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The Efficacy and Safety of Tamsulosin and Tadalafil Combination Therapy Compared with Tadalafil Alone for Patients with Benign Prostatic Hyperplasia

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ABSTRACT

Background: Benign prostatic hyperplasia (BPH) is a common urologic condition in aging men that often manifests as lower urinary tract symptoms (LUTS). Pharmacological management includes α1-adrenoceptor blockers like tamsulosin and phosphodiesterase type 5 inhibitors (PDE5-Is) like tadalafil. Recent studies suggest combination therapy may offer greater symptom relief. **Objective**: To compare the efficacy and safety of combination therapy with tamsulosin and tadalafil versus tadalafil monotherapy in patients with BPH-related LUTS. **Methods**: This literature review included randomized controlled trials and prospective studies published between 2008 and 2022. Databases such as PubMed, MEDLINE, Embase, and Cochrane Library were searched using relevant keywords. Twelve studies met the inclusion criteria and were narratively analyzed. **Results**: Most studies showed that combination therapy was more effective than monotherapy in improving IPSS scores, Qmax, and sexual function, especially in patients with coexisting erectile dysfunction. Fixed-dose combination therapy also improved patient adherence and satisfaction. While tadalafil monotherapy remained effective, particularly in men with mild-to-moderate symptoms, its effect was less consistent in severe LUTS. **Conclusion**: Combination therapy of tamsulosin and tadalafil provides superior clinical benefit in managing LUTS/BPH, especially in men with concurrent ED. It is generally well tolerated, but individualized therapy based on symptom severity, prostate size, and comorbidities is essential.
Keyword: benign prostatic hyperplasia, combination therapy, LUTS, tadalafil, tamsulosin

ABSTRAK

Latar Belakang: Hiperplasia prostat jinak (BPH) merupakan kondisi urologis yang umum pada pria lanjut usia dan sering menyebabkan gejala saluran kemih bagian bawah (LUTS). Penatalaksanaan farmakologis meliputi penggunaan *α1-adrenoceptor blocker* seperti tamsulosin dan penyekat fosfodiesterase tipe 5 (PDE5-I) seperti tadalafil. Studi terbaru menunjukkan bahwa terapi kombinasi dapat memberikan perbaikan gejala yang lebih baik. **Tujuan**: Membandingkan efektivitas dan keamanan terapi kombinasi tamsulosin dan tadalafil dengan monoterapi tadalafil pada pasien dengan LUTS akibat BPH. **Metode**: Tinjauan pustaka ini mencakup uji klinis terkontrol acak dan studi prospektif yang diterbitkan antara tahun 2008 hingga 2022. Basis data seperti PubMed, MEDLINE, Embase, dan Cochrane Library digunakan dengan kata kunci relevan. Dua belas studi memenuhi kriteria inklusi dan dianalisis secara naratif. **Hasil**: Sebagian besar studi menunjukkan bahwa terapi kombinasi lebih efektif dibandingkan monoterapi dalam meningkatkan skor IPSS, Qmax, dan fungsi seksual, terutama pada pasien dengan disfungsi ereksi. Terapi kombinasi dosis tetap juga meningkatkan kepatuhan dan kepuasan pasien. Meskipun monoterapi tadalafil tetap efektif, efeknya kurang konsisten pada gejala LUTS yang berat. **Kesimpulan**: Terapi kombinasi tamsulosin dan tadalafil memberikan manfaat klinis yang lebih baik dalam penanganan LUTS/BPH, khususnya pada pasien dengan disfungsi ereksi. Terapi ini umumnya ditoleransi dengan baik, namun pilihan terapi harus

disesuaikan secara individual berdasarkan tingkat keparahan gejala, ukuran prostat, dan komorbiditas.
Kata Kunci: hiperplasia prostat jinak, LUTS, tamsulosin, tadalafil, terapi kombinasi

1. Introduction

Lower urinary tract symptoms (LUTS) in older men are commonly caused by benign prostatic hyperplasia (BPH), a non-malignant growth or hyperplasia of prostate tissue. The prevalence of BPH at autopsy has been shown to increase with age. For males in their 60s, the histological prevalence of BPH is as high as 50% to 60%, and it rises to 80% to 90% for men older than 70 years of age. Treatment options for men with symptomatic BPH include medication and surgery as well as watchful waiting which will be determined by the patient's level of illness burden by an International Prostate Symptom Score (IPSS) following a thorough review of all available alternatives and their associated risks and benefits.[1]

Guidelines of the European Association of Urology recommend both α1-adrenoceptor blockers (α1-blockers) and phosphodiesterase type 5 inhibitors (PDE5-Is) as first-line pharmacological therapies for managing LUTS related to BPH.[2] Tamsulosin, an α1-adrenoceptor blocker, blocks adrenergic receptors which caused smooth muscles in bladder neck and prostate to be relaxed, so it will lower BPH complaints and raise the maximal flow rate. Nevertheless, in certain patients with BPH, tamsulosin monotherapy yields suboptimal symptomatic improvement. Consequently, alternative treatment strategies—such as combination or add-on therapies with other agents targeting LUTS—are being explored for these individuals.[3]

Tadalafil, a PDE5-I commonly used for the treatment of erectile dysfunction (ED), has also been approved for managing the signs and symptoms of BPH-related LUTS. The therapeutic effects of PDE5-Is on LUTS are attributed to the inhibition of PDE5 isoenzymes found in the bladder, prostate, urethra, and associated vasculature. This inhibition leads to increased intracellular nitric oxide–cyclic guanosine monophosphate (NO–cGMP) levels, resulting in smooth muscle relaxation, enhanced blood flow, and diminished afferent signaling from the urogenital tract.[4]

Clinical trials have suggested that the combination of tadalafil and tamsulosin may provide superior symptom relief and improvement in urinary flow parameters compared to tadalafil alone. For example, Oelke *et al.* (2012) demonstrated significantly improved IPSS reductions and quality of life outcomes with combination therapy compared to monotherapy.[5] Similarly, Singh *et al.* (2014) reported enhanced efficacy of combination therapy without a significant increase in adverse events.[6]

Despite these findings, clinical implementation of combination therapy remains cautious due to concerns regarding safety, cost, and generalizability of results to broader patient populations. Additionally, long-term safety data and head-to-head comparisons with tadalafil monotherapy are still limited. The European Association of Urology (EAU) 2020 guidelines recognize the potential of such combinations but highlight the need for more robust evidence before widespread adoption, particularly among patients without concomitant erectile dysfunction.[7]

Given the increasing prevalence of BPH and its impact on aging populations, further evaluation of combination therapy's efficacy and safety is warranted. Therefore, the objective of this review is to evaluate the current evidence comparing the efficacy of tamsulosin and tadalafil combination therapy with tadalafil monotherapy in improving LUTS in patients with BPH.

2. Method

2.1 Study Design

This study was designed as a narrative literature review aimed at evaluating and comparing the efficacy and safety of tamsulosin and tadalafil combination therapy versus tadalafil monotherapy for the treatment of LUTS associated with BPH in adult male patients.

2.2 Data Sources and Search Strategy

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A comprehensive literature search was conducted using electronic databases including PubMed, MEDLINE, Cochrane Library, and Embase from 2008 to 2024. The search was performed using a combination of Medical Subject Headings (MeSH) and free-text terms: ("Benign Prostatic Hyperplasia" OR "BPH") AND ("Tamsulosin") AND ("Tadalafil"). The search was limited to studies published in English and conducted on human subjects.

2.3 Eligibility Criteria

Studies were included based on the following criteria:

a. Population: Adult male patients with LUTS suggestive of BPH, with or without ED.
b. Intervention: Combination therapy involving tamsulosin and tadalafil, or monotherapy with either agent.
c. Comparators: Tadalafil monotherapy, tamsulosin monotherapy, or placebo.
d. Outcomes: At least one reported outcome related to efficacy (e.g., IPSS, Qmax, PVR), safety (e.g., adverse events), or sexual function (e.g., erectile or ejaculatory function).
e. Study Design: Randomized controlled trials (RCTs)

Exclusion criteria included:

a. Studies involving patients with prostate cancer or neurogenic bladder.
b. Case reports, editorials, conference abstracts, or studies lacking comparative outcomes.

2.4 Study Selection and Data Extraction

Two reviewers independently screened titles and abstracts to identify potentially relevant articles. Full-text reviews were conducted for studies that met inclusion criteria. Discrepancies were resolved through discussion or consultation with a third reviewer. Data were extracted using a standardized data extraction form, including information on study design, sample size, patient characteristics, interventions, outcome measures, and adverse events.

The databases searching result showed that there were 78 articles appeared. After first exclusion based on study design and, a total of 27 articles were screened as proper studies to be evaluated based on the suitability of the title and abstract with the topic and based on eligibility dan exclusion criteria. From those articles, 12 articles were selected as eligible articles for further evaluation and data extraction (Figure 1).

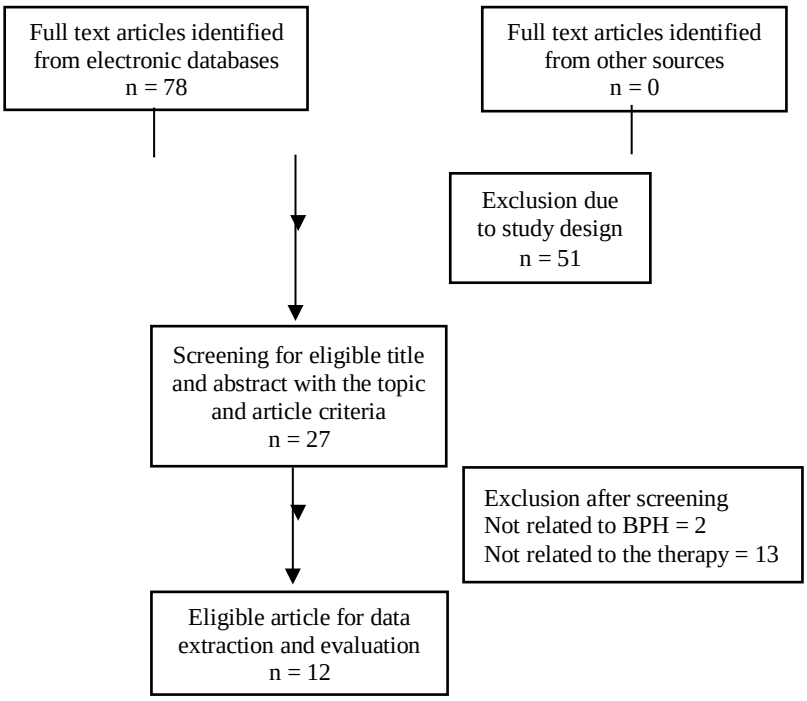

Figure 1. Literature Review Flowchart Diagram

2.5 Data Synthesis and Analysis

Due to heterogeneity in study designs, outcome measures, and treatment durations, a qualitative synthesis of findings was conducted. Outcomes of interest were narratively compared, focusing on trends in symptom improvement (e.g., changes in IPSS and Qmax) and safety profiles between the combination therapy and monotherapy groups.

3. Discussion

This literature review evaluated and compared the efficacy and safety of combination therapy using tamsulosin and tadalafil versus tadalafil monotherapy in patients with BPH presenting with LUTS. A total of twelve clinical studies were included, consisting primarily of randomized controlled trials, placebo-controlled trials, and prospective studies published between 2008 and 2022. The selected studies varied in sample size (ranging from 26 to 612 participants), geographic focus, and intervention design. Summary of the selected studies are included on Table 1.

Table 1. Summary of Included Studies on Tadalafil and Tamsulosin for BPH-LUTS

Study	Design	Size	Intervention vs Comparator	Population	Key Outcomes	Main Findings
AbdelRazek *et al.* [10]	RCT	308	Tadalafil vs Silodosin vs Combination	Men >50 years with LUTS/BPH	IPSS, Qmax, IIEF, PVR	Combination therapy superior to either monotherapy in all outcomes; well tolerated.
Baghani Aval *et al.* [11]	RCT, double-blind	80	Tamsulosin + Tadalafil vs Tamsulosin + Placebo	Men with AUR due to BPH	Catheter-free rate	No significant difference at 24h or 1 week; both arms well tolerated.
Oelke *et al.* [12]	RCT, placebo-controlled	511	Tadalafil vs Tamsulosin vs Placebo	Men ≥45 years with LUTS/BPH	Treatment Satisfaction, IPSS, Qmax	Tadalafil improved treatment satisfaction; tamsulosin did not differ from placebo.
Negoro *et al* [13]	RCT, crossover	26	Tamsulosin + Tadalafil vs Tamsulosin + Placebo	Men ≥50 years with small prostate & persistent LUTS	IPSS, Qmax, IIEF-5	Tadalafil add-on significantly improved total IPSS and voiding symptoms.
Oelke *et al* [14]	RCT	511	Tadalafil vs Tamsulosin vs Placebo	Men ≥45 years with LUTS/BPH ± ED	IPSS, Qmax, IIEF, TSS-BPH	Both active arms improved IPSS; tadalafil also improved erectile function and satisfaction.
Giuliano *et al.* [15]	RCT	310	Tadalafil vs Tamsulosin vs Placebo	Men with LUTS/BPH and ED	IIEF domains, ejaculation, satisfaction	Tadalafil improved orgasm, ejaculation, and satisfaction; tamsulosin worsened some

						sexual outcomes.
Yokoyama *et al.* [4]	RCT	612	Tadalafil 2.5 & 5 mg vs Tamsulosin 0.2 mg vs Placebo	Asian men ≥45 years with LUTS/BPH	IPSS, Qmax, BII, QoL	Tadalafil 5 mg improved LUTS with good tolerability; tamsulosin less effective on flow metrics.
Singh *et al.* [16]	Open-label RCT	100	Tadalafil 5 mg vs Tamsulosin 0.4 mg	Men >45 years with LUTS-BPH (IPSS >7)	IPSS, Qmax, PVR, QoL, IIEF	Both drugs effective; tadalafil better on storage symptoms, tamsulosin better on QoL
Singh *et al.* [17]	Prospective RCT (3-arm)	133	Tadalafil 10 mg, Tamsulosin 0.4 mg, Combination	Men >45 years with LUTS–BPH (IPSS >8, PSA ≤4)	IPSS, Qmax, PVR, QoL, IIEF	Combination therapy showed greatest improvement; all treatments improved LUTS and erectile function
Kim *et al.* [18]	Double-blind RCT	510	FDC Tamsulosin/Tadalafil vs Tadalafil 5 mg	Men >50 years with LUTS (IPSS ≥13) and ED	IPSS, IIEF-EF, Qmax, PVR, QoL	FDC 0.4/5 mg superior for LUTS, non-inferior for ED; safe and improved compliance
Bechara *et al.* [19]	Double-blind RCT	27	Tamsulosin 0.4 mg vs Tamsulosin 0.4 mg + Tadalafil 20 mg	Men >50 years with LUTS/BPH	IPSS, IPSS-QOL, Qmax, PVR, IIEF-EF, GAQ	Tamsulosin 0.4 mg/day plus tadalafil 20 mg/day was more effective than tamsulosin 0.4 mg/day alone to improve LUTS and ED
Karami *et al.* [20]	RCT	183	Tadalafil 20 mg, Tamsulosin 0.4 mg, and Tamsulosin 0.4 mg + Tadalafil 20 mg	All patients with LUTS, BPH, and any grade of ED	Prostate volume, PSA, PVR, IPSS, LUTS severity, Qmax, IIEF and ED severity	Combination of tamsulosin and tadalafil are better than their separate use and recommended because of its synergistic effects, well

	toleration and safety.

Abbreviations
BPH = Benign Prostatic Hyperplasia
LUTS = Lower Urinary Tract Symptoms
IPSS = International Prostate Symptom Score
Qmax = Maximum Urinary Flow Rate
IIEF = International Index of Erectile Function
PVR = Post-Void Residual
ED = Erectile Dysfunction
RCT = Randomized Controlled Trial
AUR = Acute Urinary Retention
BII = BPH Impact Index
TSS-BPH = Treatment Satisfaction Scale for BPH
PSA = Prostate Specific Antigen

BPH is a non-malignant enlargement of the prostate gland, primarily due to hyperplasia of epithelial and stromal cells in the periurethral transition zone. Histologically, it is characterized by increased cellular proliferation, while clinically it manifests through LUTS, including urinary frequency, urgency, nocturia, weak stream, and incomplete emptying, caused by urethral compression due to gland enlargement.[8]

The pathophysiology involves static and dynamic components. The static aspect is due to proliferation of stromal and epithelial cells in the transition zone of the prostate causing physical compression of the urethra and mechanical obstruction of urine flow.[8] The dynamic component is associated with increased smooth muscle tone mediated by alpha-adrenergic receptors. This elevated tone contributes to functional obstruction and is a target for several pharmacologic therapies aimed at improving urinary flow and reducing LUTS.[9]

Most studies reported that combination therapy yielded superior improvements in symptom scores (primarily the IPSS), urinary flow parameters (Qmax), quality of life, and in some cases, sexual function (e.g., IIEF scores), compared to tadalafil monotherapy. While tadalafil alone was also effective, particularly in patients with comorbid ED, its efficacy in isolation appeared comparatively modest in patients with more severe LUTS or limited α-blocker response.

The observed superiority of combination therapy can be explained by its mechanistic synergy. Tamsulosin, a selective α1-adrenoceptor antagonist, targets dynamic obstruction in the prostatic urethra by relaxing smooth muscle in the prostate and bladder neck. In contrast, tadalafil, a PDE5-I, exerts its effects via the NO–cGMP signaling pathway, resulting in smooth muscle relaxation in the lower urinary tract and improved tissue perfusion in the pelvic region. This dual pathway enables the combination to target both voiding dysfunction and vascular contributions to LUTS, especially relevant in aging males with endothelial dysfunction.[4]

Regarding tolerability, both agents were generally well accepted as for α-blockers may cause ejaculatory disorders, dizziness, or orthostatic hypotension, while tadalafil's sexual benefits make it favorable for patients affected by α-blocker-induced sexual side effects.[21][22]

Multiple high-quality RCTs reinforce this hypothesis. AbdelRazek *et al.* (2022) found that combining tadalafil with silodosin significantly improved IPSS, Qmax, and erectile function compared to either agent alone. However, as the overall improvements in LUTS IPSS and ED (IIEF) were similar in the three treatment arms, therapy may become increasingly patient-oriented and personalized. More precise counseling and medications might be offered in daily clinical practice. Tadalafil 5 mg daily was well tolerated both in monotherapy and in combination with silodosin 8 mg.[10]

Bechara *et al*. (2008) showed that tamsulosin 0.4 mg/day combined with tadalafil 20 mg/day for 6 weeks improved voiding symptoms and erectile function more than tamsulosin alone.[19] Similarly, Singh et al. (2014) and Karami et al. (2016) found that tamsulosin 0.4 mg/day combined with tadalafil 10–20 mg/day was more effective than either drug alone in relieving LUTS and ED, supporting the synergy of this combination.[16][20]

Negoro *et al.* (2019) demonstrated that even in small prostates with persistent LUTS, tadalafil add-on reduced symptoms significantly, particularly voiding complaints. The improvement is showed in Figure 2. Decreasing IPSS total scores without significant effects on Qmax is a characteristic effect of PDE5-I compared with α1-

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adrenoceptor blockers. PDE5-I have variable effects on LUTS which may lead to the add-on effects of tadalafil on tamsulosin.[13]

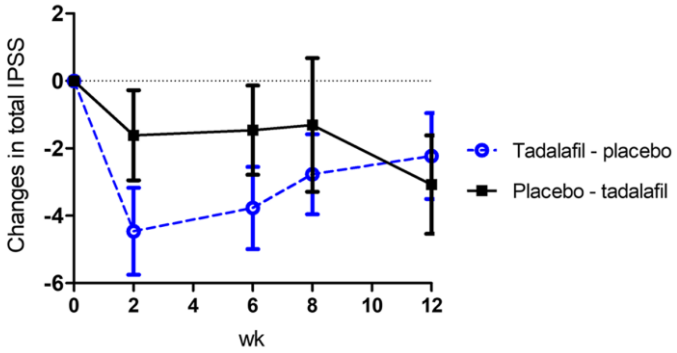

Figure 2. Changes in total IPSS from baseline [13]

Oelke *et al.* (2012) further supported the efficacy of tadalafil monotherapy compared to tamsulosin, while highlighting its added benefit in improving erectile function—a domain where α1-blockers are generally neutral or even detrimental. Tadalafil significantly improved ED compared with placebo in sexually active men with ED, while tamsulosin did not. Figure 3 showed improvements that tadalafil and tamsulosin similarly reduced the symptoms at 4 and 12 week.[14] Kim *et al.* (2017) assessed whether a fixed-dose combination (FDC) of tamsulosin 0.4 mg and tadalafil 5 mg (FDC 0,4/5 mg) or tamsulosin 0.2 mg and tadalafil 5 mg (FDC 0,2/5 mg) offers superior benefits compared to tadalafil monotherapy (5 mg daily) in men with LUTS due to BPH who also have ED. The tamsulosin/tadalafil (FDC 0.4/5 mg) offers enhanced LUTS improvement over tadalafil alone, while preserving erectile function and maintaining good tolerability.[18]

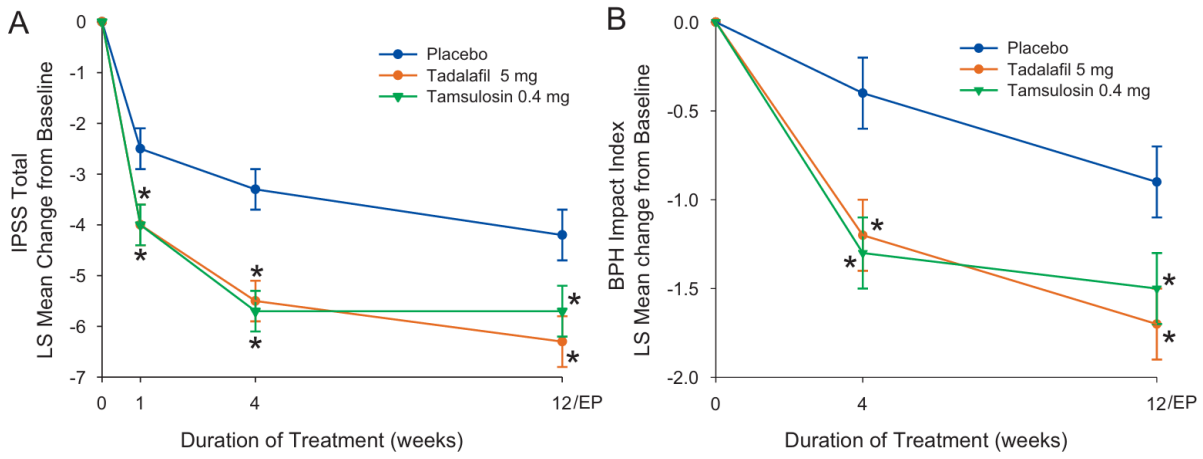

Figure 3. Changes from baseline in (A) total IPSS and (B) BPH Impact Index[14]

Singh et al. (2020) found tadalafil 5 mg and tamsulosin 0.4 mg were similarly effective for moderate-to-severe LUTS. Tadalafil offers an alternative, especially for patients with concurrent ED, given its comparable efficacy and safety profile.[16] On the contrary, Baghani Aval *et al.* (2018) found that adding tadalafil in patients with acute urinary retention did not significantly improve catheter-free rates, questioning its role in mechanically obstructive settings. Its muscle relaxant effect on the detrusor may counteract benefits on bladder neck opening, although higher doses might yield better outcomes.[11]

Tadalafil's sexual benefits are noteworthy. In the study by Giuliano *et al.* (2013), tadalafil also enhanced ejaculatory and orgasmic function, distinguishing it from tamsulosin, which showed a neutral to negative impact on sexual satisfaction. These findings affirm tadalafil's role in managing patients with overlapping LUTS and sexual dysfunction—an increasingly recognized clinical phenotype.[15]

These findings align with the 2020 EAU Guidelines, which recommend individualized treatment for men with moderate-to-severe LUTS and ED. While both drugs are guideline-endorsed, evidence supports tailored combination therapy for selected patients.[7]

The findings of this review have clear relevance for clinical practice. Combination therapy with tamsulosin and tadalafil should be considered in men with moderate-to-severe LUTS who have an insufficient response to monotherapy, particularly when associated with concurrent ED. The potential for simultaneous improvement in urinary symptoms, sexual function, and patient-perceived satisfaction may lead to greater adherence and overall quality of life. However, treatment selection must consider patient-specific factors such as cardiovascular comorbidities, baseline blood pressure, medication tolerability, cost, and individual preference.

The methodological limitations of the reviewed studies warrant careful consideration. Most trials were of short duration (typically 12 weeks), limiting the ability to assess long-term efficacy, safety, and adherence. Several studies, such as those by Yokoyama et al. (2012), were conducted exclusively in Asian populations, potentially limiting the generalizability of findings to broader global cohorts. There was considerable heterogeneity in the α1-blocker agents used (e.g., tamsulosin, silodosin), dosages, and baseline patient characteristics (e.g., prostate volume, presence or absence of ED), which complicates direct comparison across studies.

Additionally, outcome measures varied. While IPSS and Qmax were consistently used, other important metrics such as PVR, treatment satisfaction, nocturia episodes, and sexual function were inconsistently reported. Many trials also lacked head-to-head comparisons between fixed-dose combinations versus separate agent administration, and few studies rigorously evaluated health economics or patient adherence over time.

This review has several limitations. It included only peer-reviewed studies published in English, potentially introducing selection and language bias. The absence of a meta-analysis due to clinical heterogeneity precluded quantitative synthesis of effect sizes. Although the included studies were generally high in methodological quality, gray literature and unpublished trials were not considered, which could lead to an overrepresentation of positive outcomes (publication bias). Additionally, the review relied primarily on clinical endpoints; real-world effectiveness data remain limited.

Larger, longer-term RCTs are needed to evaluate the durability and safety of combination therapy. Comparative studies across different α1-blocker–PDE5-I regimens and delivery formats (fixed vs. free combination) are warranted. Real-world studies should assess adherence, cost-effectiveness, and subgroup responses (e.g., based on prostate size, sexual activity, comorbidities) to support personalized therapy.

4. Conclusion

This literature review highlights that combination therapy using tamsulosin and tadalafil is more effective than tadalafil monotherapy in improving LUTS due to BPH, particularly in men with coexisting erectile dysfunction. The therapeutic synergy between the α1-blocker's smooth muscle relaxation and the PDE5-I's vascular and neuro-modulatory effects offers enhanced symptom control and patient satisfaction. Further research should focus on long-term safety data, cost-effectiveness, and real-world adherence across diverse populations. The evolving evidence base supports the integration of personalized, multimodal strategies in the pharmacologic management of BPH-related LUTS.

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