# EVALUATING THE EFFECTS OF TADALAFIL ON LOWER URINARY TRACT SYMPTOMS DUE TO BENIGN PROSTATIC HYPERPLASIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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***ABSTRACT***

***Objective:*** *This review aims to assess tadalafil's efficacy and safety in managing BPH-LUTS, providing insights for clinical practice.* ***Material &Methods:*** *A systematic search strategy was conducted across several electronic reference databases (PubMed, Google Scholar, Proquest, and Cochrane) and included articles published between 2014-2024. Duplicate publications, review articles, and incomplete articles were excluded.* ***Results:*** *Database search yielded 302 articles, which were systematically eliminated, leaving 10 relevant articles. A total of 1.645 patients were involved in the 10 included studies. Of the 10 included studies, 9 were single-center studies and 1 was a multi-center study. Of all the studies, 7 were randomized controlled trials, 2 were observational trials, and 1 was a cohort study. From the meta-analysis test, it was found that the increase in IPSS 12 weeks after therapy was no different when administering tadalafil and tamsulosin.* ***Conclusion:*** *In conclusion, tadalafil monotherapy demonstrates comparable efficacy to tamsulosin in treating LUTS/BPH, with its approval stemming from its effectiveness in managing ED. The IPSS score between tadalafil and tamsulosin is considered similar statistically. Studies suggest synergistic effects when combined with alpha-blockers, offering promise for patients with concurrent conditions. Safety findings support its utility across diverse populations.*

***Keywords:*** *BPH, LUTS, tadalafil.*

***ABSTRAK***

***Tujuan:*** *Tinjauan ini bertujuan untuk mengevaluasi kemanjuran dan keamanan tadalafil dalam mengelola BPH-LUTS, memberikan wawasan untuk praktik klinis.* ***Bahan & Cara:*** *Strategi pencarian sistematik dilakukan di beberapa basis data referensi elektronik (PubMed, Google Scholar, Proquest, dan Cochrane) dan mencakup artikel yang diterbitkan antara tahun 2014-2024. Publikasi duplikat, artikel ulasan, dan artikel yang tidak lengkap di eksklusikan.* ***Hasil:****Pencarian basis data menghasilkan 302 artikel, yang secara sistematis dihilangkan, meninggalkan 10 artikel yang relevan. Sebanyak 1.645 pasien terlibat dalam 10 studi yang termasuk. Dari 10 studi yang termasuk, 9 adalah studi pusat tunggal dan 1 adalah studi multi-pusat. Dari semua studi, 7 adalah uji coba teracak terkontrol, 2 adalah uji observasional, dan 1 adalah studi kohort. Dari uji meta-analisis, ditemukan bahwa peningkatan skor IPSS setelah 12 minggu terapi tidak berbeda antara pemberian tadalafil dan tamsulosin.* ***Simpulan:*** *Sebagai kesimpulan, monoterapi tadalafil menunjukkan kemanjuran yang sebanding dengan tamsulosin dalam mengobati LUTS/BPH, dengan persetujuan yang berasal dari efektivitasnya dalam mengelola disfungsi ereksi (ED). Skor IPSS antara tadalafil dan tamsulosin dianggap serupa secara statistik. Studi menunjukkan efek sinergis ketika dikombinasikan dengan α-blockers, menawarkan harapan untuk pasien dengan kondisi bersamaan. Temuan keamanan mendukung utilitasnya di berbagai populasi.*

***Kata Kunci:*** *BPH, LUTS, tadalafil.*

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## INTRODUCTION

Benign prostatic hyperplasia (BPH) is a condition characterized by non-malignant enlargement of the prostate gland, primarily due to the proliferation of epithelial and smooth muscle cells within the prostate's transition zone.[1] This enlargement often precipitates lower urinary tract symptoms (LUTS), encompassing storage, voiding, and post-micturition symptoms. The prevalence of secondary LUTS attributable to BPH (BPH-LUTS) is notably high among elderly men globally, including in regions such as Asia, the United States, and Japan, where it significantly impacts daily

activities and quality of life.[2-3]

Pharmacological management of BPH-LUTS typically initiates with α-adrenergic blockers (α-blockers), often augmented with 5-α-reductase inhibitors (5ARIs) in cases of prostatic enlargement. While α-blockers offer prompt relief within weeks, 5ARIs exhibit a slower onset of action, necessitating long-term administration to mitigate urinary retention and avoid surgical interventions. Despite their efficacy, a subset of individuals may exhibit inadequate response or experience adverse effects, including sexual dysfunction.[4-5]

Concurrently, tadalafil, a phosphodiesterase type 5 (PDE5) inhibitor traditionally indicated for erectile dysfunction (ED), has garnered approval for once-daily administration to alleviate BPH-LUTS symptoms.[6] Its mechanism of action involves smooth muscle relaxation within the prostate and bladder, mirroring the therapeutic effects of α-blockers. Clinical guidelines from renowned urological associations endorse tadalafil's efficacy, underpinned by Level 1 evidence derived from robust randomized controlled trials predominantly featuring tadalafil.[7-8]

## OBJECTIVE

Nevertheless, a comprehensive systematic evaluation of tadalafil's efficacy and safety profile in BPH-LUTS patients is imperative to inform evidence-based clinical decision-making. Hence, this study aims to meticulously examine the impact of tadalafil administration on lower urinary tract symptoms in individuals afflicted by benign prostatic hyperplasia. Through rigorous scrutiny of existing literature and synthesis of pertinent data, this systematic review endeavors to furnish valuable insights into tadalafil's role as a therapeutic option in managing BPH-LUTS, thus contributing to optimized patient care.

## MATERIAL &METHODS

To obtain a comprehensive dataset on all publications evaluating the effects of tadalafil on lower urinary tract symptoms due to benign prostatic hyperplasia, we did a systematic literature search starting until April 2024 in PubMed, Google Scholar, Proquest, and Cochrane. This study included original articles including cohort, cross-sectional, case-control, and randomized control trials discussing the effects of tadalafil on lower urinary tract symptoms due to benign prostatic hyperplasia. The detailed search terms used are mentioned in this research protocol and can be found in the supplementary appendix. The presentation adhered to the PRISMA Statement (Figure 1).

The investigation was conducted in English, using keywords related to the effects of tadalafil on lower urinary tract symptoms due to benign prostatic hyperplasia, with the keywords used "tadalafil" OR "phosphodiesterase type 5 inhibitor" OR "PDE5" AND "lower urinary tract symptoms" OR "LUTS" AND "benign prostatic hyperplasia" OR "BPH" OR "BPH-LUTS". The search was performed with a combination of some or all of these keywords, both in the title and abstract of the article. Search is limited to publications in the period 2019 to 2024.

The titles and abstracts of the papers that could be discovered in the databases were separately examined by two writers. The research's included and excluded articles complied with the established criteria. Our systematic review's inclusion criteria were: (1) original papers; and (2) research looking into the effects of tadalafil on lower urinary tract symptoms due to benign prostatic hyperplasia. Letters, notes, case series, conference abstracts, conference publications, and literature reviews were not included. Articles in full text were located.

A standardized table that contains the names of the authors, the year the research was published, the study design, the study setting, the number of subjects, the therapy utilized, and the main conclusions of each study was used to extract the data. Following the process of finding and sorting articles using search terms, a manual examination of the articles was conducted, taking into account the relevancy of the title and abstract. After reading the whole text of the article and inserting the pertinent data in the data extraction table, articles that satisfy the ambiguous inclusion and exclusion criteria will be subjected to further analysis. The outcomes from the included papers will be compared with previous systematic reviews' findings and existing research.

The quality of the studies was appraised independently by two authors using Risk of Bias 2 (RoB2) for the trial and the Modified Newcastle-Ottawa Scale (NOS) for cohort. A score of 0-9 was allocated to each study, with studies having a total score of >7 defined as high quality. Any disagreement in the quality assessment was resolved by discussion with a third author.

**Statistical analytic**

The main outcome assessed from the intervention was the IPSS score (IPSS storage, IPSS voiding and IPSS quality of life). Outcomes taken after 12 weeks or 3 months of intervention. Meta-analysis testing was carried out by measuring the effect size after administering Tadalafil (treatment group) and Tamsulosin (control group) therapy to LUTS patients. Each study group was tested for Hedges' g effect size with a CI of 95%. A p value <0.05 is interpreted as a statistically significant difference. Heterogeneity was estimated with the Cochran Q test and the degree of heterogeneity was expressed as I2. An I2 value >75% was assessed as high heterogeneity. Analysis was carried out with STATA 17.0.

## RESULTS

A systematic search was carried out and yielded 302 articles (Fig. 1). A total of 118 articles remained, after rechecking and excluding duplicate articles. A total of 41 articles were eligible for this study. Then, after a comprehensive review of the full-text articles, the remaining 10 articles were included in this study. The database search results are described in Table 1 and Figure 1. The summary of each included study is described in Table 2.

Of the 10 included studies, 7 were randomized controlled trials, 2 were observational trials, and 1 was a cohort study.

A total of 1645 patients were involved in the 10 included studies. Of the 10 included studies, 9 were single-center studies and 1 was a multi-center study.

In the meta-analysis test, the effect size was measured on continuous variables, namely mean and SD data in the included studies. The group that received tadalafil therapy was the treatment group and the group that received tamsulosin was the control group.

### 1. IPSS voiding

Research by Zhang, 2018 and Sebastian, 2019 compared the administration of Tadalafil and Tamsulosin as LUTS therapy. From the results of statistical tests, it was found that there was a p value> 0.05 which indicated that there were no significant differences between the two groups after the meta-analysis test was carried out. The IPSS voiding effect size value in this meta-analysis is -0.12 (95% CI -0.29-0.05).

From the heterogeneity test, an I2 value of 0% is obtained, which means there is almost no heterogeneity between publications.

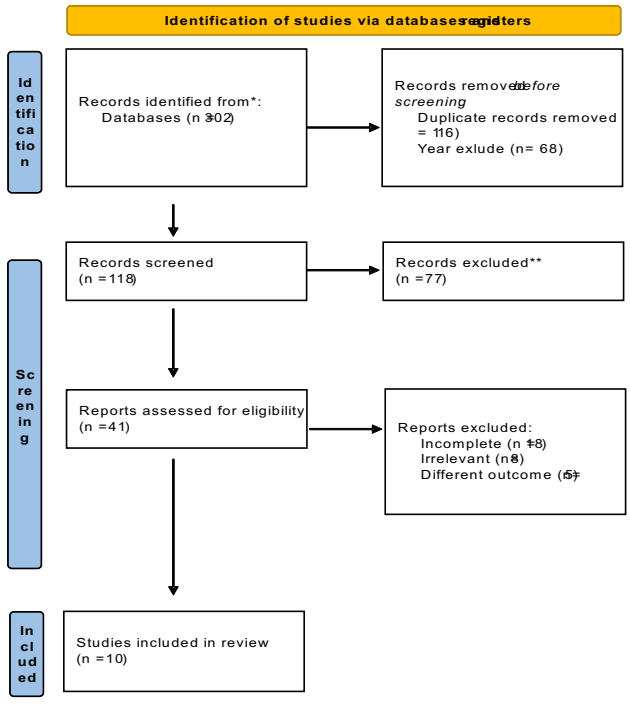


**Figure 1.** Systematic Search.

From research by Zhang, 2018 and Sebastian, 2019, a p value of 0.34 was obtained, indicating that there was no significant difference between the two management groups regarding the IPSS storage score. The effect size obtained for the IPSS storage variable was 0.02 (95% CI -0.15-0.19).

The heterogeneity value in this test is 0%, which means that there is almost no heterogeneity between publications.

Regarding the quality of life variable, the test results obtained a p value of 0.28, which means there is no significant difference in quality of life in the two treatment groups. The effect size value in testing the IPSS QoL variable is -0.02 (95% CI -0.19-0.14).

Testing for heterogeneity in the IPSS QOL variable is 0%, which means there is almost no heterogeneity between publications.

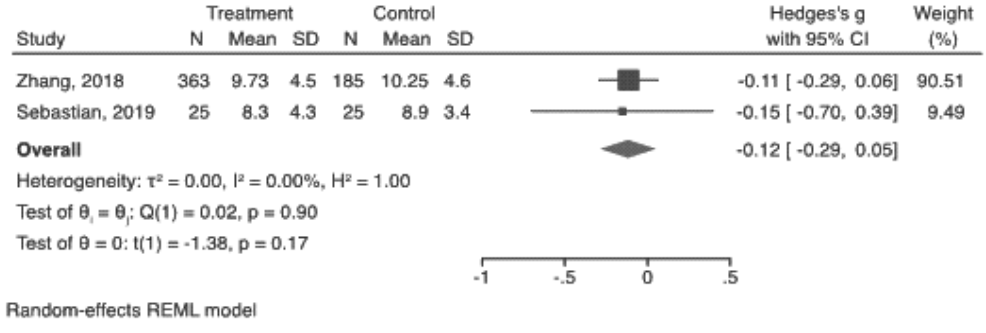


**Figure 2.** Meta-analysis of IPSS voiding after 3 month of Tadalafil vs Tamsulosin.

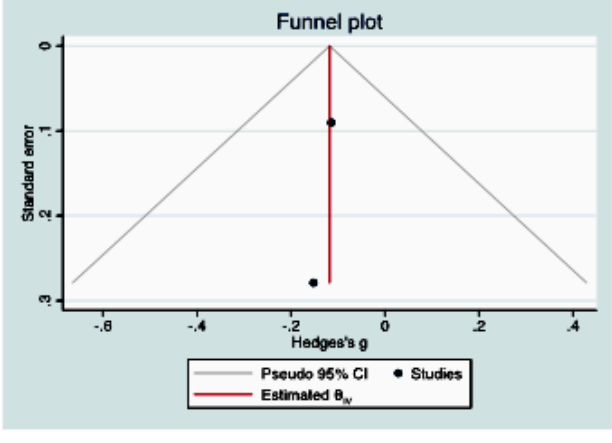


**Figure 3.** Funnel plot of IPSS voiding after 3 month of Tadalafil vs Tamsulosin.

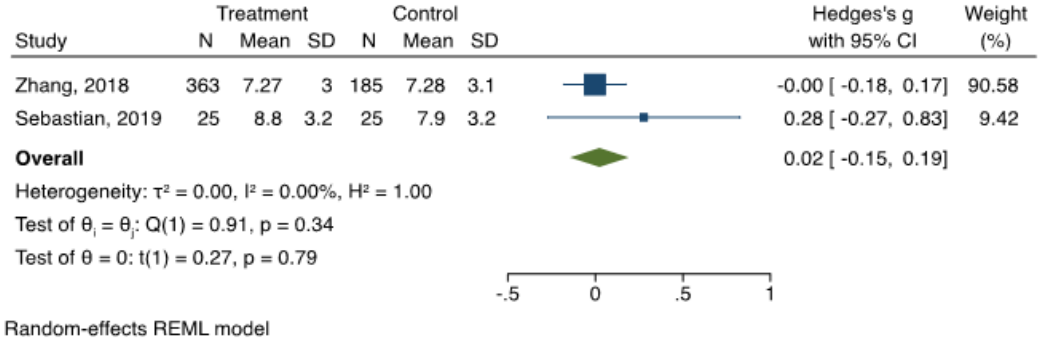


**Figure 4.** Meta-analysis of IPSS storage after 3 month of Tadalafil vs Tamsulosin.

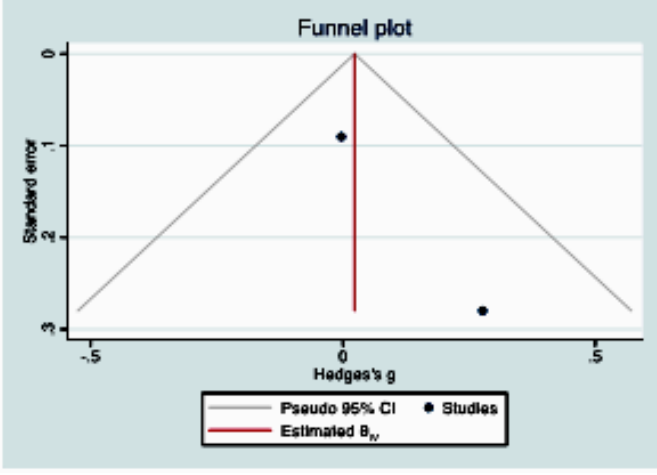


**Figure 5.** Funnel plot of IPSS storage after 3 month of Tadalafil vs Tamsulosin.

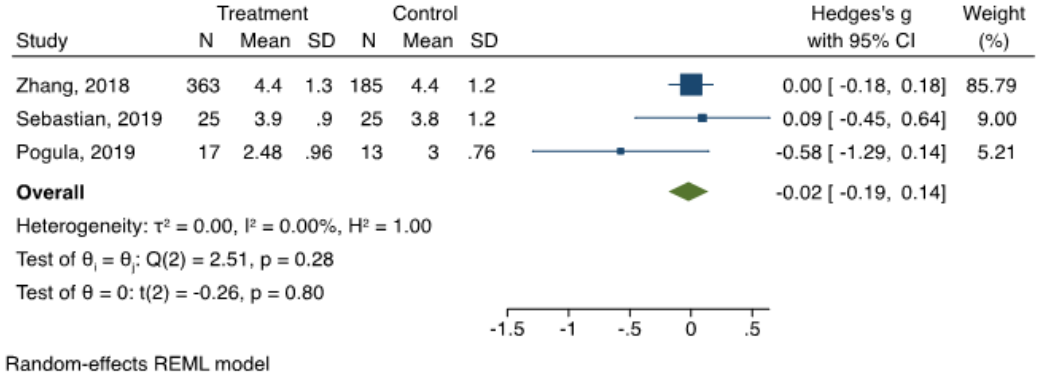


**Figure 6.** Meta-analysis of IPSS QoL after 3 month of Tadalafil vs Tamsulosin.

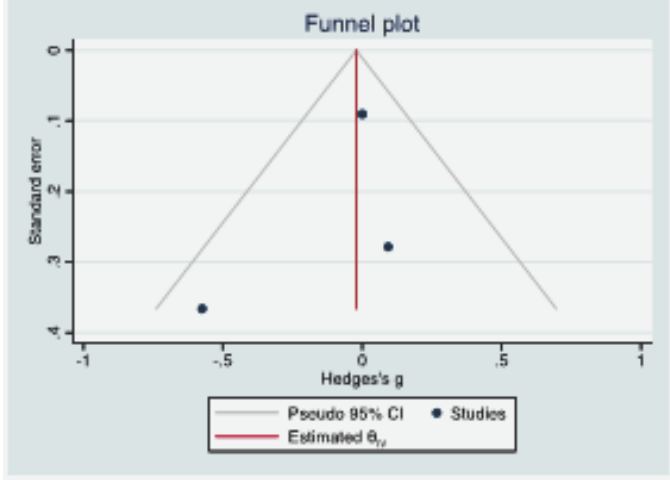


**Figure 7**. Funnel plot of IPSS QoL after 3 month of Tadalafil vs Tamsulosin.

**Table 1.** Study Characteristics and Finding

| Author | Design | Country | Arms | Subject | Age | Follow up Period | Δ IPSS | Δ Q Max | ΔIIEF score | PVR | Complication |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **AbdelRazek et al, 2022**[9] | Randomized Controlled Trial | Egypt | Group A: Tadalafil 5 mg | 101 | 61.7 ± 4.6 | 3 months | 3.6 ± 1.9 | 7.2 ± 2.0 | 5.9 ± 2.4 | 11.1 ± 7.1 | Headache, nasal congestion, ocular hyperemia, myalgia, dizziness, flushing |
| | | | Group B: Silodosin 8 mg | 102 | 62.9 ± 5.6 | | 4.1 ± 2.2 | 8.1 ± 2.3 | 7.4 ± 2.1 | 13.3 ± 6.4 | Retrograde ejaculation, headache, nasal congestion, ocular hyperemia, myalgia, dizziness, |
| | | | Group C: Combination | 105 | 62.6 ± 5.4 | | 5.6 ± 2.8 | 8.7 ± 2.0 | 7.0 ± 2.3 | 15.5 ± 6.4 | palpitation, dyspepsia, peripheral edema, flushing, orthostatic hypotention |
| **Sebastianelli et al, 2021**[10] | Prospective trial | Italy | TAD: tadalafil 5 mg | 25 | 64.4 ± 8.3 | 24 weeks | 5.56 | 1.86 | 4.64 | - | Headache, back pain, dyspepsia |
| | | | TAM: tamsulosin 0.4 mg | 25 | 67.0 ± 7.8 | | 5.24 | 1.96 | 0.72 | - | Headache, nasopharyngitis, back pain, ejaculatory dysfunction |
| **Nasef et al, 2021**[11] | Randomized Controlled Trial | Egypt | Group A: Tadalafil 5 mg and tamsulosin 0.4 mg | 41 | 60.51±6.93 | 6 months | 8.03 | 3.85 | - | 29.32 | Backache, blurred vision, headache, hypotension |
| | | | Group B: Tamsulosin 0.4 mg and placebo | 41 | 62.05±6.87 | | 0 | -0.02 | - | 2.44 | - |
| **Nagasubramanian et al, 2020**[12] | Randomized Controlled Trial | India | Tadalafil 5 mg and tamsulosin 0.4 mg | 69 | 58.87 ± 8.16 | 3 months | 6.42 | 3.13 | 4.34 | 1.06 | Myalgia, dyspepsia |
| | | | Tamsulosin 0.4 mg and placebo | 71 | 61.28 ± 8.23 | | 3.57 | 1.24 | 0.67 | 6.88 | Myalgia, dyspepsia, retrograde ejaculation |
| **Negoro et al, 2020**[13] | Randomized Controlled Trial | Japan | Tadalafil 5 mg and tamsulosin 0.4 mg | 13 | 73 (65-85) | 6 weeks | 3.42 | 0.99 | 1.2 | 4.7 | - |
| | | | Tamsulosin 0.4 mg and placebo | 13 | 70 (50-80) | | 1.85 | 0.42 | -0.07 | 15 | |
| **Sebastianelli et al, 2019**[14] | Observational Trial | Italy | Tadalafil 5 mg and tamsulosin 0.4 mg | 50 | 65.7 ± 9.1 | 12 weeks | 7 | 4.2 | 5.7 | - | Treatment-emergent adverse event (22%): headache, back pain, dizziness, dyspepsia, ejaculatory dysfunction |
| | | | Tamsulosin 0.4 mg and placebo | 25 | 65.5 ± 6.3 | | 5.2 | 2.2 | 6.1 | - | Treatment-emergent adverse event (16%): headache, nasopharyngitis, back pain |
| **Matsukawa et al, 2019**[15] | Prospective cohort | Japan | Tadalafil 5 mg/day | 105 | 70.7 ± 7.5 44.5 | 3 months | 5.4 | 2 | - | 20 | Headache, erection problems, dizziness |
| | | | | | | 12 months | 6.9 | 2.9 | - | 27 | |
| **Zhang et al, 2019**[16] | Randomized Controlled Trial | China | Tadalafil 5 mg | 363 | 61.8 ± 7.3 | 12 months | 5.49 | 5.24 | - | - | Nasopharyngitis , dizziness, back pain |
| | | | Placebo | 361 | 61.8 ± 7.4 | | 4.08 | 1.88 | - | - | |
| **Pogula et al, 2019**[17] | Randomized Controlled Trial | India | Tadalafil 5 mg | 50 | 59.40 ± 8.84 | 12 weeks | 0.62 | 2.4 | - | 12 | - |
| | | | Tamsulosin 0.4 mg | 50 | 63.66 ± 9.05 | | 2.76 | 4 | - | 59 | |
| **Pattanaik et al, 2019**[18] | Randomized Controlled Trial | India | Tadalafil 10 mg | 36 | 60.30±8.073 | 12 weeks | 4.84±5.12 | 0.00± 0.27 | 3.42± 4.83 | 17.47± 100.42 | Epigastric discomfort, myalgias, cals pain, decreased seminal volume, herpes zoster |
| | | | Tamsulosin 0.4 mg | | 60.65±7.849 | | 4.88±4.99 | 0.05± 0.20 | 1.87± 4.17 | 38.69± 90.41 | Epigastric discomfort |

IPSS: International Prostate Symptom Score, IIEF: International Index of Erectile Function, PVR: Post Void Residual

## DISCUSSION

The current approach to treating moderate to severe LUTS/BPH typically involves starting with medication and reserving surgery for cases where medication isn't effective.[4] Tamsulosin is highly regarded for its effectiveness in this regard, as it selectively relaxes smooth muscles in the bladder, neck, and prostate by blocking a1 receptors. In Western countries, a daily dose of 0.4mg of tamsulosin is commonly used alongside PDE5 Is for its safety and efficacy, as recommended by the European Association of Urology guidelines. Studies have shown that tamsulosin can significantly improve symptom scores by 4-6 points.[19-20]

Similarly, studies indicate that tadalafil monotherapy can reduce total IPSS scores by an average of 4.7-6.4 points, showing comparable effectiveness to tamsulosin in treating moderate to severe LUTS/BPH, as suggested by Oelke's study.[21] Tadalafil, the sole PDE5 inhibitor used for BPH treatment, was initially intended for erectile dysfunction in 2003 but was later found to be effective in managing LUTS/BPH. Consequently, it gained FDA approval in 2011 for alleviating BPH symptoms, particularly when accompanied by ED. A study involving 1,058 patients with LUTS/BPH randomly assigned to receive tadalafil (2.5, 5, 10, or 20mg) or a placebo daily demonstrated significant symptom improvement across all doses compared to the placebo, with the 5mg dose showing a favorable risk-benefit profile. This 5mg daily dose is now considered standard for tadalafil.[7,22]

Multiple randomized controlled trials have showcased the significant reduction of IPSS score, improvement in both storage and voiding LUTS, and enhancement of patients' quality of life through the administration of PDE5 inhibitors.[9-18] However, across most trials, their impact on Qmax did not notably deviate from that of the placebo. Similarly, as per a meta-analysis conducted by Gacci et al., while IPSS and IIEF scores displayed significant improvement with PDE5 inhibitors, Qmax did not exhibit significant changes.[23] The results of the meta-analysis in this study showed that there were no significant differences in IPSS voiding, storage and QoL between LUTS patients who received tadalafil and tamsulosin. However, there was improvement at 3 months post therapy but it was not significantly different between the two therapy groups.

Laydner et al., in the initial systematic review addressing PDE5 inhibitors for LUTS linked with benign prostatic enlargement, noted enhancements in IPSS and IIEF-5 scores but no significant alteration in Qmax. Nonetheless, a study by Roehrborn et al. in 2014, assessing the efficacy of once-daily tadalafil at 5 mg, observed a slight yet notable increase in Qmax. Improvement in storage symptoms, particularly the relief of nocturia, contributed significantly to enhanced QoL.[9,24]

In a recent investigation conducted by Abdel Razek et al., it was discovered that Tadalafil on its own led to a significant reduction in the overall IPSS and an enhancement in Qmaxover 12 weeks; however, the combination of tadalafil and silodosin yielded superior improvements in voiding symptoms. The inaugural meta-analysis exploring the efficacy of PDE5 inhibitors in managing both ED and LUTS demonstrated enhancements in IPSS score and Qmax, along with the IIEF score, among men treated with a combination of alpha-blockers and PDE5 inhibitors compared to those solely receiving alpha-blockers. These statistically notable outcomes underscored the significant therapeutic impact of tadalafil in ameliorating LUTS, yet the specific mechanisms of action remain unclear.[9]

The PDE5 enzyme is present in various anatomical structures including the bladder, urethra, corpora cavernosa, prostate, ureter, and kidney.[25] Matsukawa et al. conducted a urodynamic study that revealed tadalafil's significant improvement in bladder outlet obstruction and bladder storage function. Furthermore, in vitro studies demonstrated that PDE5 inhibitors induce relaxation of smooth muscles in the bladder, neck, and prostate, and decrease detrusor muscle overactivity. The relaxant effect on the bladder neck and urethra mediated by the NO-cGMP signaling pathway potentially leads to symptom relief in LUTS/BPH patients. Other implicated mechanisms include decreased activation of the RhoA/Rho kinase pathway, improved oxygenation, regulation of proliferation and transdifferentiation, modulation of bladder and prostate afferent nerves along with autonomic nervous system overactivity, and anti-inflammatory effects.[15]

The corpus cavernosum, bladder, and prostate share similar pathophysiological pathways, leading to a frequent co-occurrence of LUTS/BPH and ED, particularly prevalent among older men. Notably, LUTS is recognized as a risk factor for ED. While many PDE5 inhibitors operate through comparable mechanisms, tadalafil stands out as the sole PDE5I approved for BPH treatment due to its

safety, tolerability, and prolonged duration of action. However, a study by Broderick et al. involving over 1,000 men revealed that tadalafil demonstrated similar effectiveness in alleviating LUTS/BPH in men with or without concurrent ED. This suggests that tadalafil's impact on LUTS may not primarily stem from its action on ED.[26] Nonetheless, reports indicate that tadalafil enhances tamsulosin's inhibitory effects on neurogenic contractions in the bladder, neck, and prostate. Additionally, studies suggesting an additional relaxation effect on the corpus cavernosum with combined treatment of alpha-blockers and tadalafil hint at potential synergistic effects between these medications, particularly beneficial for individuals experiencing both LUTS/BPH and ED. Hence, when either alpha blockers or tadalafil alone fail to provide adequate efficacy, combination therapy with both agents could be considered.[27-28]

A study conducted by Zhang et al. involving both Asian and Caucasian populations revealed that Tadalafil 5 mg once daily was well received, with safety profiles consistent with previous findings in studies of tadalafil among Asian and Caucasian individuals with BPH-LUTS, whether accompanied by ED or not. Adverse events were minimal and predominantly mild to moderate in severity. The only adverse event reported in over 2% of patients in the tadalafil group and occurring more frequently than in the placebo group was nasopharyngitis. Similarly, adverse events in the tamsulosin treatment group were uncommon. In summary, the 5 mg once-daily dosage of tadalafil was well tolerated and led to significant improvements in both BPH-LUTS and ED over a 12-week period in this predominantly Chinese male cohort. These findings align with results from studies conducted on non-Asian men with BPH-LUTS and ED.[16]

Our study has certain limitations that warrant acknowledgment. We did not confine our analysis solely to studies pitting tadalafil against a placebo. To reinforce the efficacy and safety of tadalafil monotherapy in ameliorating LUTS/BPH compared to active control, it is essential to undertake larger-scale, meticulously designed, and long-term prospective clinical trials incorporating comprehensive indicators.

## CONCLUSION

Tadalafil monotherapy has shown comparable efficacy to tamsulosin in alleviating LUTS/BPH, underscoring its significance. IPSS score of voiding, storage and QoL between tadalafil and tamsulosin is considered similar statistically. Notably, tadalafil's approval for BPH treatment stemmed from its efficacy in managing ED, highlighting the overlap between these conditions. Despite significant improvements observed with PDE5 inhibitors in various trials, their impact on Qmax remains inconclusive. However, studies suggest potential synergistic effects when alpha-blockers are combined with tadalafil, especially beneficial for patients with concurrent LUTS/BPH and ED. Safety and efficacy findings of tadalafil in Asian and Caucasian populations corroborate its utility across diverse demographics.

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