

Efficacy and safety comparison between silodosin and tamsulosin as medical expulsive therapy for distal ureteral stones

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ABSTRACT

BACKGROUND Ureteral stones are a common urological condition causing significant discomfort and morbidity. Medical expulsive therapy (MET) is a noninvasive approach to facilitate the passage of stones. This study aimed to compare the efficacy and safety of silodosin and tamsulosin as MET in patients with distal ureteral stones (DUS).

METHODS We searched CINAHL, Cochrane Library, PubMed, and ScienceDirect for randomized controlled trials (RCTs) on the administration of silodosin and tamsulosin for DUS. The primary outcomes analyzed were stone expulsion rates and expulsion times, measured as risk ratio (RR) and mean difference (MD), respectively. Statistical analyses were performed using Review Manager 5.4 and STATA 17.

RESULTS 14 RCTs comprising 1,535 patients (770 received silodosin) met the inclusion criteria. The silodosin group had notably higher stone expulsion rates (RR 1.20, 95% confidence interval [CI] 1.13–1.27, $p < 0.00001$, $I^2 = 37\%$), shorter expulsion times (MD -2.98 , 95% CI -4.35 – -1.62 , $p < 0.01$, $I^2 = 85\%$), and fewer colicky pain episodes (MD -0.35 , 95% CI -0.59 – -0.10 , $p < 0.01$, $I^2 = 83\%$) than the tamsulosin group. Retrograde ejaculation was the only adverse event that had a significant difference between both groups, statistically favoring tamsulosin (RR 1.61, 95% CI 1.12–2.33, $p = 0.01$, $I^2 = 0\%$).

CONCLUSIONS Silodosin should be preferred as the first-line MET agent for DUS owing to its better expulsion rate, shorter stone expulsion time, and fewer colicky pain episodes. However, tamsulosin may be used in selected cases where patients experience retrograde ejaculation after receiving silodosin.

KEYWORDS silodosin, tamsulosin, ureterolithiasis

Urolithiasis, a common urological condition, has been steadily increasing globally over recent decades, with prevalence rates ranging from 5–19.1% in Asian countries.¹ While predominantly affecting men at a 2:1 ratio, urolithiasis is increasingly observed among women.^{2,3} A high incidence rate is observed among individuals aged 30–50 years.⁴ The treatment for ureteral stones should be tailored according to the patient's symptoms and associated complications. This includes conservative measures, such as monitoring

for spontaneous stone passage, medications (medical expulsive therapy [MET]), lithotripsy using extracorporeal shock wave modality, as well as invasive procedures, such as ureteroscopic lithotripsy and open/laparoscopic ureterolithotomy.⁵

The size, shape, and location of the stone in the ureter affect the success rate of spontaneous stone passage.⁶ Several studies have documented an acceptably high likelihood of spontaneous stone expulsion ranging from 71–98% when the stone size

is <5 mm. However, for sizes between 5–10 mm, the rate of spontaneous passage was considerably lower, ranging from 25–53% in reported cases.⁷ MET, a cost-effective and conservative approach for treating small distal ureteral stones (DUS) in specific patients, can be performed in outpatient clinics, potentially minimizing the need for surgery. Campschroer et al⁸ discovered that MET was more effective for larger stones (>5 mm) than for smaller stones (<5 mm). The 2022 European Association of Urology guidelines stated that MET can involve various drug classes, including adrenergic alpha-antagonists, phosphodiesterase type 5 (PDE5) inhibitors, and calcium channel blockers. Currently, adrenergic alpha-antagonists are the sole recommended monotherapy as they effectively increase the stone expulsion rate in DUS >5 mm (level of evidence 1a).⁹ Compared to a placebo, these drugs exhibit a greater stone expulsion rate and reduce the duration required for spontaneous passage.⁹

Adrenergic alpha-antagonists are predominantly used in MET treatment; among these drugs, tamsulosin has been extensively studied and the most commonly used drug for several years. It is a selective adrenergic alpha-antagonist with equal affinity to both α -1A and α -1D receptors, enhancing the stone expulsion rate and reducing the expulsion time.¹⁰ Multiple studies have associated silodosin as a highly selective alpha-1 adrenergic receptor antagonists (α 1-AR antagonist),

compared to tamsulosin, to further enhance stone expulsion in patients with DUS.¹¹ The choice of drugs used in the MET has sparked debate because of conflicting results among studies. Although adrenergic alpha-antagonists are preferred for MET, discussions on drugs that yield significant results remain unclear. Therefore, this study aimed to compare the efficacy and safety of tamsulosin and silodosin as MET in patients with DUS.

METHODS

Extensive research was conducted across electronic medical databases, including the CINAHL, Cochrane Library, PubMed, and ScienceDirect, in September 2022. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (Figure 1) using medical subject heading terms, such as “distal ureteral stone,” “silodosin,” AND “tamsulosin.” All authors were involved in the search and selection of the studies. The protocol for this review was registered in the PROSPERO (CRD42022350797).

Eligibility criteria

This study included all English-written, accessible, randomized controlled trials (RCTs). It assessed patients with DUS treated with silodosin and

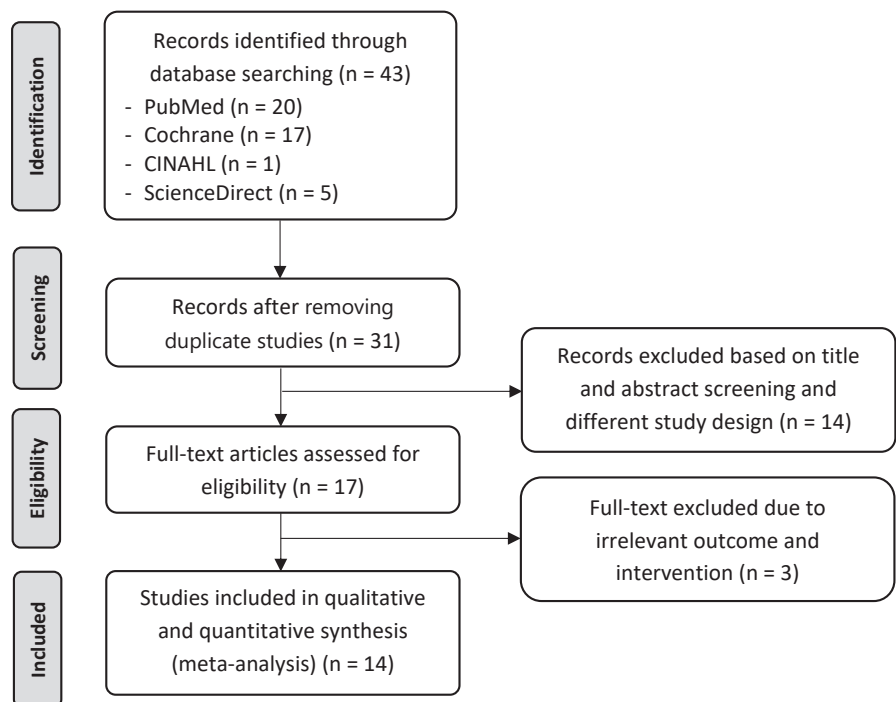


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Antony 2017	+	+	+	?	?	+	-
AS 2016	?	?	?	+	?	+	-
Dell'Atti 2015	+	+	?	+	?	+	+
Egalaly 2016	+	+	?	+	+	+	+
Georgescu 2015	+	+	?	+	+	+	+
Gharib 2018	?	?	?	+	+	+	?
Gupta 2013	+	+	?	+	+	+	+
Gur 2021	?	?	?	+	+	+	?
Kumar 2015	+	+	+	+	+	+	+
Priyanka 2017	+	+	?	+	+	+	-
Rahman 2017	+	+	?	+	+	+	+
Reddy 2016	?	?	?	+	?	+	?
Sharma 2016	?	+	?	-	+	+	-
Soliman 2021	+	+	+	+	+	+	+

Figure 2. Summary of study quality assessment using Cochrane risk-of-bias tool

tamsulosin and was published within the last decade. The exclusion criteria were unavailable full-texts, non-prospective studies, and irrelevant results. The observed results aimed to include at least one of the following aspects: stone expulsion rate, stone expulsion time, colicky pain episodes, and adverse events experienced by the patients. The stone expulsion rate was defined as the passage of the stone through the external urethral sphincter and quantified as the risk ratio (RR). Stone expulsion time

was determined from the initial drug administration until the stone expulsion event occurred. Stone expulsion time and colicky pain episodes were quantified as the mean difference (MD) because both were categorized as continuous data. All adverse events were quantified as RR.

Data collection and statistical analysis

Studies were incorporated following the eligibility criteria and assessed for possible duplication using the EndNote software (Clarivate Analytics, USA). The included studies were assessed qualitatively using the Cochrane risk-of-bias tool (Figure 2). Study heterogeneity was assessed using the I² test, considering the heterogeneity of >50% as significant. Therefore, a random effects model was used in the analysis. A fixed effects model was used when the heterogeneity was insignificant. Analyses were performed using Review Manager 5.4 (Cochrane Collaboration, UK) and STATA 17 (StataCorp, USA) software.

RESULTS

Table 1 lists 14 RCTs involving 1,535 patients (770 patients who received silodosin) who met the inclusion criteria.

Stone expulsion rate

A fixed effects analysis model was preferred because of insignificant heterogeneity in both groups (I² = 37%). Analysis in Figure 3 demonstrated a significant stone expulsion rate, where the silodosin group was considered more than the tamsulosin group (RR 1.20, 95% confidence interval [CI]: 1.13–1.27, and p<0.00001).

Stone expulsion time and pain episodes

Three studies comprising 940 patients were divided into silodosin (n = 522) and tamsulosin (n = 418) groups to assess the stone expulsion time (Figure 4a). Combined analysis demonstrated that the stone expulsion time was shorter in the silodosin group (MD -2.98, 95% CI: -4.35--1.62, and p<0.0001) than in the tamsulosin group. Based on the random effects model (I² = 83%), the silodosin group experienced significantly fewer pain episodes than the tamsulosin group (MD -0.35, 95% CI -0.59--0.10, and p = 0.005) (Figure 4b).

Table 1. Summary of the studies

First author, year	Country	Design	Stone size (mm), mean (SD)		Intervention dose (mg/day)		Co-medication	Follow-up period (weeks)
			Silodosin	Tamsulosin	Silodosin	Tamsulosin		
AS, ¹² 2016	India	RCT	7.0 (1.5)	7.0 (2.0)	8	0.4	Diclofenac 50–100 mg	4
Antony, ¹³ 2017	India	RCT	NA	NA	8	0.4	NA	2
Dell'Atti, ¹⁴ 2015	Italy	RCT	5.82 (1.66)	5.37 (1.33)	8	0.4	Diclofenac 100 mg/ paracetamol 1,000 mg/tramadol 100 mg	3
Elgalaly, ¹¹ 2016	Egypt	RCT	5.4 (1.5)	5.6 (1.2)	8	0.4	Diclofenac 50 mg	4
Georgescu, ¹⁵ 2015	Romania	RCT	5.32 (2.09)	5.08 (2.09)	8	0.4	Diclofenac 50 mg	4
Gharib, ¹⁶ 2018	Egypt	RCT	7.47 (1.41)	7.54 (4.3)	8	0.4	Diclofenac 75 mg	4
Gupta, ¹⁷ 2013	India	RCT	6.6 (1.8)	7.0 (2.3)	8	0.4	Diclofenac 100 mg	4
Gur, ¹⁸ 2021	Turkey	RCT	NA	NA	8	0.4	Metamizole 1 mg	4
Kumar, ¹⁹ 2015	India	RCT	7.50 (1.30)	7.44 (1.20)	8	0.4	Diclofenac 50 mg	4
Priyanka, ²⁰ 2017	India	RCT	NA	NA	8	0.4	Diclofenac 50–100 mg	4
Rahman, ²¹ 2017	India	RCT	7.4 (1.30)	7.5 (1.20)	8	0.4	Diclofenac 50 mg	4
Reddy, ²² 2016	India	RCT	NA	NA	8	0.4	Diclofenac 75 mg	4
Sharma, ²³ 2016	India	RCT	NA	NA	8	0.4	Diclofenac (dose NA)	4
Soliman, ²⁴ 2021	Egypt	RCT	6.2 (1.2)	6.3 (0.9)	4	0.4	Ibuprofen 4–10 mg	4

NA=not available; RCT=randomized controlled trial; SD=standard deviation

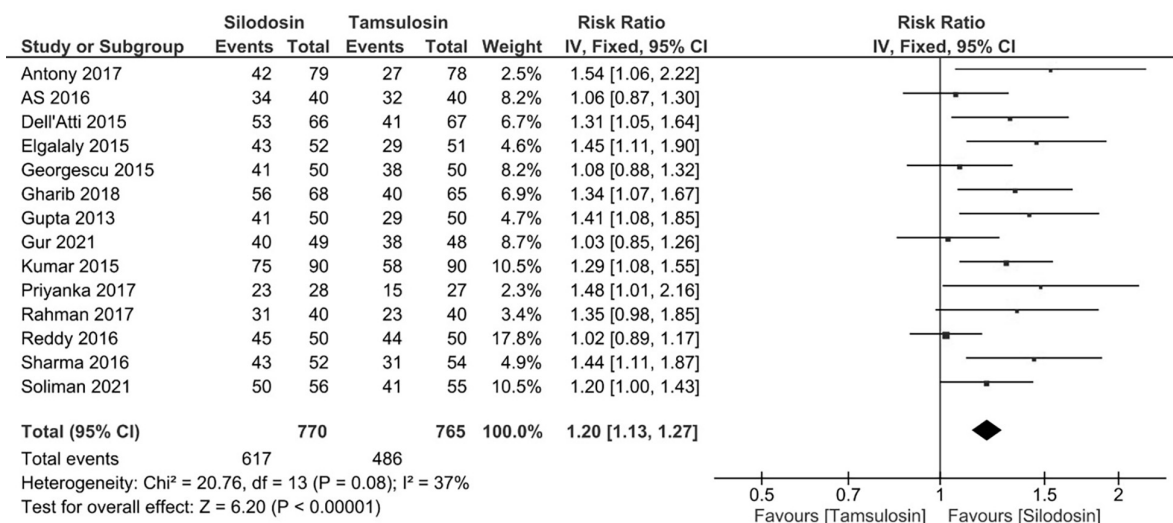


Figure 3. Forest plot of silodosin and tamsulosin effects on stone expulsion rate. CI=confidence interval

Adverse events

The most commonly reported adverse events were retrograde ejaculation, postural hypotension, dizziness, and headaches (Figure 5). However, only retrograde ejaculation was shown significantly different across the groups. The combined analysis revealed a reduced risk of retrograde ejaculation (RR 1.61, 95% CI: 1.12–2.33, p = 0.01, and I² = 0%) in the tamsulosin group.

DISCUSSION

In this study, silodosin was associated with an increased stone expulsion rate and a reduced stone expulsion time in patients with DUS. Additionally, patients in the silodosin group experienced a significantly reduced colicky pain episode. Patients in both groups experienced similar incidences of adverse events (postural hypotension, dizziness, and

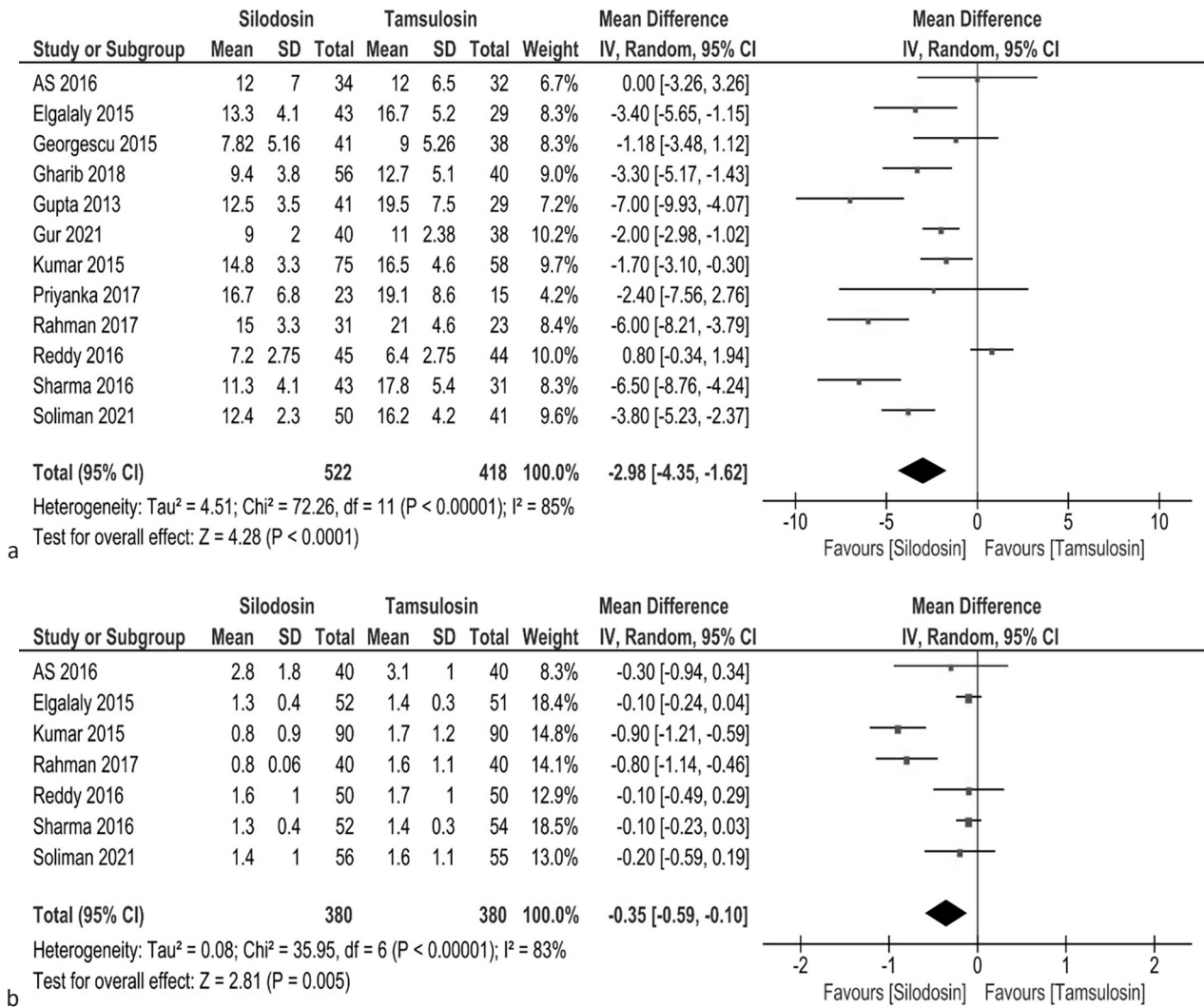


Figure 4. Forest plot of silodosin and tamsulosin effects on stone expulsion time (a) and pain episodes (b). CI=confidence interval; SD=standard deviation

headache). However, the incidence of retrograde ejaculation was considerably higher in the silodosin group.¹¹⁻²⁴

Alpha-adrenergic receptors are observed throughout the human ureter, predominantly in the distal ureter.²⁵ Stimulation of these receptors increases the force of contraction of the ureter and the ureteral peristaltic frequency. The human ureter comprises three alpha-1 receptor subtypes (α1A, α1B, and α1D). The alpha-1D-adrenergic receptor (α1D-AR) is predominantly observed throughout the ureter. In the distal ureter, alpha-1A-adrenergic receptors (α1A-AR) concentration is higher than that of alpha-1B-adrenergic receptors (α1B-AR).²⁵ Because α1A-AR antagonists are selective for the detrusor and distal ureter, they have been used to facilitate stone expulsion and pain alleviation through various mechanisms, such as

reducing ureteral spasms, decreasing the frequency of peristaltic contraction, elevating proximal pressure to the stone, and relaxing the ureteral section around the stone. In conjunction with the fluid bolus volume supplied through the ureter, α1-AR antagonists may facilitate stone passage.²⁶

Tamsulosin and silodosin are the widely assessed α1-AR antagonists used for ureteral stone treatment. Tamsulosin exhibits a 10-fold higher affinity for inhibiting α1A-AR and α1D-AR than for inhibiting α1B-AR. In contrast, silodosin is highly selective in inhibiting α1A-AR, demonstrating the highest uroselectivity, which exhibits a 162-fold greater affinity for α1A-AR over α1B-AR and an approximately 50-fold higher affinity for α1A-AR than for α1D-AR.²⁷ Based on these results, this study revealed a higher increase in stone expulsion rate and a shorter mean stone expulsion time

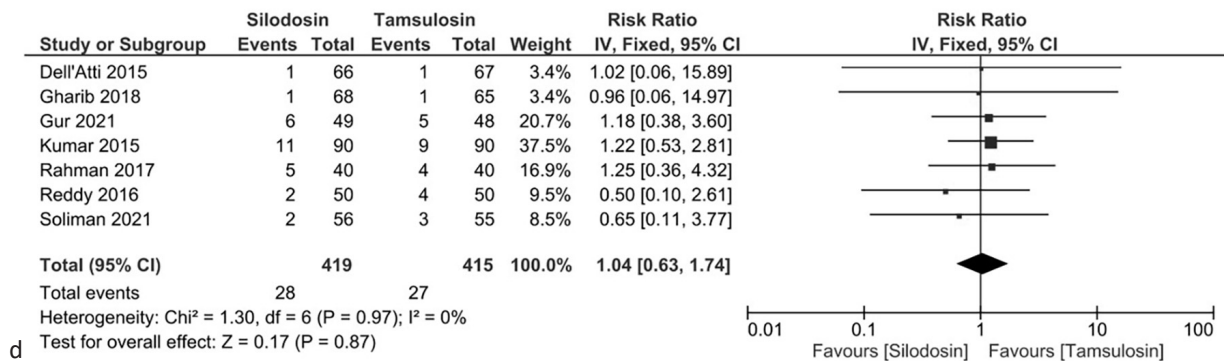
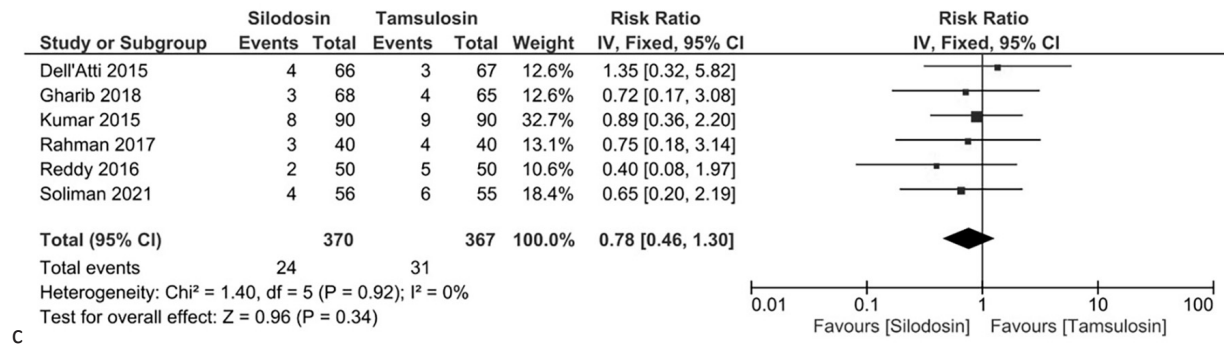
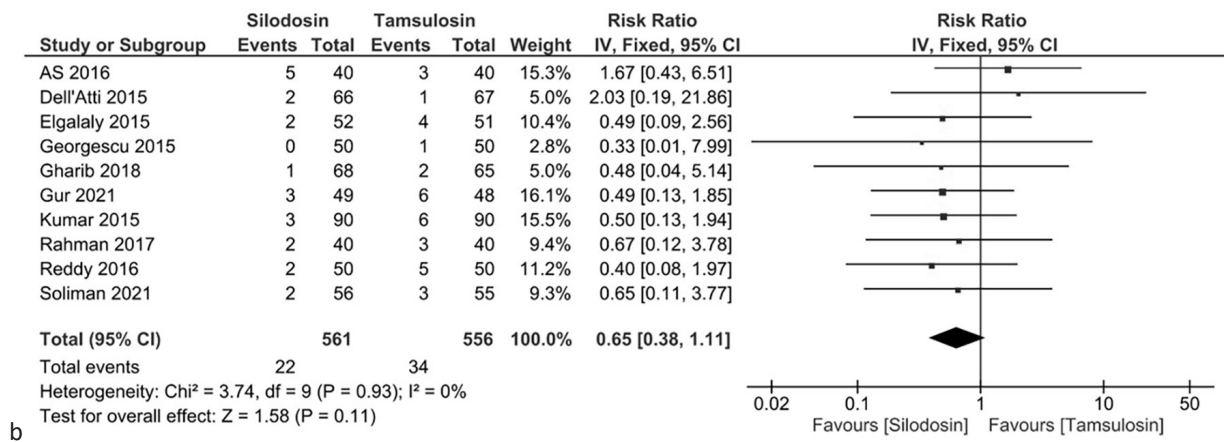
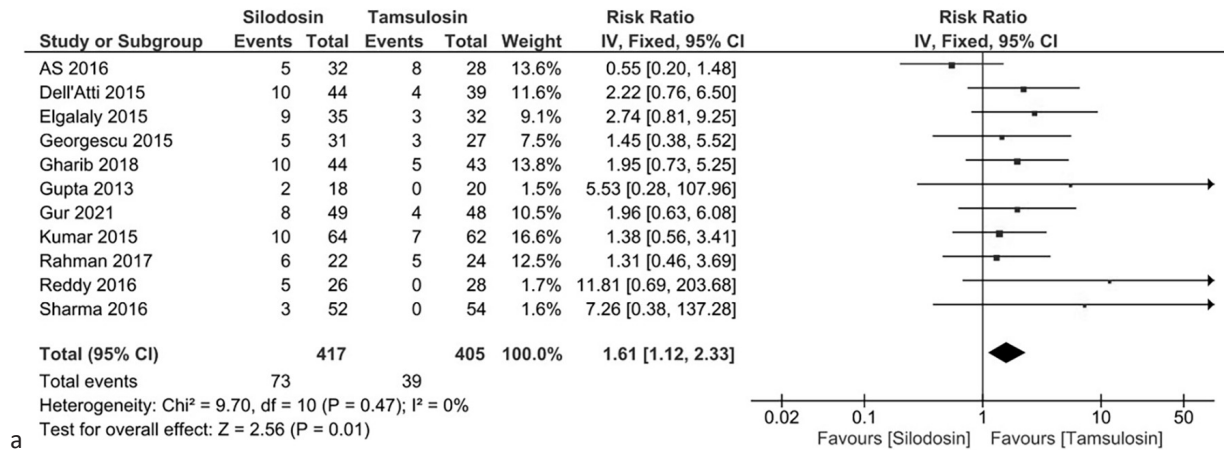


Figure 5. Forest plot of silodosin and tamsulosin effects on retrograde ejaculation (a), postural hypotension (b), dizziness (c), and headache (d) as adverse events. CI=confidence interval

in the silodosin group. Furthermore, a highly selective α 1A-AR blocker is associated with fewer cardiovascular side effects than a nonselective blocker.²⁸

Colicky pain may cause discomfort in patients with ureteral stones due to increased intra-ureteral pressure at the site of stone obstruction.²⁸ The use of alpha-blockers for ureteral stone expulsion may reduce colicky pain episodes through three mechanisms: (1) facilitating stone expulsion by reducing the frequency and extent of peristaltic contractions; (2) reducing intra-ureteral pressure associated with ureteral obstruction; and (3) inhibiting pain-mediating C fibers. However, the dominant mechanism underlying pain reduction remains unknown. During therapy, the silodosin group exhibited a reduced analgesic demand compared to the average dosage used.^{11,16,19} Kumar et al¹⁹ reported results confirming a significant pain-relieving effect of the silodosin group, evident in their reduced frequency of pain episodes. These findings may be associated with the higher uroselectivity of silodosin than that of tamsulosin.

Patients using either silodosin or tamsulosin for ureteral stones experienced similar adverse effects, including orthostatic hypotension, dizziness, headache, and retrograde ejaculation. Although the occurrences of orthostatic hypotension, dizziness, and headache were identical in both groups, retrograde ejaculation was markedly increased in the silodosin group. The predominant alpha-1 subtype observed in large vascularization is α 1B-AR, which is crucial for blood vessel contraction and blood pressure regulation.¹² Both silodosin and tamsulosin inhibit this receptor, resulting in blood vessel dilation, increased postural hypotension, headache, and dizziness.

Retrograde ejaculation is directly associated with smooth muscle relaxation induced by α 1-AR antagonists. Smooth muscle relaxation in the lower urinary and genital tracts may result in the entrance of semen into the bladder during ejaculation instead of flowing along the urethra.¹⁹ Although retrograde ejaculation is a significant adverse event correlated with α 1-AR antagonists, it should also be considered an indicator of medication efficacy rather than an adverse event. Gupta et al¹⁷ indicated that patients who experienced significant relief from lower urinary tract symptoms had a greater chance of experiencing retrograde ejaculation. Therefore, retrograde ejaculation can indirectly indicate whether a specific drug effectively affects smooth muscle relaxation.

This study had a few limitations. Owing to the limited availability of articles, studies from regions outside Europe, Asia, and Africa were excluded, potentially affecting the external validity of this study. Furthermore, none of the reviewed studies assessed the comparative efficacy between male and female patients. In contrast, variations in urethral length may affect the time required for complete stone expulsion. Further studies involving broader demographic groups are required to comprehensively understand the efficacy of these drugs as MET agents.

In conclusion, silodosin is indicated as the primary MET agent used in patients with DUS. Tamsulosin is a viable alternative when silodosin is unavailable or when the patient experiences difficulty with retrograde ejaculation, which occasionally occurs following the initiation of silodosin therapy.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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