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THE EFFICACY AND SAFETY OF SILODOSIN FOR THE TREATMENT OF BENIGN HYPERPLASIA PROSTATE: A SYSTEMATIC REVIEW

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Abstract

Background: *BPH is a prevalent and costly condition affecting the quality of life for older men. α adrenoceptor antagonists provide effective relief for bothersome symptoms but do not prevent the need for surgery or acute urinary obstruction. Silodosin, a newer α1 adrenoceptor antagonist, offers comparable symptom relief to tamulosin*

Aim: *This systematic review evaluates the efficacy and safety of silodosin for the treatment of benign prostatic hyperplasia (BPH) and its suitability for daily clinical practice..*

Methods: *This systematic review examined the use of silodosin in men with benign prostatic hyperplasia (BPH). Multiple databases were searched for relevant literature. (PubMed and Cochrane Library)*

Results: *This systematic review included four randomized trials involving 2504 patients with benign prostatic hyperplasia. The analysis showed that silodosin demonstrated significant improvements in International Prostate Symptom Score, specifically in storage and voiding symptoms, compared to placebo.*

Conclusion: *Silodosin shows efficacy and safety for treating benign prostatic hyperplasia (BPH), but the higher incidence of retrograde ejaculation warrants further high-quality, long-term studies, including direct comparisons with tamsulosin.*

Keywords: *BPH, silodosin, systematic review*

INTRODUCTION

Benign prostatic hyperplasia (BPH) is primarily characterized by non-cancerous enlargement of the prostate gland, affecting nearly 70% of men by the age of 70.[1] Among them, approximately half experience prostate enlargement, leading to bladder outlet obstruction and lower urinary tract symptoms. The direct costs associated with managing BPH in the United States alone surpass $1 billion annually and continue to rise.[2] This prevalent and costly condition significantly impacts the quality of life for older men, with lower urinary tract symptoms, particularly nocturia, increasing the risk of falls and fractures. Thus, the primary objective of BPH treatment is to alleviate bothersome symptoms and prevent disease progression, such as acute urinary retention.[3]

Traditionally, surgical intervention was reserved for men with severe symptoms or complications of bladder outlet obstruction. However, with the introduction of effective drugs, the identification and treatment of men with milder symptoms have become more feasible. As a result, lower urinary tract symptoms related to BPH are now acknowledged as a chronic medical condition that can be managed through lifestyle changes and medication. Primary care physicians play a pivotal role in the care of BPH patients, as they handle more than two-thirds of new cases.[4]

One of the commonly used medication is α adrenoceptor antagonists. These medications are commonly prescribed for men with bothersome lower urinary tract symptoms (LUTS). These medications bind to α1 adrenoceptors in the prostate, inhibiting its smooth muscle contraction and reducing symptom severity. They may also affect urethral smooth muscle, decreasing outlet resistance. Around 60% of men experience meaningful improvement in urinary symptoms within a month of starting α adrenoceptor antagonist treatment. These drugs are popular due to their rapid onset of action and independence from prostate size. They are well-tolerated and can provide long-term relief, although they do not prevent the need for surgical intervention or the risk of acute urinary obstruction.[5,6]

Silodosin is a recently developed α1 adrenoceptor antagonist that offers comparable and long-lasting relief from symptoms, similar to tamulosin. Compared to alfuzosin, silodosin has a potential advantage in terms of cardiac tolerability, as it does not typically prolong the QT interval, reducing the risk of cardiac arrhythmias in specific populations. However, it is important to note that silodosin is associated with a higher incidence of retrograde ejaculation. Additionally, dosage adjustments are necessary for patients with renal insufficiency.[7,8]

There is no recent review about the efficacy and safety of silodosin, also comparing this medication to other α1 adrenoceptor antagonist. Here, we aim to systematically review the efficacy and safety of silodosin, whether it is recommended to use in daily practice as choices of benign prostate hyperplasia or not.

Method

Search Strategy

This study is a systematic review was conducted to gather literature on the use of silodosin for treating men with benign prostatic hyperplasia (BPH). The search was conducted in multiple databases, including PubMed (2010-December 2020) and the Cochrane Library (2020, Issue 12). The search terms used were "silodosin" AND ("benign prostatic hyperplasia" OR "benign prostatic hypertrophy"). Additionally, the references of the included studies were checked to identify any additional relevant studies. The titles and abstracts of the identified literatures were independently reviewed by two reviewers to determine their relevance to the review. Studies that were not applicable were excluded. The selection process guideline was according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020.

Table 1. Literature search strategy

Database	Keywords	Results
PubMed	"silodosin" AND ("benign prostatic hyperplasia" OR "benign prostatic hypertrophy")	9876
Cochrane Library	"silodosin" AND ("benign prostatic hyperplasia" OR "benign prostatic hypertrophy")	8182

Eligibility Criteria

Type of studies

In this systematic review, literatures that specifically focused on men with BPH and compared the efficacy and safety of silodosin with other medical treatments for BPH were included. However, literatures that did not match with guidelines were excluded.

Populations

We included studies involving BPH patients. Participants were not restricted in terms of age, ethnicity, or another social status. We excluded studies that did not exclude lower urinary tract patients other than BPH because they were thought to influence the intervention's outcome.

Interventions and Comparison

The intervention given was silodosin and the comparator group was placebo and other medication for BPH.

Outcome

The primary outcome measures we considered were the changes in the International Prostate Symptom Score (IPSS), quality of life (QoL) score, peak urine maximum flow rate (Qmax), as well as the impact on QoL related to urinary

symptoms and adverse effects. These measures were used to assess the effectiveness and safety of silodosin compared to alternative treatments in managing BPH.

Quality assessment

The quality of each study's methodology was evaluated based on the manner in which patients were assigned to the study's arms, the secrecy of allocation procedures, blinding, and data loss due to attrition. The studies were then classified qualitatively in accordance with the 2019 guidelines published in the Cochrane Handbook for Systematic Reviews of Interventions. Based on the quality assessment criteria, each study was assigned to one of the three following categories: A: if all quality criteria were adequately met, the study was deemed to have a low risk of bias; B: if one or more quality criteria was only partially met or unclear, the study was deemed to have a moderate risk of bias; and C: if one or more criteria were not met, or not included, the study was deemed to have a high risk of bias.

Results

The combined search strategies identified four literature studies that met the inclusion criteria, involving a total of 2504 patients (1109 in the silodosin group, 736 in the placebo group, and 659 in the tamsulosin group) (Figure 1). All of these studies were multicenter, randomized, double-blind trials with a duration of 12 weeks. Three of the four studies were placebo-controlled, while three studies compared the effectiveness of 8 mg silodosin with 0.2 mg tamsulosin. One literature study was conducted in USA, one was conducted in Europe, and the remaining two studies were conducted in Asia. Detailed characteristics and quality assessments of these four literature studies are summarized in Table 2.

The databases search identified a total of 18.058 articles (Table 1). Of these, 100 articles passed the screening process, resulting in 20 articles for full-text assessment. Among them, 11 articles did not evaluate the outcome of interest reslting in 9 articles for full text assesment. And finally there is 4 studies included in this systematic review (Figure 1).

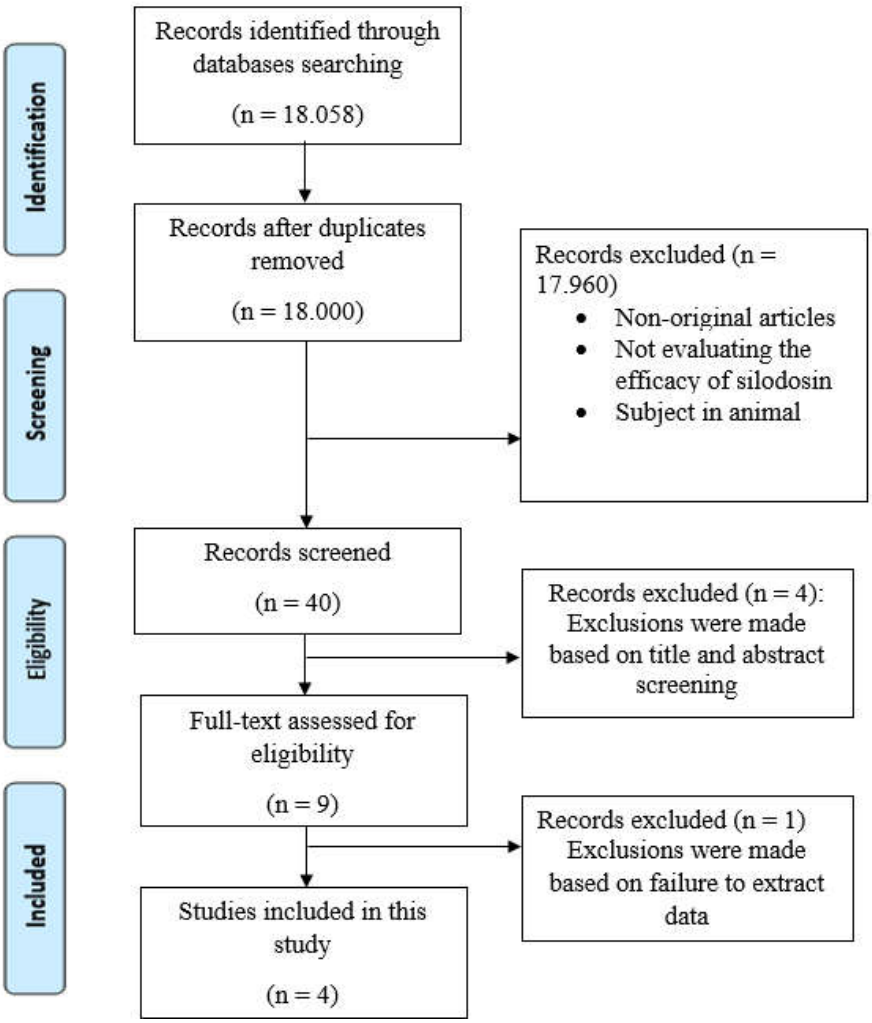

Figure 1. PRISMA flow diagram

Table 2. Summary of included studies

Author (Year)	Intervention	Mean age	Study duration (week)	Total IPSS	QoL score	Qmax
Hazra (2014)[9]	Silodosin (n=26) Tamsulosin (n=27)	61.4±7.88 62.6±7.55	12	18.4±3.94 18.3±4.08	4.3±0.8 4.2±0.8	9.8±2.5 9.9±2.6
Capitanio (2013)[10]	Placebo (n=457) Silodosin (n=466)	64.7±8.1 64.6±8.1	12	21.3±4.9 21.3±5.1	None	8.9±2.8 8.7±2.6
Chapple (2011)[11]	Silodosin (n=87) Tamsulosin (n=83)	67.5±9.3 65.0±8.8	12	19.3±4.5 19.8±4.5	3.8±0.8 3.7±0.8	10.3±2.8 10.6±2.8
Yu (2011)[12]	Placebo (n=190) Silodosin (n=381) Tamsulosin (n=384)	66.0±7.37 65.8±7.70 65.9±7.41	12	19.3±4.33 19.1±4.23 18.9±4.37	4.0±1.00 3.9±1.01 3.9±1.09	10.32±2.816 10.78±2.726 10.27±2.726

Discussion

Lower urinary tract symptoms (LUTS) commonly affect aging males, with benign prostatic hyperplasia (BPH) being the leading cause. While surgery is the definitive treatment for symptomatic BPH, it carries the risk of complications, including permanent urinary incontinence. As a result, alpha-blockers have emerged as the preferred initial pharmacological approach for managing BPH. Silodosin, a recently introduced α1A-adrenoceptor blocker, has gained recognition in the medical field for its efficacy in alleviating BPH.[1]

This systematic review represents the first assessment of silodosin's effectiveness and safety in treating benign prostatic hyperplasia (BPH). Silodosin, an approved alpha1A-blocker for BPH, demonstrated significant improvements in the International Prostate Symptom Score (IPSS), quality of life (QoL) score, and peak urine maximum flow rate (Qmax) compared to placebo. However, it was associated with a higher occurrence of ejaculation disorder. When compared to tamsulosin, silodosin showed comparable efficacy but a higher incidence of ejaculation disorder.

According to the findings of this systematic review, silodosin exhibited superiority over placebo and comparability to tamsulosin in reducing the total International Prostate Symptom Score (IPSS). The difference in IPSS reduction between the silodosin and tamsulosin groups was 21.4 (95% CI: 22.11-0.18). Thus, 8 mg silodosin is considered as effective as the recommended 0.2 mg tamsulosin dosage in Asian countries. Silodosin effectively alleviated both voiding and storage symptoms. Furthermore, significant differences were observed in the improvement of quality of life (QoL) scores between the silodosin group and both the placebo and 0.2 mg tamsulosin groups.

The selective blocking of alpha1A-adrenergic receptors (alpha1A-ARs) by silodosin induces relaxation of prostatic and urethral smooth muscles, resulting in the amelioration of voiding symptoms associated with benign prostatic hyperplasia (BPH). Silodosin has also demonstrated inhibitory effects on detrusor overactivity, potentially benefiting storage symptoms.[13]

Yuan et al. conducted a study on the effectiveness and safety of tamsulosin for BPH treatment. The results showed that tamsulosin, at doses of 0.4mg and 0.8mg, significantly improved the Boyarsky symptom score and peak urine flow compared to placebo. In this systematic review, silodosin at a dose of 8mg, also had a significant positive effect on the IPSS and peak urine flow compared to placebo. Additionally, when comparing silodosin to tamsulosin, silodosin showed similar efficacy in terms of IPSS, peak urine flow, and QoL score. However, the incidence of ejaculation disorder was higher with silodosin compared to 0.2mg tamsulosin. The adverse effect of ejaculation disorder can be explained by the high selectivity of silodosin for the alpha1A-AR subtype. It is worth noting that silodosin did not have any negative cardiovascular effects, which can be considered an advantage compared to tamsulosin, which has a higher selectivity for the alpha1B-AR.[14]

To the best of our knowledge, this is the first systematic review evaluating efficacy and safety of silodosin to treat BPH. This systematic review serves as a usefull tool for future knowledge whether silodosin can be an option for pharmacologic treatment of BPH. However, this systematic review has certain limitations. Firstly, the quality of the included studies is moderate. Secondly, the duration of all the studies was relatively short, only 12 weeks. Thirdly, the dosages of tamsulosin (0.2 mg) and silodosin (4 mg twice a day) used in the included studies differ from the dosages commonly used in Europe and the United States (0.4 mg tamsulosin and 8 mg silodosin once daily).

Conclusion

The findings of this systematic review indicate that silodosin demonstrates efficacy and safety as a treatment for benign prostatic hyperplasia (BPH) in men. However, it should be noted that the incidence of retrograde ejaculation was higher in the silodosin group compared to both the placebo and tamsulosin treatment groups. To validate these findings, it is recommended that future research includes higher-quality and long-term studies. Additionally, comparative studies directly comparing the efficacy of 8 mg silodosin with 0.4 mg tamsulosin would be beneficial.

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