hypokalemia that can cause tachyarrhythmia and epileptic seizures (see ▶ Chap. 17). In severe acidosis (pH < 7.1), bicarbonate has to be infused.

19.11 Questions and Answers

Questions

Which assignment of drug classes for DM treatment to mechanism of action is *NOT* correct?

A. Insulins – Increase of cellular glucose uptake
B. Glitazones – Antagonists at PPAR-α
C. Gliflozins – Inhibition of SGLT2
D. Gliptins – Inhibition of DPP4
E. Sulfonylureas – Inhibition of ATP-dependent potassium channels

Answers

A. Insulin reduces blood glucose concentration. Glucagon and EPI are functional insulin antagonists and increase blood glucose concentration.
B. Glitazones are PPAR-γ agonists. Lipid-lowering drugs of the fibrate class are PPAR-α agonists. PPAR-α antagonists are not used clinically.
C. Via inhibition of this glucose transporter, renal glucose elimination is increased.
D. Via DPP4 inhibition, GLP-1 degradation is reduced, enhancing glucose-dependent insulin secretion from B cells.
E. Via inhibition of potassium channels, sulfonylureas stimulate insulin secretion. Since insulin secretion is glucose-independent, the risk of hypoglycemia is high.

Assignment **B** is not correct.

19.12 Exercises

A 64-year-old male patient (BMI 34.9) is diagnosed with hypertension (185/110 mm Hg), dyslipidemia, and type 2 DM. The HbA_{1C} value is 8.9%. The patient reports that he feels lethargic and is not moving around anymore a lot. Whenever possible, he uses the car and elevators.

Questions

1. Which antidiabetic is the drug of choice in this patient?
2. Which additional measures should be implemented in the patient?

Answers

1. The patient is obese and suffers from hypertension, dyslipidemia, and DM. The DM must have been ongoing for quite a while since the HbA_{1C} value is very high. All symptoms of a metabolic syndrome are present. Based on the clinical symptoms, you can reasonably assume the presence of insulin resistance. In this situation, metformin is the most appropriate drug. It can improve insulin resistance without increasing body weight or causing hypoglycemia. Clinical studies have documented a decrease in mortality in type 2 DM patients under metformin therapy.
2. It is critical to educate the patient about the nature of the type 2 DM. The patient needs to understand that a long-term calorie-restricted diet will lead to weight reduction which is the key to improvement insulin resistance. The patient should be counseled by a dietitian. In addition, the patient must initiate an appropriate exercise program including, e.g., swimming and Nordic walking. Moderate exercise positively affects insulin resistance. Moreover, it is essential to treat hypertension. Because of micro- and macroangiopathy, DM is a major risk factor for hypertension and its complications. For the patient, ACEIs or AT_1R antagonists are drugs of choice, combined with class B, C, and D drugs as needed. Dyslipidemia needs to be treated as well. HMG-CoA reductase inhibitors constitute an option.

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Drugs for Treatment of Osteoporosis

R. Seifert, *Basic Knowledge of Pharmacology*, https://doi.org/10.1007/978-3-030-18899-3_20

Osteoporosis is the result of excessive activity of osteoclasts in relation to osteoblasts. The therapeutic goal is to correct this disbalance. This is accomplished by exposure to sun light, reduction of tobacco and ethanol consumption, supplementation of vitamin D_3 and calcium, and appropriate physical activity. Several drugs including classic cytostatics, thyroid hormones, PPIs, and GCR agonists promote osteoporosis. Therapy of osteoporosis is performed with bisphosphonates which inhibit osteoclasts. Postmenopausal osteoporosis is treated with SERMs and inhibitors of the RANK/RANKL interaction. The latter drugs are also used in osteoporosis due to hormone ablation in prostate carcinoma. Osteoblast activity can be increased by the N-terminal fragment of PTH.

Key Points

1. GCR agonists, T4, classic cytostatics, heparin, aromatase inhibitors, AR antagonists, PPIs, antacids, lithium, ethanol, and nicotine promote osteoporosis.
2. Bisphosphonates inhibit osteoclasts.
3. Bisphosphonates have to be administered on an empty stomach, in upright position and with ample water.
4. SERMs inhibit osteoclasts and are used in postmenopausal osteoporosis.
5. Denosumab inhibits osteoclasts via blockade of RANK/RANKL interaction.
6. Denosumab is used in postmenopausal osteoporosis and hormone ablation in prostate carcinoma.
7. Teriparatide stimulates osteoblasts and can be used intermittently for up to 24 months.
8. Calcium and vitamin D_3 are the basis of osteoporosis therapy.

20.1 Pathophysiology of Osteoporosis and Pharmacological Interventions

Bones are dynamic support structures consisting of the periost, pars compacta, and pars spongiosa. They are permanently remodeled according to the current demands, i.e., the level of physical activity. Osteoblasts act anabolically and osteoclasts catabolically. For physiological bone remodeling, a balanced action of both cell types is required. Adequate physical activity is essential for proper bone function.

Osteoporosis is a very common disease in which the activity of osteoclasts is too high in relation to that of osteoblasts. ◘ Figure 20.1 shows this disbalance, drugs, and diseases that promote osteoporosis and pharmacological interventions. ◘ Table 20.1 lists selected drugs for treatment of osteoporosis. The disease is characterized by reduced bone density and increased bone fragility so that even small traumatic events result in pathological fractures that lead to immobilization and complications such as thrombosis (see ▶ Chap. 18) or pneumonia (see ▶ Chap. 33). This may be lethal. In addition, fractures heal only poorly in osteoporotic bone and are difficult to treat surgically. Therefore, prophylaxis of osteoporosis by a healthy lifestyle and avoidance of drugs that can promote osteoporosis has high priority. Prophylaxis and therapy of osteoporosis have to be performed on a long-term basis. Therefore, good efficacy and tolerability of drugs are essential. In addition, costs should not be too high because large portions of the population are affected by osteoporosis.

Primary osteoporosis is the most common disease form, is divided into two subforms, and accounts for 95% of all cases. Type I postmenopausal osteoporosis is due to the decrease in estrogen concentration (see ▶ Chap. 24). In this case, mostly the pars spongiosa is degraded. Type II osteoporosis is also referred to as senile osteoporosis and is predominantly due to vitamin D deficiency. This subform affects women and men about equally. Both, the pars spongiosa and the pars compacta are degraded. Secondary osteoporosis accounts for about 5% of all cases and is caused by hyperthyroidism (see ▶ Chap. 21), Cushing disease (see ▶ Chap. 11), CKD and loop diuretics (see ▶ Chap. 12), classic cytostatics (see ▶ Chap. 32), heparin (see ▶ Chap. 18), GCR agonists (see ▶ Chap. 11), PPIs (see ▶ Chap. 13), AR antagonists and aromatase inhibitors (see ▶ Chap. 24), as well as SGLT-2 inhibitors (see ▶ Chap. 19). Physical inactivity, confinement in bed, vitamin D or calcium deficiency, lack of sunlight exposure, and consumption of ethanol and

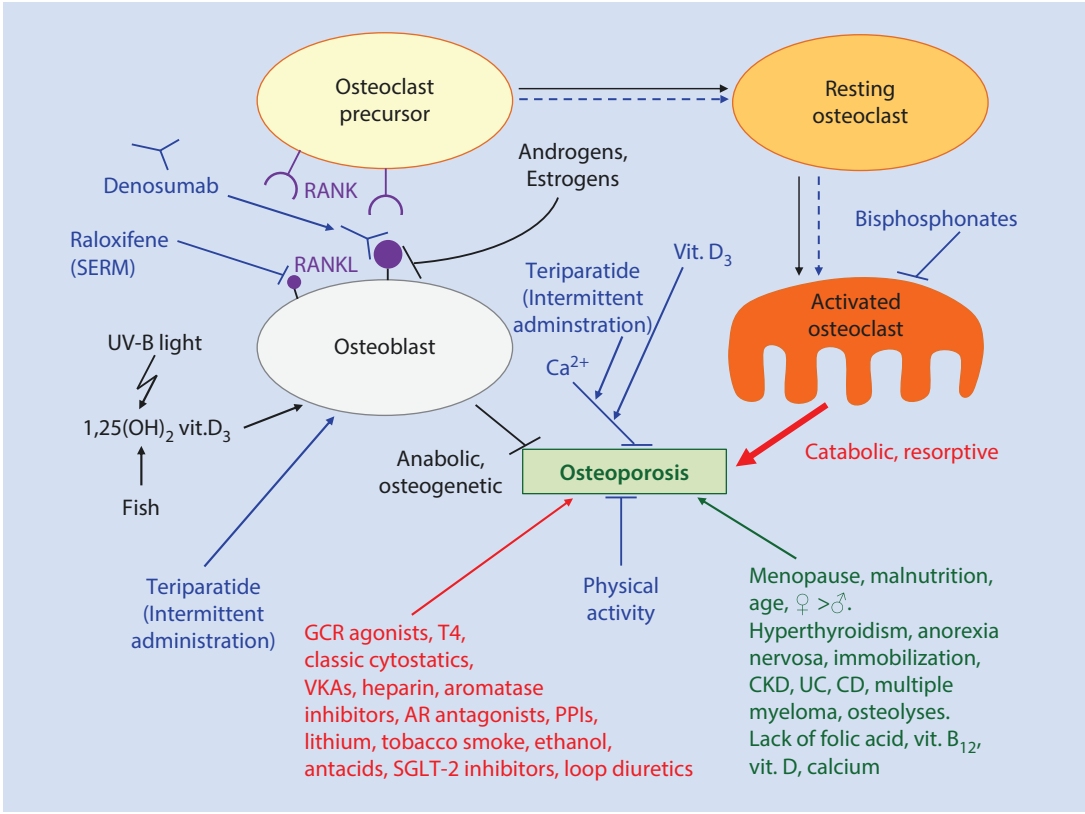

Fig. 20.1 Pathophysiology of osteoporosis: Pharmacological interventions and drugs as well as diseases that promote osteoporosis. Try to avoid drugs that can cause osteoporosis and eliminate risk factors! The application of bisphosphonates is not trivial and can cause serious ADRs

tobacco promote osteoporosis. Prophylaxis and basic therapy of osteoporosis rest on elimination of the risk factors and sufficient supply of vitamin D_3 and calcium. In addition, therapeutic strategies aim at inhibiting osteoclast activity (antiresorptive therapy). Bisphosphonates, SERMs, and denosumab act via this mechanism. Moreover, osteoblast activity can be increased (osteoanabolic therapy) by teriparatide and vitamin D_3.

20.2 Vitamin D_3 and Calcium

$1,25(OH)_2D_3$ (calcitriol) is the most important antiosteoporotic hormone. It binds to an NR (see ▶ Chap. 1), increases intestinal calcium absorption, and decreases renal calcium elimination. As a result, more calcium is available for bone mineralization. In addition, osteoblast activity is stimulated. Calcitriol is produced from vitamin D_3 (cholecalciferol) that is taken up with food (e.g., fish) or formed from 7-dehydrocholesterol via UV-B irradiation of the skin. Cholecalciferol is converted to 25(OH) vitamin D_3 in the liver and to calcitriol in the kidney. Therefore, calcitriol is substituted in CKD (see ▶ Chap. 12).

Daily intake of 800–1000 IU vitamin D_3 constitutes the basic prophylaxis and therapy of osteoporosis. Since enhanced intestinal calcium absorption represents a significant portion of the effect of calcitriol, sufficient calcium supply is important. Preferentially, calcium should be provided with the food, e.g., milk or milk products (or calcium-containing mineral water for vegans). Alternatively, calcium in a daily amount of 1000 mg can be administered as dietary supplement. Overdoses of calcium (>2 g/day) and/or vitamin D_3 may result in calcium overload, leading to hypercalcemia, hypercalciuria, and urolithiasis. Hypercalcemia manifests itself as nervousness, fatigue, and tachycardia as well as increased toxicity of Na^+/K^+-ATPase inhibitors (see ▶ Chaps. 4 and 16).

Table 20.1 Overview of selected drugs for treatment of osteoporosis

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Alendronate	This pyrophosphate analog is taken up by osteoclasts and incorporated in AMP to form a dysfunctional ATP analog	Induces apoptosis of osteoclasts resulting in an antiresorptive effect	All types of osteoporosis, osteolyses in tumor diseases, Paget's disease	Poor absorption which is further reduced by calcium, antacids, and milk; mucosal erosions in the esophagus, nausea, and vomiting. This is the reason why alendronate has to be taken p.o. on an empty stomach in an upright position with ample water. Rare but dangerous: jawbone osteonecroses after dental/jaw surgeries	2, 13, 32
Calcium carbonate	Amplifies the effect of vitamin D_3	Enhances intestinal absorption of calcium resulting in increased bone mineralization	Very inexpensive basic therapy and prevention of osteoporosis; administered in combination with vitamin D_3; preferably consume calcium-rich food instead of expensive food supplements	Hypercalcemia, hypercalciuria, urolithiasis, increased toxicity of Na^+/K^+-ATPase inhibitors	12, 16, 23
Denosumab	Monoclonal antibody inhibiting the RANK/RANKL interaction	Inhibits formation, function and survival of osteoclasts	Postmenopausal osteoporosis, osteoporosis in metastatic prostate carcinoma after hormone ablation therapy	Hypocalcemia, cataract, diverticulitis, jawbone osteonecroses, atypical femoral fractures	12, 24, 32
Raloxifene	SERM with ER agonist effects on the skeletal, cardiovascular, and cerebral system and ER antagonist effects on the uterus and mammary gland	Inhibits osteoclast function (antiresorptive effect) by inhibiting RANKL expression	Postmenopausal osteoporosis	Hot flashes, flu-like symptoms, thromboembolisms (strokes)	18, 24

Teriparatide	N-terminal fragment of PTH activating the PTH receptor	Stimulates intestinal calcium absorption and tubular calcium reabsorption; intermittent administration increases osteoblast activity	Therapy of osteoporosis for a maximum of 24 months	Hypercalcemia, vertigo, headache, musculoskeletal pain, nausea, increased toxicity of Na^+/K^+-ATPase inhibitors	12, 16
Vitamin D_3	Conversion to $1,25(OH)_2$ vitamin D_3 (calcitriol) and activation of the nuclear calcitriol receptor	Enhances intestinal calcium absorption and inhibits renal calcium elimination; stimulates osteoblast activity	Very inexpensive basic therapy and prophylaxis of osteoporosis. Ensure sufficient calcium intake. In case of renal insufficiency, calcitriol has to be administered	Hypercalcemia, hypercalciuria, urolithiasis, increased toxicity of Na^+/K^+-ATPase inhibitors	12, 16, 23

20.3 Bisphosphonates

Bisphosphonates are phosphate analogs. Alendronate is a representative drug of this class. Bisphosphonates bind to hydroxyl apatite in the bone and are transported into osteoclasts and incorporated into AMP. Since the pyrophosphate group of ATP is substituted by a bisphosphonate, metabolically dysfunctional ATP analogs are formed. Therefore, bisphosphonates induce osteoclast apoptosis and act antiresorptively. They are used in all types of osteoporosis including bone metastases and long-term GCR agonist therapy, osteogenesis imperfecta, and Paget's disease. Long-term therapy with bisphosphonates can reduce the incidence of the particularly problematic hip fractures in postmenopausal women by more than 50%. Sufficient vitamin D_3 and calcium supply for osteogenesis is important as well.

For efficacy of bisphosphonates, it is critical to strictly adhere to a defined application protocol. Because of their hydrophilicity, bisphosphonates are only poorly absorbed following p.o. administration (0.3–4%, see ▶ Chap. 2). Since they can form insoluble complexes with calcium and other salts, bisphosphonates have to be given on the empty stomach with a sufficient volume of water (about 200 ml; no milk, no juice) about 30 minutes before breakfast. Drug administration has to be performed in an upright position (sitting or standing). Thereafter, the patient must not lie down again because bisphosphonates can cause serious esophagus erosions that may develop into ulcerations and strictures. Bisphosphonates also cause ulcerations in the pharynx, stomach, and duodenum. Following dental or jawbone surgery, osteonecrosis can occur in patients treated with bisphosphonates.

Bisphosphonates have a half-life of months to years since they accumulate in a deep compartment, i.e., the bone matrix (see ▶ Chap. 2). In parallel to the elimination from the bone, the antiresorptive effects of bisphosphonates decline. Since their elimination occurs via the kidney, they are contraindicated in CKD. Further contraindications are GERD and PUD (see ▶ Chap. 13), inability to sit upright, hypocalcemia, pregnancy, and lactation.

Because of the complex formation with salts, calcium supplements must be taken not earlier than 2 hours after bisphosphonate application. Bisphosphonates increase the ulcerogenic effects of COX inhibitors in the GI tract (see ▶ Chaps. 10 and 13).

20.4 Selective Estrogen Receptor Modulators (SERMs)

The interaction of RANKL with its receptor RANK is important for differentiation of osteoblast precursors to activated osteoclasts. Estrogens suppress RANKL expression on osteoblasts and, hence, RANK/RANKL interaction. Thus, in women with sufficient estrogen production, osteoclast activity is suppressed. In menopause, the suppressing estrogen effect disappears. Consequently, osteoclast activity increases, and postmenopausal osteoporosis develops (see ▶ Chap. 24).

SERMs differentially act on the ER subtypes ERα and ERβ (see ▶ Chap. 24). The SERMs used in postmenopausal osteoporosis are antagonists at ERα expressed in the uterus and the mammary gland and agonists at ERβ expressed in the bone, CNS, and blood vessels. Raloxifene is a prototype of this drug class. It inhibits RANKL expression and acts antiresorptively. However, the agonist effects at ERβ in blood vessels increase the stroke risk (see ▶ Chaps. 18 and 24). Accordingly, raloxifene is contraindicated in patients with serious cardiovascular diseases. Via the agonist effects of raloxifene at ERβ in the CNS, hot flushes and flu-like symptoms can occur.

20.5 Denosumab

Denosumab is a human monoclonal antibody that binds to RANKL expressed on osteoblasts, thereby preventing the interaction of the ligand with its receptor RANK on osteoclasts. Since the RANK/RANKL interaction is important for differentiation of osteoclast precursors to activated osteoclasts as well as for the function of activated osteoclasts, denosumab inhibits osteoclast activity and induces an antiresorptive effect. Thus, denosumab acts functionally similarly on the bone as SERMs, the difference being that ERs are not involved in the pharmacological effects.

Denosumab can be used as alternative to SERMs in postmenopausal osteoporosis. Like lack of estrogen effects, androgen ablation (performed in hormone-positive prostate carcinoma) increases osteoclast activity and increases osteoporosis risk. Therefore, denosumab can be used in men with prostate carcinoma undergoing a therapy with AR antagonists (see ▶ Chaps. 24 and 32).

Denosumab is injected s.c. every 6 months. Cataract, diverticulitis, bone osteonecrosis, atypical femoral fractures, allergic reactions, and hypocalcemia are rare ADRs.

20.6 Teriparatide

PTH is synthesized in the parathyroid gland and released in hypocalcemia. It increases intestinal and renal calcium absorption. Teriparatide is the N-terminal 34 amino acid fragment of PTH. If applied intermittently, it stimulates osteoblast activity and acts anabolically in addition to the calcium-elevating effects. Teriparatide is administered s.c. for up to 24 months. It is predominantly used in postmenopausal osteoporosis and high fracture risk. Hypercalcemia, nausea, vertigo, headache, and limb pain are ADRs. Hypercalcemia increases the toxicity of Na^+/K^+-ATPase inhibitors (see ▶ Chaps. 4 and 16). Teriparatide is contraindicated in manifest hypercalcemia, CKD, bone metastases, and Paget's disease.

20.7 Questions and Answers

Questions

Which assignment of drug class to effect on bone structure is *NOT* correct?

A. SERMs – antiresorptive effect
B. AR antagonists – osteoporosis prophylaxis in healthy men
C. Inhibitors of RANK/RANKL interaction – osteoporosis prophylaxis in metastasizing prostate carcinoma
D. Bisphosphonates – therapy and prophylaxis of osteolytic lesions in multiple myeloma
E. Teriparatide – osteoanabolic effect in osteoporosis

Answers

A. SERMs inhibit osteoclasts and can be used in postmenopausal osteoporosis.
B. Androgens act osteoanabolically. AR antagonists are used in prostate carcinoma patients but not healthy men. AR antagonists promote the development of osteoporosis.
C. Inhibitors of RANK/RANKL interactions act antiresorptively and inhibit development of osteoporosis.
D. Bisphosphonates reduce osteoclast activity and counteract osteolytic lesions in multiple myeloma.
E. The osteoanabolic effects of teriparatide can be used for up to 24 months. The risk of hypercalcemia has to be considered.

Assignment **B** is not correct.

20.8 Exercises

A 72-year-old woman has been treated for 3 years with alendronate for postmenopausal osteoporosis. Her family physician transfers her to your gastroenterology office because she complains of heartburn. In esophagoscopy you see severe mucosal erosions in the distal esophagus. Inspection of the stomach does not yield any pathological findings. For hypertension, the patient additionally takes ramipril and, once in a while, one half tablet of diphenhydramine for treatment of insomnia. Previously she had taken long walks with her dog. However, after the dog's death 6 months ago, she stopped this habit. Instead she has started again to smoke cigarettes.

Questions

1. What are your initial therapeutic measures?
2. Which long-term therapeutic options do you have?

Answers

1. Most likely, the erosions are the result of incorrect alendronate application. The drug must be taken on the empty stomach with sufficient volumes of water and in an upright position to ensure sufficient absorption and to avoid

mucosal damage in the GI tract. You educate the patient about the proper procedure for alendronate administration. You should also inform the family physician about proper alendronate application because it looks like that he is not aware of the problems that can arise when correct procedures are not implemented. In about 4 weeks, you perform a control esophagoscopy. Ramipril is an unproblematic drug in this context. Diphenhydramine, in high doses, could cause GI motility problems due to M_xR antagonism, but in the low doses applied, this drug should be unproblematic as well.

2. It appears that the patient does not yet receive a basic therapy with vitamin D_3 and calcium. The family physician should implement such a therapy. In addition, the patient should be motivated to restart an exercise program commensurate with her physical capabilities to strengthen the skeletal muscles and to prevent osteoporosis deterioration. One option would be the purchase of another dog. Joining a senior exercise group is another option. Such a group would also foster social contacts. The patient must be advised to quit smoking.

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Drugs for Treatment of Thyroid Gland Diseases

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The thyroid hormones T4 and T3 regulate nearly every body function. Thyrocytes take up iodide and incorporate it into tyrosine residues of thyroglobulin via TPO. Iodinated tyrosine residues are condensed to yield T3 and T4. Following proteolytic cleavage of thyroglobulin, T3 and T4 are secreted into the blood. In the liver, T4 is deiodinated into the biologically active T3. Hyperthyroidism is due to increased synthesis of T4 and T3. Stimulation of the TSHR with autoantibodies is one cause of hyperthyroidism. It is treated with TPO inhibitors. For goiter prophylaxis (inhibition of TSH secretion), potassium iodide and low-dose T4 are administered. Alternatively, hyperthyroidism can be treated with ^{131}iodide, selectively destroying thyrocytes with energy-rich β-radiation. Cardiovascular symptoms of hyperthyroidism (tachycardia and hypertension) can be treated with β_1AR antagonists, agitation with benzodiazepines, and diarrhea with loperamide. In hypothyroidism, synthesis of T4 and T3 is reduced. Hashimoto's autoimmune thyroiditis and iodine-deficiency goiter are common causes of hypothyroidism. This disease is treated with T4 because it ensures more consistent effects than T3. In case of iodide deficiency, potassium iodide is substituted.

Key Points

1. Hyperthyroidism is treated with thionamides or ^{131}iodide.
2. Thionamides inhibit TPO and, thereby, T3 and T4 synthesis.
3. Agranulocytosis is the most serious ADR of thionamides.
4. T4 is a prohormone of T3.
5. ^{131}Iodide destroys thyrocytes via β-radiation.
6. In hyperthyroidism, goiter prophylaxis with T4 has to be performed.
7. β_1AR antagonists can be used for treatment of cardiovascular hyperthyroidism symptoms.
8. Benzodiazepines can be used to treat agitation in hyperthyroidism.
9. Loperamide can be used for treatment of diarrhea in hyperthyroidism.
10. Hypothyroidism is treated with T4.
11. T4 and thyroid extracts are abused for weight reduction; this can result in arrhythmias and hypertension.
12. Amiodarone can induce hyper- or hypothyroidism, iodine-containing contrast media hyperthyroidism, and lithium hypothyroidism.

21.1 Physiology of the Thyroid Gland

TSH, which is secreted from the hypophysis, regulates synthesis and secretion of the thyroid hormones T4 and T3. T4 is the biologically inactive prohormone of T3. In the liver, deiodases convert T4 to T3. Via negative feedback T3 inhibits TSH secretion in the hypophysis and, thereby, ensures that the thyroid gland is not excessively stimulated. Long-term TSH stimulation enhances thyrocyte proliferation, culminating in goiter development. This does not only constitute a cosmetic but also a functional problem. Hypo- or hyperthyroidism can cause benign adenomas or malignant tumors. ◘ Figure 21.1 provides an overview of regulation of T4 and T3 secretion, functions of T3, hyper- and hypothyroidism, and pharmacological interventions.

T3 mediates its effects via an NR that regulates gene transcription and protein biosynthesis (see ▶ Chap. 1). Accordingly, thyroid hormones act slowly, and pharmacological interventions show effects only after a latency of several days. On the one hand, this allows for smooth and well-tolerated treatment, but on the other hand, it is very difficult to address acute symptoms due to excessive thyroid hormone action.

Thyroid hormones regulate nearly every body function. T3 is essential for an even-tempered mood and normal intellectual capability. In the cardiovascular system, T3 leads to increased β_1AR expression. As a result, tachycardia and hypertension develop (see ▶ Chaps. 15 and 17). T3 is essential for normal GI tract motility. In the liver, T3 regulates glucose and lipid metabolism, ensures normal basal metabolic rate, and regulates body temperature. It influences muscle metabolism and contractility. In addition, T3 is important for proper function of the reproductive organs, skel-

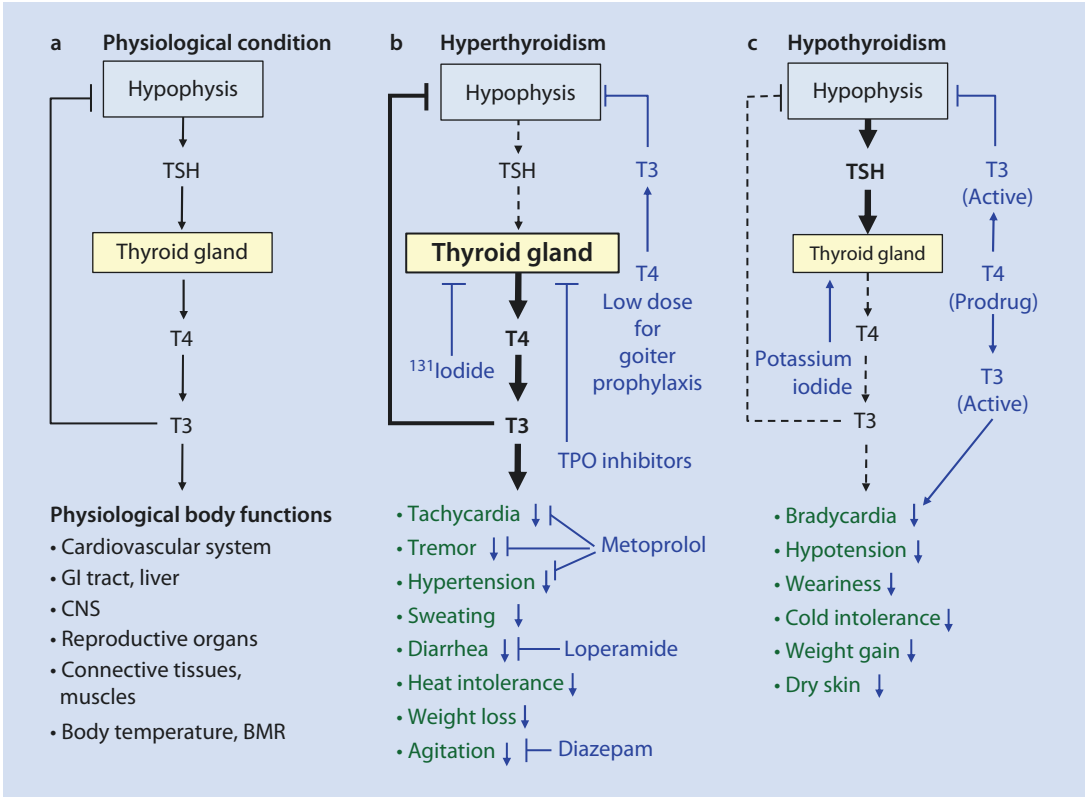

Fig. 21.1 **a–c** Regulation of T4 and T3 secretion, functions of T3, and pharmacological interventions. **a** Physiological situation. **b** Hyperthyroidism. **c** Hypothyroidism; BMR basic metabolic rate. Both hypothyroidism and hyperthyroidism can be treated easily and economically

eton, connective tissue, and skin. Therefore, hypo- and hyperthyroidism manifest themselves at multiple organs (see Fig. 21.1b, c).

Figure 21.2 provides an overview of synthesis and metabolism of T4 and T3, pathophysiological changes, pharmacological interventions, and toxicological problems. Iodide is actively taken up into thyrocytes via a transporter and translocated into the colloid vesicles where TPO oxidizes it to iodine and subsequently incorporates it into tyrosine residues of thyroglobulin. TPO condensates two diiodinated tyrosine residues (diiodothyronine) to T4, and a monoiodinated tyrosine residue (monoiodothyronine) is coupled with a diiodothyronine residue to T3. Thyroglobulin is then taken up into thyrocytes where proteolytic cleavage of T3 and T4 takes place. Both hormones are secreted into the blood where T3 and T4 are bound to T3-/T4-binding globulin. T3 is biologically active and regulates target cells, whereas the biologically inactive T4 first has to be converted to T3 in the liver. T3 possesses a much shorter plasma half-life (about 24 hours) than T4 (about 7 days). Table 21.1 summarizes important properties of selected drugs for treatment of thyroid gland diseases.

21.2 Pathophysiology and Pharmacotherapy of Hyperthyroidism

In hyperthyroidism secretion of T3 and T4 is elevated (see Fig. 21.1b). Causes are autonomous adenomas of the thyroid gland as consequence of iodide deficiency, goiter, or Graves' disease. In Graves' disease, stimulatory antibodies against the TSHR are formed, activating function and proliferation of thyrocytes (see Fig. 21.2). Constitutively active mutations in the TSHR are another cause of hyperthyroidism. This implies that the TSHR is active and stimulates the thyroid gland even in the absence of TSH. TSH-secreting hypophyseal adenomas and certain drugs can

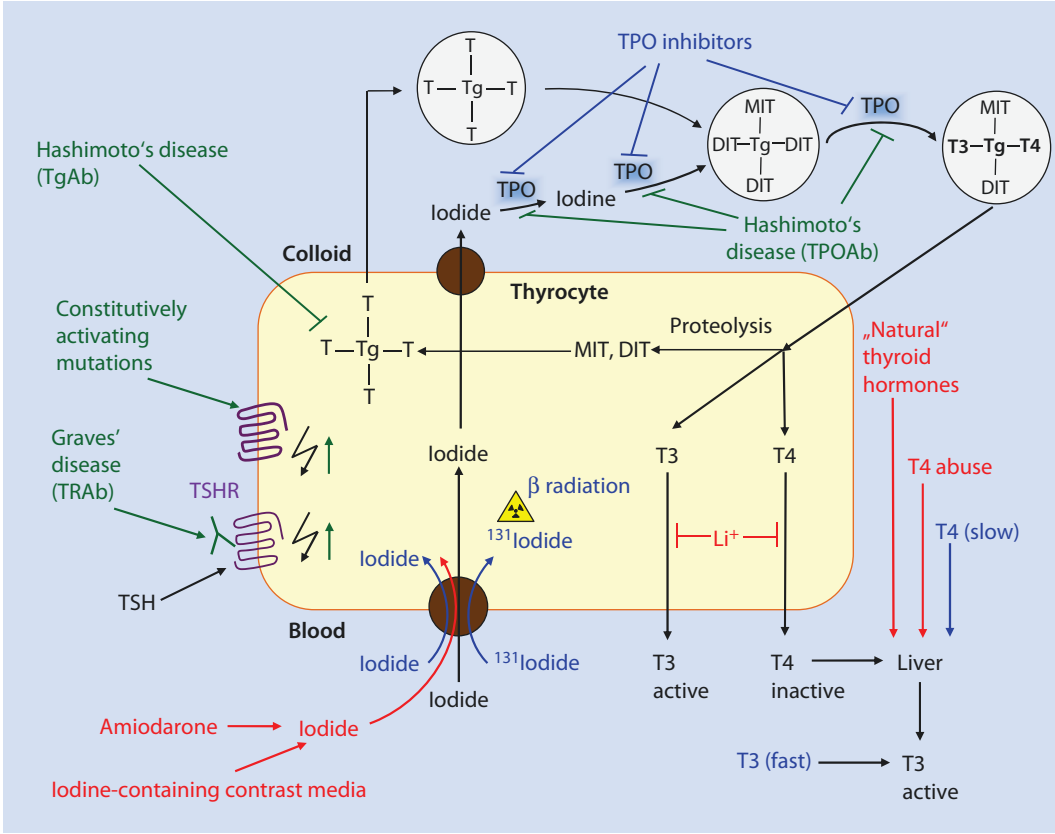

Fig. 21.2 Synthesis and metabolism of T4 and T3, pathophysiological changes, pharmacological interventions, and toxicological problems. Tg thyroglobulin, MIT monoiodothyronine, DIT diiodothyronine, TBG T3/T4-binding globulin, TPOAb antibody against TPO, TGAb antibody against thyroglobulin, TRAb antibody against TSHR

cause hyperthyroidism as well. Among these drugs are iodine-containing contrast media (see ▶ Chap. 12) and amiodarone (see Fig. 21.2 and ▶ Chap. 17). The increased iodine supply leads to enhanced synthesis of T3 and T4.

Cardinal symptoms of hyperthyroidism are tachycardia, hypertension, and tremor as a consequence of enhanced β_1AR expression. In addition, agitation, diarrhea, heat intolerance, weight loss, hyperthermia, sweating, voracious appetite, hyperglycemia, steatohepatitis, alopecia, osteoporosis, infertility, and myopathy can develop. A particular problem is the abuse of T4 for weight reduction in euthyreotic persons. Since T4 does not exhibit organ selectivity, all other organs are affected in addition to the desired weight loss. Tachycardia, hypertension, and CHF can develop (see ▶ Chaps. 15, 16, and 17). The consumption of "natural" thyroid hormones from desiccated animal thyroid glands is problematic as well. Such formulations are broadly advertised on the Internet but do not possess a clearly defined content of T3 and T4. Moreover, these preparations can be purchased without a prescription. As a result, life-threatening thyrotoxic crisis can develop.

Hyperthyroidism is treated with TPO-inhibiting thionamides, thiamazole being a prototype. These drugs inhibit iodide oxidation, incorporation of iodine into thyroglobulin, and coupling of MIT + DIT to T3 and of DIT + DIT to T4. Thiamazole (plasma half-life 6–12 hours) is administered once daily and propylthiouracil (plasma half-life of 2 hours) twice daily. Carbimazole is a thiamazole prodrug (see ▶ Chap. 2). After initiation of a thionamide therapy, still much T3-/T4-containing thyroglobulin is available. Moreover, T3 exerts its effects via an NR (see ▶ Chap. 1). Therefore, a 1- to 2-week latency until onset of drug action exists. Because thionamides induce long-term inhibition of T3

Table 21.1 Overview of selected drugs for treatment of thyroid gland diseases

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
^{131}Iodide	Energy-rich β emitter	Selective uptake by the thyroid gland leading to irreversible destruction of thyrocytes	Hyperthyroidism which does not respond to TPO inhibitors; thyroid carcinoma	Hypothyroidism; low toxicity outside the thyroid gland	32
Diazepam	Allosteric $GABA_AR$ modulator	Sedative-hypnotic, anxiolytic	Agitation associated with hyperthyroidism	Daytime sedation, impaired driving ability, ataxia; risk of physical and psychological addiction during long-term treatment	25
Loperamide	Peripherally acting MOR agonist	Slows intestinal motility, thereby enhancing the absorption of water and electrolytes	Diarrhea in hyperthyroidism	Constipation with long-term application. Ensure sufficient water and electrolyte supply and high-fiber foods	13
Metoprolol	β_1AR antagonist	Negative inotropic, chronotropic, and dromotropic effects on the heart	Tachycardia, hypertension, and tremor in hyperthyroidism	Bradycardia, AV block, hypotension, bronchoconstriction in asthmatic patients and unrecognized hypoglycemia in diabetic patients	1, 5, 15, 16, 17
Potassium iodide (100–200 µg/day)	Iodide supply for T3 and T4 synthesis	Increased T3 and T4 synthesis	Iodine-deficiency goiter	Hyperthyroidism due to overdose with long-term use	
T3	Biologically active thyroid hormone	Activation of the NR for thyroid hormones, modulation of various body functions (plasma half-life of approx. 24 hours)	Not to be used in long-term treatment of hypothyroidism and in combination with TPO inhibitors because of its short plasma half-life/too fluctuating effects. Used in myxedema, a rare complication of hypothyroidism, requiring a rapid onset of action	Symptoms of hyperthyroidism as with T4, but more rapid onset of action	5, 13, 15, 16, 25

(continued)

Table 21.1 (continued)

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
T4	Prohormone that is converted to the biologically active T3	Conversion to T3 with a plasma half-life of approx. 7 days	Long-term therapy of hypothyroidism; combination with TPO inhibitors to inhibit TSH secretion (goiter prophylaxis). It is important to take T4 in the morning on an empty stomach	Hyperthyroidism due to overdose (weight loss, heat intolerance, agitation, diarrhea, tremor and tachycardia, diarrhea)	5, 13, 15, 16, 25
Thiamazole	TPO inhibition	Reduction of T3 and T4 synthesis	Hyperthyroidism; combination with T4 to inhibit TSH secretion (goiter prophylaxis)	Hypothyroidism due to overdose (weight gain, cold intolerance, weariness, bradycardia, constipation), exanthemas, arthralgia, fever, nausea, vomiting, liver damage, vasculitis, agranulocytosis (hemograms)	4, 13

and T4 synthesis, the negative feedback of T3 on the hypophysis is abrogated, resulting in increased TSH secretion (see ◘ Fig. 21.1b). This leads to enhanced thyrocyte proliferation, clinically presenting as goiter. This ADR can be prevented by adding low doses of T4 to the thionamide therapy. T4 has to be dosed in such a way that the patient, as a result of the combined effects of endogenous and exogenous thyroid hormones, is euthyreotic. T3 is not suitable for goiter prophylaxis because its effects can only be poorly controlled due to its short plasma half-life.

Frequent and mild ADRs of TPO inhibitors are exanthemas, arthralgia, fever, nausea, and vomiting. In about 0.3–0.6% of the patients, more serious ADRs including liver damage, vasculitis, and leukopenia, developing into life-threatening agranulocytosis, can occur. Under thionamide therapy, regular hemograms have to be performed. In case of agranulocytosis, TPO inhibitors must be discontinued. Granulocytopoiesis can be stimulated with G-CSF (see ▶ Chap. 4).

If hyperthyroidism cannot be treated with TPO inhibitors or if serious ADRs occur, radiotherapy with the energy-rich β-emitter ^{131}iodide constitutes an alternative. This therapy can also be implemented in thyroid carcinoma that is not accessible to surgery. Like nonradioactive iodide, ^{131}iodide is taken up in thyrocytes and sequestered into the colloid (see ◘ Fig. 21.2). The radioisotope has a physical half-life of 8 days and a range of action of 5 mm in thyroid gland tissue. Via enrichment of ^{131}iodide in thyrocytes and colloid, DNA strand breaks and irreversible destruction of thyroid gland tissue are induced. There is a 2–3-month latency between initiation of therapy and clinical onset of action. In case of complete thyroid gland destruction, hypothyroidism can develop, requiring substitution with T4. Pregnancy, lactation, and severe hyperthyroidism without prior treatment are contraindications for ^{131}iodide therapy. Overall, due to the strong enrichment in the thyroid gland and the short range of action of the β-radiation, ^{131}iodide exhibits only little toxicity in organs other than the thyroid gland.

The latency between therapy start and onset of drug action constitutes a practical problem in therapy of hyperthyroidism. The latency has to be bridged by minimization of hyperthyroidism symptoms. For treatment of tachycardia, hypertension, and tremor, β_1AR antagonists are feasible (see ▶ Chaps. 5, 15, and 17). For therapy of agitation, benzodiazepines (see ▶ Chap. 25) can be used. In case of diarrhea, water and electrolytes are substituted (see ▶ Chap. 13). The peripherally acting MOR agonist loperamide reduces GI tract motility and improves diarrhea (see ▶ Chap. 13). Hyperthermia must be treated by controlled cooling of the body.

21.3 Pathophysiology and Pharmacotherapy of Hypothyroidism

Hypothyroidism is frequent (prevalence 1–5%) and can be treated readily. Hashimoto's autoimmune thyroiditis is an important cause. In this disease, autoantibodies against TPO (90% of the patients) and thyroglobulin (50% of the patients) are formed. Insufficient supply of iodide with food and drinking water is another important cause for hypothyroidism. Iodide deficiency is a problem worldwide including remote inland areas and certain equatorial and mountain regions. Iodide deficiency goiter can be prevented by using iodized salt. Hypothyroidism can also occur postsurgically, after irradiation of the thyroid gland with ^{131}iodide, under therapy with TPO inhibitors, and as ADR of certain drugs such as lithium (see ◘ Fig. 21.2 and ▶ Chap. 28), amiodarone (see ◘ Fig. 21.2 and ▶ Chap. 17), or the targeted tumor therapeutic sunitinib (see ▶ Chap. 32). In hypothyroidism, the inhibitory effect of T3 on TSH secretion is reduced. As a result, thyrocyte proliferation is enhanced and goiter develops (see ◘ Fig. 21.1c).

Weariness, reduced intellectual capability, memory impairment, constipation, weight gain, cold sensitivity, bradycardia, hypotension, CHF, myxedema, alopecia, hoarseness, and dry, cold, and exfoliative skin are cardinal symptoms of hypothyroidism.

Hypothyroidism can be readily treated with T4. It has a plasma half-life of about 7 days and is converted to T3 in the body on demand. Therapy with T3 should only be performed in the very rare myxedema coma because for long-term therapy, the effects of T3 are too fluctuating and uncomfortable for the patient. Therapy of hypothyroidism is started with a dose of about 25 μg of T4 per day. This daily dose is increased weekly by an additional 25–50 μg one until a daily dose of about 1.5 μg/kg has been reached. Under T4 therapy

euthyreosis should be attained. In addition, TSH secretion must be suppressed to avoid further stimulation of thyrocytes (goiter prophylaxis). In iodide deficiency, substitution with potassium iodide has to be performed if supplementation with iodized salt and iodide-containing food items such as sea food is not sufficient. Early indicators for successful hypothyroidism therapy are weight loss with concomitant increase in appetite, motor activity, blood pressure, and HR. Later, skin symptoms and hoarseness improve.

From a practical point of view, it is important that T4 absorption is most reliable on an empty stomach. T4 must be administered about 30 minutes prior to breakfast with a glass of water. In pregnancy and in gastritis due to *Helicobacter pylori* infection (see ▶ Chap. 13), the T4 dose must be increased. By contrast, the T4 dose must be decreased in CHD to reduce the MI risk (see ▶ Chap. 16). Cholestyramine, antacids, and iron salts diminish T4 absorption. T4 can reduce the efficacy of insulin and oral antidiabetics (see ▶ Chap. 19). Drugs extensively bound to plasma proteins such as VKAs (see ▶ Chap. 18) and phenytoin (see ▶ Chap. 25) compete with T3 and T4 for binding to transport proteins in the blood and, thereby, increase the portion of the unbound and hence biologically active T3, leading to hyperthyroidism (see ▶ Chap. 2).

In principle, therapy with T4 is very affordable, but costs can vary dramatically from country to country. Over the past years, strong centralization of T4 production worldwide has taken place. If for centrally produced drugs quality and/or quantity problems occur, global supply problems emerge because of the lack of alternatives. This situation has resulted in supply problems for several important drugs including T4, the antibiotics amoxicillin and piperacillin (see ▶ Chap. 33), classic cytostatics like cyclophosphamide (see ▶ Chap. 32), and ASA low-dose for i.v. therapy of MI (see ▶ Chap. 16).

21.4 Questions and Answers

Questions

Which statement on pharmacotherapy of hyperthyroidism is *NOT* correct?

A. Benzodiazepines can be used to induce sedation.
B. TPO inhibitors can cause agranulocytosis.
C. Administration of T4 is contraindicated.
D. β_1AR antagonists can be used for treatment of tachycardia.
E. Amiodarone can deteriorate arrhythmias in hyperthyroidism.

Answers

A. In hyperthyroidism, agitation is common. This condition can be treated with long-acting benzodiazepines (e.g., diazepam) before the psychological situation improves upon onset of action of the TPO inhibitors.
B. Agranulocytosis is an ADR of TPO inhibitors. Therefore, under a therapy with TPO inhibitors, regular hemograms have to be performed.
C. TPO inhibitors are combined with low-dose T4 to keep the TSH concentration low and, thereby, to prevent thyrocyte proliferation (goiter prophylaxis).
D. Under T4 therapy, β_1AR expression is increased, resulting in tachycardia and hypertension. These consequences of T4 action can be alleviated with β_1AR antagonists.
E. Amiodarone is contraindicated in hyperthyroidism because it contains iodine and can deteriorate clinical symptoms.

Statement **C** is not correct.

21.5 Exercises

A 25-year-old female patient visits you in your general practitioner office. The patient is apathetic and complains of fatigue and inability to focus, weight gain, constipation, and increased sensitivity to cold. You diagnose bradycardia (HR 45/minute). Laboratory tests reveal a substantial increase in the plasma TSH concentration, a substantial decrease of T3 and T4 concentration, and high concentrations of antibodies against TPO. The ultrasound reveals an irregular structure of the thyroid gland.

Questions

1. What is your diagnosis and how do you proceed therapeutically?
2. Which ADRs can T4 cause?

Answers

1. The patient suffers from severe hypothyroidism caused by Hashimoto's autoimmune thyroiditis. You treat the patient with T4, the dose of which is increased incrementally. You begin with a daily dose of 25 µg. This dose can be increased every week by 25 µg per day until a daily maintenance dose of about 1.5 µg/kg has been reached. It is important that T4 is administered in the morning on an empty stomach with water and that the patient waits at least 30 minutes until having breakfast. During the therapy you regularly check for improvement of disease symptoms. Additionally, you control (every 6 weeks) the plasma TSH concentration. This parameter should decrease and reach low normal values. In Hashimoto's thyroiditis, no immunosuppressive therapy is conducted.
2. The therapeutic goal is to reach euthyreosis. T4 overdosing causes hyperthyroidism. Cardinal symptoms are weight loss, heat intolerance, agitation, diarrhea, tremor, and tachycardia. In this case, the T4 dose must be reduced again.

Further Reading

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Drugs for Treatment of Dyslipidemias

R. Seifert, *Basic Knowledge of Pharmacology*, https://doi.org/10.1007/978-3-030-18899-3_22

Hypercholesterolemia is an important risk factor in the pathogenesis of atherosclerosis which, in turn, is a major cause for MI, stroke, and PAD. Thus, reduction of plasma LDL cholesterol is of great importance for the prevention of cardiovascular diseases. Basis of therapy and prevention of atherosclerosis is a healthy and balanced diet, normal body weight, an active lifestyle, and abstinence from tobacco. The HMG-CoA reductase inhibitors (statins) constitute the most important and best-validated drug class for LDL cholesterol reduction. They inhibit cholesterol synthesis in the liver. The most important ADR of these drugs is myopathy which is due to enhanced bioavailability. Simultaneous administration of CYP3A4 and OATPB1 inhibitors increases bioavailability of HMG-CoA reductase inhibitors. Inhibition of cholesterol absorption, bile acid sequestration, PPAR-α activation, and PCSK9 inhibition are complementary approaches to reduce LDL cholesterol.

Key Points

1. HMG-CoA reductase inhibitors decrease LDL cholesterol effectively and economically.
2. HMG-CoA reductase inhibitors decrease cardiovascular mortality.
3. A risk score considering age, sex, tobacco use, and BP determines indication for HMG-CoA reductase inhibitors.
4. The use of HMG-CoA reductase inhibitors has to be integrated into an overall concept including lifestyle, reduction of overweight, and treatment of cardiovascular risk factors.
5. HMG-CoA reductase inhibitors can cause myopathy.
6. The myopathy risk is increased by simultaneous administration of CYP3A4 and OATPB1 inhibitors.
7. Ezetimibe inhibits intestinal cholesterol absorption and is combined with HMG-CoA reductase inhibitors in most cases.
8. Cholestyramine binds bile acids and interrupts the enterohepatic cycle.
9. Fenofibrate is a PPAR-α agonist and is used in mixed hyperlipidemia and hypertriglyceridemia.
10. Evolocumab inhibits PCSK9 and should be used only in resistant hypercholesterolemia because of high therapy costs.

22.1 Pathogenesis of Atherosclerosis and Pharmacological Interventions

Cholesterol is a sterol lipid that plays an essential role for all membrane functions. In addition, it is the substrate for the synthesis of bile acids and vitamin D_3 (see ▶ Chap. 20), mineralocorticoids (see ▶ Chap. 15), GCR agonists (see ▶ Chap. 11), and sex hormones (see ▶ Chap. 24). The transport of cholesterol in the blood is mediated via lipoproteins. The major fraction (about 700–900 mg) of the daily requirement of cholesterol is synthesized in the liver; the remainder (about 250 mg) is provided with the food. Cholesterol elimination is predominantly mediated via the bile, with a substantial fraction of cholesterol (about 400 mg) being converted into bile acids which are important for absorption of lipid-soluble vitamins, fatty acids, and triglycerides. Cholesterol transport to the liver is predominantly mediated via low-density lipoprotein (LDL). LDL cholesterol is taken up into the liver via the LDL receptor.

Hypercholesterolemia (LDL cholesterol >3.4 mmol/l) is an important risk factor in the pathogenesis of atherosclerosis with deleterious complications including MI (see ▶ Chap. 16), stroke, and PAD. In many countries, more than 50% of the population have hypercholesterolemia. ◘ Figure 22.1 schematically depicts the pathogenesis of atherosclerosis and pharmacological interventions. The most frequent form of hypercholesterolemia is the type IIa. This type is of polygenetic origin and promoted by risk factors including an unbalanced diet, DM, obesity, excessive ethanol consumption, and a sedentary lifestyle. Various drugs can facilitate development of hypercholesterolemia as well. Among these drugs are GCR agonists (see ▶ Chap. 11) and oral contraceptives (see ▶ Chap. 24). LDL cholesterol is

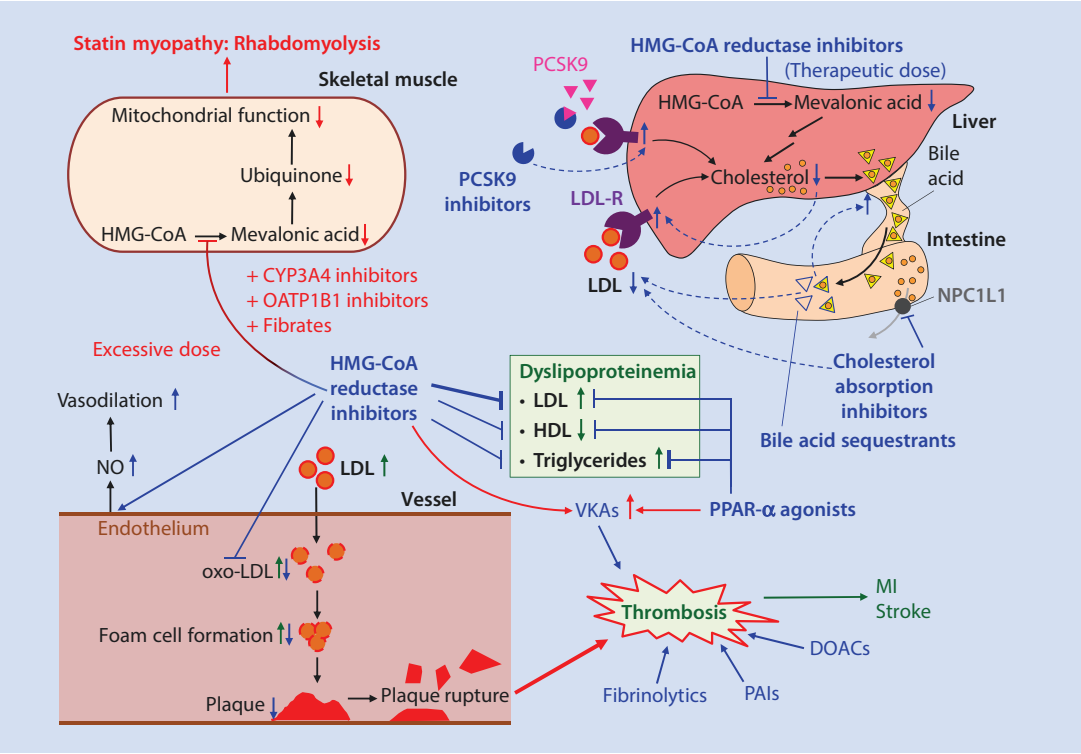

Fig. 22.1 Pathogenesis of atherosclerosis and pharmacological interventions. Beware of the uncritical use of HMG-CoA reductase inhibitors without proper indication! They can cause serious statin myopathy!

Before prescribing a HMG-CoA reductase inhibitor, assess the cardiovascular risk score of the patient. Just hypercholesterolemia without any other cardiovascular risk factors does not justify the use of these drugs

oxidized in the endothelium. Oxo-LDL cholesterol is taken up into macrophages that are converted to foam cells which generate an inflammatory response leading to subendothelial plaques. Rupture of these plaques causes thrombosis with the complications MI and stroke (see ▶ Chaps. 16 and 18).

Additional risk factors in the pathogenesis of cardiovascular diseases are hypertension (see ▶ Chap. 15), high age (women >60 years; men >50 years), type 2 DM (see ▶ Chap. 19), tobacco smoking (see ▶ Chap. 5), and dyslipidemia. p-mGPCR antagonists (see ▶ Chap. 29) and antiviral protease inhibitors (see ▶ Chap. 34) can deteriorate dyslipidemia. A reduction of the high-density lipoprotein (HDL) cholesterol (<1.2 mmol/l for women and <1.0 mmol/l for men) and elevation of triglycerides >1.7 mmol/l are unfavorable for the development of atherosclerosis as well.

Table 22.1 provides an overview of selected drugs for treatment of hypercholesterolemia and other dyslipidemias. Various drugs reduce LDL cholesterol, the HMG-CoA reductase inhibitors being the most important class (see ▶ Sect. 22.2). In comparison, inhibitors of cholesterol absorption (see ▶ Sect. 22.3), bile acid sequestrants (see ▶ Sect. 22.4), PPAR-α agonists (see ▶ Sect. 22.5), and PCSK9 inhibitors (see ▶ Sect. 22.6) are of lesser importance. HMG-CoA reductase inhibitors and PPAR-α agonists also moderately increase HDL cholesterol. HMG-CoA reductase inhibitors, inhibitors of cholesterol absorption, and PPAR-α agonists additionally reduce triglyceride concentration in the plasma to a different extent. The effects of lipid-lowering drugs exhibit a delayed onset of action of several days, and maximum effects are reached only after several weeks. But this is unproblematic because the lipid-lowering therapy is of preventive nature.

Therapy of hypercholesterolemia is performed under consideration of additional cardiovascular risk factors. Among these factors are age (for men the risk of MI and stroke increases consider-

Table 22.1 Overview of selected drugs for treatment of lipid metabolism disorders

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Cholestyramine	Basic polymer which binds bile acids in the intestine and, hence, interrupts the enterohepatic circulation	Total cholesterol: ↓ LDL: 12–34%↓ HDL: → Triglycerides: →↓	Adjunctive therapy in primary hypercholesterolemia; pruritus/icterus in partial biliary obstruction	Constipation, steatorrhea, hypovitaminoses of the fat-soluble vitamins A, D, E, and K; should be combined with HMG-CoA reductase inhibitors because of compensatory overexpression of HMG-CoA reductase	2, 12, 13
Evolocumab	Monoclonal antibody which inhibits PCSK9. As a consequence, more LDL receptors are expressed in the liver	Total cholesterol: ↓ LDL: 50–60%↓ HDL: → Triglycerides: →	Primary hypercholesterolemia and mixed dyslipidemia, if HMG-CoA reductase inhibitors are contraindicated or do not provide sufficient results if administered alone	Allergic reactions (e.g., at the injection site), respiratory complaints, infections of the upper respiratory tract	
Ezetimibe	Inhibition of intestinal cholesterol absorption via NPC1L1	Total cholesterol: 15%↓ LDL: 8–20%↓ HDL: → Triglycerides: 10%↓	Primary hypercholesterolemia and homozygous familial hypercholesterolemia (also in combination with HMG-CoA reductase inhibitors)	Hepatotoxicity, GI disturbances, vertigo	
Fenofibrate	PPAR-α agonist causing changes in expression of genes involved in lipid metabolism	Total cholesterol: 11%↓ LDL: 8%↓ HDL: 10%↑ Triglycerides: 36%↓	Mixed hyperlipidemia, severe hypertriglyceridemia	Hepatotoxicity, GI disturbances, myopathy, and rhabdomyolysis (increased risk if combined with HMG-CoA reductase inhibitors)	12
Simvastatin	Inhibition of HMG-CoA reductase and, hence, reduction of cholesterol synthesis in the liver. In addition, LDL cholesterol uptake by the liver is enhanced, endothelial NO synthesis is stimulated, and LDL cholesterol oxidation is inhibited	Total cholesterol: 15–40%↓ LDL: 20–60%↓ HDL: 2–14%↑ Triglycerides: 10–30%↓	Primary hypercholesterolemia (particularly type IIa), mixed dyslipidemia, secondary prevention after MI and stroke	Myopathy in statin monotherapy: 5% transient creatine kinase increase; 1% creatine kinase increase <tenfold; 0,5% creatine kinase increase >tenfold; 0.01% fulminant rhabdomyolysis and kidney failure; combination with PPAR-α agonists and with CYP3A4 and OATPB1 inhibitors increases the risk of myopathy; GI disturbances, headache, hepatotoxicity	2, 12, 15, 16, 18

ably earlier than for women), blood pressure, and tobacco smoking. The first measures in patients with elevated LDL cholesterol without additional risk factors are implementation of a healthy diet and an active lifestyle. This includes weight reduction, limitation of ethanol consumption, a diet with restricted saturated fat, abstaining from soft drinks and tobacco, and inclusion of sufficient fibers and unsaturated fats into the diet. If additional risk factors are present, a pharmacotherapy suited to the individual type of dyslipidemia is initiated.

In general, an HMG-CoA reductase inhibitor is the drug of first choice. Efficient pharmacotherapy of hypercholesterolemia reduces cardiovascular mortality. This has been demonstrated in particular for HMG-CoA reductase inhibitors. As a general rule, LDL cholesterol should be reduced more aggressively, the more risk factors are present. In high-risk patients, LDL cholesterol should be reduced to levels <1.8 mmol/l or at least by 50%. It is equally important to treat hypertension (see ▶ Chap. 15), insulin resistance (see ▶ Chap. 19), and thromboembolism (see ▶ Chap. 18).

22.2 HMG-CoA Reductase Inhibitors

The most important drug class for treatment of dyslipidemia are the HMG-CoA reductase inhibitors (statins). Their effectiveness in the prevention of cardiovascular diseases has been proven, and safe and affordable treatment of large patient cohorts is feasible. ◘ Figure 22.1 shows the mechanism of action, ADRs, and interactions of HMG-CoA reductase inhibitors.

HMG-CoA reductase is the key enzyme for cholesterol synthesis in the liver, catalyzing the conversion of HMG-CoA to mevalonic acid which is converted to cholesterol via multiple steps. HMG-CoA reductase inhibitors block the rate-limiting, irreversible step of cholesterol synthesis. As a consequence, hepatic cholesterol concentration declines. In order to compensate for cholesterol depletion, the expression of LDL receptors on the plasma membrane is increased. These receptors mediate enhanced uptake of LDL cholesterol into the liver. In parallel, LDL cholesterol concentration in the plasma is reduced, and pathogenesis of atherosclerosis is delayed. HMG-CoA reductase inhibitors can lower LDL cholesterol by up to 50%. They also moderately reduce triglycerides and, to a small extent, increase HDL cholesterol. Thus, HMG-CoA reductase inhibitors all in all possess a beneficial effect on most types of dyslipidemia which are complex and often include, besides LDL increase, HDL reduction and triglyceride elevation. In addition, HMG-CoA reductase inhibitors promote vasodilation by increased expression of endothelial NO synthase (see ▶ Chap. 9). Moreover, they have antioxidative effects, thereby inhibiting inflammation and plaque formation. HMG-CoA reductase inhibitors are the most commonly prescribed drugs for treatment of dyslipidemia. They reduce overall mortality by 30% and mortality due to MI by 42%. Since hypercholesterolemia is a risk factor requiring long-term therapy, good tolerability of the drugs is important.

Simvastatin is a prototypical HMG-CoA reductase inhibitor. It is a lacton prodrug that is taken up into the liver by OATP1B1 and converted to the active metabolite (hydrolysis of the lacton ring). Simvastatin possesses a very large first-pass effect, i.e., CYP3A4 inactivates already >95% of the drug during the first liver passage (see ▶ Chap. 2). In case of simvastatin, this effect is desired since the effect of the drug is largely confined to the liver. If the bioavailability of simvastatin is increased by co-administered drugs, enhanced systemic ADRs can occur. The skeletal muscle is an important target for ADRs of HMG-CoA reductase inhibitors where they inhibit ubiquinone synthesis and, as a result, compromise energy metabolism. This can lead to myopathy, starting with muscle pain. If unrecognized and untreated, rhabdomyolysis, myoglobinemia, kidney failure, and death may result (see ▶ Chap. 12). In laboratory tests, myopathy is diagnosed by elevation of creatine kinase and myoglobin in plasma. PPAR-α agonists which can induce myopathy themselves may aggravate myopathy caused by statins (see ▶ Sect. 22.5). HMG-CoA reductase inhibitors enhance the effects of VKAs and the risk of hemorrhage.

The myopathy risk is particularly large with high doses of HMG-CoA reductase inhibitors and comedication with CYP3A4 and OATP1B1 inhibitors (see ▶ Chap. 2). Under these conditions, simvastatin is taken up by the liver to a smaller extent, so that higher concentrations of the drug become systemically available. Clinically important CYP3A4 inhibitors are erythromycin, ketoconazole, and the bitter substance naringin

from grapefruit juice. Ciclosporin, erythromycin, and ketoconazole are clinically important OATP1B1 inhibitors. That high bioavailability is relevant for toxicity of HMG-CoA reductase inhibitors is highlighted by the case of cerivastatin with a bioavailability of 60%. In combination with the PPAR-α agonist gemfibrozil which inhibits cerivastatin degradation via CYP2C8 and hepatic uptake via OATP1B1, more than 50 patients worldwide died as a consequence of severe rhabdomyolysis. This serious interaction became infamous as the Lipobay® scandal and resulted in the withdrawal of cerivastatin from the drug market.

In addition to simvastatin, other HMG-CoA reductase inhibitors are used clinically. Among these drugs are atorvastatin and pravastatin. With respect to the maximally achievable reduction of LDL cholesterol, the drugs are comparable, but they differ from each other in terms of potency (drug dose, see ▶ Chap. 1). Dosing of HMG-CoA reductase inhibitors is adjusted to the desired LDL-cholesterol reduction. Interactions with CYP3A4 inhibitors are more pronounced for atorvastatin than for pravastatin. HMG-CoA reductase inhibitors should be administered in the evening because cholesterol synthesis is maximal during the night.

Another dose-dependent ADR of HMG-CoA reductase inhibitors is hepatotoxicity. Dose-independent ADRs are GI problems and headache. HMG-CoA reductase inhibitors are contraindicated in patients with liver diseases and myopathy. HMG-CoA reductase inhibitors should not be applied during pregnancy and the lactation period because of possible teratogenic effects.

22.3 Inhibitors of Cholesterol Absorption

In the intestine, cholesterol is absorbed via NPC1L1. This transporter is inhibited by cholesterol absorption inhibitors. Ezetimibe is the prototype of this drug class. As a consequence of the cholesterol deficiency, cholesterol is extracted more efficiently from the plasma into the liver. LDL cholesterol is reduced moderately (about 20%), and triglycerides are lowered to a still lesser extent. Inhibition of cholesterol absorption in the intestine causes a compensatory increase in hepatic cholesterol synthesis. In addition to the only moderate effect on LDL cholesterol, this is another reason why ezetimibe is usually combined with HMG-CoA reductase inhibitors in hypercholesterolemia. Ezetimibe has no effect on absorption of triglycerides, fatty acids, and fat-soluble vitamins. Overall, the ADRs of ezetimibe are moderate. GI problems, headache, transaminase increases, and myopathy (mostly if the drug is combined with HMG-CoA reductase inhibitors) are observed. Ezetimibe can enhance the effects of VKAs. During pregnancy and lactation period, ezetimibe is contraindicated.

22.4 Bile Acid Sequestrants

Bile acid sequestrants are basic, non-absorbable polymers that bind bile acids in the intestine. Cholestyramine is the prototype of this drug class. Due to interruption of the enterohepatic circulation (see ▶ Chap. 2), bile acids are eliminated to a greater extent from the organism, leading to a compensatory increase in hepatic bile acid synthesis. Since bile acid synthesis starts from cholesterol, the latter is extracted more efficiently from the plasma, and a reduction of LDL cholesterol by about 25% results. Because of this only moderate effect, cholestyramine is usually combined with HMG-CoA reductase inhibitors to counteract the compensatory increase in HMG-CoA reductase expression under cholestyramine. The drug can also be used in chologenic diarrhea and partial bile duct occlusion for elimination of bile acids from the organism (see ▶ Chap. 13).

The daily cholestyramine dose amounts to 4–24 g. The drug is ingested with liquids prior to meals. Cholestyramine is not absorbed and eliminated with the feces. The drug can cause constipation (see ▶ Chap. 13), steatorrhea, and inhibition of absorption of the fat-soluble vitamins A, D, E, and K. Accordingly, these vitamins need to be substituted. Moreover, cholestyramine inhibits absorption of T4 (see ▶ Chap. 21) and doxycycline (see ▶ Chap. 33). Therefore, T4 and doxycycline have to be administered either 1 hour prior to or 4 hours after cholestyramine (see ▶ Chap. 2). The drug is contraindicated in constipation, ileus, and complete bile duct occlusion. During pregnancy, cholestyramine should only be used cautiously.

22.5 PPAR-α Agonists

PPAR-α belongs to the class of NRs (see ▶ Chap. 1) and is activated by PPAR-α agonists (fibrates). The receptor forms a heterodimer with the retinoid X receptor (RXR). This heterodimer binds to specific recognition sequences in the DNA and regulates the expression of various genes involved in lipid metabolism. Expression of acetyl-CoA synthase, regulating fatty acid oxidation, is modulated, and lipoprotein lipase and some proteins involved in lipid transport are induced. The result of these changes in gene expression is a moderate reduction of LDL cholesterol, a moderate HDL cholesterol elevation, and a prominent (30–50%) decline of triglycerides. Because of this profile, PPAR-α agonists are predominantly used in mixed hyperlipoproteinemia and severe and diet-refractory hypertriglyceridemia. Fenofibrate is a prototype of this drug class. PPAR-α agonists can cause GI problems and phototoxic reactions. Predominantly in combination with HMG-CoA reductase inhibitors, increases in transaminases and myopathies can occur. PPAR-α agonists enhance the effects of VKAs and sulfonylureas and are contraindicated in liver and gall bladder diseases.

22.6 PCSK9 Inhibitors

PCSK9 is synthesized in the liver and circulates in the blood. It binds to the hepatic LDL receptor and is internalized as complex with the receptor into the liver. In the liver PCSK9 degrades the LDL receptor. Evolocumab is a monoclonal antibody that binds and neutralizes circulating PCSK9. Accordingly, degradation of internalized LDL receptors is prevented, and LDL receptor expression is increased. As a result, LDL cholesterol is reduced by 50–60%. Evolocumab is indicated in forms of hypercholesterolemia where HMG-CoA reductase inhibitors are contraindicated or insufficiently efficient. It is also used in the rare familial homozygous hypercholesterolemia. The high treatment costs with evolocumab are a current topic of controversial discussion. Depending on the country, annual therapy costs of up to $ 15,000 per patient can accrue, whereas the annual costs for simvastatin (40 mg/day) amount to about $ 100 or less. These pharmacoeconomic aspects must be considered in view of the worldwide high prevalence of hypercholesterolemia and the mostly lifelong need for drug therapy.

Evolocumab is injected s.c. every 2 weeks or monthly. Allergic reactions at the injection site, respiratory problems, and infections of the upper airways and back pain are common ADRs.

22.7 Questions and Answers

Questions

Which statement on HMG-CoA reductase inhibitors (statins) is correct?

A. Statins effectively increase HDL cholesterol.
B. Statins should be prescribed for every male >60 years.
C. Statins possess excellent bioavailability.
D. Statins possess pleiotropic effects.
E. Because of the risk of interactions, statins should not be combined with ACEIs.

Answers

A. Statins increase HDL cholesterol only weakly. Their major effect is the reduction of LDL cholesterol (20–60%).
B. Prescription of statins follows a score integrating age, sex, LDL cholesterol, tobacco use, and BP. High age and male sex alone do not justify statin prescription. This is important in view of the fact that in certain countries, the prescription of statins is aggressively promoted.
C. Therapeutically used statins possess low bioavailability. Statins with high bioavailability possess a high risk for statin myopathy.
D. Statins inhibit hepatic cholesterol synthesis and stimulate compensatory hepatic LDL uptake. In addition, statins stimulate NO production in endothelial cells and inhibit LDL cholesterol oxidation.
E. BP reduction constitutes a major component of atherosclerosis therapy. Therefore, for pharmacodynamic reasons, the combination of statins with ACEIs is useful.

Answer **D** is correct.

22.8 Exercises

A 68-year-old male patient who had previously suffered posterior MI has been treated with 80 mg of simvastatin per day for 2 years due to hypercholesterolemia type IIa. So far, the patient has tolerated the therapy well. Because of an acute bronchitis, the family physician has prescribed a 7-day therapy with erythromycin. After 3 days, the patient complains of severe pain in the thighs. This is the reason why the patient visits you in your orthopedics office.

Questions

1. What is the most likely cause for the pain and how do you proceed diagnostically?
2. How do you proceed with respect to the medication?

Answers

1. The patient receives a relatively large simvastatin dose. This drug has only a low bioavailability and, in general, does not impair ubiquinone synthesis in the skeletal muscles. Erythromycin is an inhibitor of CYP3A4 and OATP1B1. As a result, simvastatin uptake and metabolism in the liver are inhibited. Accordingly, bioavailability increases, and because of inhibition of ubiquinone synthesis in the skeletal muscles, statin myopathy can develop. To verify the suspected diagnosis, you determine creatine kinase and myoglobin concentration in the plasma and creatinine concentration or, even better, creatinine clearance to detect kidney failure early. Close cooperation with the family physician is required.
2. This is a common drug interaction. You immediately terminate erythromycin and substitute it by an antibiotic (preferably on the basis of an antibiogram) that does not cause interactions with CYP3A4 or OAT1B1. Amoxicillin is such an alternative, but prior to therapy start, you must exclude that the patient suffers from penicillin allergy. If the patient does not have biochemical evidence for myopathy, you do not have to stop simvastatin because bioavailability should decrease again after therapy cessation. If there are already biochemical signs for statin myopathy, you stop the statin therapy until symptoms disappear. You could also try to reduce the dose to 40 or 60 mg/day. Most importantly, you must inform the patient about other possible drugs and food items (e.g., naringin in grapefruit juice) that can cause statin myopathy. Close cooperation with the family physician is required.

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Drugs for Treatment of Gout

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23

Gout is characterized by precipitation of uric acid, the end product of purine metabolism, in joints, soft tissues, and the urinary system. The symptoms of acute gout are monoarthritis with severe pain, restricted joint mobility, and hyperthermia. This condition can be effectively treated with COX inhibitors, GCR agonists, as well as microtubule and IL-1 inhibitors. Symptoms of chronic gout are polyarthritis with rest pain and impaired mobility. A calorie- and purine-reduced diet is the basis of long-term gout therapy. Uricostastic drugs (XO inhibitors) alone or in combination with uricosuric drugs (inhibitors of URAT1) are used for long-term gout therapy. With rigorous diet and stringent pharmacotherapy, gout has a good prognosis.

Key Points

1. Hyperuricemia without symptoms does not require pharmacotherapy.
2. PZA, EMB, thiazide, and loop diuretics can cause asymptomatic hyperuricemia.
3. In tumor lysis syndrome under therapy with classic cytostatic drugs, severe hyperuricemia can develop.
4. Acute gout is treated with COX inhibitors, GCR agonists, or microtubule and IL-1 inhibitors.
5. A calorie- and purine-reduced diet is the basis of gout therapy.
6. Uricostatic and uricosuric drugs are used for treatment of chronic gout.
7. Uricostatic drugs inhibit XO.
8. Allopurinol and febuxostat are uricostatic drugs.
9. Uricostatic drugs enhance the ADRs of 6-MP and azathioprine due to inhibition of their degradation.
10. Uricosuric drugs inhibit URAT1.
11. Benzbromarone and lesinurad are URAT1 inhibitors.
12. Initially, chronic gout is treated with allopurinol.
13. If the effect of allopurinol is not sufficient, benzbromarone or lesinurad are added.
14. As alternative to allopurinol, the more potent febuxostat can be used.

23.1 Pathophysiology of Gout

The prevalence of gout strongly depends on the diet. Whereas gout is almost unknown in countries with malnutrition, the prevalence of gout reaches 1–2% in countries with supernutrition, and up to 20% of the population in such countries have asymptomatic hyperuricemia. With increasing age, gout prevalence rises, reaching more than 7% in 65-year-old patients in some countries. Like type 2 DM, gout is the result of an unhealthy lifestyle. Accordingly, lifestyle adjustments are the key to successful gout treatment. Pharmacotherapy should only be implemented if diet alone is not successful. ◘ Table 23.1 summarizes selected drugs for gout treatment.

Gout is a disorder of purine metabolism. All gout symptoms are caused by uric acid (urate), the end product of purine metabolism (◘ Fig. 23.1). ATP is degraded to hypoxanthine via inosine and GTP to xanthine via guanine. XO converts hypoxanthine to xanthine and xanthine to uric acid which is subject to glomerular filtration. In the proximal tubule, uric acid is reabsorbed via URAT1 at the apical side. At the basolateral side, it is exchanged via OAT1 against various anions (◘ Fig. 23.2). Further distally in the tubule, uric acid is actively secreted.

Uric acid possesses only limited solubility in biological fluids. If its concentration exceeds 400 µmol/l, it precipitates and forms crystals. The solubility of uric acid increases with the temperature. Therefore, it precipitates to a greater extent in cooler acral regions such as the finger and foot joints or ears than in internal organs. Since uric acid is a weak acid, the risk of crystallization is higher at low pH. Uric acid deposits in soft tissues are designated as tophi. In addition, uric acid crystals can form in the urinary tract (urolithiasis) (see ◘ Fig. 23.2). This can lead to CKD (see ▶ Chap. 12) and severe colic pain. Reno-ureteral colics can be treated with butylscopolamine (see ▶ Chap. 5), GTN (see ▶ Chap. 9), and metamizole (see ▶ Chap. 10).

In about 90% of all gout cases, reduced renal elimination of uric acid is the cause. The remaining cases are due to excessive uric acid formation. Massive accumulation of uric acid can occur in the context of a therapy with classic cytostatics where many tumor cells are lyzed and large amounts of purine bases arise (see ▶ Chap. 32).

Table 23.1 Overview of selected drugs for treatment of acute and chronic gout

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Allopurinol	Inhibition of XO (only moderate selectivity)	Uricostatic effect by inhibition of xanthine and uric acid synthesis	Chronic gout, dose reduction in CKD	Nausea, vomiting, diarrhea, liver function abnormalities, allergic reactions (type IV)	3, 11, 12, 32
Benzbromarone	Inhibition of various transporters, e.g., URAT1	Uricosuric effect by enhanced renal elimination of uric acid	Chronic gout, as adjunctive therapy for patients who do not sufficiently respond to allopurinol alone. Ensure sufficient fluid intake and urine alkalization	Nausea, vomiting, loss of appetite, headache, allergic reactions, risk of urate crystal precipitations in the urinary tract with insufficient fluid intake	12
Canakinumab	Monoclonal antibody neutralizing IL-1	Anti-inflammatory effect by inhibition of IL-1 effects	Acute gout if ibuprofen, prednisolone, and colchicine are not tolerated or contraindicated	Infections of the urinary and respiratory tract, local reactions at the injection site	11, 33
Colchicine (low dose)	Inhibition of microtubule formation	Indirect anti-inflammatory effect by inhibition of leukocyte migration and phagocytosis	Acute gout	Nausea, vomiting, diarrhea with electrolyte loss (acute). More rarely, hair loss, liver, kidney, and CNS function abnormalities (chronic) are observed	13, 32
Febuxostat	Inhibition of XO (high selectivity)	Uricostatic effect by inhibition of xanthine and uric acid synthesis	Chronic gout if allopurinol is not tolerated or is ineffective; higher efficacy than allopurinol	Nausea, vomiting, diarrhea, headache, allergic reactions, increased cardiovascular risk?	11, 12, 32
Ibuprofen	COX inhibitor, inhibition of PGE_2 synthesis	Analgesic and anti-inflammatory effect	Acute gout	PUD, CKD, hypertension	10, 12, 13, 15
Lesinurad	Selective inhibition of URAT1	Uricosuric effect by enhanced renal elimination of uric acid	Chronic gout, adjunct therapy for patients who do not sufficiently respond to allopurinol alone. Ensure sufficient fluid supply and urine alkalization	GERD, headache, fever, renal dysfunctions	12
Prednisolone	Potent synthetic GCR agonist, inhibition of PG and LT synthesis, inhibition of cytokine release	Anti-inflammatory effect	Acute gout	No risk of adrenal gland suppression and Cushing's syndrome in short-term therapy	11

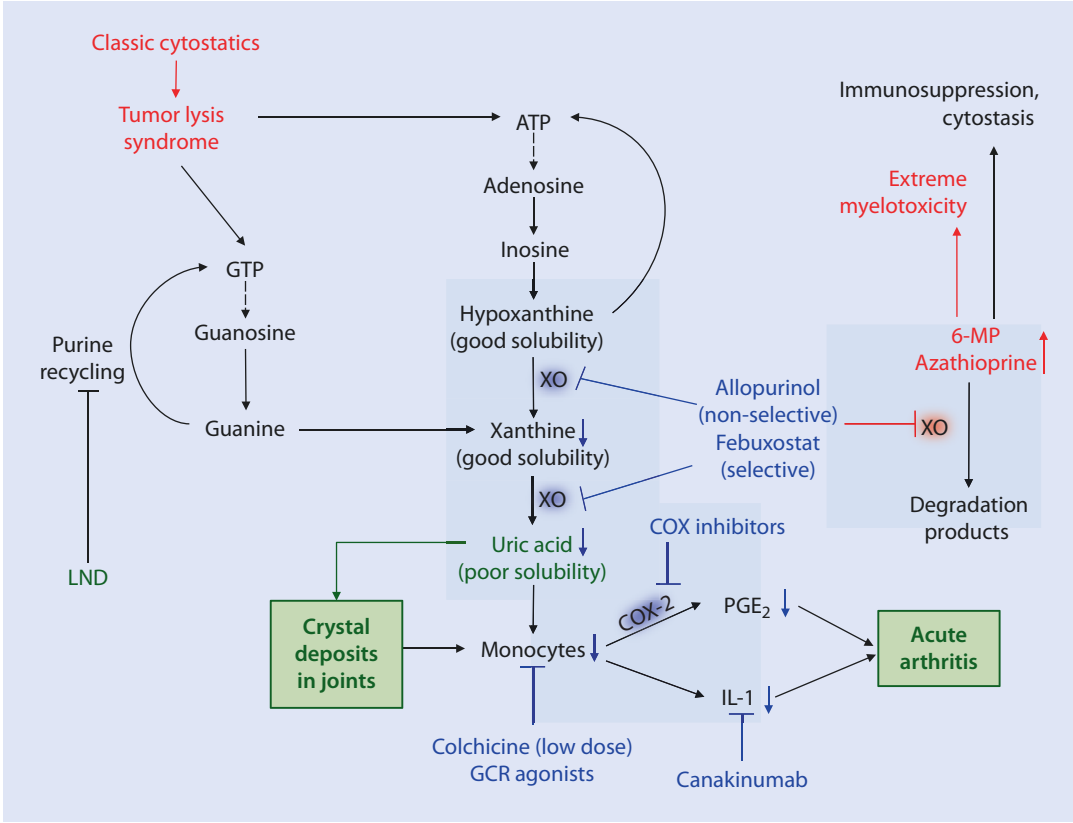

Fig. 23.1 Overview of (patho)physiology of purine degradation, pathogenesis of gouty arthritis, as well as pharmacological interventions and toxicological problems. LND, Lesch-Nyhan disease. Acute gout must be diagnosed and treated early! Do not overdose colchicine; it is very toxic

Lesch-Nyhan disease is a rare cause for uric acid overproduction. In this X-chromosomally inherited disease, recycling of purine bases is impaired. The urine must be alkalized, and XO must be inhibited to prevent uric acid precipitation (see Figs. 23.1 and 23.2). At a plasma uric acid concentration <400 µmol/l, gout incidence is 0.1%. It increases to 0.5% at concentrations between 400 and 525 µmol/l and to 5% at concentrations >525 µmol/l. The anti-TB drugs PZA and EMB (see ▶ Chap. 33) as well as thiazide and loop diuretics can cause hyperuricemia (see ▶ Chap. 12) that is symptomless in most cases.

Asymptomatic hyperuricemia does not require pharmacotherapy. However, in many cases, it is treated with the intention to prevent acute and chronic gout. The effectiveness of treatment is not proven, and ADRs of anti-gout drugs must be considered.

Gout is divided into four stages. In the first stage which does not require pharmacotherapy, symptomless uric acid precipitations in the joints, soft tissues, and kidney develop. In the second stage, acute gout develops, often presenting as monoarthritis. The affected joint is massively swollen, erythematous, and painful and exhibits restricted mobility. Uric acid crystals cause an acute inflammatory response in the joint (see Fig. 23.1). The symptoms develop within 24 hours and subside within 14 days. The third stage, also referred to as intercritical period, encompasses the time between acute gout episodes. Additional deposits of uric acid in joints, soft tissues, and the kidney develop, but the patient is symptomless. In the fourth stage, polyarthritis with rest pain and serious immobility develop. In addition, CKD and reno-ureteral colics, caused by uric acid crystals, occur.

The diagnosis "gout" is made on the basis of the classic clinical symptoms in the joints, the clinical course, and the detection of tophi and uric acid crystals in the joints. An elevated plasma uric

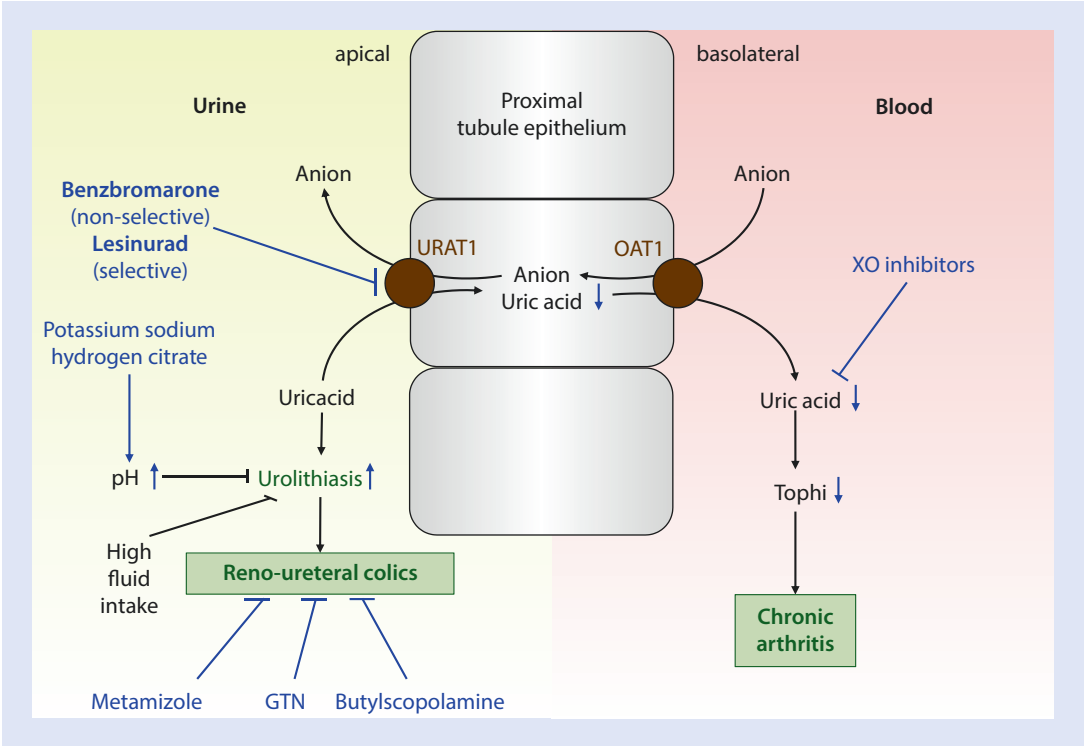

Fig. 23.2 Uric acid secretion in the kidney, urolithiasis, reno-ureteral colics, and pharmacological interventions. Reno-ureteral colic pain is an emergency that must be treated immediately and effectively! You can use several drug classes for colic pain

acid concentration provides further evidence for the presence of gout, but it does not prove the diagnosis. In fact, gout can be present even with normal uric acid plasma concentrations. Gout has to be treated from the second stage on.

23.2 Drugs for Treatment of Acute Gout

Acute gout is characterized by a very painful monoarthritis in a foot or hand joint. Without therapy, an acute gout attack lasts for 3–14 days. The therapeutic goal is to suppress the acute inflammation as quickly as possible and to restore mobility of the affected joint. As a general measure, the joint should be immobilized in an elevated position and chilled with cold packs. The earlier the therapy begins, the more rapidly the inflammation subsides. Thus, therapy should start not later than 12–24 hours after onset of symptoms.

Acute gout can be effectively treated with nonselective COX inhibitors such as ibuprofen (Table 23.1). It is important to apply sufficiently high drug doses (see ▶ Chap. 10). Typical ADRs of COX inhibitors are PUD, edema, impairment of kidney function, and hypertension. The risk of PUD can be controlled by PPIs (see ▶ Chap. 13), and hypertension can be effectively controlled by antihypertensive drugs (see ▶ Chap. 15). During short-term therapy with COX inhibitors, ADRs are generally acceptable. In CKD, e.g., caused by urolithiasis, COX inhibitors must not be administered (see ▶ Chap. 12). In general, a 5–10 day therapy with a nonselective COX inhibitor is sufficient to treat acute gout. The effect of COX inhibitors is mediated by inhibition of COX-2, resulting in reduced PGE_2 formation. PGE_2 causes hyperemia and sensitizes pain receptors (see ▶ Chap. 10). Because of the high risk for thromboembolic complications, e.g., stroke and MI, selective COX-2 inhibitors (prototype celecoxib) should be generally avoided, specifically in gout (see ▶ Chaps. 10, 11, and 18).

As an alternative to COX inhibitors, a GCR agonist such as prednisolone in a dose of 30–35 mg per day (corresponding to a cortisol equivalence dose of 150–175 mg) can be applied

for 5 days (see ▶ Chap. 11). Typical ADRs are PUD (see ▶ Chap. 13), deterioration of DM (see ▶ Chap. 19), and increase in blood pressure (see ▶ Chap. 15). The risk of developing a Cushing's syndrome is minimal during short-term therapy with GCR agonists. They are contraindicated in infections, in poorly controlled DM and/or hypertension, and in ulcerating wounds.

In acute gout, monocytes and neutrophils migrate into the site of inflammation. Cell migration depends on intact microtubules. Colchicine, a constituent of the autumn crocus, inhibits microtubule polymerization, thereby reducing leukocyte migration, and phagocytosis. In order to exert an effect in acute gout, colchicine must be administered during the first 24 hours after onset of symptoms since otherwise the infiltration of leukocytes into the joint has already been completed. Because of serious ADRs, colchicine must only be given in low doses. If colchicine is administered in high doses, serious intoxications can result.

Colchicine has cytostatic effects on rapidly proliferating cells (see ▶ Chap. 32), manifesting themselves by nausea, vomiting, and diarrhea. During long-term and high-dose colchicine therapy, alopecia and malfunction of the liver, kidney, and CNS can develop. In liver failure and CKD, colchicine must be given in reduced doses. In children, autumn colchicine intoxications are common because they may accidentally eat the attractive-looking but toxic autumn crocus (see ◘ Fig. 23.1).

Uric acid crystals activate leukocytes and cause release of proinflammatory cytokines, specifically IL-1. Thus, neutralization of IL-1 constitutes a rational approach to treat acute gout. Canakinumab is a humanized monoclonal antibody that binds and neutralizes IL-1. The antibody must be administered parenterally and is an effective therapeutic alternative if COX inhibitors, GCR agonists, and colchicine have insufficient effects or are contraindicated.

23.3 Drugs for Treatment of Chronic Gout

Once the acute gout symptoms have subsided, comprehensive diagnostics to assess the extent of gout are performed. In addition to determination of the plasma uric acid concentration, a search for tophi and uric acid crystals in the joints and urinary system has to be conducted. Kidney function must be evaluated because gout can impair its integrity. Accordingly, the dose of drugs may have to be adjusted (see ▶ Chap. 12). A low-calorie and low-purine diet is the basis of the long-term therapy of gout. Overweight and the consumption of meat, entrails, crustaceans, ethanol (particularly beer and liquors), and fructose-containing soft drinks must be reduced substantially. In patients suffering from urolithiasis, sufficient consumption of fluids (e.g., tea, mineral water) is important (see ◘ Fig. 23.2). In case of more than two acute gout attacks per year, urolithiasis and tophi, a long-term pharmacotherapy must be implemented. The plasma concentration of uric acid should be reduced <400 µmol/l.

The standard drug for treatment of chronic gout is allopurinol that has been in clinical use for more than 50 years. Accordingly, several generic formulations are available, allowing cost-effective long-term therapy. Allopurinol is an uricostatic drug that inhibits XO and, thereby, prevents conversion of hypoxanthine to xanthine and of xanthine to uric acid (see ◘ Fig. 23.1). Xanthine and hypoxanthine possess a higher solubility in biological fluids than uric acid. As a result, the risk of formation of uric acid crystals is reduced. Allopurinol causes GI problems and allergic reactions, particularly type IV reactions (see ▶ Chap. 3). In CKD, the allopurinol dose must be lowered. The therapy starts with low doses of allopurinol which can be increased up to 800 mg/day. Tumor lysis syndrome (see ▶ Sect. 23.1 and ◘ Fig. 23.1) and Lesch-Nyhan disease are treated with allopurinol as well.

If the effect of allopurinol is insufficient, the drug can be combined with a uricosuric drug such as benzbromarone (see ◘ Fig. 23.2) which inhibits various transporters. For its efficacy in gout, inhibition of URAT1 at the apical membrane of the tubule is essential. Via this mechanism, the reuptake of uric acid from the tubule lumen into the organism is prevented, synergistically supporting the effect of allopurinol. Since uricosuric drugs increase the uric acid concentration in the tubule, sufficient administration of fluids and urine alkalization are essential to avoid crystal formation in the urinary system. Uricosuric drugs cause GI problems and headache.

If the combination of allopurinol + benzbromarone is not sufficiently effective or in case of allopurinol intolerance, therapy with the new

XO inhibitor febuxostat constitutes an option (see ◘ Fig. 23.1 and ◘ Table 23.1). The drug possesses a higher selectivity for XO than allopurinol and is more potent. Lesinurad, a new uricostatic drug that inhibits URAT1 with higher selectivity than benzbromarone, is used in gout patients in combination with allopurinol if the latter drug alone is insufficiently effective. The cardiovascular risk profile of lesinurad still needs to be evaluated. In CKD and tumor lysis syndrome, it is contraindicated because of the risk of formation of uric acid crystals in the urinary system. Compared to allopurinol and benzbromarone, the therapy costs with febuxostat and lesinurad are high.

A dangerous interaction of XO inhibitors with 6-MP and its prodrug azathioprine (see ▶ Chaps. 11 and 32) must be kept in mind. 6-MP is inactivated via XO. If a patient treated for gout with allopurinol or febuxostat additionally receives 6-MP or azathioprine because of a tumor or an autoimmune disease, massive ADRs, most notably anemia, leukopenia, and thrombocytopenia, can develop (see ◘ Fig. 23.1). In order to avoid this interaction, the doses of 6-MP and azathioprine must be reduced substantially.

23.4 Questions and Answers

Questions

Which statement on the mechanism of action of drugs for treatment of gout is correct?

A. Allopurinol – inhibition of hypoxanthine synthesis
B. Colchicine – inhibition of actin cytoskeleton formation
C. Lesinurad – inhibition of URAT1
D. Benzbromarone – forced diuresis
E. Ibuprofen – inhibition of LTB_4 synthesis

Answers

A. Allopurinol inhibits XO and, thereby, formation of the poorly water-soluble uric acid. Hypoxanthine which is well water-soluble accumulates and is eliminated to a greater extent renally.
B. Colchicine does not interfere with the formation of the actin cytoskeleton but with the formation of microtubules. These are important for migration of leukocytes into the site of inflammation.
C. Selective inhibition of URAT1 enhances uric acid elimination in the urine and constitutes a promising new approach for treatment of chronic gout.
D. Benzbromarone inhibits various transporters including URAT1, but the drug does not globally stimulate diuresis.
E. Ibuprofen is a well-suited COX inhibitor for treatment of acute gout and, via COX-2 inhibition at the site of inflammation, reduces PGE_2 formation. This mediator induces vasodilation and increases pain perception and contributes substantially to the symptoms of acute gout. LTB_4 synthesis is mediated by LOX, but this enzyme is not inhibited by ibuprofen.

Answer **C** is correct.

23.5 Exercises

A 66-year-old obese woman visits you in your orthopedics office and complains about severe pain in the left forefoot that has flared up yesterday. The physical exam reveals a strongly swollen and erythematous metatarsophalangeal joint of the left big toe. Upon gentle touching, the pain becomes more severe, and the joint mobility is severely restricted.

Questions

1. What is your suspected diagnosis and how do you proceed therapeutically in this acute situation?
2. How do you then proceed diagnostically and therapeutically?

Answers

1. The patient has the classic symptoms of acute gouty monoarthritis. You immediately initiate a therapy. The earlier therapy is initiated, the more successful is the outcome. A pragmatic start is the prescription of the COX inhibitor ibuprofen which is very effective and can be well controlled. The maximum daily dose of ibuprofen is 2.4 g. This daily dose can be

split into doses of 0.4 g, 0.6 g, or 0.8 g. If the patient has a PUD or GERD history, you should additionally prescribe a PPI such as pantoprazole. The therapy should be conducted for 5–10 days until the symptoms disappear. Additionally, the patient should keep the affected foot in an elevated position and should regularly apply cold packs. Alternatively to ibuprofen, a 5-day therapy with a GCR agonist such as prednisolone (30–35 mg/day) could be performed. Short-term therapy with a high-dose GCR agonist is not associated with an increased risk for occurrence of a Cushing's syndrome. The application of colchicine (low dose) constitutes another therapeutic option.

2. You search for tophi, e.g., in the ears, and determine the plasma concentration of uric acid. Moreover, using imaging techniques, you search for urate precipitations or erosions that are typical for gout. In parallel with an increase in plasma uric acid concentration, the risk of acute gout increases. After the acute symptoms of the disease have subsided, you explain to the patient the pathophysiology of gout commensurate with the intellectual level and, in collaboration with a dietitian, change the dietary habits. Purine-rich food such as meat and entrails should be avoided, and vegetarian protein sources should be integrated. Moreover, consumption of ethanol and soft drinks must be reduced. Furthermore, a drug therapy with the uricostatic drug allopurinol is initiated. If the effect on plasma uric acid concentration is insufficient, you can add a uricostatic drug such as benzbromarone. In severe cases, the uricostatic drug febuxostat should be used. The URAT1-selective inhibitor lesinurad constitutes a further novel therapeutic option.

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Sex Hormones: Hormonal Contraception and Hormone Replacement Therapy

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The most important sex hormones are the ER agonist estradiol, the PR agonist progesterone, and the AR agonist 5α-dihydrotestosterone. Estradiol is synthesized by aromatase from progesterone metabolites and testosterone. Estradiol and testosterone regulate multiple organ functions, whereas progesterone predominantly regulates female sex organs. In case of deficiency, the appropriate hormones are substituted. Synthetic ER agonists and PR agonists are widely used for hormonal contraception. The micropill is a combination of low-dose ethinylestradiol and a PR agonist, e.g., levonorgestrel or desogestrel. The minipills contain levonorgestrel or desogestrel, and IUDs levonorgestrel. The morning-after pill is based on, e.g., high-dose levonorgestrel. PR agonists inhibit ovulation, increase viscosity of cervical secretion, and render the endometrium less hospitable for nidation. ER agonists also inhibit ovulation and increase PR expression. Hormonal contraceptives differ from each other in their Pearl index and ADRs. The PR antagonist mifepristone is used as abortifacient in several countries. Inhibitors of steroid-5α reductase reduce synthesis of 5α-dihydrotestosterone and are used in the therapy of androgenic alopecia and BPH. The ER antagonist clomiphene is applied to induce ovulation, the AR antagonist cyproterone in hypersexuality, severe acne, and transsexuality. Flutamide is used in non-resectable prostate cancer.

Key Points

1. The micropill with low-dose ethinylestradiol and levonorgestrel has fewer ADRs than the classic pill with high ER agonist and PR agonist doses.
2. ER agonist/PR agonist-containing contraceptives can cause weight gain, mood swings, loss of libido, breast pain, liver dysfunction, and thromboembolism.
3. The minipill containing a PR agonist must be administered on a very precise schedule.
4. Spotting and intermenstrual hemorrhages are common ADRs of the minipill.
5. The "new" minipill contains desogestrel and is safer than the "old" minipill with levonorgestrel.
6. IUDs continuously release levonorgestrel.
7. For IUDs, mechanical complications need to be considered in addition to ADRs of PR agonists.
8. The morning-after pill with a high-dose PR agonist is administered as emergency contraception.
9. ER agonists modulate many organ functions. As a result of estrogen deficiency, numerous health problems can develop in menopause.
10. Symptoms in peri- and postmenopause are treated in an individualized manner with ER and PR agonists.
11. Therapy of peri- and postmenopausal symptoms is supported by a healthy lifestyle.
12. Estrogen substitution in peri- and postmenopause can increase the risk of mammary carcinoma and DVT and should be conducted only for a limited period of time.

24.1 Physiology of Sex Hormones

The most important sex hormones are the ER agonist estradiol, the PR agonist progesterone, and the AR agonist 5α-dihydrotestosterone. They mediate their biological effects via NRs that regulate gene transcription (see ▶ Chap. 1). Accordingly, therapeutically administered sex hormones possess a delayed onset of action. ◘ Figure 24.1 provides an overview of synthesis of sex hormones, important physiological effects, and pharmacological interventions.

Sex hormones are derived from cholesterol which is converted into pregnenolone, serving as precursor of progesterone which does not only exerts hormonal effects by itself but also constitutes a precursor of the estrogens and androgens. Via 17α-hydroxyprogesterone, the intermediate 4-androstene-3,17-dione is formed which is then converted to estradiol via aromatase. The 17β-hydroxysteroid dehydrogenase converts

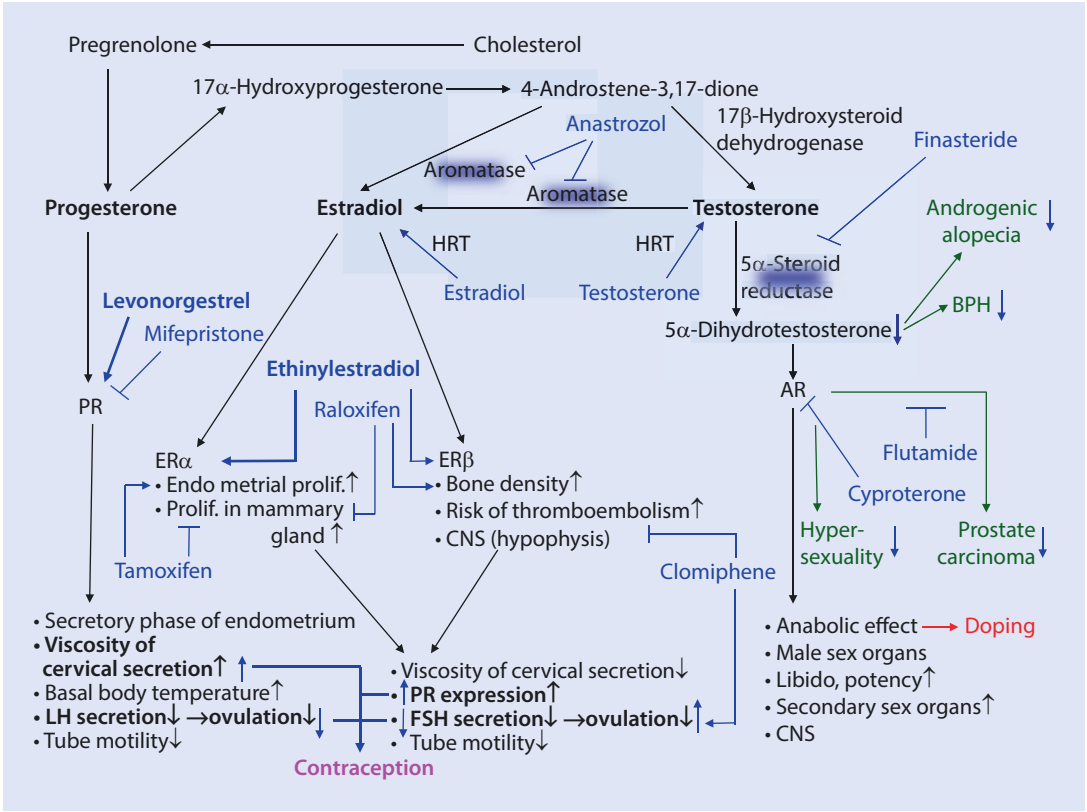

Fig. 24.1 Synthesis and physiological effects of sex hormones: pharmacological effects. ER and PR agonists are used for contraception and HRT. ER antagonists are used to induce ovulation. PR antagonists are used for abortion. SERMs are used for osteoporosis and ER-positive mammary carcinoma. Aromatase inhibitors are used for ER-positive mammary carcinoma as well. AR agonists are used for HRT in men. AR agonists with strong anabolic component are abused for doping! AR antagonists are used in AR-positive prostate carcinoma, hypersexuality, and transsexuality. 5α-steroid reductase inhibitors are used in BPH and androgenic alopecia

4-androsten-3,17-dione to testosterone. On the one hand, testosterone is another precursor for estradiol (conversion by aromatase), and on the other hand, it is converted to the potent 5α-dihydrotestosterone by 5α-steroid reductase. Estradiol is produced in the ovarian follicles, progesterone in the ovarian corpus luteum, and testosterone in the Leydig cells of the testes. What all sex hormones have in common is that they inhibit the release of FSH and LH in the hypophysis. An exception is the preovulatory estrogen peak which triggers ovulation.

Estradiol regulates many organ functions and acts via the ER subtypes ERα and ERβ. These receptors possess a different tissue distribution which is exploited pharmacologically. Important locations are the endometrium and the mammary gland for ERα and the bones and the CNS for ERβ. Estradiol inhibits osteoclasts and has protective effects against osteoporosis (see ▶ Chap. 22). It increases coagulability of the blood (see ▶ Chap. 18), promotes water retention, and possesses antiatherogenic effects. Estradiol stimulates endometrium proliferation and increases the fluidity of cervical secretion and the motility of the uterus and uterine tubes, supporting egg transport. Estradiol possesses anabolic effects on female sex organs, is responsible for formation of secondary sexual characteristics (e.g., mammary gland growth), and increases PR expression.

Progesterone is responsible for secretory conversion of the endometrium and support of endometrium function in pregnancy. It increases the viscosity of cervical secretions, thereby impeding penetration of sperms. Progesterone enhances body temperature and decreases motility of uterine tubes. The increase in body temperature and the changes in viscosity of cervical secretions

during the menstrual cycle are used as biological indicators for certain non-hormonal contraceptive methods.

Testosterone and the more potent 5α-dihydrotestosterone (see ▶ Chap. 1) possess anabolic effects on skeletal muscles and bones and cause epiphyseal closure. They increase hematopoiesis and activity of sebaceous glands. Occlusion of the excretory ducts of these glands can promote acne. Androgens play a role in male sex behavior and promote growth of the prostate gland, seminal vesicle, and testes. Androgens are important for sperm maturation and expression of secondary male sexual characteristics (e.g., dense body hair) as well as normal libido and fertility.

24.2 Pharmacological Interventions

In principle, synthesis and function of sex hormones can be influenced pharmacologically via two approaches, either via enzyme inhibitors that block the function of certain enzymes of hormone synthesis or via ligands of sex hormone receptors which are either activated, antagonized, or modulated (see ◘ Fig. 24.1). ◘ Table 24.1 shows selected drugs that indirectly or directly mediate their effects via sex hormone receptors.

Aromatase inhibitors (prototype anastrozole) inhibit estradiol synthesis. This effect is exploited in the therapy of ER-positive mammary carcinoma (see ▶ Chap. 32). Steroid-5α reductase inhibitors (prototype finasteride) reduce synthesis of 5α-dihydrotestosterone. As a result, the AR-mediated inhibition of head hair follicles is alleviated, and proliferation of prostate gland cells is reduced. Accordingly, steroid-5α reductase inhibitors can be used for treatment of androgenetic alopecia and BPH. Long-term and high-dose therapy with azole antimycotics can reduce sex hormone synthesis via CYP inhibition and cause hormone deficiency symptoms (see ▶ Chap. 35).

Estradiol possesses a high first-pass effect. Therefore, it has to be administered in special formulations (e.g., vaginally, cutaneously, or p.o. as prodrug) in order to achieve pharmacological effects. Estradiol and estradiol prodrugs are predominantly used in HRT (see ▶ Sect. 24.4). In contrast, ethinylestradiol does not undergo first-pass metabolism and can therefore be administered for oral hormonal contraception (see ▶ Sect. 24.3). Clomiphene is an ER antagonist which prevents the negative feedback of estradiol on the hypophysis and supports maturation of ovarian follicles and ovulation via increased FSH and LH secretion, respectively. These effects can be used in women wishing to become pregnant. However, this method also bears the risk of multiple pregnancies. Estradiol and ethinylestradiol do not discriminate between ERα and ERβ in contrast to SERMs. Raloxifene preferentially activates ERβ in the bone and antagonizes ERα in the mammary gland. This profile can be used for therapy of postmenopausal osteoporosis and prevention of mammary carcinoma (see ▶ Chap. 20). In contrast, tamoxifen exhibits agonistic effects at ERα in the endometrium and antagonistic effects at ERα in the mammary gland. This profile is exploited in the therapy of hormone-sensitive mammary carcinoma.

Progesterone possesses a high first-pass effect which has to be considered, e.g., in peri- and postmenopausal HRT. In contrast, the synthetic gestagen levonorgestrel has a very good bioavailability and can therefore be used for various applications in hormonal contraception (see ▶ Sect. 24.3). Mifepristone is a PR antagonist. It alleviates the prosecretory effect of progesterone in the endometrium and leads to apoptosis of the endometrium. This effect is used for induction of abortion in combination with the PG misoprostol.

Testosterone is only poorly bioavailable after p.o. administration. Therefore, it has to be applied in specific formulations, e.g., patches, p.o. prodrugs or i.m. injections. Testosterone is predominantly used in male hypogonadism.

Particularly androgens with strong anabolic component in relation to the virilizing effects (anabolics) are abused mainly in athletic sports and by sprinters to enhance performance (doping). A prototypical anabolic is the naturally occurring nandrolone (19-nortestosterone). Anabolics have serious ADRs such as depression, acne, hypertension including complications such as MI and stroke, as well as liver damage culminating in hepatocellular carcinoma. Testicular atrophy and infertility due to suppressed FSH and LH secretion can occur. In women, hirsutism, clitoris hypertrophy, virilization of the voice, and hypersexuality can develop. In contrast to AR agonists, AR antagonists exhibit important medical applications. Flutamide is used in AR-positive prostate cancer

Table 24.1 Overview of selected drugs acting via sex hormone receptors

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Clomiphene	Synthetic ER antagonist	Inhibits the negative feedback of ER agonists on FSH and LH release from the hypophysis, thus promoting follicle development and ovulation(s)	Ovulation induction in anovulatory patients with desire for children and with an otherwise intact endocrine system	Hot flashes, visual disturbances, multiple pregnancies due to multiple ovulations, ovarial cysts. Contraindicated in patients with hypophyseal and ovarian tumors and in pregnancy	
Cyproterone	Synthetic AR antagonist (and PR agonist)	Libido and potency↓, spermatogenesis↓, hirsutism↓, sebaceous gland activity↓, muscular system↓, prostate growth↓, Breast growth↑ (femalization, hormonal castration)	Hypersexuality, severe forms of acne, severe hirsutism, alopecia in females, transgender hormone therapy	In males: Libido and potency↓, spermatogenesis↓, gynecomasty, weariness In females: Intermenstrual hemorrhages, weight gain, depression In males and females: Thromboembolisms (particularly in combination with ethinylestradiol) and hepatotoxicity	18, 28, 32
Estradiol	The most important naturally occurring ER agonist; shorter duration of effect than ethinylestradiol	Regulates multiple organ functions: CNS, mood and memory ↑; breast, elasticity↑; metabolism, protection against atherosclerosis and MI; vagina, epithelial proliferation ↑, pH↓, and pelvic stabilization; skin, elasticity ↑; abundant head hair; bone and muscle formation; normal cardiovascular function	Local and systemic treatment of peri- and postmenopausal complaints; as monotherapy or in combination with gestagens; various dosing schemes and dosage forms are available; an individual and symptom-related therapy is important. Use in transgender hormone therapy	Increased risk for mammary and endometrial carcinoma and for thromboembolic diseases (stroke and MI), particularly with systemic high-dose therapy over many years; no increased risk if applied vaginally	2, 16, 18
Ethinylestradiol	Synthetic ER agonist with small first-pass effect	FSH secretion↓ → inhibition of ovulation, stabilization of the endometrium, expression of PR expression↑ → effects of gestagen↑	Mostly administered in combination with a gestagen in contraception and in regulation of menstrual cycle, in primary and secondary amenorrhea	Breast pain, increased breast sensitivity, vulvovaginitis (candidiasis). Contraindications: Hormone-dependent mammary and endometrial carcinoma, liver adenoma, pancreatitis, dyslipidemia, thromboembolisms, insufficiently treated hypertension, vaginal hemorrhages of unknown origin, severe migraine	2, 6, 15, 16, 18, 22, 32, 35

(continued)

Table 24.1 (continued)

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Finasteride	5α-steroid reductase inhibitor	Reduced synthesis of 5α-dihydrotestosterone being a very potent AR agonist; reduces hair loss and inhibits growth of an enlarged prostate gland	Androgenic alopecia and BPH	Gynecomasty, increased breast sensitivity; if administered in doses of 5 mg per day, 1–10% of BPH patients complain of decreased libido, ED and reduced ejaculate volume, depression; ADRs are not always reversible (post-finasteride syndrome)	9, 28
Levonorgestrel	Synthetic second-generation PR agonist	LH secretion ↓ → inhibition of ovulation, viscosity of cervical secretions ↑ → sperm penetration↓, changes in endometrial secretion, tube motility ↓	As contraceptive: Often in combination with an ER agonist, but also as PR agonist-only pill (minipill). Menstrual cycle regulation, endometriosis. Applied in postmenopausal HRT in combination with ER agonists. In high doses as postcoital emergency contraception after up to 72 hours of unprotected intercourse	Weariness, breast tenderness, headache, weight gain, spotting; nausea and vomiting in postcoital emergency contraception	
Mifepristone	Synthetic PR antagonist	Endometrial degeneration within few hours, opening of the cervix within 36–48 hours, consecutive death of the embryo	Abortifacient for the whole pregnancy (preferably up to 9 weeks of gestation); in combination with misoprostol to induce uterine contractions and to expel the contents of the uterus 36–48 hours after mifepristone administration	Heavy hemorrhages, hot flashes, headache (mifepristone); nausea, vomiting, diarrhea and severe uterine colics (misoprostol)	10

Progesterone	Most important naturally occurring PR agonist; shorter duration of effect than levonorgestrel because of high first-pass effect	Mainly synthesized in the second half of the menstrual cycle and in pregnancy. Stimulates endometrial secretion, maintains pregnancy, inhibits FSH and LH secretion and, hence, maturation of further follicles (inhibition of ovulation)	Postmenopausal HRT, protection of the endometrium and regulation of uterine hemorrhages	Weariness, breast tenderness, weight gain, spotting	
Testosterone	Naturally occurring AR agonist; precursor of the more potent 5α-dihydrotestosterone	Regulates multiple organ functions: Prostate growth and function↑, sperm maturation, libido and potency ↑, secondary sexual characteristics ↑, male sexual behavior, anabolic effect, bone maturation, epiphyseal closure, hematopoiesis, secretion of sebaceous glands↑	Substitution in hypogonadism and delayed puberty. Because of its high first-pass effect testosterone is applied as patch, gel, i.m. injection of the prodrug; use in transgender hormone therapy	Thromboembolisms (stroke, MI), dyslipidemia, gynecomasty (conversion to estrogens by aromatase), depression, aggression, alopecia, hirsutism, steroid acne, testicle size and spermatogenesis↓, liver diseases, stimulation of androgen-dependent tumors (prostate carcinoma)	2, 15, 16, 18, 28, 32

This table does not list the SERMs raloxifene and tamoxifen, the aromatase inhibitor anastrozole, and the AR antagonist flutamide. Raloxifene is discussed in ► Chap. 20; tamoxifen, anastrozole, and flutamide are discussed in ► Chap. 32

to inhibit tumor growth (see ▶ Chap. 32). Cyproterone is applied in hypersexuality, severe acne, and hirsutism and to support formation of secondary sexual characteristics in transsexual patients.

24.3 Hormonal Contraceptives

The development of effective, safe, and conveniently applicable contraceptives for women considerably contributed to the reduction of birthrate in industrialized countries since the late 1960s. ◘ Table 24.2 provides an overview of selected hormonal contraceptive methods including safety, ADRs, and contraindications. Worldwide, there are substantial cultural differences in the use and acceptance of contraceptive methods. Despite intense efforts, so far it has not yet been possible to develop a safe and effective male contraceptive.

Hormonal contraception uses the physiological effects of ER and PR agonists in such a way that pregnancy does not occur despite sexual intercourse. A possible infection with sexually transmitted diseases such as gonorrhea (see ▶ Chap. 33) or HIV (see ▶ Chap. 34) is therefore not prevented by oral contraceptives. This requires the use of condoms which further increases the safety of hormonal contraceptives. The Pearl index, i.e., the number of pregnancies per 100 women years, is used as a measure to quantify the safety of contraceptive methods. Without contraception, the Pearl index of fertile women ranges between 30 and 80, i.e., 30–80 of 100 women become pregnant within a calendar year.

The estradiol concentration rises strongly within the first half of the menstrual cycle and triggers ovulation via induction of an LH peak. Thereafter, the estradiol concentration declines rapidly to remain on a lower plateau in the second half of the cycle. In the first half, the progesterone concentration is very low and increases substantially after ovulation. Upon cessation of the luteal body function, estradiol and progesterone concentrations decline sharply, causing apoptosis of the endometrium and its expulsion from the vagina (menstruation). Together, estradiol and progesterone inhibit FSH and LH secretion in the second half of the menstrual cycle and prevent maturation of additional follicles and another ovulation potentially interfering with nidation of a blastocyst. As additional protective mechanism against multiple fertilizations, the cervical secretions become viscous under the influence of progesterone and prevent penetration of sperms into the uterus.

In case of the classic monophasic contraceptive pill, a fixed combination of a synthetic ER agonist and a synthetic PR agonist is applied daily over 21 days. This combination very effectively inhibits ovulation and increases viscosity of cervical secretions. In the following 7 days, either no pill or a placebo is administered. Because of the decline of the concentration of synthetic ER and PR agonist, a withdrawal hemorrhage occurs. Often, this hemorrhage is weaker than the regular menstruation. For this reason, hormonal contraceptives are frequently used to regulate menstrual cycle length. The monophasic preparations have a high contraceptive safety but a low tolerability because of the lack of adaptation of the sex hormone doses to the physiological menstrual cycle. The first contraceptive pills contained high doses of synthetic ER and PR agonists, causing many ADRs, specifically thromboembolic events (see ▶ Chap. 18). Moreover, the menstrual cycle was often irregular after cessation of contraceptive application because the hypophyseal function was strongly suppressed. Accordingly, it could take several months until a desired pregnancy occurred.

In order to improve tolerability of oral contraceptives without reducing their safety, two-phase pills were developed. In these formulations, the ER agonist dose is kept constant over the menstrual cycle, and the gestagen dose is kept low in the first cycle half and high in the second half. These formulations are more tolerable than the one-phase pills but are not yet optimal.

In three-phase pills, the ER and PR agonist doses are further decreased. The ER agonist dose is low in the first and third of the cycle and higher in the second third, while the progesterone dose increases stepwise from third to third. If applied correctly, the Pearl index of this method is <1, but due to accidental omission of pill administration, the true Pearl index rather straddles between 1 and 12.

Patients must be educated about the importance of regular pill administration for contraceptive safety. In addition, they need to be informed that loss of efficacy can take place under certain conditions. Particularly, drugs that increase CYP

Table 24.2 Comparison of various hormonal contraceptive methods: a basis for consultation

Parameter	Micropill	Minipill and new minipill	IUD	Morning-after pill (emergency contraception)
Drug content	Low-dose ER agonist (mostly ethinylestradiol, < 50 µg/pill) + low-dose PR agonist (e.g. levonorgestrel ((2) generation) or desogestrel ((3) generation). Two-phase micropills or three-phase micropills with more favorable adaption to the natural cycle	Levonorgestrel (minipill) and desogestrel (new minipill) The minipill requires strict adherence to pill taking schedule (not more than 3 hours past the typical time); higher flexibility with the new minipill	Intrauterine device which continuously releases levonorgestrel over a period of 5 years	Single dose of 1.5 mg levonorgestrel within 12–72 hours after unprotected intercourse; not to be confused with the abortion pill (mifepristone + misoprostol). As an alternative, ulipristal can be used
Mechanism of action	Inhibition of ovulation; cervical secretions become more viscous so that the passage of sperms is impeded	Impedes passage of sperms through the cervix and causes modifications of the endometrium (inhibition of nidation). Desogestrel additionally inhibits ovulation	T-shaped plastic device which inhibits nidation and continuously releases levonorgestrel. Thus, the passage of sperms through the cervix is impeded and the endometrium is modified (inhibition of nidation). Ovulation may be inhibited	Inhibits ovulation, possibly also the transport of sperms and of the egg in the tubes, prevents nidation
Pearl index	0.1–0.9 (perfect-use Pearl index); the typical-use Pearl index often is only 1–12 due to irregular pill intake	Minipill Pearl index: approx. 4; new minipill Pearl index: 0.4 (perfect use)	0.2	If taken within 24 hours after unprotected intercourse: 0.6% pregnancies; on day 2: 1.2% pregnancies; on day 3: 2.7% pregnancies
Indications	Standard contraceptive method in healthy women who have no risk factors	Patients who cannot take ER agonist-containing anti-contraceptives (due to hypertension, thromboembolism, tobacco consumption, ER agonist-depending tumors)	Instead of minipill or new minipill; menstrual complaints, endometriosis. Not method of choice in women wishing to have children later	Postcoital emergency contraception after unprotected intercourse

(continued)

Table 24.2 (continued)

Parameter	Micropill	Minipill and new minipill	IUD	Morning-after pill (emergency contraception)
ADRs	Significantly reduced ER and PR agonist doses (as compared to the classic pill); hence, less ADRs. Nausea, vomiting, weight loss, increased appetite, edema, migraine, breast pain, mood swings, loss of libido, hypertension, thromboses, disturbances of liver function; micropills with desogestrel have a higher cardiovascular risk than pills with levonorgestrel; benign liver adenoma (reversible), increased reversible risk for mammary carcinoma; reduced risk for endometrial, ovarian and colorectal carcinoma	Intermenstrual hemorrhages and spottings, amenorrhea, mood swings, depression, nausea, acne, weight gain, changes in skin, hirsutism (androgynous effect)	IUD expulsion (approx. 7% in the first 2 months of use), damage to the uterus when the device is inserted, uterus perforation, migration into the abdominal cavity, headache, pelvic pain, hypermenorrhea, oligomenorrhea, amenorrhea, spottings and intermenstrual hemorrhages, vulvovaginitis; in addition, typical gestagen ADRs as with the minipill	Nausea, vomiting, menstrual irregularities, typical gestagen short-term side effects (see minipill), no long-term ADRs due to one-time administration
Interactions	Drug effect is reduced by CYP inducers (e.g. phenytoin, carbamazepine, RMP, St. John's wort), MCP, diarrhea (antibiotics), activated charcoal	Drug effect is reduced by CYP inducers, diarrhea (antibiotics), activated charcoal	Due to local endometrial administration of the drug there is only a low risk of interactions	Unreliable absorption of the drug in GI disorders such as nausea, vomiting and diarrhea
Contraindications	Previous DVT, pulmonary embolism, stroke, MI, insufficiently treated cardiovascular diseases (particularly hypertension), DM, hormone-dependent tumors, pregnancy and lactancy, liver diseases, abnormal vaginal hemorrhages. Relative contraindications: Smokers and age > 35 years	DVT, pulmonary embolism, hormone-sensitive tumors, liver diseases, abnormal vaginal hemorrhages, pregnancy	DVT, pulmonary embolism, hormone-sensitive tumors, liver diseases, abnormal vaginal hemorrhages, pregnancy, uterine malformations, endometritis, cervicitis	Not applicable

Discuss frankly the advantages and disadvantages of contraceptive methods! Make an individualized decision! Emphasize the importance of adherence for safety and discuss family planning

expression such as NIPEs (see ▶ Chap. 25), certain antibiotics (see ▶ Chap. 33) or St. John's wort, diarrhea, and drugs that increase GI motility can reduce contraceptive safety.

In general, a micropill should be prescribed for contraception of a healthy young woman who has not yet completed her family planning. Due to the low ER and PR agonist doses, ADRs are minimal. The risk for certain tumors (hepatic adenoma and mammary carcinoma) is elevated, whereas the risk for other tumors (endometrial cancer, ovarian cancer, and colon carcinoma) is decreased. Overall, the altered tumor risks neutralize each other.

It is important to identify women who are not candidates for the micropill. These are women with a history of thromboembolic diseases (see ▶ Chap. 18), with insufficiently treated cardiovascular diseases, particularly hypertension (see ▶ Chap. 15), DM (see ▶ Chap. 19) and hormone-sensitive tumors, breastfeeding mothers, and tobacco smokers as well as in pregnancy. It is an advantage of the low drug doses in the micropill that following cessation of contraceptive intake, the normal menstrual cycle starts without problems in most patients, enabling women to become pregnant rapidly at their discretion. Levonorgestrel, a prototypical second-generation gestagen, possesses a lower cardiovascular risk than desogestrel, a typical third-generation one. This has to be considered when choosing the best hormonal contraceptive for each woman. If a given micropill shows suboptimal tolerability, another micropill with a different composition should be tried. For the efficacy of two-phase and three-phase pills, it is essential to strictly adhere to the order of pills in the blister pack provided by the pharmaceutical manufacturer.

In case of too many ADRs despite testing various ER/PR agonist combinations or of contraindications, switching to the minipill is an alternative. It contains levonorgestrel, increasing viscosity of cervical secretions. Endometrium changes unfavorable for nidation and inhibition of ovulation may contribute to contraception. The need for very regular pill administration (tolerance just 3 hours) is disadvantageous and explains the higher Pearl index. In addition, spotting and intermenstrual hemorrhage may occur. Otherwise, ADRs due to the ER agonist are absent from the minipill, particularly thromboembolic events. It has to be kept in mind that levonorgestrel possesses an androgenic component, causing head hair thinning and hirsutism. The contraceptive safety of the "new" minipill, containing desogestrel, is higher (Pearl index 0.4) than for the "classic" minipill with levonorgestrel. This is due to more effective inhibition of ovulation. However, the cardiovascular risk with desogestrel is higher.

Patients with problematic adherence or intolerance for the classic or new minipill could be offered an IUD. This is a T-shaped intrauterine device containing a levonorgestrel depot that releases the gestagen for a period of up to 5 years. IUDs have an excellent safety (Pearl index 0.2) which is also due to the fact that the device mechanically impedes nidation. In principle, the ADRs are similar to those of the minipill. Menstruation with an IUD is weaker than normal. Because of the local drug release, the risk for drug interactions is low. In up to 7% of the patients, the IUD is expelled from the uterus within the first 2 months. In addition, uterus injuries including perforation, possibly requiring hysterectomy, may occur. Thus, IUDs are not the hormonal contraceptive method of choice in patients who have not yet completed their family planning. IUD insertion and removal have to be performed by the gynecologist.

Postcoital contraception(morning-after pill) is subject to very different cultural acceptance in various countries. Postcoital contraceptives contain a high dose of a gestagen such as levonorgestrel that effectively inhibits uterine tube motility and changes the endometrium unfavorably for nidation. In some countries, postcoital contraceptives are available without prescription, reducing the barrier for availability and rapid administration. The earlier the postcoital contraceptive is administered, the higher is its efficacy. It is important that women, physicians, and pharmacists are informed about this crucial point. If administered within the first 24 hours after sexual intercourse, the probability of a pregnancy is just 0.6% and increases up to 2.7% after 72 hours. Since postcoital contraceptives are administered only once, no long-term ADRs occur. Short-term ADRs include transient menstrual cycle irregularities, nausea, and vomiting. Low-threshold accessibility of postcoital contraceptives decreases risky legal (but very unpleasant) abortions performed with mifepristone + misoprostol or high-risk illegal abortions.

24.4 Hormone Replacement Therapy (HRT) for Women

Menopause is a physiological event. Starting from the age of about 45 years, follicle maturation decreases. This reduces the probability of a pregnancy and results in a gradual decline of plasma estradiol and progesterone concentrations. Due to the reduced negative feedback of ER and PR agonists on the hypophysis, FSH concentration increases, but this cannot anymore compensate the physiological reduction of ovarian function. Menopause is the last ovary-controlled menstruation. The onset of menopause differs substantially among different countries, ranging from about 44 to 55 years. Prior to menopause, the menstrual cycle becomes more irregular and menstruation becomes weaker. Menopause is defined retrospectively once no menstruation took place for 12 months. As a consequence of the decreasing concentrations of sex hormones, physical and psychological changes occur. ◘ Table 24.3 summarizes important

◘ **Table 24.3** Key facts on HRT in peri- and postmenopause: A basis for consultation

Parameter	Important facts
Symptoms of peri- and postmenopause	*Skin and hair:* Wrinkles and dry skin, thinning of head hair and hair loss; facial hair, hirsutism due to relative androgen excess *CNS:* Nervousness, sleeping disorders, irritability, less physical ability, memory impairment, depression, loss of libido *Breast:* Reduced elasticity *Cardiovascular system:* Palpitation, sudden sweating, hot flashes, vertigo *Metabolism:* Dyslipidemia, increased risk of MI and stroke *Vagina:* Dryness, dyspareunia *Pelvic floor:* Muscle weakness and descensus uteri *Bones:* Demineralization, osteoporosis *Skeletal muscles:* Decrease in muscle mass
Available drug formulations	*Estrogen single-drug formulations:* Tablets, patches, gels, nasal spray, injections, vaginal tablets, vaginal suppositories, vaginal cremes, vaginal ovules *Estrogen/gestagen combinations:* Tablets, patches *Gestagen single-drug formulations:* Tablets
Indications	Indication, formulation, and dose of the preparation as well as duration of treatment have to be adapted to the individual symptoms by considering other existing diseases, ADRs, and contraindications. As a general rule, hormonal preparations should be dosed as low as possible for the shortest duration; do not generally refrain from prescription
Advantages	Positive effects on peri- and postmenopausal complaints, less atrophies, and infections in the urogenital tract, enhanced sexual activity and libido, improved mood (fewer depressions), and reduced risk for colorectal carcinoma (ER agonist + PR agonist)
Disadvantages (ADRs)	Increased risk for mamma carcinoma, DVT, pulmonary embolism, cholecystitis
Absolute contraindications	ER-positive mammary carcinoma, acute thromboembolic diseases, undiagnosed vaginal hemorrhage
Relative contraindications	Liver diseases, dyslipidemia, hypertension and ER agonist intake, status post thrombosis, uterine myoma
Alternatives to hormonal replacement therapy	No scientific evidence for clinical effectiveness of herbal preparations from yams, hop, or black cohosh. Use bisphosphonates or raloxifene in osteoporosis (see ► Chap. 20); depression and mood swings can be treated with NE/5-HT enhancers, NIPEs, and lithium, respectively (see ► Chap. 28)
Healthy lifestyle recommendations	Avoid overweight, eat a healthy and balanced diet, drink only moderate amounts of ethanol (red wine, no liquors), do regular physical exercises, avoid smoking, eat food rich in calcium and vitamin D to prevent osteoporosis

Take you time to discuss frankly the advantages and disadvantages of HRT for each woman. Make an individualized decision! Beware of a globally negative attitude toward HRT! Phytoestrogens do not possess proven efficacy and do not constitute a rational alternative. HRT works best in conjunction with a healthy lifestyle

symptoms of peri- and postmenopause and therapeutic options, ADRs, and contraindications.

About one third of all women transit through menopause without problems and do not require a specific pharmacotherapy. However, the remaining two thirds have symptoms, the severity of which varies substantially. If vulvovaginal complaints dominate, the therapy of choice is vaginal application of ER agonists (without a PR agonist). For this indication, a number of effective and well-tolerated formulations with just minimal ADRs are available. Thus, local ER agonist formulations can be prescribed generously. A systemic therapy with ER/PR agonist combinations should be reserved for patients complaining of hot flushes, sweating, sleep disorders, headache, depression, and loss of libido and of physical capability. A positive effect of ER agonist substitution is protection against osteoporosis (see ► Chap. 20). Every systemic hormone therapy should be supported by a healthy lifestyle including sufficient supply of calcium and vitamins, physical activities, and abstinence from tobacco smoking.

Systemic peri- and postmenopausal HRT is very effective, but the results of the Women's Health Initiative (WHI) study tainted the positive sides of HRT, having resulted in broad skepticism of women and physicians alike toward HRT. Uncritical reports in the media contributed to the negative perception. The WHI study revealed that during a 10-year HRT, 6 additional women in a cohort of 1000 women fell sick of mammary carcinoma. However, this risk is small if one considers that as a result of obesity, ethanol consumption, a sedentary lifestyle, and tobacco smoking, additional 123 women fell sick of that disease. These aspects have not been properly discussed in the media. In any case, the WHI study has convincingly demonstrated the importance of a healthy lifestyle for mammary carcinoma prevention. Thus, peri- and postmenopausal women with substantially reduced life quality and complaints should be offered systemic HRT. As a consequence of the negative perception of HRT, alternative approaches including therapy with plant extracts and phytoestrogens have flourished and developed into a very profitable business. However, evidence for effectiveness is lacking for these approaches so that they cannot be recommend from a pharmacological point of view.

Prior to HRT initiation, contraindications have to be excluded. As a general rule, the minimally effective dose should be established for each patient who wishes HRT, and therapy should be conducted for the shortest period of time possible. A projected therapy time of 2 years is a reasonable starting point. With such a conservative approach, the positive aspects of HRT exceed ADRs. After a year, therapy should be evaluated and adjusted according to the prevailing symptoms. Concomitant diseases, ADRs, and comedications must be considered.

Systemic HRT should be initiated by a gynecologist. It is differentiated into continuous, cyclic, and sequential HRT. Continuous HRT with ER agonists should only be performed in hysterectomized patients because otherwise the risk for endometrial carcinoma increases. In patients with atrophic endometrium, continuous therapy with an ER agonist + PR agonist is feasible without the risk of uterine hemorrhage. In the cyclic sequential therapy, an ER agonist is applied cyclically for 7 days with a subsequent pause of 7 days. During the last 10–14 days of the cycle, a PR agonist is additionally given. Alternatively, ER agonists can be administered continuously. Following PR agonist cessation, a withdrawal hemorrhage occurs. In newer schemes, the ER agonist is given continuously, and the PR agonist is applied for 3 days followed by a 3-day pause. With this scheme, most patients do not develop uterine hemorrhage.

For implementation of HRT, numerous formulations are available, allowing for individualized therapy. Estradiol possesses a large first-pass effect (see ► Chap. 2). This can be circumvented if specific formulations such as patches or gels are applied onto the skin. Alternatively, estradiol ester or conjugated ER agonists can be administered p.o. These formulations possess a higher bioavailability. Complementary gestagen formulations that can be combined with ER agonists are available as well, allowing for flexible and individualized therapeutic schemes. Lastly, fixed combinations of ER and PR agonists for oral or transdermal application are available.

24.5 Questions and Answers

Questions

Which assignment of drug to ADR is correct?

A. Ethinylestradiol – increased risk for thromboembolism
B. Mifepristone – support of the secretory phase of the endometrium
C. Finasteride – hypersexuality

D. Levonorgestrel – triggering of ovulation
E. Clomiphene – increased mammary carcinoma risk

Answers

A. Ethinylestradiol increases the risk for thromboembolism. In order to minimize this risk, the dose of ethinylestradiol in oral contraceptives should be as low as possible (<50 µg/pill; micropill). Patients with increased risk for thromboembolism (e.g., tobacco smokers, known DVT, CHD) should not take ethinylestradiol-containing oral contraceptives.
B. Mifepristone is a PR antagonist inhibiting the secretory phase of the endometrium. The endometrium is expelled. This effect is used in abortion.
C. Finasteride inhibits steroid-5α reductase and the synthesis of the biologically active 5α-dihydrotestosterone. Accordingly, libido decreases (hyposexuality).
D. Levonorgestrel is a PR agonist and inhibits LH secretion, thereby suppressing ovulation.
E. Clomiphene is an ER antagonist and is used to trigger ovulation. Clomiphene would reduce the mammary carcinoma risk if it were given as long-term therapy. However, such application is not indicated because osteoporosis risk would increase as well.

Answer **A** is correct.

24.6 Exercises

A 53-year-old woman visits you in your gynecological office. She reports that she had her last menstruation 14 months ago. In general, she feels well with one exception: During the last year, her vagina has become dry, causing pain during sexual intercourse. For this reason, she did not have sex with her husband for the past 6 months. Both she and her husband suffer from this situation. The patient is very health-conscious and has taken black cohosh extracts to alleviate the symptoms, but the medication has not helped. In no case, she wants to take a HRT because her friend, about the same age, has recently fallen sick with mammary carcinoma. The gynecological exam does not reveal pathological findings except for very modest vulvovaginal atrophy and vaginal dryness.

Questions

1. What is your diagnosis and how do you proceed therapeutically?
2. For which type of health problems you have to consider a p.o. ER agonist or ER agonist/PR agonist therapy and which risks does such a therapy have?

Answers

1. The patient is postmenopausal because the last menstruation dates back longer than 1 year. As a consequence of menopause and the associated reduction of estrogen production, a (physiological) vulvovaginal atrophy develops. You explain the patient that it is possible to revert these changes with a local ER agonist therapy and to improve the quality of her sex life. You additionally point out that with no treatment, additional problems such as involuntary urination, itch, burning sensation, and infections of the lower urogenital tract can develop and that these symptoms can considerably decrease life quality. Furthermore, you considerately tell the patient that there is no evidence for an effect of black cohosh extracts in vulvovaginal atrophy. Last but not least, you point out that local ER agonist treatment does not have systemic effects such as increased mammary carcinoma risk.
2. Oral HRT is an option if the patient suffers from agitation, sleep disorders, irritability, reduced physical capacity, memory impairment, palpitations, hot flushes, sweating, and dizziness. In the end, the individual complaints determine whether the patient opts for HRT or not. A relatively small increase in mammary carcinoma risk can result because of HRT. However, in the media, this risk was exaggerated and caused substantial

uncertainty in peri- and postmenopausal women. You propose to conduct a low-dose HRT for about a year if the symptoms warrant such a decision and then try to terminate the therapy. If HRT is used for a short period of time and at low doses, the risks are small, particularly if the patient has an active and healthy lifestyle.

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Neuron Inhibitors with Pleiotropic Effects and Allosteric $GABA_AR$ Modulators

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Many neuropsychiatric diseases including polyneuropathies, trigeminal neuralgia, schizophrenia, bipolar disorder, personality disorders, and epilepsies are characterized by pathological neuronal activity. The goal of pharmacotherapy is to normalize neuronal activity by inhibition of excitatory and activation of inhibitory neurons. This goal is reached with NIPEs, comprising SCBs, CCBs, and inhibitors of glutamatergic neurotransmission. NIPEs are used empirically in the rapidly expanding scope of neuropsychiatric indications. The application of NIPEs must be integrated into a therapeutic concept encompassing TDM, a regulated lifestyle and avoidance of deteriorating factors. NIPEs possess drug-specific indications and ADRs. Barbiturates, benzodiazepines, and Z-drugs are allosteric $GABA_AR$ modulators. Benzodiazepines have sedative-hypnotic, anxiolytic, muscle-relaxing, and antiepileptic effects. Z-drugs possess sedative hypnotic effects. Benzodiazepines and Z-drugs can cause psychological and physical addiction, requiring judicious prescription. Long-term application of benzodiazepines and Z-drugs must be avoided. Due to their very small therapeutic index, barbiturates should only be used in exceptional situations.

Key Points

1. Many neuropsychiatric diseases are characterized by a disbalance between excitatory and inhibitory neurotransmitters.
2. These diseases encompass polyneuropathies, trigeminal neuralgia, schizophrenia, bipolar disorder, personality disorders, post-traumatic stress reactions, and epilepsies.
3. NIPEs are effective drugs for the treatment of these diseases and are used empirically.
4. NIPEs comprise SCBs, CCBs, and inhibitors of glutamatergic neurotransmission.
5. Because of the recent expansion of indications for NIPEs, the traditional term "antiepileptics" should not be used anymore.
6. Certain NIPEs, most notably valproic acid, are teratogenic. Nonetheless, epilepsy must be treated during pregnancy.
7. Benzodiazepines, barbiturates, and Z-drugs modulate $GABA_AR$ allosterically with different pharmacological profiles.
8. The prescription of benzodiazepines and Z-drugs in insomnia must fulfill stringent criteria.
9. Triazolam and the Z-drug zolpidem are short-acting and used for difficulties falling asleep.
10. Midazolam is used in premedication and induction of anesthesia.
11. The medium/long-acting oxazepam is used for difficulties to sleep through the night.
12. The long-acting diazepam is used for anxiolysis, sedation, muscle relaxation and the life-threatening status epilepticus.

25.1 Neuropsychiatric Diseases with Neuronal Imbalance: Neuron Inhibitors with Pleiotropic Effects (NIPEs) as Pharmacological Strategy

Normal function of the CNS depends on a balance between inhibitory and excitatory neurons. GABA is the most important inhibitory NT. The $GABA_AR$ is a ligand-gated chloride channel. Glutamate is the most important excitatory NT. The AMPAR (receptor for α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) is a particularly relevant glutamate receptor and constitutes a ligand-gated sodium channel, mediating depolarization.

A change in the equilibrium of inhibitory and excitatory populations can result in numerous neuropsychiatric diseases, depending on which specific CNS region is affected. Clinically, a neuronal disequilibrium can result in diseases as diverse as migraine, trigeminal neuralgia, cluster headache, polyneuropathies, fibromyalgia, restless leg syndrome, bipolar disorder (see ▶ Chap. 28), schizophrenia (see ▶ Chap. 29), borderline personality disorder, post-traumatic stress disorder, depersonalization disorder, and epilepsies.

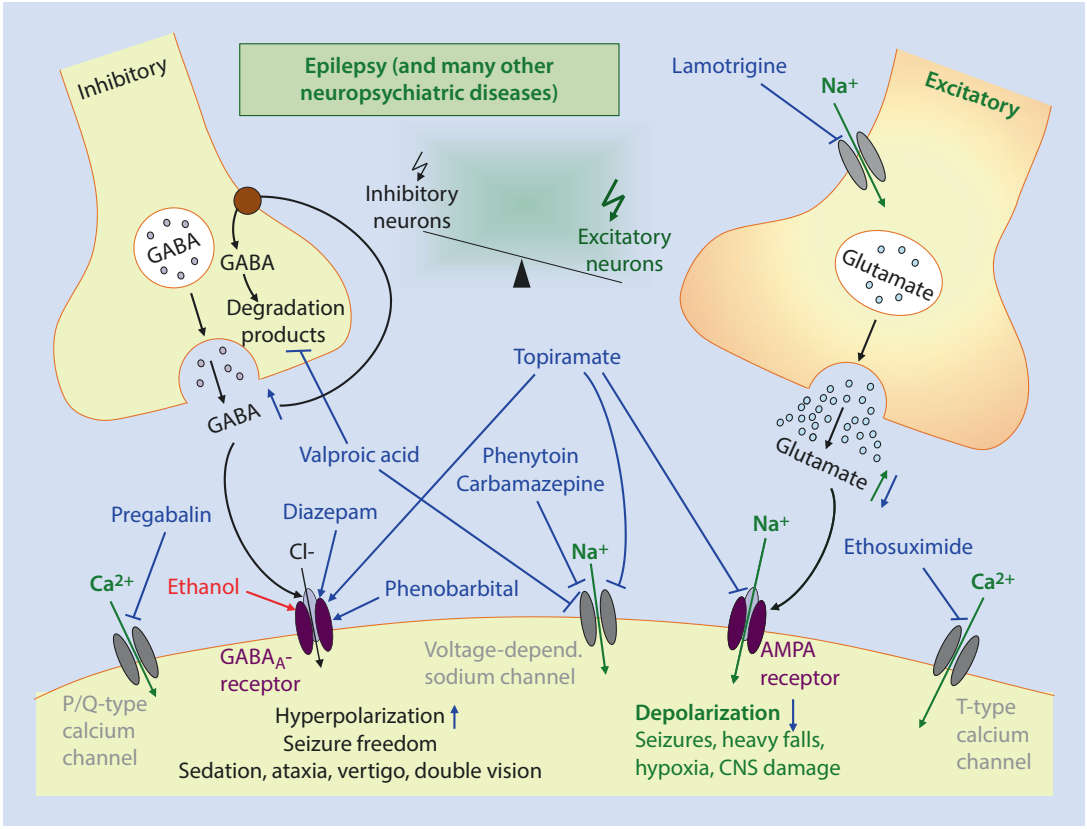

Fig. 25.1 Pathophysiology of epilepsies and pharmacological interventions. Phenobarbital and diazepam belong to the allosteric $GABA_AR$ modulators; the other drugs shown here belong to the NIPEs. This model of an imbalance between excitatory and inhibitory neurons and the efficacy of NIPEs can be transferred to many other important neuropsychiatric diseases including anxiety disorders, obsessive-compulsive disorders, schizophrenia (▶ Chap. 29), bipolar disorder (▶ Chap. 28), and neuropathic pain (▶ Chap. 10)

At first glance, these diseases appear to have little in common. However, the empirical finding that a certain group of drugs, the "neuron inhibitors with pleiotropic effects (NIPEs)" (traditionally designated as "antiepileptics"), are quite effective in these disorders indicates that they have a common pathophysiological background. This is an example how pharmacology does not only improve therapy of severe diseases but also improves our knowledge on pathophysiology. It should be noted that not all of the medical uses of NIPEs for neuropsychiatric diseases are officially approved by drug agencies. In many cases, neurologists and psychiatrists use these drugs "off-label" in patients and see how the condition improves. Thus, an empirical pharmacological approach to neuropsychiatric diseases with NIPEs offers the chance for clinical improvement. Should a drug fail, the physician can switch the patient to another drug. Clinical responses are often difficult to predict.

25.2 Epilepsies as Paradigm for Diseases with Neuronal Imbalance and Treated with NIPEs

Among the diseases mentioned above, the role of inhibitory and excitatory NTs is best understood for epilepsies (Fig. 25.1). Therefore, these diseases are discussed in greater detail as paradigm for the other diseases.

The therapeutic goal in epilepsy (and the other aforementioned diseases) is to restore the equilibrium between inhibitory and excitatory neurons. This is accomplished by supporting the function of GABAergic neurons and inhibition of glutamatergic neurons or by the blockade of ion channels mediating depolarization (see Fig. 25.1).

About 6 of 1000 humans suffer from epilepsy. With effective treatment, about two thirds of the

patients can be rendered seizure-free or at least improved in terms of a reduced seizure frequency. Focal seizures are confined to one side of the CNS. Generalized seizures affect both sides and manifest themselves as tonic-clonic or absence seizures. Pre-, peri-, or postnatal CNS lesions, meningitis, encephalitis, tumors, hemorrhage, hypocalcemia, hypoxia, hypoglycemia (see ▶ Chap. 19), hypertensive emergencies (see ▶ Chap. 15), ethanol intoxication or withdrawal, vitamin B_6 deficiency under INH therapy (see ▶ Chap. 33), rhythmic acoustic or optical stimuli, sleep withdrawal, or sudden termination of therapy with NIPEs or benzodiazepines can cause seizures. In addition, indirect sympathomimetics (see ▶ Chap. 5), PDE inhibitors (see ▶ Chap. 14), indirect dopamimetics (see ▶ Chap. 8), M_xR antagonists, NSMRIs, mGPCR antagonists (see ▶ Chaps. 5, 28, and 29), penicillins, and cephalosporins in high doses as well as quinolones (see ▶ Chap. 33) can induce seizures as well.

Whenever possible, the cause of seizures should be eliminated. Therapy of epilepsies is performed empirically with NIPEs according to the specific type of seizure. The specific properties of NIPEs are discussed in ▶ Sect. 25.3 and ◘ Table 25.1. For each patient, an individualized balance between therapeutic effects (the optimum is freedom from seizures) and ADRs has to be established. Since many NIPEs are involved in drug interactions, TDM is important. Drug doses should be increased incrementally. After 3 years of freedom from seizures, gradual tapering off of the NIPE over 2 years can be attempted. NIPEs have a small therapeutic index. Therefore, their prescription belongs into the hands of the neurologist who also has to be informed about every drug prescription by other physicians and OTC drugs because of potential drug interactions.

For optimal treatment it is essential that patients keep a seizure diary. Abstinence from ethanol, intoxicants, sedatives, as well as epileptogenic drugs and stimuli, e.g., stroboscopic light in discotheques, must be strictly followed. In addition, patients have to adhere to a regulated lifestyle. Discontinuation of NIPEs in puberty and pregnancy can deteriorate epilepsy. Regular controls of the function of the liver, kidney, and the hematopoietic system are essential. Strict implementation of these general rules is important for the success of the pharmacological treatment of epilepsies.

Status epilepticus is a life-threatening condition characterized by recurrent tonic-clonic seizures. Between seizures, the patient remains unconscious. Hypoxia develops due to respiratory depression and respiratory tract obstruction with secretions, ultimately leading to serious organ damage, particularly of the CNS. A major cause for status epilepticus is the abrupt discontinuation of NIPEs. Therefore, termination of NIPE treatment must be performed stepwise. Status epilepticus is treated with the allosteric $GABA_AR$ modulator diazepam (see ▶ Sect. 25.4).

25.3 Selected NIPEs

◘ Table 25.1 summarizes the properties of important NIPEs. Among these drugs, lamotrigine and pregabalin appear to possess the best relation between therapeutic effects and ADRs. Therefore, the drugs are widely used for several indications. "Classic" NIPEs such as phenytoin, carbamazepine, and valproic acid are effective drugs as well, but they are more problematic in terms of their ADRs. Accordingly, they should be used judiciously. Some NIPES such as ethosuximide have only very limited clinical use. All NIPEs can cause sedation, ataxia, vertigo, and double vision. Because of the sedative effect of all NIPEs, the capability to drive a car or to operate a machine is reduced. The sedative effect is potentiated by ethanol. Therefore, consumption of ethanol must be avoided. For each patient, an individual balance between therapeutic effects and ADRs has to be found, i.e., the drug dose should be increased incrementally and titrated carefully. Therapy must be terminated gradually as well because otherwise, disease symptoms may reoccur. This is particularly true for epilepsies. Certain NIPEs possess drug-specific ADRs (see ◘ Table 25.1).

Lamotrigine predominantly acts via blockade of sodium channels in glutamatergic neurons and the additional inhibition of glutamate release from them. As a result, especially the activity of excitatory neurons is decreased. Lamotrigine is broadly used in neurology and psychiatry. Its uses comprise focal seizures, bipolar disorder (see ▶ Chap. 28), cluster headache (see ▶ Chap. 10), migraine prophylaxis (see ▶ Chap. 6), polyneuropathies (see ▶ Chap. 10), borderline personality

Table 25.1 Overview of selected NIPEs

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Carbamazepine	SCB	Antiepileptic effect, mainly inhibits pathological neuronal activity	All types of seizures except absence seizures, bipolar disorder, schizophrenia, trigeminal neuralgia	Sedation, ataxia, double vision, leukopenia, loss of efficacy due to CYP induction	1, 2, 10, 28, 29
Ethosuximide	T-type CCB	Antiepileptic effect, mainly inhibits pathological neuronal activity	Absence seizures	Sedation, ataxia, double vision, nausea, leukopenia, allergies	
Lamotrigine	Inhibition of glutamate release via SBC	Antiepileptic effect, mainly inhibits pathologically active glutamatergic neurons; mood stabilization	Focal seizures, adjunct therapy of refractory epilepsy, alternative to valproic acid in women wishing to have children, mood stabilization in bipolar disorder, migraine prophylaxis, schizophrenia	Sedation, ataxia, double vision, vertigo, exanthemas	1, 6, 28, 29
Phenytoin	SCB	Antiepileptic effect; mainly inhibition of pathological neuronal activity	All types of seizures except absence seizures, trigeminal neuralgia	Sedation, ataxia, double vision, gingival hyperplasia, hypertrichosis, exanthemas, anemia, leukopenia, loss of efficacy due to enzyme induction	1, 2, 10
Pregabalin	P/Q-type CSB, no effect on $GABA_AR$ (in contrast to the suggestive drug name)	Antiepileptic effect; inhibition of pathological activity of different neuronal systems (NE, substance P, glutamate)	Neuropathic pain, generalized anxiety disorders, adjunct therapy of epilepsies, fibromyalgia, restless leg syndrome, many new uses are currently explored	Sedation, ataxia, double vision, vertigo, ED, addictive potential	1, 10, 28

(continued)

Table 25.1 (continued)

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Topiramate	Allosteric antagonism at AMPAR, additional SCB, and allosteric modulation of $GABA_AR$	Antiepileptic effect; mainly inhibition of pathologically active glutamatergic neurons	Adjunct therapy of focal and generalized seizures; migraine prophylaxis	Sedation, ataxia, double vision, vertigo, teratogenicity	1, 6
Valproic acid	SCB, inhibition of GABA degradation	Antiepileptic effect; mainly inhibition of pathologically active neurons; enhances activity of GABAergic neurons. Mood-stabilizing effect	Generalized seizures, mood stabilization in bipolar disorder migraine prophylaxis, schizophrenia	Sedation, ataxia, double vision, hair loss, liver damage, thrombopenia, teratogenicity (spina bifida). Nonetheless, pregnancy/wish to become pregnant is not a contraindication	1, 28, 29

For NIPEs, the indications (both approved and off-label) increase continuously. The list of indications provided here is incomplete. Among the drugs listed, pregabalin possesses the greatest risk of abuse Considering the high prescription numbers for pregabalin, abuse increases! Be alarmed when patients are actively requesting pregabalin without a clear indication

disorders, depersonalization disorder, and post-traumatic stress disorder.

Pregabalin blocks P/Q-type calcium channels. Despite the fact that the drug name pregabalin contains the word "GABA," the drug does not act via $GABA_AR$ (see ◘ Fig. 25.1). The drug is used as add-on therapy in epilepsies when the initially prescribed NIPE is not sufficiently effective. Pregabalin is very broadly prescribed for polyneuropathies, particularly diabetic polyneuropathy (see ▶ Chaps. 10 and 19) and post-herpetic polyneuropathy (see ▶ Chap. 34). The drug is also used in generalized anxiety disorders, social anxiety disorders, bipolar disorder (see ▶ Chap. 28), fibromyalgia, and restless leg syndrome. Pregabalin possesses less addictive potential than benzodiazepines (see ▶ Sect. 25.4), but with increasing therapeutic use of pregabalin, also its abuse increases. In many patients, pregabalin is prescribed off-label, and it is expected that the number of approved (and unapproved) indications of pregabalin continues to increase. Pregabalin is also an example for large differences in drug prices in different countries. Specifically, in the USA, therapy costs are more than 50-fold higher than in the UK.

Phenytoin has been successfully used for decades in the therapy of epilepsies. The drug blocks sodium channels changing from the resting to the active and then back to the inactive state. Due to preferential binding to the inactive state, phenytoin predominantly inhibits the activity of pathologically active neurons. The drug is effective in all types of epilepsy except for absence seizures. In addition to various types of epilepsies, phenytoin can be used for the treatment of trigeminal neuralgia (see ▶ Chaps. 1 and 10).

Because of the induction of CYP3A4 (see ▶ Chap. 2), phenytoin can reduce the effects of concomitantly applied drugs metabolized via this enzyme. In addition, the dose of phenytoin must be increased due to accelerated inactivation. Phenytoin possesses numerous ADRs. Hirsutism is cosmetically very disturbing in women. Another specific ADR is gingival hyperplasia which is not only cosmetically bothersome but also predisposing for periodontopathies and loss of teeth. Therefore, excellent dental hygiene is important. Excessive gingival hyperplasia must be removed surgically, and phenytoin must be exchanged against another NIPE drug in an overlapping manner.

Carbamazepine possesses a similar mechanism of action as phenytoin. Carbamazepine is used for various types of epilepsies, bipolar disorder (see ▶ Chap. 28), schizophrenia (see ▶ Chap. 29), and trigeminal neuralgia (see ▶ Chaps. 1 and 10). It also reduces its own efficacy as a result of CYP3A4 induction, requiring an increase in dose during long-term therapy (see ▶ Chap. 2).

Valproic acid blocks sodium channels and additionally inhibits GABA degradation with subsequent increased GABAergic neuronal activity, thereby counterbalancing pathological activity of excitatory neurons. Valproic acid is effective in generalized seizures. In addition, it is used as mood stabilizer in bipolar disorder (see ▶ Chap. 28) and schizophrenia (see ▶ Chap. 29). Valproic acid can also be used for prevention of migraine (see ▶ Chap. 6). Valproic acid possesses the highest risk for teratogenic effects among all NIPEs if administered during pregnancy. It can cause numerous malformations in the embryo, among them the most common and most serious being neural tube defects (spina bifida).

Despite potential teratogenic effects, a therapy with NIPEs must not be discontinued in pregnant women since the risk of seizures increases in pregnancy. Therefore, education of epileptic women with a desire to have children about the benefit-risk ratio of an NIPE drug therapy during pregnancy is important. It must also be emphasized that seizures due to nonadherence increase the risk of hypoxic CNS damage in the embryo and fetus. Commensurate with this special therapeutic situation, neurological and gynecological controls during pregnancy in epileptic women have to be very tight. As prophylaxis of neural tube defects, administration of folic acid supplements is required.

Topiramate blocks glutamatergic neurotransmission via allosteric AMPAR antagonism. In addition, the drug blocks sodium channels and activates the $GABA_AR$ allosterically. Topiramate is used as add-on therapy in epilepsies if the primarily applied drugs are insufficiently effective. Topiramate can also be used in migraine prophylaxis (see ▶ Chap. 6).

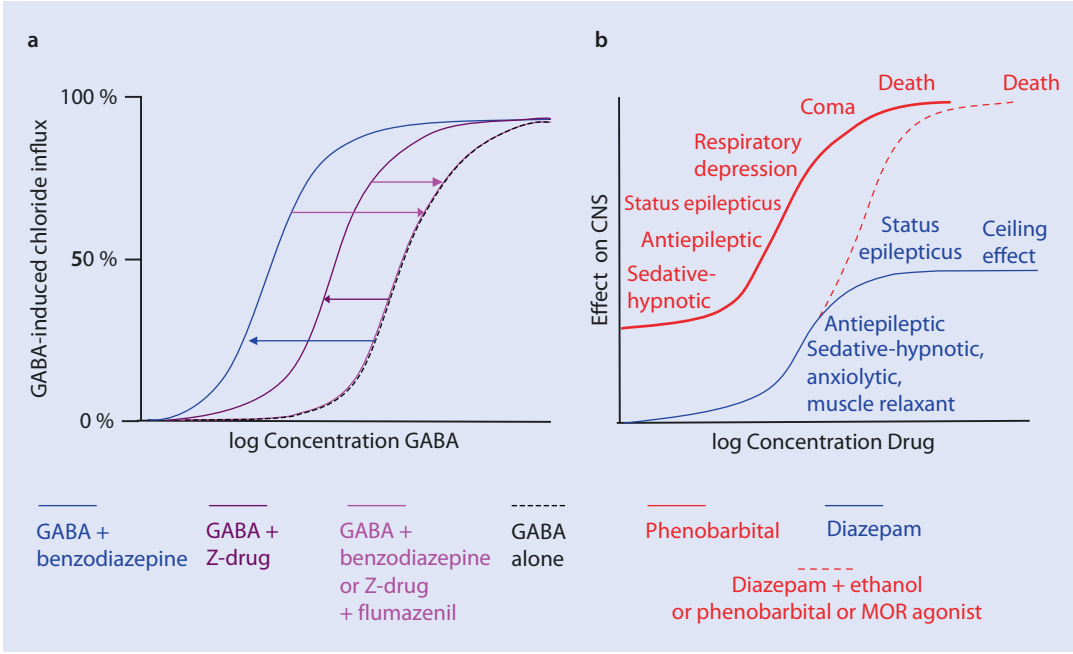

Fig. 25.2 **a**, **b** Pharmacological profiles of benzodiazepines, Z-drugs, flumazenil, and barbiturates. **a** Allosteric interactions of benzodiazepines, Z-drugs, and flumazenil with GABA at $GABA_AR$. **b** Comparison of pharmacological profiles of diazepam and phenobarbital. Barbiturates possess a much higher risk of intoxication than benzodiazepines. Flumazenil is an antidote for benzodiazepines and Z-drugs but not for barbiturates. See also Fig. 1.4. Barbiturates are unsafe for routine use

25.4 Allosteric $GABA_AR$ Modulators

The $GABA_AR$ consists of five subunits (two α, two β, and one γ). GABA binds to the α-subunit. Its binding site is positively and allosterically modulated by benzodiazepines and Z-drugs (binding to the γ-subunit) as well as barbiturates, the injection narcotic propofol (see ▶ Chap. 27), and ethanol, all binding to the β-subunit.

Benzodiazepines shift the concentration-response curve for GABA to the left, i.e., they render the receptor more sensitive to a given concentration of GABA without changing the maximally achievable receptor activation (Fig. 25.2a). Accordingly, the pharmacological effects of benzodiazepines depend on the presence of GABA. They possess anxiolytic, sedative-hypnotic, muscle-relaxing, and antiepileptic effects. With increasing doses, no respiratory depression develops (ceiling effect) (Fig. 25.2b). Therefore, it is very difficult to commit suicide even with high doses of benzodiazepines. The Z-drugs (non-benzodiazepines) address a similar binding site as benzodiazepines but possess only partial-agonistic effects (see ▶ Chap. 1). Z-drugs at maximally effective concentration shift the concentration-response curve for GABA also to the left but to a lesser extent than benzodiazepines (see Fig.25.2a). Accordingly, the therapeutic effects and ADRs of Z-drugs are smaller than those of benzodiazepines. Zolpidem is a representative Z-drug. It has only a short duration of action. Accordingly, zolpidem is predominantly used in mild difficulties falling asleep. It has no anxiolytic effects.

In contrast to benzodiazepines and Z-drugs, barbiturates possess pharmacological effects in the absence of GABA (Fig. 25.2b). At low doses, a sedative-hypnotic effect is observed, followed by antiepileptic effects in higher doses. At very high doses, loss of consciousness and finally coma and death occur. Barbiturates do not pos-

sess the ceiling effect of benzodiazepines. Therefore, overdosed barbiturates can cause death much easier than benzodiazepines. In addition, they do not possess anxiolytic and muscle-relaxing effects. Moreover, they adversely alter sleep physiology by suppressing REM (rapid eye movement) phases being relevant for dreaming. For all these reasons, the use of barbiturates is mostly restricted to the induction of anesthesia and to refractory epilepsies. There is no antidote for barbiturate intoxication. Until they are eliminated, the patient has to be mechanically ventilated. In contrast to barbiturates, the effects of benzodiazepines and Z-drugs can be rapidly reverted by the antagonist flumazenil (see ◘ Fig. 25.2a and ▶ Chap. 4). Thus, treatment of intoxications with benzodiazepines and Z-drugs is easier than therapy of barbiturate intoxication. However, suicide with benzodiazepines can be committed if the patient additionally ingests MOR agonists (see ▶ Chap. 11) or allosteric modulators acting on the β-subunit of the $GABA_AR$ such as ethanol, barbiturates, or propofol.

Qualitatively, all benzodiazepines possess the same pharmacological effects. However, due to differences in pharmacokinetics and modes of drug application, individual benzodiazepines have different indications (◘ Table 25.2). Benzodiazepines are divided into short-acting, medium/long-acting, and long-acting drugs. Short-acting benzodiazepines are used predominantly for treatment of difficulties falling asleep. The short-acting midazolam is applied in premedication prior to surgery and in induction of anesthesia (see ▶ Chap. 27). Medium/long-acting benzodiazepines are used for treatment of difficulties sleeping through the night and for sedation and anxiolysis, e.g., for support of initial therapy of depression (see ▶ Chap. 28). The long-acting diazepam is used for muscle relaxation in muscular tension (e.g., lumbar disc hernia) and in central spasticity and tetanus and for supporting initial therapy of depression. The antiepileptic effect of diazepam is used in status epilepticus.

The most common use of benzodiazepines and Z-drugs is the treatment of various types of insomnia. Before prescribing these drugs, general measures such as sleeping in a cool and quite room as well as avoidance of long periods of sleep during the day have to be implemented. Benzodiazepines and Z-drugs must be prescribed at the lowest dose and for the shortest period of time possible. The drugs must be tapered off and must not be terminated abruptly because of the risk of rebound insomnia and withdrawal symptoms. All contraindications need to be considered. In general, short-acting drugs should be preferentially prescribed in all cases of insomnia to avoid sedation during the day and hangover.

The ADRs of benzodiazepines and Z-drugs are the result of excessive $GABA_AR$ activation. Particularly for the drugs with longer duration of action, sedation during the day, hangover, confusion, and loss of libido are common. The capability to drive a car or to operate a machine is reduced. If benzodiazepines are taken together with large amounts of ethanol, respiratory depression, coma, and death can occur. In elderly patients, ataxia and heavy falls are common. In respiratory tract obstruction, pre-existing CNS damage, and concomitant therapy with MOR agonists (see ▶ Chap. 10), the risk of respiratory depression is increased. In children and elderly patients, benzodiazepines must be used cautiously because paradoxical agitation can occur. Anterograde amnesia, particularly following i.v. injection of benzodiazepines or in combination with ethanol, is another very dangerous ADR. Patients with anterograde amnesia can cause serious traffic accidents without having a recollection of the event. In addition, anterograde amnesia can be intentionally abused for sexual acts. In newborn babies, the floppy infant syndrome can develop, manifesting itself with respiratory depression and difficulties to suckle.

Long-term use of benzodiazepines causes psychological and physical addiction. Upon withdrawal, seizures and severe states of agitation can occur. Benzodiazepines are commonly used as surrogate drugs by heroin addicts. This abuse is a common cause for pharmacy break-ins. Benzodiazepines are contraindicated in myasthenia gravis, ataxia, sleep apnea, and obstructive respiratory tract diseases.

Table 25.2 Overview of selected allosteric $GABA_AR$ modulators

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Diazepam	Benzodiazepine, allosteric modulation of $GABA_AR$ (higher intrinsic activity than Z-drugs)	Sedative-hypnotic, anxiolytic, muscle relaxant, antiepileptic (very long duration of action: 48–96 hours)	Versatile benzodiazepine. Daytime sedation, anxiolysis to reduce anxiety in mental disorders, relaxation of muscle spasms (lumbar disc hernia, lumboischialgia), status epilepticus	Sedation, physical and psychological addiction, tolerance with loss of efficacy and withdrawal symptoms, paradoxical agitation in children and elderly patients, retrograde amnesia	4, 10, 28
Flumazenil	Competes with benzodiazepines and Z-drugs for allosteric binding to $GABA_AR$	Counteracts the effects of benzodiazepines and Z-drugs	Life-threatening intoxication by benzodiazepines and Z-drugs, particularly in case of respiratory arrest	Treatment of an intoxication with long-acting benzodiazepines may require repeated administration of flumazenil due to its short duration of action (2 hours) to prevent recurrent symptoms of overdose	3
Midazolam	Benzodiazepine, allosteric modulation of $GABA_AR$ (higher intrinsic activity than Z-drugs)	Sedative-hypnotic, anxiolytic (short duration of action: 2–3 hours), antiepileptic	Difficulty in falling asleep, premedication in surgery (p.o. administration), anesthetization (i.v. administration), sedation in MI (nasal spray; status epilepticus (nasal spray)	Insomnia after discontinuation, daytime sleepiness, addiction, paradoxical insomnia in children and elderly patients, anterograde amnesia (particularly with i.v. injection and rapid penetration into the CNS), respiratory depression, retrograde amnesia	1, 27
Oxazepam	Benzodiazepine, allosteric modulation of $GABA_AR$ (higher intrinsic activity than Z-drugs)	Sedative-hypnotic, anxiolytic (intermediate-long duration of action: 8–12 hours)	Difficulty to sleep through the night	Insomnia after discontinuation, daytime sleepiness, addiction, paradoxical insomnia in children and elderly people, retrograde amnesia	1

Phenobarbital	Allosteric modulation of $GABA_AR$ (different binding site than diazepam)	Antiepileptic effect, enhances function of GABAergic neurons (only sedative and antiepileptic effect; no anxiolysis and no muscle relaxation)	All types of seizures except absence seizures. Because of the small therapeutic index and loss of response in long-term treatment, phenobarbital is only used as drug of last resort	Sedation, ataxia, double vision, risk of respiratory depression in case of overdose; loss of efficacy due to CYP induction during long-term therapy	1, 2
Triazolam	Benzodiazepine, allosteric modulation of $GABA_AR$ (higher intrinsic activity than Z-drugs)	Sedative-hypnotic, anxiolytic (short duration of action: 2–5 hours)	Difficulty to fall asleep	Insomnia after discontinuation, daytime sleepiness, addiction, paradoxical insomnia in children and elderly people, retrograde amnesia	1
Zolpidem	Z-drug, allosteric modulation of $GABA_AR$ (lower intrinsic activity than benzodiazepines)	Sedative-hypnotic (very short duration of action: 1.5–2.5 hours), not anxiolytic	Minor difficulty to fall asleep; lower effect than benzodiazepines due to partial agonism	Overall less ADRs than benzodiazepines due to partial agonism, retrograde amnesia	1

All drugs listed here show synergistic interactions with MOR agonists (see ► Chap. 10) and ethanol. The ability to drive cars and operate machines can be substantially impaired! Anterograde amnesia is a dangerous ADR of benzodiazepines and Z-drugs

25.5 Questions and Answers

Questions

Which assignment of drug to indication is correct?

A. Zolpidem – difficulties sleeping through
B. Triazolam – status epilepticus
C. Diazepam – muscle relaxation in lumbar disc hernia
D. Midazolam – long-term therapy of generalized seizures
E. Oxazepam – difficulties falling asleep

Answers

A. Because of its short duration of action (1.5–2.5 hours), zolpidem is only suitable for treatment of difficulties falling asleep. For difficulties sleeping through, oxazepam is better suited because of its longer duration of action (8–12 hours).

B. Triazolam possesses a short duration of action (2–5 hours). Therefore, it is used for difficulties falling asleep. For therapy of status epilepticus, diazepam is suitable. It possesses a long duration of action (48–96 hours) and is available in suitable formulations (solutions for i.v. injection, suppositories for rectal administration).

C. In lumbar disc hernia, a very painful reflectory muscular tension develops that causes a malposition of the back, further deteriorating the pain in a vicious cycle. This cycle must be broken by administration of highly effective analgesics (metamizole + COX inhibitor + MOR agonist) and muscle relaxants. For muscle relaxation, diazepam is particularly well suited because of its long duration of action.

D. Midazolam possesses only a short duration of action (2–3 hours). Therefore, it is not suitable for long-term treatment. In general, benzodiazepines are not suitable for long-term treatment of epilepsies because of the development of tolerance.

E. Because of its intermediate-long duration of action (8–12 hours), oxazepam is suitable for difficulties sleeping through. However, for this indication, sedation during the day constitutes an ADR.

Answer **C** is correct.

25.6 Exercises

A 29-year-old woman has been treated with valproic acid for 3 years for generalized tonic-clonic seizures. Under this therapy, the patient is free from seizures and tolerates the drug well. A year ago, the woman married. Now she wishes to become pregnant. From the gynecological perspective, there are no concerns. The patient visits you in your neurology office and asks for advice regarding the desire to have children.

Questions

1. Which advice do you give the patient?
2. Which alternative therapeutic options can you offer?

Answers

1. Generalized seizures must be treated in pregnancy. The risk for seizures is increased, and accordingly, the risk for the mother (risk of accidents, injuries, and hypoxia) and the embryo/fetus (predominantly CNS hypoxia) increases as well. Since the patient is well treated with valproic acid, she should continue this therapy. You must inform the patient about the fact that under valproic acid therapy, the risk for teratogenic effects amounts to 7%. Neuronal tube defects are the most common teratogenic effect. Since the teratogenic effects of valproic acid are dose-dependent, the patient should be adjusted to the smallest dose possible. In addition, the drug should be given as a sustained-release formulation. Moreover, as preventive measure against neuronal tube defects, folic acid must be substituted. Lastly, close gynecological controls (ultrasound exams) during pregnancy are required to detect potential malformations as early as possible.
2. Because of its high efficacy (75% of all pregnant patients are free from seizures), valproic acid is the drug of choice during pregnancy. Carbamazepine and lamotrigine possess a lower teratogenic risk (about 2–3%), but the rate of freedom from seizures is also lower (70% under carbamazepine and 60% under lamotrigine). These risks have to be weighed against each other because increased frequency of seizures can be teratogenic as well as a result of hypoxia.

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Local Anesthetics

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26

Local anesthetics are weak bases with a cationic and a hydrophobic moiety. In the uncharged form they diffuse across the plasma membrane. Intracellularly, in the charged (cationic) form, local anesthetics block sodium channels, thereby interrupting pain transmission. At low pH, present in inflammation and traumatized tissue, the efficacy of local anesthetics is reduced. Individual drugs differ from each other in their duration of action. EPI prolongs the effects of local anesthetics and reduces their toxicity in the heart and CNS. Ester local anesthetics cause para group allergies and should not be used anymore but replaced by much less allergenic amide local anesthetics. Local anesthetics are used for topical, infiltration, nerve block, spinal, and epidural anesthesia.

Key Points

1. Local anesthetics block voltage-dependent sodium channels.
2. The efficacy of local anesthetics is reduced in inflamed and traumatized tissue.
3. Only amide local anesthetics should be used.
4. Lidocaine is a short-acting local anesthetic.
5. Bupivacaine is a long-acting local anesthetic.
6. Local anesthetics can be cardio- and neurotoxic.
7. Vasoconstrictors prolong the duration of action of local anesthetics and reduce toxicity.
8. EPI is the most important vasoconstrictor.
9. Different types of local anesthesia exist.

26.1 Mechanism of Action of Local Anesthetics

The major use of local anesthetics is to interrupt pain transmission during surgical procedures. Pain transmission is mediated via thinly myelinated afferent neurons and based on a depolarizing sodium entry via voltage-dependent sodium channels. Local anesthetics interrupt transmission of the action potential in all peripheral and central neurons by blockade of these channels. The sensitivity of neurons toward blockade by local anesthetics depends on the thickness of the neuron and its myelination. The thinner a neuron, the thinner its myelin sheath and the more readily neurotransmission is blocked. C fibers have a thickness of about 1 µm, B fibers of about 3 µm, and A fibers of about 5–15 µm. Pain transmission is predominantly mediated via C fibers, temperature transmission via B fibers, and transmission of touch and proprioception via A fibers. Accordingly, local anesthetics block sensory qualities in the order pain > cold/heat > touch > proprioception. However, the very thickly myelinated motor neurons are blocked as well, leading to muscular paralysis. Postganglionic fibers of the sympathetic nervous system belong to class C so that injection of a local anesthetic close to a sympathetic ganglion can result in a serious drop in BP (see ▶ Chaps. 5 and 15).

Figure 26.1 shows the mechanism of action of local anesthetics. These drugs are weak bases with pK_a values of ca. 8. They possess a tertiary or quaternary nitrogen and a hydrophobic moiety. Local anesthetics are soluble only as acid salts. In injection vials, local anesthetics are present in the protonated (charged) form at a pH of 4–6. In healthy tissue, the pH is around 7.4. Accordingly, protonation of local anesthetics decreases in tissues, and the portion of the deprotonated (uncharged) form increases. In the uncharged form, the local anesthetic is lipophilic and can diffuse across the plasma membrane (transport form). In the cell, again, an equilibrium between the charged and uncharged form establishes. The charged form is pharmacologically active and blocks the sodium channel pore from the intracellular side by ion bonds and hydrophobic interactions.

The efficacy of local anesthetics depends on tissue pH (Fig. 26.1b). In elective surgery in otherwise healthy tissue without trauma or inflammation, equilibration of the two forms of local anesthetics proceeds very efficiently, ensuring excellent anesthesia. However, if surgery has to be performed in inflamed or injured tissue with decreased pH, formation of the transport form of the local anesthetic is impeded. As a consequence, fewer local anesthetic molecules in the pharmacologically active form approach the site

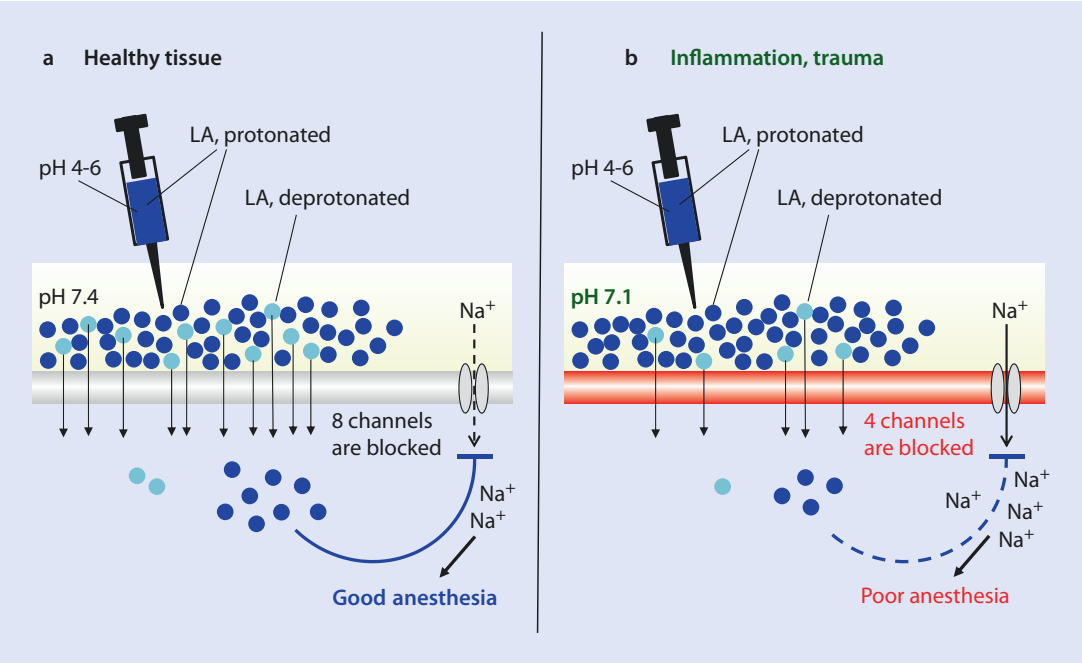

Fig. 26.1 Mechanism of action of local anesthetics. **a** High efficacy of LAs as SCBs in healthy tissue. **b** Low efficacy of LAs as SCBs in inflamed or traumatized tissue. LA, local anesthetic. Never directly anesthetize traumatized or inflamed tissue! The local anesthesia does not work, and both you and your patient will be stressed! In trauma or inflammation, use a nerve block anesthesia

of action, and anesthesia is reduced. The surgeon can try to solve this problem by injecting larger amounts of the local anesthetic solution. However, this practice also increases the risk of ADRs. Therefore, whenever possible, local anesthetics should be applied proximally to the injured or inflamed tissue, but not in the inflamed or injured tissue itself.

26.2 Important Local Anesthetics, Applications, and ADRs

Local anesthetics are classified into esters and amides. Esters are hydrolyzed in the tissue by esterases. p-Aminobenzoic acid is a strongly allergenic degradation product of ester local anesthetics. It exhibits cross-allergies with sulfonamides and preservatives (see ▶ Chap. 3). Therefore, ester local anesthetics should not be used anymore. Preservatives in local anesthetic solutions can be allergenic as well (see ▶ Chap. 3). Therefore, single-use vials without preservatives should be used whenever possible. Amide local anesthetics are degraded in the liver.

A clinically useful local anesthetic must fulfill several criteria. It has to be sterilizable, water-soluble, tissue-friendly, and nontoxic. In addition, it must exhibit a rapid and excellent anesthetic effect that must be reversible. The amide local anesthetics fulfill these criteria to a large extent. Lidocaine is a prototypical short-acting and bupivacaine a prototypical long-acting local anesthetic. Table 26.1 summarizes important pharmacological properties of lidocaine and bupivacaine. In dentistry, articaine is broadly used because it penetrates well into the bone.

Lidocaine is a universally applicable local anesthetic. It can be used in topical anesthesia, e.g., in the eye, where it blocks pain transmission in corneal and conjunctival sensory neurons. Lidocaine can also be applied for infiltration anesthesia in dentistry or for surgical procedures at the body surface. In the latter case, predominantly pain transmission in the subcutis is blocked.

In nerve block anesthesia, lidocaine inhibits pain transmission in sensory and mixed peripheral nerves. This type of anesthesia is broadly used in dentistry and surgery of the

Table 26.1 Overview of selected local anesthetics

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Bupivacaine	Long-acting blockade of voltage-dependent sodium channels from the inside of the plasma membrane	The order of loss of peripheral nerve function is pain > cold/heat > touch > proprioception > motor function. Onset of action after 5–10 minutes, duration of action up to 400 minutes	Mainly spinal and epidural anesthesia	See lidocaine	2, 3, 5, 17, 25
Lidocaine	Short-acting blockade of voltage-dependent sodium channels from the inside of the plasma membrane	The order of loss of peripheral nerve function is pain > cold/heat > touch > proprioception > motor function. Onset of action after 4–8 minutes, duration of action 60–120 minutes. The duration of action may be prolonged to up to 4 hours by addition of vasoconstrictors (EPI)	Standard local anesthetic. All types of local anesthesia (surface, infiltration, nerve block, spinal and epidural anesthesia)	Tachyarrhythmias and bradyarrhythmias, negative inotropy, cardiovascular failure; CNS symptoms including loss of consciousness, seizures, coma, and respiratory arrest. Early symptoms of CNS effects: nausea, vomiting, euphoria, anxiety, and vertigo. Allergic reactions occur only rarely and are mostly caused by preservatives	2, 3, 5, 17, 25

arms and legs. For gynecological or urological procedures and knee surgery, spinal anesthesia is often applied in which lidocaine is injected into the subarachnoid space and inhibits pain transmission in the spinal nerves. In epidural anesthesia, the local anesthetic is injected into the epidural space. Applications are similar to those of spinal anesthesia. Infiltration, nerve block, spinal, and epidural anesthesia can be performed with or without EPI. Bupivacaine is predominantly used in spinal and epidural anesthesia.

Upon accidental intravasal injection of local anesthetics, systemic ADRs can develop. In order to avoid such ADRs, it is essential that the local anesthetic is injected slowly and with regular aspiration to ensure that accidental puncture of a blood vessel does not occur. The risk of ADRs can also be reduced by the application of vasoconstrictors (see ▶ Sect. 26.3).

In the heart, local anesthetics act like class I antiarrhythmic drugs and cause negative chronotropic, negative dromotropic, and negative inotropic effects (see ▶ Chap. 17). Heart function can be compromised until cardiac arrest occurs. Tachyarrhythmias can develop as well.

In principle, local anesthetics interrupt transmission in every neuron. They penetrate the BBB (see ▶ Chap. 2) and can compromise CNS functions. Initially inhibitory neurons are affected. The early symptoms of CNS intoxication by local anesthetics are nausea, vomiting, urge to speak excessively, anxiety, agitation, restlessness, and loss of orientation. Later, seizures occur. In serious cases of intoxication, excitatory neurons in the CNS are impaired as well, leading to respiratory depression and coma.

Treatment of systemic ADRs of local anesthetics is symptomatic because there is no spe-

cific antidote. In case of ADRs in the heart and CNS, administration of the local anesthetic must be terminated immediately. Vital functions of the patient must be secured. Lateral positioning and keeping free the airways are the most important measures. If available, oxygen can be inhaled. Seizures are treated with diazepam (i.v. or rectally, see ▶ Chap. 25), and the patient must be protected from injuries. Treatment of arrhythmias is difficult. In most cases, it is sufficient to check basic cardiovascular parameters (BP, HR, ECG) and wait for spontaneous termination of the arrhythmia following drug inactivation in the liver in order to avoid administration of another pro-arrhythmogenic antiarrhythmic drug (see ▶ Chap. 15). In cardiac arrest, cardiopulmonary resuscitation has to be performed.

26.3 Vasoconstrictors in Local Anesthesia

The local anesthetic effects of lidocaine and bupivacaine are terminated by diffusion from the site of injection. Additionally, these drugs induce vasodilation. This facilitates elimination of the drug from the injection site and shortens their duration of action which, accordingly, may be prolonged by the addition of vasoconstrictors to local anesthetics (see ▶ Chap. 5). EPI contracts blood vessels via the α_1AR. The addition of EPI to local anesthetics also lowers the risk of ADRs in the heart and CNS. Moreover, EPI reduces hemorrhage in the area of surgery, improving oversight and lowering the risk of surgery-induced tissue damage. Due to the vasoconstriction, the dose of the local anesthetic can be reduced, further diminishing the risk of systemic toxicity. Thus, the addition of EPI to local anesthetics avoids stress for the physician and patient and renders local anesthesia more effective and safe. In dentistry, EPI is used at concentrations of 5–10 µg/ml, in general surgery at concentrations of 2–10 µg/ml.

In many countries the use of EPI as vasoconstrictor in acral body regions (nose, ears, fingers, toes, penis) is discouraged because of the assumed risk of tissue necrosis. However, evidence from various surgical disciplines indicates that EPI is safe and improves results. In addition, accidental injection of EPI from EPI pens for anaphylactic shock (see ▶ Chap. 3) into fingers did not result in tissue necrosis. Thus, the previously held view that EPI is contraindicated in acral body regions is not valid anymore.

In patients treated with NSMRIs and SSNRIs, local anesthetics with EPI additive must be used cautiously. EPI that is absorbed into the systemic circulation is not taken up neuronally but can lead to tachycardia and increases in BP (see ▶ Chaps. 5 and 28). Under therapy with MAOIs, EPI is not degraded and can cause ADRs. In such situations the vasoconstrictor octapressin can be applied as alternative. However, it possesses a smaller efficacy than EPI. NE is contraindicated as additive to local anesthetics because of the strong vasoconstriction (missing vasodilation via the β_2AR, see ▶ Chap. 5) that can cause necrosis even in tissues well supplied with blood. Collectively, the key for effective and safe local anesthesia with an added vasoconstrictor is the avoidance of accidental intravasal injection.

26.4 Questions and Answers

Questions

Which statement on amide local anesthetics is correct?

A. Amide local anesthetics are weak acids.
B. Amide local anesthetics have a higher efficacy at low tissue pH.
C. Amide local anesthetics bind to the extracellular side of sodium channels.
D. Amide local anesthetics inhibit potassium channels.
E. Amide local anesthetics are degraded in the liver.

Answers

A. Amide local anesthetics are weak bases with pK_a values of ~8. This implies that at physiological pH (7.4), most of the drug molecules are protonated (positively charged). Both the presence of protonated and deprotonated forms of the local anesthetic is important for its pharmacological effects.
B. At lower pH most of the local anesthetic molecules are protonated. Accordingly,

the portion of deprotonated but membrane-permeable molecules is exceedingly small, and the absolute number of intracellularly available local anesthetic molecules is strongly reduced. The clinical result is reduced anesthetic efficacy.

C. Amide local anesthetics bind to the intracellular side of sodium channels.

D. Amide local anesthetics block voltage-dependent sodium channels.

E. Ester local anesthetics are rapidly degraded in the tissue by esterases. Amide local anesthetics are degraded in the liver by amidases.

Answer **E** is correct.

26.5 Exercises

A 28-year-old healthy man suffered a 5-cm-long and heavily bleeding incisional wound at the left lower arm. In the emergency room, the intern surgically closes the wound with several stitches. Prior to surgery, the intern has generously infiltrated the injured area with lidocaine (without EPI additive). About 30 minutes after wound closure, the patient suffers generalized seizures.

Questions

1. How do you explain the patient's seizures?
2. Which additional therapeutic measures do you take?

Answers

1. The most likely cause for the seizures is that lidocaine in a high concentration accidentally entered the systemic circulation because of the missing vasoconstrictor. Lidocaine then reached the CNS and inhibited inhibitory neurons, resulting in agitation and seizures. This complication could have been avoided if a local anesthetic with EPI additive had been administered.
2. There is no antidote for local anesthetics. The most important measure is to keep the respiratory tract open and prevent the patient from injuries by proper positioning. Administration of oxygen with a nasal tube is useful, too. To terminate the seizures, diazepam can be administered i.v. or rectally. However, the seizures should be self-limiting because lidocaine rapidly diffuses out of the CNS and is transported to the liver where inactivation takes place. It is also a good idea to have the patient examined neurologically to exclude a CNS disease that may have facilitated the occurrence of seizures.

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Inhalation and Injection Anesthetics

R. Seifert, *Basic Knowledge of Pharmacology*, https://doi.org/10.1007/978-3-030-18899-3_27

Inhalation and injection anesthetics are used for anesthesia and in emergency and intensive care medicine. The available anesthetics have different properties. They can be combined with each other and with other drug classes such as muscle relaxants and MOR agonists in order to obtain optimal anesthesia for each patient. Inhalation anesthetics modulate membrane properties globally. Modern inhalation anesthetics possess good controllability. Nitrous oxide possesses low potency and good analgesia. Sevoflurane possesses high potency, a good hypnotic effect, and does not irritate mucosal membranes. Desflurane is a standard inhalation anesthetic but is not suitable for induction of anesthesia. For this purpose, thiopental is broadly used in uncomplicated cases. In anesthesia, midazolam is often applied because of its sedative-hypnotic and anxiolytic effects. Ketamine is used because of its dissociative-anesthetic effects. Propofol is widely applied and has a good sedative-hypnotic but no analgesic effect.

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Key Points

1. Inhalation anesthetics modulate membrane properties globally.
2. The higher the potency of an inhalation anesthetic, the lower is the minimally effective alveolar concentration.
3. The lower the blood/gas distribution coefficient, the better is the controllability of anesthesia.
4. Anesthetics + muscle relaxants + MOR agonists render anesthesia safe.
5. Malignant hyperthermia is a rare but life-threatening ADR of haloethers.
6. Malignant hyperthermia is treated with dantrolene.
7. Modern inhalation anesthetics possess good controllability.
8. Nitrous oxide possesses low potency and a good analgesic effect.
9. Sevoflurane and desflurane possess high potency and a good hypnotic effect.
10. Thiopental has sedative-hypnotic but no anxiolytic effects.
11. Midazolam has sedative-hypnotic and anxiolytic effects.
12. Ketamine induces dissociative anesthesia.
13. Propofol has sedative-hypnotic effects.

27.1 Principles of Inhalation Anesthesia

Inhalation anesthetics are mainly used in anesthesia to allow for the execution of surgical procedures. For this purpose, evaporated gases or volatile drugs are inhaled via a respiratory mask or an endotracheal tube. The goal of anesthesia is to eliminate consciousness and to induce analgesia as well as relaxation of the skeletal muscles.

An ideal inhalation anesthetic should neither be explosive nor combustible and should possess a high therapeutic index, a rapid onset of action, good controllability, good analgesia, and muscle relaxation. It should suppress reflexes in the oropharynx and have neither an unpleasant smell nor induce an excitation stage. The anesthetic should be devoid of ADRs in the cardiovascular system, liver, kidney, and respiratory tract (mucosal irritation). Lastly, inhalation anesthetics should be devoid of occupational hazards for the operation room personnel. Modern inhalation anesthetics fulfill most of these criteria.

By combination of inhalation anesthetics with injection anesthetics (see ▶ Sect. 27.3), muscle relaxants (see ▶ Chap. 5), and MOR agonists (see ▶ Chap. 10), good anesthesia with acceptable ADRs can be accomplished in almost all cases. The goal of the anesthetist is to achieve an optimal anesthesia for every patient under consideration of the specific indication and concomitant diseases. ◘ Table 27.1 summarizes the properties of important inhalation and injection narcotics.

In contrast to most other drug classes (see ▶ Chap. 1), there is no specific pharmacological target for inhalation anesthetics. These drugs alter membrane properties globally and inhibit propagation of the action potential and NT release from neurons. The more lipophilic an anesthetic is, the more potent is the drug, i.e., the lower is the minimally effective alveolar concentration (see ▶ Chap. 1). Anesthetics rapidly reach the CNS since it is very rich in lipids. During long-lasting anesthesia, anesthetics can accumulate in adipose tissue and generate a depot (see ▶ Chap. 2).

For safety of anesthesia, good controllability is essential. The lower the blood/gas distribution coefficient of an inhalation anesthetic, the faster is the onset and termination of anesthesia and the more flexibly can anesthesia be adapted to current requirements. All modern inhalation anesthetics can be controlled very well.

Table 27.1 Overview of selected inhalation and injection narcotics

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Desflurane	Inhalation anesthetic: changes membrane properties, no specific target	Lower potency than sevoflurane, very rapid onset of action, depth of anesthesia can be controlled very easily, weak analgesic and muscle relaxant effect, few effects on the cardiovascular system	Standard inhalation anesthetic for surgery. Not to be used for induction of anesthesia because of respiratory tract irritation	Overall good tolerability, postoperative nausea and vomiting, malignant hyperthermia	4
Ketamine	Allosteric NMDAR antagonist, pleiotropic effects	Mainly sedative-hypnotic and analgesic effect (dissociative anesthesia), acute antidepressive effects	Induction of anesthesia, often used in combined anesthesia, analgesia in pediatric surgery and emergency medicine, analgesia for intubated ICU patients, intubation of patients with status asthmaticus (bronchodilatory effect), chronic pain, used as acute antidepressant drug (nasal spray) in the USA	As protective reflexes are retained, there is only a small risk of respiratory arrest. Rise in BP and HR due to inhibition of catecholamine re-uptake. Hallucinations, IOP rise, addiction potential	5, 10, 15, 28
Midazolam	Benzodiazepine, allosteric $GABA_AR$ modulator, different binding site than thiopental	Sedative-hypnotic, anxiolytic, muscle relaxant, and antiepileptic effect; no analgesic effect	Premedication, induction of anesthesia, mainly used because of its sedative-hypnotic and anxiolytic effect, often used in combined anesthesia, used in diagnostic procedures (e.g., endoscopy), status epilepticus	Anterograde amnesia (may lead to uncontrolled actions and unjustified accusations on the part of the patient) and respiratory depression. Abuse may lead to physical and psychological addiction with withdrawal symptoms	4, 25
Nitrous oxide	Inhalation anesthetic, changes membrane properties, no specific target	Low potency, rapid onset of action, depth of anesthesia can be easily controlled, good analgesic effect, weak narcotic effect	Short, painful surgeries, used in combined anesthesia	Diffusion hypoxia, vitamin B_{12} deficiency after frequent administration	

(continued)

Table 27.1 (continued)

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Propofol	Allosteric $GABA_AR$ modulator and nAChR antagonist	Sedative-hypnotic effect, no analgesic effect	Often used in combined anesthesia, endoscopy, combination with MOR agonists (additional analgesia), sedation in intensive care medicine, pediatric anesthesia, component of TIVA, therapy of malignant hyperthermia	Falling asleep and awakening are pleasant; no risk of malignant hyperthermia, risk of respiratory depression and BP drop, anaphylactic shock, euphoria, abuse potential	3, 4, 7, 10
Sevoflurane	Inhalation anesthetic, changes membrane properties, no specific target	High potency, rapid onset of action, depth of anesthesia can be easily controlled, good hypnotic effect, weak analgesic and muscle relaxant effect	Standard inhalation anesthetic for surgeries, well suited for induction of anesthesia because it causes no respiratory tract irritation, often used in pediatric anesthesia	Overall good tolerability, particularly no respiratory tract irritation, postoperative nausea and vomiting, malignant hyperthermia	4
Thiopental	Barbiturate, allosteric $GABA_AR$ modulator, different binding site than midazolam	Sedative-hypnotic effect	Induction of anesthesia in uncomplicated patients, drug of last resort in patients with increased intracranial pressure and status epilepticus	Respiratory depression, respiratory arrest, anaphylactic shock, hyperalgesia, tissue necrosis after paravasal injection, accumulation after repeated administration	2, 3, 7, 25

Ketamine, midazolam, and propofol have abuse and addiction potential. Be alarmed when patients are actively requesting prescription of these drugs without proper indication

27.2 Important Inhalation Anesthetics

Nitrous oxide (N_2O, laughing gas) has a sweet smell; is not combustible; does not irritate mucosal membranes; has no ADRs in the cardiovascular system, liver, and kidney; and does not cause malignant hyperthermia (see below). Nitrous oxide oxidizes vitamin B_{12}. If applied for periods >6 hours, methionine biosynthesis and methylation reactions are inhibited. However, this issue is not clinically relevant during short-term application of nitrous oxide.

Nitrous oxide possesses only low potency so that general anesthesia with this gas alone cannot be accomplished. At concentrations >20% in the anesthetic gas mixture, nitrous oxide exhibits good analgesic and weak anesthetic effects. Commonly, it is used in combination with oxygen in a 1:1 ratio to induce analgesia for short surgical procedures or to alleviate pain during labor. Nitrous oxide is also used to support analgesia in

combination with other inhalation anesthetics such as sevoflurane and desflurane. By combining various gases, the concentration of each gas in the anesthetic gas mixture can be reduced so that the overall risk of ADRs declines.

Since nitrous oxide possesses a low blood/gas distribution coefficient (0.47), onset and end of anesthesia are fast. Thus, inhalation anesthesia with nitrous oxide can be controlled very well, and the risk of respiratory depression is low. Nitrous oxide diffuses rapidly into gas-containing body compartments. This can result in pressure increases in the middle ear, paranasal sinuses, and the intestine. If nitrous oxide is applied at high concentrations, diffusion hypoxia may develop during termination of anesthesia. This can be prevented by increasing the oxygen concentration in the respiratory gas mixture.

Nitrous oxide is a greenhouse gas that contributes to global warming. Contamination of the atmosphere with environmentally problematic anesthetic gases could be avoided with closed anesthesia systems. However, these systems are very expensive and available only in few hospitals.

Sevoflurane and desflurane are broadly used inhalation anesthetics. They are liquid drugs with a high vapor pressure and a low boiling point. Haloethers are colorless, not combustible, chemically inert, and stable against light exposure. They are stored in special color-coded containers and added to the anesthetic gas mixture with special vaporizers. Haloethers possess good hypnotic but only poor analgesic and muscle-relaxing effects. Therefore, they are usually combined with nitrous oxide (see above), MOR agonists (see ▶ Chap. 10), and muscle relaxants (see ▶ Chap. 5) to induce optimal anesthesia. Depending on the concentration, haloethers induce loss of consciousness, respiratory depression, and suppression of reflexes. Postoperative ADRs of haloethers are nausea, vomiting, and increase of intracranial pressure. Therefore, haloethers should not be given to patients with known susceptibility to these incidents. Instead, total intravenous anesthesia (TIVA) should be performed.

Sevoflurane possesses a low blood/gas distribution coefficient. Therefore, controllability is very good. With a minimally effective alveolar concentration of 1.7%, sevoflurane is much more potent than nitrous oxide. It does not irritate mucosal membranes and is therefore suitable for induction of anesthesia. Because of its pleasant smell, sevoflurane is often used in pediatric anesthesia. It is metabolized to a small extent in the liver, but there is no known organ toxicity. Sevoflurane is a greenhouse gas with a residence time in the atmosphere of 1 year.

Desflurane is a standard inhalation anesthetic. It possesses a blood/gas distribution coefficient of 0.42. Thus, anesthesia with desflurane can be well controlled. Desflurane is less potent than sevoflurane and has a minimally effective alveolar concentration of 6%. In contrast to sevoflurane, desflurane irritates mucosal membranes and is therefore not suitable for induction of anesthesia. It can cause laryngo- and bronchospasm. Desflurane is barely metabolized. Accordingly, it can also be applied in patients with impaired liver function and affects the cardiovascular system only marginally. Because of its chemical stability, the residence time of desflurane in the atmosphere is very long (14 years).

Malignant hyperthermia (frequency 1:20,000) is a rare but life-threatening complication of haloethers. Most cases are due to mutations in the ryanodine receptor of the sarcoplasmic reticulum. Haloethers can induce massive calcium release from the sarcoplasmic reticulum causing muscular rigidity, rhabdomyolysis, hyperthermia, acidosis, hyperkalemia, kidney failure, activation of the sympathetic nervous system, and eventually shock and death. Upon onset of the first symptoms of malignant hyperthermia, administration of the causative drug must be terminated immediately. For maintenance of anesthesia, nitrous oxide, propofol, midazolam, MOR agonists, and non-depolarizing muscle relaxants can be used.

Dantrolene inhibits calcium release from the sarcoplasmic reticulum and must be immediately administered as antidote (see ▶ Chap. 4). In addition, controlled hypothermia and symptomatic correction of acidosis, hyperkalemia, as well as cardiovascular function must be implemented. Dantrolene must be available ready for i.v. injection during each inhalation anesthesia with a potential trigger. In the preoperation discussion, previous anesthetic accidents in the patient and in family members must be proactively addressed. Overall, the frequency of malignant hyperthermia is declining because problematic drugs such as the inhalation anesthetic halothane and the depolarizing muscle relaxant succinylcholine (see ▶ Chap. 5) are not used anymore or only rarely and because TIVA is available.

The noble gas xenon is chemically highly inert and possesses good anesthetic properties. Controllability is excellent, but the potency is low. Therefore, rather high xenon concentrations must be applied, increasing the risk of diffusion hypoxia. Apart from this issue, xenon does not possess any ADRs. The high costs of xenon due to its very low abundance in the earth atmosphere are the major disadvantage, but they could be mitigated by the routine use of closed anesthesia systems. A major advantage of xenon compared to nitrous oxide and haloethers is the lack of greenhouse burden.

27.3 Important Injection Anesthetics

A problem of inhalation anesthesia is the latency between the start of anesthetic gas inhalation and the onset of action. Moreover, certain gases such as desflurane are not suitable for induction of anesthesia, and a potentially dangerous excitatory stage must be avoided during the induction phase. Therefore, anesthesia is often induced with an injection anesthetic before onset of action of the inhalation anesthetic.

Thiopental is a barbiturate (see ▶ Chap. 25). It allosterically modulates the $GABA_AR$. This leads to hyperpolarization and inhibition of neuronal activity. Thiopental has sedative-hypnotic effects and is often used in anesthesia induction in otherwise healthy patients. It has no anxiolytic and no analgesic effects (rather hyperalgesic ones) and does not relax muscles. Thiopental is the drug of last resort in status epilepticus. In addition, it reduces the intracranial pressure. This effect is used in intracranial edema. Thiopental is very lipophilic and penetrates the BBB very rapidly so that loss of consciousness sets in within few seconds after injection.

Thiopental may lead to respiratory depression up to respiratory arrest. Due to its CAD properties, thiopental can activate mast cells with subsequent anaphylactic shock (see ▶ Chaps. 3 and 7). Since thiopental solutions are highly basic (pH > 10), accidental paravasal or intra-arterial injection can cause painful tissue necrosis.

After i.v. injection, thiopental is rapidly distributed from the blood into the CNS and later from the skeletal muscles and ultimately into the adipose tissue. In adipose tissue, thiopental accumulates after repeated or long-term administration (see ▶ Chap. 2). In the liver, it is converted to the active metabolite pentobarbital, causing additional prolongation of its effects. Long-term therapy with thiopental causes CYP induction, accelerating inactivation of barbiturates and other drugs (see ▶ Chap. 2).

Midazolam belongs to the benzodiazepines (see ▶ Chap. 25) and modulates the $GABA_AR$ allosterically like thiopental. Since the binding sites for thiopental and midazolam differ (see ▶ Chap. 25), the drugs possess different pharmacological effects. Midazolam has sedative-hypnotic, antiepileptic, anxiolytic, and muscle-relaxing, but no analgesic effects. It is frequently used in premedication and induction of anesthesia. Its anxiolytic effects are particularly valuable in anesthesia as well as in emergency and intensive care medicine. Midazolam can cause anterograde amnesia. On the one hand, this can be a desired effect (lack of memory of a surgical procedure), but on the other hand, it can be abused, e.g., for sexual acts. Because of the anterograde amnesia, it is mandatory that the physician administers midazolam in the presence of another person, e.g., an operating room nurse, to protect herself/himself against accusations from the patient.

Midazolam can be combined with other drugs such as MOR agonists. Its antiepileptic effect is used to terminate epileptic seizures. Midazolam can be applied p.o. and i.v. In higher doses, it may lead to respiratory depression that can be alleviated with the antidote flumazenil (see ▶ Chap. 4). Midazolam may cause psychological and physical addiction and withdrawal symptoms upon termination of drug administration.

Ketamine is a negative allosteric modulator at the NMDAR at which glutamate is the endogenous agonist. Ketamine causes a dissociative anesthesia, i.e., it has sedative-hypnotic and analgesic effects while preserving protective reflexes. This pharmacological profile can be applied for induction of anesthesia and as adjunct in spinal and epidural anesthesia. In emergency medicine, ketamine is predominantly used because of its analgesic effects that complement well with the effects of midazolam. Moreover, ketamine is of high importance in the treatment of chronic pain (see ▶ Chap. 10). In pediatric patients, ketamine is

mostly used without midazolam which can cause paradoxical agitation in children (see ▶ Chap. 25). Since ketamine also has bronchodilating effects, it can be given in combination with muscle relaxants for intubation in refractory epileptic status (see ▶ Chap. 14).

Ketamine can be administered p.o., sublingually, intranasally, i.m., and i.v. Following i.v. injection, analgesia and loss of consciousness set in rapidly and last for about 10 minutes. Thereafter, the analgesic effect is dominant and retrograde amnesia develops.

Since ketamine inhibits catecholamine reuptake into synapses, it may cause increases in BP and HF. Its stabilizing effect on circulation can be used in patients without accompanying cardiovascular diseases. However, the risk for MI increases in patients with CHD because of higher oxygen consumption. Ketamine also increases the IOP (see ▶ Chap. 31) and intracranial pressure. Therefore, it must not be administered in patients with eye and brain injuries. Nausea, vomiting, hypersalivation, visual disturbances, light-headedness, motor restlessness, and hallucinations (bad trips) are common ADRs. By combining ketamine with benzodiazepines, nightmares can be at least partially suppressed. Because of the hallucinogenic effects, ketamine possesses the potential for addiction.

Propofol is an allosteric $GABA_AR$ modulator and, in higher concentrations, a nAChR antagonist. It has sedative-hypnotic, but no analgesic, effects. Therefore, propofol is often combined with MOR agonists. It is poorly water-soluble and hence applied as an emulsion. Because of its lipophilicity, it penetrates the BBB rapidly. With propofol, the onset and termination of anesthesia are more pleasant than with other injection narcotics. It is used, for example, for induction or maintenance of TIVA and as adjunct medication during endoscopy. The controllability of propofol is very good, and the drug is well suited to conduct anesthesia in patients with risk for and with manifest malignant hyperthermia.

Nausea and vomiting are rare ADRs of propofol. Respiratory depression, decrease in BP, and anaphylactic shock (see ▶ Chaps. 3 and 7) may occur. Injection of propofol can be painful. It may induce dreams, often of sexual content, as well as euphoria, therefore possessing potential for predominantly psychological addiction.

27.4 Questions and Answers

Questions

Which statement on inhalation and injection narcotics is *NOT* correct?

A. Nitrous oxide is well suited as single drug for general anesthesia.
B. Sevoflurane does not irritate mucosal membranes.
C. Desflurane has a very rapid onset of action.
D. Ketamine causes dissociative anesthesia.
E. Propofol possesses low water solubility.

Answers

A. Nitrous oxide possesses a low anesthetic potency so that with this drug alone no sufficiently high concentrations for general anesthesia can be obtained. Nitrous oxide can be used in combination with oxygen to achieve good analgesia.
B. In contrast to other haloethers, sevoflurane does not irritate mucosal membranes. Therefore, it can also be used for induction of anesthesia.
C. Desflurane possesses a low blood/gas distribution coefficient and, accordingly, a rapid onset of action.
D. Dissociative anesthesia is a special property of ketamine. It induces unconsciousness and analgesia while preserving reflexes.
E. Because of its poor water solubility, propofol must be applied i.v. as an emulsion.

Statement **A** is not correct.

27.5 Exercises

A 49-year-old woman undergoes outpatient meniscectomy in the right knee. As requested by the patient, the procedure is performed in spinal anesthesia. After the surgery, which was performed without any complications, the patient complains that for the time in the operating room, she has no memory. She suspects that she has been sexually abused.

Questions

1. What happened to the patient?
2. How can the physician avoid problems related to anterograde amnesia?

Answers

1. Evidently, the patient suffered an anterograde amnesia. Most likely, the amnesia is due to midazolam which is a common component of anesthetic procedures.
2. It is crucial to inform the patient about the fact that following midazolam administration, anterograde amnesia can occur. In order to deal with accusations about assumed sexual abuse during anesthesia, it is essential that always a second person (e.g., operating room nurse) is present. Moreover, it is essential to document the preoperation discussion and obtain informed consent of the patient.

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Drugs for Treatment of Depression and Bipolar Disorder

R. Seifert, *Basic Knowledge of Pharmacology*, https://doi.org/10.1007/978-3-030-18899-3_28

Depression is a very common psychiatric disease caused by stress, early childhood psychotrauma, (epi)genetic factors, and personality characteristics. It is characterized by a functional NE and 5-HT deficit and impaired hippocampal neurogenesis. Therapy of depression comprises psychotherapeutic and pharmacological approaches. The goal of pharmacotherapy is normalization of the NT deficit with NE/5-HT enhancers comprising the NSMRIs, SSRIs, SSNRIs, α_2AR antagonists, and MAOIs. Between initiation of therapy and onset of clinical effects is a latency of several weeks during which the suicide risk is high. NE/5-HT enhancers have group-specific ADRs that can cause serious intoxications. Bipolar disorder is characterized by switches between depressive and manic phases. The alkali metal ion lithium and the NIPEs valproic acid and lamotrigine have mood-stabilizing effects. For successful therapy of depression and bipolar disorder, early diagnosis, early start of therapy, sufficient doses of drugs, and patient instruction are crucial. During the past decade, numerous new neuropsychiatric indications for NE/5-HT enhancers and lithium have emerged. Conversely, p-mGPCR antagonists, traditionally used in schizophrenia, are now increasingly used for the treatment of refractory depression and bipolar disorder.

Key Points

1. Stress, early childhood psychotrauma, (epi)genetic factors, and personality traits can cause depression.
2. Depression is characterized by a functional NE and 5-HT deficit.
3. As a consequence of the NT deficit, hippocampal neurogenesis is impaired.
4. High-dose GCR agonists can cause depression.
5. The NE/5-HT enhancers comprising the NSMRIs, SSRIs, SSNRIs, MAOIs, and α_2AR antagonists correct the NT deficit.
6. There is a latency between start of therapy and onset of clinical effects.
7. The delayed clinical effects are due to neurogenesis requiring a certain time.
8. NE/5-HT enhancers can cause life-threatening intoxications.
9. Combination of MAOIs with NSMRIs, SSRIs, SSNRIs, or α_2AR antagonists is dangerous.
10. Depression is initially treated with SSRIs, in the second stage with SSNRIs or α_2AR antagonists and in the third stage with NSMRIs.
11. MAOIs are drugs of last resort for refractory patients.
12. Lithium, valproic acid, and lamotrigine stabilize mood in bipolar disorder.
13. Numerous new indications for NE/5-HT enhancers have emerged. Therefore, the traditional term "antidepressants" should be avoided.
14. Some new indications for lithium have been established. Therefore, the traditional term "mood stabilizer" should be avoided.
15. p-mGPCR antagonists are now used more often in patients with refractory depression.

28.1 Pathophysiology of Depression and Pharmacotherapeutic Concepts

Depression is a common psychiatric disease with a life prevalence of about 10%. Women are affected twice as often as men. Depression causes economic problems and adversely affects relations of the patient with the partner, family, friends, and colleagues at work. The major symptoms of depression are:

1. Depressive mood
2. Loss of interest and anhedonia
3. Loss of motivation and excessive fatigability

Additional symptoms are:

1. Reduced ability to concentrate
2. Reduced self-confidence
3. Feeling of guilt
4. Sleep disorders
5. Loss of appetite
6. Motor inhibition or agitation
7. Suicidal thoughts and suicide attempts

Mild depression is characterized by two major and one or two additional symptoms, moderate depression by two major and two to four additional symptoms and severe depression by three major and five or more additional symptoms.

Therapy is performed symptomatically according to the severity of the disease. Table 28.1 provides an overview of selected NE/5-HT enhancers, comprising NSMRIs, SSRIs, SSNRIs, α_2AR antagonists, and MAOIs. They are predominantly used in moderate to severe depression. NE/5-HT enhancers are chosen according to their pharmacological profile in relation to the clinical symptoms. In the case of inefficacy after a 6–8 week treatment, the patient should be switched to

Table 28.1 Overview of selected drugs for treatment of depression and bipolar disorder

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
NE/5-HT enhancers					
Amitriptyline	NSMRI	Mood enhancing, sedative	Moderate to severe depression (level 3), anxiety disorders, migraine prophylaxis, neuropathic pain, nocturnal enuresis	ADRs result from the increased NE and 5-HT concentrations in the synaptic cleft, antimuscarinic syndrome, orthostatic hypotension	1, 4, 5, 13, 31
Citalopram	SSRI	Mainly mood lifting	Moderate depression (level 1), anxiety disorders, obsessive-compulsive disorders, panic disorders, phobia, post-traumatic stress disorder, phobia, adjunct therapy for schizophrenia	ADRs result from the increased 5-HT concentration in the synaptic cleft; serotonin syndrome with overdose or when combined with MAOIs	1, 6, 29
Imipramine	NSMRI	Mood-enhancing, motivating, and sedative effects are balanced	Moderate to severe depression (level 3), co-analgesic for severe pain (e.g., tumor pain)	See amitriptyline	4, 5, 13, 31
Mirtazapine	α_2AR antagonist	Mood enhancing and motivating	Moderate to severe depression (level 2), anxiety disorders, obsessive-compulsive disorders, panic disorders, phobia, adjunct therapy for schizophrenia	ADRs result from the increased NE concentration in the synaptic cleft	5, 6, 29
Moclobemide	Reversible MAO-A inhibitor	Highly mood enhancing and motivating	Refractory depression (level 4), refractory anxiety, and panic disorders	ADRs result from the increased NE and 5-HT concentrations in the synaptic cleft; serotonin syndrome when combined with NSMRIs, SSRIs, and SSNRIs	5, 6

(continued)

Table 28.1 (continued)

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Tranylcypromine	Irreversible MAO-A/B inhibitor	Highly mood lifting and motivating	Refractory depression (level 4), refractory anxiety, and panic disorders	ADRs result from the increased NE and 5-HT concentrations in the synaptic cleft; serotonin syndrome when combined with NSMRIs, SSRIs, and SSNRIs; life-threatening hypertension when combined with tyramine-containing food	5, 6
Venlafaxine	SSNRI	Mood lifting and activating	Moderate to severe depression (level 2), polyneuropathies, anxiety disorders, obsessive-compulsive disorders, panic disorders, phobia, adjunct therapy for schizophrenia	ADRs result from the increased NE and 5-HT concentrations in the synaptic cleft	5
Alkali metal ions					
Lithium	Unknown (pleiotropic modulation of signal transduction cascades)	Mood stabilizing	Therapy and prophylaxis of bipolar disorder (effective against depression and mania), reduction of suicide risk, augmentation in treatment of depression	Lithium affects many organ systems (cardiovascular system, CNS, kidney, thyroid gland); TDM is required because of low therapeutic index. Teratogenicity, but, if indicated, treatment should be continued during pregnancy	4, 12, 21
NIPEs					
Lamotrigine	Inhibition of glutamate release by SCB	Mood stabilizing also antiepileptic effects	Prophylaxis of recurrent depressions, neuropathic pain, various types of epilepsies, borderline personality disorder, post-traumatic stress disorder, cluster headache, migraine prophylaxis	Sedation, vertigo, double vision, ataxia	6, 25, 29

(continued)

Table 28.1 (continued)

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Valproic acid	SCB, inhibition of GABA degradation, inhibition of histone deacetylase	Mood stabilizing also antiepileptic effects	Prophylaxis of recurring manic phases, migraine prophylaxis, various types of epilepsies, schizophrenia	Sedation, vertigo, double vision, ataxia, tremor, teratogenic effects (strict indication criteria in pregnancy)	6, 25, 29
p-mGPCR antagonists (non-NSMRIs)					
Trimipramine	α_xAR, H_xR, M_xR, D_xR, and 5-HT_xR antagonism	Highly sedative (hypnotic) and anxiolytic	Mainly anxious-agitated depression, schizophrenia	Antimuscarinic syndrome, orthostatic hypotension; antiadrenergic effects, antiserotonergic and antidopaminergic effects	1, 5, 6, 7, 8, 29

ADRs as a consequence of increased NE concentration in the synaptic cleft: BP and HR increase, agitation, tremor, and loss of appetite. ADRs as a consequence of increased 5-HT concentration in the synaptic cleft: nausea, vomiting, headache, weight loss, and sexual dysfunction. These ADRs are particularly prominent during the early phase of pharmacotherapy. Other mGPCR antagonists for treatment of acute mania and refractory depression are discussed in ► Chap. 29

another drug. Suicidal patients must be admitted to a psychiatric hospital and never be handed economy-sized packs of NE/5-HT enhancers.

The clinical efficacy of NE/5-HT enhancers is a subject of controversial discussion. A bias leading to preferential publication of clinical studies with positive outcome, sponsoring of studies by drug companies, and lack of studies without conflict of financial interest are justified points of critique. In addition, the placebo effect (see ► Chap. 1) is very relevant in the treatment of depression. A current meta-analysis states that 20–40% of placebo-treated and 40–60% of depressive patients treated with NE/5-HT enhancers show an improvement after 6–8 weeks. These data show that altogether NE/5-HT enhancers exhibit moderate clinical efficacy. However, additional drug company-independent high-quality clinical studies are required to draw a definitive conclusion regarding the efficacy of NE/5-HT enhancers. A problem in the determination of the efficacy is the possibility that the clinical diagnosis "depression" includes a number of molecularly distinct disease entities that exhibit differential accessibility to NE/5-HT enhancers. Accordingly, a molecular diagnosis of depression would be highly desirable and allow the development of targeted therapeutics in analogy to the therapy of tumor diseases (see ► Chap. 32).

As a result of a patient-specific combination of (epi)genetic factors, psychosocial stress (early childhood development, life events, daily stress), and personality traits, an as yet incompletely understood pathophysiological mechanism leads to a functional deficit of the NTs NE and 5-HT (Fig. 28.1). The NE deficit results in loss of motor activity, motivation, interest, and ability to concentrate (see ► Chap. 5), while the 5-HT deficit predominantly causes depressive mood (see ► Chap. 6). Both deficits in conjunction lead to difficulties to cope with daily stress, anxiety, and sleep disorders. Stress vulnerability results in activation of the neuroendocrine system with an elevated plasma cortisol concentration.

A permanently increased cortisol concentration is deleterious and leads to neuronal apoptosis in the hippocampus. In parallel, neuro- and synaptogenesis are impaired. For this reason,

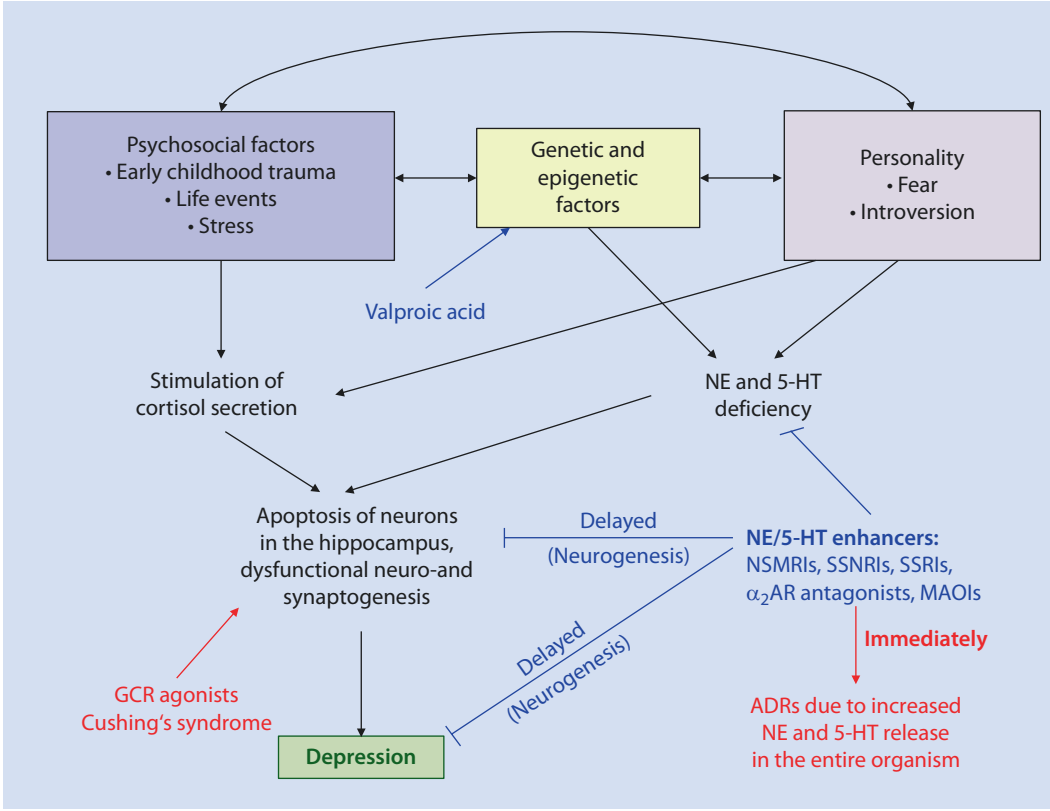


Fig. 28.1 Pathophysiology of depression and pharmacological interventions. It should be noted that this scheme does not explain the effects of p-mGPCR antagonists in depression. Based on the efficacy of drugs, it also appears that several psychiatric diseases including anxiety disorders, obsessive-compulsive disorders, and schizophrenia possess an at least partially similar pathophysiology as depression

many patients treated with GCR agonists in high doses because of a tumor, autoimmune disease, or organ transplantation suffer from depression (see ▶ Chaps. 11 and 32). In addition, HCV patients treated with peginterferon α-2a (see ▶ Chap. 34) and patients with endogenously increased cortisol production (Cushing's syndrome) may be depressive as well.

An intact hippocampus is essential for a balanced mood and normal motivation. An insufficiently treated depression can result in serious hippocampal damage. Therefore, early diagnosis and rapid initiation of treatment are keys to successful management of depression. Pharmacological and psychotherapeutic measures complement each other. Light therapy, sports and autogenic training, and, in serious cases, deep brain stimulation and electroconvulsive therapy (ECT) are effective as well. Most likely, the ECT also works via increased NE and 5-HT release, but this treatment has, unjustifiably, a bad reputation.

The latency between the start of therapy and the onset of clinical efficacy constitutes a major problem in the management of depression with NE/5-HT enhancers, NIPEs, and lithium (see ▶ Sects. 28.2, 28.3, 28.4, 28.5, 28.6, and 28.7). In this period, which may take several weeks, patients often suffer from serious ADRs. In addition, the suicide risk is increased because motivation normalizes before the depressive mood improves. Initially, a long-term therapy with NE/5-HT enhancers can be supported with a short-term course of benzodiazepines (see ▶ Chap. 25) to reduce the suicide risk. Long-term treatment with benzodiazepines is not an option because it leads to tolerance and addiction.

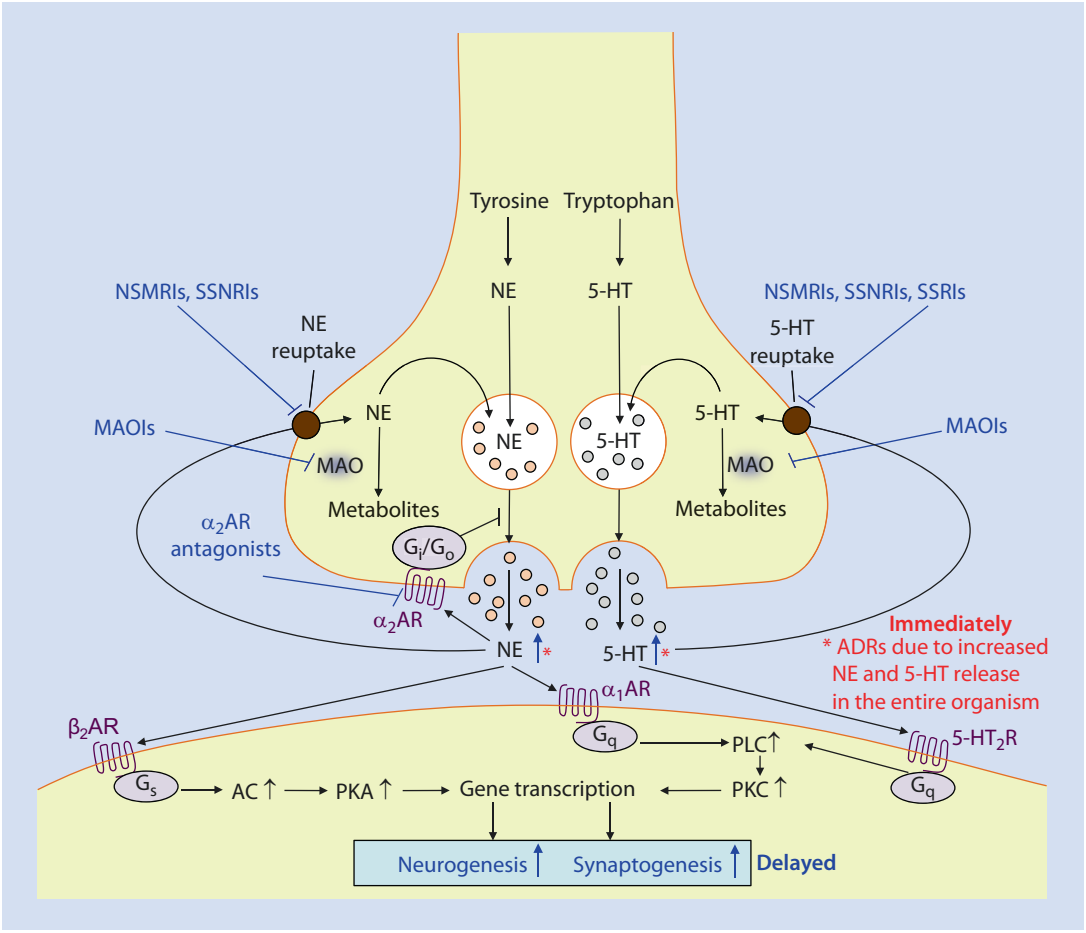
Particularly at the beginning of a therapy with NE/5-HT enhancers, patients must be closely guided by the physician and supported with psychotherapeutic measures. The dose of NE/5-HT enhancers should be increased gradually at the beginning and decreased gradually at the end of a

therapy. The minimum therapy length is about three months. If a drug therapy is terminated abruptly, the symptoms of depression can flare up.

Because of the delayed effect onset of NE/5-HT enhancers, intense efforts are directed toward the development of drugs with an immediate clinical effect. One approach is to exploit allosteric NMDAR antagonism of the injection anesthetic ketamine (see ▶ Chap. 27) in low doses. An enantiomer of ketamine has been approved as nasal spray for the acute treatment of depression in the USA, and this treatment has become very popular within a short period of time. However, ketamine is not available globally, and it has serious ADRs and addiction potential (see ▶ Chap. 27).

Traumatic events during childhood can lead to epigenetic changes such as reduced histone acetylation, resulting in impaired neurogenesis and synaptogenesis. Accordingly, these processes could be stimulated with histone deacetylase inhibitors. Valproic acid exhibits such effect (see ▶ Sect. 28.7). As an alternative approach, antagonism at the GCR is exploited. The hormone oxytocin improves social behavior and reduces anxiety. These therapeutic approaches are currently under clinical investigation. The development of new drugs for depression is difficult because animal models possess only limited validity.

The cause for the latency between start of a therapy with NE/5-HT enhancers and onset of clinical effects is that first neuro- and synaptogenesis have to take place via activation of postsynaptic α_xARs, β_xARs, and 5-HT$_x$Rs (◘ Figs. 28.1 and 28.2). This is a process lasting several weeks. The patient has to be adequately educated about that lag phase to ensure adherence and about ADRs. In contrast need time! You must explain to your patient that there is a lag time between the start of therapy with NE/5-HT enhancers and onset on clinical effects



◘ **Fig. 28.2** Targets of NE/5-HT enhancers in the noradrenergic and serotoninergic synapse. See also ◘ Figs. 5.4 and 6.1. Neurogenesis and synaptogenesis

to benzodiazepines, NE/5-HT enhancers do not cause addiction (see ▶ Chap. 25) and usually do not require a dose increase during long-term therapy. Symptoms occurring after abrupt termination of therapy with NE/5-HT enhancers are often a reflection of the reoccurring depression. Therefore, such therapy should be terminated gradually.

28.2 NSMRIs

NSMRIs act at the noradrenergic and serotonergic synapse (Fig. 28.2). They inhibit neuronal re-uptake of NE and 5-HT from the synaptic cleft into the presynaptic neuron. Via this mechanism, the synaptic concentration of both NTs is increased immediately. This explains the instantaneously occurring ADRs: NE mediates an increase in BP and HF, loss of appetite, restlessness, and tremor; 5-HT causes nausea, vomiting, sleep disorders, headache, weight loss, and sexual dysfunction. These ADRs are unpleasant for the patient, particularly in view of the fact that the therapeutic effects set in only after several weeks.

Figure 28.3 shows the pharmacological profile of selected NE/5-HT enhancers. The inhibition curves of drugs for various targets are depicted. The more potently a drug binds to its pharmacological target, the lower is the drug dose required to elicit a clinical effect. The NSMRI amitriptyline is a very potent H_1R antagonist (see ▶ Chap. 1). Therefore, the drug causes sedation already in very low doses (see ▶ Chap. 7). This effect can be exploited in agitated patients. In higher doses neuronal re-uptake of NE and 5-HT is inhibited, mediating the long-term improvement of mood. The H_1R antagonism of amitriptyline largely compensates the stimulatory effect on motivation mediated via inhibition of NE re-uptake. Long-term H_1R antagonism is also associated with increased appetite leading to obesity (see ▶ Chaps. 7 and 29). Imipramine has a mood-lifting effect, too, does not sedate patients, and increases motivation more effectively than amitriptyline.

In clinically relevant doses, NSMRIs also antagonize M_xRs and α_1AR, resulting in ADRs. Because of these effects, the drugs are referred to

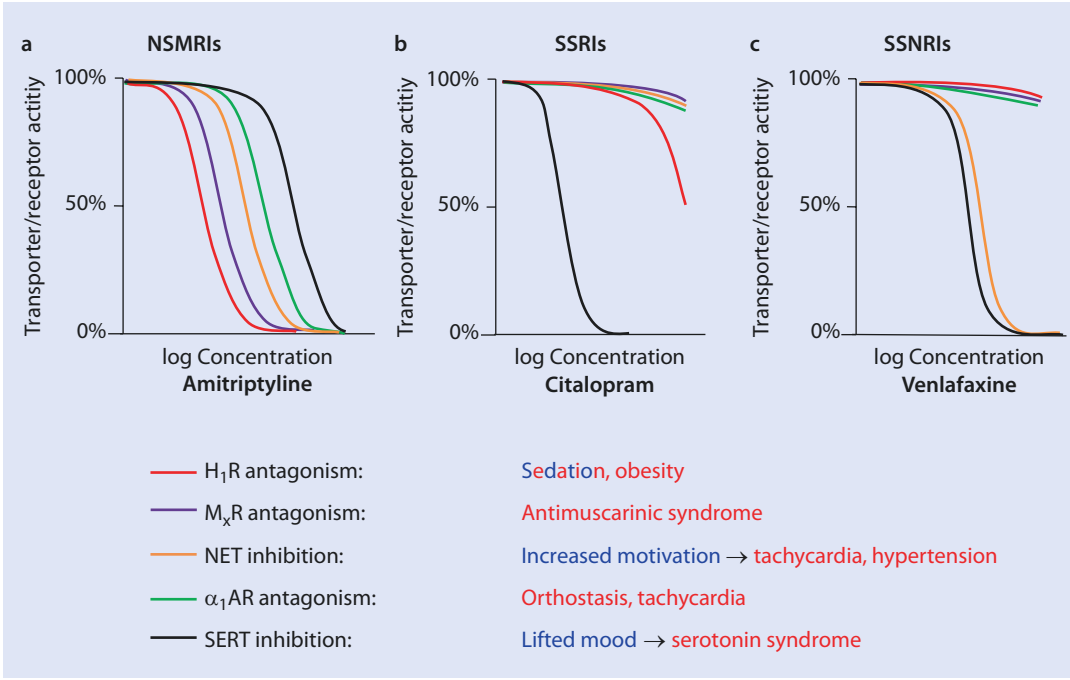


Fig. 28.3 Pharmacological profiles of selected NE/5-HT enhancers. **a** Amitriptyline. **b** Citalopram. **c** Venlafaxine. See also Table 29.1. These drugs can be used in multiple psychiatric indications including anxiety disorders and obsessive-compulsive disorders. This figure shows how useful knowledge of basic pharmacological principles is to explain clinical effects of drugs! If you do not understand the connection between inhibitory potencies of drugs for the various targets and clinical effects, go back to ▶ Chap. 1

as *nonselective* monoamine re-uptake inhibitors. M_xR antagonism leads to an antimuscarinic syndrome (see ▶ Chap. 5). α_1AR antagonism mediates a decrease in BP and orthostatic hypotension with reflex tachycardia that is aggravated by M_xR antagonism. During long-term therapy, these effects often become smaller and the therapeutic effects dominate. However, serious intoxications can develop as a result of NSMRI overdosing (see ▶ Chap. 4). Due to their lipophilicity, high plasma protein binding, large distribution volume, and long plasma half-life, NSMRIs cannot be eliminated with dialysis or forced diuresis.

Compared to SSRIs, NSMRIs possess a higher clinical efficacy, but because of their ADRs, they are usually prescribed only in the third stage after SSRIs (stage 1) and SSNRIs or α_2AR antagonists (stage 2). Prescription of NSMRIs should be reserved for the psychiatrist.

28.3 SSRIs

The undesired M_xR and α_xAR antagonism of NSMRIs resulted in the development of NE/5-HT enhancers devoid of these ADRs. SSRIs inhibit 5-HT re-uptake with high potency, but not NE re-uptake, and do not antagonize M_xRs, α_1AR, and H_1R (◘ Fig. 28.3). This pharmacological profile explains the term *selective* 5-HT re-uptake inhibitor. Sertraline and citalopram are prototypical SSRIs. Because of the missing effect on NE re-uptake, they have a mood-lifting effect but do not increase motivation. According to the mechanism of action, typical ADRs of SSRIs are due to an excess of 5-HT in the CNS manifesting themselves as nausea, vomiting, sleep disorders, weight loss, and sexual dysfunction. Globally, SSRIs are the most widely used NE/5-HT enhancers. They can be prescribed more readily by general practitioners in order to overcome the initial barrier of patients with depression to seek professional help. However, SSRIs possess a lower clinical efficacy than NSMRIs.

In addition, their toxicity should not be underestimated. Accidental or suicidal ingestion of large amounts of SSRIs causes a life-threatening serotonin syndrome that can only be treated symptomatically (see ▶ Chaps. 4 and 6). SSRIs should be used cautiously in adolescents. The suicide risk in this patient group is high and requires close supervision by the physician and psychotherapeutic measures.

28.4 SSNRIs

By analogy to SSRIs, selective NE re-uptake inhibitors (SNRIs) exist. Reboxetine is a prototype. However, the clinical efficacy of these drugs is insufficient. Based on the principle of SSRIs and SNRIs, dually selective 5-HT/NE re-uptake inhibitors (SSNRIs) were developed. Duloxetine and venlafaxine are prototypes of this drug class. In contrast to NSMRIs, SSNRIs do not possess antagonistic effects at M_xRs and α_1AR (◘ Fig. 28.3). Accordingly, the ADRs of these drugs are essentially due to the elevated NE and 5-HT concentration in the synaptic cleft.

Many patients assume that plant-derived drugs are safe because of their natural origin. However, this is not necessarily the case. Extracts from St. John's wort (*Hypericum perforatum*) used for the treatment of depression are a good example for this misconception. The pharmacologically active constituent of St. John's wort is hyperforin, which inhibits NE and 5-HT re-uptake. It also stimulates CYP3A4 expression via the pregnane X receptor. This process accelerates elimination of ciclosporin, VKAs, and oral contraceptives (see ▶ Chaps. 11, 18, and 24) and reduces their effects.

28.5 α_2AR Antagonists

NE release in the synapse is regulated by a negative feedback mechanism (see ▶ Chap. 5). Specifically, NE inhibits its neuronal release via the α_2AR (◘ Fig. 28.2). This effect is mediated via G_i/G_o proteins with subsequent inhibition of calcium channels and activation of potassium channels. α_2AR antagonists eliminate this feedback and, thereby, increase NE release indirectly, resulting in long-term stimulation of hippocampal neuro- and synaptogenesis. Mirtazapine is a prototypical α_2AR antagonist. It is mood-lifting and improves motivation. ADRs are the result of increased NE release (agitation, increase in BP and HF), but often they are only transient. α_2AR antagonists are used in the second stage of pharmacotherapy of depression.

28.6 Monoamine Oxidase Inhibitors (MAOIs)

There are severe cases of depression in which SSRIs, SSNRIs, α_2AR antagonists, and NSMRIs are ineffective. In these refractory cases, MAOIs can be administered. They inhibit degradation of NE and 5-HT, thereby increasing the concentration of both NTs in the synaptic cleft. MAOIs have prominent mood-lifting effects and they strongly improve motivation.

MAO exists in two isoforms, i.e., MAO-A and MAO-B. MAO-A is predominantly responsible for degradation of NE and 5-HT and MAO-B especially for DA degradation (see ▶ Chap. 8). In severe depression, the dual and irreversibly acting MAO-A and MAO-B inhibitor tranylcypromine is used. The reversible MAO-A inhibitor moclobemide is an alternative.

MAOIs must not be combined with other NSMRIs, SSRIs, and SSNRIs because a life-threatening serotonin syndrome can develop (see ▶ Chap. 6). Another peculiarity of MAOIs is the dangerous interaction with indirect sympathomimetic drugs (see ▶ Chap. 5). If a patient treated with a MAOI eats food containing tyramine such as cheese, nuts, or chocolate or drinks red wine, the NE released by tyramine is not degraded anymore, and life-threatening hypertensive emergencies can occur. Therefore, patients treated with MAOIs must not consume tyramine-containing food or drinks. Because of the risks, prescription of MAOIs belongs into the hands of the psychiatrist.

28.7 Pathophysiology of Bipolar Disorder

Bipolar disorder is characterized by excessive fluctuations of mood, motivation, and activity going far beyond normal variability. These fluctuations manifest themselves in either depressive or manic phases (◘ Fig. 28.4). Bipolar disorder is frequent; about 3–4% of the population are affected by the disease at least once in life. It causes massive economic and social damage. The high suicidality during depressive phases is a serious problem. Manic phases are characterized by lack of self-criticism, loss of sense of reality, megalomania, reduced need of sleep, urge to talk, flight of ideas, distraction, and risky behaviors, ultimately rendering the patients into big personal, social, and financial problems. Bipolar disorder is divided into two forms. Hypomania is often characterized by creativity. In many cases, bipolar disorder is diagnosed only with a latency of many years. Often, patients lack insight into the illness. This renders initiation of pharmacotherapy impossible until a catastrophic event due to the disease happens.

The pathogenesis of bipolar disorder is incompletely understood so that only symptomatic treatment is possible. Genetic, social, anatomical, and biochemical factors as well as abuse of illicit drugs contribute to pathogenesis. The function of several NTs and downstream signaling mechanism is altered. Excessive activity of G_q-PLC-coupled GPCRs and reduced neuronal plasticity with increased apoptosis of neurons in the prefrontal cortex may be involved in the pathogenesis. Hyperthyroidism can deteriorate bipolar disorder (see ▶ Chap. 21).

In acute mania, mGPCR antagonists (see ▶ Chap. 29) as well as valproic acid (see ▶ Chap. 25) are effective. mGPCR antagonists are effective against agitation and hallucinations. Differentiation between mania and schizophrenia is sometimes difficult, but therapeutic measures are similar anyway.

28.8 Lithium and NIPEs

As soon as acute mania subsides, recurrence prevention with the alkali metal ion lithium or a NIPE must be implemented. Bipolar disorder with rapid or very rapid phase transitions can be particularly well improved with these drugs. NIPEs inhibit activity of pathologically active neurons with a certain selectivity (see ▶ Chap. 25). This effect can be exploited in bipolar disorder. Valproic acid has a predominant prophylactic effect on the occurrence of manic phases, whereas lamotrigine preferentially prevents depressive phases. Lithium reduces occurrence of both manic and depressive phases and lowers suicide risk. Another advantage is that therapy with lithium is inexpensive so that long-term therapy of patients even in countries with little financial resources can be performed.

Patients with bipolar disorder must never be handed economy-sized packs of NE/5-HT enhancers, mGPCR antagonists, NIPEs, and

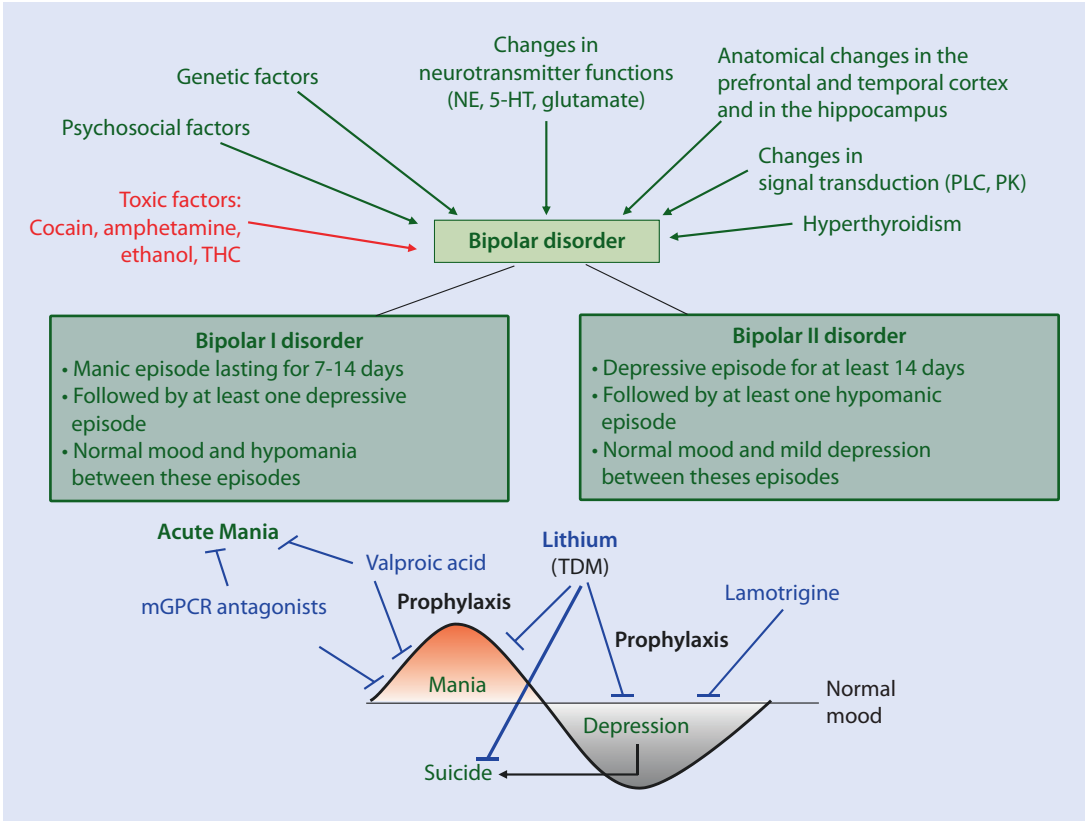


Fig. 28.4 Pathophysiology of bipolar disorder and pharmacological interventions. NIPEs are discussed in ▶ Chap. 25, and mGPCR antagonists are discussed in ▶ Chap. 29. Because of the preventive effect of lithium on suicidality, it is used despite its small therapeutic index

lithium to avoid suicide attempts. The patient has to be admitted to a psychiatric hospital if suicide is imminent. In severe depression, lithium can be combined with NE/5-HT enhancers (lithium augmentation).

The mechanism of action of lithium is unknown. Its clinical effects become apparent after a latency period of about 2 weeks. One hypothesis states that lithium impedes recycling of inositol by inhibiting a phosphatase so that less substrate is available for PLC and the activity of G_q-PLC-coupled GPCRs is reduced. Another hypothesis assumes that lithium inhibits the activity of a protein kinase involved in neuronal apoptosis. Most likely lithium possesses a pleiotropic mechanism of action.

Lithium has a small therapeutic index (see ▶ Chap. 1), requiring TDM. Therapeutic plasma lithium concentrations range between 0.5 and 1.0 mmol/l. Lithium shows a similar distribution in the body as sodium. However, it possesses a lower affinity to ion pumps than sodium so that it accumulates intracellularly and is eliminated more slowly via the kidney. The plasma half-life of lithium is 24 hours. Because of its distribution in the entire organism, lithium possesses many ADRs including tremor, slurred speech, confusion, epileptic seizures, arrhythmias, hypotension, polydipsia, thirst, polyuria, weight gain, edema, and hypothyroidism (see ▶ Chap. 21). Lithium can be readily eliminated from the organism via dialysis in case of intoxication (see ▶ Chap. 4). It is contraindicated in CHF and MI (see ▶ Chap. 16) and CKD (see ▶ Chap. 12). Renal lithium elimination is retarded by RAAS inhibitors (see ▶ Chaps. 15 and 16), COX inhibitors (see ▶ Chaps. 10 and 11), and diuretics (see ▶ Chap. 12). A diet poor in sodium reduces and a sodium-rich diet increases renal lithium elimination. A stable social environment improves adherence and the success of a lithium therapy.

28.9 Nontraditional Indications of NE/5-HT Enhancers and Lithium

Although depression is the most common psychiatric disease globally, there are many other psychiatric diseases for which no pharmacotherapy has been available. Among these diseases are anxiety disorders, obsessive-compulsive disorders, panic disorders, and post-traumatic stress disorder. The latter disease is particularly prevalent in soldiers and war victims. The clinical symptoms observed in these diseases overlap, in part, with certain symptoms found in patients with depression (see ▶ Sect. 28.1). The high medical need of pharmacotherapies for these diseases together with the overlap in symptoms with depression initiated empirical testing of NE/5-HT enhancers, initially as off-label treatment, for these conditions. In fact, several drugs are effective in these conditions, but there is a lot of trial and error in finding the best treatment for any given patient with a specific disease (see ▶ Chap. 1 and ◘ Table 1.4).

A major obstacle for a more rational use of NE/5-HT enhancers in the abovementioned diseases is that our knowledge about their pathophysiology is very poor. However, the at least partial success of NE/5-HT enhancers in psychiatric diseases beyond depression indicates that there is also at least a partial overlap in pathophysiological changes (see ◘ Figs. 28.1 and 28.2). By analogy to depression, MAOIs are used in refractory cases of anxiety and panic disorders (see ▶ Chap. 1 and ◘ Table 1.4).

The partial success of NE/5-HT enhancers in various psychiatric diseases with high medical need stimulated further exploratory testing of these drugs in other diseases with few or no treatment option. In fact, it turned out that these drugs are, to different degrees and in a drug- and patient-specific manner, effective in various debilitating diseases including polyneuropathies and migraine (prophylaxis, not acute attack) (see ▶ Chap. 1 and ◘ Table 1.4). The pathophysiology of these diseases is also poorly understood. With respect to clinical symptoms, there is little overlap between polyneuropathies and migraine on the one hand and depression, anxiety, and panic disorders on the other hand. Thus, it appears that neurons respond to different types of "stress" and "damage" in a relatively uniform manner, the different clinical symptoms reflecting different localization of the "stress" and "damage" in the CNS. In aggregate, empirical testing of NE/5-HT enhancers in various neuropsychiatric conditions has shed some light on their underlying pathophysiological mechanisms. This knowledge may guide the development of more efficacious drugs with larger therapeutic index.

Along the same line, the use of lithium is expanding beyond bipolar disorder. Since the efficacy of pharmacotherapy of depression is unsatisfying in many cases, various pharmacotherapeutic strategies were tested empirically. Since the MAOIs are problematic drugs for refractory depression (see ▶ Chaps. 5 and 6 and ▶ Sect. 28.6), it was attempted to combine other NE/5-HT enhancers with lithium, and this strategy works in at least some patients. This therapy is referred to as lithium augmentation. The efficacy of lithium in depression prompted its use in schizophrenia, and, again, the drug turned out to be effective in some patients. AD is another disease with high medical need for an effective pharmacotherapy (see ▶ Chap. 30). Accordingly, efforts are underway to examine the use of lithium in AD and other neurodegenerative diseases as neuroprotective drug. However, these studies are too premature to allow for a definitive conclusion. It should be kept in mind that in pharmacotherapy of psychiatric diseases, often "soft" parameters such as improved mood and improved behavior are measured, but these parameters are hard to quantify.

28.10 Treatment of Depression with p-mGPCR Antagonists

Treatment of depression with p-mGPCR antagonists started from an unexpected observation: The NSMRIs, amitriptyline and imipramine, are well-established and reasonably effective drugs in moderate to severe depression (see ◘ Figs. 28.1, 28.2, and 28.3). It turned out that trimipramine, structurally very closely related to imipramine, is also an effective antidepressant but only a low-potency inhibitor of NET and SERT. Thus, trimipramine is not a classic NE/5-HT enhancer. Instead, trimipramine is a potent antagonist at D_xRs,

5-HT$_x$Rs, and H$_1$R (see ▶ Chaps. 5, 6, 7, and 8). Therefore, it has been designated as non-NSMRI (see ◘ Table 1.4). But this is a negative definition of a drug class. Trimipramine actually belongs to the class of p-mGPCR antagonists, predominantly used in schizophrenia (see ▶ Chap. 29). Via H$_1$R antagonism, trimipramine exerts a sedative effect. It is also anxiolytic. Because of this effect, trimipramine is often used in depressive patients with anxiety and agitation. It additionally exhibits antagonism at α_xARs and M$_x$Rs, explaining ADRs (see ▶ Chap. 5). As expected from its pharmacological properties as p-mGPCR antagonist, trimipramine possesses also antipsychotic effects.

The serendipitous identification of the p-mGPCR antagonist trimipramine as an antidepressant drug came as a surprise and does not readily fit into established pathophysiological concepts of depression outlined in ▶ Sects. 28.1, 28.2, 28.3, 28.4, 28.5, and 28.6 and illustrated in ◘ Figs. 28.1 and 28.2. However, based on the limited efficacy of NE/5-HT enhancers in depression, it is also clear that the pathophysiological concepts of depression are too simplistic and, again, pharmacology aided the development of new disease concepts. Based on the efficacy of trimipramine in depression, it became evident that there must be some overlap in the pathophysiology of depression and schizophrenia at the molecular level. With respect to clinical symptoms, quite often mixed forms of depression and schizophrenia are observed. These observations were the starting point for very broad clinical testing of numerous p-mGPCR antagonists in refractory depression and mixed forms of depression and schizophrenia. In some patients with refractory depression, NE/5-HT enhancers and mGPCR antagonists are combined, with mixed results. From a pharmacological perspective, such a drug combination is problematic because the enhanced release of NE and 5-HT is, at least in part, antagonized by the p-mGPCR antagonist. Some depressive patients are also treated with D$_2$R-mGPCR antagonists.

Overall, the clinical data on the use of p-mGPCR antagonists in depression are very heterogeneous, and as with many other psychiatric diseases, a lot of trial and error testing has to be performed until a suitable p-mGPCR antagonist for a depressive patient has been identified. These recent clinical developments highlight the importance of abandoning the traditional terms "antidepressants" and "antipsychotics" to avoid confusion. There is too much overlap in the indications of these drugs. A mechanistic and neutral classification of drugs renders it much easier to prescribe drugs to patients without placing the stigma of "depression" or "schizophrenia" on them. In this regard, neutral names for drug classes increase adherence to pharmacotherapy.

28.11 Questions and Answers

Questions

Which statement on SSRIs is correct?

A. SSRIs exhibit ADRs predominantly during later stages of therapy.
B. In severe depression, the combination of a SSRI + MAOI is the last resort.
C. SSRIs are more effective in depression than NSMRIs.
D. SSRIs can promote synaptogenesis in the hippocampus.
E. SSRIs inhibit 5-HT re-uptake in parallel with the therapeutic effects.

Answers

A. SSRIs exhibit ADRs such as nausea, vomiting, sleep disorders, and headache predominantly at the beginning of the therapy.
B. The combination of a SSRI + MAOI is contraindicated and can cause a life-threatening serotonin syndrome.
C. NSMRIs possess a higher clinical efficacy than SSRIs.
D. Synaptogenesis constitutes a major therapeutic effect of SSRIs.
E. Formation of new synapses does not occur until several weeks after start of therapy. This explains the delayed onset of action of NE/5-HT enhancers. The phase between start of therapy and onset of clinical effects is dangerous because increased motivation in parallel with not yet elevated mood can activate suicidal tendencies.

Answer **D** is correct.

28.12 Exercises

As an emergency physician you are called to a 38-year-old female patient who attempted to commit suicide. The patient has the following symptoms: somnolence, tachycardia, BP 100/60 mm Hg, mydriasis, hot and dry skin, lack of intestinal sounds, and large bladder upon palpation. In the vicinity of the patient, you do not find any tablets or empty blisters that could provide hints for the cause of the clinical symptoms.

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Questions

1. What is the most likely cause of the symptoms, how do you confirm your suspected diagnosis, and what are your immediate therapeutic measures?
2. How can you avoid suicide attempts in the patient in the future?

Answers

1. It is not uncommon that patients after start of a therapy with NE/5-HT enhancers, deterioration of depression, or insufficient drug therapy commit suicide attempts with the prescribed drugs. The patient shows symptoms that are caused by H_1R antagonism (sedation), α_1AR antagonism (hypotension and reflex tachycardia), as well as M_xR antagonism (tachycardia, mydriasis, hot and dry skin, lack of intestinal sounds, large bladder). These symptoms suggest that the patient has taken an overdose of the NSMRI amitriptyline. You can attempt primary poison elimination (gastric lavage in intubation anesthesia and application of activated charcoal) or secondary poison elimination (only application of activated charcoal or additional plasmapheresis). Tablet remainders, blood, and urine are tested for the presence of amitriptyline. An elevated plasma amitriptyline concentration confirms the diagnosis. It is also important to balance water and electrolytes properly.
2. It is crucial that the physician stays in regular and close contact with the patient to recognize suicidal tendencies as early as possible. All suicidal thoughts have to be taken seriously. In case of imminent suicide, the patient must be admitted to a psychiatric hospital. It has also to be evaluated whether the drug dose is sufficient or needs to be increased. In outpatient management it is important to integrate family members into the therapeutic concept. It is crucial that the patient does not have uncontrolled access to NE/5-HT enhancers. Tablets should be taken under supervision. Prescription of economy-sized tablet packages must be strictly avoided in suicidal patients.

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Drugs for Treatment of Schizophrenia

R. Seifert, *Basic Knowledge of Pharmacology*, https://doi.org/10.1007/978-3-030-18899-3_29

Schizophrenia is a psychiatric disease with a global prevalence of 1%. Often, the disease manifests itself in early adulthood. Severe positive and particularly negative symptoms render it very difficult for the patient to cope with the demands of daily life and to keep the relation to reality. Schizophrenia is characterized by an imbalance in neuronal activity, particularly overactivity of the dopaminergic and serotonergic system. D_2R-mGPCR antagonists predominantly antagonize the D_2R, and p-mGPCR antagonists antagonize several GPCRs including the D_4R and 5-HT_{2A}R. D_2R-mGPCR antagonists preferentially improve positive symptoms, p-mGPCR antagonists also negative symptoms. Thanks to mGPCR antagonists, nowadays many more schizophrenics can be treated as outpatients than previously. D_2R-mGPCR antagonists predominantly cause EPSs; p-mGPCR antagonists especially lead to metabolic syndrome. mGPCR antagonists are chosen on an individual basis and aim at obtaining an optimal balance between antipsychotic effects and few ADRs with high adherence and good quality of life. During the past decade, numerous new neuropsychiatric indications for mGPCR antagonists have emerged. Conversely, NE/5-HT enhancers, lithium, and NIPEs, traditionally used in depression and bipolar disorder, are now increasingly used for the treatment of refractory schizophrenia.

Key Points

1. Schizophrenia is characterized by excessive activity of the dopaminergic and serotonergic system.
2. mGPCR antagonists have antipsychotic effects and are classified into D_2R-mGPCR antagonists and p-mGPCR antagonists.
3. D_2R-mGPCR antagonists differ from each other in terms of potency but not clinical efficacy.
4. Therapeutic effects and EPSs of D_2R-mGPCR antagonists are mediated via D_2R antagonism.
5. p-mGPCR antagonists act via antagonism at multiple GPCRs including D_4R and 5-HT_{2A}R.
6. p-mGPCR antagonists induce fewer EPSs than D_2R-mGPCR antagonists, but more often a metabolic syndrome.
7. mGPCR antagonists antagonize M_xRs, α_1AR, and H_1R with different potency, yielding both therapeutic effects and ADRs.
8. mGPCR antagonists are prescribed on an individual basis to obtain an optimal balance between therapeutic effects and ADRs.
9. Numerous new indications for mGPCR antagonists have emerged. Therefore, the traditional term "antipsychotics" should be avoided.
10. Likewise, the traditional terms "typical antipsychotics" for D_2R-mGPCR antagonists and "atypical antipsychotics" for p-mGPCR antagonists are very problematic.
11. NE/5-HT enhancers, lithium, and NIPEs are increasingly used in patients with refractory schizophrenia.

29.1 Pathophysiology of Schizophrenia and Pharmacotherapeutic Concepts

Schizophrenia is a very common psychosis with a global prevalence of 1%. It affects women and men with about the same frequency. Schizophrenia is life-destroying because 65% of all new cases affect humans prior to completion of their 30th year of age. Life expectancy is reduced by about 15 years because of accidents, suicides, and diseases as consequence of social decline. Schizophrenia compromises all areas of thinking and psyche fundamentally so that patients lose the ability to cope with the demands of life in partnership, family, and profession and to keep the relation to reality. There are also mixed forms of depression, bipolar disorder (see ▶ Chap. 28), and schizophrenia.

Figure 29.1 shows the pathophysiology of schizophrenia and pharmacological interventions derived from these concepts. The disease has multifactorial causes. According to the diathesis-stress model, humans differ from each other in their ability to compensate stress factors and toxic influences. With a good balance between stressors and resilience, the individual is mentally healthy.

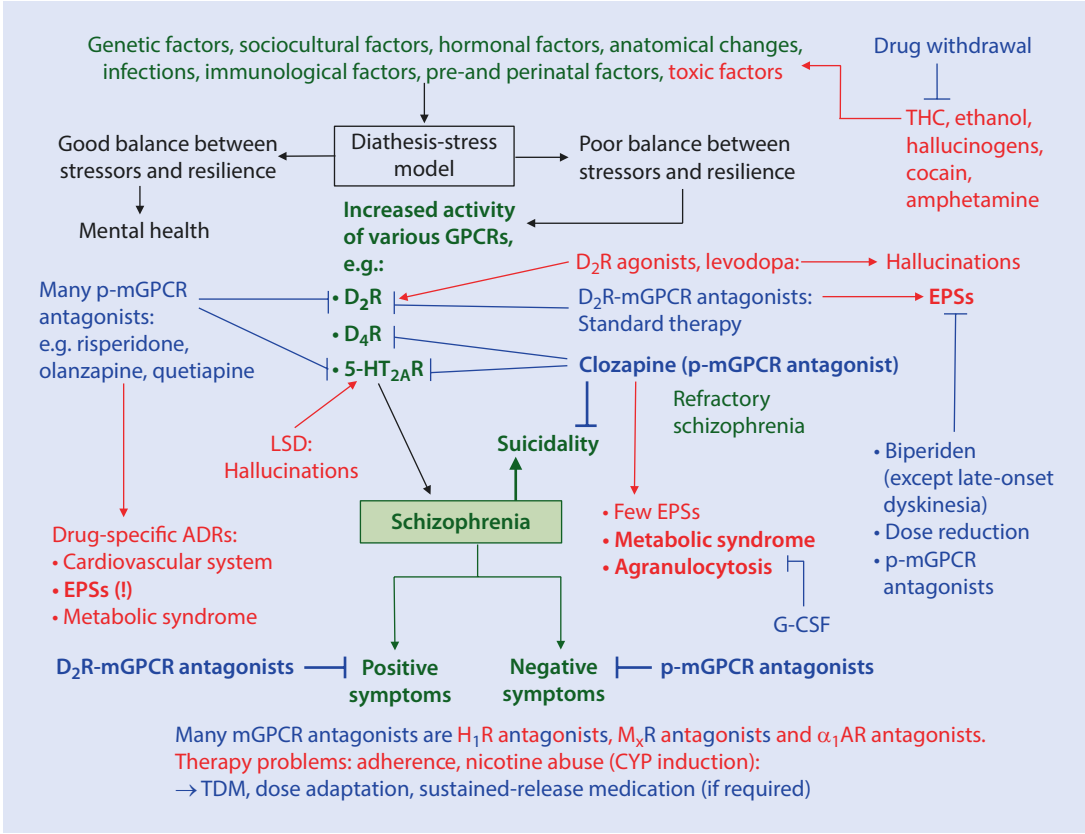

Fig. 29.1 Pathophysiology of schizophrenia and pharmacological interventions. H_1R antagonism of many mGPCR antagonists can be desired (sedation in agitated patients) or can be an ADR (daytime sedation, sleepiness, obesity). M_xR antagonism can be desired (less EPSs) or can be an ADR (antimuscarinic syndrome). The figure does not show the effects of NE/5-HT enhancers, lithium, and NIPEs in refractory schizophrenia. D_2R-mGPCR antagonists and p-mGPCR antagonists complement each other in drug therapy. Newer drugs are not necessarily better! The clinical efficacy of clozapine in schizophrenia is still unsurpassed! The major problem of clozapine is the control of agranulocytosis! However, in adherent patients, this problem can be managed

If stressors dominate in relation to resilience, schizophrenia may develop. As a consequence, a disbalance in the activity of several GPCRs including D_2R, D_4R (see ▶ Chap. 8) and 5-HT_{2A}R (see ▶ Chap. 6) develops. Consumption of illicit drugs such as THC (see ▶ Chap. 10), ethanol, and hallucinogens (e.g., LSD, see ▶ Chap. 6) and the abuse of indirect sympathomimetics (see ▶ Chap. 5) can facilitate development of schizophrenia.

For pharmacotherapy it is important to discriminate between positive (or plus) symptoms and negative (or minus) symptoms. Positive symptoms are often impressive and include hallucinations, paranoia, motor stereotypies, mutism, stupor, thought inspirations, thought withdrawal, and disorganized speech. Negative symptoms are clinically less impressive. Flattening of emotions, apathy, loss of interest, social withdrawal, loss of will, and anhedonia are typical negative symptoms. For long-term prognosis, they are more important, but less accessible to pharmacotherapy than positive symptoms.

Schizophrenia is characterized by overactivity of dopaminergic neurons in the mesolimbic system (see ▶ Chap. 8). This overactivity predominantly concerns the D_2R. Accordingly, D_2R-mGPCR antagonists are effective antipsychotics. The DA hypothesis of schizophrenia is corroborated by pharmacological data. There is a linear correlation between the daily antipsychotically effective dose of D_2R-mGPCR antagonists and their potency at the D_2R. The lower the daily dose of the respective drug, the higher is its potency at the D_2R (Fig. 29.2a). D_2R-mGPCR antagonists compete with DA at the D_2R and prevent receptor activation (Fig. 29.2b). For an antipsychotic effect, about

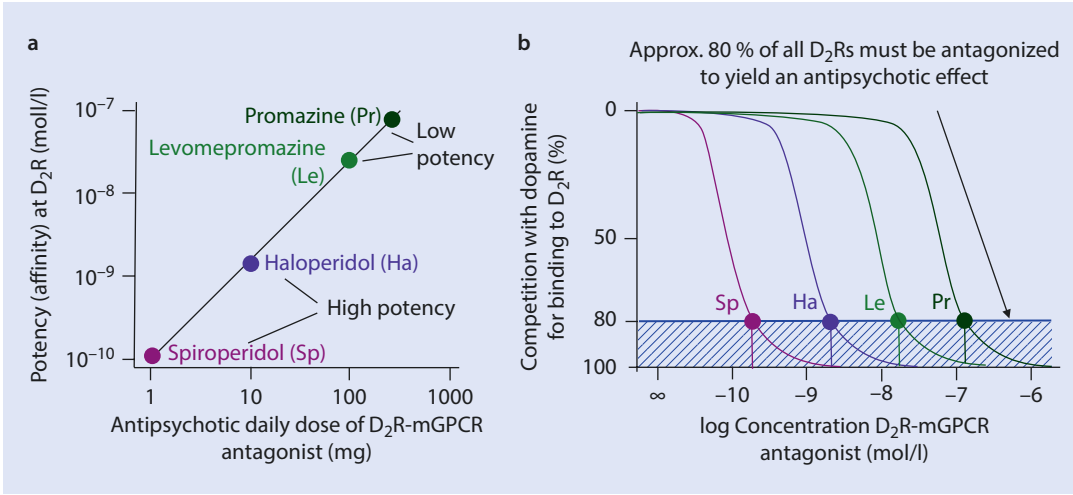

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Fig. 29.2 DA hypothesis of schizophrenia. **a** Correlation of daily antipsychotic dose of D_2R-mGPCR antagonists with D_2R potency. **b** Inhibition curves for various D_2R-mGPCR antagonists at the D_2R. See also Fig. 1.2. Spiroperidol is a D_2R-mGPCR antagonist marketed only in Japan. The various D_2R-mGPCR antagonists differ from each other only the daily dose but not maximum antipsychotic efficacy! High potency just means low antipsychotically effective dose, and low potency means large antipsychotically effective dose! Study again ► Chaps. 1 and 10 if this concept is not clear to you

80% of all D_2Rs have to be occupied with an antagonist. The clinical efficacy of D_2R-mGPCR antagonists is comparable. The DA hypothesis is also supported by the fact that levodopa and D_2R agonists can cause hallucinations (see ► Chap. 8).

Table 29.1 provides an overview of selected mGPCR antagonists. The lack of selectivity for an individual GPCR is not necessarily a therapeutic disadvantage. Rather, the results are drug-specific pharmacological profiles that can be specifically used in various psychiatric diseases. Because of their complex effects and ADRs, prescription of mGPCR antagonists belongs into the hand of the psychiatrist. In particular, ADRs on the cardiovascular system and metabolism require close collaboration with the internist.

Due to their lipophilicity, all mGPCR antagonists are well absorbed following oral administration. They possess high plasma protein binding and large volumes of distribution. In intoxications, mGPCR antagonists cannot be eliminated from the organism by dialysis (see ► Chap. 4). Intoxications are treated symptomatically. In general, mGPCR antagonists have a long plasma half-life and are extensively metabolized in the liver. Metabolites are eliminated via the kidney.

Parts of several societies still consider mGPCR antagonists as "chemical straightjacket." However, the opposite is true. If schizophrenic patients are treated with mGPCR antagonists under close psychiatric supervision and TDM, psychotic symptoms can be reasonably well controlled in most patients. This allows many of them to lead a decent life outside of closed psychiatric institutions. D_2R-mGPCR antagonists can often improve positive symptoms, while p-mGPCR antagonists tend to better improve negative symptoms.

mGPCR antagonists do neither cause addiction nor tolerance. This is an important but not well-known point that must be clearly communicated to patients and their relatives. The term "psychoactive drugs" is used as an umbrella to include the addiction-causing benzodiazepines (see ► Chap. 25), NE/5-HT enhancers (see ► Chap. 28), as well as mGPCR antagonists, the latter two groups not causing addiction. However, this umbrella term is problematic because it incorrectly suggests that all three drug classes have similar pharmacological properties, particularly with respect to addiction and tolerance.

Because of the lack of tolerance, long-term therapy with mGPCR antagonists usually does not require substantial increases in drug dose. mGPCR antagonists typically show a rapid onset of action, specifically with regard to positive symptoms. This drug property can be exploited in

Table 29.1 Overview of selected mGPCR antagonists

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
D_2R-mGPCR antagonists					
Chlorprothixene	Low-potency D_2R-mGPCR antagonist (thioxanthene in terms of chemical structure)	Antipsychotic, sedative	Mainly agitation in acute psychosis, chronic pain	Orthostatic dysregulation, severe antimuscarinic syndrome, but low risk for acute dystonia and parkinsonoid because of high M_xR potency	4, 5, 7, 8, 10, 13
Haloperidol	High-potency D_2R-mGPCR antagonist (butyrophenone in terms of chemical structure)	Strong antipsychotic effect, mainly on positive symptoms; suppression of motor activity, but no sedation; co-analgesic effect	Acute and chronic psychosis, particularly schizophrenia and acute mania; chronic pain; vomiting; no indication for "sedation" of agitated patients with dementia	Strong orthostatic dysregulation, only mild antimuscarinic syndrome, high risk for EPSs, hyperprolactinemia with galactorrhea, QT prolongation and TdP	4, 5, 6, 8, 10, 13, 17, 27, 30
Levomepromazine	Low-potency D_2R-mGPCR antagonist (phenothiazine in terms of chemical structure)	Antipsychotic, sedative	Mainly agitation in acute psychosis	Orthostatic dysregulation, antimuscarinic syndrome	4, 5, 7, 8, 13, 31
p-mGPCR antagonists					
Clozapine	p-mGPCR antagonist, high D_4R potency, pleiotropic GPCR profile	Antipsychotic effect on positive and negative symptoms, clinically proven reduction of suicide risk	Refractory schizophrenia or severe ADRs after administration of typical antipsychotics	Antimuscarinic syndrome, sedation, orthostatic dysregulation, only few EPSs, metabolic syndrome, agranulocytosis, seizures, weight gain	4, 5, 7, 13, 19, 22, 25, 28
Olanzapine	p-mGPCR antagonist, pleiotropic GPCR profile; the chemical structure is similar to that of clozapine; 5-HT_3R antagonist	Antipsychotic, antiemetic	Schizophrenia, bipolar disorder, obsessive-compulsive disorders, chemotherapy-induced vomiting, refractory depression	Sedation, metabolic syndrome, orthostatic dysregulation, EPSs, low risk of agranulocytosis, weight gain	6, 7, 8, 19, 22, 28, 32

(continued)

Table 29.1 (continued)

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Quetiapine	p-mGPCR antagonist; mainly 5-HT_{2A}R, D_2R and H_1R antagonism, inhibition of NE re-uptake	Antipsychotic effect; sedation due to H_1R antagonism	Schizophrenia, bipolar disorder, obsessive-compulsive disorders, depression, Tourette syndrome, anxiety disorders	Sedation, edema, hypotension, constipation, restless legs syndrome, QT time prolongation, SJS, antimuscarinic syndrome	3, 5, 17, 28
Risperidone	p-mGPCR antagonist, high 5-HT_{2A}R potency, moderate D_2R potency	Antipsychotic, co-analgesic	Chronic schizophrenia and schizoaffective psychosis, obsessive-compulsive disorders, chronic pain, bipolar disorder, autism	Sedation, orthostatic dysregulation, low risk for EPSs	5, 10, 28

The table does not list NE/5-HT enhancers, lithium, and NIPEs for treatment of refractory schizophrenia. These drugs are discussed in ► Chaps. 25 and 28

psychiatric emergencies. The antipsychotic drug dose is adjusted to the clinical symptoms and should provide a good compromise between therapeutic effects and ADRs. Termination of drug therapy is performed gradually. For patients with problematic adherence, certain mGPCR antagonists are available as i.m. sustained release formulations (see ► Chap. 2).

29.2 D_2R-mGPCR Antagonists

Traditionally, D_2R-mGPCR antagonists have been designated as "typical antipsychotics" to describe the fact that these drugs are used in schizophrenia and cause EPSs (see ► Chap. 1). However, for two important reasons, this term should be dropped. First, D_2R-mGPCR antagonists are now used in many more indications than schizophrenia (see ► Sect. 29.4), and even the "atypical antipsychotics" can cause EPSs (see ► Sect. 29.3).

D_2R-mGPCR antagonists are the gold standard for treatment of schizophrenia. They improve the positive more effectively than the negative symptoms. A substantial advantage of these drugs is that their therapeutic effects and ADRs have been known for decades. Moreover, many inexpensive generic drugs are available in this group, rendering long-term treatment of patients feasible even in countries with limited financial resources.

Depending on their potency at the D_2R and the daily dose, low-potency (e.g., levomepromazine, chlorprothixene, promethazine, pipamperone), medium-potency (e.g., melperone), and high-potency D_2R-mGPCR antagonists (e.g., haloperidol, spiroperidol, benperidol, flupentixol, and fluphenazine) are differentiated (see ► Chap. 1). This classification is very useful for prescription and provides important information on the required daily antipsychotic dose (Fig. 29.2b). D_2R-mGPCR antagonists can also be classified according to their chemical structure, i.e., into phenothiazines (e.g., levomepromazine, fluphenazine, and promethazine), thioxanthenes (e.g., chlorprothixene and flupentixol), and butyrophenones (e.g., haloperidol, melperone, and pipamperone). However this classification is not relevant for clinical use.

A common property of all D_2R-mGPCR antagonists is that they exert their therapeutic effects predominantly via D_2R antagonism

(■ Table 29.2) which is also responsible for the EPSs. These movement disorders are differentiated into early (acute dystonia, parkinsonoid) and late EPSs (akathisia and tardive dyskinesia) (■ Table 29.3). EPSs are very common. Up to 30% of all treated patients are affected, and particularly late EPSs are difficult to alleviate. The M_xR antagonist biperiden can mitigate EPSs except for tardive dyskinesia.

The low-potency D_2R-mGPCR antagonist levomepromazine additionally possesses sedative effects that are due to H_1R antagonism (see ▶ Chap. 7). These effects can be used for treatment of psychoses associated with agitation. Levomepromazine also antagonizes M_xRs with medium potency. On the one hand, this effect entails the risk of an antimuscarinic syndrome (see ▶ Chap. 5) but reduces, on the other hand,

■ **Table 29.2** Comparison of various mGPCR antagonists at selected biogenic amine receptors

Drug	D_2R and D_4R: antipsychotic effect D_2R: EPSs	α_1AR: orthostatic hypotension, tachycardia	H_1R: sedation, obesity	M_xR: antimuscarinic syndrome and protection against EPSs
Chlorprothixene	D_2R (low potency)	High potency	Moderate potency	High potency
Clozapine	D_4R (high potency)	Moderate potency	Moderate potency	Moderate potency
Haloperidol	D_2R (high potency)	Moderate potency	Very low potency	Low potency
Levomepromazine	D_2R (low potency)	Moderate potency	Moderate potency	Moderate potency

See also ■ Fig. 28.3. The different potencies of mGPCR antagonists at various GPCRs explain their therapeutic effects and ADRs at clinically relevant antipsychotic drug doses

■ **Table 29.3** EPSs caused by D_2R-mGPCR antagonists and to a lesser extent by p-mGPCR antagonists

Parameter	Acute dystonia	Parkinsonoid	Akathisia	Tardive dyskinesia
Onset after start of therapy	Day 1–5	Day 5–30	Months-years	Months-years, even after discontinuation
Frequency	10–30%	15–20%	20%	20%
Symptoms	Hyperkinesia of mimic muscles, torticollis, ocular dyskinesia	Rigor, akinesia, anxiety, irritability	Inability to sit and stand still; urge to walk restlessly	Chronic hyperkinetic movement disorder (choreoathetosis); chewing, smacking, and sucking movements
Therapy	M_xR antagonist biperiden	M_xR antagonist biperiden, dose reduction, switch to p-mGPCR antagonists	M_xR antagonist biperiden, dose reduction, switch to p-mGPCR antagonists	Switch to a D_2R-mGPCR antagonist of higher potency or clozapine; difficult to treat; hence, prevention is more important than therapy

EPSs are a major problem in the therapy of schizophrenia with mGPCR antagonists! Keep in mind that also the p-mGPCR antagonists ("atypical antipsychotics"), in contrast to general belief, can cause EPSs! The differentiation between "typical" and "atypical antipsychotics" is artificial and scientifically not justified, but it is deeply rooted in medical language

the risk of acute dystonia and parkinsonoid (Tables 29.2 and 29.3). Chlorprothixene possesses a similar pharmacological profile as levomepromazine. Its higher potency at M_xRs further lowers the EPS risk at the expense of a higher risk of an antimuscarinic syndrome.

In contrast to levomepromazine, haloperidol possesses no clinically relevant sedation because of its low potency at the H_1R. Its low potency at M_xRs correlates with a low risk for an antimuscarinic syndrome, but an accordingly increased EPS risk (Table 29.2). Hyperprolactinemia is a consequence of the potent D_2R antagonism of haloperidol. This can lead to galactorrhea, even in men, resulting in substantial adherence problems (see ▶ Chap. 9). Haloperidol causes damping of motor activity and disconnection of the patient from his/her hallucinations. These effects are often mistaken for sedation caused by assumed (but nonexistent) H_1R antagonism.

In order to obtain a rapid antipsychotic effect, haloperidol should be administered p.o. in the form of drops. For long-term therapy, tablets are used. The i.v. administration of haloperidol is dangerous, can cause life-threatening TdP (see ▶ Chap. 17), and must therefore be performed very slowly under ECG control. It should be reserved to the most serious psychiatric emergencies such as acute schizophrenia with severe hallucinations or mania with massive paranoia.

A common property of all mGPCR antagonists is their α_1AR antagonism (Table 29.2). This component does not contribute to therapeutic efficacy but only to ADRs. Specifically, orthostatic hypotension with reflex tachycardia develops. Patients with EPSs under therapy with D_2R-mGPCR antagonists can suffer serious falls and injuries. Reflex tachycardia is aggravated by M_xR antagonism of mGPCR antagonists and may pass into serious tachyarrhythmias (see ▶ Chap. 17). For prevention of arrhythmias, patients treated with mGPCR antagonists must have regular cardiological checkups. In the ECG, prolongation of the QT interval is an important risk indicator for TdP.

29.3 p-mGPCR Antagonists

Traditionally, p-mGPCR antagonists have been designated as "atypical antipsychotics" to describe the fact that these drugs are used in schizophrenia and DO NOT cause EPSs (see ▶ Chap. 1). However, for two important reasons, this term should be dropped. First, p-mGPCR antagonists are used in many more indications than schizophrenia (see ▶ Sect. 29.4), and even the "atypical antipsychotics" can cause EPSs. This is due to the fact that certain p-mGPCR antagonists are also quite potent D_2R antagonists. And D_2R antagonism mediates EPSs (see ▶ Sect. 29.2). Nonawareness of this important fact decreases drug safety of p-mGPCR antagonists and increases the risk of development of unrecognized EPSs, mistaken as motor stereotypies of schizophrenia.

p-mGPCR antagonists have pleiotropic neuropsychiatric effects mediated by multiple GPCRs. The effects of p-mGPCR antagonists are more complex than those of D_2R-mGPCR antagonists, and they predominantly improve negative symptoms in schizophrenia. Every p-mGPCR antagonist possesses a drug-specific pharmacological profile from which indications and ADRs can be partially derived, but overall, the assignment of the profile to the clinical use is not as straightforward as for D_2R-mGPCR antagonists. In addition, clinical studies on efficacy of p-mGPCR antagonists are rather heterogeneous and partially inconclusive. In several cases, direct comparisons with D_2R-mGPCR antagonists are missing. As a consequence, the clinical use of p-mGPCR antagonists is largely determined by individual experience of a psychiatrist with a given drug. Moreover, marketing by drug companies and "community fashions" rather than validated clinical studies often influence prescription of p-mGPCR antagonists. This is reflected by rapidly changing prescription trends and different prescription patterns in various countries.

An important ADR common to many p-mGPCR antagonists is the metabolic syndrome, i.e., the combination of obesity, DM, dyslipidemia, and hypertension (see ▶ Chaps. 15, 19, and 22). This syndrome is caused by an increase in appetite and is mediated via H_1R and 5-HT_{2A}R antagonism (see ▶ Chaps. 6 and 7). Patients treated with p-mGPCR antagonists must be educated about the risk of metabolic syndrome and urged to adhere to a healthy lifestyle with a balanced diet and sufficient exercise. However, because of the underlying psychiatric disorder, this is often difficult to implement, particularly in view of the fact that many psychiatric patients are heavy tobacco or THC smokers, thereby further reducing their

physical fitness. Hypertension, DM, and dyslipidemia in patients under p-mGPCR antagonists must be treated. It must be kept in mind that the risk of drug interactions increases due to polypharmacy. Therefore, it is important to conduct TDM of mGPCR antagonists in patients treated with multiple drugs.

Numerous p-mGPCR antagonists are available. Even for the psychiatrist, it is difficult to have a complete overview of all drugs. As general rule, introduction of a new p-mGPCR antagonist does not automatically imply that it is more efficacious than already approved mGPCR antagonists. Our lack of in-depth knowledge about the pathophysiology of schizophrenia has substantially hampered development of more effective and safer mGPCR antagonists than those being currently available.

Olanzapine, quetiapine, and risperidone are widely prescribed mGPCR antagonists. Olanzapine has a pleiotropic pharmacological GPCR antagonist profile and is additionally a 5-HT_3R antagonist. For this reason, olanzapine is also used in chemotherapy-induced vomiting (see ▶ Chaps. 6 and 32). Overall, the clinical use of olanzapine is burdened by several ADRs including EPSs and weight gain, and its clinical superiority relative to D_2R-mGPCR antagonists is not proven. For quetiapine, D_2R and 5-HT_{2A}R antagonism is dominant. Via H_1R antagonism, it induces strong sedation. The EPS risk is small. In case of risperidone, dual antagonism at D_2R and 5-HT_{2A}R is important for antipsychotic effects as well. The drug does not possess higher clinical efficacy in schizophrenia than D_2R-mGPCR antagonists. Risperidone is also used as co-analgesic (see ▶ Chap. 10).

Clozapine is a very valuable and very effective p-mGPCR antagonist for refractory patients. It possesses low potency at the D_2R in favor of high D_4R potency. D_4R antagonism mediates a part of the antipsychotic effects. Low D_2R and medium M_xR potency ensure low EPS risks. 5-HT_{2A}R antagonism contributes to the antipsychotic effects. Clozapine reduces suicidality and mortality in schizophrenia. Such convincing clinical effects have not been demonstrated for any other mGPCR antagonist. The potent H_1R antagonism of clozapine mediates sedation and an increase in appetite; α_1AR causes orthostatic hypotension.

Agranulocytosis is a serious ADR of clozapine that occurs dose-dependently in about 1–2% of the patients. Therefore, a weekly hemogram has to be performed during the first 18 weeks under clozapine therapy. At a granulocyte concentration <500/µl, therapy has to be terminated, and clozapine must be replaced by another mGPCR antagonist. Agranulocytosis can be treated with G-CSF (▶ Chaps. 4 and 32). It is the major reason that clozapine, despite its clinical superiority, is often only used as drug of last resort. For successful application of clozapine, it is essential to ensure excellent adherence and regular hemograms. A major advantage of the drug is that it has been in clinical use for decades. Because of this experience, ADRs are well characterized. Furthermore, inexpensive generic clozapine formulations are available. Clozapine therapy is a classic case where the specialist (psychiatrist) needs to collaborate with the general practitioner performing the hemograms.

29.4 Nontraditional Indications of mGPCR Antagonists

mGPCR antagonists have been used for multiple indications for many years. The use of D_2R-mGPCR antagonists in acute mania is well established (see ▶ Chap. 28). These drugs are also used, with mixed success, in the treatment of anxiety disorders, personality disorders, and obsessive-compulsive disorders (see ▶ Chap. 1).

In nonpsychotic patients, mGPCR antagonists cause emotional disconnection from the actual life situation, i.e., the patient develops a certain degree of indifference. As an example, serious pain is perceived as less agonizing. This effect can be exploited in the therapy of tumor patients. Haloperidol is often successfully used as co-analgesic (see ▶ Chap. 10). In addition, disconnection of the patient from pain perception with preserved responsiveness is exploited in neuroleptanalgesia (see ▶ Chap. 27). This type of analgesia is often used in neurosurgery when it is necessary to communicate with the patient to avoid injury of critical neuronal structures or to place intracerebral electrodes correctly. Additionally, D_2R-mGPCR antagonists are potent antiemetics and used in the treatment of vomiting caused by classic cytostatic drugs (see ▶ Chaps. 6 and 32).

The unexpected finding that the p-mGPCR antagonist trimipramine, chemically closely related to the NSMRI imipramine, exhibits antide-

pressive effects (see ▶ Chap. 28) initiated interests of psychiatrists in exploring other indications for these drugs, often on an off-label and trial and error basis. The group of clinically used p-mGPCR antagonists is quite large (at least different 20 drugs) and very heterogeneous. Thus, it is conceivable that when all these drugs are examined under different conditions and doses in multiple psychiatric diseases with different comorbidities and comedications, very large and confusing datasets are generated. Accordingly, a final assessment of the value of p-mGPCR antagonists in "nontraditional" psychiatric indications cannot yet been made. However, these drugs are used empirically and with mixed success in diseases including bipolar disorder, depression, anxiety disorders, Tourette syndrome, chronic pain, autism, and obsessive-compulsive disorder. Clinically, the aforementioned diseases have some overlap with schizophrenia, and the clinical efficacy of p-mGPCR antagonists suggests that there is also a partial overlap in pathophysiology. It is expected that the scope of indications of p-mGPCR antagonists, all possessing unique pharmacological properties, will further increase over the next years.

29.5 Treatment of Schizophrenia with NE/5-HT Enhancers, Lithium, and NIPEs

As has been pointed out in ▶ 29.1, the pathophysiology of schizophrenia is as yet incompletely understood. In ▶ Sects. 29.2 and 29.3, it was discussed that the clinical efficacy of mGPCR antagonists is variable and that, in many cases, serious ADRs limit pharmacotherapy. This unsatisfying situation was the starting point for searching for improved pharmacotherapeutic strategies in refractory schizophrenia. Similar to the strategies in refractory depression, refractory schizophrenia can be treated by adding NE/5-HT enhancers, lithium, or NIPEs to p-mGPCR antagonists. In addition, various p-mGPCR antagonists are combined. The results of clinical studies on these drug combinations are heterogeneous, but for some patients, improvements can be achieved. As already discussed in ▶ Chap. 28, from a pharmacological point of view, the combination of NE/5-HT enhancers and p-mGPCR antagonists is questionable.

29.6 Questions and Answers

Questions

Which statement on mGPCR antagonists is *NOT* correct?

A. Levomepromazine is a highly potent D_2R-mGPCR antagonist.
B. Haloperidol can cause akathisia.
C. Olanzapine can cause a metabolic syndrome.
D. Clozapine is a p-mGPCR antagonist with high potency for the D_4R.
E. Risperidone is a p-mGPCR antagonist with high potency for the $5\text{-}HT_{2A}R$.

Answers

A. Levomepromazine antagonizes the D_2R with low potency. Accordingly, levomepromazine must be administered in higher doses than high-potency D_2R-mGPCR antagonists such as haloperidol to obtain an antipsychotic effect.
B. Akathisia is a common ADR of haloperidol. This ADR is treated by reducing the drug dose or switching to another mGPCR antagonist. It can also be attempted to reduce akathisia by adding the M_xR antagonist biperiden.
C. Olanzapine is a p-mGPCR antagonist. It possesses a lower EPS risk than D_2R-mGPCR antagonists. Conversely, the risk for metabolic syndrome is increased. Hypertension, dyslipidemia, and DM must be treated pharmacologically. The drug dose may have to be reduced, or the patient may have to be switched to another mGPCR antagonist.
D. In contrast to D_2R-mGPCR antagonists, clozapine antagonizes the D_4R with high potency, but it antagonizes the D_2R only with low potency. Clozapine is a p-mGPCR antagonist.
E. The antipsychotic effect of risperidone is predominantly due to its antagonism at the $5\text{-}HT_{2A}R$. Risperidone is a p-mGPCR antagonist. Conversely, $5\text{-}HT_{2A}R$ agonists such as LSD cause hallucinations.

Statement **A** is not correct.

29.7 Exercises

As 25-year-old female medical student is admitted to the psychiatric emergency room with paranoia, acoustic hallucinations, lack of the mimic expression, and overall rigidity of the body musculature. It is difficult to take the medical history.

Questions

1. What is your suspected diagnosis and what is your first therapeutic measure?
2. Which problems can arise during long-term therapy with haloperidol?

Answers

1. Probably, the patient suffers from acute schizophrenia. Overall, positive symptoms dominate, but because of the difficulties to record the medical history, it cannot be readily assessed to which extent negative symptoms are present. Due to the severity of the disease and potential suicidality, you admit the patient into the hospital. You initiate a therapy with a highly potent D_2R-mGPCR antagonist such as haloperidol (initially drops, later tablets). The drug should rapidly improve the positive symptoms. You should avoid i.v. injection of haloperidol because life-threatening TdP may occur. Once the acute symptoms of psychosis are controlled, the patient may be more accessible for detailed interviews about other symptoms and background information on the disease.
2. You should try to identify the minimally effective dose of haloperidol to obtain a good compromise between antipsychotic effects and ADRs. Acceptance of the therapy by the patient is essential to obtain good adherence. Otherwise, the psychosis may flare up again. EPSs are typical ADRs of haloperidol. In this case, the dose must be reduced, or the patient must be switched to another mGPCR antagonist. In addition, haloperidol can cause orthostatic dysregulation.

Further Reading

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Drugs for the Treatment of Alzheimer's Disease

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Globally, dementias constitute an increasingly important medical problem. The most common dementia is AD. It is characterized by the formation of protein aggregates, i.e., amyloid plaques and tau tangles. Currently, a causative treatment of AD is impossible. AChEIs and allosteric NMDAR antagonists moderately improve symptoms but do not affect the natural course of AD. New therapeutic strategies aim at preventing tau aggregation and amyloid plaque formation and at stabilizing microtubules. A healthy diet, an active lifestyle, and the efficient treatment of hypertension, dyslipidemia, and DM can prevent or at least delay development of all forms of dementia.

Key Points

1. Tau aggregates and amyloid plaques are characteristics of AD and pharmacological targets.
2. Impaired calcium homeostasis, mitochondrial dysfunction, and ROS formation are pathogenetic factors that could be targeted.
3. AD can be treated symptomatically with AChEIs, allosteric nAChR agonists, and allosteric NMDAR antagonists.
4. Currently available AD drugs exhibit only limited efficacy.
5. The use of high-potency D_2R-mGPCR antagonists in dementia is dangerous.

30.1 Pathophysiology of Dementias and Pharmacotherapeutic Concepts

Dementias are, like PD (see ▶ Chap. 8), neurodegenerative diseases. Since societies in Europe, North America, and East Asia experience a substantial demographic shift toward an aging population, the number of patients with dementias will increase dramatically over the next decades. Dementias are chronic so that nursing expenses will increase exponentially. The situation is further aggravated by a paucity of qualified nurses. Thus, there is an urgent need for effective pharmacotherapy of dementias. Unfortunately, the currently available drugs (◘ Table 30.1) have only, at best, very modest effects. Meanwhile, the problem has been recognized by the pharmaceutical industry, and intense efforts are underway to develop new drugs for dementias.

Dementia is characterized by loss of short-term memory, confusion, loss of orientation, impaired ability to think critically, alterations of sleep-wake cycles, and emotional lability with depression and aggression; the latter often directed toward nurses and family members.

The most common dementia is AD (about 70% of all cases). The disease is characterized by tau aggregates (tangles) and amyloid plaques. The plaques spread diffusely in the CNS starting in the cortex and then propagating into the midbrain, brain stem, and cerebellum. Tau aggregates first develop in the brain stem and later in the cortex. Accumulation of tau aggregates and amyloid plaques precedes clinical symptoms often by many years. Accordingly, much brain tissue has already been damaged irreversibly when the first clinical symptoms occur, so that an effective therapy comes too late. This situation renders it necessary to diagnose AD before the onset of clinical symptoms, i.e., by detecting amyloid plaques with imaging techniques or by assessing biomarkers in blood or cerebrospinal fluid. Vascular dementia (about 30% of all cases) is the second most common dementia. Clinical differentiation between AD and vascular dementia is difficult and can only be made postmortem in most cases by histological analysis.

Additional factors play a role in the pathogenesis of neurodegenerative diseases. Calcium homeostasis is of particular importance in this regard. Physiologically, there is a 1,000–10,000-fold calcium concentration gradient between the extracellular and intracellular space. If homeostasis is impaired, e.g., by reduced brain perfusion and consequently lower ATP synthesis, the gradient cannot be maintained anymore, and the intracellular calcium concentration increases. This results in higher release of the excitatory NT glutamate which is neurotoxic at high concentrations and damages predominantly cholinergic neurons in AD (◘ Fig. 30.1). Calcium additionally impairs mitochondrial function via formation of ROS. Therefore, an important concept for therapy of neurodegenerative disorders is to develop drugs that improve mitochondrial function. The antioxidant idebenone is effective in certain neurodegenerative diseases such as the Leber hereditary optic neuropathy (LHON).

Table 30.1 Overview of selected drugs for treatment of AD

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Donepezil	Reversible AChE inhibition	Only moderate improvement of cognitive deficits in AD; no causative therapy	AD	Muscarinic syndrome	4, 5, 13
Galantamine	Allosteric enhancement of nAChR function and reversible AChE inhibition	Only moderate improvement of cognitive deficits in AD; no causative therapy	AD	Muscarinic syndrome	1, 4, 5, 13
Memantine	Allosteric NMDAR antagonist	Only moderate improvement of cognitive deficits in AD; no causative therapy	AD	Sedation, confusion, unrest, hallucinations, seizures, nausea, constipation, vomiting	1, 13

None of the drugs listed here is clinically convincing!

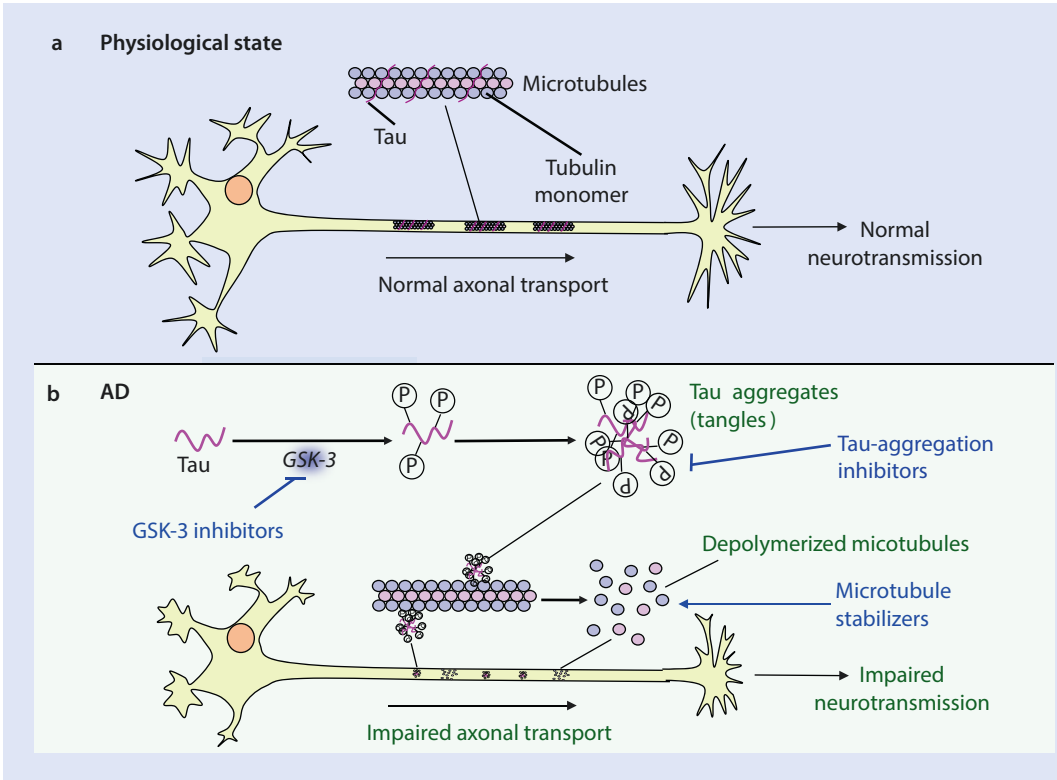

Fig. 30.1 Tau aggregates as pharmacological targets in AD. **a** Normal function of tau. **b** Tau aggregates in AD and pharmacological targets. Current pharmacotherapy of AD is very frustrating! This figure shows some strategies how to improve pharmacotherapy by targeting tau

Psychoactive drugs should be prescribed very restrictively in AD patients. Doses should be increased incrementally, and the lowest effective dose should be used to avoid ADRs and drug interactions. Benzodiazepines usually have sedative-anxiolytic effects (see ▶ Chap. 25), but in AD patients they can cause paradoxical agitation. This is also the case for NE/5-HT enhancers improving motivation. High-potency D_2R-mGPCR antagonists (see ▶ Chap. 29) are too often used in AD patients for "sedation." However, particularly haloperidol has no sedating effect but rather further disconnects AD patients from reality. In addition, highly potent D_2R-mGPCR antagonists can cause serious EPSs and cardiovascular problems (see ▶ Chaps. 17 and 29).

Because of the unsatisfying pharmacotherapy of AD, prophylaxis and supportive therapy are particularly important. The patient should remain independent as long as possible, and the residence in a nursing home should be as short as possible. Moderate calorie uptake and a Mediterranean diet with lots of vegetables, fruits, fish, and olive oil, moderate consumption of red wine and caffeine-containing beverages, and as much mental and physical activity as possible are recommended. Tobacco smoking should be avoided because of damaging effects of tobacco ingredients on blood vessels (see ▶ Chaps. 5, 9, 15, 16, 18, and 22).

Another component of AD management is to appropriately treat concomitant internal diseases such as hypertension (see ▶ Chap. 15), CHD and CHF (see ▶ Chap. 16), DM (see ▶ Chap. 19), and dyslipidemia (see ▶ Chap. 22). These measures positively affect the course of AD.

The development of effective drugs for AD is difficult for several reasons:

1. The disease is heterogeneous, i.e., there are hereditary and non-hereditary forms.
2. The pathophysiology of AD is as yet incompletely understood.
3. Symptoms appear not before substantial CNS damage has occurred.
4. Therapeutic effects are only observed in the long run. Accordingly, it is difficult and expensive to conduct high-quality clinical studies.
5. AD symptoms are psychiatric and, therefore, subjective.
6. AD animal models only incompletely recapitulate AD in humans.

30.2 Currently Used Drugs

There is no causative pharmacological therapy for AD and other dementias. The currently available drugs act symptomatically, and their efficacy is at best only moderate. The major problem is that therapy usually starts in late disease stages where irreversible CNS damage has already taken place. There is no evidence that any of the drugs discussed below is superior to another drug. In contrast to other indications (see, e.g., ▶ Chap. 15), combination therapy in AD has no advantages compared to single drug treatment.

In AD, cholinergic neurons are particularly affected. By analogy to restoring dopaminergic neuronal function in PD (see ▶ Chap. 9), therapy of AD aims at supporting cholinergic neuronal functions. This can be accomplished by inhibiting ACh degradation and with nAChR agonists (see ▶ Chap. 5). Donepezil is the prototypical AChEI used in AD. Since it does not only inhibit AChE in the CNS but also in the entire organism, a muscarinic syndrome can develop (see ▶ Chap. 5). This ADR is problematic in AD patients and must be assessed in relation to a relatively small benefit for cognitive function. Therefore, donepezil must be dosed cautiously and incrementally. Drug intake must be controlled regularly. As an alternative to donepezil, the alkaloid galantamine from *Galanthus nivalis* can be used. Like donepezil, galantamine inhibits AChE and positively modulates the nAChR, i.e., it allosterically enhances the effects of ACh (by analogy to benzodiazepines at the $GABA_A$R, see ▶ Chaps. 1, 5, and 25). The ADRs of galantamine are similar to those of donepezil.

An important component of neurodegenerative diseases including AD is the impaired calcium homeostasis, ultimately leading to enhanced NMDAR activation (see ▶ Sect. 30.1). The NMDAR belongs to the ligand-gated ion channels (see ▶ Chap. 1) and is activated by glutamate. As a result, calcium influx into neurons is enhanced. The term NMDAR is derived from the synthetic glutamate analog, N-methyl-D-aspartate (NMDA), that very potently and effectively activates these receptors. NMDA is neurotoxic. Accordingly, NMDAR antagonists should be neuroprotective, i.e., they should particularly improve the functions of cholinergic neurons in AD. Memantine is an allosteric NMDAR antagonist, i.e., it reduces the sensitivity of the receptor for glutamate.

Despite the convincing mechanism of action of memantine, its clinical efficacy is not. A certain cognitive improvement can be achieved, but the declining natural course of AD cannot be halted. In addition, memantine has several ADRs (see Table 30.1) that have to be weighed against its cognition-enhancing effects.

30.3 Pharmacological Strategies to Reduce Tau Aggregates

Tau is a filamentous protein that is wrapped around tubulin monomers to stabilize microtubules. Intact microtubules are essential for neuronal function, particularly for transport of vesicles and nutrients from the cell body to the synapses (Fig. 30.1a). In several neuropsychiatric diseases, tau becomes hyperphosphorylated for as yet incompletely understood reasons. The protein kinase GSK-3 plays a key role in this process (Fig. 30.1b). Hyperphosphorylated tau cannot fulfill its normal function for microtubules and aggregates anymore (formation of tangles). As a result, microtubules depolymerize and axon transport is impaired. Accordingly, inhibition of GSK-3 and tau aggregation and stabilization of microtubules are pharmacological strategies for treatment of AD and other neurodegenerative diseases associated with tau aggregation. Lithium (see ▶ Chap. 28) and valproic acid (see ▶ Chap. 25) have multiple mechanisms of action and, among other effects, inhibit GSK-3.

30.4 Pharmacological Strategies to Reduce Amyloid Plaques

Since amyloid plaques are found in the CNS of all AD patients, most efforts are directed toward inhibition of amyloid formation or elimination of amyloid from the organism. Amyloid consists of two peptides. Progressive aggregation of these peptides sustains a neurodegenerative process. The amyloid precursor protein (APP), an integral membrane protein with unknown function (Fig. 30.2), is the substrate for Aβ40/42 formation. Under

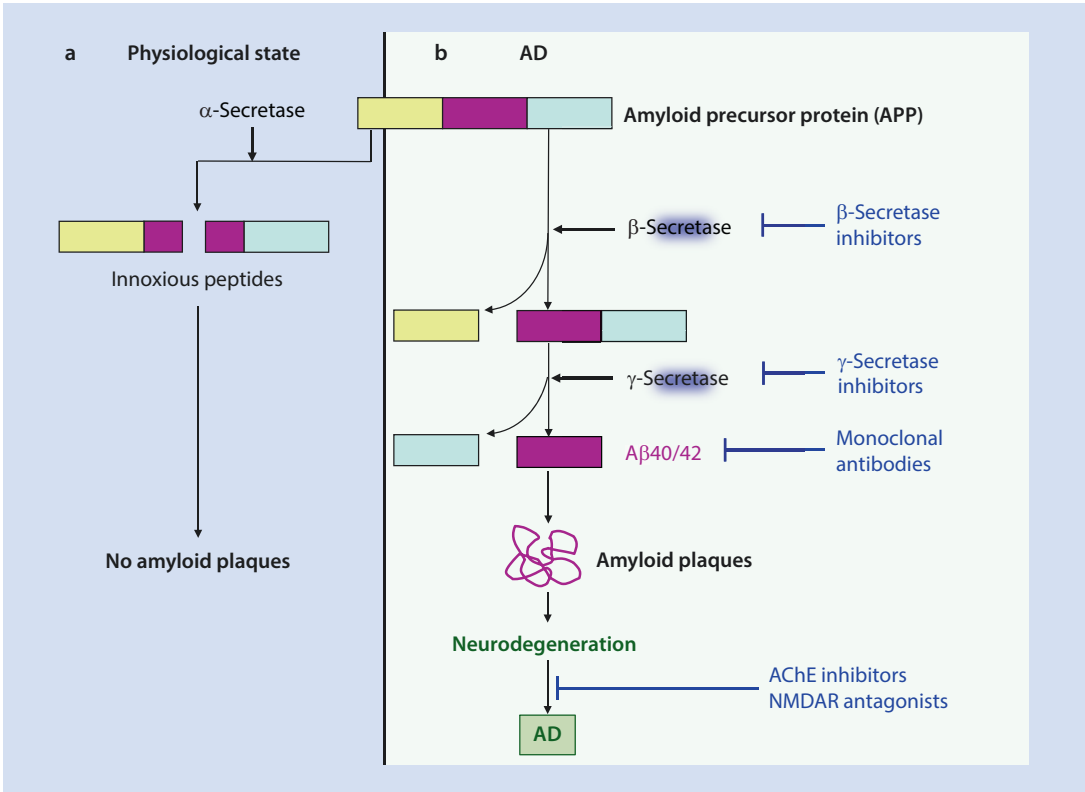

Fig. 30.2 Amyloid plaques as pharmacological targets in AD. **a** Physiological situation. **b** Situation in AD and pharmacological targets. Current pharmacotherapy of AD is very frustrating! This figure shows some strategies how to improve pharmacotherapy by targeting Aβ40/42

physiological conditions, APP is degraded to innoxious peptides by α-secretase. For as yet unknown reasons, the degradation pathway is switched in AD where β-secretase initially cleaves off N-terminal parts of APP and γ-secretase then cleaves off the C-terminal part. The central remainders of this cleavage process are Aβ40 and Aβ42 which then aggregate. Therefore, one pharmacological approach is to inhibit β- and/or γ-secretase. However, this approach is problematic because secretases are also involved in the degradation of other proteins. Therefore, secretase inhibitors can cause serious ADRs.

Current efforts are directed toward neutralization of Aβ40/42 via monoclonal antibodies. Based on their physicochemical properties (high molecular mass, high density of charges, see ▶ Chap. 2), antibodies cannot penetrate the BBB by diffusion. Rather, antibodies are taken up into the CNS via cellular transport processes. Clinical studies with antibodies against Aβ40/42 are performed, but for the reasons discussed in ▶ Sect. 30.1, they are labor-intensive. An advantage of the studies with Aβ antibodies is that the reduction of Aβ in the CNS can be visualized with high-resolution imaging techniques. An important strategy in the clinical assessment of Aβ antibodies is to administer them to patients with hereditary AD forms already before clinical symptoms occur. Should the clinical studies with Aβ antibodies be successful, therapy will probably be expensive because of the very high development costs. It will therefore be a challenge for all healthcare systems confronted with high AD prevalence whether they can afford treating large number of patients for a long period of time.

30.5 Questions and Answers

Questions

Which class of drug is, in principle, suitable for treatment of AD?

A. Allosteric NMDAR agonists
B. Microtubule-depolymerizing drugs
C. Stimulators of tau aggregation
D. nAChR antagonists
E. Monoclonal Aβ antibodies

Answers

A. Allosteric NMDAR antagonists can be used; agonists would deteriorate the symptoms.
B. Microtubule-stabilizing drugs could be useful; depolymerizing drugs would deteriorate the disease.
C. Inhibitors of tau aggregation could improve AD symptoms; stimulators would deteriorate the disease.
D. Allosteric nAChR agonists like galantamine can improve AD symptoms; antagonists would deteriorate symptoms.
E. Monoclonal Aβ antibodies constitute a pathophysiologically supported therapeutic approach. Currently, clinical studies are conducted to evaluate the validity of the concept.

Answer **E** is correct.

30.6 Exercises

A 92-year-old patient with AD is treated with donepezil to improve his memory. The drug works moderately. After about 6 months, the patient develops insomnia which is treated with amitriptyline with an intermediately high dose. Thereafter, cognitive functions decline substantially.

Questions

1. How can the loss of efficacy of donepezil after initiation of therapy with amitriptyline be explained?
2. How do you proceed with the patient?

Answers

1. Donepezil inhibits AChE and improves the impaired cholinergic neurotransmission in AD. This moderately improves cognitive function. Amitriptyline induces sedation via H_1R antagonism. This effect can be exploited in insomnia. However, in higher doses the drug also antagonizes M_xRs and, thereby, annihilates the effect of the AChEI on memory.

2. Both donepezil and amitriptyline act only symptomatically. Polypharmacy increases the risk of ADRs and interactions. The risk is particularly large for geriatric patients. Accordingly, it has to be evaluated critically whether therapy with one or two of the drugs can be terminated. Cognitive performance can be improved by stimulating daily activities such as physiotherapy, ergotherapy, singing, games, interactions with family members and friends, and appropriate reading of newspapers and books and by treatment of underlying internal diseases. Insomnia can be improved by keeping daytime sleep periods short. In addition, the design of the bedroom should be checked. Sufficient darkening of the windows, a comfortable bed with elevated headboard, low room temperature, and avoidance of traffic noise all contribute to good sleep quality. Should you come to the conclusion that drug therapy is indicated, donepezil can be substituted by the NMDAR antagonist memantine. In addition, amitriptyline should be prescribed at a very low dose so that only the H_1R is antagonized, but not M_xRs. Alternatively, a first-generation H_1R antagonist such as diphenhydramine could be applied.

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Drugs for the Treatment of Glaucoma and Age-Related Macular Degeneration

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Demographic changes in many countries increase the prevalence of degenerative eye diseases causing blindness and loss of independence. Glaucoma and AMD are the most important diseases leading to blindness. In an open-angle glaucoma, outflow of aqueous humor is reduced in relation to humor production. IOP reduction by 30–50% prevents disease progression. Increase of trabecular and uveoscleral humor outflow by FPR agonists is the most effective therapy. In case of insufficient effects, further drug classes increasing outflow or decreasing production of humor can be added. AMD is differentiated into the more common non-exudative and the less common but much more dangerous exudative form. In the latter, the growth factor VEGF is released, causing choroidal neovascularization with subsequent hemorrhage and scarring. Regular intravitreal injection of VEGF inhibitors can prevent disease progression. The high therapy costs constitute a huge pharmacoeconomic problem. For successful treatment of glaucoma and AMD, adherence is critical.

Key Points

1. FPR agonists increase trabecular and uveoscleral aqueous humor outflow.
2. FPR agonists are the most effective drugs for IOP reduction.
3. FPR agonists can cause iris discoloration and elongation of eye lashes.
4. β_xAR antagonists inhibit aqueous humor production.
5. CAH inhibitors reduce aqueous humor production and can cause dysgeusia and allergies.
6. α_2AR agonists inhibit aqueous humor production and increase uveoscleral humor outflow.
7. In case of insufficient IOP reduction, drug classes are combined.
8. M_xR agonists are only used in narrow-angle glaucoma.
9. In acute glaucoma attack, osmotic diuretics are used.
10. Neovascularization in exudative AMD can be prevented by VEGF inhibitors.
11. Therapy with VEGF inhibitors can cause glaucoma, cataract, and endophthalmitis.

31.1 Pathophysiology of Glaucoma

The demographic change in aging societies entails that the prevalence of neurodegenerative diseases increases (see ► Chaps. 8 and 30). Degenerative eye diseases impede independence and life quality of patients and lead to accidents and high nursing costs. Therefore, a good visual function is crucial for aging humans. Globally, glaucoma is the most frequent cause for blindness. Many cases remain undiagnosed. Glaucoma prevalence increases with age and amounts to about 3.5% in 40–80-year-old people. Therefore, glaucoma treatment has high priority.

Glaucoma is characterized by a disbalance of aqueous humor production and absorption (outflow in the anterior chamber). ◘ Figure 31.1 shows the pathophysiology of glaucoma and pharmacological interventions. ◘ Table 31.1 summarizes selected drugs for glaucoma treatment.

The major risk factor for glaucoma development is increased IOP. Accordingly, to reduce IOP is the most important aim of pharmacological intervention. Myopia, low cornea thickness, poorly controlled hypertension (see ► Chap. 15), other eye diseases, a positive family history, and DM (see ► Chap. 19) favor glaucoma development.

IOP is regulated by the balance between aqueous humor production in the ciliary body, trabecular absorption in Schlemm's canal, and uveoscleral outflow. The humor is important for proper function of the lens and the cornea. For aqueous humor production, two enzymes are critical, i.e., CAH and Na^+/K^+-ATPase, regulating bicarbonate and sodium secretion, respectively. The ATPase is under stimulatory control of the β_2AR and inhibitory control of the α_2AR. The humor is transported between the posterior side of the iris and the lens to the anterior eye chamber where trabecular and uveoscleral absorption takes place.

In the rare narrow-angle glaucoma, Schlemm's canal is constricted and humor outflow is reduced. No apparent pathological changes appear in the very common open-angle glaucoma, but nonetheless, humor outflow is reduced in relation to humor production. As consequence of the disbalance, the IOP, usually ranging between 10 and 21 mm Hg, is increased. It is determined by tonometry. A long-lasting IOP increase leads to damage of the optic disc and excavation. This is diagnosed by fundoscopy, kinking of blood vessels being a hallmark. Initially, patients do not

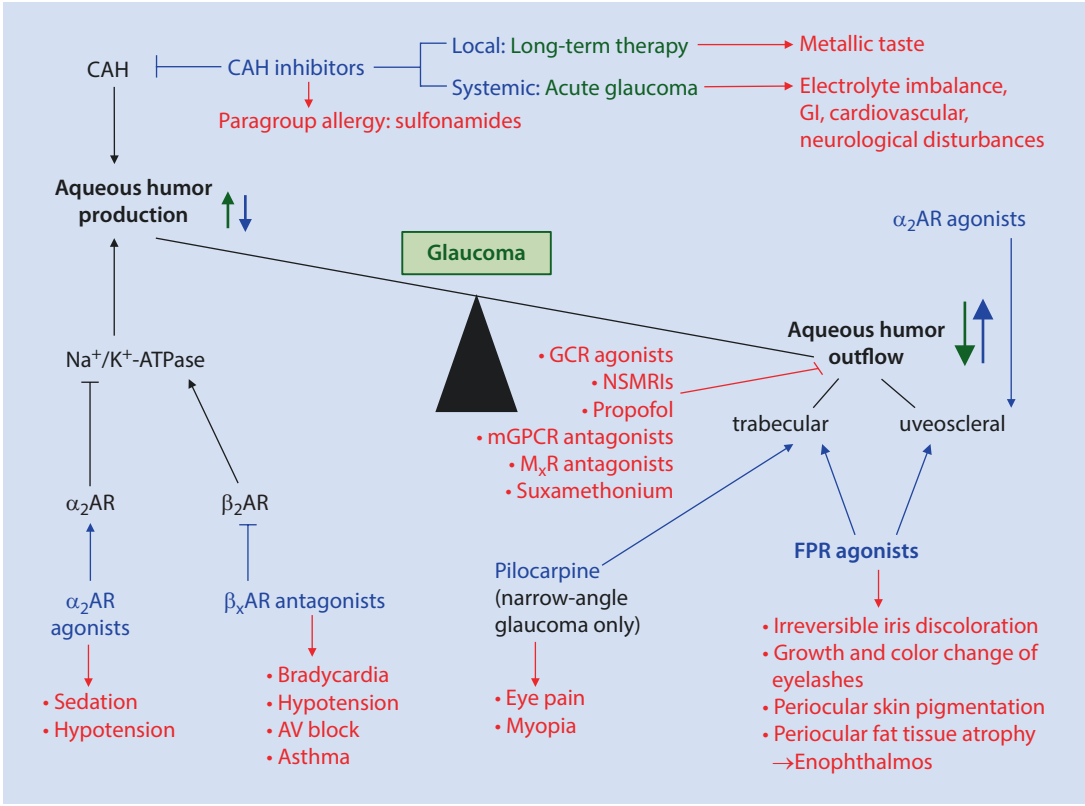

Fig. 31.1 Pathophysiology of glaucoma: pharmacological interventions. FPR agonists are the most important drug class for glaucoma treatment! Glaucoma can be treated effectively and economically

have symptoms. When time goes by, increasing peripheral scotomas develop, ultimately affecting central vision. Scotomas are diagnosed by perimetry. In many cases, glaucoma develops in spite of an IOP within the normal range. Nonetheless, IOP is crucial for therapy because an effective pressure reduction delays disease progression even with apparently "normal" values. An important cause for glaucoma pathogenesis is systemic or local long-term therapy with GCR agonists (see ▶ Chap. 11) which inhibit humor outflow.

M_xR antagonists cause mydriasis (see ▶ Chap.5). For fundoscopy or eye surgery, the pupil is often dilated locally with these drugs (tropicamide, short acting; atropine, long acting). Mydriasis causes constriction of Schlemm's canal and can lead to rapid IOP increases. Therefore M_xR antagonists must be applied cautiously and under IOP control in glaucoma patients.

Many drugs used in various indications have an M_xR-antagonistic component. Such drugs are biperiden used for PD treatment (see ▶ Chap. 8), NSMRIs (see ▶ Chap. 28), and mGPCR antagonists (see ▶ Chaps. 2 and 29). In addition, systemically applied atropine for treatment of AV block can increase the IOP (see ▶ Chaps. 5 and 17). In patients treated with the above drugs, the IOP must be determined regularly.

In extreme cases, the IOP can increase up to 80 mm Hg. Patients complain about severe headache and eye pain, severe vision impairment, nausea, and vomiting. A massive and rapid increase in IOP is referred to as acute glaucoma attack. In this case, an immediate and effective IOP reduction is required. To achieve this goal, several pharmacotherapeutic strategies are available (see ▶ Sect. 31.2).

31.2 Pharmacotherapy of Glaucoma

Glaucoma progression can be prevented if the IOP is reduced by 30–50%, regardless of the initial pressure. The most important pharmacological aim for therapy of open-angle glaucoma is to

Table 31.1 Overview of selected drugs for treatment of glaucoma and exudative AMD

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Glaucoma					
Brimonidine	α_2AR agonist	Inhibition of aqueous humor production and increase of uveoscleral aqueous humor outflow; IOP decrease of approx. 25%	Open-angle glaucoma (topical)	Sedation, hypotension	5
Brinzolamide	CAH inhibitor	Inhibition of aqueous humor production; IOD decrease of 20–25%	Open-angle glaucoma (topical); in acute glaucoma attack, acetazolamide is systemically administered	Local: metallic taste, allergization (para group allergy), multiple organ disorders after systemic administration of acetazolamide	3
Latanoprost	FPR agonist	Increased trabecular and uveoscleral aqueous humor outflow; IOP decrease of up to 40%	Open-angle glaucoma (topical); drug of first choice	Local: irreversible iris color change, growth and color change of eyelashes, periocular skin pigmentation and fat tissue atrophy (enophthalmos)	
Pilocarpine	M_xR agonist	Induction of miosis which opens the Schlemm's canal and thus increases outflow of trabecular aqueous humor	Narrow-angle glaucoma (topical)	Myopia, eye pain	5
Timolol	β_xAR antagonist; for treatment of glaucoma, β_2AR antagonism is of therapeutic relevance	Inhibition of aqueous humor production; IOP decrease of 20–25%	Open-angle glaucoma (topical)	Bradycardia, hypotension, AV block, asthma	1, 5, 15, 16, 17
Exudative AMD					
Aflibercept	Extracellular domain of the VEGFR which binds to VEGF	Inhibition of choroidal neovascularization in exudative AMD	Exudative AMD (intravitreal injection), comparable efficacy as ranibizumab and bevacizumab; very expensive therapy	Glaucoma, cataract, endophthalmitis	32, 33

Table 31.1 (continued)

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Ranibizumab	Antibody fragment which binds to VEGF	Inhibition of choroidal neovascularization in exudative AMD	Exudative AMD (intravitreal injection), comparable efficacy as aflibercept and bevacizumab; very expensive therapy	Glaucoma, cataract, endophthalmitis	32, 33
Bevacizumab	Antibody which binds to VEGF	Inhibition of choroidal neovascularization in exudative AMD	Exudative AMD (intravitreal injection), comparable efficacy as aflibercept and ranibizumab; affordable off-label (!) therapy	Glaucoma, cataract, endophthalmitis	32, 33

For all of the listed drugs, poor adherence leads to disease progression. Three drugs are effective in AMD, but only the two expensive drugs are approved! Nonetheless, off-label treatment with the much less expensive bevacizumab is similarly effective. Therefore, bevacizumab is used quite commonly in AMD patients

increase aqueous humor outflow. The FPR stimulates humor outflow increase via the trabecular network and the uveoscleral system. With FPR agonists, an IOP reduction up to 40% can be achieved. The improved outflow dynamics ameliorate the ability of the eye to cope with IOP peaks, e.g., as a consequence of BP fluctuations (see ▶ Chap. 15). Moreover, the production of aqueous humor, being important for eye function, remains unaffected by FPR agonists. They are well tolerated and have to be applied only once daily. Therefore, FPR agonists (prototype latanoprost) are the drug class of first choice. The failure rate is <20%. Multiple-use FPR agonist formulations with preservatives and single-use formulations without potentially allergenic preservatives are available. FPR agonists have only local ADRs (see ◘ Fig. 31.1 and ◘ Table 31.1). In order to ensure high adherence, patients must be educated about ADRs.

If FPR agonists do not achieve a sufficient IOP reduction, other drug classes are used, e.g., β_xAR antagonists (prototype timolol). They can be applied either alone or in combination with FPR agonists with the goal to keep therapy as simple as possible. β_xAR antagonists mediate their effects in glaucoma via the β_2AR, causing inhibition of Na^+/K^+-ATPase and of aqueous humor production. In case of systemic β_xAR antagonist absorption, bradycardia, hypotension, AV block, and asthma can develop (see ▶ Chaps. 14, 15, 16, and 17). To avoid these ADRs, the dose should be as low as possible. Moreover, following ocular application of drugs, manual pressure should be exerted on the lower tear duct for few seconds to avoid drug outflow into the nose. β_xAR antagonists reduce IOP by 20–25%.

CAH inhibitors constitute a therapeutic alternative to β_xAR antagonists. They inhibit aqueous humor production as well. Brinzolamide is a prototypical CAH inhibitor. It reduces IOP by 20–25%. Dysgeusia (metallic taste) is the most important ADR of local administration. CAH inhibitors can cause para group allergies. Here, cross-allergies with sulfonamides can develop (See ▶ Chaps. 3 and 33).

α_2AR agonists (prototype brimonidine) reduce IOP up to 25% via a dual mechanism. On

the one hand, they inhibit Na^+/K^+-ATPase (functional antagonism with β_2AR), and on the other hand, they increase uveoscleral humor outflow. The most important ADRs of α_2AR agonists upon systemic absorption are sedation and hypotension (see ▶ Chap. 15). Combination preparations of β_xAR antagonists + CAH inhibitors or α_2AR agonists are available. They are used if IOP reduction by FPR agonists is not sufficient.

Pilocarpine is an M_xR agonist and a classic drug for treatment of glaucoma (see ▶ Chap. 5). However, it often causes eye pain and myopia and is therefore still used only in narrow-angle glaucoma. The use of AChEIs (see ▶ Chap. 5) in glaucoma is obsolete because more effective drugs with a higher therapeutic index (see ▶ Chap. 1) are available.

Acute glaucoma attack is an ophthalmological emergency that must be treated immediately. Osmotic diuretics applied i.v. reduce IOP rapidly. This reduction is accomplished via water extraction from the ocular bulb. In addition, CAH inhibitors can be administered systemically. However, this is burdened with numerous ADRs due to the ubiquitous expression of CAH (see ◘ Fig. 31.1). In acute glaucoma attack, the drugs discussed above are also used locally. In case of inefficiency of drug treatment, surgical measures must be implemented.

31.3 Pathophysiology of Age-Related Macular Degeneration (AMD)

Exudative AMD is the most important cause for blindness in >50 years old humans in industrialized countries. Because of the frequency of the disease, drugs for treatment of exudative AMD belong to the best-selling drugs globally. ◘ Figure 31.2 shows the pathophysiology of AMD and pharmacological interventions. ◘ Table 31.1 summarizes selected drugs for treatment of exudative AMD. The most important risk factor for AMD is tobacco smoking. In addition to age, excessive UV exposure and insufficiently treated hypertension (see ▶ Chap. 15) are risk factors, too. Accordingly, treatment of hypertension also contributes to AMD prophylaxis. A healthy balanced diet with ample fruits, vegetables, and fish is recommended.

There are two AMD forms. The non-exudative (dry) form accounts for about 80% of the cases but only to about 5–10% of all cases of blindness. Disease progression is slow and vision impairment is insidious. Lipofuscin deposits are found in the choroidea. There is no specific pharmacotherapy for non-exudative AMD.

Exudative (wet) AMD accounts for about 20% of the disease cases but 90–95% of all cases of blindness. In this disease form, VEGF is released, resulting in choroidal neovascularization (neoangiogenesis). However, the newly generated blood vessels are fragile so that hemorrhages with subsequent detachment of the retina from the choroidea occur. In the end stage, scarring develops, and the disease can transit into non-exudative AMD. Distorted vision is an early sign of AMD that can be easily recognized by the patient her/himself by looking at grid structures. Acute hemorrhages cause rapid and substantial vision loss. Central vision is particularly affected; the ability to read and to perceive contrasts decreases. Patients become more sensitive to glare and adapt less rapidly to changing light conditions. The grid vision test, fundoscopy, and perimetry are important for diagnosis.

31.4 Pharmacotherapy of AMD

Prior to the elucidation of the role of VEGF in neovascularization in exudative AMD, therapy was restricted to vessel sclerotherapy. Nowadays, exudative AMD can be treated with VEGF inhibitors on the basis of validated pathophysiological concepts. For inhibition of VEGF-mediated neovascularization, three drugs are available (see ◘ Fig. 31.2 and ◘ Table 31.1).

Ranibizumab is a VEGF-binding antibody fragment devoid of the Fc portion. It prevents interaction of VEGF with the VEGFR. As a result, neovascularization is inhibited. Ranibizumab is injected intravitreally under local anesthesia with an extremely fine needle. Most patients tolerate the treatment well, but injection must be performed under meticulous hygienic conditions to avoid development of bacterial endophthalmitis which is dangerous and difficult to treat and can cause irreversible loss of vision. Glaucoma and cataract are additional ADRs of ranibizumab and other VEGF inhibitors.

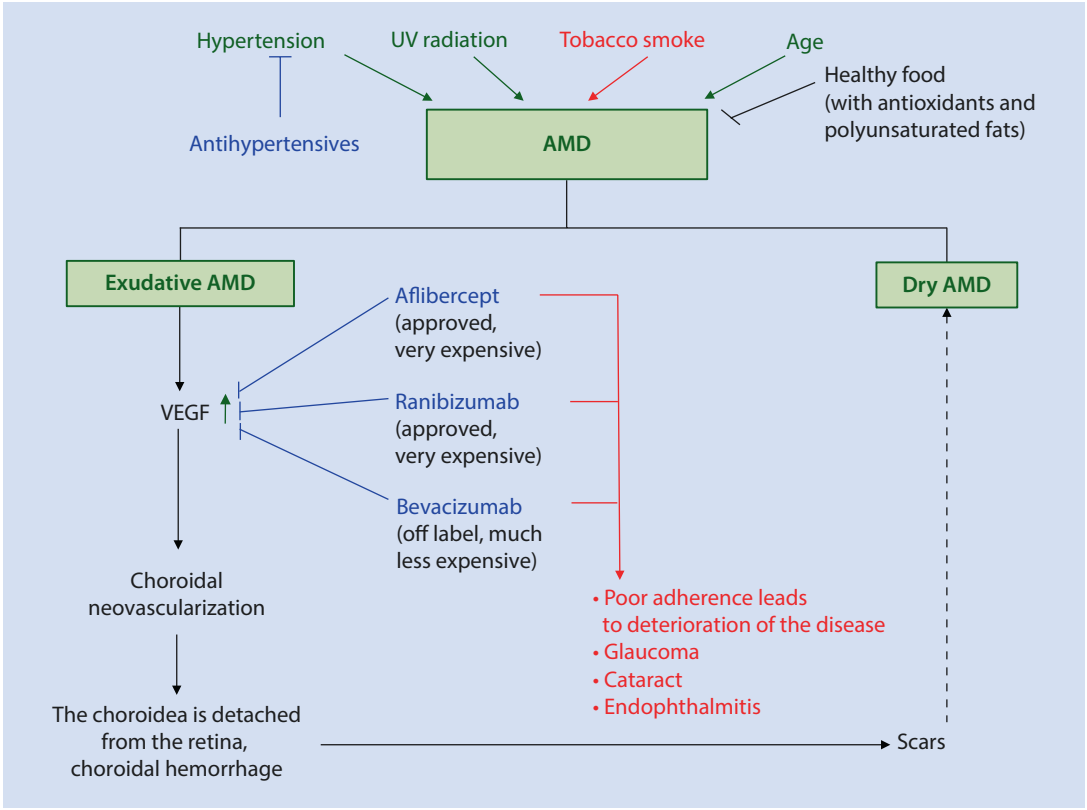

Fig. 31.2 Pathophysiology of AMD: pharmacological interventions. Inhibition of VEGF is the key to successful therapy of AMD. Off-label treatment of AMD with bevacizumab is affordable and safe! Many ophthalmologists perform this off-label treatment for cost reasons instead of prescribing more expensive alternatives! Approval of bevacizumab for AMD would be most desirable and is scientifically justified

Ranibizumab was developed under the assumption that an antibody fragment can diffuse more readily in the vitreous body than a complete antibody with Fc portion. Bevacizumab is such a complete antibody and is approved for the treatment of numerous types of cancer (see ▶ Chap. 32). In contrast to the original assumption, ranibizumab and bevacizumab possess similar efficacy in exudative AMD, but only ranibizumab is approved for AMD. There is a pharmacoeconomic controversy whether the lack of approval of bevacizumab for AMD is justified since treatment costs with ranibizumab are much higher. Because of the large price difference, bevacizumab is very often used off-label in AMD patients. However, possible ADRs are then the risk of the ophthalmologist. This example illustrates how profit-oriented price policies of pharmaceutical companies may pose problems for effective drug therapy.

Aflibercept is an alternative to ranibizumab and bevacizumab. It represents the ligand-binding domain of the VEGFR that neutralizes free VEGF. However, the high therapy costs of aflibercept are of concern as well. In view of the increasing prevalence of exudative AMD, of the need for effective and affordable long-term treatment, and of the detrimental consequences of blindness, global pressure should be exerted both on pharmaceutical companies and drug approval authorities to obtain approval of bevacizumab for exudative AMD.

Regular intravitreal injections of VEGF inhibitors in 1–3 month intervals can prevent AMD progression and even improve vision, particularly in early disease stages. However, high adherence is required for such success. Accordingly, under "real-world" conditions, the success rates of VEGF inhibitors in exudative AMD are not as compelling as in clinical studies.

In order to circumvent adherence problems, efforts are directed toward the development of gene therapeutics. It is the goal to introduce genetically modified adenoviruses into the choroidea which then continuously produce VEGF inhibitors. However, these therapeutic strategies are still in their infancy.

31.5 Questions and Answers

Questions

Which assignment of drug class to effect on the eye is correct?

A. M_xR agonists – mydriasis
B. CAH inhibitors – inhibition of tear production
C. FPR agonists – stimulation of uveoscleral and trabecular aqueous humor outflow
D. β_xAR antagonists – stimulation of trabecular humor outflow
E. α_2AR agonists – rapid IOP reduction in acute glaucoma attack

Answers

A. M_xR agonists dilate the canal of Schlemm and, thereby, increase humor outflow. M_xR agonists are only used in narrow-angle glaucoma due to ADRs.
B. CAH inhibitors reduce aqueous humor production in the ciliary body and, thereby, decrease IOP.
C. Stimulation of uveoscleral and trabecular humor outflow by FPR agonists constitutes the most effective approach to decrease IOP.
D. β_xAR antagonists, like CAH inhibitors, inhibit aqueous humor production in the ciliary body and, thereby, decrease IOP.
E. Osmotic diuretics are used for rapid IOP reduction in acute glaucoma attack. They bind water and reduce the ocular bulb volume. For long-term therapy, osmotic diuretics are not suitable because of their ADRs (most prominently systemic dehydration).

Answer **C** is correct.

31.6 Exercises

A 56-year-old man visits you in your ophthalmic practice and complains that in the periphery he sees black shadows that have become larger during the last year. He has no pain, and otherwise, he is healthy. Inspection of the eyes does not reveal abnormalities. Tonometry reveals an IOP of 20 mm Hg for the left eye and 12 mm Hg for the right eye. Fundoscopy of the left eye shows papillar excavation with kinking of the blood vessels. The anterior chamber of the left eye looks normal. Perimetry shows a sickle-shaped peripheral scotoma of the left eye. Examination of the right eye yields normal results.

Questions

1. What is your diagnosis and how do you proceed initially?
2. Which therapeutic options do you have, should the patient not respond to the initial therapy?

Answers

1. The patient suffers from open-angle glaucoma of the left eye. This is the most common glaucoma form. The fundoscopic and perimetric results are crucial for securing the diagnosis. The IOP is still "normal," but even with an apparently normal IOP, glaucoma can develop. Disease progression can be prevented if IOP is reduced by 30–50%. Thus, in the patient, IOP should be decreased to 10–14 mm Hg. You initiate a therapy with latanoprost and check IOP regularly. Latanoprost is applied only once daily (in the evening) into the eye and exhibits good efficacy in most patients. The drug does not exhibit systemic ADRs. It is important to educate the patient about the fact that only stringent adherence prevents deterioration of vision. It is equally important to discuss with the patient the possible local ADRs of latanoprost.
2. In case of insufficient IOP reduction, a combination of FPR agonist + β_xAR

antagonist (e.g., timolol) can be administered. Fixed drug combinations, facilitating application and increasing adherence, are available. Addition of a β_xAR antagonist to the regime decreases IOP by another 20%. Should even this therapy not be sufficient, a CAH inhibitor like brinzolamide and an α_2AR agonist like brimonidine can be integrated.

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Drugs for the Treatment of Malignant Tumor Diseases

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Malignant tumors are characterized by a disbalance between proliferation and apoptosis/differentiation of cells toward the former process. At the checkpoint between the G1 and S phase of the cell cycle, many signaling pathways regulating cell proliferation converge. Pharmacological interventions for tumor therapy are based on (1) cell cycle inhibition by classic cytostatics and (2) promotion of apoptosis, stimulation of immune processes, and inhibition of angiogenesis and of pathways stimulating proliferation by targeted therapeutics. Classic cytostatics have common ADRs, e.g., nausea, vomiting, fatigue syndrome, bone marrow suppression, inhibition of epithelial cell proliferation, teratogenicity and carcinogenicity, as well as drug-specific ADRs. Targeted therapeutics have serious drug-specific ADRs. To avoid development of tumor resistance, higher efficacy and reduced toxicity, classic cytostatics, and targeted therapeutics are often combined. Palliative treatment of pain and treatment of vomiting and impaired hematopoiesis are of great importance in tumor therapy. The dramatically increasing costs for targeted therapeutics constitute an important pharmacoeconomic problem in tumor therapy globally.

Key Points

1. Many malignant tumor diseases cannot be cured, but don't forget palliative pain treatment!
2. Antiemetic therapy during treatment with classic cytostatics is very important!
3. In most tumor diseases, a combination of classic cytostatics and targeted therapeutics is used.
4. Targeted therapeutics have many "unusual" ADRs!
5. Cyclophosphamide is a cell cycle-blocking alkylating agent causing serious vomiting.
6. Cisplatin cross-links DNA and induces vomiting, oto-, nephro-, and neurotoxicity.
7. Doxorubicin intercalates into DNA and is cardiotoxic.
8. MTX inhibits tetrahydrofolate synthesis and is myelo- and hepatotoxic.
9. 5-FU is a pyrimidine antagonist; 6-MP is a purine antagonist.
10. XO inhibitors potentiate myelotoxicity of 6-MP.
11. Vinblastine inhibits microtubule function and is neurotoxic.
12. Paclitaxel stabilizes microtubules, is neurotoxic, and can cause allergic reactions.
13. Etoposide inhibits TOPO-II and can induce leukemias.
14. Tamoxifen is a SERM used in ER-positive mammary carcinoma.
15. Anastrozole inhibits estrogen synthesis and is used in ER-positive mammary carcinoma.
16. Flutamide is an AR antagonist used in prostate carcinoma.
17. Olaparib induces apoptosis via PARP1 inhibition.
18. Carfilzomib induces apoptosis via proteasome inhibition.
19. Panobinostat induces apoptosis via HDC inhibition.
20. IL-2, rituximab, and pembrolizumab induce apoptosis via immune cell modulation.
21. Lenalidomide is immunomodulatory and antiangiogenic in multiple myeloma.
22. ATRA and ATO induce differentiation and apoptosis in acute promyelocytic leukemia.
23. Bevacizumab and ramucirumab are antiangiogenic via VEGFR blockade.
24. Trastuzumab is effective in HER2-positive mammary carcinoma and is cardiotoxic.
25. Imatinib inhibits BCR-ABL in chronic myelogenous leukemia.
26. Sunitinib inhibits multiple TKs and possesses a broad spectrum of toxicity.
27. Erlotinib inhibits the EGFR; antineoplastic efficacy correlates with the severity of exanthemas.
28. Palbociclib reduces proliferation via CDK inhibition.
29. Vemurafenib selectively inhibits a constitutively active Raf mutant in melanomas.

32.1 Pathophysiology of Malignant Tumors and Pharmacological Interventions

Malignant tumors (neoplasias, cancers) are classified into epithelial tumors (carcinomas), mesenchymal tumors (sarcomas), and hematopoietic tumors (leukemias, lymphomas). Globally, ca. 20 million new cancer cases are diagnosed, and ca. 10 million patients die from cancer annually. About 20% of all humans fall victim to cancer in their lifetime. In industrialized countries, the most important cancer types in women are mammary carcinoma > lung carcinoma > colorectal carcinoma. In men the order is lung carcinoma > colorectal carcinoma > prostate carcinoma. Figure 32.1 provides an overview of the regulation of tumor cell proliferation and pharmacological interventions.

In neoplasias, the balance between cell proliferation and apoptosis is shifted toward proliferation, and the immune system is ineffective at eliminating tumor cells. Tumor cell proliferation depends on sufficient oxygen and nutrient supply ensured by neoangiogenesis. The shift toward proliferation is mediated by mutations and altered expression of protective tumor suppressor genes and pathogenic oncogenes. Mutations are hereditary or acquired. Tobacco smoking, excessive consumption of alcoholic beverages, unbalanced diet, viruses, ionizing radiation (e.g., X-ray or UV radiation), as well as chemicals (e.g., asbestos, benzene, polycyclic aromatic hydrocarbons, and many drugs used in tumor therapy (Tables 32.1 and 32.2)) can cause neoplasias.

The classic strategy to treat cancer takes advantage of the fact that most tumors possess a high proliferation rate. Classic cytostatics inhibit

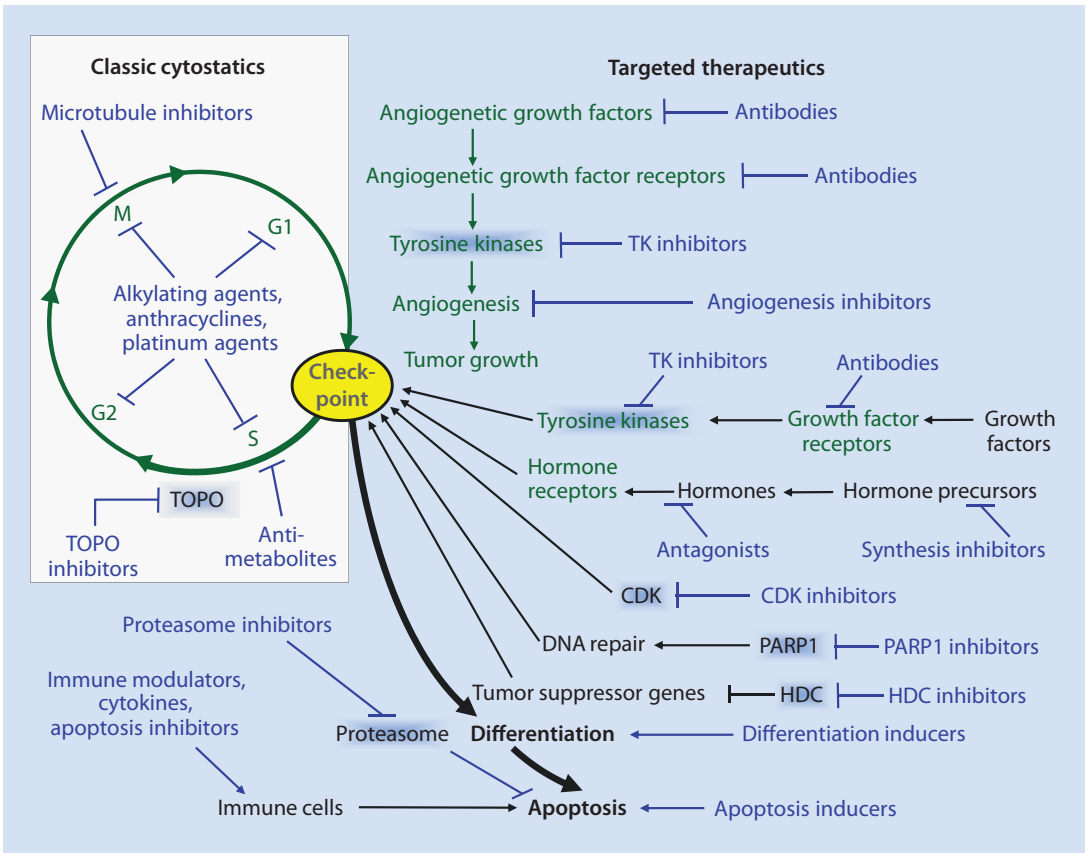

Fig. 32.1 Regulation of tumor cell proliferation and targets for classic cytostatics and targeted therapeutics. *Gray* background, targets for classic cytostatics; *blue* background, targets at the checkpoint of the cell cycle and in angiogenesis. The number of drugs directly or indirectly affecting the checkpoint of the cell cycle between the G1 and S phase is increasing exponentially! Checkpoint inhibitors belong into the hands of the oncologist and have many unusual ADRs

Table 32.1 Overview of selected classic cytostatics

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
5-FU	Pyrimidine antagonist; inhibition of thymidylate synthase; 5-FU is incorporated as a wrong base into DNA and RNA, thereby leading to abnormal base pairing and chain disruption	Cell cycle block, apoptosis, genotoxicity	Very inexpensive cytostatic for many indications (colorectal esophageal, stomach, pancreatic, mammary, cervix carcinoma, basalioma)	Vomiting, diarrhea, myelotoxicity, acute cerebellar syndrome, hand-foot syndrome (palmar-plantar erythrodysesthesia, > 10%!)	6, 13
6-MP	Purine antagonist; 6-MP is incorporated as a wrong base into DNA and RNA and causes abnormal base pairing and chain disruption	Cell cycle block, apoptosis, genotoxicity. The immunosuppressive effect is used for treatment of autoimmunopathies	Relatively inexpensive cytostatic for some indications (acute lymphoblastic leukemia, chronic myeloid leukemia); low-dose treatment of autoimmune diseases (UC, CD)	Myelotoxicity and hepatotoxicity; 6-MP degradation by XO; dose reduction if co-administered with allopurinol	11, 12, 23
Cisplatin	Cross-linking of DNA strands (preferably N7 of guanine and adenine)	Cell cycle block, apoptosis, genotoxicity	Seminoma; ovarian, mammary, bladder carcinoma; head and neck tumors, esophageal carcinoma	Excessive vomiting, nephrotoxicity, ototoxicity, peripheral neuropathy	6, 12
Cyclophosphamide	Alkylation of guanine with subsequent DNA cross-linking	Cell cycle block, apoptosis, genotoxicity. The immunosuppressive effect is used for treatment of autoimmunopathies (low dose)	Very inexpensive cytostatic for many indications (lymphoma, multiple myeloma, leukemias, ovary and mammary carcinomas, small-cell lung carcinoma, neuroblastoma); low-dose treatment of autoimmune diseases	Excessive vomiting, urotoxic effect of the metabolite acrolein (antidote: MESNA)	4, 11, 12
Doxorubicin (adriamycin)	Intercalation into DNA and RNA, inhibition of TOPO-II, enhanced ROS generation	Cell cycle block, apoptosis, genotoxicity	Mammary carcinoma, Kaposi's sarcoma, lymphoma, acute lymphatic leukemia	Cardiotoxicity (type 2, reversible arrhythmia; type 1, dose-dependent irreversible cardiomyopathy)	16, 17

Etoposide	Inhibition of TOPO-II and subsequent DNA unwinding, inhibition of DNA religation	Cell cycle block, apoptosis, genotoxicity	Relatively inexpensive cytostatic for various tumors (Kaposi's sarcoma, Ewing's sarcoma, lung carcinoma, glioblastoma multiforme, seminoma, lymphoma, leukemia)	Allergic reactions, mixed-lineage leukemia after 1–3 years	3
Irinotecan	Inhibition of TOPO-I	Cell cycle block, apoptosis, genotoxicity	Mainly colorectal carcinoma	Muscarinic syndrome, diarrhea	4, 5
MTX	Inhibition of dihydrofolate reductase and subsequent inhibition of synthesis of thymidine, purine bases, methionine, and serine	Cell cycle block, apoptosis, genotoxicity. The immunosuppressive effect is used for treatment of autoimmunopathies	Very inexpensive cytostatic for many indications (mammary carcinoma, head and neck tumors, leukemias, lymphoma, osteosarcoma, bladder carcinoma), low-dose treatment of autoimmune diseases	Myelotoxicity, hepatotoxicity, mucositis (folinic acid supplementation to reduce ADRs, especially myelotoxicity)	4, 11
Paclitaxel	Microtubule stabilization; inhibition of spindle assembly and cell cycle arrest in metaphase of mitosis	Cell cycle block, apoptosis, genotoxicity. The antiproliferative effect on the intima prevents the restenosis of coronary stents (coating)	Relatively inexpensive cytostatic for various tumors (ovary, mammary, lung, bladder, esophageal carcinoma)	Hypersensitivity reactions after infusion with Cremophor EL (premedication with H_1R and H_2R antagonists and GCR agonists), polyneuropathy	3, 16
Vinblastine	Inhibition **of** microtubule polymerization; inhibition of spindle assembly and cell cycle arrest in metaphase of mitosis	Cell cycle block, apoptosis, genotoxicity	Relatively inexpensive cytostatic for various tumors (Hodgkin lymphoma, seminoma, melanoma, lung carcinoma, bladder carcinoma, brain tumors)	Neurotoxicity (polyneuropathy), myelotoxicity	23

Table 32.2 Overview of selected targeted therapeutics

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Anastrozole	Inhibition of aromatase (reduced conversion of testosterone to estrogen in the adrenal gland and in adipose tissue)	Inhibition of mammary carcinoma cell proliferation	Advanced postmenopausal mammary carcinoma	Osteoporosis, hot flashes, headache, fatigue, exanthemas, arthralgias, insomnia	24
ATO	Multimerization and, thus, inactivation of the PML/RARα fusion protein	Derepression of genes which predominantly control apoptosis (and to a lesser extent differentiation) of promyelocytes	Acute promyelocytic leukemia; the combination of ATRA and ATO is very successful (remission rate of 90%)	Carcinogenicity due to inhibition of gene repair mechanisms and impairment of energy metabolism	
ATRA	Binds to the PML/RARα fusion protein in tumor cells; binding to the retinoic acid receptor in normal body cells	Derepression of genes which control differentiation of promyelocytes to neutrophil granulocytes; improved keratinocyte differentiation in acne	Acute promyelocytic leukemia; remission rate of 80%; combination with ATO; acne (local and systemic therapy)	Differentiation syndrome (accumulation of neutrophil granulocytes in the lung) with acute respiratory failure; teratogenicity (contraception is required)	
Bevacizumab	Monoclonal antibody which binds and functionally inactivates VEGF	Inhibition of tumor angiogenesis and, hence, restricted oxygen and nutrition supply of the tumor	Metastatic colorectal and mammary carcinoma, advanced renal cell carcinoma, non-small-cell bronchial carcinoma, advanced gynecological carcinoma; off-label use in exudative AMD	Hypertension, proteinuria, fatigue, GI disorders (including ileus and perforation), wound healing disorders, thromboembolism	15, 18, 31
Carfilzomib	Proteasome inhibition and, thus, degradation of excessive and incorrectly folded proteins	Apoptosis	Multiple myeloma	Respiratory tract infections, GI disturbances, herpes zoster reactivation, polyneuropathy	33, 34
Erlotinib	Selective inhibition of HER2 TK	Inhibition of tumor cell proliferation, inhibition of metastasis	First-line therapy of non-small-cell bronchial carcinoma with L858R mutation and metastatic pancreatic carcinoma	Diarrhea, acneiform exanthemas (associated with successful therapy), interstitial lung disease	13

Flutamide	Nonsteroidal AR antagonist	Inhibition of proliferation of prostate carcinoma cells; apart from that antiandrogenic effects in women	Adjuvant therapy in prostate carcinoma, palliative therapy in advanced prostate carcinoma; treatment of hirsutism and polycystic ovary in women	Hepatotoxicity, muscle atrophy, osteoporosis, anemia, gynecomastia, hot flashes, weight gain, ED, loss of libido (chemical castration)	24
IL-2	T-cell activation	Immune modulation (in combination with HA)	Acute myeloid leukemia	Flu-like symptoms, thyroiditis, mental disorders, GI disturbances, respiratory tract diseases	7
Imatinib	Inhibition of several TKs (constitutively activated BCR-ABL, c-kit, PDGFR)	Inhibition of tumor cell proliferation, apoptosis	Chronic myeloid leukemia, GI stroma tumors, chronic eosinophilic leukemia, mastocytosis	Nausea, vomiting, muscle spasms, headache, edema, hypertension, allergic reactions, neutropenia, thrombopenia, interactions with CYP3A4 inducers and inhibitors	2, 3
Lenalidomide	Binding to ubiquitin E3 ligase with subsequent degradation of specific transcription factors	Immune modulation, antiangiogenic effect, apoptosis	Multiple myeloma, myelodysplastic syndrome, mantle cell lymphoma	Thromboembolisms, SJS, teratogenicity, fatigue, risk of acute myeloid leukemia (2% after 2 years; 4% after 3 years)	18
Olaparib	Inhibition of PARP1 and, thus, of DNA repair	Cell cycle blockade, apoptosis	Tumors with mutations in the tumor suppressor genes BRCA1 and 2 (ovary, fallopian tube, peritoneal carcinoma)	Loss of appetite, nausea, vomiting, anemia, fatigue	
Palbociclib	Selective inhibition of CDK4 and CDK6	Inhibition of tumor cell proliferation, inhibition of metastasis	Therapy of the advanced and metastatic ER-positive and HER2-negative mammary carcinoma, combination with aromatase inhibitors or SERMs	Myelotoxicity. As the drug has been approved only recently, the list of ADRs is still incomplete	
Panobinostat	HDC inhibition and, thus, enhanced expression of tumor suppressor genes	Apoptosis	Multiple myeloma (drug of last resort if other drugs fail)	GI disturbances, susceptibility to infections, neutro- and thrombopenia	
Pembrolizumab	Monoclonal antibody against the T-cell antigen PD-1 (programmed cell death receptor 1)	Inhibition of tumor-specific T-cell apoptosis; enhancement of tumor-specific immune reactions	Unresectable or metastatic melanoma and other advanced tumors which overexpress the PD1 ligand	Severe infusion reactions, autoimmune reactions of many organs (e.g., skin, kidney, blood vessels, liver, endocrine organs)	3, 11

(continued)

Table 32.2 (continued)

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Ramucirumab	Monoclonal antibody against VEGFR 2	Inhibition of tumor angiogenesis and, hence, restricted oxygen and nutrition supply of the tumor	Gastric, colorectal, non-small-cell lung carcinoma	Diarrhea, hyponatremia, headache, hypertension	15
Rituximab	Monoclonal antibody against the B-lymphocyte antigen CD20	Complement-dependent cytotoxicity, antibody-dependent phagocytosis and cytotoxicity, immunosuppression, B cell depletion	Chronic lymphocyte leukemia, B cell lymphoma, non-Hodgkin lymphoma, immunosuppression in autoimmune diseases (e.g., rheumatoid arthritis)	Allergic reactions, hypotension, TEN, susceptibility to infections, activation of hepatitis B, PML	3, 34
Sunitinib	Inhibition of several TKs (PDGFR, VEGFR, c-kit, RET)	Inhibition of tumor cell proliferation and angiogenesis, inhibition of metastasis	GI stroma tumors, renal cell carcinoma, pancreatic neuroendocrine tumors	Hypothyroidism, fatigue, diarrhea, mucositis, dysgeusia, hypertension, palmar-plantar erythrodysesthesia, thromboembolism	15, 18, 21
Tamoxifen	The active metabolite is endoxifen (mediated by CYP2D6). SERM with antagonistic ER effect on the mammary gland and agonistic ER effect on bones, endometrium and cardiovascular system	Inhibition of mammary carcinoma cell proliferation	Adjuvant therapy of mammary carcinoma and metastatic mammary carcinoma	Hot flashes, GI disturbances, water retention, endometrial hyperplasia (increased risk for endometrial carcinoma)	24
Trastuzumab	Monoclonal antibody against HER2 (ErbB2)	Inhibition of HER2-activated pathways which promote proliferation	HER2-positive metastatic mammary carcinoma; combination with paclitaxel, which inhibits HER2 insertion into membranes, and tamoxifen for treatment of ER-positive tumors	Cardiotoxicity, allergic reactions, fever, susceptibility to infections, headache, insomnia	3, 16
Vemurafenib	Selective inhibition of the TK B-Raf with V600E mutation	Inhibition of tumor cell proliferation, inhibition of metastasis, apoptosis	Advanced and metastatic melanoma (V600E mutation in 60% of melanoma)	Fatigue, arthralgia, dermal toxicity (photosensitivity), exanthemas, hyperkeratosis, squamous cell carcinoma	3

cell proliferation by targeting the cell cycle. Various drug groups (alkylating agents, anthracyclines, platinum compounds) act in all cell cycle phases, antimetabolites and TOPO inhibitors selectively in the S phase, and microtubule inhibitors in the M phase. All these drugs do not differentiate between tumor cells and normal cells with a high proliferation rate (e.g., skin, mucosa, hematopoietic cells), resulting in numerous ADRs (see ▶ Sect. 32.3). ◘ Table 32.1 summarizes selected classic cytostatics. Therapy with cytostatics is often performed in cycles (few days of therapy, several days of pause) to facilitate regeneration of normal cells.

Because of the lack of selectivity of classic cytostatics for tumor cells and the serious ADRs, much effort is directed toward the development of targeted antineoplastic drugs (targeted therapeutics). These drugs address specific molecular alterations in tumor cells, inhibit angiogenesis, or strengthen the immune system (see ▶ Sect. 32.4). Many biochemical changes in tumor cells affect signaling pathways converging at the checkpoint between the G1 and S phase, regulating whether a cell enters proliferation or undergoes differentiation with subsequent apoptosis (◘ Fig. 32.1). Although targeted therapeutics do not possess the typical ADRs of classic cytostatics, nonetheless, they have serious drug-specific ADRs. ◘ Table 32.2 summarizes selected targeted therapeutics. This class of therapeutics constitutes one of the most active fields of drug design and approval.

Development of resistance is a major problem in tumor therapy. Via increased expression of MRPs, tumor cells can export numerous low-molecular mass antineoplastic drugs, rendering them ineffective. Tumor cells with high MRP expression have a strong advantage for selection and multiply therefore rapidly. Unfortunately, it is currently not possible to potently and selectively inhibit MRPs to enhance the efficacy of antineoplastic drugs. In addition, reduced cellular uptake, increased metabolic drug inactivation, and lower expression of target receptors contribute to development of tumor resistance. Mutation of target proteins under selection pressure is another important resistance mechanism, causing that the drug does not bind anymore to the target. Via this mechanism, tumor cells with mutated target proteins gain strong selection advantages. In the meantime, PK inhibitors selectively inhibiting certain mutated PKs have been developed. To at least delay resistance development, several drugs are usually combined with each other in modern cancer therapy.

32.2 Principles of Tumor Therapy

The earlier therapy of a tumor is initiated, the better are the chances for tumor elimination. For successful tumor therapy, precise cytological and molecular classification of the tumor (expression of specific receptors and/or mutations in oncogenes or TKs) and exact staging according to the TNM (*t*umor, lymph *n*ode, *m*etastasis) classification are essential. An optimal treatment strategy can only be implemented if all these parameters are known. For most tumors, specific therapeutic schemes are available. However, due to the improved molecular tumor diagnostics, to the approval of many new drugs, and to clinical studies of increasing complexity, therapeutic strategies change much more rapidly than in any other field of pharmacology. These schemes are far beyond basic knowledge and will be therefore not reviewed in this textbook. The focus of this chapter is the discussion of selected representative drugs with different mechanisms of action.

Whenever possible, the primary tumor, affected lymph nodes, and metastases should be removed surgically. In addition, targeted irradiation of a tumor or radioisotope treatment (e.g., ^{131}iodide in case of thyroid carcinoma, see ▶ Chap. 21) can be effective. It is the goal to eliminate the tumor (curative therapy). To achieve this goal, aggressive therapy entailing numerous serious ADRs has to be implemented. Early diagnosed melanomas and carcinomas of the mammary gland, thyroid gland, and prostate gland and testes tumors have a good prognosis. In contrast, prognosis of carcinomas of the esophagus, lung, and pancreas and of brain tumors is poor.

In advanced neoplasias or in tumors with poor prognosis, palliative therapy is performed to achieve temporary remissions, to delay progression, and to increase the survival time and the quality of life. In clinical studies, the efficacy of antineoplastic therapy is measured as progression-free survival time or, clinically more relevant, overall survival time.

For many neoplasias, survival rates have improved very substantially during the past years.

Most classic cytostatics are relatively inexpensive. By analogy to antibiotics (see ▶ Chap. 33), the small profits associated with the production and distribution of classic cytostatics have resulted in the concentration of global drug production in few locations. In case of problems with production, e.g., due to quality problems, the continuous supply of cytostatics has become erratic in several cases. In contrast, most targeted therapeutics are still under patent protection, and drug companies can reap large profits. In many industrialized countries, very high prices for these drugs can be achieved. The cost explosion for targeted therapeutics has resulted in intensive discussions about the cost-benefit ratio and affordability of modern tumor therapy. The comparison of the efficacy of various drugs in tumor therapy has become increasingly difficult due to the ongoing dissolution of classic phase 1–3 studies into complex study protocols with multiple subgroups.

In addition to tumor therapy with classic cytostatics and targeted therapeutics, palliative therapy of tumor-associated symptoms and drug-induced ADRs is of great importance. It is the goal to alleviate pain and improve quality of life. A good palliative therapy will allow patients to remain independent in their homes for a relatively long period of time.

Most tumor patients suffer from severe pain, specifically in advanced and final stages. In stage 1 of the WHO pain management plan, non-MOR analgesics are used, considering ADRs and contraindications (see ▶ Chap. 10). In stage 2, MOR agonists with low efficacy such as tramadol are added, and in stage 3 MOR agonists with higher efficacy (buprenorphine < morphine and fentanyl) are applied (see ▶ Chap. 10). Analgesics should be administered regularly p.o. In advanced tumor stages, pump systems are used, delivering the analgesics continuously i.v. or s.c. In case of acute pain, the patient can administer himself/herself extra-analgesic doses within certain limits.

In addition, co-analgesics are used in all stages of tumor pain therapy. Among these drugs are denosumab and bisphosphonates for bone metastases (see ▶ Chap. 20), mGPCR antagonists (see ▶ Chap. 29), NSMRIs, NIPEs (see ▶ Chap. 28), and benzodiazepines (see ▶ Chap. 25) as well as ketamine for severe and neuropathic pain. For cytostatic-induced vomiting, 5-HT_3R antagonists (early vomiting) and NK_1R antagonists (late vomiting) (see ▶ Chap. 6) are used. D_2R antagonists (see ▶ Chaps. 8 and 29) are antiemetic as well. GCR agonists (see ▶ Chap. 11) possess antiemetic and anti-inflammatory effects.

Classic cytostatics suppress hematopoiesis, becoming obvious 10–14 days after initiation of therapy. In case of severe neutropenia, resulting in increased susceptibility to infections, G-CSF can be applied. In anemia, erythrocyte concentrates are given. In case of thrombopenia (< 10.000/µl), platelet concentrates are administered. Severe mucositis is treated with the keratinocyte-stimulating factor palifermin. Bacterial (see ▶ Chap. 33), viral (see ▶ Chap.34), and fungal infections (see ▶ Chap. 35) are medicated with appropriate drugs. Several cytostatics, particularly vinblastine, cause tissue necrosis in case of paravenous injection. Therefore, cytostatics are applied via a central venous catheter.

32.3 Classic Cytostatics

Classic cytostatics are dosed based on body surface area. They have a common spectrum of ADRs including fatigue syndrome, nausea, and vomiting. A physical exercise program commensurate with the physical capability of the patient can control the fatigue syndrome. Nausea and vomiting may be treated with antiemetics (see ▶ Sect. 32.2). The development of modern antiemetics and implementation of physical exercise programs have substantially increased tolerability of therapy with cytostatics (see ▶ Chap. 6). In many cases, tumor therapy can be performed as outpatient treatment.

Cytostatics inhibit epithelial cell proliferation, resulting in mucositis, stomatitis, esophagitis, enteritis, and alopecia. They also inhibit the proliferation of hematopoietic stem cells, leading to granulocytopenia, anemia, and thrombopenia. These ADRs can be treated specifically (see ▶ Sect. 32.2).

More and more tumor patients are "cured," i.e., they survive for at least 5 years after the tumor diagnosis. Since classic cytostatics are also carcinogenic, an increasing number of patients fall sick of secondary neoplasias, e.g., lymphomas, many years after being "cured." Additionally, cytostatics are teratogenic so that safe contraception has to be ensured during therapy. In tumor patients desiring to have children, germ cells can be collected and cryoconserved prior to chemotherapy.

After chemotherapy, in vitro fertilization may be performed. Cytostatics induce azoospermia and amenorrhea. They are immunosuppressive. For some drugs, e.g., MTX, cyclophosphamide, and 6-MP, this effect is used therapeutically in autoimmune diseases (see ▶ Chap. 11), but applied doses are much lower than in neoplasias. The immunosuppressive effect of cytostatics in high-dose therapy increases susceptibility to infections which is further augmented by suppression of hematopoiesis. In case of massive degradation of tumor cells under cytostatics, purine bases can accumulate excessively. They are metabolized via XO to uric acid. Accordingly, tumor lysis syndrome associated with the symptoms of acute or chronic gout can develop (see ▶ Chaps. 12 and 23). It can be treated with uricostatics. If children are treated with cytostatics, growth inhibition may result. All classic cytostatics possess the above ADRs, but there are quantitative differences between individual drugs. In addition, drug-specific ADRs occur (◘ Table 32.1).

Cyclophosphamide is a prototypical alkylating agent. In the liver, it is converted via CYP2B6 to the active metabolite aldophosphamide (see ▶ Chap. 2) which is then cleaved nonenzymatically into the alkylating aziridinium ion and acrolein. The aziridinium ion alkylates nitrogen at the 7-position of the guanine ring, leading to inter- and intrastrand DNA cross-linking. As a result, DNA polymerases are inhibited, and DNA strand breaks occur. In 5–10% of all patients, cyclophosphamide leads to hemorrhagic cystitis caused by acrolein. The antidote 2-mercaptoethansulfonate (MESNA) binds to acrolein in the blood (see ▶ Chap. 4). The complex is filtered in the glomeruli and cannot penetrate anymore into the urothelial cells. The urotoxicity of cyclophosphamide is further reduced if the patients drink ample fluids, diluting acrolein and increasing diuresis (see ▶ Chap. 12). Carmustine is a lipophilic alkylating agent that penetrates the BBB and is used for CNS tumors.

Platinum compounds (prototype cisplatin) cross-link DNA strands preferentially via the nitrogen at the 7-position of guanine and adenine rings and lead to similar consequences as alkylating agents. Nausea and vomiting are the most important ADRs. Therefore, an effective antiemetic therapy is particularly important. Moreover, platinum compounds are nephro- and ototoxic. Great caution must be exerted if additional nephro- and ototoxic drugs are applied (see ▶ Chaps. 12 and 33).

Doxorubicin (adriamycin) is a prototypical anthracycline. These drugs intercalate into DNA and RNA, thereby inhibiting both DNA polymerase and RNA polymerase. In addition, they inhibit TOPO-II and generate ROS which damage DNA. Doxorubicin exhibits high cardiotoxicity. At the beginning of anthracycline therapy, reversible arrhythmias can occur. Later, irreversible cardiomyopathy may develop which occurs predominantly in patients in whom a cumulative drug dose of 550 mg/m^2 body surface has been exceeded. Therefore, it is essential to monitor heart function of doxorubicin-treated patients. In case of preexisting arrhythmias or CHF, doxorubicin must not be used. Bleomycin possesses a similar mechanism of action. It is less cardiotoxic than doxorubicin but induces severe lung fibrosis. In addition, bleomycin is dermatotoxic. Allergic reactions, hyperpigmentation, edema, and ulcerations can occur as well.

Antimetabolites interrupt the cell cycle in the S phase. The folate antagonist MTX, the pyrimidine antagonist 5-FU, and the purine antagonist 6-MP are prototypes of this drug class. MTX possesses a 1000-fold higher affinity to dihydrofolate reductase than dihydrofolate and inhibits the enzyme competitively. As a result, cells are depleted of tetrahydrofolate which is required for synthesis of pyrimidines, purines, and the amino acids serine and methionine. MTX is very myelotoxic and hepatotoxic and can cause loss of memory (chemo brain). Toxicity can be reduced if folinic acid (5-formyl tetrahydrofolate) is administered as antidote 24 hours after MTX application. The application of folinic acid is also referred to as leucovorin or citrovorum factor rescue. In contrast, the cytostatic effects of 5-FU are potentiated by folinic acid. This effect is exploited in certain chemotherapy regimes. MTX is eliminated renally. Sufficient intake of fluids and alkaline urine pH are essential to avoid crystallization of MTX in the kidney (see ▶ Chap. 12). Penicillins and benzbromarone inhibit MTX elimination. Accordingly, drug doses have to be adjusted or drugs need to be applied in a staggered manner.

The purine antagonist 6-MP is phosphorylated to 6-MP monophosphate via hypoxanthine phosphoribosyl transferase (HPRT). Further phos-

phorylation results in 6-MP triphosphate. This nucleotide with a wrong base is integrated into DNA and RNA. Via impaired base paring, caused by the larger size of sulfur relative to oxygen, chain termination occurs. 6-MP degradation is mediated by XO and thiopurine methyltransferase (TPMT). In patients treated with an XO inhibitor because of tumor lysis syndrome, 6-MP toxicity is increased considerably (see ▶ Chap. 23). There are clinically relevant TPMT polymorphisms. About 10% of the population have a substantially reduced TPMT activity, and in 0.3%, the enzyme is absent. In these patients, myelotoxicity of 6-MP is increased substantially. Therefore, TPMT activity must be determined prior to therapy with 6-MP, and the drug dose must be adjusted (see ▶ Chap. 2). Clinically relevant polymorphisms also play a role in the therapy with 5-FU. This drug is inactivated by dihydropyridine dehydrogenase (DPD). In about 8% of the population, DPD activity is reduced, resulting in substantially increased 5-FU toxicity. In these, patients, the 5-FU dose must be lowered.

Vinblastine is a vinca alkaloid depolymerizing microtubules. This results in inhibition of the spindle apparatus and arrest of mitosis in the metaphase. Since microtubules are also important for axon transport (see ▶ Chap. 30), vinblastine causes polyneuropathy. This ADR becomes manifest in motor, sensory, and autonomic nerve disturbances. Therefore, vinblastine must not be used in patients with preexisting polyneuropathies. Under therapy with vinblastine, neurological control exams are required.

Paclitaxel inhibits mitosis in the metaphase via microtubule stabilization. It causes allergic reactions that are usually due to the solvent macrogol glycerol ricinolate (Cremophor EL) (see ▶ Chap. 3). The risk of allergic reactions is reduced by infusion of nanoparticle-bound paclitaxel. The drug is metabolized via CYP3A4. Under simultaneous therapy with CYP3A4 inhibitors (e.g., erythromycin or ketoconazole), ADRs of paclitaxel are augmented (see ▶ Chap. 2). Like vinblastine, paclitaxel is neurotoxic. Docetaxel is structurally related to paclitaxel and is highly dermatotoxic.

Etoposide is a prototypical TOPO-II inhibitor, preventing unwinding of DNA and thereby inhibiting the cell cycle in the S phase. Etoposide is exported from tumor cells via MRPs. As a result of increased MRP expression, tumor cell resistance against etoposide develops. Conversely, MRP inhibitors such as verapamil or dronedarone increase etoposide toxicity (see ▶ Chap. 2). Etoposide can cause type I allergies (see ▶ Chap. 3). Therefore, it must be infused slowly, and both cardiovascular and respiratory function must be controlled. Etoposide can also induce translocations on chromosome 11, causing generation of mixed-lineage leukemias. These drug-induced leukemias are difficult to treat.

Irinotecan is a prototypical TOPO-I inhibitor. It is a prodrug that is converted to the active metabolite by esterases. Irinotecan is often used in colorectal cancer. It causes diarrhea (see ▶ Chap. 13). Early diarrhea is the result of AChE inhibition. Late diarrhea is due to a direct toxic effect on the mucosa. AChE inhibition can also induce a muscarinic syndrome (see ▶ Chap. 5) for which atropine is an antidote (see ▶ Chap. 4).

32.4 Targeted Therapeutics

Whereas classic cytostatics possess many common ADRs, the situation for targeted therapeutics is much more complex (◘ Table 32.2). Each drug has a unique ADR spectrum. Targeted therapeutics are often combined with classic cytostatics. Since targeted therapeutics address molecularly defined mechanisms, their indications are often more restricted than those of classic cytostatics. Detailed molecular diagnostics are required to ensure that the target is present in the tumor.

Some targeted therapeutics affect mechanisms relevant for every tumor. Among these drugs are inhibitors of neoangiogenesis. This process is necessary to provide the tumor with oxygen and nutrients. VEGF is one of the most important angiogenic growth factors. It binds to the VEGFR which stimulates angiogenesis via its TK domain. This process can be inhibited at various levels. There are antibodies that neutralize VEGF (e.g., bevacizumab). Other antibodies (e.g., ramucirumab) bind to the VEGFR and prevent ligand-receptor interaction. TK inhibitors (e.g., sunitinib) block the catalytic activity of the receptor-regulated TK domain (see ▶ Chap. 1). Antiangiogenic drugs cause cardiovascular ADRs such as thromboembolism (see ▶ Chap. 18) and hypertension (see ▶ Chap. 15).

Many targeted therapeutics act at the checkpoint between the G1 and the S phase, mediat-

ing whether a cell multiplies or differentiates and enters apoptosis. Overexpressed sex hormone receptors play a major role in the regulation of tumor proliferation. ER activation can drive proliferation of mammary carcinoma cells. The SERM tamoxifen antagonizes the ER on mammary carcinoma cells, whereas the drug acts as an agonist at the ER in the bone, endometrium, and cardiovascular system. Another approach is to inhibit estrogen synthesis with aromatase inhibitors (anastrozole) (see ▶ Chap. 24). Many prostate carcinoma cells overexpress the AR. Accordingly, tumor cell proliferation can be reduced by AR antagonists such as flutamide (see ▶ Chap. 24). Since the AR is expressed in all organs, flutamide possesses multiple ADRs.

TK-linked growth factor receptors play a central role in tumor cell proliferation. Therefore, many targeted therapeutics address these receptors. Trastuzumab is an antibody binding to HER2, thereby blocking its function. The drug can be used to treat mammary carcinomas overexpressing HER2. Many TK/PK inhibitors have been developed. In addition to the already mentioned sunitinib, erlotinib belongs into this group. Certain drugs potently inhibit the activity of constitutively active PKs that drive tumor cell proliferation. The classic example is imatinib, inhibiting the fusion protein BCR-ABL in chronic myelogenous leukemia. Another example is vemurafenib which inhibits the activity of Raf bearing a specific point mutation. However, since most PK inhibitors inhibit several PKs more or less potently, they possess a broad spectrum of ADRs, ranging from fatigue to endocrine problems (hypothyroidism with sunitinib) and induction of squamous cell carcinoma (vemurafenib). In case of erlotinib, the antineoplastic efficacy correlates with the severity of an acneiform exanthemas.

Recently, the first inhibitor of CDK4 and CDK6 has been approved (palbociclib). These protein kinases play a central role at the G1/S phase checkpoint. Repair of DNA damage in tumor cells occurs via PARP1. Inhibitors of this enzyme (prototype olaparib) reduce proliferation of certain tumors. Another approach in targeted tumor therapy is to modulate histone acetylation. Histones form complexes with DNA, thereby regulating gene expression. The HDAC inhibitor panobinostat enhances expression of certain tumor suppressor genes and, thereby, inhibits proliferation, ultimately leading to apoptosis. All these drugs also possess numerous ADRs.

Further strategies in targeted tumor therapy are modulation of cell differentiation, protein degradation, and apoptosis. All-trans retinoic acid (ATRA) binds to the PML-RARα fusion protein in promyelocytic leukemia cells and abrogates the differentiation blockade. As a result, the lack of neutrophils, important cells for host defense, is alleviated. Arsenic trioxide (ATO) inactivates the fusion protein PML-RARα and induces apoptosis. With the combination of ATRA + ATO, excellent therapeutic results can be obtained in acute promyelocytic leukemia, previously characterized by a very poor prognosis. However, this therapy is also burdened with serious ADRs. Accumulation of neutrophils in the lung can lead to respiratory failure. In addition, ATRA is teratogenic, requiring safe contraception. ATO is carcinogenic so that secondary neoplasias can develop.

B cells express the receptor CD20, mediating proliferation. Via binding to CD20, rituximab blocks proliferation signals in tumor cells expressing CD20 at high levels. Hence, B cell lymphoma cells and non-Hodgkin lymphoma cells undergo apoptosis. However, since CD20 is not only expressed in tumor cells but also in normal immune cells, rituximab possesses many ADRs.

The proteasome is responsible for degradation of misfolded and excessive proteins. Inhibition of this essential cell function by carfilzomib causes "littering" of tumor cells with subsequent apoptosis. This mechanism is used in the therapy of multiple myeloma. Because of the general importance of the proteasome for cell biology, pharmacological intervention into this process causes many ADRs as well.

A major task of the immune system is the elimination of tumor cells. However, particularly in late tumor stages, the immune system is no longer capable of properly performing this function. In view of the fact that classic cytostatics cause immunosuppression and thereby counteract tumor cell elimination, new therapeutic strategies aim at improving immune defense and indirectly enhancing tumor cell apoptosis. IL-2 activates T cells and, in combination with HA (see ▶ Chap. 7), enhances tumor cell elimination in acute myelogenous leukemia. Lenalidomide possesses antiangiogenic and immunomodulatory effects, thereby facilitating tumor cell apoptosis. This approach has resulted in substantial improvement of the

prognosis in multiple myeloma. However, lenalidomide possesses serious ADRs. The drug is teratogenic, requiring safe contraception. In addition, lenalidomide is carcinogenic, i.e., it increases the risk of the development of acute myelogenous leukemia. Moreover, because of its antiangiogenic effect, lenalidomide causes thromboembolism (see ► Chap. 18).

A final example for immunological approaches in tumor therapy is provided by pembrolizumab. This antibody inhibits apoptosis of tumor-specific T cells, thereby enhancing tumor cell apoptosis. This strategy is used in unresectable malignant melanoma. However, because this therapy constitutes a fundamental intervention in immune cell mechanisms, it is also burdened with serious ADRs, specifically autoimmune reactions (see ► Chap. 11). The ADRs have to be carefully weighed against the expected therapeutic benefit and the high costs.

32.5 Questions and Answers

Questions

Which statement on the mechanism of action of targeted therapeutics is *NOT* correct?

A. Lenalidomide is immunomodulatory and inhibits angiogenesis.
B. Palbociclib inhibits CDKs.
C. Vemurafenib inhibits BCR-ABL.
D. Olaparib inhibits PARP1.
E. Sunitinib inhibits various tyrosine kinases.

Answers

A. Via this mechanism of action lenalidomide has improved substantially the survival time of patients with multiple myeloma (plasmacytoma).
B. CDKs regulate the cell cycle. Palbociclib inhibits CDK4 and CDK6 and is used in the therapy of ER-positive/HER-negative locally advanced metastasizing mammary carcinoma.
C. Vemurafenib selectively inhibits Raf with a point mutation (V600E). This TK is constitutively active and, thereby, stimulates proliferation of certain melanomas.
D. PARP1 is important for repairing DNA damage. As a result of PARP1 inhibition, DNA damage in tumor cells cannot be repaired anymore, and tumor cells undergo apoptosis.
E. Sunitinib inhibits several TKs including PDGFR, VEGFR and c-Kit. Among other indications, sunitinib is used for treatment of GI stroma and neuroendocrine tumors.

Statement **C** is not correct.

32.6 Exercises

A 63-year-old male patient with metastasizing colorectal carcinoma receives a combination chemotherapy of 5-FU + oxaliplatin + folinic acid (FOLFOX). Suddenly, the patient develops fever. In the hemogram you diagnose neutropenia (400 neutrophils/µl).

Questions

1. How do you proceed diagnostically?
2. How do you proceed therapeutically?

Answers

1. The combination of fever and neutropenia suggests that the patient suffers from a bacterial infection. You try to identify the source of infection. You draw blood to start a blood culture with the goal to identify the responsible bacterium and prepare an antibiogram.
2. To improve neutropenia, G-CSF should be administered. This growth factor stimulates maturation of neutrophils in the bone marrow and improves the function of circulating neutrophils. Thus, G-CSF should alleviate neutropenia and improve host defense. If the status of the patient is poor, antibiotic therapy targeting the suspected pathogenic bacterium should be initiated prior to having the results of the antibiogram. Once the acute situation is under control, the cytostatic therapy has to be re-evaluated. The cytostatic regimen could be modified, G-CSF could be injected regularly, or targeted therapeutics without risk for neutropenia could be administered. VEGF inhibitors constitute drug candidates for the patient.

Further Reading

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Drugs for the Treatment of Bacterial Infections

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Bacterial infections can cause serious diseases. Because bacteria differ substantially from human cells, in principle, bacterial infections can be treated very effectively with antibiotics. However, bacterial resistance against antibiotics as consequence of uncritical use of these drugs constitutes a major clinical problem. This has resulted in the development of multidrug-resistant strains, e.g., MRSA, causing serious hospital infections. β-Lactams (penicillins, cephalosporins, and carbapenems) and vancomycin inhibit cell wall synthesis and are bactericidal. Quinolones inhibit bacterial gyrases and are bactericidal. Nitroimidazoles, forming DNA adducts, are bactericidal as well. Via inhibition of protein biosynthesis, aminoglycosides are bactericidal; macrolide antibiotics, lincosamides, and tetracyclines are bacteriostatic. The Anti-TB drugs INH, RMP, PZA, SM, and bedaquiline are bactericidal; EMB is bacteriostatic. The dihydrofolate reductase inhibitor TMP is bacteriostatic. Successful treatment of bacterial infections depends on sufficient duration of therapy and dose of antibiotics. These drugs can cause disturbances of GI microbiota, allergies, and drug-specific ADRs.

33

Key Points

1. Use antibiotics critically and only when a bacterial disease is present!
2. Use antibiotics for a sufficiently long period of time to avoid development of resistances!
3. Try to validate your antibacterial therapy on an antibiogram!
4. Try to avoid sulfonamides whenever possible because these drugs are very allergenic!
5. Before you start an antibacterial therapy, ask the patient for known allergies!
6. Uncomplicated urinary tract infections in women can be treated with fosfomycin.
7. Amoxicillin, macrolide antibiotics, and doxycycline are used for treatment of community-acquired pneumonia.
8. Borreliosis is treated with doxycycline, amoxicillin, or cefuroxime.
9. *Pseudomonas aeruginosa* is a common cause of sepsis and is treated with piperacillin + tazobactam, ceftazidime, or meropenem.
10. Pseudomembranous enterocolitis is caused by *Clostridium difficile* and is treated with metronidazole or vancomycin.
11. TB is treated for 2 months with a combination of INH + RMP + EMB + PZA and for 4 months with INH + RMP.
12. Penicillins differ from each other in terms of acid stability, penicillinase resistance, and spectrum of activity.
13. Cephalosporins are classified into three generations according to their spectrum of activity.
14. Meropenem is used in severe mixed infections and sepsis.
15. Penicillins and cephalosporins possess a high allergy risk, but because of their generally high efficacy, they are used nonetheless.
16. Vancomycin is used in MRSA and pseudomembranous enterocolitis.
17. Quinolones can cause serious ADRs in the CNS and tendinopathies.
18. Metronidazole is effective against anaerobic bacteria and is neurotoxic.
19. Erythromycin is effective against pathogens causing respiratory tract infections and can cause drug interactions via CYP inhibition.
20. Aminoglycosides are used in severe infections and are oto- and nephrotoxic.
21. Most Anti-TB drugs are hepatotoxic.
22. INH causes polyneuropathy, RMP induces the flu syndrome, PZA induces hyperuricemia, and EMB causes optic nerve damage.

33.1 Principles of Antibacterial Chemotherapy

Antibacterial chemotherapeutics (antibiotics) are used for the treatment of bacterially caused diseases. Unfortunately, these drugs are often administered uncritically, resulting in the obfuscation of clinical symptoms, ADRs (e.g., diarrhea or allergies), and the development of resistance against many bacterial strains. Development of resistance constitutes a major problem because only very few new antibiotics have been introduced into the

clinic during the past decades. Antibiotics are not feasible for the treatment of viral or fungal infections or to alleviate fever. Nonetheless, these misuses of antibiotics are common in medical practice.

Prior to therapy with antibiotics, a careful diagnosis commensurate with the severity of the disease has to be performed. In cases of severe infections, e.g., nosocomial infections, sepsis, and infections in immunocompromised patients, suitable material for cultivation and resistance testing of pathogenic bacteria (antibiogram) has to be obtained prior to therapy start.

In most cases, the physician does not wait until arrival of the time-consuming microbiological analysis, because in the meantime the condition of the patient may deteriorate. In general, therapy is initiated with an antibiotic empirically effective in the given disease. When choosing an antibiotic, probable efficacy, ADRs, contraindications, and drug interactions are considered. In many cases, antibiotics can be applied p.o. In severe infections and/or in case of unfavorable pharmacokinetic properties (e.g., penicillin G, gentamicin), antibiotics have to be administered parenterally, mostly i.v. ◘ Table 33.1 provides a summary of selected bacterial infections and antibiotics suitable for their treatment. ◘ Table 33.2 summarizes pharmacological properties of selected antibiotics.

Antibiotics are divided into bacteriostatic and bactericidal drugs (◘ Fig. 33.1). β-Lactams, glycopeptides, aminoglycosides, and quinolones belong into the latter group. In case of β-lactams, bacterial kill kinetics is time-dependent, in case of aminoglycosides and quinolones concentration-dependent. Under certain circumstances, a population of bacteria refractory to bactericidal antibiotics prevails (persisters). Thus, the disease may re-emerge after termination of therapy even in case of bactericidal drugs. Bacteriostatic antibiotics inhibit only the proliferation of bacteria, but do not kill the pathogens. Accordingly, participation of the immune system is required to recover from a bacterial infection. Therefore, immunosuppressed patients are preferably treated with bactericidal antibiotics (see ▶ Chap. 11). From the minimum inhibitory concentration (MIC) determined in vitro, important information about the choice of antibiotic for the patient is derived.

In principle, bacterial infections can be treated easily because bacteria differ from human cells substantially. ◘ Figure 33.2 shows the most important bacterial targets of antibiotics. Many bacteria possess a cell wall. Therefore, inhibition of cell wall synthesis by penicillins, cephalosporins, carbapenems and by the glycopeptide vancomycin is a very effective and selective method for therapy of bacterial infections. For replication of bacterial DNA, gyrases (topoisomerases) are required, superspiralizing DNA. They differ substantially from human topoisomerases. Thus, gyrase inhibitors of the quinolone class are also very effective antibiotics. Nitroimidazoles like metronidazole inhibit DNA replication as well. Since bacterial ribosomes differ structurally from human ribosomes, bacterial protein biosynthesis constitutes another excellent pharmacological target. Tetracyclines, macrolides, lincosamides, and aminoglycosides act via this mechanism. Due to structural differences between bacterial and human dihydrofolate reductase, inhibition of the bacterial enzyme is an additional way of antibiotic therapy. Anti-TB drugs have different targets (see ◘ Fig. 33.2).

Antibiotics can interfere with the organ-specific microbiota of the human organism. Important examples for this interference are disturbances of the GI microbiota, causing diarrhea and pseudomembranous enterocolitis (see ◘ Table 33.1) or impairment of the vaginal microbiota, facilitating superinfection with *Candida albicans*.

Resistance is defined as the lack of sensitivity of a pathogenic bacterium against an antibiotic, i.e., the MIC is above the concentration that can be reached in plasma. Both natural and acquired resistances against antibiotics exist. Acquired resistances can be propagated via single or multiple mutations in bacterial genes or extrachromosomally via plasmids. Either the bacterial targets are mutated in such a way that they do no longer effectively bind the antibiotic or antibiotics are inactivated or exported from bacteria. Development of resistance is facilitated by a number of factors. Among these are deficient hospital hygiene (specifically insufficient hand disinfection), uncritical and excessive use of antibiotics, wrong indication, too low drug dosing, too short therapy, poor patient adherence, and routine "prophylactic" use of antibiotics, e.g., in large-scale livestock farming. Particularly dangerous are hospital infections caused by methicillin-resistant (or, more correctly, multidrug-resistant) *Staphylococcus aureus* (MRSA) for which only limited therapeutic options are available.

Table 33.1 Overview of selected bacterial infections in humans

Parameter	Acute uncomplicated urinary tract infection in women	Community-acquired pneumonia (CAP)	Borreliosis	Sepsis	Pseudomembranous enterocolitis (antibiotic-associated colitis)	Infection with MRSAs	TB
Epidemiology	Incidence in younger women; approx. 5%	Globally a leading cause of mortality; precise number vary substantially in different geographic regions	Occurs widely in the Northern Hemisphere	Globally approx. 18 million cases/year	4–8 patients/1000 hospitalized patients	Globally a leading cause of mortality and morbidity; precise numbers very substantially in different geographic regions	Approx. 9 million new cases/year and 1.3 million deaths globally
Transmission	Mainly bacteria of the endogenous intestinal flora	Mainly bacteria of the endogenous flora of the upper airways	Bite of infected ticks; mainly March–October; often the tick bite remains unnoticed	Mainly bacteria from an endogenous source	By staff or patients in hospitals, doctor's offices and nursing homes or endogenous flora	Hospitals, nursing homes, agriculture, waste water treatment plants	Mainly droplet infection (sputum of infected persons)
Risk factors	Sexual activity, pregnancy, DM, antibiotic therapy, spermicides, pessaries	Hypertension, CHD, CHF, preceding influenza, older adults (>60 years), COPD, long-term oxygen therapy at home	Outdoor activities without adequate clothing (short trousers, no shoes, short-sleeved shirts, clothing with dark and rough fabrics), contact with domestic and wild animals	Immunosuppression, cytostatic therapy, older adults, inadequate surgical treatment of a sepsis focus. The risk of septic infection is often underestimated	Damage of endogenous intestinal flora by antibiotic therapy (especially quinolones and cephalosporins); therapy with PPIs	Poor hand disinfection, no protective clothing, uncritical use of antibiotics in hospitals, doctor's offices, and animal breeding facilities	Immunosuppression (most frequently with HIV infection), homelessness, consumption of illicit drugs, ethanol consumption, prison inmates, poverty, deficits in healthcare systems (e.g., Eastern Europe)

Clinical symptoms	Alguria, pruritus, urge to urinate, pollakiuria, macro–/microhematuria	Fever, cough, sputum, radiographic pulmonary infiltrates	Stage 1: Skin infection (erythema migrans (migrating redness)), nonspecific general symptoms	Fever above 39 °C or body temperature below 36 °C, tachycardia, tachypnea, leukocytosis or leukopenia, rod-shaped granulocytes	Diarrhea, abdominal spasms, fever, leukocytosis, wall thickening of a long segment of the colon (sonography, computed tomography)	Dermal infections (furuncles, carbuncles), pyomyositis, pneumonia, endocarditis	Primary TB of the lung with lymph node swellings, weariness, weakness, weight loss, cough, sputum, low-grade fever, night sweats
Complications	Chronification, pyelonephritis, sepsis. In case of insufficient or incorrect treatment, multidrug-resistant bacteria are selected	Sepsis, heart failure, respiratory failure, multiple organ failure	If stage 1 is not detected and treated, the infection enters stage 2: neuroborreliosis (e.g., facial palsy, meningitis, encephalitis). Stage 3: chronic stage which affects many organs and joints	Heart failure, multiple organ failure	Dehydration, toxic megacolon, colon perforation, septic shock	Sepsis, toxic shock syndrome	Secondary TB with destruction of the lung, organ TB (e.g., CNS, liver, bones), sepsis
Antibiotic therapy	Short-term therapy with TMP (the combination with sulfamethoxazole has too many ADRs), fosfomycin (epoxide antibiotic), nitrofurantoin (nitrofuran antibiotic), ciprofloxacin	Therapy according to the severity of the disease: Mild CAP: amoxicillin, a macrolide (clarithromycin, azithromycin) or doxycycline. Moderately severe CAP: Ceftriaxone, cefuroxime or amoxicillin + clavulanic acid, quinolones (moxifloxacin, levofloxacin). Duration of therapy: mostly 5–7 days	2–3-week therapy with doxycycline (not in pregnancy, lactation; children <8 years because of harmful drug accumulation in bones and teeth!), amoxicillin, or cefuroxime. In severe cases, treatment with cefotaxime (broad-spectrum cephalosporin) i.v.	Before starting therapy, draw blood cultures, perform an antibiogram (results after 24–28 hours), and immediately start with an empiric antimicrobial therapy (i.v.) based on the suspected pathogen Example: *Pseudomonas aeruginosa*: Piperacillin + tazobactam or ceftazidime or meropenem. Adapt the therapy once the antibiogram is analyzed. Duration of therapy: 7–10 days	Discontinue the antibiotic that has triggered the clinical symptoms, therapy with metronidazole for 10 days. In severe cases, vancomycin is the drug of last resort	Use drugs of last resort such as vancomycin, daptomycin, and tigecycline	After definitive diagnosis start a 2-month therapy with INH + RMP + EMB + PZA; continue for further 4 months with INH + RMP. SM is the drug of last resort. In multidrug-resistant TB, administer capreomycin and kanamycin (aminoglycosides), ciprofloxacin and moxifloxacin (quinolones), ethionamide and prothionamide (thionamides), 4-aminosalicylic acid (PAS) and cycloserine or bedaquiline

Table 33.2 Overview of selected antibiotics

Drug	Mechanism of action	Important effect (sensitive pathogens)	Important indications	Important ADRs	Further contexts in Chaps.
Amoxicillin	See penicillin G	As penicillin G, plus enterococci, *Haemophilus influenzae*, *Proteus mirabilis*	Infections with sensitive pathogens. Acid-stable (suitable for p.o. administration). Penicillinase-labile. Therefore, amoxicillin is often combined with the penicillinase inhibitor clavulanic acid, which has no intrinsic antimicrobial activity	See penicillin V	3, 12, 13
Bedaquiline	Bactericidal effect, inhibition of ATP synthase and hence impairment of bacterial energy metabolism	Multidrug-resistant strains of *Mycobacterium tuberculosis* and *Mycobacterium leprae*	TB and leprosy caused by multidrug-resistant strains	Nausea, arthralgia, headache; QT prolongation with TdP	17
Cefazolin	See penicillin G	First-generation cephalosporin(*Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli*)	Infections with sensitive pathogens, parenteral administration	Allergies (1–2%), 5–8% cross allergy with penicillins, GI disturbances (diarrhea), nephrotoxicity if combined with aminoglycosides	3, 12, 13
Ceftazidime	See penicillin G	Third-generation cephalosporin active against *Pseudomonas aeruginosa*	Particularly infections with *Pseudomonas aeruginosa*; acid-labile, hence parenteral administration	See cefazolin	3, 12, 13
Ceftriaxone	See penicillin G	Broad-spectrum cephalosporin (third generation) with a broader spectrum of activity than second-generation cephalosporins (e.g., gonococci, meningococci, and *Enterococcus cloacae*)	Infections with sensitive pathogens, parenteral administration	See cefazolin	3, 12, 13

Cefuroxime	See penicillin G	Second-generation cephalosporin with an extended spectrum of activity due its β-lactamase stability (*Haemophilus influenzae*)	Infections with sensitive pathogens, parenteral administration; For p.o. administration, cefuroximaxetil, a lipophilic prodrug, can be used	See cefazolin	3, 12, 13
Ciprofloxacin	Bactericidal effect, quinolone, inhibition of DNA gyrase (TOPO-II)	Broad-spectrum antibiotic, including treatment of *Escherichia coli*, *Klebsiella pneumoniae*, *Haemophilus influenzae* and *Pseudomonas aeruginosa*	Infections with sensitive pathogens, p.o. administration and good tissue penetration	Impaired absorption of calcium, magnesium and iron; GI disturbances (15%), CNS disturbances (5%) (confusion, hallucinations, psychoses, epileptic seizures), allergy, phototoxic reactions, tendinopathies	2, 3, 13
Clindamycin	Bacteriostatic effect, lincosamide, inhibition of the bacterial protein synthesis	Staphylococci, streptococci, anaerobic gram-negative bacteria (e.g., *Bacteroides, Fusobacterium*)	Infections with sensitive pathogens, suitable for p.a. administration, good tissue penetration	GI disturbances (diarrhea, vomiting, nausea, increased risk of pseudomembranous enterocolitis; increases effect of hyperpolarizing and depolarizing muscle relaxants	5
Doxycycline	Bacteriostatic effect, tetracycline, inhibition of bacterial protein biosynthesis	Particularly chlamydias and mycoplasmas, *Borrelia burgdorferi*	Infections with sensitive pathogens, p.o. administration, good tissue penetration	Chelates calcium, magnesium and iron; accumulation in bones and teeth of the embryo/fetus if administered during pregnancy (contraindication!), GI disturbances, photodermatoses	2
EMB	Bacteriostatic effect, inhibition of cell wall synthesis	*Mycobacterium tuberculosis*, *Mycobacterium leprae*	TB, leprosy	Damage to the optic nerve (decreased acuity, disturbed color vision, scotoma, optic atrophy), hyperuricemia, liver damage	23
Erythromycin	Bacteriostatic effect, macrolide antibiotic, inhibition of bacterial protein biosynthesis	Streptococci, *Haemophilus influenzae*, legionellae, mycoplasmas, chlamydias	Infections with sensitive pathogens; p.o. and parenteral administration, good tissue penetration (except liquor)	Drug interactions due to CYP3A4 and CYP1A2 inhibition, GI disturbances, liver damage	2, 13, 17
Flucloxacillin	See penicillin G	*Staphylococcus aureus*	Infections with sensitive *Staphylococcus aureus* strains, but NOT with MRSA strains; acid-stable and penicillinase resistant; suitable for p.o. administration	See penicillin V	3, 12, 13

(continued)

Table 33.2 (continued)

Drug	Mechanism of action	Important effect (sensitive pathogens)	Important indications	Important ADRs	Further contexts in Chaps.
Fosfomycin	Bactericidal effect, epoxide antibiotic, inhibition of cell wall synthesis, no cross-resistance to β-*lactamase-producing bacteria*	Broad-spectrum antibiotic, active against both gram-positive and gram-negative bacteria including *Escherichia coli*, *Citrobacter*, and *Proteus* species	Single high-dose therapy of uncomplicated urinary tract infections (highly concentrated in urine, high efficacy at low pH). Not to be used for long-term therapy because of fast development of bacterial resistance	Overall good tolerability and few ADRs	
Gentamicin	Bactericidal effect, aminoglycoside, inhibition of bacterial protein biosynthesis	*Escherichia coli*, *Klebsiella pneumoniae*; synergistic effect with penicillins for treatment of streptococci, enterococci, *Listeria monocytogenes* and *Pseudomonas aeruginosa*	Life-threatening infections with sensitive pathogens (mainly sepsis); parenteral administration; poor tissue penetration, no liquor penetration	Irreversible ototoxicity (hearing loss, ataxia) due to accumulation in the perilymph, reversible nephrotoxicity which is amplified by administration of loop diuretics, ciclosporin, vancomycin and amphotericin B; rarely, neuromuscular blockade	13
INH	Bactericidal effect on proliferating pathogens; inhibition of cell wall synthesis and of DNA synthesis	*Mycobacterium tuberculosis*, *Mycobacterium leprae*	TB, leprosy; p.o. administration and good tissue penetration	Neurotoxicity (headache, mental disorders) and polyneuropathy (paresthesias of hands and feet) caused by functional vitamin B_6 antagonism; thus, vitamin B_6 has to be prophylactically administered; hepatotoxicity; GI disturbances (5%) and dermatologic problems (2%)	4
Meropenem	See penicillin G; carbapenem which is stable to renal dehydropeptidase	Broad-spectrum antibiotic, active against both gram-positive and gram-negative bacteria including *Pseudomonas aeruginosa* and anaerobic bacteria	Severe mixed infections, sepsis, parenteral administration	See penicillin G	3, 12, 13

Metronidazole	Bactericidal effect, nitroimidazole, formation of covalent DNA adducts	Prodrug which is activated under anaerobic conditions; hence, strong effect on anaerobic pathogens	Infections caused by anaerobic bacteria; p.o. administration and good tissue penetration	Metallic taste, stomatitis, ethanol intolerance, neurotoxicity especially after long-term treatment (headache, ataxia, paresthesia). Hence, maximum duration of treatment: 10–14 days (e.g., in the Italian triple therapy of *Helicobacter pylori* infection)	13
Penicillin G	Bactericidal effect, inhibition of cell wall synthesis	Streptococci, meningococci, gonococci, anaerobic bacteria	Streptococci infections, meningitis, gonorrhea, soft tissue infections caused by anaerobic bacteria; acid-labile and hence only parenteral application. Mainly for treatment of severe infections, as high plasma concentrations can be achieved.	Allergies (1–10% urticaria, 1: 100,000 anaphylactic shock), diarrhea, pseudomembranous enterocolitis, neurotoxicity following high doses and in patients with CKD	3, 12, 13
Penicillin V	See penicillin G	See penicillin G	See penicillin G; acid-stable and hence suitable for p.o. administration; less severe infections	See penicillin G; risk of GI disturbances is higher than with penicillin G	3, 12, 13
Piperacillin	See penicillin G	Broad-spectrum activity including treatment of *Pseudomonas aeruginosa*	Sepsis and nosocomial infections, parenteral application; penicillinase-labile (combination with clavulanic acid)	See penicillin G	3, 12, 13
PZA	Bactericidal effect, intrabacterial accumulation of pyrazinecarboxylic acid (interference with NAD synthesis), effect is dependent on pH	*Mycobacterium tuberculosis*, *Mycobacterium leprae*	TB, leprosy	Hyperuricemia, liver damage, GI disturbances, skin reactions	23

(continued)

Table 33.2 (continued)

Drug	Mechanism of action	Important effect (sensitive pathogens)	Important indications	Important ADRs	Further contexts in Chaps.
RMP	Bactericidal effect on proliferating pathogens, inhibition of bacterial RNA polymerase and hence protein biosynthesis	*Mycobacterium tuberculosis*, *Mycobacterium leprae*, plus staphylococci, enterococci, legionellae	TB, leprosy and other infections with sensitive pathogens; p.o. administration and good tissue penetration	Flu syndrome with intermittent drug intake; hepatotoxicity particularly with high doses or in combination with INH (control of liver enzymes), GI disturbances, dermatologic problems, orange-colored body fluids; reduced efficacy of oral contraceptives and VKAs due to CYP induction	2, 18, 19, 24
TMP	Bacteriostatic effect, inhibition of dihydrofolic acid synthesis	Broad-spectrum antibiotic against gram-positive and gram-negative pathogens	Mainly uncomplicated urinary tract infections in women. By combination with sulfamethoxazole (cotrimoxazole) the spectrum of activity can be considerably extended (even to treatment of *Toxoplasma gondii* and *Pneumocystis jirovecii*)	GI disturbances; markedly more severe ADRs if combined with sulfamethoxazole; allergies (up to 10%), SJS, photosensitivity, granulocytopenia and thrombopenia	3
Vancomycin	Bactericidal effect on proliferating pathogens, glycopeptide antibiotic, inhibition of cell wall synthesis, cross-resistance to *β-lactamase-producing bacteria*	*Staphylococcus aureus*, coagulase-negative staphylococci, streptococci and enterococci	Drug of last resort for infections with sensitive pathogens, including MRSAs; parenteral application; p.o. administration only for treatment of pseudomembranous enterocolitis	Ototoxicity (accumulation in renal insufficiency, nephrotoxicity, red man syndrome caused by too fast infusion of vancomycin	3, 12
SM	See gentamicin	*Mycobacterium tuberculosis*, *Mycobacterium leprae*, see also gentamicin	TB, leprosy (drug of last resort); i.m. administration	See gentamicin; intermittent administration reduces ototoxicity	13

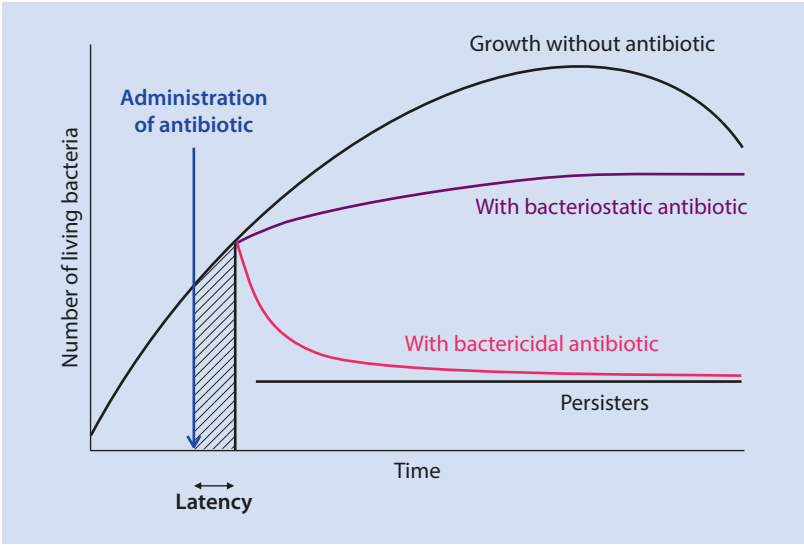

Fig. 33.1 Bactericidal and bacteriostatic effects of antibacterial chemotherapeutics. Use antibiotics only when bacteria cause a disease! The presence of bacteria without disease is no reason for chemotherapy! If you decide to treat an infection, do so for a sufficiently long period of time!

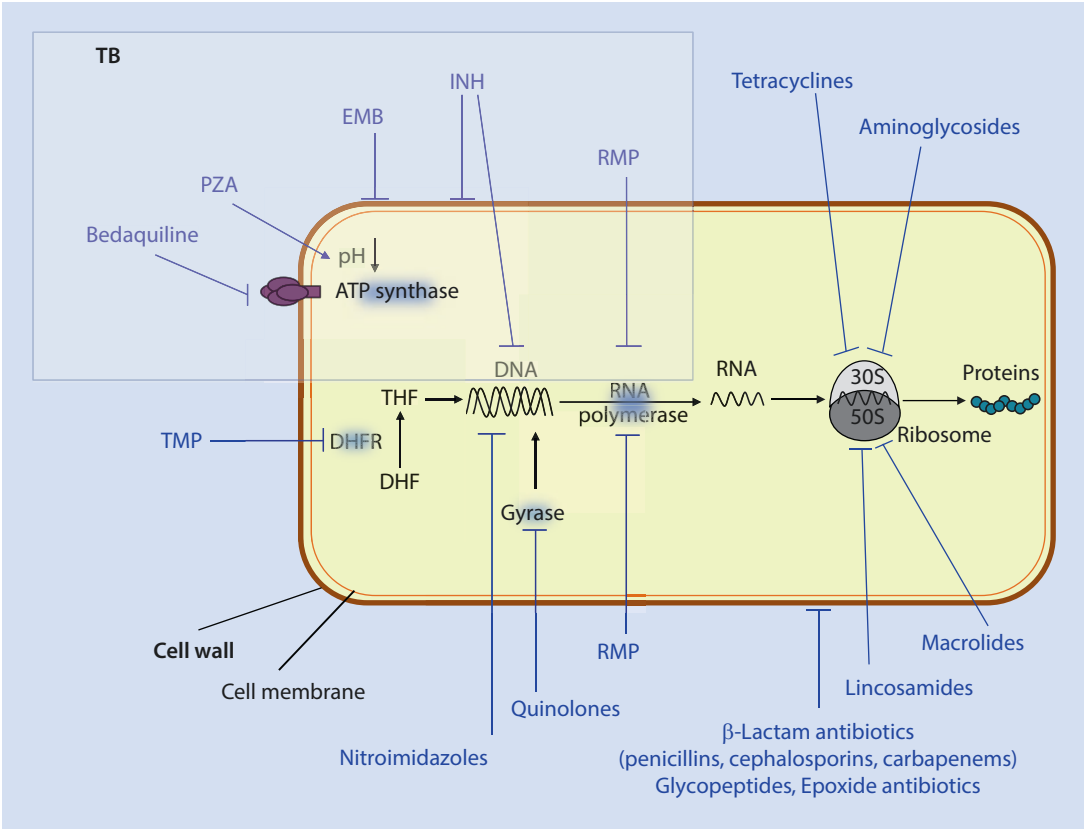

Fig. 33.2 Pharmacological targets of antibacterial chemotherapeutics. DHF dihydrofolate, DHFR dihydrofolate reductase, THF tetrahydrofolate. *Light blue background*, targets of Anti-TB drugs; *blue background*, general targets of antibiotics. Choose the antibiotic according to the bacterium causing the disease! Choose an antibiotic based on an antibiogram, if possible!

33.2 Important Bacterial Infections and Their Pharmacotherapy

Antibiotics should only be used if bacteria actually cause a disease. Just the presence of bacteria without clinical symptoms does not justify the use of antibiotics except for well-defined situations, e.g., endocarditis prophylaxis in patients with mechanical heart valves undergoing dental surgery. Prior to every antibacterial chemotherapy, the medical history, physical examination, laboratory tests, and diagnostic imaging are required. If possible, microscopic, immunological, or molecular biological verification of the pathogen should be performed. Prior to chemotherapy, suitable biological material (e.g., urine, sputum, blood, or swabs) should be collected to identify the pathogen and determine its sensitivity to antibiotics. Bacterial infections are very diverse with respect to the pathogen, incidence, severity, complications, and duration of therapy (see ◘ Table 33.1).

The uncomplicated urinary tract infection in women belongs to the most common infectious diseases. The symptoms are unambiguous in most cases encompassing alguria and pollakiuria, and diagnostics is straightforward (chemical and microscopic analysis of the urine). The disease is caused by *Escherichia coli* from the colon in most cases and can be empirically treated with a single dose of fosfomycin (see ▶ Sect. 33.3). In case of recurrent infections or severe courses (e.g., pyelonephritis), urine must be collected prior to therapy for pathogen identification and antibiogram.

The community-acquired pneumonia (CAP) often leads to hospitalization, and more than 10% of the patients admitted to the hospital ultimately die. Therefore, rapid diagnostics and onset of therapy are particularly important. Pathogenic bacteria are identified in the sputum. For initial empirical therapy, amoxicillin (see ▶ Sect. 33.3), macrolides, or tetracyclines (see ▶ Sect. 33.5) are used. In severe cases, certain cephalosporins (see ▶ Sect. 33.3) and quinolones (see ▶ Sect. 33.4) are administered. CAP must be treated for a sufficiently long period of time (5–7 days).

Borreliosis is caused by the spirochete *Borrelia burgdorferi* and occurs widely in the Northern Hemisphere due to tick bites. Borreliosis should not be confused with the virally caused tick-borne encephalitis. In most cases, the diagnosis of borreliosis is made by the typical medical history and the pathognomonic erythema migrans. The later borreliosis is diagnosed, e.g., in the stage of neuroborreliosis, the more difficult and less successful is the chemotherapy. In case of erythema migrans, a 2- to 3-week treatment with a tetracycline (see ▶ Sect. 33.5) or a β-lactam (amoxicillin, cefuroxime) (see ▶ Sect. 33.5) is performed.

Sepsis is a life-threatening disease accompanied by dysfunction of multiple organs and an excessive immunological reaction due to the bacterial infection. Hospitalized patients with immunosuppression are at particularly high risk. It is crucial to diagnose sepsis as quickly as possible and to rapidly initiate an i.v. antibiotic chemotherapy. Blood cultures must be obtained prior to therapy to identify the pathogen and prepare an antibiogram. However, the physician must not wait for the results of this analysis but immediately initiate a chemotherapy targeting the most likely pathogen based on the clinical situation. *Pseudomonas aeruginosa* is a common cause of sepsis. Until the results of the antibiogram are available, a therapy with piperacillin + tazobactam, ceftazidime, or meropenem is performed (see ▶ Sect. 33.3). The therapy is adjusted to the antibiogram once the results are available.

Antibacterial chemotherapy may seriously compromise GI microbiota. In mild cases, diarrhea may occur. In severe cases, overgrowth with the anaerobic bacterium *Clostridium difficile* occurs, secreting various toxins and causing a potentially life-threatening pseudomembranous enterocolitis (see ▶ Chap. 13). *Clostridium difficile* is propagated in hospitals via sanitary facilities and personnel. Strict hygiene and cautious use of antibiotics are keys to prevent spreading of pseudomembranous enterocolitis. The disease can lead to severe loss of water and electrolytes, culminating in multiple organ failure. The causative antibiotic must be discontinued immediately, and water and electrolytes must be substituted (see ▶ Chap. 13). Moreover, metronidazole, effective against anaerobic bacteria (see ▶ Sect. 33.4), has to be administered for 10 days. Vancomycin constitutes an alternative to metronidazole.

Staphylococcus aureus can cause severe skin and organ infections culminating in sepsis. Penicillins effective against the bacterium are available (e.g., flucloxacillin), but because of uncritical use of antibiotics and insufficient hygiene, strains of *Staphylococcus aureus* with

multiple resistances against β-lactam antibiotics, tetracyclines, aminoglycosides, and macrolides have developed (MRSA). These pathogens can cause most severe and intractable hospital infections. Antibiotics of last resort such as vancomycin (see ▶ Sect. 33.3), daptomycin, or tigecycline are used in such cases. Daptomycin inserts into bacterial membranes, and tigecycline inhibits protein biosynthesis.

The bacterial infections discussed so far require relatively short treatment durations (one day until 3 weeks). In contrast, TB must be treated for a very long period of time. Therefore, anti-TB drugs require good tolerability and patient adherence to ensure cure of the disease and to avoid development of resistant strains. Tuberculosis is caused by *Mycobacterium tuberculosis* which grows very slowly compared to other bacteria (duplication time 15–20 hours versus 15–20 minutes) and preferentially multiplies intracellularly. Moreover, necroses develop in the tissue where mycobacteria proliferate. These factors impede with accessibility of mycobacteria for drugs. Therefore, therapy of TB is performed for 2 months with a quadruple combination (INH + RMP + PZA + EMB) and for additional 4 months with a combination of INH + RMP (see ▶ Sect. 33.7). The combination of drugs with different mechanisms of action delays development of resistance. ADRs constitute another problem in TB therapy. The most important anti-TB drugs can lead to liver damage. INH may additionally induce damage in the peripheral and central nervous system, and EMB can cause visual problems.

As a result of inconsistent TB therapy, many mycobacterial strains with resistance against standard anti-TB drugs have emerged. Several drugs with limited efficacy and poor tolerability are available for treatment of multidrug-resistant TB. Bedaquiline is a promising new drug in this field. The aminoglycoside streptomycin must be administered i.v. and is burdened with severe oto- and nephrotoxicity.

33.3 Antibiotics Inhibiting Cell Wall Biosynthesis

β-Lactams (penicillins, cephalosporins, and carbapenems), the glycopeptide vancomycin, and the epoxide fosfomycin inhibit cell wall biosynthesis. All antibiotics targeting cell wall synthesis are bactericidal. β-Lactam antibiotics inhibit D-alanine transpeptidases which are specific for bacteria, resulting in inhibition of mucopeptide cross-linking with subsequent water influx in bacteria and cell bursting. Vancomycin forms complexes with terminal murein peptide complexes, reducing mucopeptide cross-linking as well. Fosfomycin inhibits UDP-acetylglucosamine enolpyruvyl transferase and, thereby, bacterial peptidoglycan biosynthesis.

Penicillin G is effective against streptococci, meningococci, and certain anaerobic bacteria. Because of its acid lability, the drug is not absorbed following oral administration. Therefore, penicillin G has to be administered several times per day as i.v. short infusion (plasma half-life 30–60 minutes). Painful vein irritation may occur during infusion. Penicillins are eliminated via glomerular filtration and tubular secretion without metabolism. They do not cross the BBB except in meningitis. Therefore, penicillin G can be used in meningococcal meningitis (see ▶ Chap. 2). Because of the disadvantageous necessity of frequent i.v. infusions, i.m. sustained-release preparations are available (benzathine penicillin, duration of action about 20 days). In addition, the acid-stable penicillin V was developed for oral therapy of mild infections with susceptible pathogens or for oral termination of a parenteral therapy with penicillin G. Flucloxacillin is an acid-stable isoxazolyl penicillin with resistance toward penicillinase and is effective against penicillinase-producing *Staphylococcus aureus*, but not against MRSA strains.

In comparison to penicillin G, the acid-stable aminopenicillin amoxicillin possesses a broader spectrum of activity including some gram-negative bacteria. However, amoxicillin is not resistant to penicillinases. This disadvantage is compensated by combination with penicillinase inhibitors such as clavulanic acid. Amoxicillin + clavulanic acid is one of the most important antibiotics because it can be used in many common bacterial infections including urinary tract and airway infections as well as borreliosis. Amoxicillin possesses a bioavailability of 90% and is eliminated renally with a half-life of 2 hours. The dose amounts to 0.5–1 g three times per day. Resistance develops slowly. Amoxicillin is a relatively inexpensive antibiotic. Accordingly, profit margins of the pharmaceutical industry are small. This has resulted in the

concentration of amoxicillin production in few factories globally. Hence, technical problems in the production process of amoxicillin have resulted in shortages of amoxicillin supply worldwide.

Compared to amoxicillin, piperacillin possesses a broader spectrum of activity against gram-negative bacteria, among them problem pathogens such as *Pseudomonas aeruginosa*. Because of its acid lability, piperacillin must be administered parenterally. Therefore, its use is essentially restricted to hospitalized patients. Piperacillin is often combined with the β-lactamase inhibitor tazobactam to treat severe hospital infections or sepsis. As with amoxicillin, shortages in the global supply with piperacillin have occurred.

The most important ADR of penicillins are allergies, particularly type I allergies. About 1–10% of all treated patients fall victim to urticaria. An anaphylactic shock occurs at a frequency of 1:100,000 and is effectively treated with EPI (see ▶ Chap. 3). It is therefore important to ask patients for known penicillin allergy prior to drug treatment. In case of doubt, penicillins and other β-lactam antibiotics must not be administered. In such a situation, alternative drug classes without risk for cross allergy such as macrolides and tetracyclines have to be given. The allergy risk is particularly high in case of penicillin application on mucosal membranes, constituting a serious medical error.

In addition, disturbances of the GI microbiota can cause diarrhea. Particularly with high doses of penicillins, pseudomembranous enterocolitis may occur. In extremely high doses (>30 million IU/day, applied only very rarely), neurotoxic symptoms can develop, particularly in patients with reduced kidney function resulting in delayed penicillin elimination (see ▶ Chap. 12).

With respect to the mechanism of action, slow development of resistance, renal elimination, and ADRs, cephalosporins are similar to penicillins. They are not inactivated by penicillinases but in many cases by more broadly acting β-lactamases produced by gram-negative bacteria. Since 5–8% of all patients show cross-allergy between cephalosporins and penicillins, caution must be exerted when switching between the two drug groups in case of a known allergy against either group (see ▶ Chap. 3).

Cefaclor is a first-generation cephalosporin that can be administered p.o. in infections with susceptible strains of staphylococci, streptococci, and certain gram-negative pathogens. The second-generation cephalosporin cefuroxime possesses a broader spectrum of activity against gram-negative bacteria due to its β-lactamase stability. Ceftriaxone is a third-generation cephalosporin with yet broader activity against gram-negative bacteria. The drug must be administered i.v. Ceftazidime belongs to the third-generation cephalosporins as well and possesses high efficacy against pathogenic *Pseudomonas aeruginosa* strains.

The glycopeptide vancomycin is a valuable last-resort antibiotic which should only be used in special situations so that the resistance situation does not further deteriorate. Important indications for vancomycin are MRSA infections (i.v. application) and pseudomembranous enterocolitis (p.o. administration). Vancomycin is eliminated renally without metabolism. The drug is oto- and nephrotoxic (see ▶ Chap. 12). Vancomycin can cause a red man syndrome. To avoid this ADR, it is important to infuse vancomycin i.v. very slowly. There are no cross-allergies with penicillins and cephalosporins.

Because of rapid resistance development, fosfomycin is not suitable for long-term administration. It is predominantly used in the first-line treatment of uncomplicated urinary tract infections in women. Fosfomycin covers the spectrum of bacteria usually causing the disease well. Moreover, the drug accumulates in urine and is effective at low pH. Fosfomycin is well tolerated and applied as a single high dose.

33.4 Antibiotics Inhibiting DNA Replication

Quinolones inhibit the bacterial gyrase (topoisomerase) TOPO-II. In addition, the drugs inhibit transcription. Quinolones are bactericidal. Ciprofloxacin is the prototype. It can be administered p.o. and possesses good tissue permeability. It is eliminated renally and intestinally without modification. The half-life is 3–6 hours. Ciprofloxacin possesses a broad spectrum of activity including several pathogenic gram-negative bacteria. Quinolones are widely used in airway and urinary tract infections. Because of their ADRs, they should only be used if pathogen sensitivity has been confirmed with an antibiogram. Levofloxacin exhibits enhanced

activity against gram-positive and atypical pathogens. Moxifloxacin additionally affects anaerobic bacteria.

Quinolones possess several ADRs. In up to 15% of the patients, GI disturbances are observed; in about 5% of the patients, CNS problems (confusion, hallucinations, seizures, psychoses) occur. Allergies, hepatotoxic reactions, QT prolongations (see ▶ Chap. 17), and phototoxic reactions are observed as well. Therefore, patients treated with quinolones must avoid intense UV light. Tendinopathies are a very specific ADR of quinolones, typically emerging after therapy for weeks to months. Tendon pain, escalating into tendon rupture, can occur. Old patients and patients treated with GCR agonists are at particular risk. The quinolone-induced tendinopathy is due to inhibition of proliferation and migration of tenocytes and activation of collagen-degrading matrix metalloproteases. Thus, long-term treatment with quinolones must be avoided. These serious ADRs of quinolones are a consequence of uncritical prescription and are regularly discussed in the media.

The nitroimidazole metronidazole is bactericidal via inhibition of DNA replication as well. Metronidazole is a prodrug that is activated in bacteria under anaerobic conditions. It induces DNA strand breaks via formation of covalent adducts with bases. Metronidazole possesses very good bioavailability (80%) and tissue permeability, including liquor, peritoneum, and abscesses. The drug is metabolized in the liver and eliminated via the bile with a half-life of 7 hours. Metronidazole is effective against anaerobic bacteria. It is predominantly used in infections caused by anaerobic bacteria including pseudomembranous enterocolitis, fistulae in CD (see ▶ Chap. 13), abscesses, and periodontitis.

Metronidazole can cause dysgeusia, glossitis, and stomatitis. The urine can turn reddish-brown in color. Metronidazole leads to ethanol intolerance. At high doses, it is neurotoxic (ataxia, headache, peripheral neuropathy). Therefore, therapy with metronidazole should not be conducted for longer periods of time than 10–14 days. According to theory, metronidazole should be mutagenic. However, epidemiological studies have not shown an increased risk for tumors. Nonetheless, metronidazole is contraindicated in pregnancy and during lactation.

33.5 Antibiotics Inhibiting Protein Biosynthesis

The macrolides are the most important antibiotics in this group. They bind to the 50S subunit of bacterial ribosomes and inhibit protein biosynthesis. However, resistance develops rapidly. Macrolides are bacteriostatic and possess good tissue permeability except for liquor. The drugs are effective against intra- and extracellular pathogens. They have a broad spectrum of activity including streptococci, *Haemophilus influenzae*, and bacteria without cell wall as mycoplasma, chlamydia, and legionella. Macrolides are often used in airway infections, e.g., tonsillitis, sinusitis, otitis media, bronchitis, and pneumonia (see ▶ Chap. 4), erysipela, and acne. For urinary tract infections, macrolides are not suitable. They constitute an alternative to β-lactams in case of resistance or allergies. Macrolides can be used during pregnancy.

Erythromycin is the prototypical macrolide. It can be administered p.o. and possesses a half-life of 2 hours. The drug is metabolized in the liver and eliminated via the bile. Erythromycin can accelerate intestinal passage time. This prokinetic effect is due to agonism at the motilin receptor and used off-label in case of missing efficacy of MCP in GI stasis and nausea (see ▶ Chaps. 6, 8, and 13). Erythromycin may cause liver damage (transaminase increase and cholestasis). The drug inhibits CYP3A4 and CYP1A2, leading to delayed elimination of other drugs metabolized by these enzymes and to drug accumulation (see ▶ Chap. 2). Erythromycin exhibits relevant interactions with ciclosporin (see ▶ Chap. 11), carbamazepine, and valproic acid (see ▶ Chap. 25) as well as HMG-CoA reductase inhibitors (see ▶ Chap. 22). Before prescription of erythromycin, it is therefore important to obtain a precise drug record to avoid dangerous drug interactions and, above all, to ask for drugs prescribed by physicians of other specialties, e.g., NIPEs (neurologists). Erythromycin prolongs the QT interval and can promote TdP (see ▶ Chap. 17). Clarithromycin possesses a prolonged half-life (6 hours) but still inhibits CYPs. Azithromycin has a half-life of 2–4 days and is devoid of CYP interactions.

Lincosamides (prototype clindamycin) inhibit protein biosynthesis via binding to the 50S subunit of bacterial ribosomes. Clindamycin is bacteriostatic, absorbed following oral administration,

andpossesses good tissue permeability. It is applied as alternative to macrolides in case of penicillin allergy. Clindamycin is effective against several staphylococci and gram-negative anaerobic bacteria. Accordingly, it can be used in dental, soft tissue, and skin infections as well as in osteomyelitis. Compared to other antibiotics, clindamycin possesses an increased risk for pseudomembranous enterocolitis. Therefore, it is not a first-choice antibiotic, and its use should be corroborated by a positive antibiogram.

Tetracyclines inhibit protein biosynthesis via binding to the 30S subunit of bacterial ribosomes. They are bacteriostatic and possess a broad spectrum of activity against intra- and extracellular pathogens. Doxycycline is the prototype. It has a bioavailability of 80–95% and a half-life of 20 hours. Doxycycline is administered p.o. once daily, simplifying therapy substantially. The drug possesses good tissue permeability. Doxycycline is broadly used in mild infections of the respiratory and urinary tract, acne, and borreliosis. Tetracyclines are an alternative to β-lactams in case of poor tolerability, allergies, or resistances.

Tetracyclines form complexes with divalent cations (calcium, iron, and magnesium). Salts of these cations must not be administered simultaneously with tetracyclines because of mutual inhibition of absorption (see ► Chap. 2). Often, patients use OTC calcium preparations for prophylaxis of osteoporosis (see ► Chap. 20) or magnesium for spasmolysis and sedation. Accordingly, the physician and pharmacist must inform patients about interactions with divalent cations when prescribing tetracyclines.

Overall, tetracyclines are well tolerated. GI problems are the most common ADRs. However, some specific ADRs must be regarded. Tetracyclines can cause photosensitization. Therefore, patients have to be educated prior to therapy with doxycycline that strong exposure to UV light must be strictly avoided. Implementation of appropriate protection measures is necessary.

Tetracyclines are contraindicated in pregnancy, during lactation, and in children up to 8 years because accumulation into bones and teeth can take place, leading to discoloration and decreasing stability and growth of these hard tissues. For these patients, β-lactams and macrolides constitute safe alternatives.

Aminoglycosides inhibit protein biosynthesis via formation of nonsense proteins. They exhibit a concentration-dependent bactericidal effect. This first exposure effects typically allow for a once-daily drug dose. Apart from the p.o. application for intestinal sterilization, aminoglycosides are administered parenterally, restricting their use to severe infections in the hospital. Aminoglycosides and β-lactams possess synergistic bactericidal effects being exploited in severe infections such as sepsis and osteomyelitis.

Aminoglycosides are hydrophilic and not bound to plasma proteins. The drugs possess poor tissue permeability and BBB penetration and do not reach intracellular pathogens. They are not metabolized and are eliminated via glomerular filtration with a half-life of 2 hours. Gentamicin is a prototypical aminoglycoside. It possesses a broad spectrum of activity, particularly in combination with penicillins. Tobramycin is more effective against *Pseudomonas aeruginosa*. Aminoglycosides accumulate in the perilymph of the inner ear and are ototoxic. Irreversible disturbances of equilibrium and hearing deficits can develop. In addition, nephrotoxicity can occur. In CKD, elimination of aminoglycosides is delayed. Nephrotoxicity of aminoglycosides is enhanced by other nephrotoxic drugs such as loop diuretics, ciclosporin, vancomycin, and amphotericin B (see ► Chap. 12). To avoid oto- and nephrotoxic effects, in CKD, TDM-based dose reduction is necessary.

33.6 Antibiotics Inhibiting Dihydrofolate Reductase

Tetrahydrofolate is a coenzyme for biosynthesis of purine and pyrimidine bases as precursors of DNA and RNA. Tetrahydrofolate is generated from dihydrofolate via reduction by dihydrofolate reductase. TMP inhibits bacterial dihydrofolate reductase with high potency (see ► Chap. 1). In the end, bacterial DNA synthesis is impeded. TMP is bacteriostatic and possesses a broad spectrum of activity against gram-positive and gram-negative pathogens and is predominantly used for the treatment of uncomplicated urinary tract and upper airway infections. However, resistance to TMP has become a serious problem due to uncritical use, substantially diminishing its

usefulness. TMP is well tolerated. GI problems are the most common ADRs. Allergies are observed as well.

Sulfonamides (prototype sulfamethoxazole) inhibit dihydrofolate synthesis. The combination of TMP + sulfamethoxazole has a synergistic bactericidal effect, but should only be applied in bacterial infections if there is no other alternative and if a positive antibiogram is available. The reason for the suggested restrictive use of the combination is the fact that sulfonamides possess a very high risk (10% of all patients) for allergic reactions, SJS and TEN being the most dangerous ones (see ▶ Chap. 3). Unfortunately, the combination of TMP + sulfamethoxazole is still widely and uncritically used in many countries, resulting in many avoidable SJS and TEN cases.

33.7 Anti-TB Drugs

INH is taken up into mycobacteria and is intracellularly converted to isonicotinic acid. Consequently, an NAD adduct is formed, inhibiting synthesis of bacterial DNA and mycolic acid, the latter being important for cell wall formation. INH is bactericidal against proliferating mycobacteria. About 10% of the strains are resistant to INH because of reduced penetration of the drug into the bacterial cell. INH possesses a bioavailability of 90%. It exhibits good tissue penetration and reaches the liquor and necrotizing granulomas. INH is inactivated in the liver via arylamine N-acetyltransferase-2 (NATR2). Headache, psychological problems, and polyneuropathy, the latter as consequence of functional antagonism with vitamin B_6, are common ADRs. For prophylaxis of neuropathy, vitamin B_6 is administered. This is particularly important in patients with increased risk for neurological ADRs such as alcoholics, with DM and with serious neurological diseases. INH increases liver transaminases, and in 1% of the patients hepatitis develops, in 2% acne and exanthemas emerge, and in 5% they suffer from GI problems. Under therapy with INH, close neurological, hepatological, and dermatological control exams are important.

RMP inhibits bacterial RNA polymerases and, thereby, protein biosynthesis. It is bactericidal on proliferating and intracellular pathogens. RMP exhibits efficacy not only against mycobacteria but also against streptococci, staphylococci, enterococci, and legionella. Thus, RMP possesses a much broader spectrum of activity than any other anti-TB drug. It shows only a low susceptibility to resistance development. RMP penetrates into all tissues including liquor and is eliminated via the bile after hepatic metabolism. The plasma half-life is 3–5 hours, but decreases to 1.5 hours during long-term therapy since RMP induces CYPs and, thereby, its own inactivation (see ▶ Chap. 2). CYP induction by RMP also concerns other drugs being inactivated by these enzymes. For example, the effects of VKAs, oral contraceptives, GCR agonists, and certain anti-HIV drugs are reduced. The dose of these drugs has to be adjusted accordingly, or the patient should be switched to alternatives devoid of CYP interactions. RMP can cause exanthemas and GI problems. In case of poor adherence, a flu syndrome can develop. In high doses and particularly in combination with INH, RMP can cause transaminase and bilirubin increase as well as liver damage. Accordingly, liver function has to be controlled during therapy with RMP. Furthermore, a harmless orange discoloration of body fluids can develop.

PZA is converted to pyrazine carbonic acid accumulating in mycobacteria. Like INH, PZA interferes with NAD metabolism. It exhibits bactericidal effects on mycobacteria including persisters in macrophages. The drug shows good tissue permeability and reaches the liquor. It is metabolized in the liver and eliminated renally. The plasma half-life is 10 hours. In most patients PZA causes asymptomatic hyperuricemia requiring no treatment (see ▶ Chap. 23). Like INH and RMP, PZA is hepatotoxic. In addition, GI problems and phototoxic skin reactions are noted.

EMB inhibits biosynthesis of polysaccharides of the mycobacterial cell wall and is bacteriostatic in proliferating mycobacteria. It shows good tissue permeability and accumulates in erythrocytes. The bioavailability is 80%. EMB is predominantly eliminated renally. Resistance development is rare, and there is no cross-resistance with other anti-TB drugs. Therefore, EMB is a valuable component of antimycobacterial combination therapies. The most important ADR of EMB is optic nerve damage, compromising color vision, acuity, and facial field. Accordingly,

the patient must have regular ophthalmological control exams. In addition, asymptomatic hyperuricemia (see ▶ Chap. 23) and liver damage may occur.

33.8 Questions and Answers

Questions

Which class of antibiotics acts via inhibition of DNA replication?

A. Cephalosporins
B. Quinolones
C. Penicillins
D. Tetracyclines
E. Glycopeptides

Answers

A. Cephalosporins inhibit cell wall synthesis.
B. Quinolones inhibit the bacterial gyrase which is responsible for DNA spiralization. Hence, the DNA loses its compact structure, impeding with its replication.
C. Penicillins inhibit cell wall synthesis.
D. Via binding to the 30S subunit of bacterial ribosomes, tetracyclines inhibit protein biosynthesis.
E. Glycopeptides inhibit cell wall synthesis.

Answer **B** is correct.

33.9 Exercises

A 34-year-old man visits you in your dermatology practice and shows you a round red efflorescence with a pale center and a diameter of about 5 cm on his left lower leg. The efflorescence and the pale center have grown recently. The medical history reveals that about 3 weeks ago, the patient was hiking in Carinthia (Southern Austria). The patient has no other clinical symptoms.

Questions

1. How do you proceed diagnostically?
2. Which complications can occur if you do not initiate a therapy and how do you proceed if the patient shows up just until serious systemic symptoms are present?

Answers

1. The medical history is typical for borreliosis. In Carinthia, ticks are often infected with *Borrelia burgdorferi*. Ticks transmit the bacteria to humans when biting and sucking blood. Often, as in the present case, the patient did not even recognize the tick bite. In such cases, patient informations about outdoor activities provide hints for tick bites. The patient has the typical signs of an erythema migrans which is pathognomonic for borreliosis. Based on the clinical symptoms, an antibacterial chemotherapy has to be initiated immediately. In addition, laboratory tests can be performed, but they are not always unambiguous. Doxycycline is the drug of choice and is administered orally for 2–3 weeks. The most important contraindications (pregnancy, lactation, age < 8 years) are not relevant in this case. You ask the patient whether he has a known tetracycline allergy. As a consequence of the tetracycline therapy, the GI microbiota may be disturbed, resulting in diarrhea. You have to inform the patient that during tetracycline therapy, direct sun exposure has to be avoided and sun protection measures (sun hat, long-sleeved shirts, and pants) have to be implemented to prevent phototoxic reactions. In case of tetracycline allergy or unavoidable sun exposure for professional reasons, amoxicillin or cefuroxime axetil can be prescribed.
2. If borreliosis is not diagnosed and treated early, neuroborreliosis can develop. In addition, arthritis and carditis may occur. In this case, a treatment in the hospital with a 3–4 week course of an i.v. applied cephalosporin (e.g., ceftriaxone) is necessary.

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Drugs for the Treatment of Viral Infections

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Viruses possess a DNA- or RNA-encoded genome and depend on host cell metabolism for their reproduction. Virus uptake, DNA and RNA replication, integration of virus DNA into the host genome, proteolytic processes, and endogenous virus defense mechanisms are targets for virustatics. HSV, VZV, HIV, and HCV are important human pathogenic viruses. Aciclovir inhibits viral DNA polymerase and is used for treatment of HSV and VZV infections. HIV infection is treated with drug combinations, NRTIs, NNRTIs, INIs, and PIs being the most important drug classes. The combination therapy (HAART) is very effective, but the metabolic ADRs of PIs are severe. HCV infection is also treated with drug combinations. The efficacy of HCV therapy has improved substantially during the past years, but the currently high costs have ignited global discussions about financial sustainability of healthcare systems. Inhibitors of viral RNA polymerase, NS5B, the viral phosphoprotein NS5A, and of viral proteases, as well as IFN, increasing the virus defense, are the most important drug classes for HCV therapy.

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Key Points

1. For all virus infections, rapid initiation of therapy is important to avoid generalization or complications.
2. HSV causes herpes labialis and genital herpes, being treated locally with aciclovir.
3. VZV causes segmental herpes zoster as reactivation of the infection; herpes zoster can be treated p.o. with aciclovir in most cases.
4. HIV causes an immunodeficiency syndrome which can be well treated with a combination of mechanistically distinct virustatics.
5. In general, anti-HIV drugs are well tolerated during long-term therapy, metabolic changes under PIs constituting the largest problem.
6. HCV causes a chronic hepatitis which can be cured with a combination of mechanistically distinct drugs.
7. The currently high costs for HCV drugs constitute a global challenge for healthcare systems.

34.1 Overview of Viral Infections and Pharmacological Interventions

Viruses are infectious particles without cytoplasm, ribosomes, and mitochondria which can multiply only in a host cell, causing cell lysis, pycnosis, and intracellular inclusions. Viruses possess a DNA- or RNA-coded genome being replicated in the host cell. They adhere to host cells via receptors and are endocytosed. The DNA or RNA is uncoated and replicated, and viral proteins are synthesized, taking advantage of cellular ribosomes. The viral proteins are then processed by specific viral proteases. In case of HIV, the viral DNA is permanently integrated into the host genome. New viruses are delivered into the blood, either via lysis or secretion.

Viruses can cause many diseases in humans, from trivial to lethal. For some virus diseases, vaccinations are available; others are accessible to pharmacotherapy. ◘ Table 34.1 provides an overview of some important virus diseases in humans and effective drugs. ◘ Table 34.2 summarizes the pharmacological properties of selected virustatics. ◘ Figures 34.1 and 34.2 provide overviews of pharmacological targets for treatment of infection with HIV and HCV, respectively.

Virustatics inhibit virus proliferation, but they do not kill viruses. This implies that a functionally intact immune system is required for successful therapy of a virus disease. Therefore, immunocompromised patients are particularly susceptible to virus infections (see ▶ Chap. 11). The goal of antiviral therapy is to terminate virus proliferation as soon as possible and with few ADRs. The therapy should be as targeted, timely, and rigorous as possible. It is critical to conduct the therapy for a sufficient period of time to avoid development of resistances that are mostly due to mutations in the target proteins of the drugs. Resistance plays a particularly important role in the therapy of HIV.

The virus life cycle offers several opportunities for pharmacological interventions. Specific viral enzymes can be inhibited: in case of DNA, viral DNA polymerase, in case of RNA, viral reverse transcriptases or RNA polymerases. Inhibition of reverse transcriptase by NRTIs and NNRTIs is of great importance for the treatment of HIV infection. For treatment of HCV infection, nucleoside and non-nucleoside inhibitors of RNA

Table 34.1 Overview of important virus infections in humans

Parameter	HSV	VZV	HIV	HCV
Epidemiology	Approx. 90% of the population is HSV-1-positive; 3–23% is HSV-2-positive	Approx. 4% of patients have a VZV reactivation; 25% of HIV patients; 8% of kidney/heart transplant patients	Approx. 37 million patients globally; approx. 1.8 million new infections/year; approx. One million deaths/year	Approx. 143 million patients globally; approx. 3–4 million new infections/year; approx. 200,000 deaths/year due to hepatocellular carcinoma
Pathogenic characteristics	Herpes viruses, HSV-1 and HSV-2, double-stranded DNA virus with capsid. Primary infection often without any clinical symptoms. The virus persists lifelong	Herpes virus (HHV-3), double-stranded DNA virus with capsid. Primary infection often in childhood (chickenpox). The pathogen persists lifelong in sensory nerve roots	Retrovirus with single-stranded RNA (HIV-1 and HIV-2) and single-or double-stranded DNA intermediates in the host. The pathogen is integrated into the host genome, and new virus particles are released	Oncovirus (carcinogenic virus) with single-stranded RNA. Numerous genotypes. High rate of chronification and high risk of liver cirrhosis and hepatocellular carcinoma
Transmission	Saliva, smear infection, contact with mucosal membranes	Droplet infection, smear infection, or contact with zoster secretions	Needle-stick injuries, drug injection with used syringes, unprotected sexual intercourse	Parenteral, by transfer of contaminated blood, needle-stick injuries, liver transplantation, drug injection with used syringes. Partly unknown ways of transmission
Risk factors	Reactivation due to emotional stress, immunosuppression, HIV infection, sexual activity in case of HSV-2	Reactivation caused by emotional stress, immunosuppression, HIV infection, tumor diseases, DM and UV light, higher age	Illicit drug consumption, anal intercourse (particularly the receptive partner is affected), needle-stick injuries	Illicit drug consumption, hemophilia, frequent blood transfusions, needle-stick injuries, tattooings and piercings with contaminated instruments, anal intercourse
Typical manifestations	Herpes labialis and genitalis (formation of painful blisters)	Herpes zoster (initially, unspecific symptoms, burning and pain alongside the dermatomes. Later, formation of blisters which slowly dry)	The virus affects and destroys CD4-positive T-helper cells, leading to unspecific flu-like symptoms which, at a later stage, are followed by opportunistic infections (HCMV, mycoses, *Pneumocystis jirovecii* infection), CNS symptoms, cachexia	Initially, unspecific flu-like symptoms with discomfort in the right upper abdomen, in some cases dark urine and clay-colored stool; in 70% of the cases, progression to chronic stages of the disease

(continued)

Table 34.1 (continued)

Parameter	HSV	VZV	HIV	HCV
Complications	Eczema herpeticum, facial nerve paresis; encephalitis and retinitis in immunosuppressed patients, neonatal herpes simplex	Zoster oticus, zoster ophthalmicus, zoster genitalis, zoster disseminatus, zoster encephalitis; postherpetic neuralgia	Kaposi's sarcoma, malignant lymphoma, HIV encephalopathy, wasting syndrome	In 25% of the cases, progression to liver cirrhosis, more rarely to hepatocellular carcinoma, secondary autoimmune diseases
Effective virustatics	Aciclovir, local or systemic (p.o.) application	Aciclovir, p.o. or i.v.	Maraviroc (entry inhibitor), tenofovir (NRTI), efavirenz (NNRTI), raltegravir (INI), atazanavir (PI), enfuvirtide (FI); combination therapy with three drugs from at least two different drug classes (HAART)	Sofosbuvir and dasabuvir (NS5B inhibitors), ledipasvir (NS5A inhibitor), simeprevir (PI), ribavirin, peginterferon α-2α; genotype-based combination therapy

Table 34.2 Overview of selected virustatics

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
HSV, VZV					
Aciclovir	Antimetabolite; induces DNA chain termination and, hence, inhibition of viral DNA polymerase	Inhibits viral DNA replication	HSV, VZV	Vertigo, headache, nausea, vomiting; stinging and burning after local application, renal disorders after i.v. administration (crystallization of the drug in the kidney)	12
HIV					
Atazanavir	PI	Inhibits processing of polyproteins to structural viral proteins, reverse transcriptase and integrase, thereby inhibiting maturation of new virus particles	HIV	Nausea, vomiting, lipodystrophy (hyperlipidemia, peripheral lipodystrophy and abdominal increase in adipose tissue, insulin resistance, DM), hepatic changes, neurological disorders	19, 22

Table 34.2 (continued)

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Efavirenz	NNRTI	Inhibits transcription of viral RNA to double-stranded DNA	HIV	CNS effects (up to 40%): vertigo, fatigue, nightmares, depression; exanthemas, teratogenicity	
Enfuvirtide	Inhibits fusion of HIV-1 with the host cell (binds to gp41)	Inhibits infection of the host cell with HIV-1	HIV-1 (currently rarely used, but conceptually important)	Generally well-tolerated; local reactions at injection site	
Maraviroc	Allosteric CCR5 coreceptor antagonist (entry inhibitor)	Inhibits entry of the virus into the host cell	HIV (currently rarely used, but conceptually important)	Nausea, vomiting, hepatotoxicity	1
Raltegravir	INI	Inhibits integration of the viral DNA into the host genome	HIV	Nausea, vomiting, diarrhea, headache, fever	
Tenofovir	NRTI	Inhibits transcription of the viral RNA to double-stranded DNA	HIV	Nausea, vomiting, headache, vertigo, lactate acidosis, hepatomegaly, renal disturbances	12
HCV					
Dasabuvir	RNA polymerase inhibitor (NS5B inhibitor)	Inhibits viral RNA synthesis	HCV genotype 1	Generally well-tolerated, nausea, itching, sleep disturbances	
Ledipasvir	Inhibitor of the viral phosphoprotein NS5A	Inhibits binding of the phosphoprotein to the RNA, thus inhibiting RNA polymerase	HCV genotypes 1, 3, 4, and 6	Generally well-tolerated, fatigue, headache	
Peginterferon α-2a	Long-acting IFN derivative; pegylation stabilizes IFN and protects it from proteolytic degradation	Stimulates T cells and, hence, the immune system against HCV	HCV (all genotypes)	Flu-like symptoms (fever, musculoskeletal pain, fatigue), more rarely autoimmune reactions, hair loss and weight loss, depression	2

(continued)

Table 34.2 (continued)

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Ribavirin	Antimetabolite; inhibits viral RNA polymerase and GTP biosynthesis; effects on the immune system	Antiviral effect which is mediated by various and so far largely unknown mechanisms	HCV (all genotypes) and other viruses, e.g., influenza and herpes viruses	Very common: Reversible hemato-lytic anemia, loss of appetite, sleepless-ness, depression, myelotoxicity, teratogenicity	3
Simeprevir	Inhibitor of the viral protease	Inhibits the initial cleavage of viral protein precur-sors which are essential for the replication of virus particles	HCV genotype 1 and 4	Generally well-tolerated, fatigue, headache, itching, sensitivity to UV light	
Sofosbuvir	RNA polymerase inhibitor (NS5B inhibitor)	Inhibits viral RNA synthesis	HCV (all genotypes)	Fatigue, headache, nausea, anemia	

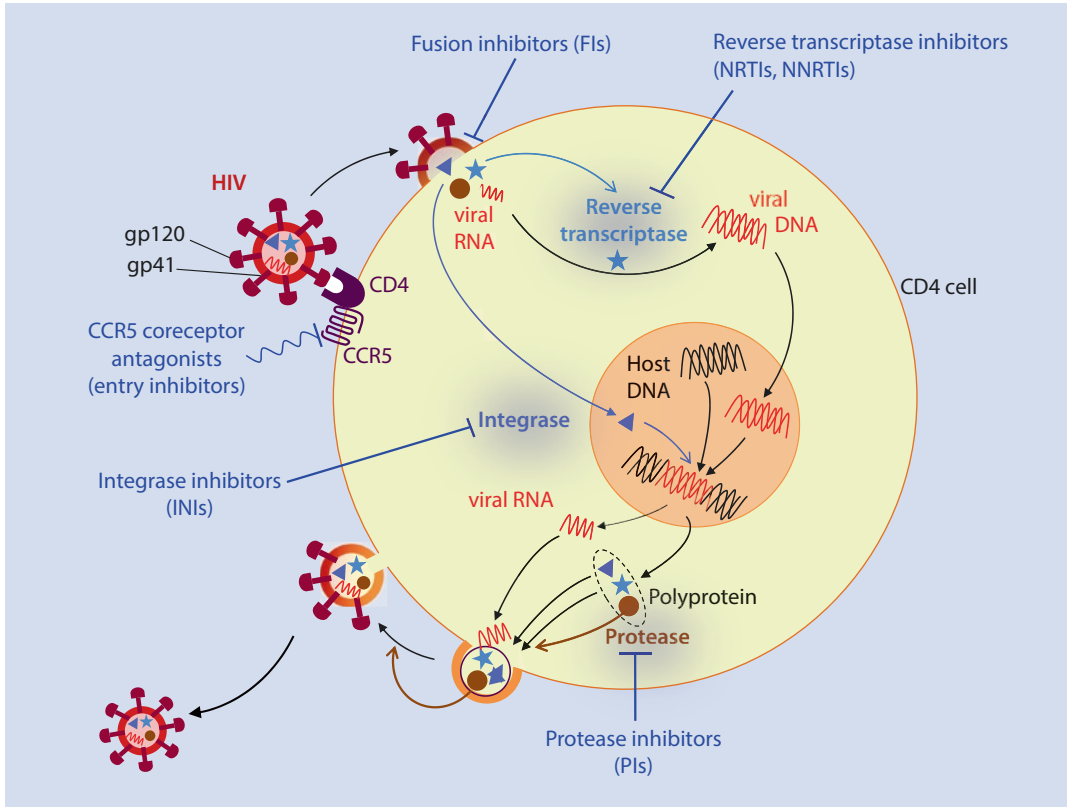

Fig. 34.1 Pharmacological targets of anti-HIV drugs. With the combination of several drugs with different mechanisms (HAART), an HIV infection in most patients can be reasonably well controlled, and AIDS can be avoided

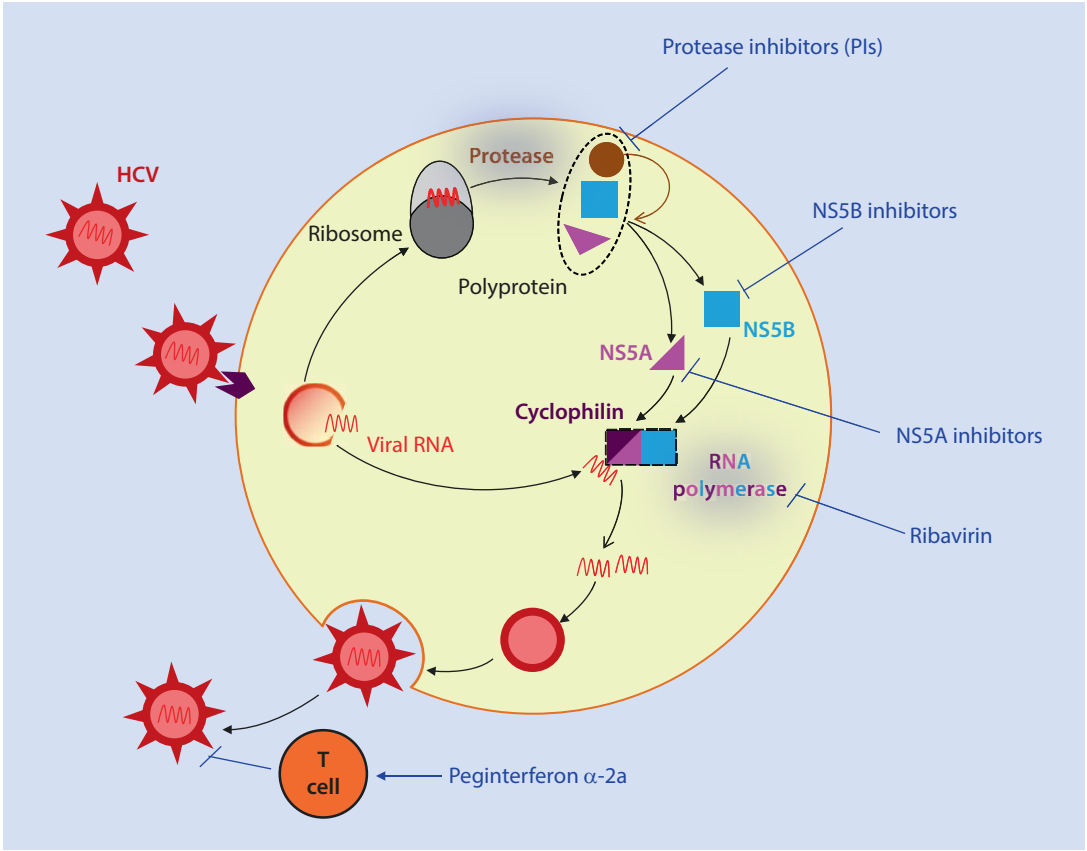

Fig. 34.2 Pharmacological targets of anti-HCV drugs. With the combination of drugs from various classes, an HCV infection can now be cured in most cases. However, the treatment costs are very high

polymerase are relevant. Proteolytic processing of virus proteins represents another important target. PIs inhibit maturation of virus particles in HIV infection and impede processing of virus proteins important for formation of the active RNA polymerase in HCV infection. INIs play a role in the therapy of HIV infection because the viral DNA is permanently integrated into the host DNA in this disease. Virus-specific proteins are suitable pharmacological targets as well. The non-structural phosphoprotein NS5A is an example for this concept. Finally, virus entry into host cells can be targeted pharmacologically.

34.2 Virustatics for Treatment of Herpes Virus Infections

HSV and VZV are crucial human-pathogenic viruses (see Table 34.1). The most important strategy for therapy of herpes virus infections is the inhibition of DNA polymerases (prototype aciclovir). This drug is a deoxyguanosine analog devoid of the cyclic ribosyl moiety and, accordingly, the 3′-hydroxyl group which is important for DNA chain elongation. In herpes virus-infected cells, aciclovir is phosphorylated to the monophosphate by the viral, but not by the host cell thymidine kinase. As a result, high selectivity of the drug for infected cells is accomplished. Cellular kinases catalyze further phosphorylation of the drug to the triphosphate which is then very effectively integrated into virus DNA instead of GTP by the viral DNA polymerase. Because of the missing 3′-hydroxyl group, DNA strand termination occurs. The human DNA polymerase binds aciclovir triphosphate much less potently than the viral enzyme. Because of this profile, aciclovir exhibits selectivity for herpes virus-infected cells. The mechanism of aciclovir action has been successfully transferred to the NRTIs for HIV infection (see ▶ Sect. 34.3).

No mutagenic, teratogenic, or carcinogenic effects of aciclovir in humans have been observed. Thus, aciclovir is a safe drug. The most common ADRs are vertigo, headache, nausea and vomiting, as well as burning sensation when applied topically. Although aciclovir has been broadly used for many years, resistance against aciclovir is not a significant clinical problem.

Aciclovir can be used in many diseases caused by herpes viruses. Locally, the drug is used for therapy of herpes labialis, genital herpes, and herpes keratitis. Depending on the drug concentration and package size, several aciclovir preparations are available OTC in various countries.

Severe herpes simplex infections and VZV reactivations, e.g., herpes zoster, must be treated p.o. or i.v. with aciclovir. Its bioavailability is low (<50%) and the half-life short (3 hours). Accordingly, large drug doses have to be administered in short intervals in oral therapy. Aciclovir is eliminated by glomerular filtration and tubular secretion. Rapid i.v. infusion of large amounts of aciclovir can cause drug precipitation, resulting in colicky pain and kidney dysfunction. Therefore, sufficient fluid intake is essential during systemic aciclovir therapy (see ▶ Chap. 12). Since the patent for aciclovir expired a long time ago, several inexpensive generic preparations are available in many countries. Ganciclovir possesses a similar mechanism of action as aciclovir and is predominantly used in infections with the human cytomegalic virus (HCMV).

34.3 Virustatics for Treatment of HIV Infections

Since HIV is a retrovirus, anti-HIV therapy is also designated as anti-retroviral therapy. Anti-HIV drugs target various steps of HIV replication. HIV binds to CD4 of T cells via the surface protein gp120. This results in a conformational change in the transmembrane protein gp41 and subsequent virus-host cell fusion that can be inhibited by the FI enfuvirtide. The chemokine receptor CCR5 participates as coreceptor in the infection of monocytes by HIV. Allosteric binding of maraviroc to CCR5 prevents HIV entry into host cells. Currently, these two mechanisms do not play a major role in HIV therapy.

Following fusion with the host cell, reverse transcriptase (RT) is released from the virus, transcribing virus mRNA into double-stranded DNA. Since RT differs substantially from human DNA and RNA polymerases, selective NRTIs and NNRTIs could be developed. The NRTI mechanism is analogous to the mechanism of aciclovir (DNA strand termination, see ▶ Sect. 34.2). Abacavir is an NRTI which can cause severe type-IV reactions (ABC-HSR) if administered to patients with certain HLA polymorphisms (see ▶ Chap. 3). Accordingly, their presence must be excluded prior to therapy with abacavir. This is an example of personalized medicine, contributing to increased efficacy and safety of drugs.

NRTIs are phosphorylated to nucleoside triphosphates and inhibit reverse transcriptase with high potency. In contrast, human DNA polymerase is inhibited by the drugs only with low potency (see ▶ Chap. 1). NNRTIs inhibit reverse transcriptase without preceding phosphorylation. Resistance development is faster for NNRTIs than for NRTIs.

Virus DNA is integrated into the human genome via the viral integrase. This enzyme can be selectively inhibited as well (INIs).

Provirus DNA is transcribed into RNA, leading to the synthesis of viral polyproteins. mRNA and viral proteins are assembled to a new virus in a maturation process in which viral protease plays a key role. This enzyme can be inhibited as well (PIs), but the selectivity of PIs for the virus target is not as high as that of NRTIs, NNRTIs, and INIs. Accordingly, PIs have serious ADRs. They can cause metabolic disturbances such as dyslipidemia, abdominal adipose tissue accumulation, insulin resistance, and DM (see ▶ Chaps. 19 and 22).

Anti-HIV therapy has to be performed lifelong. The goal is to reduce the concentration of HIV < 50 viruses/ml blood and to increase the concentration of CD4-positive T cells, ensuring nearly normal function of the immune system. HIV infection cannot be cured pharmacologically because the virus DNA is permanently integrated into the host cell DNA.

Untreated HIV infection leads to an acquired immunodeficiency syndrome (AIDS) characterized by opportunistic infections and otherwise rare tumors. AIDS substantially decreases quality of life and exhibits high long-term mortality. As a result of the modern combination therapy with various anti-HIV drugs (HAART), morbidity and mortality of the HIV infection have decreased

substantially. The combination therapy has to be performed with high adherence. The combination of drugs delays development of resistance. The earlier HAART is initiated, the higher are the success rates. In HAART, at least three drugs from two different classes are combined. Anti-HIV therapy is expensive, but programs have been implemented to provide developing countries with affordable drugs.

In general, long-term HAART is well tolerated. Mild ADRs such as loss of appetite, GI stasis, nausea, diarrhea, and vomiting are frequent. The multitude of available drugs allows for individually assembled drug combinations, considering efficacy and ADRs. Good tolerability of the therapy is essential to ensure high adherence and to avoid development of resistance. Because of its complexity, HAART belongs into the hands of HIV specialists.

34.4 Virustatics for Treatment of Hepatitis C

HCV is a single-stranded mRNA virus. Following entry into host cells, the mRNA is translated into a polyprotein coding for a viral protease, the RNA polymerase NS5B, and the nonstructural phosphoprotein NS5A. The viral protease plays a critical role in the cleavage of the polyprotein into its individual components and, therefore, represents an excellent drug target. HCV PIs are very effective and generally well tolerated drugs. Together with cyclophilin, NS5A and NS5B form a complex which exhibits RNA polymerase activity. Ribavirin is the classic inhibitor of HCV RNA polymerase. The drug works in analogy to the mechanism of aciclovir (RNA strand termination). In addition, ribavirin inhibits GTP synthesis and modulates the immune system. The new generation of RNA polymerase inhibitors comprises NS5B inhibitors and NS5A inhibitors.

Another classic approach for therapy of HCV infection is stimulation of T cells with IFN-α 2a, enhancing HCV elimination. IFN conjugated with polyethylene glycol (peginterferon-α 2a) is used clinically. Pegylation increases the half-life of IFN (see ▶ Chap. 2). Accordingly, the intervals of IFN application can be prolonged, and therapy costs are reduced.

Until few years ago, HCV infection was difficult to treat. In many cases, the infection resulted in chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Liver transplantation was the only cure. However, this therapy is associated with high costs and risks and could be offered only to few patients due to the limited availability of donor organs. The standard therapy of HCV infection was a 24–48 (72)-week treatment with peginterferon-α 2a + ribavirin. Depending on the genotype of HCV, 50–80% of the patients could be cured, genotypes 2 and 3 being more sensitive than genotype 1. Unfortunately, the therapy was poorly tolerated. Peginterferon-α 2a can frequently cause flu-like symptoms, autoimmune phenomena, fatigue, hair loss, thyroid gland dysfunction, depression, and anxiety. In depressive patients an additional antidepressive therapy had to be initiated (see ▶ Chap. 28). The major ADR of ribavirin is hemolysis, requiring dose reduction and resulting in reduced antiviral efficacy. Ribavirin can also cause neuropsychiatric problems (anorexia, sleeplessness, depression). Moreover, the drug is myelotoxic and teratogenic.

The introduction of new anti-HCV drugs of the class of NS5A-, protease, and particularly NS5B inhibitors has substantially improved efficacy and tolerability of anti-HCV therapy. It is performed according to the virus genotype and the extent of liver damage. A standard therapy for genotypes 1, 4, 5, and 6 is a 12-week course of peginterferon-α 2a + ribavirin + sofosbuvir. For genotypes 2 and 3, a 12-week course of ribavarin + sofosbuvir is an option. For genotypes 1 and 4, sofosbuvir + ledipasvir can be used; for genotypes 5 and 6, ledipasvir + sofosbuvir + ribavirin. As a result of these improvements, many HCV patients can now be cured.

However, the currently very high costs for anti-HCV drugs are a major problem for many healthcare systems, and anti-HCV therapy is not available to all patients in several countries. It has been criticized that drug companies take advantage of the high efficacy of new HCV drugs to reap inappropriately high profits. Related to this, surveillance agencies and insurance companies are often considered as too powerless to enforce moderate drug prices. In this complex discussion, it has to be taken into consideration that now for the first time, a cure of HCV infection is feasible for most patients, and that substantial follow-up costs due to liver cirrhosis, hepatocellular carcinoma, and liver transplantation do not accrue anymore. Moreover, the quality of life and

employability of HCV patients has improved substantially. Due to its complexity and high costs, the therapy of HCV infection belongs into the hands of the hepatologist.

34.5 Questions and Answers

Questions

Which statement on pharmacotherapy of the HIV infection is correct?

A. Integrase inhibitors (INIs) block integration of virus RNA into the host cell DNA.
B. Protease inhibitors (PIs) inhibit initial disintegration of the HIV in the host cell.
C. Inhibitors of the viral phosphoprotein NS5A inhibit docking of HIV to host cells.
D. Non-nucleosidic reverse transcriptase inhibitors (NNRTIs) cause lipodystrophy.
E. Allosteric CCR5 coreceptor antagonists prevent HIV uptake into host cells.

Answers

A. Initially, the HIV-RNA has to be transcribed in double-stranded DNA by reverse transcriptase. The integrase mediates integration of the HIV-DNA into the host cell DNA.
B. PIs inhibit the viral protease and, thereby, maturation of new HIV particles.
C. Inhibitors of the viral phosphoprotein NS5A inhibit amplification of HCV, but not HIV.
D. Lipodystrophy is a typical ADR of PIs.
E. Maraviroc is a typical drug of this group. It is also referred to as entry inhibitor.

Answer **E** is correct.

34.6 Exercises

A 37-year-old woman visits you in your dermatology practice. About 3 days ago, she noticed burning segmental pain on the right thorax, radiating from the spine to the center of the sternum. Just recently, 15 groups of about 3–4 blisters each along the burning segment have flared up. Upon request the patient tells you that she had chickenpox in childhood. In general, she has been healthy, but during the past 3 weeks, she has experienced a lot of problems with her boss at work and at home with her husband and the children. The children were vaccinated against chickenpox.

Questions

1. How do you proceed therapeutically?
2. How would you proceed if the clinical symptoms generalized?

Answers

1. Most likely, the patient suffers from herpes zoster affecting the intercostal nerves. The complaints, the medical history (herpes zoster activation by stress), and the results of the physical exam are pathognomonic so that further diagnostic measures are not necessary. You immediately initiate a therapy with aciclovir (5 × 800 mg/day for 7 days). You inform the patient that adherence to the therapy is crucial for rapid alleviation of the clinical symptoms and to avoid development of postherpetic neuralgia. To mitigate the pain, you additionally prescribe a COX inhibitor such as ibuprofen (4 × 400–600 mg/day). The patient should avoid contact with pregnant women and should not become pregnant during the therapy with aciclovir. In otherwise healthy patients, aciclovir is generally well tolerated. You educate the patient about potential ADRs of aciclovir and ibuprofen. The patient should avoid stress situations during therapy and come to your office immediately should the symptoms in the diseased area deteriorate or should new symptoms occur. Generalization of the herpes zoster must be avoided. However, this complication is rather unlikely because the aciclovir dose prescribed is sufficiently high and because the patient apparently is not immunocompromised. The patient should drink sufficient volumes of fluids of her choice to avoid crystallization of aciclovir in the kidney.
2. A generalized herpes zoster is life-threatening and cannot be treated on an outpatient basis. In such a case, the patient is immediately admitted to a

hospital. The patient is then treated with i.v. infusions of aciclovir. Monitoring kidney function is important because aciclovir is eliminated renally and can crystallize in the kidney and ureter. In case of severe pain, analgesics according to the WHO scheme are prescribed. The therapy includes MOR agonists and co-analgesics. In addition, it must be clarified whether a hitherto unrecognized immunodeficiency has caused deterioration of the herpes zoster.

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Drugs for the Treatment of Fungal Infections

R. Seifert, *Basic Knowledge of Pharmacology*, https://doi.org/10.1007/978-3-030-18899-3_35

Mycoses are caused by dermatophytes, yeast, mold, or ascomycetes. In mycoses, the immune system is weakened, allowing overgrowth of fungi. The similarities between fungi and human cells handicap selective killing of fungi. Azole antimycotics inhibit ergosterol synthesis and impair function of the fungal plasma membrane. Azoles are fungistatic in local and invasive candidiasis and cryptococcosis. They inhibit CYPs and cause drug interactions. Amphotericin B forms complexes with ergosterol and increases plasma membrane permeability, being also the cause for high toxicity. The drug is fungicidal in many invasive mycoses. Caspofungin inhibits synthesis of cell wall constituents and is less toxic than amphotericin B. It is fungistatic or fungicidal in invasive mycoses including infection with *Pneumocystis jirovecii*.

Key Points

1. Weakening of the immune system by classic cytostatics, immunosuppressants, GCR agonists, tumor diseases, and HIV facilitates development of mycoses.
2. Superficial mycoses caused by dermatophytes are treated with azole antimycotics.
3. *Candida albicans* can cause superficial and invasive mycoses.
4. Superficial candidiasis is treated with azole antimycotics and nystatin.
5. Invasive candidiasis is treated with azole antimycotics, amphotericin B, caspofungin, and flucytosine.
6. Invasive cryptococcosis is treated with azole antimycotics, amphotericin B, and flucytosine.
7. *Pneumocystis jirovecii* infections are treated with caspofungin and cotrimoxazole.
8. Invasive aspergillosis is treated with azole antimycotics, amphotericin B, and caspofungin.

35.1 Overview of Important Fungal Infections and Their Pharmacotherapy

Mycoses are caused by fungi that infest human tissues as parasites. Fungi possess a nucleus and form cell clusters. They are closer related to human cells than bacteria. For this reason, it is much more difficult to selectively kill fungi than bacteria (see ▶ Chap. 33). Accordingly, only few antimycotic drug classes for clinical use are available. One of the few selective targets for antimycotics is the cell wall. ◘ Figure 35.1 shows the structure of the plasma membrane and the cell wall of fungi and the targets of drugs at these sites. ◘ Table 35.1 provides an overview of important mycoses, and ◘ Table 35.2 lists selected antimycotics.

Mycoses particularly develop in immunocompromised patients. Among them are elderly people, prematurely born babies, and patients after organ or bone marrow transplantation, with autoimmune diseases, DM, HIV, or bacterial sepsis. Several drug classes including cytostatics, GCR agonists, immunosuppressants, and broad-spectrum antibacterial chemotherapeutics can facilitate development of mycoses (see ▶ Chaps. 11, 19, and 34). SGLT2 inhibitors can promote vulvovaginal infections due to increased excretion of glucose in the urine, altering microbiota and providing nutrient for fungi (see ▶ Chap. 19). Moreover, major surgeries and parenteral nutrition may facilitate the development of mycoses.

Dermatophytes cause superficial infections of the skin, hairs, and nails. These mycoses are not life-threatening and represent the most common type of mycoses. Globally, up to 25% of the human population suffer from dermatophyte infections. Both insufficient and excessive hygiene favor these diseases as do hyperhidrosis and use of public showers, saunas, and swimming pools. Dermatophyte infections are treated locally with azole antimycotics. For long-term therapeutic success, elimination of factors favoring the diseases is essential.

Candida species are the second most common cause of mycoses. The most important pathogens are *Candida albicans* and *Cryptococcus neoformans*.

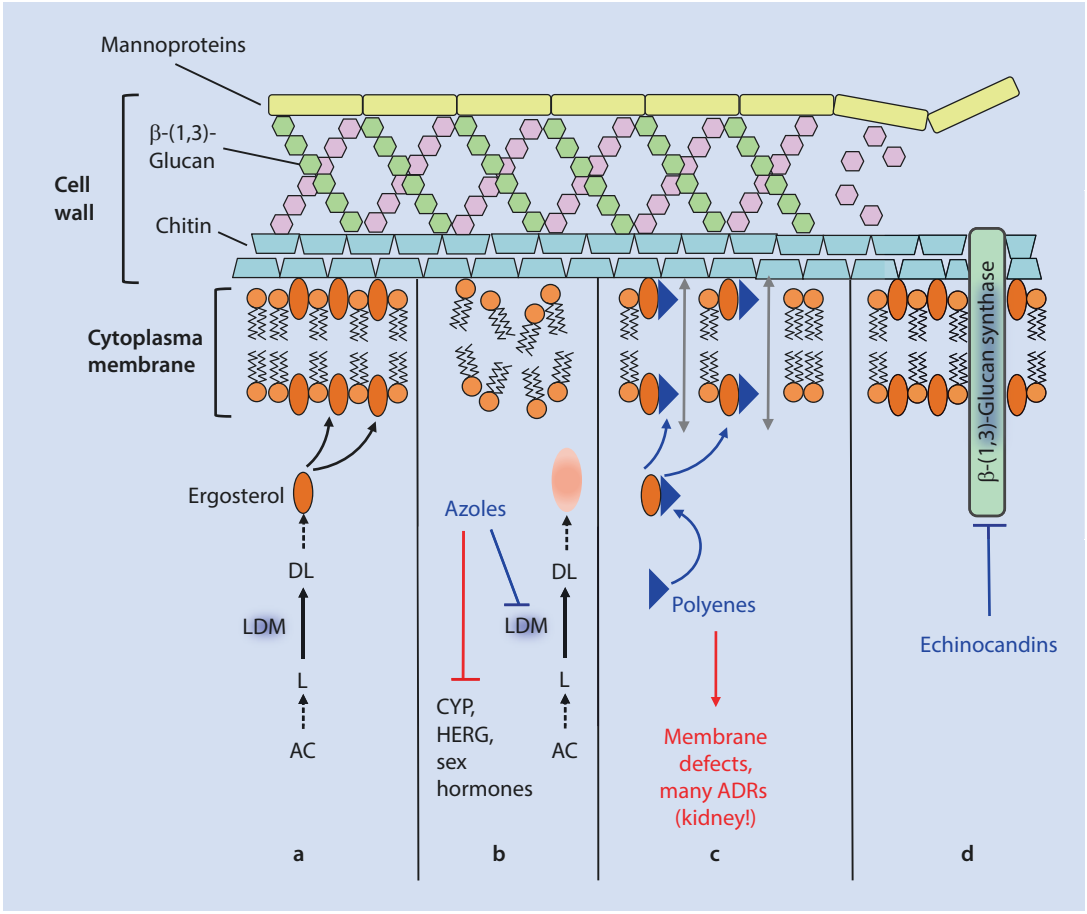

Fig. 35.1 **a–d** Structure of the plasma membrane and cell wall of fungi and targets of antimycotics. **a** Physiological situation. **b** Azole antimycotics. **c** Polyene antimycotics. **d** Echinocandins. AC acetyl coenzyme A, L lanosterol, DL 14-α-demethyl-lanosterol, LDM lanosterol-14-α-demethylase. Fungi and mammalian cells are very similar. For this reason, we have only a limited arsenal of drugs for fungal infections

Candida albicans can cause superficial mycoses of mucosal membranes and invasive mycoses. Common superficial diseases are candidiasis of the mouth, tongue, palate, vagina, and vulva. These diseases are favored by the same factors as dermatophyte infections. A particularly important cause for oral candidiasis is the incorrect application of IGCR agonists for treatment of asthma (see ▶ Chap. 14), i.e., the deposition of substantial IGCR agonist amounts in the mouth. In addition to acquisition of the correct inhalation technique, rinsing of the mouth with water after IGCR agonist application reduces the candidiasis risk.

Vulvovaginitis in premenopausal women is very common. Frequent causes are therapy with antibacterial chemotherapeutics, compromising local microbiota (e.g., *Lactobacillus iners* or *Lactobacillus crispatus*), therapy with oral contraceptives having high ER agonist content (see ▶ Chap. 24), pregnancy, and insufficient or excessive intimate hygiene. Oral and vulvovaginal candidiasis can be treated locally with azole antimycotics and nystatin.

Invasive candidiasis occurs predominantly in immunocompromised patients and is burdened with high lethality. The disease is treated with azole antimycotics, amphotericin B, caspofungin, or flucytosine. *Cryptococcus neoformans* belongs to yeast pathogens as well and affects predominantly lungs and meninges. Cryptococcosis therapy is performed with azole antimycotics, amphotericin B, and flucytosine as drug of last resort.

Mold fungi are less common causes of mycoses. The most important pathogen is *Aspergillus*

Table 35.1 Overview of important mycoses in humans

Parameter	Dermatophytes	Yeasts	Molds	Ascomycetes
Epidemiology	Overall 25% of the population worldwide is affected (all disease entities)	50–75% of all women of reproductive age worldwide experience at least one vulvovaginal mycosis in their lives. Worldwide >400,000 life-threatening infections/year caused by invasive candidiasis and > 1,000,000 infections/year caused by cryptococcosis	Worldwide >200,000 life-threatening cases of aspergillosis per year	Worldwide >400,000 life-threatening infections/year; common in HIV patients
Lethality	No	45–75% with invasive candidiasis; 20–70% with cryptococcosis	30–95%, depending on the localization	20–80%
Most common types of fungi	Trichophyton species, Microsporum species, *Epidermophyton floccosum*	*Candida albicans, Cryptococcus neoformans*	*Aspergillus fumigatus*	*Pneumocystis jirovecii* (trophozoites forming cysts and containing spores)
Typical manifestation	Superficial infections of skin, hair, and nails	Superficial candidiasis of the skin and mucous membranes, invasive candidiasis, cryptococcosis	Skin, ears, respiratory tract, lung; rarely heart, kidney, and CNS	Invasive infection of the lung
Representative diseases	Tinea pedis, onychomycosis, Tinea capitis	Vulvovaginal mycosis, stomatitis (thrush), invasive candidiasis affecting lung, heart, stomach, intestine, liver, spleen, CNS; pulmonary and meningeal cryptococcosis	Aspergilloma, allergic bronchopulmonary aspergillosis, invasive aspergillosis with different degrees of severity	Interstitial pneumocystis pneumonia
Disease-favoring factors	Insufficient or exaggerated hygiene, hyperhidrosis, weakend immune system, use of public showers, saunas or pools; elderly people	Oral contraceptives, insufficient or excessive hygiene (vaginal mycosis); therapy with antibiotics, GCR agonists, classic cytostatics, immunosuppressants; SGLT-2 inhibitors, tumor diseases, HIV infection, s/p organ transplantation, autoimmune diseases	Therapy with antibiotics, GCR agonists, classic cytostatics, immunosuppressants. Oral contraceptives, insufficient or exaggerated hygiene, tumor diseases, HIV infection, s/p organ transplantation, autoimmune diseases	Immunosuppression in HIV infection is an important risk factor

Table 35.1 (continued)

Parameter	Dermatophytes	Yeasts	Molds	Ascomycetes
Effective antimycotics	Clotrimazole, itraconazole (local application)	Clotrimazole, fluconazole, and nystatin for local treatment of superficial candidiasis; itraconazole, fluconazole, amphotericin B, caspofungin, and flucytosine for systemic treatment of invasive candidiasis; amphotericin B, flucytosine, fluconazole, and itraconazole for systemic treatment of cryptococcosis	Amphotericin B, itraconazole and caspofungin (systemic application)	Caspofungin and cotrimoxazole for systemic treatment of pneumocystis pneumonia

Table 35.2 Overview of selected antimycotics

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Amphotericin B	Complex formation with ergosterol in the cell membrane and pore formation; fungicidal	Increases the permeability of the cell membrane for water, ions, and small molecules. Hence, resistance to amphotericin B is rare	Very broad spectrum of action in local and invasive mycoses (exceptions dermatophytes and *Pneumocystis jirovecii*)	Severe ADRs because of the unspecific mechanism of action. In case of overdose: respiratory depression and cardiac arrest, disturbance of hematopoiesis, nausea, vomiting, exanthemas, hypokalemia, hypotension, liver and kidney damage	12, 13
Caspofungin	Inhibition of β-(1,3)-D-glucan synthase; fungicidal (fungistatic activity against *Aspergillus fumigatus*)	Disrupts cell wall formation	Systemic therapy of invasive mycoses caused by *Candida albicans, Pneumocystis jirovecii*, and *Aspergillus fumigatus*	Relatively well tolerated: fever, inflammations at the injection site, exanthemas, nausea, vomiting, anemia, headache, elevated transaminases, hypokalemia	12
Clotrimazole	See fluconazole	See fluconazole	Local therapy of superficial infections with dermatophytes and *Candida albicans*	No systemic ADRs after local application on small areas	2, 17, 24

(continued)

Table 35.2 (continued)

Drug	Mechanism of action	Important effects	Important indications	Important ADRs	Further contexts in Chaps.
Fluconazole	Inhibition of lanosterol 14α-demethylase, fungistatic	Integrates nonphysiological sterols into the cell membrane and thus disrupts cell membrane function	Superficial and invasive candidiasis, cryptococcosis, not effective against *Aspergillus fumigatus*	Inhibits various CYPs and thus increases concentration of CYP substrates. Nausea, vomiting, hepatic dysfunction, arrhythmias, allergy; in high doses, inhibition of sex hormone synthesis leading to gynecomastia and oligospermia (men) and menstrual disturbances (women)	2, 17, 24
Flucytosine	Pyrimidine derivative which is integrated into the mRNA and inhibits thymidylate synthesis	Inhibits protein biosynthesis and DNA replication	Systemic therapy of invasive mycoses with sensitive strains of *Candida albicans* and *Cryptococcus neoformans*. Due to rapidly emerging resistance, flucytosine is used in combination with amphotericin B; antimycotic of last resort	Anemia, leukopenia, thrombopenia, vomiting, diarrhea, allergic skin reactions, weariness, fever, hepatotoxicity	34
Itraconazole	See fluconazole	See fluconazole	Local therapy of superficial infections with dermatophytes and *Candida albicans*, *Aspergillus*	See fluconazole	2, 17, 24
Nystatin	See amphotericin B	See amphotericin B	Local therapy of dermal, intestinal, and vaginal mycoses; not systemic application	Nausea, vomiting, and diarrhea after p.o. administration. No systemic ADRs because nystatin is not absorbed from the GI tract or skin	13

fumigatus. Aspergillus species can affect many organs. Aspergillomas are encapsulated conglomerates of fungi, mucus, and human cells in preformed body cavities. They are treated surgically. Allergic bronchopulmonary aspergillosis predominantly occurs in patients with asthma (see ▶ Chap. 19) and is treated with allergen avoidance and GCR agonists. In addition, invasive aspergillosis affecting many organs can develop. The disease is treated with azole antimycotics, amphotericin B, and caspofungin.

Pneumocystis jirovecii belongs to the ascomycetes and causes an interstitial pneumonia, the most common opportunistic infection in HIV

patients (see ▶ Chap. 34). Since the pathogen contains cholesterol instead of ergosterol in the plasma membrane, azole antimycotics and amphotericin B cannot be applied. However, caspofungin is effective and also cotrimoxazole, inhibiting tetrahydrofolate synthesis (see ▶ Chap. 33).

Diagnosis of mycoses is often difficult because the clinical symptoms are arbitrary. This constitutes a serious problem, because invasive mycoses exhibit high lethality. In general, the physician cannot wait until a precise microbiological diagnosis has been made and the antibiogram is available. For success of antimycotic therapy, early onset is important. Therefore, if invasive mycosis is suspected in patients at high risk, antimycotic therapy is initiated. In this case, about 60–70% of invasive infections can be cured. However, bacterial infections result in a substantially higher cure rate. The reason for the unsatisfying situation is that patients with invasive mycoses are immunocompromised in most cases (see ▶ Chap. 11). In high-risk patients, antimycotic prophylaxis is an option as well.

35.2 Azole Antimycotics

Azole antibiotics contain either imidazole or triazole groups. Some drugs such as clotrimazole, econazole, and tioconazole are exclusively used topically. Other drugs such as fluconazole and itraconazole are applied both topically or systemically. Azole antimycotics inhibit the lanosterol-14-α-demethylase, catalyzing the conversion of lanosterol to 14-α-demethyl-lanosterol. Via this mechanism, the formation of ergosterol is impaired. Since ergosterol is essential for membrane integrity, azole antimycotics compromise the membrane function. They are fungistatic. The onset of action is slow because of the underlying indirect effect on membrane integrity. Human 14-α-demethylase is inhibited less potently than the fungal enzyme (see ▶ Chap. 1). Local therapy with the drugs is generally well tolerated.

Certain azole antimycotics inhibit CYP3A4 (see ▶ Chap. 2). This is relevant in systemic therapy. In case of co-application of drugs metabolized via CYP3A4, e.g., ciclosporin and tacrolimus, their organ toxicity can be increased, requiring dose reduction. Moreover, comedication with TdP-causing drugs metabolized via CYP3A4 can be problematic (see ▶ Chap. 17).

In systemic therapy with azole antimycotics, nausea, vomiting, and diarrhea are common ADRs (5–10%). Azole antimycotics are potentially hepatotoxic. In high doses or during long-term therapy, they can inhibit sex hormone synthesis via CYP inhibition, resulting in gynecomastia and oligospermia (men) or menstrual disorders (women) (see ▶ Chap. 24). Because of teratogenic effects, systemic therapy with azole antimycotics in pregnancy and lactation is contraindicated.

Fluconazole can be administered topically, p.o., and parenterally. It inhibits CYP3A4, CYP2C9, and CYP2C19. Fluconazole is used in superficial and invasive mycoses. Because of good penetration into the liquor, it can also be applied in meningeal cryptococcosis. In *Aspergillus* infections, fluconazole is ineffective. It has a bioavailability of 90%, very low plasma protein binding, and a half-life of 24–30 hours. The drug is predominantly eliminated via the kidney. In CKD, the dose of fluconazole must be reduced (see ▶ Chap. 12).

Itraconazole can be applied locally, p.o., and parenterally. It is effective in superficial mycoses caused by dermatophytes and *Candida albicans* as well as in invasive aspergillosis. The drug has a lower bioavailability (50–55%) than fluconazole and a half-life of 15–36 hours. Itraconazole is metabolized via CYP3A4, thereby causing drug interactions.

35.3 Polyene Antimycotics

Amphotericin B is the prototypical polyene antimycotic. It is an amphiphilic drug with both hydrophilic and hydrophobic domains and forms complexes with ergosterol in the plasma membrane. As a result, pores with permeability for water, ions, and low-molecular mass substances are formed. Thus, concentration gradients for electrolytes are abrogated, and nutrients are lost from cells. Because of this direct mechanism of action (in contrast to azole antimycotics), amphotericin B has a rapid onset of action and is fungicidal. It possesses a broad spectrum of activity excluding only dermatophytes and *Pneumocystis jirovecii*. Amphotericin B is used in severe invasive mycoses, particularly for emergency therapy of life-threatening infections. Because of the protein-independent mechanism of action, the risk of resistance development is low.

In contrast to azole antimycotics, amphotericin B cannot be applied p.o., but is administered i.v. or locally for superficial infections. Plasma protein binding is very high (95%), entailing a high risk of interactions with other highly protein-bound drugs (see ▶ Chap. 2). The half-life is about 18–24 hours. Amphotericin B also binds to cholesterol in the plasma membrane of human cells, causing serious ADRs. In toxic doses, amphotericin B leads to respiratory and cardiovascular arrest. There is no antidote. Because of the serious ADRs, incremental dosage increase is necessary. Common ADRs are nausea and vomiting, anemia, liver, and kidney damage with hypokalemia as well as ototoxicity. Nephrotoxicity of amphotericin B is enhanced by other nephrotoxic drugs such as aminoglycosides, ciclosporin, and cytostatics (see ▶ Chap. 12). Thiazide and loop diuretics and GCR agonists aggravate hypokalemia. Exanthemas may occur as well. Because of the numerous ADRs, liposomal preparations of amphotericin B with reduced toxicity have been developed. The nephrotoxicity is also reduced by infusion of 1–1.5 l of 0.9% NaCl solution per day. During amphotericin B infusion, fever, chills, and red man syndrome can occur.

Nystatin is very toxic. Therefore, the drug is exclusively used for local mycoses of the skin, the GI tract, and the vagina. Nystatin is not absorbed following oral administration and causes diarrhea, vomiting, and nausea.

35.4 Echinocandins

Echinocandins are semisynthetic lipopeptides inhibiting the fungal β-(1,3)-D glucan synthase and, thereby, cell wall formation. Echinocandins are fungicidal, in infections with *Aspergillus fumigatus* fungistatic. Caspofungin is the prototype of this drug class. It is used in invasive candidiasis and aspergillosis. The drug is also effective in *Pneumocystis jirovecii* infections. Because of its poor absorption following oral administration, caspofungin is applied i.v. The high plasma protein binding may cause interactions with other highly protein-bound drugs (see ▶ Chap. 2). Ciclosporin increases, and RMP decreases caspofungin plasma concentration. Caspofungin lowers tacrolimus concentration. It possesses less serious ADRs than amphotericin B. Fever, inflammatory reactions at the site of infusion, exanthemas, nausea, vomiting, anemia, headache, transaminase increase, and hypokalemia are observed.

35.5 Questions and Answers

Questions

Which assignment of antimycotic drug to mechanism of action is *NOT* correct?

A. Caspofungin – inhibition of peptidoglycan biosynthesis
B. Amphotericin B – pore formation in the cell membrane
C. Flucytosine – inhibition of protein biosynthesis
D. Fluconazole – inhibition of ergosterol synthesis
E. Nystatin – complex formation with ergosterol

Answers

A. Penicillins inhibit bacterial peptidoglycan (murein) biosynthesis. Murein is part of bacterial cell walls. Caspofungin is an echinocandin and inhibits the synthesis of β-1,3-glucans, important constituents of fungal cell walls.
B. Amphotericin B and nystatin (see answer E) form complexes with ergosterol, causing an increase in the permeability of the fungal plasma membrane for water, ions, and low-molecular mass substances.
C. Flucytosine is taken up into fungal cells, deaminated to 5-FU, and integrated into the mRNA, thereby inhibiting protein biosynthesis.
D. Fluconazole belongs to the azole antimycotics and inhibits ergosterol biosynthesis by targeting lanosterol-14-α-demethylase.
E. Nystatin possesses the same mechanism of action as amphotericin B (see answer B). Because of its high systemic toxicity, nystatin is only used locally.

Statement **A** is not correct.

35.6 Exercises

A 30-year-old woman visits you in your gynecologist's office, complaining about pruritus in the genital area, burning sensation while urinating, and pain during sexual intercourse. She has not had these problems before. The patient reports that until 2 days ago, she has taken an antibiotic (clarithromycin), prescribed by her general practitioner, because of a severe bronchitis. The physical exams reveal white, crumbly, and odorless vaginal discharge and white plaques on the vaginal mucosa and the vulva, the latter being erythematous. The patient is afraid of possible ADRs of a pharmacotherapy because she wishes to become pregnant. For this reason, she has stopped taking the micropill 2 months ago. Upon request, the patient reports that her husband has no complaints.

Questions

1. How do you proceed diagnostically and therapeutically?
2. Which drug classes can increase the likelihood of vaginal mycosis?

Answers

1. Based on the medical history and the physical exam, the patient most likely suffers from vulvovaginal candidiasis as a result of disturbed microbiota following antibacterial chemotherapy. To confirm the diagnosis, you take a vaginal smear and examine it microscopically to identify fungi. In addition, using a pH indicator strip, you determine the pH of the vaginal secretions. The pH is 4.2 (reference values 4.0–4.4). The additional application of probiotics is not necessary. Since vulvovaginitis has occurred for the first time, additional diagnostics are not required. You prescribe a single-dose therapy of clotrimazole as vaginal suppository and cream. Her husband should apply the cream onto the glans penis as well to avoid balanitis and the risk of ping-pong infections during sexual intercourse. The therapy should alleviate the clinical symptoms rapidly. You can put the patient at ease that local therapy of candidiasis with clotrimazole is safe, even in pregnancy. You also take the opportunity to educate the patient about appropriate intimate hygiene (e.g., avoiding sprays, direct contact of the vagina with wash lotions and moist chambers, wearing breathable cotton panties) to prevent additional disease episodes.
2. Systemically and locally applied antibacterial chemotherapeutics can increase the probability of vulvovaginal mycosis. The same is true for GCR agonists. Oral contraceptives with high ER agonist content favor candidiasis as well. Moreover, systemically applied SGLT2 inhibitors, classic cytostatics, and immunosuppressants (e.g., low- and high-dose 6-MP, MTX, and cyclophosphamide) can increase the probability of vulvovaginal mycosis.

Further Reading

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Integrative Case Studies

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Having studied the preceding 35 chapters of this textbook, the student should have a solid knowledge of key pharmacological principles and of the most important drugs. The next step then is to apply this knowledge in real-world situations. One important aspect in this regard is effective communication about pharmacology and drugs with patients and other health professionals (e.g., physicians and pharmacists). This ensures drug efficacy, adherence, and minimization of ADRs. The integrative case studies discussed in this chapter highlight important problems encountered in medical practice. Interactions of drugs with food items, inappropriate therapy with antibiotics, drug underdosing and overdosing, ADRs due to incomplete BBB, optimization of medication plans, and drug abuse are discussed.

Key Points

1. Beware of interactions of food items with drugs!
2. Use antibacterial chemotherapeutics critically!
3. Do not use drugs in subtherapeutic doses!
4. Beware of the incomplete BBB in toddlers!
5. Critically review medication plans!
6. Beware of the increasing abuse of drugs!
7. Do not overdose drugs!
8. Critically assess long-term medications!
9. Drugs can cause ADRs that are mistaken as "disease" symptoms!
10. In many cases, fewer drugs are better!
11. Consider all therapeutic alternatives including non-pharmacological measures!
12. Educate and inform patients about drug effects including ADRs!

36.1 Lessons from History: Arrhythmias After Tropical Fruit Party

In 1988, a 37-year-old male lawyer, so far without any cardiovascular problems, was admitted to the emergency room with a very rapid, irregular, and shallow pulse. The ECG showed a classic TdP. Cardioversion restores normal sinus rhythm. From the medical history, you learned that the patient took a tablet of terfenadine once in a while for allergic conjunctivitis. He did not take other drugs. So far, he tolerated terfenadine well. However, yesterday terfenadine did not work. Therefore, he took three tablets, but even the high dose failed. Further questioning reveals that the day before yesterday, his wife and he had attended a "tropical fruit party." At the party he drank a lot of grapefruit juice.

36.2 Questions and Answers

Questions

1. How do you explain the lack of efficacy of terfenadine on the allergic symptoms and the occurrence of TdP?
2. How can further TdP episodes be prevented?

Answers

1. Terfenadine is a prodrug of the H_1R antagonist fexofenadine which is used for the treatment of allergic conjunctivitis. Conversion of terfenadine is mediated via CYP3A4. However, this conversion was reduced because the patient drank a lot of grapefruit juice on the preceding evening. Grapefruit juice contains the bitter substance naringin which inhibits CYP3A4. This explains the lack of anti-allergic effect of terfenadine. The patient then tripled the terfenadine dose. The accumulating terfenadine blocked cardiac HERG channels, causing delayed repolarization and triggering TdP.
2. The patient is an academic. Thus, you should be able to communicate to him the explanations under point 1. You explicitly warn the patient to avoid renewed intake of grapefruit juice + terfenadine. Because of TdP, terfenadine was withdrawn from the drug market. Moreover, you transfer the patient to a cardiologist for a cardiac checkup. Specifically, ECG abnormalities (e.g., long-QT syndrome favoring occurrence of TdP) should be excluded.

36.3 Generalized Pruritus and Lack of Antibiotic Efficacy in Uncomplicated Cystitis

A 22-year-old female patient visits you in your urology office complaining about dysuria, oliguria, and pollakiuria. The patient does neither have fever nor pain in the renal bed. The medical history is otherwise inconspicuous. Analysis of the urine reveals the presence of many leukocytes and rod-shaped bacteria. You diagnose an uncomplicated cystitis caused by gram-negative bacteria, presumably *Escherichia coli*. You order an antibiogram, advise the patient to drink ample fluids, and prescribe a combination of trimethoprim + sulfamethoxazole (cotrimoxazole). The patient is advised to take the antibiotic for 3 days. The day after tomorrow, the patient visits you again. The clinical symptoms are still there, and moreover, a generalized pruritus has occurred. Inspection of the skin reveals generalized urticaria with scratching artifacts.

36.4 Questions and Answers

Questions

1. How do you explain the lack of efficacy of the antibiotic and the pruritus?
2. How do you proceed to improve the cystitis symptoms and to mitigate the pruritus?

Answers

1. In general, an antibiotic effective against a pathogenic bacterium improves the cystitis symptoms within 24 hours. Since this is not the case here, you can suspect that the pathogen is a bacterium exhibiting resistance against cotrimoxazole. The antibiogram will answer this question. However, since the patient still has clinical symptoms, you cannot wait until the results of the antibiogram are available. The pruritus and the urticaria are typical symptoms of a type I allergic reaction. The allergy was most likely caused by the sulfonamide sulfamethoxazole. Because of the high risk for allergies, sulfonamides should not be used in uncomplicated urinary tract infections.
2. You immediately terminate cotrimoxazole and replace if by fosfomycin. This drug is effective as single-dose therapy in many cases of uncomplicated urinary tract infection in women. With the new therapy, the clinical symptoms should improve rapidly. Termination of cotrimoxazole should also improve urticaria and pruritus rapidly. Against the pruritus, you should prescribe the second-generation H_1R antagonist fexofenadine. If the pruritus also affects the quality of sleep, a first-generation H_1R antagonist penetrating the BBB such as clemastine constitutes a therapeutic alternative.

You should report the ADR to your national drug surveillance agency. Moreover, you inform the patient about the possible cause of the urticaria and provide the patient with an allergy pass after confirming the allergy with a re-exposition in a skin test. You also must inform the patient that in the future, she must never take again sulfonamides or drugs cross-reacting with sulfonamides such as sulfasalazine, ester-type local anesthetics, or CAH inhibitors. Lastly, you inform the patient that in case of acute deterioration of the symptoms (dyspnea, cardiovascular problems), she should immediately come to the emergency room. The urticaria may transit into an anaphylactic shock.

36.5 Pain Despite Therapy with Analgesics

A 23-year-old otherwise healthy female ski downhill racer suffers a right knee injury during a training run resulting in rupture of the cruciate anterior ligament. In order to enable the racer to resume skiing as quickly as possible, the ligament was reconstructed arthroscopically. After the surgery the patient has been taking 500 mg paracetamol in the morning and in the evening. Despite the therapy with analgesics, the patient complains of pain, swelling of the right knee, and limited mobility.

36.6 Questions and Answers

Questions

1. Why does the patient have complaints despite analgesic therapy?
2. How do you proceed to treat the patient more effectively?
3. Do MOR agonists constitute an alternative?

Answers

1. Here, two common medication errors occurred. (1) The patient did not receive the correct analgesic. (2) The selected analgesic was given at an insufficient dose, most likely because of fear of ADRs. Paracetamol has only an analgesic effect, but no anti-inflammatory effect. Following knee injury with subsequent surgery, a substantial inflammatory reaction is present, resulting in edema and limited mobility of the joint. In order to achieve a good analgesic effect of paracetamol, the drug would have to be administered in much higher doses, i.e., 1 g three to four times per day. However, even with the high dose, no anti-inflammatory effect would be achieved.
2. Since the patient is otherwise healthy, there are no restrictions with regard to the choice of analgesic. For the current situation, administration of ibuprofen (0.6 g three to four times per day) is well suited. Ibuprofen exhibits good controllability and belongs to the group of COX inhibitors. In contrast to paracetamol, ibuprofen also exhibits a good anti-inflammatory effect. Accordingly, under ibuprofen, the knee swelling should decline rapidly. The improved joint mobility facilitates the accompanying physiotherapy and overall remobilization. The therapy with ibuprofen should not be conducted for more than 2 weeks because otherwise kidney perfusion may be impaired, resulting in sodium and water retention (edema). In addition, PUD may develop. The latter ADR can be counteracted with prophylactic administration of a PPI. You should inform the patient that in her specific situation, the high-dose and short-term treatment with ibuprofen is useful and should be well tolerated.
3. In some countries, particularly in the USA, MOR agonists have been prescribed uncritically for different types of pain. Often, the indication was not well-defined. This has resulted in the massive development of MOR agonist abuse and addiction (opioid crisis). MOR agonists do not have the anti-inflammatory component of the COX inhibitors, which is crucial in this particular case. Thus, MOR agonists should only be (cautiously) used if there are clearly defined contraindications for paracetamol or COX inhibitors. In some countries, metamizole can be prescribed as alternative to paracetamol. Metamizole possesses a higher analgesic efficacy than paracetamol. However, because of the (very low) risk of agranulocytosis and anaphylactic shock (during i.v. injection), metamizole is not available in all countries. This situation contributed to the excessive prescription of MOR agonists possessing other ADRs.

36.7 Toddler with GI Infection and Spasmodic Torticollis in the Emergency Room

Michael is a 2-year-old toddler who attends a day-care facility. Both parents work full-time. In the facility, a virus is going around, causing GI symptoms, predominantly nausea and vomiting. Today, Michael has become affected as well. His father picks him up. During the entire trip back home, Michael vomits. He is feeling weak and tired. The father is not sure what to do. The pediatrics office is already closed. At home, in the medicine cabinet, the father finds MCP drops. He recalls that his wife is taking these drops when she suffers from nausea during a migraine attack. Thus, the father assumes that the drops will help his son as well. The father succeeds at administering Michael 15 drops of MCP, sweetened with syrup. In fact, Michael stops vomiting after about 30 minutes, and the child seems to get better. Suddenly,

Michael starts crying, and the father gets frightened because Michael pulls his head close to the right shoulder. The neck is painful, but Michael cannot change his head position. Immediately, the father drives to the emergency room with Michael and tells the physician on duty what happened. At first glance you diagnose a spasmodic torticollis.

36.8 Questions and Answers

Questions

1. Is there a connection between the intake of MCP and the spasmodic torticollis?
2. How can you treat the spasmodic torticollis?
3. How do you treat the GI infection?

Answers

1. MCP is a D_2R agonist that does not penetrate well the BBB in school children, adolescents, and adults. Via D_2Rs in the chemoreceptor trigger zone, MCP exhibits an antiemetic effect. In toddlers, MCP penetrates the BBB well and, via antagonism at D_2Rs in the extrapyramidal system, can cause acute dyskinesias, spasmodic torticollis being a prototypical manifestation.
2. The spasmodic torticollis is self-limiting, i.e., after MCP elimination from the CNS, the dyskinesia disappears. In case of a very painful spasmodic torticollis, you can inject the M_xR antagonist biperiden i.v. This stops the torticollis very rapidly. However, biperiden can cause an antimuscarinic syndrome (e.g., mydriasis, xerostomia, urinary retention, constipation, hot and dry skin). It is important to educate the father about the link between MCP intake and the symptoms, their relative harmlessness, and the need for avoidance of future MCP applications.
3. In a toddler, the most important aspect in the treatment is dehydration with HWO rehydration solution. Fever can be reduced with paracetamol, vomiting with the $5\text{-}HT_3R$ antagonist ondansetron. First-generation H_1R antagonists are antiemetic as well and promote sleep.

36.9 Critical Assessment of a Medication Plan

Recently, you have taken over the country ambulance from a colleague, and you get to know the patients. For the first time, Mr. John Rattlesnake visits you in your office. In his files you find the diagnoses hypertension, stable CHD, and condition after hip replacement left leg. Currently, the patient receives the following medication:

1. One puff GTN spray buccally in the morning
2. 5 mg ramipril in the morning
3. 100 mg ASA in the morning
4. 190 mg sustained-release metoprolol in the morning, and
5. 50 mg amitriptyline in the evening

The physical exam reveals a blood pressure of 125/75 mm Hg. The patient does not suffer from AP but feels dizzy in the morning. In addition he complains that his face is getting red in the morning quite regularly and that his mouth is pretty dry. Moreover, he is constipated, and despite summer time, his fingers feel cold.

36.10 Questions and Answers

Questions

1. Could the patient's complaints be due to the medication?
2. Is there an appropriate indication for all drugs?
3. How can you optimize the medication?

Answers

1. The dizziness and the morning flush are probably due to short-term vasodilation caused by the NO donor GTN. The cold fingers are probably due to the high dose of metoprolol. In high doses, metoprolol antagonizes the β_2AR, abrogating a vasodilatory mechanism predominantly relevant in acral body regions. Xerostomia and constipation are probably the result of M_xR antagonism of amitriptyline and are part of a classic antimuscarinic syndrome.
2. A major indication for GTN is AP. There is no proof for efficacy of NO donors in long-term CHD therapy. Since the patient

does not suffer from AP, there is no indication for GTN. In contrast, the use of ramipril, metoprolol, and ASA is justified (hypertension and CHD). Amitriptyline is an NSMRI and is used for therapy of depression (high doses) and sleep disorders (low doses). Since there is no evidence for depression or sleep disorders in the patient, amitriptyline can be discontinued.

3. It is quite common that drugs are prescribed over many years without critically assessing their indication. This case illustrates that drugs administered without proper indication can cause unpleasant ADRs. Thus, a change in the attending physician or admittance to a hospital are always good opportunities to evaluate the appropriateness of a medication. Discontinuation of GTN and amitriptyline will lead to cessation of the respective ADRs. The dose of metoprolol is rather high. Thus, you can stepwise reduce the metoprolol dose over a period of several weeks, regularly checking the BP and potential AP attacks. This strategy should improve the cold finger sensation. If required, you could increase the ramipril dose to 10 mg, but then you need to check that no hypokalemia is developing.

36.11 Ballerina with Nervousness and Hypertension

A 20-year-old professional ballerina visits you in your general practitioner office because she has become very nervous recently. Additionally, she suffers from palpitations. You measure a BP of 160/90 mm Hg and a resting HR of 100/minute. The patient's skin is warm and sweaty. Her body mass index is 17 kg/m^2. The patient denies the intake of prescription drugs. Previously, she had used laxatives to keep her body weight constant, but she has stopped doing this because she has heard about negative consequences of laxative use from a colleague. Instead, she is now taking natural thyroid gland powder bought on the Internet. On her bowel movements, the natural hormones seem to have the same effect as laxatives.

36.12 Questions and Answers

Questions

1. What is your tentative diagnosis?
2. How do you proceed diagnostically?
3. How do you proceed therapeutically?

Answers

1. Your tentative diagnosis is hyperthyroidism as a consequence of uncontrolled intake of "natural" and supposedly "healthy" hormones. "Natural" thyroid hormone preparations, e.g., from bovine thyroid gland, do not possess a clearly defined T3 and T4 content. Therefore, the intake of such preparations is dangerous and can lead to unpredictable effects. Such preparations have no place in pharmacotherapy. However, such preparations can be easily purchased without prescription from Internet vendors. Many Internet websites uncritically advertise "natural" thyroid hormones and do not properly inform about drug doses and ADRs.
2. In order to confirm the diagnosis, you determine the plasma concentrations of TSH, T3, and T4. TSH should be reduced, and T3 and T4 should be elevated. Sonography should show a small thyroid gland, and technetium uptake into the thyroid gland should also be low because of the missing TSH stimulation.
3. You educate the patient about the link between the complaints and the intake of "natural" thyroid hormones. You also tell the patient that in the long term, hyperthyroidism has negative consequences for the function of all organ systems. You request that the patient stops taking the thyroid hormones and check within a time period of about 6 months, whether the patient becomes euthyroid again. It is critical that you inform the patient about the symptoms of both hypothyroidism and hyperthyroidism. You check thyroid gland function regularly in terms of hormone concentrations and scintigraphy. Should hypothyroidism develop, the patient must be treated with T4 at a clearly defined daily dose.

The reason for the intake of "natural" thyroid hormones was the desire to maintain a low body weight expected for a professional ballerina. You inform the patient about the fact that her body mass index is already below normal values and that a further reduction of the body weight has negative long-term consequences including increased risk for osteoporosis. In order to facilitate implementation of normal eating habits and normal body weight, you transfer the patient to a dietician specialized in counseling of athletes.

36.13 Gestational DM Due to Fenoterol Infusion?

A 36-year-old woman with normal body weight is admitted to the hospital department of obstetrics because of premature labor in the 26th week of pregnancy. Otherwise the woman is healthy. Particularly, there are no abnormalities in cardiovascular and metabolic function. Therefore, the patient receives a fenoterol infusion with a dose of 3 µg/minute. With this therapy, premature labor ceases. On the one hand, the patient is relieved, but on the other hand, the patient complains about palpitations. You measure a resting HR of 98/minute. Furthermore, laboratory tests reveal hyperglycemia (10 mmol/l). You immediately inject 4 IU insulin i.v.

36.14 Questions and Answers

Questions

1. Does the patient have a gestational DM?
2. How do you explain the tachycardia of the patient?
3. Is the injection of insulin indicated?
4. How can you optimize the tocolytic therapy?

Answers

1. It is most unlikely that in an otherwise healthy patient with normal body weight, suddenly gestational DM develops. The most likely explanation for the hyperglycemia is that fenoterol has been administered at a rather high dose. The therapeutic range is between 0.5 and 3.0 µg/minute. The patient receives a dose at the upper therapeutic limit. At these doses, one must anticipate that not only the β_2AR in the uterus is activated but also the β_2AR in the liver. This receptor mediates glycogenolysis and hyperglycemia. However, this ADR has nothing to do with a gestational DM.
2. Tachycardia is the result of activation of cardiac β_1ARs. At high doses, fenoterol is not selective for the β_2AR but also activates the β_1AR.
3. The administration of insulin is not indicated because the hyperglycemia is only a short-term ADR. Short-term hyperglycemia should not be confused with a long-term dysbalance of glucose metabolism observed in DM. The short-term hyperglycemia does not have negative consequences for the mother and the fetus. The i.v. injection of insulin in the absence of a DM entails the risk that hyperglycemia rapidly switches into hypoglycemia which is dangerous. Hypoglycemia can cause epileptic seizures in the mother, resulting in respiratory depression and fetal hypoxia.
4. Although tocolysis with fenoterol is successful, at least two different ADRs occurred. Therefore, the fenoterol dose should be reduced. After all, a compromise between tocolysis and acceptable ADRs will have to be found. At lower doses, fenoterol selectively activates the β_2AR, so that at least the cardiac ADRs mediated by the β_1AR can be avoided. A reasonable approach is to titrate the patient in a medium dose range (about 1 µg/minute) and to wait how effective this dose is. The advantage of fenoterol is that the drug acts within few minutes so that dose adjustment can be performed very quickly as well.

36.15 Meaningful Long-Term Therapy with Pantoprazole?

A 48-year-old male professional oboe player suffers from deteriorating GERD. In addition, the oboe player often eats late after concerts. Because of GERD the patient visits you in your gastroenter-

ology office. Apart from mild esophagitis, you do not see abnormalities in esophagoscopy. You prescribe pantoprazole tablets (40 mg) which the patient takes in the morning. With this therapy, the complaints improve. Within 3 weeks the symptoms have disappeared completely, and the patient can do his job and adhere to his lifestyle as usual. Because of its apparently good tolerability, the patient has now taken pantoprazole for a period of 10 years. However, slowly the patient gets a numb feeling and tingling sensation at the finger tips, and he develops more and more problems at operating the instrument flaps correctly. This resulted in a reduced level of musical performance. He gets into trouble with his colleagues and the conductor, suspecting that the oboe player has become an alcoholic. However, this is not the case. Because you have difficulties at interpreting the situation properly, you transfer the patient to a neurologist. He diagnoses a peripheral polyneuropathy.

36.16 Questions and Answers

Questions

1. What is the most likely reason for the polyneuropathy?
2. How do you proceed diagnostically?
3. How do you proceed therapeutically?

Answers

1. Oboe playing causes an increase in intra-abdominal pressure and can promote development of GERD. The GERD symptoms are effectively alleviated by PPIs. The decade-long PPI intake has elevated the intragastral pH. A consequence of this change is impaired absorption of vitamin B_{12}. This vitamin deficiency can lead to polyneuropathy and megaloblastic anemia.
2. The diagnosis is confirmed by measuring the plasma concentration of vitamin B_{12}. Reference values range between 120 and 180 pmol/l. In case of the patient, the concentration is 60 pmol/l. Thus, a laboratory test could confirm the clinical diagnosis.
3. Oral or parenteral vitamin B_{12} supplementation is of highest therapeutic priority to compensate for the vitamin deficiency and revert the neurological symptoms. You also have to check whether the indication for long-term PPI administration is still given. It is appropriate to make a PPI withdrawal trial and observe whether GERD symptoms reoccur. Should this be the case, you can consider an alternating low-dose PPI therapy (e.g., 20 mg pantoprazole every other day) instead of the high-dose therapy. You also need to check whether the patient can change lifestyle habits promoting GERD. One factor is already known from the medical history, i.e., the late meals before going to bed. Dose reduction or discontinuation of the PPI is not only indicated because of the vitamin B_{12} deficiency but also because of the fact that long-term PPI therapy can cause other ADRs such as susceptibility to certain GI infections or osteoporosis.

36.17 Nervous Breakdown After Nocturnal Computer Sessions

The 14-year-old Luca is among the best performers in the computer game "monster kill" being played in a global network. The sessions are usually held between 10 p.m. and 2 a.m. After having won the Italian championship, Luca has become European champion. Now, Luca wishes to become World champion. Luca's younger brother Fabiano (12 years) has been treated with MPH (20 mg in the morning) for 3 months because of ADHD. Luca recognizes that Fabiano can focus better with MPH. Luca plans to use this effect for his computer gaming activities. Unnoticed by his parents, he steals an MPH tablet before the next session and realizes that he is more successful. He is getting closer to his goal of becoming the World champion. The intake of MPH becomes a routine for Luca. Prior to the eighth-final, he steals an entire blister pack, and after ingestion of two tablets, he wins. Before the fourth-final, two tablets are not sufficient anymore, but with three tablets, he manages to win. Prior to the semifinal, Luca takes four tablets, just to be sure. He wins, but just barely. After the game, Luca is very nervous.

Prior to the final, Luca is extremely nervous, lacks appetite, and has difficulties to focus. For this final game, Luca has saved seven tablets, and he takes them all. However, the desired effect did not appear, and he suffered a devastating defeat. The next morning, Luca's parents find their son in the bed, anxious, crying, shaking, and completely exhausted.

36.18 Questions and Answers

Questions

1. How do you explain the unfortunate end of Luca's monster kill career?
2. How could the nervous breakdown have been avoided?
3. Which prerequisites must be given for prescription of MPH?

Answers

1. This is a classic case of tachyphylaxis following intake of the indirect dopamimetic drug MPH. Regular administration of MPH causes emptying of DA-containing vesicles in neurons. To a certain extent and for a limited time, this effect can be compensated by a dose increase, but ultimately, vesicles are empty, and the desired effect fails to appear. Instead, a withdrawal syndrome including nervousness, anxiety, concentration problems, and depression manifests.
2. Luca's parents should have kept MPH in a closed medicine cabinet and counted the tablets. Possibly, the physician who prescribed the drug for Fabiano did not explicitly mention the risk of MPH misuse by "healthy" persons. In addition, the pharmacist should have informed Luca's parents accordingly.
3. MPH is not only effective in ADHD patients but in every person. In order to avoid abuse, it is essential that the diagnosis "ADHD" is made by a trained child and youth psychiatrist. The uncritical prescription of MPH by non-specialized physicians explains the increasing prescriptions of MPH in many countries.

36.19 Sufficient Analgesic Therapy for Metastasizing Mammary Carcinoma?

A 65-year-old woman with a mammary carcinoma metastasizing into the liver, lung, skin, and bones wishes no further therapy with classic cytostatics or targeted therapeutics. She just would like to receive palliative therapy in a hospice. The patient suffers from severe bone pain, both during rest and when walking. Her general practitioner prescribed the following pain medication:

1. 400 mg ibuprofen in the morning
2. 20 drops tramadol (100 mg/ml) in the morning, at noon, and in the evening

You have been asked to direct the palliative treatment in the hospice.

36.20 Questions and Answers

Questions

1. Is the analgesic therapy sufficient?
2. Which options for analgesic therapy do you have?
3. How do you estimate the risk of MOR agonist addiction in the patient?
4. Which is the most important ADR of analgesics that you have to consider?

Answers

1. The current analgesic therapy is insufficient. The therapeutic goal is to abrogate the pain. Ibuprofen is administered at a very low dose (just 400 mg) and too infrequently (just once daily). Tramadol is only a weak partial MOR agonist with insufficient analgesic efficacy.
2. Since the patient suffers from an incurable disease in the final stage, all options of analgesic therapy should be used. If the patient tolerates ibuprofen, the drug can be administered up to 4 × 600 mg/day. In addition, in some countries, metamizole can be prescribed at doses up to 4 × 1 g/day. The patient should also be regularly given a high-efficacy MOR agonist such as hydromorphone. The dose of

hydromorphone can be increased substantially to override a possible MOR desensitization. It is critical to administer the analgesics regularly. In case that this therapy is insufficient, for pain peaks fentanyl lollipops can be administered. Should this therapy still be inadequate, additional therapeutic alternatives can be offered. For bone metastases, bisphosphonates or denosumab can be applied. α_2AR agonists have sedating and analgesic effects. In case of anxiety, benzodiazepines are indicated; in case of depression, NSMRIs are effective. mGPCR antagonists distance the patient's psyche from the objective pain perception.

3. The risk of MOR agonist addiction is largely overestimated in terminal tumor patients. Dysphoria is more common than euphoria. In case of MOR desensitization, the drug dose can be increased substantially.
4. The most important ADR is severe constipation that develops rapidly under MOR agonist therapy. Therefore, it is very important to proactively address this ADR. One possibility is to administer osmolaxatives such as macrogol. Alternatively, intestinal motility can be increased with the peripherally acting MOR antagonist methylnaltrexone. Sufficient fluid intake, a diet high in fibers, and adequate physical activity support prevention of constipation.

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The "100 List" of Drugs

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Numerous drug lists with different foci exist. This chapter discusses 100 important drugs ("100 List"). Every physician must know the drugs listed here. The list was compiled to cover as many important indications and medical fields as possible within the chosen constraints. General medicine has a key role in integrating medications from all medical specialties. Whenever possible, inexpensive generic drugs were listed, facilitating prescription even in resource-poor countries. The chapter covers drugs for emergency, acute, short-term, and long-term use. Unique drugs are emphasized. Risk of abuse, cultural differences in use, pricing, and availability of drugs are discussed as well. The chapter also highlights 20 drugs that every physician should prescribe. These drugs cover some medical emergencies, hypertension, important GI diseases, asthma, migraine, depression, type I allergies, pain, and some bacterial infections. For various reasons, certain drugs, e.g., COX-2 inhibitors, drugs for treatment of AD, DOACs, THC, and newer p-mGPCR antagonists, were not included in the "100 List."

Key Points

1. In the "100 List," most medical indications are covered at least in part.
2. The "100 List" constitutes the core of pharmacological knowledge for every physician.
3. Whenever possible, a physician should prescribe well-known and inexpensive generic drugs.
4. Be reluctant to prescribe expensive new drugs without long-term clinical experience!
5. In most medical fields, basic pharmacotherapy can be readily performed with <15 drugs.
6. Every physician must know the unique drugs.
7. Many indications are served with multiple structurally related drugs, often with only limited advantages compared to the prototype.
8. Prescribe only few drugs, but know these drugs very well!
9. Dare to be minimalistic in your prescription behavior!
10. Prescribe drugs for which evidence of efficacy, both in clinical studies and real-world settings, is available!
11. Drug prices may vary tremendously among different countries.
12. Availability of drugs (prescription, OTC, non-availability) varies substantially among different countries.
13. Pharmacotherapy is a cultural construct and varies substantially among different countries.
14. Be aware that therapeutic guidelines from learned societies are not necessarily neutral. They may be influenced by commercial interests of individuals participating in these guidelines.
15. The fewer drugs you prescribe, the lower is the risk of ADRs and drug interactions!
16. Treatment of autoimmune diseases, prevention of transplant rejection, and malignant tumors belongs into the hands of specialists because it often requires prescription of many expensive drugs.
17. In general, newly introduced immunomodulatory drugs and targeted therapeutics for malignant tumor diseases are very expensive.
18. Drugs for HCV infection are very expensive, too.
19. Beware of the risk of drug abuse!
20. Drug abuse may concern many areas of life, even unexpected ones!
21. Areas of drug abuse change rapidly!
22. Be very cautious when prescribing controlled drugs!
23. Always ensure that you have a proper indication for your prescription, particularly for controlled drugs! Check whether the patient is faking a medical condition!
24. Be skeptical when patients specifically request a certain drug with potential for abuse!
25. Be aware of the fact that even OTC drugs can cause serious ADRs and intoxications!
26. Drug prescription becomes more and more specialized; this constitutes a problem for recognizing ADRs and drug interactions!

27. Always ask the patient which other drugs including OTC drugs he/she takes before you prescribe a drug!
28. The increasing specialization of medicine increases the probability of interfering prescriptions from many physicians.

37.1 How the "100 List" Was Compiled

This book discusses about 400 drugs. The list of drugs in the appendix of this book sorts the drugs according to mechanisms of action and book chapters. Thus, the list is systematic and aims at being comprehensive. In several cases two or even more drugs are listed, e.g., a historic prototype and a commonly prescribed drug. The list in the appendix predominantly serves to assigning mechanisms of actions to drugs.

A major problem of modern pharmacology is the increasing specialization of medical fields and increasing number of drugs, specifically in immunopharmacology (see ▶ Chap. 11) and tumor pharmacology (see ▶ Chap. 32). Thus, it becomes more and more difficult for the physician to maintain an overview of all available drugs. In some countries, several thousand different drugs are marketed. In an attempt to provide the overview, the WHO has put together a list of essential medicines, comprising more than 550 different drugs [1]. This list serves as basis for essential medicine lists for many countries and organizations. For example, the *Médecins sans Frontières* has compiled a list with about 275 drugs [2], and even in a resource-poor countries like Afghanistan, still more than 200 drugs are listed [3]. In some countries, lists on the top 100 drugs in terms of prescription numbers are published [4]. Other lists sort the top 100 drugs according to commercial parameters, specifically sales [5].

The purpose of this chapter is to summarize the preceding 36 chapters from an overarching perspective and critically discuss a list of 100 important drugs ("100 List") that every physician, regardless of specialization, must know (◘ Table 37.1). The table lists the drugs in alphabetical order. To each drug, the drug class and a number are assigned. The goal of the list is to cover as many indications and medical fields as possible within the preset number of 100 entries. Several important drug lists (see [4, 5]) limit themselves to 100 entries, serving as model for the present list.

The "100 List" aims at covering drugs for which good clinical evidence for efficacy is available. In general, generic drugs are much less expensive than drugs marketed under a registered trade name. The "100 List" also provides information about the uniqueness of drugs and availability of structurally related drugs. In addition, data on clinical applications, important medical fields, risk of abuse, cultural differences in drug use, pricing, and availability are provided. Given in bold italics are 20 drugs that every physician, regardless of specialization, should prescribe. These drugs (see ▶ Sect. 37.10) cover some very important indications. For systematic discussion of any given drug, the reader is referred to the respective chapters listed in the last column of ◘ Table 37.1.

37.2 Important Indications Covered by the "100 List"

The "100 List" covers, among others, the broad indications:

- Pain (5, 17, 18, 28, 33, 44, 48, 53, 55, 60, 64, 68, 78, 97)
- Autoimmune diseases and prevention of transplant rejection (2, 11, 16, 23, 31, 69, 71, 79)
- GI diseases (11, 15, 18, 62–64, 75–77)
- Respiratory tract diseases (8, 16, 36, 42, 85–87, 94, 99)
- Cardiovascular diseases (6, 7, 10, 22, 27, 28, 39, 40, 46, 48, 66, 83, 87, 88, 90, 100)
- Endocrine diseases (3, 33, 47, 51, 52, 65, 92, 95)
- Gynecological indications (18, 43, 45, 54, 59)
- Type I allergies (21, 32, 40,85, 86, 94, 99)
- Neurological diseases (5, 14, 15, 20, 35, 55, 58, 53, 63, 64, 72, 91, 97)
- Psychiatric diseases (5, 14, 20, 25, 28, 29, 35, 49, 55, 61, 70, 96, 97)
- Malignant tumor diseases (13, 31, 33, 44, 49, 50, 69, 71, 75)
- Bacterial infections (8, 24, 26, 36, 28, 42, 45, 51, 67, 77, 81, 84, 98)
- Viral infections (1, 12, 37, 57, 82, 89, 93)

Table 37.1 The "100 List" of drugs

No.	Drug	Drug class	Important Indications	Structurally similar drugs	Clinical application	Important medical fields	Risk of abuse	Cultural differences	Pricing	Availability	Further contexts in Chaps.
1	**Aciclovir**	Virustatics	HZV and VZV infections	+	S	DEN, DER, GM, GYN, NEU, ONC, OPH, OTO			+	P, OTC	34
2	**Adalimumab**	TNF inhibitors	Autoimmune diseases	+	L	DER, GE, RHEU		+++	++++	P	11
3	**Alendronate**	Bisphospho-nates	Osteoporosis, tumor osteolyses	++	L	GM, ONC, ORT			++	P	20
4	**Allopurinol**	Uricostatics	Chronic gout	(+)	L	GM, ONC, RHEU			+	P	23
5	**Amitriptyline**	NSMRIs	Depression, anxiety disorders, neuropathic pain, migraine prophylaxis	++	L	GM, NEU, PSY		++	+	P	28
6	**Amiodarone**	Class I–IV antiarrhythmics	VT, MI (selected patients only)	(+)	E, A, S, L	CAR			+	P	16, 17
7	***Amlodipine***	***CCBs***	***Hypertension***	++	***L***	***CAR, GM***			+	***P***	***15***
8	***Amoxicillin + clavulanic acid***	***Antibacterial chemother-apeutics***	***Infections with sensitive bacteria***	+	***S***	***GM, GYN, PED, PUL, OTO, URO***			+	***P***	***33***
9	**Amphotericin B**	Antimycotics	Local and invasive mycoses	(+)	S	DEN, GM, NEPH, ONC, RHEU			+	P	35
10	***ASA***	***Irreversible COX inhibitors (PAIs)***	***Low-dose: Secondary prevention of MI and stroke; NOT primary prevention***	***Unique***	***E, S, A, L***	***CAR, GM, NEU***	***SELF***	+	*(+)*	***P, OTC***	***16, 18***

11	**5-ASA**	Anti-inflammatory drugs	UC; NOT CD	Unique	S, L	GE			+	P	13
12	**Atazanavir**	Virustatics	HIV infection	++	L	HIV		+	+ to +++	P	34
13	**Bevacizumab**	VEGF inhibitors	Malignant tumors, AMD (inexpensive off-label use instead of ranibizumab and aflibercept)	+	L	ONC, OPH		+++	+++	P	31, 32
14	**Biperiden**	M_xR antagonists	PD, D_2R-mGPCR antagonist-induced EPSs	+	S, L	NEU, PSY			+	P	5, 8, 29
15	**Botulinum neurotoxin**	Ach release inhibitors	Dystonias	Unique	L	GE, NEU, OTO	COS	+++	+++	P, F	5
16	**Budesonide**	GCR agonists	UC, type I allergies (bronchial asthma, conjunctivitis, rhinitis)	+	L	GE, OPH, OTO, PUL			+	P	11, 13, 14
17	**Buprenorphine**	Partial MOR agonists	Intermediate-severe tumor pain, intermediate-severe postsurgical pain	+	S, L	GM, ONC, SUR	MOR	+	+	C	10, 32
18	**Butylscopolamine**	M_xR antagonists	Colic pain	+	S	GE, GM, GYN, URO			+	P, OTC	5
19	***Candesartan***		***Hypertension, CHF, CAD, DM***	+++	L	***CAR, END, GM, NEPH***			+	***P***	***12,15–17***
20	**Carbamazepine**	NIPEs	All types of seizures except for absence seizures, bipolar disorder, schizophrenia, trigeminal neuralgia	(+)	L	NEU, PSY			+	P	25

(continued)

Table 37.1 (continued)

No.	Drug	Drug class	Important Indications	Structurally similar drugs	Clinical application	Important medical fields	Risk of abuse	Cultural differences	Pricing	Availability	Further contexts in Chaps.
21	*Cetirizine*	*Second-generation H_1R antagonists*	*Type I allergies (conjunctivitis, rhinitis, urticaria)*	+++	*A, S, L*	*DER, GM, OTO, PED, PUL*			+	*P, OTC*	*3, 7*
22	*Chlorthalidone*	*Thiazide diuretics*	*Hypertension, CHF*	+	*L*	*CAR, GM, NEPH*	*ATH*	+	+	*P*	*12, 15–17*
23	**Ciclosporin**	Calcineurin inhibitors	Autoimmune diseases, prevention of transplant rejection	++	L	DER, NEPH, RHEU		+	++	P	11, 12
24	**Ciprofloxacin**	Antibacterial chemotherapeutics	Infections with sensitive bacteria	+++	S	GM, GYN, PUL, URO		+	+	P	33
25	*Citalopram*	*SSRIs*	*Depression (initial therapy), anxiety disorders, obsessive-compulsive disorders, panic disorders, schizophrenia, post-traumatic stress disorder*	+++	*L*	*GM, PSY*		+	+	*P*	*28*
26	**Clindamycin**	Antibacterial chemotherapeutics	Infection with sensitive bacteria	(+)	S	DEN, DER, GM, PUL, SUR		+	+	P	33
27	**Clopidogrel**	Irreversible $P2Y_{12}R$ antagonists (PAIs)	Secondary prevention of MI and stroke (sometimes + ASA)	++	A, L	CAR, GM, NEU		+	+	P	18

28	**Clonidine**	α_2AR agonists	Hypertensive emergency, various pain states, drug withdrawal	+	E, A, L	CAR, ANE, PSY, SUR	SUB		+	P	5, 15
29	**Clozapine**	p-mGPCR antagonists	Refractory schizophrenia or ADRs after D_2R-mGPCR antagonists, bipolar disorder	+++	L	PSY		+	+	P	29
30	**Cotrimoxazole**	Antibacterial chemotherapeutics	*Pneumocystis jirovecii* infection	Unique	L	GYN, HIV, URO		+	+	P	33, 35
31	**Cyclophosphamide**	Classic cytostatics	Autoimmunopathies (low dose); malignant tumors (high dose)	(+)	A, L	DER, GE, NEPH, ONC, PUL, RHEUM		+	+	P	11, 32
32	**Diphenhydramine**	First-generation H_1R antagonist	Type I allergies (conjunctivitis, rhinitis, urticaria), kinetosis, sleep disorders	+++	A	DER, GM, OTO, PED, PUL	SUB	+	+	P, OTC	3, 7
33	**Denosumab**	RANKL inhibitors	Postmenopausal osteoporosis, osteolysis in prostate carcinoma	Unique	L	GM, ONC, ORTH			+++	P	20, 32
34	**Desflurane**	Inhalation anesthetics	Inhalation anesthesia (halothane in poor countries, WHO list)	+	A	ANE		+	+	P	27

(continued)

Table 37.1 (continued)

No.	Drug	Drug class	Important Indications	Structurally similar drugs	Clinical application	Important medical fields	Risk of abuse	Cultural differences	Pricing	Availability	Further contexts in Chaps.
35	**Diazepam**	Allosteric $GABA_AR$ modulators	Status epilepticus, sedation, anxiolysis, muscle relaxation	+++	E, A, S	GM, NEU, ONC, ORT, PSY	SUB	+	+	P	25
36	**Doxycycline**	Antibacterial chemotherapeutics	Infection with sensitive bacteria	(+)	A	DER, GM, PUL		+	+	P	33
37	**Efavirenz**	Virustatics	HIV infection	++	L	HIV		+	+ to +++	P	34
38	**EMB**	Antibacterial chemotherapeutics	TB, leprosy	Unique	L	DER, GM, PUL			+	P	34
39	**Enoxaparin**	LMWHs	Prevention of thromboembolic diseases	++	A, L	CAR, GM, GYN, SUR			+	P	18
40	***EPI***	***α_xAR and β_xAR agonists***	***Anaphylactic shock, additive to local anesthetics***	***Unique***	***E***	***ANE, DEN, DER, GM, OTO, PED, PUL, SUR***		+	***+ to ++++ (USA)***	***P***	***3, 5, 7***
41	**Epoetin**	Hematopoietic growth factors	Renal anemia	(+)	L	NEPH	ATH	++	++	P	12
42	***Erythromycin***	***Antibacterial chemotherapeutics***	***Infection with sensitive bacteria, GI stasis (off-label)***	++	***A***	***GE, GM, PUL, PED***		+	+	***P***	***13, 33***
43	**Ethinylestradiol**	ER agonists	Component of micropill for contraception	(+)	L	GYN		+++	+	P	24

44	**Fentanyl**	Full MOR agonists	Severe tumor pain, severe postsurgical pain, breakthrough pain, anesthetic procedures	+	E, A, L	ANE, GM, ONC, SUR	MOR	++	+	C	10, 32
45	***Fosfomycin***	***Antibacterial chemotherapeutics***	***Acute uncomplicated urinary tract infection in women***	***Unique***	***A***	***GM, GYN, URO***		**+**	**+**	***P***	***33***
46	**Furosemide**	Loop diuretics	Hypertension, hypertensive emergency, CKD, CHF, pulmonary edema	(+)	E, A, L	CAR, GM, NEPH	ATH	+	+	P	12, 15, 16
47	***Glucose***	***Emergency drugs for hypoglycemia***	***Acute hypoglycemia (oral; i.v. in case of unconsciousness)***	***Unique***	***E, A***	***END, GM, NEU, PED***			+	***P, OTC***	***19***
48	***GTN***	***NO donors***	***AP, MI, hypertensive emergency, colic pain, several off-label uses for vasodilation***	***(+)***	***E, A***	***CAR, GE, GM, URO***		+	+	***P***	***9, 15***
49	**Haloperidol**	D_2R-mGPCR antagonists	Schizophrenia, acute mania, tumor pain, neuropathic pain	+++	E, A, L	GM, NEU, PSY, ONC		++	+	P	10, 29
50	**Imatinib**	TK inhibitors	Chronic myelogenous leukemia, GI stromal tumors	++++	L	ONC		+	+++	P	32
51	**INH**	Antibacterial chemotherapeutics	TB, leprosy	Unique	L	GM, DER, PUL			+	P	34

(continued)

Table 37.1 (continued)

No.	Drug	Drug class	Important Indications	Structurally similar drugs	Clinical application	Important medical fields	Risk of abuse	Cultural differences	Pricing	Availability	Further contexts in Chaps.
52	**Insulin**	Short-acting insulins	Type 1 DM, ketoacidotic coma	++	E, A, L	END, GM		+	+	P	19
53	***Ibuprofen***	***COX inhibitors***	***Various types of acute pain with inflammatory component, postsurgical pain, tumor pain, fever, not chronic pain***	++	***A***	***DEN, GM, ONC, ORT, PED, RHEUM, SUR***	***SELF***	+	+	***P, OTC***	***10, 11***
54	**Itraconazole**	Antimycotics	Local and invasive mycoses	+++	A	DER, GM, GYN, ONC, PUL		+	+	P	35
55	**Lamotrigine**	NIPEs	Focal seizures, mood stabilization in bipolar disorder, neuropathic pain	+	L	GM, NEU, ONC, PSY		++	+	P	10, 28
56	**Latanoprost**	FPR agonists	Open-angle glaucoma	+	A, L	OPH	COS	+	+	P, COS	31
57	**Ledipasvir**	Virustatics	HCV infection	+	L	HEP		+	++++	P	34
58	**Levodopa + Benserazide**	DA prodrugs	PD	+	L	NEU	LIFE	+	+	P	9
59	**Levonorgestrel**	PR agonists	Component of micropill, minipill, IUD and morning-after pill for emergency contraception	(+)	E, L	GM, GYN		++++	+	P, OTC or not available	24

60	**Lidocaine**	Amide-type LAs	Universal local anesthetic for surgical and dentistry procedures	+	A	ANE, DEN, DER, GYN, SUR		+	+	P	26
61	**Lithium**	Alkali metal ions	Mood stabilization in bipolar disorder and augmentation in severe depression, schizophrenia		L	PSY		++	+	P	28
62	**Macrogol**	Laxatives	MOR agonist-induced constipation	+	L	GE, GM, ONC	SELF	+	+	P, OTC	13
63	***MCP***	***D_2R antagonists***	***Emesis (GI infections, migraine, cystostatics, morphine)***	***(+)***	***A, L***	***GE, GM, ONC, PED***		+	+	***P***	***6, 8, 13***
64	**Metamizole**	Non-MOR agonists	Moderate-severe pain without inflammatory component, tumor pain, colic pain, high fever	Unique	A, L	GE, GM, ONC, ORT, URO	SELF	+	+++	P, OTC or not available	10
65	**Metformin**	Biguanides	Type 2 DM	(+)	L	END, GM		+	++	P	19
66	***Metoprolol***	***β_1AR antagonists***	***Hypertension, CHF, CHD, AF***	***++***	***A, L***	***CAR, GM***		+	+	***P***	***5, 15–17***
67	**Metronidazole**	Antibacterial chemotherapeutics	Infections with anaerobic bacteria, pseudomembranous enterocolitis	(+)	A	DEN, DER, GE, SUR		+	+	P	33

(continued)

Table 37.1 (continued)

No.	Drug	Drug class	Important Indications	Structurally similar drugs	Clinical application	Important medical fields	Risk of abuse	Cultural differences	Pricing	Availability	Further contexts in Chaps.
68	**Morphine**	Full MOR agonists	MI, pulmonary embolism, severe tumor pain and postsurgical pain	+++	E, A, L	CAR, SUR, ONC	MOR	+	++	C	10, 16
69	**6-MP**	Classic cytostatics	Autoimmunopathies (low dose); malignant tumors (high dose)	(+)	L	DER, GE, NEPH, ONC, PUL, RHEUM		+	+	P	11, 32
70	**MPH**	Indirect dopamimetics	ADHD	(+)	L	PED, PSY	LIFE	+	+	C	8
71	**MTX**	Classic cytostatics	Autoimmune diseases (low dose); malignant tumors (high dose)		L	DER, NEPH, ONC, PUL, RHEUM		+	+	P	11, 32
72	**Neostigmine**	AChEIs	Myasthenia gravis	(+)	L	NEU		+	+	P	5
73	**Nitrous oxide**	Inhalation anesthetics	Inhalation anesthesia, (good analgesia)	Unique	A	ANE		+	+	P	27
74	**NPH insulin**	Intermediate-acting insulins	Type 1 DM	++	L	END, GM, PED		+	+	P	19
75	**Ondansetron**	5-HT_3R antagonists	Cytostatic-induced vomiting	++	A	GE, ONC		+	+	P	6, 32
76	***Oral rehydration solution***	***Oral rehydration solutions***	***Acute diarrhea, life-saving emergency therapy in cholera***	***Unique***	***E, A***	***GE, GM, PED***		+	+	***P, OTC***	***13***
77	**Pantoprazole**	PPIs	PUD, GERD, *Helicobacter pylori* infection	+++	A, L	GE, GM	SELF	+	+	P, OTC	7, 13

78	***Paracetamol***	***Non-MOR agonists***	***Mild pain without inflammatory component, intermediate fever***	***Unique***	***A, L***	***DEN, GM, SUR, PED***	***SELF***	+	+	***P, OTC***	***10***
79	**Prednisolone**	GCR agonists	Autoimmune diseases, prevention of transplant rejection	++	L	DER, NEPH, ONC, PUL, RHEUM		+	+	P	11
80	**Propofol**	Allosteric $GABA_AR$ modulators	i.v. Induction of anesthesia	+	A	ANE	SUB	+	+	P	27
81	**PZA**	Antibacterial chemotherapeutics	TB, leprosy	Unique	L	DER, GM, PUL			+	P	34
82	**Raltegravir**	Virustatics	HIV infection	++	L	HIV		+	+ to +++	P	34
83	**Ramipril**	ACEIs	Hypertension, CHF, CAD, DM	+++	L	CAR, END, GM, NEPH			+	P	12, 15–17
84	**RMP**	Antibacterial chemotherapeutics	TB, leprosy, other infections with sensitive bacteria	(+)	L	GM, R, D			+	P	34
85	***Salbutamol***	***SABAs***	***Acute asthma attack***	++	***E, A***	***GM, PED, PUL***	***ATH***	+	+	***P***	***5, 14***
86	**Salmeterol**	LABAs	Prevention of asthma attacks, COPD	++	L	GM, PED, PUL		+	+	P	5, 14
87	**Sildenafil**	PDE5 inhibitors	ED, PBH, PAH	+	A, L	PUL, URO	ATH, LIFE	++	+	P, OTC, I, F	9
88	**Simvastatin**	HMG-CoA reductase inhibitors	Hypercholesterolemia, prevention of MI	+++	L	CAR, GM	LIFE	+		P	16, 22
89	**Sofosbuvir**	Virustatics	HCV infection	+	L	HEP		+	++++	P	34

(continued)

Table 37.1 (continued)

No.	Drug	Drug class	Important Indications	Structurally similar drugs	Clinical application	Important medical fields	Risk of abuse	Cultural differences	Pricing	Availability	Further contexts in Chaps.
90	**Spironolactone**	MCRAs	CHF	(+)	L	CAR, GM, NEPH		+	+	P	15, 16
91	***Sumatriptan***	***5-HT$_{1D}$R agonists***	***Acute migraine attack***	+++	***A***	***GM, NEU***	***SELF***	+	+	***P, OTC***	***6***
92	**T4**	Thyroid hormones	Hypothyroidism, goiter prevention in hyperthyroidism	(+)	L	GM, END	LIFE	+	+	P, I	21
93	**Tenofovir**	Virustatics	HIV infection	++	L	HIV		+	+ to +++	P	34
94	**Tiotropium**	M_3R antagonists	COPD	(+)	L	GM, PUL		+	+	P	5, 14
95	**Thiamazole**	TPOIs	Hyperthyroidism	(+)	L	GM, END		+	+	P	21
96	**Tranylcypromine**	Irreversible MAOIs	Refractory depression	(+)	L	PSY		++	+	P	28
97	**Valproic acid**	NIPEs	Various types of seizures, mood stabilization in bipolar disorder, migraine prophylaxis, schizophrenia	Unique	L	NEU, PSY		++	+	P	28
98	**Vancomycin**	Antibacterial chemotherapeutics	Drug of last resort in infections with MRSA	Unique	S	DER, GE, GM			+	P	33

99	***Xylometazoline***	***α_1AR agonists***	***Allergic and viral conjunctivitis and rhinitis***	+	***A, S***	***GM, OPH, OTO, PED***	***SELF***	+	+	***P, OTC***	***3, 5, 7***
100	**Warfarin**	VKAs	Prevention of thromboembolic diseases (MI, stroke), particularly in AF	(+)	L	VAR, GM, NEU		++	(+)	P	16, 18

Drugs are listed in alphabetical order and numbered consecutively. To each drug, the drug class has been assigned. In most cases, a mechanism-based drug class name was used. In some cases, a chemistry-based name was used (61, 65)
Given in bold italics are 20 drugs that every physician should prescribe (see ► Sect. 37.9)
Column "Structurally similar drugs": unique, unique drug; (+), few similar drugs; +, some similar drugs; ++, several similar drugs; +++, many similar drugs; ++++, very many similar drugs (see ► Sect. 37.3)
Column "Clinical application": *E* life-threatening emergency, *A* acute medical situation (not life-threatening), *S* short-term treatment (1 day to 3 weeks), *L* long-term treatment (> 3 weeks) (see ► Sect. 37.4)
Column "Important medical fields": *ANE* anesthesia, *CAR* cardiology, *DEN* dentistry, *DER* dermatology, *END* endocrinology, *GE* gastroenterology, *GM* general (family) medicine, *GYN* gynecology, *HEP* hepatology, *HIV* HIV clinic, *NEPH* nephrology, *NEU* neurology, *ONC* oncology, *OPH* ophthalmology, *ORT* orthopedics, *OTO* otorhinolaryngology, *PED* pediatrics, *PSY* psychiatry, *PUL* pulmonology, *RHEU* rheumatology, *SUR* surgery, *URO* urology (see ► Sect. 37.5)
Column "Risk of abuse": *ATH* abuse in athletes to boost physical performance, *COS* abuse for cosmetic reasons, *LIFE* abuse for lifestyle reasons, *MOR* abuse in addition to MOR agonists including heroin, *SELF* risk of serious ADRs due to uncritical long-term self-medication, *SUB* abuse for substitution in MOR agonist addiction (see ► Sect. 37.6)
Column "Cultural differences": +, moderate cultural differences; ++, large cultural differences; +++, very large cultural differences; ++++, extremely large differences even entailing legal consequences (see ► Sect. 37.7)
Column "Pricing": (+), very inexpensive; +, inexpensive; moderately expensive; +++, very expensive; ++++, exceedingly expensive (see ► Sect. 37.8)
Column "Availability": *P* prescription drug, *C* controlled drug, *COS* cosmetic products, *OTC* over-the-counter drug, *I* Internet purchase, *F* risk of fake drugs (see ► Sect. 37.7)

Thus, many broad indications are covered by about 10–15 drugs, despite the limitations chosen.

In fact, for certain indications such as hypertension, all major drugs classes (A, B, C, D; see ▶ Chap. 15) are included (7, 19, 22, 66, 83). With just these few generic antihypertensive drugs, many follow-up complications can be avoided economically if the drugs are administered with high adherence. In contrast, for other indications such as targeted tumor therapy, just very few representatives (13, 50) are included because therapy of individual tumors has become too complex. Except for entries 8, 30, and 58, being combinations of two drugs, all other drugs are single entities. Several of the drugs from various indications (e.g., 5, 6, 10, 32, 49, 61, 65, 78, 100) have been used for decades so that their clinical effects, ADRs, and drug interactions are well known. The "100 List" also contains some rather new drugs (2, 13, 33, 57, 89), but their number was intentionally limited because they are usually very expensive and not available globally due to cost reasons.

Many of the drugs listed in the "100 List" are used for very common diseases such as:

- Hypertension (7, 19,22, 28, 46, 66, 83)
- CHD (10, 19, 27, 48, 66, 83, 100)
- Stroke (6, 10, 27, 100)
- PD (14, 58)
- Depression (5, 25, 35, 55, 61, 96, 97)
- Bipolar disorder (29, 49, 61, 55, 97)
- Schizophrenia (20, 25, 29, 49, 61, 97)
- Hypothyroidism (92)
- BPH (87)
- Type 2 DM (65)

But the list also includes drugs for relatively rare diseases such as:

- Myasthenia gravis (72)
- PAH (87)
- Stromal tumors (50)
- Certain autoimmune diseases (2, 23, 71)

The "100 list" does not only include diseases predominantly occurring in industrialized countries but also diseases prevalent in developing countries such as:

- HCV infection (57, 89)
- HIV (12, 37, 82)
- Opportunistic infections in HIV (30)
- TB and leprosy (38, 51, 81, 84)

Taken together, although the "100 List" cannot be comprehensive, it covers a broad spectrum of diseases from many representative fields.

37.3 Unique Drugs in the "100 List" and Structurally Related Drugs

Several drugs of the "100 List" are structurally unique and cannot be replaced by related drugs. Therefore, the drugs are particularly important. Among these drugs are ASA (10), certain analgesics (64, 78), lithium (61), certain antibiotics (30, 38, 51, 81, 84), EPI (40), and nitrous oxide (73). These drugs have been known for a long time and are available as generic drugs.

For most of the drugs in the "100 List," fewer or more structurally related analogs are available. In many cases, the structurally related drugs differ from each other in pharmacokinetic properties, less so in pharmacodynamic properties. Therefore, often drugs having structurally related analogs can be substituted against each other relatively easily. Many structurally related drugs are available in large indication areas such as cardiovascular diseases and GI diseases. For example, numerous AT_1R antagonists (19), ACEIs (83), and β_1AR antagonists (66) are available for treatment of hypertension. Along the same line, many PPIs for treatment of GERD and PUD are on the drug market (77). Similarly, migraine is a common disease, and many 5-$HT_{1D}R$ agonists (91) are available. Structurally similar drugs without therapeutic advance compared to the prototype are also referred to as "me-too compounds," the reason for their existence often being just getting a share of a big drug market.

With respect to NSMRIs (5), SSRIs (25), D_2R-mGPCR antagonists (49), and p-mGPCR antagonists (29), numerous related drugs are available as well. For psychiatric diseases, the diversity of available drugs is actually valuable because in this field, the best drug is often only identified by trial and error. The reason is that the molecular basis of the diseases is as yet incompletely understood. To some extent, the diversity of psychiatric drugs is covered in ▶ Chaps. 28 and 29 and the drug list in the appendix. The largest number of structurally related drugs is available in the field of protein kinase inhibitors, imatinib (50) being the prototype. The number of representatives in this class is

growing exponentially, each drug having a slightly different pharmacodynamic profile for target kinases, resulting in different and highly specific indications.

37.4 Clinical Application of the "100 List"

The "100 List" covers clinical applications ranging from life-threatening emergencies to long-term (lifelong) use. Evidently, for long-term use, the tolerability of the drugs must be particularly high. Among drugs with these properties are many modern antihypertensive drugs (7, 19, 22, 66, 83). Neurological diseases and psychiatric diseases also often require lifelong treatment. Unfortunately, these drugs (e.g., 5, 20, 29, 49, 58, 61) have serious ADRs, compromising tolerability and adherence. In contrast, lifelong therapy with insulin (52, 53), metformin (65), and T4 (92) is generally tolerated very well. Uncritical long-term use of certain drug classes is common, resulting in serious ADRs, e.g., polyneuropathy and osteoporosis (77); CKD, PUD, and hypertension (53); or even death due to refractory status asthmaticus (85). Therefore, it is very important to make a clear decision before prescription which duration of therapy is intended.

Several drugs are suited for treatment of acute medical conditions such as 18, 48, and 64 (colic pain), 5 (migraine attack), 64 and 78 (fewer), 85 (asthma attack), 99 (conjunctivitis and rhinitis), and 44 (acute deterioration of tumor pain).

A number of drugs listed here are intended for use in life-threatening emergencies. Amiodarone (6) can be used for treatment of TdP, ASA (10) for prevention of further thrombus growth in MI, clonidine (28) for hypertensive emergencies, diazepam (35) for status epilepticus, EPI (40) for anaphylactic shock, fentanyl (44) and morphine (68) for excruciating pain, glucose (47) for hypoglycemia, haloperidol (49) for acute schizophrenia and mania, insulin (52) for ketoacidotic coma, levonorgestrel (59) for emergency contraception, and salbutamol (85) for status asthmaticus. Last but not least, the oral rehydration solution (76) must be highlighted as emergency therapy for cholera, in which massive water and electrolyte losses can result in death within a day or less.

37.5 Important Medical Fields Covered by the "100 List"

The drugs in the "100 List" were chosen in such a way that many important medical fields are covered. Without having the ambition of being exhaustive, most fields are covered with 7–19 drugs. Specifically, 7 drugs are used in anesthesia, 15 in cardiology, 8 in dentistry, 19 in dermatology, 8 in endocrinology, 17 in gastroenterology, 11 in gynecology, 12 in nephrology, 8 in otorhinolaryngology, 15 in pediatrics, 13 in psychiatry, 11 in surgery, and 8 in urology. Some disciplines such as orthopedics need only relatively few drugs (5 entries). Some fields such as pulmonology (21 entries) and oncology (23 entries) are covered with more drugs, but specifically in oncology, the number of relevant drugs is much higher. Ophthalmology is covered with five drugs, and special fields such as hepatology (HCV infection) and treatment of HIV infection are covered with two and four drugs, respectively. While these listed drugs do not cover all indications, many areas, particularly cardiovascular diseases, are excellently served with the selected drugs, thereby satisfactorily addressing a major cause of global morbidity and mortality.

Sixty drugs were classified to be of relevance for general (family) medicine. Thus, general medicine is very heavily dependent on pharmacology. This does not automatically imply that the general practitioner has to be an expert in prescribing the respective drugs, but she/he must keep an overview on all the prescriptions written by specialists to avoid ADRs and drug interactions. In fact, this crucial integrative function of pharmacology across fields becomes increasingly lost when pharmacology classes are dissolved into so-called "integrative" and "organ-specific" teaching modules. In these modules, the focus is just on the respective organ and the relevant diseases, but mechanisms of drug action and ADRs of the respective drugs on other organs are "forgotten." This puts the general practitioner into a central position for drug safety and rational drug use and provides strong arguments for re-implementing pharmacology classes where they have been "integrated" (abandoned).

Some of the drugs in the "100 List" are used just by specialists (e.g., 6, 11, 12, 20, 29, 34, 37, 41, 43, 50, 56–58, 61, 72, 73, 80, 82, 89, 93, 96). These drugs usually serve very specialized indications, are very expensive, and/or have serious ADRs. In

contrast, several other drugs (e.g., 1, 8, 9, 28, 31, 32, 39, 40, 44, 53, 54, 69, 71, 78, 79, 99) are used very broadly across disciplines. Among these drugs are virustatics and antibiotics, analgesics, and drugs for the treatment of systemic autoimmune diseases.

37.6 Risk of Abuse of the "100 List"

Among the drugs in the "100 List," at least 26 drugs have the potential for abuse. Thus, the prescribing physician has to carefully explore before prescription whether such a risk exists. Certain substances with abuse risk (17, 44, 68, 70) are controlled substances and can be prescribed only under specific legal conditions, aiming at the reduction of abuse. However, several drugs with abuse potential are available OTC (or in cosmetic products) or can be purchased without control on the Internet. Accordingly, when a patient presents with disease symptoms, the physician has always to consider the possibility that the clinical symptoms are due to drug abuse.

The uncritical long-term use of ASA (10) can lead to severe GI hemorrhage. While the value of ASA (low dose) in the secondary prevention of MI and stroke is uncontested, primary prevention of these diseases with ASA is controversial. Along the same line, the use of simvastatin (88) and related drugs for hypercholesterolemia without the presence of other cardiovascular risk factors as primary prevention is recommended by certain physicians and learned societies. However, simvastatin can cause life-threatening rhabdomyolysis. Hence, the uncritical use of simvastatin and related drugs in primary prevention of cardiovascular diseases cannot be recommended.

Related to the uncritical use of ASA (10) is the uncritical use of PPIs (77). In order to prevent GI hemorrhage by ASA, many patients additionally consume PPIs. The number of patients taking the combination of 10 + 77 (both available OTC) for years or even decades has increased substantially. It is generally assumed that this combination is "harmless" in terms of GI hemorrhage. However, it is becoming increasingly clear that uncritical use of PPIs without proper indication can cause serious ADRs including polyneuropathy and osteoporosis.

Certain drugs (15, 56) are used for cosmetic purposes. Botulinum neurotoxin is used to smoothen wrinkles in the facial muscles, but if applied incorrectly, the toxin may induce a long-lasting loss of mimic expression. Fake "Botox" products (without active toxin) have become a serious problem. Latanoprost (56), a highly effective drug for treatment of open-angle glaucoma, causes periocular and iris discoloration and excessive growth of eyelashes. The latter effect is exploited in certain eyelash growth sera. However, if applied incorrectly and extensively, periocular discoloration may occur. This is certainly not a cosmetically desired result. In cosmetic products, the presence and/or concentration of latanoprost (or other PGs) often is not declared, rendering use of these products unpredictable with respect to their effects.

The MOR agonists listed in the "100 List" (17, 44, 68) can all cause severe addiction. Therefore, these drugs are controlled. Nonetheless, the uncritical prescription of these drugs without proper indication has resulted in the opioid crisis in the USA. Along the same line, MPH (70), an effective drug for treatment of ADHD, is broadly abused in persons without ADHD to boost their intellectual performance. This abuse has resulted in discussions about the fairness of academic exams and competition for professional positions requiring high intellectual capacity. Similarly, levodopa (58) is abused to increase intellectual performance and increase sexual desire. However, dosing of levodopa is not easy, and serious cases of hypersexuality have been reported.

Diphenhydramine (32), diazepam (35), and propofol (80) are often used as substitute drugs in persons addicted to MOR agonists because these drugs are either available OTC (32) or as prescription drug (35). Clonidine (29) has become another drug of abuse in MOR addicts to mitigate withdrawal symptoms.

It should be emphasized in this context that psychotropic drugs used for the treatment of depression (5, 25, 55), bipolar disorder (61, 97), and schizophrenia (29, 49) do usually *not* bear the risk of abuse and addiction. This is a very important point because patients may be afraid of addiction. Patient education about the fact that these drugs do not bear the risk of addiction is very important to ensure high patient adherence to the therapy. In this context, the use of mechanism-oriented names of drug classes is crucial.

Certain drugs are also abused by athletes. Specifically, diuretics (22, 46) and laxatives (62) may be abused in disciplines in which athletes are

classified according to body weight. Specifically, reduction of body weight just prior to a fight may place the athlete into a "better" weight class. However, athletes must be warned because severe water and electrolyte losses (particularly potassium!) may impede with athletic performance. Epoetin (41) and analogs have been broadly abused in endurance sports such as Nordic skiing. Now that detection of synthetic epoetin in blood has become very easy, epoetin abuse has been largely replaced by autoinfusion of previously drawn erythrocyte concentrates just prior to the competition. However, both epoetin and autoinfusion of erythrocyte concentrates entail the risk of severe thromboembolic events. Salbutamol (85) and related drugs are also often abused by endurance athletes, i.e., bicyclists. These drugs may increase the supply of oxygen to the organism and, thereby, enhance performance. In order to avoid disqualification because of doping, many endurance athletes are diagnosed with "asthma" to render the use of the drugs (85) legal. The PDE5 inhibitor sildenafil (87), used for ED, PBH, and PAH, increases pulmonary perfusion and can also increase oxygen supply to the organism. For this reason, sildenafil is increasingly abused in endurance athletes.

Another global problem is the abuse of COX inhibitors for chronic pain. Certain drugs from this class (e.g., 53) are available OTC. Their traditional labeling as "non-steroidal anti-inflammatory drugs (NSAIDs)" suggests that they can be used without harm (in contrast to the harmful steroids (GCR agonists)) for long-term treatment of inflammation-associated pain such as in arthrosis and rheumatoid arthritis (see ▶ Chaps. 1 and 10). However, long-term use of these drugs is associated with hypertension, CKD, and PUD. As a result, COX inhibitors such as ibuprofen (4) should be used only for ACUTE pain and for SHORT periods of time to avoid these debilitating ADRs. The combination of COX inhibitor + PPI (e.g., 53 + 77) is often used to mitigate the PUD problem, but as pointed out above, the long-term use of PPIs is problematic for several reasons. Thus, the long-term use of the combination of PPI + COX inhibitor is strongly discouraged.

Long-term use of high doses of paracetamol (78) may cause liver damage. Long-term use of metamizole (67) for pain may increase the risk of agranulocytosis, but the discussion on this question is controversial.

Certain drugs are also abused to meet certain societal expectations. Specifically, the pressure for perfect sexual performance around the clock has substantially increased the consumption of sildenafil (87) even in patients without ED. Since the pressure has become so large, in many countries illegal (fake) sildenafil preparations are on the market. Sildenafil preparations bought on the Internet are also often of questionable quality. In some countries, the first legal OTC preparations of sildenafil have become available.

Particularly in women, there is a high pressure on maintaining a low body weight. In certain professions (e.g., fashion models, actresses, ballerinas) a very low body weight is expected, despite certain efforts to counteract this expectation. In order to maintain a very low body weight, many women abuse diuretics (22, 46) and laxatives (62). Moreover, T4 (92) is abused to reduce body weight. However, T4 also causes hypertension and nervousness.

GPCR agonists are prone to abuse because their long-term use leads to desensitization and reduced clinical efficacy, thus promoting a dose increase (see ▶ Chap. 1). This problem is particularly relevant for MOR agonists (17, 44, 68), because the loss of efficacy of these drugs in addicts may lead to criminal acts in order to secure the financial resources for purchase (either legally or illegally) of larger quantities of MOR agonists. The uncritical use of salbutamol (85) as single drug in asthma may increase mortality. As another example, the uncritical and regular use of sumatriptan (91) for migraine attacks may lead to loss in efficacy. In such cases, migraine prophylaxis with other drugs from the "100 list" (e.g., 97) must be initiated. Another common problem is the abuse of xylometazoline (99), available OTC, for constipated nose. The drug loses its efficacy within 1–2 weeks after regular use. In cases of type I allergies causing the constipation, medication with locally acting GCR agonists (16) is indicated to alleviate the inflammation.

37.7 Cultural Differences in the Availability and Use of the "100 List"

The "100 List" is certainly not globally accepted. In fact, there are substantial cultural differences in the use of individual drugs in various countries. Different historical and religious developments of

countries, different interpretations of risks, influence of industry, financial resources, availability of drugs, geographic differences, and different views on diseases all contribute to a differential drug use. For the majority of drugs listed in the "100 List," more or less pronounced cultural differences in all major medical fields exist.

While this introductory text cannot discuss all these differences, in an increasingly globalized world, the medical and pharmacy student should be aware of the fact that pharmacotherapy is a cultural construct, where in addition to scientific evidence, many other factors play a role. Thus, one should be cautious about making statement that a given pharmacotherapy is "correct" or "wrong."

A very striking example for fundamental cultural differences in pharmacotherapy is the use and availability of emergency contraceptives (59) in various countries (see [6]). These differences are largely influenced by religious beliefs. Along the same line, cultural differences in the acceptance and use of oral contraceptives exist. Another compelling example is the availability of the analgesic metamizole (64) in various countries (see [7]). In this case, the risk of agranulocytosis is interpreted very differently. In some countries, the risk is deemed so low that the drug is available OTC, and, in other countries, the risk is estimated so high that the drug is not available at all. There are also country-specific differences in the use of various MOR agonists. Evidently, if an effective analgesic drug (i.e., metamizole) is not available in a given country, this has an impact on the use of other analgesics. Specifically, in the USA, where metamizole is not available, MOR agonists and paracetamol are very popular drugs.

The use of drugs for the treatment of psychiatric diseases such as depression, bipolar disorder, and schizophrenia also reveals country-specific differences. One reason for this situation is the fact that the quality of clinical studies on these drugs is often ambiguous so that "personal experience" of the psychiatrist dominates prescription behavior.

Several drugs are available as prescription drugs or OTC drugs (1, 10, 18, 21, 32, 47, 53, 62, 64, 76–78, 87, 91, 92, 99), again country-specific difference being relevant. For some drugs, the package size determines whether a drug is available OTC or as prescription drug. For example, in some countries paracetamol (78) is available OTC in package sizes of up to 5 or 10 g, whereas in other countries, the drug is available in virtually unlimited quantities. For ibuprofen, the dose per tablet (in general 400 mg) makes the difference whether the drug is available OTC or as prescription drug. However, if a consumer intends to use the drug in higher doses, then he/she just takes two or three instead of one 400 mg-tablet. These examples indicate that control mechanisms for commonly used non-MOR analgesics are not tight although these drugs can be quite dangerous, particularly in high doses and during long-term use.

The uncritical long-term use of OTC PPIs (77) can lead to osteoporosis and polyneuropathy, and the uncritical long-term use of M_xR antagonists (butylscopolamine (18)) can lead to constipation. High doses of OTC diphenhydramine (32) can result in an antimuscarinic syndrome and impaired ability to operate cars, and long-term use of the drug can lead to obesity. These few examples illustrate that the use of OTC drugs is not without risk. Accordingly, the pharmacist has substantial responsibility in educating patients about proper drug use, ADRs, and interactions. However, in certain countries, several drugs, most notably non-MOR agonists (53, 78) and drugs for treatment of type I allergies (32), are available in drug stores shelves without the need for consultation, enhancing the ADR risk.

Large cultural differences are also evident for VKAs. In the "100 List," warfarin is incorporated as a prototype because most clinical studies were performed with this drug. However, in certain countries (Germany), phenprocoumon is used much more widely, and the drug is actually often not designated with its generic name but with the brand name of a leading manufacturer (Marcumar®). Even more problematic, in clinical practice it is not stated that a patient is treated with phenprocoumon, but rather that the patient is "marcumarized." This traditional language use plays a major role in determining drug use in certain countries, beyond scientific evidence.

37.8 Pricing of the "100 List"

In general, the list aimed at incorporating generic drugs with affordable prices globally. With some exceptions (2, 12, 15, 40, 50, 57, 89, 93), this goal was achieved. However, the disadvantage is that due to low profit margins and pressure from

insurance companies, to name few reasons, the production of many generic drugs is now concentrated in few factories. If a technical problem occurs in such a factory, global drug supply problems arise. Supply problems have occurred for several drugs including 10, 8, 40, 53, 60, and 92.

In general, many prescription drugs, particularly newly introduced ones, are sold at much higher prices in the USA than in other countries. This issue is topic of current debates. Compared to other European countries, prices for many drugs in Germany are higher. In part, this problem can be circumvented by inexpensive re-imports, particularly for highly priced drugs. In any case, these examples illustrate that determination of drug prices is not transparent.

It has been widely criticized that prices for newly introduced drugs for autoimmunopathies, malignant tumors, and HCV infections are very high. Previously, prices for anti-HIV drugs were also high, but in the meantime, mechanisms were established to ensure that also countries with limited financial resources have better access to anti-HIV drugs.

Price issues do not only concern new drugs, but also generic drugs. As a prominent example, the exceedingly high prices for EPI pens (emergency treatment of anaphylactic shock) (40) in the USA has been widely criticized. In contrast, in the USA, exceedingly large quantities of ibuprofen and paracetamol can be purchased at very low prices, often even with heavy discounts.

As a general rule, drug prices decrease once the patent has expired and generic drugs enter the market. Since for biologicals (2, 13, 15, 41), prices are generally very high, the introduction of generic biologicals, referred to as biosimilars, leads to substantial price declines and renders therapy much more affordable even in resource-poor countries.

37.9 20 Drugs from the "100 List" that Every Physician Should Prescribe

Medicine is experiencing an exponential specialization of disciplines and subdisciplines. Accordingly, pharmacotherapy becomes more and more specialized. As a result, the common trunk of pharmacotherapeutic capabilities of every physician is reduced continuously. In order to counteract this trend, among the "100 List," 20 drugs were selected that every physician should prescribe if requested and necessary. These 20 drugs are highlighted (bold italics) in ◘ Table 37.1.

Every physician should be able to initially treat some life-threatening emergencies, i.e., hypoglycemia (47), anaphylactic shock (40), and hypertensive emergencies (28, 48), AP (48), MI (10, 48), and acute heart failure (48). In addition, a physician should be able to treat acute medical situations such as acute colic pain (48), migraine attack (91), fever (78), traumatic and inflammatory pain (53), acute diarrhea (76), nausea and vomiting (63), and various manifestations of type I allergies (21, 85, 99). Note that a single drug (48) is suitable for treatment of several emergencies (acute medical situations).

Globally, insufficiently treated hypertension constitutes a major cause for subsequent morbidity and mortality. Since hypertension is very easy to diagnose and treat (see ▶ Chap. 15), every physician should be able to at least initiate antihypertensive treatment. Among the selected antihypertensives are representative of the classes A (19), B (66), C (7), and D (22). In addition, secondary prevention of stroke and MI with ASA (10) is easy to perform.

Depression constitutes an increasingly important cause for long-term morbidity (see ▶ Chap. 28). In addition, depression does not only affect the patient but also her/his social environment, i.e., family, friends, and colleagues at work. Unfortunately, many depressive patients seek professional advice too late. Another reason for delayed depression treatment is that in many countries, patients have to wait for months until they get a regular appointment with a psychiatrist. Therefore, to facilitate depressive patients receiving proper treatment, it is suggested that every physician should be able to initiate treatment of depression with citalopram (25). This is an SSRI with many psychiatric indications. Evidently, if such a decision is made, all precautions discussed in ▶ Chaps. 6 and 28 must be followed.

For viral infections associated with fever in children, (78) is a good choice; (53) constitutes an alternative. In toddlers, MCP (63) should be avoided, but in older children, MCP can be administered based on body weight. For acute diarrhea in children, (76) is suitable, and in rhinitis, (99) can be used to facilitate respiration.

Lastly, every physician should be able to treat at least some bacterial infections based on the clinical symptoms. Treatment of an uncomplicated urinary tract infection with fosfomycin (45) is straightforward. In addition, many infections in the respiratory tract including sinusitis, tonsillitis, bronchitis, and CAP can be readily treated with a 5–7-day course with (4). In case of penicillin allergy, (42) constitutes an alternative.

37.10 Why Certain Commonly Prescribed Drugs Are Not in the "100 List"

Evidently, when the list is restricted to 100 drugs while thousands of drugs exist, decisions must not only be made which drugs must be included but also which drugs have to be omitted. As discussed before, many specialized drugs for treatment of autoimmunopathies and malignant tumors had to be omitted because they are far too specialized (and often very expensive) (see ▶ Chaps. 11 and 32). Important criteria for inclusion of a drug in the "100 List" were efficacy in clinical studies and real-world settings, reasonable ADRs, and moderate pricing. These criteria were not fulfilled for all drugs, indicating that there are still options for improvement of pharmacotherapy, most notably in psychiatry. In fact, many drug companies have abandoned their drug discovery programs for psychoactive drugs because it is very difficult to make pharmacotherapeutic advances.

Several commonly prescribed drugs were not included in the "100 List" for various reasons, but these drugs are listed in the list of generic drugs in the appendix. The "100 List" does not include THC, becoming increasing popular in several countries for pain treatment, because the clinical studies on THC are not convincing and because it is still impossible to dissociate therapeutic effects from ADRs. Moreover, THC can cause addiction and is one pathogenic factor of psychiatric diseases. The highly popular St. John's wort preparations for depression were not included because of the lack of convincing clinical evidence, undefined drug content (hyperforin) in many preparations, and the risk of drug interactions (CYP induction). Moreover, because many St. John's wort preparations are available OTC or on the Internet, proper diagnosis of depression by a physician may be delayed, aggravating the future course of the disease and rendering professional treatment more difficult.

Clozapine (29) is a "very old" p-mGPCR antagonist. Its efficacy in schizophrenia has been very well documented in clinical studies. Its major disadvantage is the risk of agranulocytosis, requiring regular hemogram controls. Since this is inconvenient, clozapine is not very popular in many countries, despite its proven efficacy. Substantial efforts were made to introduce newer p-mGPCR antagonists with higher efficacy and less ADRs. In fact, in many countries newer p-mGPCR antagonists not integrated into the "100 List" dominate current drug markets. However, the newer drugs were not included in the "100 List" because they also cause serious ADRs and most importantly, they are not clinically superior compared to clozapine. Reduction of suicidality is still the gold standard, and no drug has surpassed clozapine so far in this regard. Lastly, many of the newer drugs are more expensive than clozapine. Likewise, drugs for AD (little evidence for clinical efficacy) were not included (see ▶ Chap. 30).

With respect to cardiovascular diseases, DOACs have surpassed VKAs in terms of prescription numbers and sales in several (industrialized) countries. However, compared to VKAs, DOACs are much more expensive. Moreover, discussions have ignited whether in real-world conditions, DOACs are truly equivalent or superior to VKAs. Several studies indicate that if VKAs are used judiciously, avoiding polypharmacy and drug interactions, they are very effective and safe.

In the field of DM therapy, new drug classes (GLP-1R agonists, SGLT-2 inhibitors) have been recently introduced into the clinic. While these drug classes have therapeutic potential, they were not included in the "100 List" because in contrast to metformin, the inexpensive and clinically proven gold standard for type 2 DM, long-term studies on clinical efficacy are not yet available.

With respect to analgesics, the broadly used tramadol was not included. It is often classified as weak partial MOR agonist. It is a popular drug because it does not constitute a controlled substance. However, its clinical efficacy is often overestimated. Instead, the controversial metamizole

(64) was included into the "100 List" because it possesses a high analgesic efficacy and is suitable for long-term use without addiction risk. The case of metamizole calls for high-quality clinical studies on this drug assessing efficacy in relationship to ADRs (agranulocytosis) because, particularly in light of the opioid crisis, there is an urgent need for good and affordable analgesics without addiction risk.

Because of the problems associated with the long-term use of nonselective COX inhibitors (53) for inflammatory pain (PUD, hypertension, CKD), selective COX-2 inhibitors were developed. While COX-2 inhibitors are devoid of the PUD risk, they exhibit an increased risk for thromboembolic complications such as stroke and MI. Thus, COX-2 inhibitors do not constitute a safe alternative to COX inhibitors for long-term treatment of inflammatory pain. They should just be used for short-term treatment of pain like the COX inhibitors, but they are not superior.

37.11 Questions and Answers

Questions

Which drug should only be prescribed to selected patients by a specialist?

A. Amiodarone
B. Amlodipine
C. Candesartan
D. Chlorthalidone
E. Metoprolol

Answers

A. Amiodarone effectively prevents VT in MI patients, but the drug has a very small therapeutic index, many ADRs, and many drug interactions. Therefore, patients for amiodarone therapy have to be carefully selected.

B. Amlodipine is well-tolerated and an effective CCB for long-term treatment of hypertension. Therefore, the drug can be prescribed to large patient cohorts, even by the general practitioner.

C. Candesartan is a well-tolerated and effective AT_1R antagonist for treatment of hypertension and CHF. Therefore, the drug can be prescribed to large patient cohorts, even by the general practitioner. The most important ADR is hyperkalemia. This ADR can be readily prevented by combining the drug with chlorthalidone (see answer D).

D. Chlorthalidone is a well-tolerated and effective thiazide diuretic for treatment of hypertension and CHF. Therefore, the drug can be prescribed to large patient cohorts, even by the general practitioner. The most important ADR is hypokalemia. This ADR can be readily prevented by combining the drug with candesartan (see answer C).

E. Metoprolol is a well-tolerated and effective β_1AR antagonist for the treatment of hypertension, CHF, and CHD. Therefore, the drug can be prescribed to large cohorts of patients, even by the general practitioner. The most important ADRs are bradycardia, cardiac failure if the dose is increased to rapidly, asthma attacks, and unrecognized hypoglycemia in DM patients. However, these ADRs can be well prevented.

Answer **A** is correct.

37.12 Exercises

You work as a physician for a humanitarian organization in a country with very little financial resources. The Ministry of Health of this country asks you to assemble a list of essential drugs.

Questions

1. Which drugs from the "100 List" do you pick for the indication "cardiovascular emergencies?
2. How do justify your selection to the Ministry of Health?

Answers

1. You pick the following drugs:
   - Amiodarone
   - ASA
   - Clonidine
   - Diazepam
   - EPI
   - GTN
   - Furosemide
   - Morphine

2. All drugs are available as inexpensive generic drugs, and they have complementary indications:
   - Amiodarone: Can stop life-threatening TdP caused by drugs or heart diseases.
   - ASA (low dose): Inhibits further platelet aggregation and thrombosis in ACS and MI.
   - Clonidine: Reduces BP and sedates the patient in hypertensive emergencies.
   - Diazepam: Induces sedation and anxiolysis in patients with ACS and MI.
   - EPI: Stabilizes circulation (positive chronotropy, dromotropy, and inotropy and moderate vasodilation) in anaphylactic shock. EPI can also be used to restore cardiac function in cardiac arrest, but this indication is not uncontested.
   - GTN: Induces vasodilation and reduces dyspnea in acute heart failure and pulmonary embolism/pulmonary edema. GTN also reduces chest pain in ACS and MI and reduces BP in hypertensive emergencies.
   - Furosemide: Induces vasodilation and strong diuresis. As a result, dyspnea in acute heart failure and pulmonary embolism/edema is reduced. In addition, the drug reduces the BP in hypertensive emergencies.
   - Morphine: The drug reduces the excruciating pain and dyspnea in ACS, MI, and pulmonary embolismv/edema.

Further Reading

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Supplementary Information

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List of Generic Drugs

Drug group	Drug (INN)	Chapter
Drugs acting on the adrenergic system		**5**
α_xAR and β_xAR agonists	EPI (epinephrine), NE (norepinephrine)	1, 3, 5, 26
α_1AR agonists	Xylometazoline	1, 5
α_1AR antagonists	Doxazosin, tamsulosin	5
α_2AR agonists	Moxonidine, clonidine, methyldopa, brimonidine	5, 10, 15, 31
α_2AR antagonists	Mirtazapine	5, 28
β_1AR antagonists	Metoprolol, bisoprolol, atenolol	1, 5, 15, 16, 17
β_2AR agonists	Salbutamol (albuterol), fenoterol	1, 5, 7, 14
β_xAR antagonists	Propranolol, timolol	1, 5, 31
β_3AR agonists	Mirabegron	5, 12, 31

Drugs acting on the cholinergic system		**5**
M_xR agonists	Pilocarpine	5, 31
AChEIs	Neostigmine and pyridostigmine (peripherally acting), edrophonium (for diagnosis of myasthenia gravis), donepezil, and physostigmine (cross BBB)	2, 3, 5, 13, 30
M_xR antagonists	Atropine, scopolamine, biperiden, tiotropium, ipratropium, butylscopolamine, tropicamide (very diverse spectrum of indications)	2, 4, 5, 8, 10, 13, 14, 23, 29, 31
Antidote for intoxication with M_xR antagonists	***Physostigmine***	***4, 5***
nAChR agonists (depolarizing muscle relaxants)	Suxamethonium (succinylcholine)	5, 27
nAChR antagonists (hyperpolarizing muscle relaxants)	Alcuronium, vecuronium	5
Inhibitors of ACh release	Botulinum neurotoxin	5

Drugs acting on the serotonergic system		**6**
5-$HT_{1B/D}$R agonists (triptans)	Sumatriptan, naratriptan	6
5-HT_{2A}R antagonists	Clozapine, risperidone (both drugs are also antagonists at other GPCRs)	6, 29
5-HT_3R antagonists (setrons)	Ondansetron, granisetron	6, 32
5-HT_{2A}R agonists (hallucinogens)	LSD, psilocybin	6, 29
5-HT_4R agonists	Prucalopride	6, 13

Drugs acting on the histaminergic system		**7**
First-generation H_1R antagonists	Diphenhydramine, clemastine, dimetinden	3, 7, 14
Second-generation H_1R antagonists	Fexofenadine, loratadine, cetirizine	3, 7, 14
H_2R antagonists	Ranitidine, famotidine	7, 13
H_3R antagonists	Pitolisant	7
H_xR agonists	HA	7, 32

Drugs for treatment of allergies		**7**
Mast cell stabilizers	Cromoglicic acid, ketotifen	7, 14
Second-generation H_1R antagonists	Fexofenadine, loratadine, cetirizine	3, 7, 14
IL-5 inhibitors	Mepolizumab (antibody)	14
IgE inhibitors	Omalizumab (antibody)	14
BK_2R antagonists	Icatibant	3, 7, 15
Emergency treatment of anaphylactic shock	EPI i.v. applied by a physician or i.m. by means of a pen to be used by the patient	3, 5, 7, 14

Drugs acting on the dopaminergic system		**8**
Anti-Parkinson drugs		
DA prodrugs	Levodopa	2, 8
Dopa decarboxylase inhibitors	Carbidopa, benserazide	2, 8
D_xR agonists	Bromocriptine (ergoline D_xR agonist), pramipexole, and ropinirole (non-ergoline D_xR agonists)	8
MAO-B inhibitors	Rasagiline	8
COMT inhibitors	Entacapone	8
M_xR antagonists	Biperiden	4, 8, 29
Drugs for treatment of ADHS (indirect dopamimetics)	Methylphenidate	8
Prokinetics and antiemetics	MCP, domperidone, D_2R-mGPCR antagonists	8, 13, 29
D_2R-mGPCR antagonists	Haloperidol, fluphenazine, melperone, chlorprothixene, levomepromazine, promethazine, pipamperone	8, 29
Drugs for enhancement of renal perfusion	DA (D_xR agonist; at higher concentrations also acts as α_xAR and β_xAR agonist)	8, 12

Drugs acting on smooth muscle cells		**9, 15, 16**
NO donors	GTN, SNP	9, 13, 15, 16
Antidotes for cyanide intoxication during SNP therapy	***Sodium thiosulfate (rhodanide formation), dimethylaminophenol (DMAP; methemoglobin formation)***	***4, 9***
sGC activators	Cinaciguat	9
sGC stimulators	Riociguat	9

PDE5 inhibitors	Sildenafil, tadalafil	9, 13
L-type CCBs acting on smooth muscles cells	Nifedipine (short-acting), amlodipine (long-acting)	2, 15
Potassium channel openers	Minoxidil	15
Thiazide diuretics	Hydrochlorothiazide, chlorthalidone	15, 16
Loop diuretics	Furosemide, torasemide	15, 16
α_1AR agonists	Xylometazoline, EPI and NE (also agonists at β_xAR and α_2AR)	1, 4, 5, 7, 26
α_1AR antagonists	Doxazosin, tamsulosin	5, 15,16
AT_1R antagonists (sartans)	Candesartan, valsartan	15, 16
ET_AR antagonists (ERAs)	Bosentan	15
NEP inhibitors	Sacubitril	16

Analgesics		**10**
MOR agonists		
Weak partial MOR agonists	Tramadol	10
Moderate partial MOR agonists	Buprenorphine	10
Full MOR agonists	Morphine, fentanyl, remifentanil, hydromorphone	1, 2, 3, 4, 10, 12, 13
MOR antagonists for intoxication by MOR agonists and for preventing relapse to heroin addiction	***Naloxone, naltrexone***	***4, 10***
Non-MOR agonists		
COX inhibitors	Ibuprofen, diclofenac	3, 7, 10, 11, 18
COX-2 inhibitors (coxibs)	Celecoxib	10, 11, 12, 18
Analgesics with unknown mechanism of action	Paracetamol (acetaminophen), metamizole (novaminsulfon, dipyrone)	10, 23
Antidote for paracetamol intoxication	***Acetylcysteine***	***4, 10***
N-type CCBs	Ziconotide (ω-conotoxin)	1, 10
Partial CB_1R agonists	THC	10

Drugs for treatment of autoimmune diseases and for inhibition of transplant rejection		**11**
Systemic GCR agonists	Prednisolone, dexamethasone	3, 6, 11, 13, 14, 32
Topical GCR agonists	Budesonide, fluticasone	2, 13, 14
AICAR transformylase inhibitors	MTX (low dose)	11, 13
Inosine monophosphate dehydrogenase inhibitors	Mycophenolate	11
Purine antagonists	6-MP (low dose); azathioprine (6-MP prodrug)	11, 32
Alkylating agents	Cyclophosphamide (low dose)	11, 32

Dihydroorate dehydrogenase inhibitors	Leflunomide (teriflunomide prodrug)	11
$S1P_1R$ agonists	Fingolimod	11
Calcineurin inhibitors	Ciclosporin, tacrolimus	11, 12, 13
mTOR inhibitors	Sirolimus (rapamycin)	11, 12, 13
Drugs with antioxidant effects for treatment of MS	Dimethyl fumarate (DMF)	11
Drugs with pleiotropic effects for treatment of MS	Glatiramer acetate (GA)	11
TNF inhibitors	Infliximab and adalimumab (antibodies), etanercept (soluble TNFR fragment)	11, 13
IL-1R antagonists	Anakinra	11
Inhibitors of interaction between CD80/86 and CD28	Abatacept (fusion protein)	11
CD20 inhibitors	Rituximab (antibody)	11
CD52 inhibitors	Alemtuzumab (antibody)	11
IL-2(CD25) inhibitors	Basiliximab, daclizumab (antibodies)	11
CD3 inhibitors	Muromonab (antibody)	11
IL-12 and IL-23 inhibitors	Ustekinumab (antibody)	11
Integrin-α-4 inhibitors	Natalizumab (antibody)	11
Interferons	IFN-β	11

Drugs for treatment of CKD		**12**
Thiazide diuretics	Hydrochlorothiazide, chlorthalidone	12, 13, 15, 16
Loop diuretics	Furosemide, torasemide	12, 13, 15, 16
Potassium-sparing diuretics	Triamterene	12, 15, 16
Calcimimetics (allosteric CaSR modulators)	Cinacalcet	1, 12
Phosphate binders	Lanthanum carbonate	12
Active vitamin D_3 (1,25-$(OH)_2$-vitamin D_3)	Calcitriol	12, 20
V_2R antagonists (drugs for ADPKD)	Tolvaptan	12
Hematopoietic growth factors (drugs for renal anemia)	Epoetin, darbepoetin	12, 15, 18

Drugs for treatment of GI diseases		**13**
PPIs	Pantoprazole	2, 7, 10, 13, 18, 20, 33, 34, 35
H_2R antagonists	Ranitidine, famotidine	7, 13
Laxatives	Bisacodyl (antiresorptive and prosecretory laxative), macrogol (osmolaxative, polyethylene glycol)	10, 13

Prokinetics	MCP and domperidone (D_2R antagonists)	2, 7, 8, 3, 17
Antidiarrheals	Loperamide (peripherally acting MOR agonist)	13
Peripherally acting MOR antagonists	Methylnaltrexone (for patients who require long-term MOR agonist administration for pain management)	2, 10, 13
Spasmolytics (M_xR antagonists)	Butylscopolamine	5, 10, 13, 23
Antibiotics against *Helicobacter pylori*	Clarithromycin, amoxicillin, metronidazole	13, 33
Absorbents for primary removal of toxic substances	Activated charcoal	4, 13
Oral rehydration solutions	Glucose, Na^+, K^+, Cl^-, citrate (for diarrhea)	1, 13
Drugs for inflammatory bowel diseases	5-ASA (mesalazine, in UC), sulfasalazine (in CD)	11, 13
Antiemetics		6, 13, 32
M_xR antagonists	Scopolamine	5, 6
5-HT_3R antagonists	Ondansetron	6, 32
H_1R antagonists	Clemastine, diphenhydramine	6, 7
D_2R antagonists	MCP, domperidon	6, 8
NK_1R antagonists	Aprepitant	8, 32

Drugs for treatment of respiratory tract diseases		**14**
SABAs	Salbutamol, fenoterol	1, 2, 5, 14
LABAs	Salmeterol, formoterol	1, 2, 5, 14
SAMAs	Ipratropium	5, 14
LAMAs	Tiotropium	5, 14
PDE4 inhibitors	Roflumilast	14
PDE inhibitors/adenosine receptor antagonists	Theophylline	2, 4, 13, 14
LTRAs (lukasts)	Montelukast	7, 13
IGCR agonists (inhaled GCR agonists)	Budesonide, fluticasone	11, 14
CFTR potentiators	Ivacaftor	14
CFTR correctors	Lumacaftor	14

Drugs acting on the RAAS		**15, 16**
ACEIs	Ramipril, enalapril	12, 15, 16
AT_1R antagonists (sartans)	Candesartan, valsartan	12, 15, 16
MCRAs	Eplerenone, spironolactone	12, 15, 16

Antihypertensives		**15**
ACEIs and AT_1R antagonists (class A)		
ACEIs	Ramipril, enalapril	3, 12, 15, 16
AT_1R antagonists (sartans)	Candesartan, valsartan	3, 12, 15, 16
β_1AR antagonists (class B)		
β_1AR antagonists	Metoprolol, bisoprolol, atenolol	1, 5, 15, 16, 17
CCBs (class C)		
Long-acting L-type CCBs	Amlodipine, nitrendipine	2, 15
Short-acting L-type CCBs	Nifedipine (hypertensive emergency)	2, 15
Diuretics (class D)		
Thiazide diuretics	Hydrochlorothiazide, chlorthalidone	12, 15, 16
Loop diuretics	Furosemide, torasemide	12, 15, 16
Potassium-sparing diuretics	Triamterene	12, 15, 16
Antihypertensives of last resort	α_1AR antagonists (doxasosin), α_2AR agonists (moxonidine), potassium channel openers (minoxidil), MCRAs (eplerenone)	5, 15
Drugs for treatment of hypertensive emergencies	NO donors (GTN, SNP), short-acting L-type CCBs (nifedipine), α_2AR agonists (clonidine), loop diuretics (furosemide)	4, 5, 9, 12, 15

Drugs for treatment of chronic heart failure		**16**
ACEIs and AT_1R antagonists (class A)	ACEIs (enalapril), AT_1R antagonists (candesartan)	3, 15, 16
β_1AR antagonists (class B)	β_1AR antagonists (metoprolol)	1, 5, 15, 16, 17
Diuretics (class D)	Thiazide diuretics (hydrochlorothiazide), loop diuretics (furosemide)	12, 15, 16
MCRAs	Eplerenone	12, 15, 16
I_f channel inhibitors (class I)	HCN4 channel blockers (ivabradine)	16, 17
NEP inhibitors	Sacubitril	15, 16

Antiarrhythmics		**17**
Class Ia	Ajmaline	**17**
Class II	Metoprolol	5, 15, 16, 17
Class IV	Verapamil, diltiazem	15, 17
Classes I–IV (previously designated as class III)	Amiodarone, dronedarone	2, 17, 21
HCN4 channel blockers	Ivabradine	16, 17
M_xR antagonists	Atropine	4, 5, 17
Divalent cations	Magnesium	17

Drugs for treatment of thromboembolic diseases		**18**
UFHs	Heparin	18
Antidote for management of hemorrhage under UFH therapy	***Protamine***	***4, 18***
LMWHs	Enoxaparin	18
Heparinoids	Danaparoid	18
VKAs	Phenprocoumon (used, e.g., in Germany), warfarin (used, e.g., in the USA)	2, 13, 18
Antidote for management of VKA overdose	***Vitamin K, slow onset of action***	***4, 18***
Antidote for life-threatening hemorrhage under VKA therapy	***Concentrates of clotting factors II, IX, and X, immediate onset of action***	***4, 18***
Fibrinolytics (tissue plasminogen activators)	Alteplase	18
DOACs		
Thrombin inhibitors	Dabigatran	18
Antidote for hemorrhage under thrombin inhibitor therapy	***Idarucizumab (antibody)***	***4, 18***
Factor-Xa inhibitors (xabans)	Rivaroxaban	18
Antidote for hemorrhage under xaban therapy	***Andexanet (decoy receptor)***	***4, 18***
Antidote for management of life-threatening hemorrhage under DOAC therapy	***Concentrates of clotting factors II, IX, and X, immediate onset of action***	***4, 18***
PAIs		
Irreversible COX-1 inhibitors	ASA (low dose, approx. 100 mg/day)	13, 18
Irreversible $P2Y_{12}R$ antagonists	Clopidogrel	13, 18
Glycoprotein IIb/IIIa inhibitors	Abciximab (antibody)	16, 18
PAR1 antagonists	Vorapaxar	18

Drugs for treatment of DM		**19**
Insulins		
Short-acting insulins	Human insulin, insulin lispro	19
Intermediate–/long-acting insulins	Insulin glargin, NPH insulin (neutral protamine Hagedorn)	19
Drugs for treatment of type 2 DM		
DPP4 inhibitors (gliptins)	Sitagliptin	19
GLP-1R agonists (incretin mimetics)	Liraglutide, exenatide	19
Potassium channel blockers (sulfonylureas)	Glibenclamide	2, 19
Biguanides	Metformin	12, 19
α-Glucosidase inhibitors	Acarbose	13, 19
PPAR-γ agonists (glitazones)	Pioglitazone	1, 19
SGLT-2 inhibitors (gliflozins)	Empagliflozin	19, 33

Drugs for treatment of hypoglycemia		
Glucose	Glucose p.o. or i.v. (in case of unconsciousness)	19
Emergency drug for life-threatening hypoglycemia	Glucagon i.m. (injection by instructed person or physician)	19

Drugs for treatment of osteoporosis		20
Vitamin D	Cholecalciferol	12, 20
Bisphosphonates	Alendronate, risedronate	20
SERMs	Raloxifene (NOT tamoxifen)	20, 24
Calcium salts	Calcium carbonate	12, 20
PTH analogues	Teriparatide	20
RANKL inhibitors	Denosumab (antibody)	20, 32

Drugs for treatment of thyroid gland diseases		21
Thyroid hormones	T4 (long acting, T3 prodrug), T3 (active, short-acting)	21
TPO inhibitors (thionamides)	Thiamazole, carbimazole (thiamazole prodrug)	21
Radiopharmaceuticals	^{131}Iodide (β radiation)	21
Iodide substitution in case of iodide deficiency	Potassium iodide (low dose, 100–200 µg/day)	21

Drugs for treatment of dyslipidemias		22
Anion exchange resins	Cholestyramine	4, 22
HMG-CoA reductase inhibitors (statins)	Simvastatin, atorvastatin, pravastatin	2, 12, 22
PPAR-α agonists (fibrates)	Fenofibrate	12, 22
Cholesterol absorption inhibitors	Ezetimibe	22
PCSK9 inhibitors	Evolocumab (antibody)	22

Drugs for treatment of gout		23
Uricostatics (XO inhibitors)	Allopurinol, febuxostat	23
Uricosurics	Benzbromarone (non-selective inhibitor), lesinurad (selective URAT-1 inhibitor)	12, 23
Microtubule inhibitors	Colchicine (low dose)	23, 32
IL-1 inhibitors	Canakinumab (antibody)	23

Sex hormones: Drugs for hormonal contraception and hormone replacement		**24**
AR agonists and antagonists and enzyme inhibitors		
AR agonists	Testosterone	24
AR antagonists	Cyproterone, flutamide	24, 32
5α-steroid reductase inhibitors	Finasteride	24
ER agonists, allosteric modulators and antagonists and enzyme inhibitors		
ER agonists	Ethinylestradiol (EE), estradiol, conjugated estrogens	13, 15, 24
SERMs	Raloxifene, tamoxifen	20, 24, 32
ER antagonists	Clomiphene	24
Aromatase inhibitors	Anastrozole	24, 32
PR agonists and antagonists		
PR agonists	Levonorgestrel, desogestrel	24
PR antagonists	Mifepristone (in combination with misoprostol (PGE derivative) for termination of pregnancy)	24

Neuron inhibitors with pleiotropic effects (NIPEs) and allosteric $GABA_AR$ modulators		**25**
NIPEs		
SCBs	Carbamazepine, phenytoin, valproic acid	2, 6, 10, 25, 28
T-type CCBs	Ethosuximide	25
P/Q-type CCBs	Gabapentin, pregabalin	10, 25, 28, 29
Inhibitors of glutamatergic neurotransmission (pleiotropic mechanisms)	Topiramate, lamotrigine, levetiracetam	10, 25, 28
Allosteric $GABA_AR$ modulators		
Barbiturates	Phenobarbital, thiopental	25, 27
Benzodiazepines	Long-acting: diazepam, clonazepam; intermediate-acting: oxazepam; short-acting: midazolam, triazolam	1, 10, 13, 25, 27
Z drugs	Zolpidem	25
Antidote for benzodiazepine and Z drug intoxication	***Flumazenil***	***4*, *25*, *27***
Emergency drug for status epilepticus	Diazepam (i.v., i.m., rectal)	25

Drugs used in anesthesia		**26, 27, 5, 10, 29**
Inhalation narcotics	N_2O (nitrous oxide), sevoflurane and desflurane (haloethers)	27
Injection narcotics	Thiopental, midazolam, ketamine, propofol	27
MOR agonists	Remifentanil (TIVA), fentanyl	10
High-potency D_2R-mGPCR antagonists	Droperidol (neuroleptanalgesia)	29
Local anesthetics (amide-type)	Lidocaine and articaine (short acting), bupivacaine (long acting)	26
Vasoconstrictor additive for local anesthesia	EPI (1:100,000 – 1:200,000)	5, 26
Hyperpolarizing muscle relaxants (nAChR antagonists)	Alcuronium, vecuronium	3, 5
Depolarizing muscle relaxants (nAChR agonists)	Suxamethonium (succinylcholine)	3, 5, 7
Drugs for sinus bradycardia and AV block	Atropine (M_xR antagonist)	5, 17
Antidote for treatment of malignant hyperthermia	***Dantrolene***	***4, 27***
Antidote for respiratory depression due to treatment with nAChR antagonists	***Neostigmine***	***5***

Drugs for treatment of depression and bipolar disorder		**28**
NE/5-HT enhancers		
NSMRIs	Amitriptyline, imipramine	4, 5, 6, 13, 28
SSRIs	Citalopram, sertraline	6, 28
SSNRIs	Venlafaxine	5, 6, 28
α_2AR antagonists	Mirtazapine	5, 28
MAOIs	Moclobemide, tranylcypromine	5, 6, 28
mGPCR antagonists (non-NSMRIs)	Trimipramine	4, 5, 6, 28, 29
Alkali metal ions	Lithium	12, 21, 28
NIPEs	Lamotrigine, carbamazepine, valproic acid	25, 28

mGPCR antagonists (drugs for treatment of various neuropsychiatric disorders including schizophrenia and acute mania)		**29**
D_2R-mGPCR antagonists		
Low-potency D_2R-mGPCR antagonists	Levomepromazine, promethazine, pipamperone, chlorprothixene	4, 8, 10, 13, 29
Mid-potency D_2R-mGPCR antagonists	Melperone	4, 8, 10, 13, 29
High-potency D_2R-mGPCR antagonists	Haloperidol, fluphenazine, benperidol, flupentixol	4, 8, 10, 13, 29, 30
Antidote for EPS caused by p-mGPCR antagonists	***Biperiden***	***5, 29***
p-mGPCR antagonists	Clozapine, risperidone, olanzapine, quetiapine	6, 7, 19, 22, 29

Drugs for treatment of AD		**30**
AChEIs	Donepezil, galantamine	2, 4, 30
Allosteric nAChR modulators	Galantamine	1, 30
NMDAR antagonists	Memantine	30

Drugs for treatment of eye diseases		**31**
Glaucoma		
CAH inhibitors	Brinzolamide	31
FPR agonists	Latanoprost	31
β_xAR antagonists	Timolol (for treatment of glaucoma, only β_2AR antagonism is of relevance)	5, 31
α_2AR agonists	Brimonidine	5, 31
M_xR agonists	Pilocarpine (narrow-angle glaucoma)	5, 31
Osmotic diuretics	Mannitol (acute glaucoma attack)	31
Exudative AMD		
VEGF inhibitors	Aflibercept (soluble VEGFR fragment), ranibizumab (antibody fragment), bevacizumab (antibody, off-label use)	31, 32
Mydriatics	Tropicamide (short acting), atropine (long acting)	5

Drugs for treatment of malignant tumor diseases		**32**
Classic cytostatics		
Alkylating agents	Cyclophosphamide, carmustine	2, 32
Antidote for cyclophosphamide-induced hemorrhagic cystitis	***2-mercaptoethane sulfonate sodium (MESNA)***	***4, 32***
Platinum agents	Cisplatin, carboplatin	12, 32
DNA intercalators	Doxorubicin (adriamycin), bleomycin	32
TOPO inhibitors	Irinotecan (TOPO-I), etoposide (TOPO-II)	32
Folate antagonists	MTX	11, 12, 32, 33
Antidote to rescue cells from toxic effects of MTX	***Folinic acid***	***4, 32***
Purine antagonists	6-MP	11, 23, 32
Pyrimidine antagonists	5-FU	32
Mitotic inhibitors	Vinblastine, paclitaxel	23, 32
Growth factors for treatment of ADRs resulting from classic cytostatics		
G-CSF	***Filgrastim (also for treatment of agranulocytosis induced by TPO inhibitors, metamizole and clozapine)***	***3, 4, 10, 21, 29, 32***
Keratinocyte-stimulating factor	***Palifermin***	***32***

Targeted therapeutics		
SERMs	Tamoxifen	24, 32
Aromatase inhibitors	Anastrozole	24, 32
Cytokines	IL-2	7, 32
EGF inhibitors	Trastuzumab (antibody)	32
VEGF inhibitors	Bevacizumab, ramucirumab (antibodies)	15, 18, 31, 32
CD20 inhibitors	Rituximab (antibody)	32
PD1 inhibitors	Pembrolizumab (antibody)	32
Tyrosine kinase inhibitors	Imatinib, erlotinib, sunitinib	32
Raf-V600E inhibitors	Vemurafenib	32
Immune modulators/angiogenesis inhibitors	Lenalidomide	15, 18, 32
Differentiation and apoptosis inducers used for treatment of acute myeloid leukemia	All-trans retinoic acid (ATRA), arsenic trioxide (ATO)	32
PARP inhibitors	Olaparib	32
Proteasome inhibitors	Carfilzomib	32
HDC inhibitors	Panobinostat	32
CDK inhibitors	Palbociclib	32

Antibacterial chemotherapeutics (antibiotics)		**33**
Penicillins		
Benzylpenicillins	Penicillin G (i.v.)	3, 33
Oral penicillins	Penicillin V (p.o.)	33
Isoxazolyl penicillins	Flucloxacillin (p.o.)	33
Aminopenicillins	Amoxicillin (p.o.)	13, 33
Acylaminopenicillins	Piperacillin (i.v.)	33
Penicillin + lactamase inhibitor	Amoxicillin + clavulanic acid (p.o.), Piperacillin + tazobactam (i.v.)	33
Cephalosporins		
First-generation cephalosporins	Cefaclor (p.o.), cefazolin (i.v.)	33
Second-generation cephalosporins	Cefuroxime axetil (p.o.), cefuroxime (i.v.)	33
Third-generation cephalosporins	Ceftriaxone (i.v.)	33
Third-generation cephalosporins active against *Pseudomonas aeruginosa*	Ceftazidime (i.v.)	33
Other classes of antibiotics		
Carbapenems	Meropenem (i.v.)	33
Dihydrofolate reductase inhibitors	TMP (p.o.)	33
Quinolones	Ciprofloxacin, moxifloxacin, levofloxacin (p.o.)	13, 33
Epoxide antibiotics	Fosfomycin (p.o.)	

Macrolide antibiotics	Erythromycin, clarithromycin, azithromycin (p.o.)	2, 15, 33
Lincosamides	Clindamycin (p.o. und i.v.)	33
Tetracyclines	Doxycycline (p.o.)	2, 33
Aminoglycosides	Gentamicin, tobramycin (i.v.)	12, 33
Glycopeptide antibiotics	Vancomycin (i.v.)	12, 33
Nitroimidazoles	Metronidazole (p.o.)	13, 33
Nitrofurans	Nitrofurantoin (p.o.)	33
Antibiotics for treatment of MRSA infections	Tigecycline (p.o.), daptomycin (i.v.)	33
Anti-TB drugs		
First-line drugs	INH, RMP, PZA, EMB	33
Drugs of last resort	Streptomycin (SM), bedaquiline, cycloserine, prothionamide, para-aminosalicylic acid (PAS)	33

Antiviral chemotherapeutics (Virustatics)		**34**
HSV, VZV, HCMV		
DNA polymerase inhibitors	Aciclovir (HSV, VZV), ganciclovir (HCMV)	12, 34
HCV		
RNA polymerase inhibitors	Ribavirin	34
NS5A inhibitors	Ledipasvir	34
NS5B inhibitors	Dasabuvir, Sofosbuvir	34
Protease inhibitors (PIs)	Simeprevir	34
Interferons (IFNs)	Peginterferon α-2a	2, 34
HIV		
Entry inhibitors (allosteric CCR5 coreceptor antagonists)	Maraviroc (MVC)	1, 34
NRTIs	Tenofovir, abacavir	3, 34
NNRTIs	Efavirenz (EFV), nevirapine (NVP)	34
Integrase inhibitors (INIs)	Raltegravir (RAL), elvitegravir (EVG)	34
Protease inhibitors (PIs)	Atazanavir (ATV), darunavir (DRV), ritonavir (RTV)	2, 19, 22, 34
Fusion inhibitors (FIs)	Enfuvirtide (ENF)	34

Antimycotics		**35**
Polyene antimycotics	Nystatin, amphotericin B	12, 35
Azole antimycotics	Fluconazole, itraconazole, clotrimazole	2, 17, 35
Echinocandins	Caspofungin	35
Sulfonamide + dihydrofolate reductase inhibitors	Cotrimoxazole (TMP + sulfamethoxazole) for treatment of *Pneumocystis jirovecii* infections	33, 34, 35
Pyrimidine antagonists	Flucytosine	35

The drugs listed in this table are ordered according to the chapters in which they are discussed. Additional references to other relevant chapters are given in the last column. Some drug classes are listed several times because they are relevant for various chapters. The table uses a stringent mechanism-oriented nomenclature and, as far as possible, abstains from using traditional terms that are problematic (see abbreviation list and ▶ Chap. 1). In some cases, particularly antibiotics but also certain other drugs, they are classified according to their chemical class rather than their mechanism of action. Some antibiotics are classified according to their target bacteria. The table contains all the drugs listed in the "100 List" discussed in ▶ Chap. 37 and selected other drugs from various drug classes. Please note that this table does not intend to be comprehensive. The selected drugs are widely used in many but not all countries. Antidotes for specific drugs are highlighted in bold italics.

This table does not list certain commonly used drugs because of questionable clinical efficacy and/or high toxicity (very small therapeutic index). Among these non-considered drugs are Na^+/K^+-ATPase inhibitors ("cardiac glycosides," CHF, AF), reserpine (hypertension), class Ia and Ib antiarrhythmics, the COX inhibitor indomethacin, the ergot alkaloid ergotamine (acute migraine attack), PDE3 inhibitors (acute heart failure), nicotinic acid (dyslipidemia), orlistat (obesity), misoprostol (prevention of PUD caused by concomitant therapy with COX inhibitors), and the neuraminidase inhibitor oseltamivir (prophylaxis of influenza).

Furthermore, the table does not discuss all newly introduced drugs for treatment of autoimmunopathies and prevention or transplant rejection and targeted therapeutics for therapy of malignant tumors. Rather, the table provides examples of mechanistically distinct drugs. Furthermore, the table cannot cover all the recently approved orphan drugs for the treatment of rare diseases. However, some examples of orphan drugs have been considered.

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