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META-ANALYSIS

Promising selective alpha-1 blocker silodosin as a new therapeutic strategy for premature ejaculation and analysis of its drug adverse effect: A systematic review and meta-analysis of randomized controlled trials

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Summary ***Introduction and objectives: Premature Ejaculation (PE) occurs in 31% of men aged 18-59 years, leading to disappointment and avoidance of sexual relations. The current guideline of treatment for PE is Dapoxetine, which possesses several adverse effects causing the limitation of its long-term use. Silodosin, an alpha-1 blocker, has been proposed as a new option for treating PE due to its minimal side effects. Therefore, our study aims to assess the efficacy of silodosin in treating PE.***

Materials and methods: This systematic review and meta-analysis was in accordance with Cochrane Handbook guidelines. Comprehensive literature search was conducted in several databases including PubMed, ScienceDirect, and Cochrane Central Register of Controlled Trials. The studies were included if they met the following criteria: (1) Involving premature ejaculation patients; (2) Intervention using silodosin; (3) Comparing placebo or other therapies for PE (4) Outcome includes the Intravaginal Ejaculation Latency Time (IELT) and reported adverse events related to the therapy. Study quality was assessed using Cochrane risk-of-bias criteria. Statistical analysis in this study was performed using Review Manager 5.4

Results: A total of four studies were included in this meta-analysis. Our study showed that patients who received silodosin had a significantly longer IELT compared to control (MD: 132.54, 95% CI 51.51-213.57, p < 0.001). However, patient treated with silodosin also possessed significantly higher risk of adverse event for developing reduced semen ejaculation (OR 10.79, 95% CI 3.46-33.67, p < 0.0001).

Conclusions: Silodosin significantly increased IELT. However, it also reduced semen ejaculation as its drug adverse effect. This result supports the clinical use of silodosin as an alternative treatment for premature ejaculation.

KEY WORDS: Silodosin; Premature ejaculation; Alpha blocker; Retrograde ejaculation.

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INTRODUCTION

Ejaculation involves complex physiological processes. Premature ejaculation (PE) is defined as inability to delay ejaculation upon vaginal penetration and classified into lifelong and acquired PE (1, 2). PE affects about 31% of men aged 18-59, causing psychological effects such as disappointment, hopelessness, and avoidance of sexual relations (3).

PE treatment usually involves multimodal therapy, including behavioral, psychological, and pharmacological approaches. SSRIs including dapoxetine and paroxetine are the gold standard, but their long-term use is limited due to several adverse effects, including psychiatric and neurological complications (4, 5). Silodosin, an alpha-1 blocker, offers a new option for treating PE with minimal side effects (6). Alpha-1 blockers, as primary treatment for benign prostatic hyperplasia, are also linked to PE treatment. Recent studies show they suppress seminal emission by inhibiting smooth muscle contraction, potentially delaying ejaculation (7).

Limited research exists on silodosin's effectiveness in treating PE. Investigating silodosin as an alternative treatment for PE is crucial. Hence, we aim to assess its efficacy in treating PE.

METHODS

Literature search

On December 23, 2023, four reviewers (M.A., M.F., I.F., I.A) conducted a literature study using *PubMed*, *ScienceDirect*, and *Cochrane Library*, including additional valid studies and screening reference lists for relevant research outside of the databases if they met the criteria.

Eligibility criteria

The search was performed using keywords '(Silodosin) AND (Premature Ejaculation)'. Followed the PICO criteria: (1) populations with premature ejaculation; (2) silodosin therapy; (3) comparison with placebo or other therapies; (4) outcomes including *Intravaginal Ejaculation Latency Time* (IELT) and therapy-related adverse events; (5) randomized controlled studies; (6) published in English.

Selection process
Duplicate studies were excluded after the initial search. Four independent reviewers screened titles and abstracts for eligibility, including studies that met criteria and excluding those that didn't.
Conflicts were resolved through discussion. The screening results follow *Preferred Reporting Items for Systematic Review and Meta-Analyses* (PRISMA) guidelines.

Data collection
Each author independently extracted data, which was then cross-examined by others. Discrepancies were resolved through discussion. Authors were contacted for unclear information; non-responsive studies were withdrawn with reviewer consent. Collected data include author, year, location, design, population, sample size, mean age, intervention, control, outcomes, and adverse events.

Quality assessment
Study quality was assessed using the Cochrane risk-of-bias tool with Review Manager 5.4, classifying each point as low, high, or unclear risk.

Statistical analysis
Data were processed using Review Manager 5.4. Two meta-analyses assessed the effect and odds of silodosin *versus* placebo or other therapies. The first analysed mean differences in IELT scores, and the second analysed adverse event odds ratios, both with 95% CIs. Heterogeneity was assessed by I^2 value; a fixed-effects model was used if $I^2 < 50\%$, and a random-effects model if $I^2 \geq 50\%$. Results are shown in a Forest plot, with significance at $p < 0.05$. A funnel plot was used to evaluate publication bias. Asymmetrical distribution indicates high bias, while symmetrical distribution indicates low bias.

Results

Literature search and screening results
Using keywords, 108 studies were identified from databases, plus 5 studies outside the databases, totaling 113. After removing 22 duplicates, two reviewers screened 91 titles and abstracts, excluding 86 that didn't meet criteria. Four studies met the criteria for analysis. Full search and filter details are in Figure 1.

Characteristics of eligible studies
The four included RCTs were conducted in three countries, with a total of 358 PE patients. Most studies diagnosed PE using DSM-IV-TR and ISSM criteria. All studies administered 4 mg of silodosin 1-3 hours before intercourse. Controls included placebo (*Hodeeb et al., Bhat et al.*), Naftopidil 25 mg (*Sato et al.*), and other alpha blockers (*Akin et al.*). Outcomes measured included IELT in all studies, CGIC in three (*Sato, Bhat, Akin et al.*), PE Profile in two (*Sato, Bhat et al.*), and QOL index in one (*Akin et al.*). The most common side effect was reduced semen ejaculation. Full study characteristics are in Table 1.

Quality assessment result
The risk of bias assessment using Review Manager 5.4 showed that all studies generally had a low risk of bias (Figure 2). However, blinding bias was high in some studies due to the lack of double-blind procedures.

Figure 1.
Flow diagram of literature search and selection based on Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).

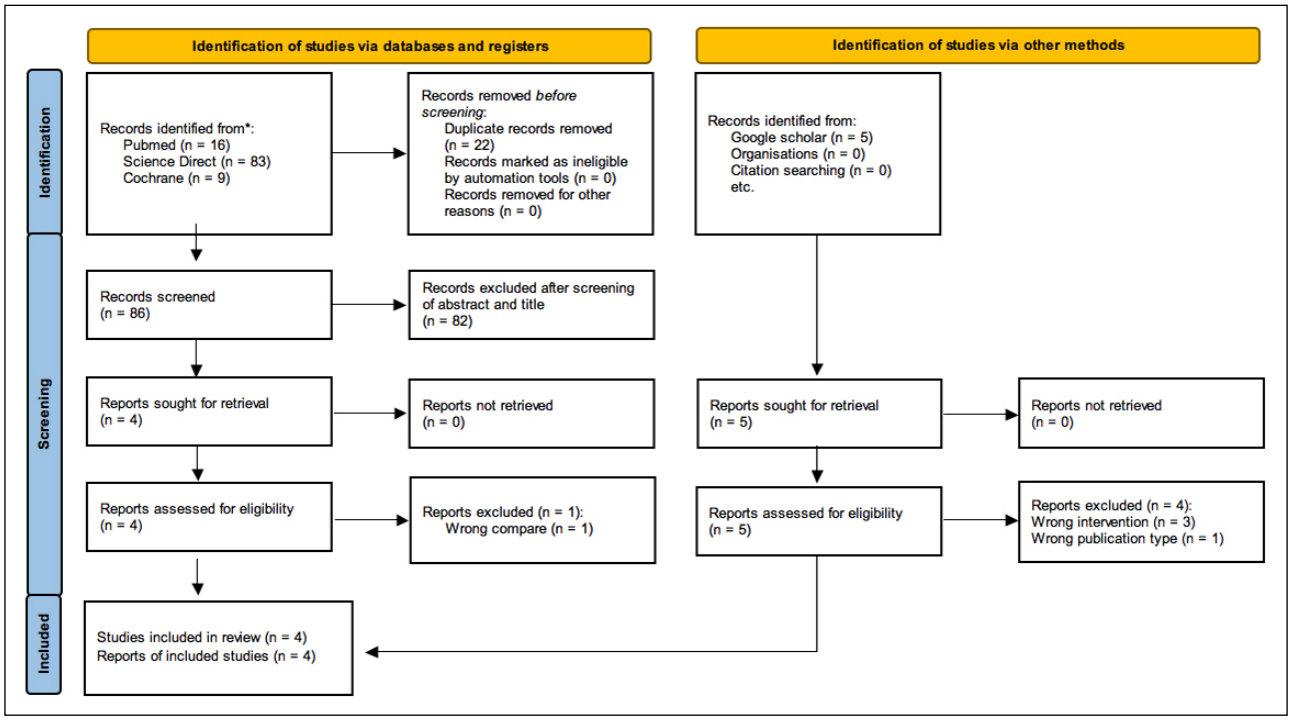


Table 1.
Collection data of included studies.

No	Author (year)	Country	Study design	Population	Mean Age (years) Silodosin	Mean Age (years) Control	Total samples (silodosin vs control)	Intervention	Control Type	Outcome Assesment	Adverse Event Reported
1	*Hodeeb et al.* (2019)	Egypt	db-RCT	PE patient diagnosed with DSM IV-TR criteria	29.39 ± 7.6	30.91 ± 7.5	160 (80 *vs* 80)	Silodosin 4 mg (2 hours before intercourse)	Placebo (2 hours before intercourse)	1. IELT 2. PE Profile	Reduced semen volume
2	*Sato et al.* (2016)	USA	RCT	PE patient	-	-	26	Silodosin 4 mg (1 hours before intercourse)	Naftopidil 25 mg (1 hours before intercourse)	1. IELT 2. CGIC 3. PE Profile	Reduced semen volum
3	*Bhat et al.* (2016)	China	RCT	Diagnosed PE patient reported unsatisfied with 'on demand' dapoxetine	32.6 ± 3.53	28.7 ± 3.14	64 (31 *vs* 33)	Silodosin 4 mg (3 hours before intercourse)	Placebo (3 hours before intercourse)	1. IELT 2. CGIC 3. PE Profile	1. Reduced semen volume 2. Uncomfortably delayed ejaculation 3. Dizziness
4.	*Akin et al.* (2013)	USA	RCT	PE patient diagnosed with DSM IV-TR criteria	49.4 ± 11.8	1. 43.3 ± 8.9 2. 46 ± 8.6 3. 44.5 ± 9.1 4. 45.7 ± 9.4	108 (21 *vs* 23 *vs* 22 *vs* 21 *vs* 21)	Silodosin 4mg (2-3 hours before intercourse)	1. Tamsulosin 0.4 mg 2. Alfuzosin 10 mg 3. Terazosin 5 mg 4. Doksazosin 4 mg (2-3 hours before intercourse)	1. IELT 2. CGIC 3. QoL Index	Reduced semen volume

db-RCT: Double Blind-Randomized Controlled Study; PE: Premature Ejaculation; DSM IV-TR: Diagnostic and Statistical Manual of Mental Disorders IV-Text Revision; ISSM: International Society of Sexual Medicine; IELT: Intravaginal Ejaculation Latency Time; CGIC: Clinical Global Impression of Change; QoL: Quality of Life.

Figure 2.
Risk of bias assessment using the Cochrane risk-of-bias tool for randomized trials.

Statistical analysis (Meta-Analysis)

Efficacy of Silodosin on IELT scores

Meta-analysis of four RCTs found that silodosin recipients had significantly longer IELT than controls (MD: 132.54, 95% CI 51.51-213.57, $p < 0.001$). Heterogeneity exceeded 50% ($p < 0.00001$, $I^2 = 98\%$), so the random-effects model was applied (Figure 3).

Silodosin reported adverse event analysis

All studies reported reduced semen ejaculation as an adverse event post-silodosin. Figure 4 displays the pooled effect size.

The Forest plot indicated heterogeneity below 50% ($p = 0.12$, $I^2 = 41\%$), favoring the fixed-effects model. Silodosin treatment significantly increased the risk of reduced semen ejaculation (OR 10.79, 95% CI 3.46-33.67, $p < 0.0001$).

Funnel Plot analysis

The funnel plot in Figures 5A and 5B shows the symmetrical shape of the study distribution, indicating a low risk of publication bias in this meta-analysis.

Figure 3.
Forest plot analysis of the silodosin effect in Intravaginal Ejaculation Latency Time (IELT).
M-H: Mantel–Haenszel, CI: Confidence interval.

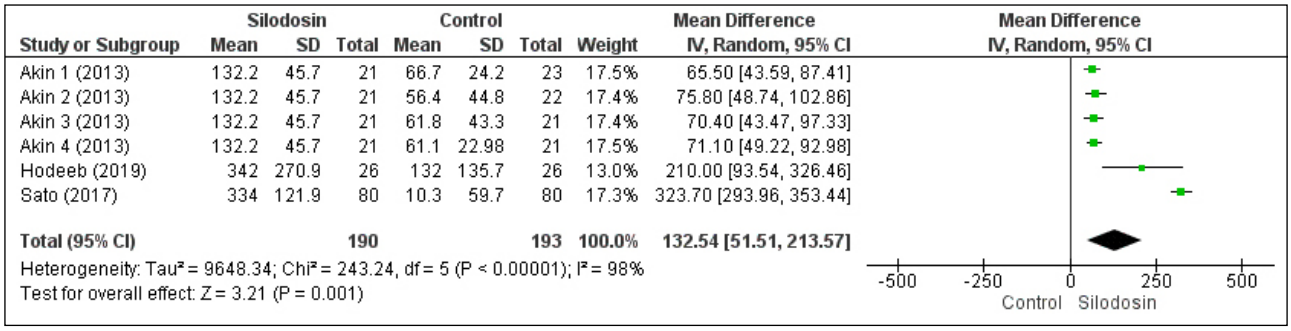


Figure 4.
Forest plot analysis of reduced semen ejaculation as a silodosin adverse event.
M-H: Mantel–Haenszel, CI: Confidence interval.

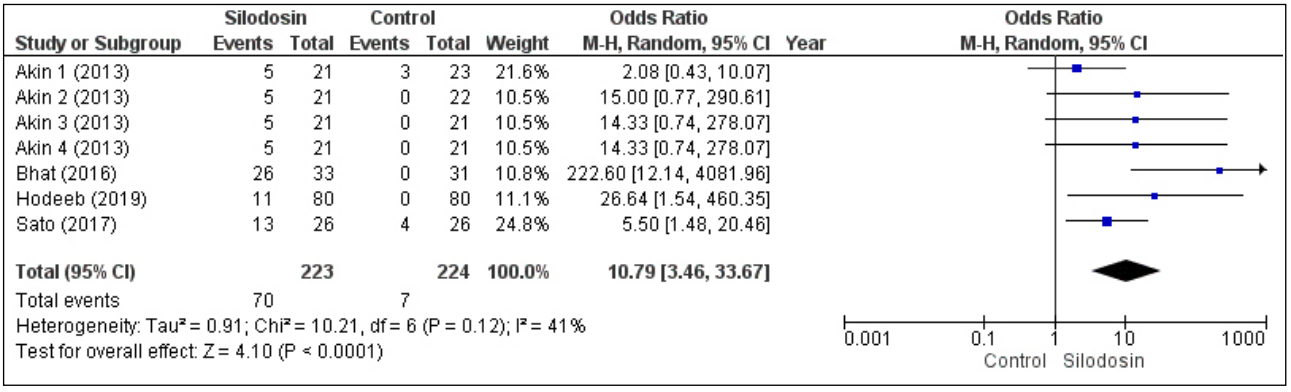
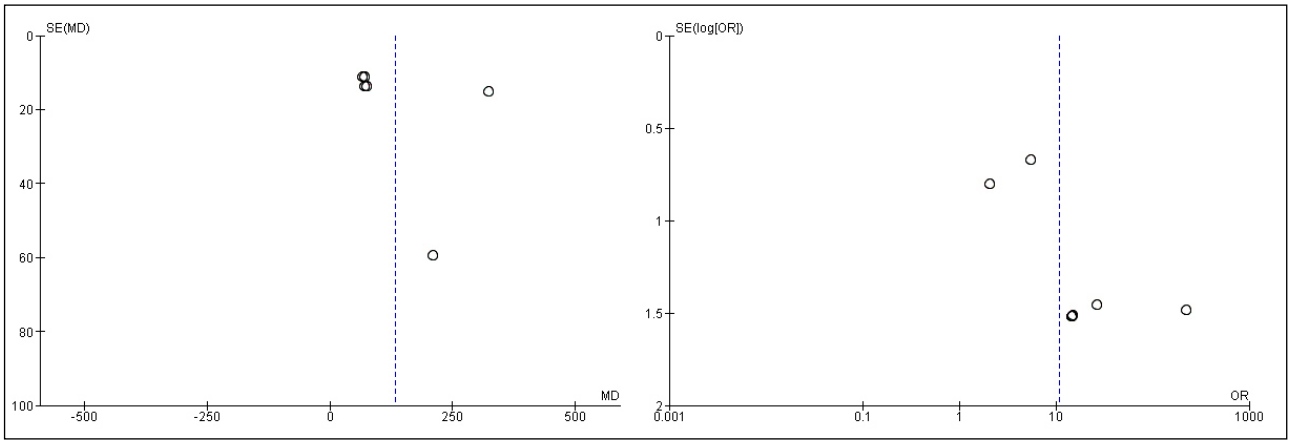


Figure 5.
Funnel plot analysis: A) Effect of silodosin on IELTs. B) Reduced semen ejaculation as silodosin adverse event.
SE: Standard Error; MD: Mean Difference; OR: Odds Ratio..



Discussion

PE is the most prevalent male sexual disorder, affecting 30% to 50% of men globally (8). PE is a common male sexual disorder, leads to negative effects including avoidance of sexual intimacy, frustration, reduced confidence with partners, and decreased quality of life (2, 3). PE treatments include oral medications like SSRIs and alpha blockers, as well as topical and behavioral therapies (9). Dapoxetine, an SSRI, treats PE by inhibiting the ejaculatory reflex. However, its significant adverse effects, like nausea, dizziness, and loss of libido, negatively impact patients' QOL (3-5). Silodosin, an alpha blocker for BPH, is highly selective for α1a adrenergic receptors and effective in treating PE (10).

In this meta-analysis, patients receiving silodosin before intercourse showed improved IELT compared to controls or those on placebo (MD: 132.54, $p < 0.001$). Alpha blockers, including silodosin, are gaining attention as alternative treatments for their ability to inhibit contractions of seminal vesicles, vas deferens, prostate, and asso-

ciated muscles, peripheral effectors in ejaculation. Silodosin's strong suppressive action on seminal emission, via its high α1A selectivity, may prolong IELT and improve ejaculatory control (11-13).

While effective for PE, Silodosin may cause mild anejaculation discomfort and reduced semen ejaculation. α1A-adrenoreceptor antagonists, including Silodosin, suppress seminal emission, possibly reducing semen production and prolonging ejaculation (12). *Roehrborn et al.* discovered that 28.1% of those experiencing retrograde ejaculation during silodosin treatment showed significant symptom improvement and enhanced peak flow rate compared to those without this side effect. This suggests silodosin effectively relaxes smooth muscles in the lower urinary and genital tracts, leading to retrograde ejaculation (14). Silodosin has fewer systemic adverse events and is more effective in treating PE than other alpha blockers (9).

Akin et al. compared PE patients given 4 mg silodosin 2-3 hours before intercourse with those on other alpha blockers: tamsulosin hydrochloride 0.4 mg, alfuzosin 10 mg, terazosin 5 mg, and doxazosin mesylate 4 mg. Silodosin significantly improved QoL, increased IELT, and decreased PEP (9). Silodosin's selectivity for alpha 1 receptors in the prostate makes it more effective in treating PE. Studies by *Sato Y et al.* and *Hodeeb et al.* support silodosin's greater improvement in PE patients, offering a promising, effective, affordable, and safe treatment avenue (11, 15)

This study has several limitations. Firstly, due to silodosin's novelty, relevant literature sources were still scarce. Secondly, the literatures that existed did not yet compare silodosin to dapoxetine, the main therapy for premature ejaculation therefore comparison of head-to-head was not available in this study. Thirdly, sample sizes varied, causing significantly high heterogeneity.

Conclusions

Silodosin significantly increased IELT. However, it causes reduced semen ejaculation as its drug adverse effect. This result supports the clinical use of silodosin as an alternative treatment for premature ejaculation. Further clinical studies evaluate the comparison of silodosin and SSRI are warranted.

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