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Review

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Therapeutic Applications of Alpha-Blockers: Pharmacology, Clinical Evidence, and Evolving Therapeutic Strategies

Jean Paule Joumaa[1], Joe Abou Jaoude[2,*], Carine El Khoury[1], Leona Antoun[1], Tony Sadek[1], Bendy Boulos[1]

[1] Faculty of Medicine and Biomedical Sciences, University of Balamand, Lebanon.
[2] Department of Urology, Lebanese American University Rizk Medical Center, Lebanon.

***Correspondence to:** Joe Abou Jaoude, MD – Department of Urology, Lebanese American University Rizk Medical Center, Lebanon. Email: joeaboujaoudee@gmail.com

Abstract: ***Background:*** Alpha blockers are alpha adrenergic antagonists commonly used in urology to treat many conditions; particularly benign prostatic hyperplasia (BPH), ureteric stones, lower urinary tract obstruction, and chronic pelvic pain syndrome (CPPS). These drugs fall into three categories: nonselective, alpha-1, and alpha-2 blockers. They primarily act on alpha-adrenergic receptors of the sympathetic nervous system, thereby decreasing the vascular tone and leading to the relaxation of the smooth muscle. Despite their high effectiveness, these medications contribute to adverse side effects like hypotension, weakness, tachycardia, and even tremors. ***Discussion:*** This review analyzes the pharmacological properties, therapeutic uses, comparative therapies, and safety profiles of alpha blockers (both selective and non-selective). The article addresses the pharmacodynamics and pharmacokinetics of the most commonly used agents like tamsulosin, silodosin, doxazosin, and alfuzosin. Additionally, a differential analysis of their therapeutic roles in monotherapies and combination therapies is presented, together with an evaluation of their clinical outcomes. Moreover, an interpretation of the determinants of treatment resistance is presented. ***Conclusion:*** Advances in precision medicine and therapeutic formulations point to potential development and highlight the limitations of current research in urology. Based on clinical evidence, this paper contributes to improved decision-making and appropriate therapeutic management with minimal invasive techniques.

Keywords: Alpha-Blockers; Benign Prostatic Hyperplasia (BPH); Lower Urinary Tract Symptoms (LUTS); Nocturia; Frequency; Urgency; Therapeutic outcomes; Combination Therapy; Treatment resistance; Precision medicine

1. Introduction

Lower Urinary Tract Symptoms or LUTS are symptoms pertinent to the urinary system, characterized by frequency, urgency, nocturia, and weak stream. Often, they are associated with benign prostatic hyperplasia (BPH), which is prevalent among aging men, increasing with age, and affecting more than 80% of men over 80 years [1]. LUTS have

been found to expose men to erectile dysfunction (ED), given that both conditions frequently occur together in middle-aged and older men [2].

Historically, BPH management was primarily surgical, including transurethral resection of the prostate (TURP), laser treatment, and open prostatectomy. With the development of pharmacotherapy, alpha-blockers (ABs) have transformed the treatment modality to less invasive approaches [3]. Alpha–blockers are now widely used in managing the moderate and severe LUTS or BPH. Recommended as first-line therapy by both the American Urological Association (AUA) and the Canadian Urological Association (CUA), alpha-blockers improves urinary obstruction by hindering the effects of norepinephrine on the alpha–adrenergic receptors of smooth muscles of the prostate and bladder neck, reducing prostatic tone and improving urinary flow [4].

The mechanism of action includes the α1A-adrenergic receptor, a G protein-coupled receptor, enabling the contraction of smooth muscle through pathways involving inositol triphosphate (IP3) and diacylglycerol (DAG). Thereby, alpha-blockers relieve LUTS symptoms through an inhibitory mode of action, causing muscular relaxation of the smooth muscle of the prostate and bladder neck [5]. Furthermore, some highly selective alpha-blockers provide additional benefits in alleviating afferent bladder signaling, offering improvements in both excretion and storage symptoms [5].

Since α1-adrenoceptors are prominently distributed along the ureter, alpha-blockers effectively ease ureteroscope procedures (URS) and decrease the need for adjunctive interventions like balloon dilation.[6] Moreover, these medications aid in stone expulsion (by lowering ureteral tone and intra-ureteral pressure), urinary tract dysfunction (by reducing urinary retention after operations), and the preservation of sexual function (better ejaculatory outcomes due to their vasodilatory effects on ED) [1,2,7–9]. Even though alpha-blockers are the cornerstone of many treatments, they are not consistently effective. In a substantial number of patients, efficacy in symptom management fails.

Diverse factors are responsible for this therapeutic variability, including drug absorption and metabolism, receptor availability and expression, dosing regimens, and treatment compliance. Compliance is decreased in younger males due to the undesirable effects of many agents on sexual function. [1,2]

This review highlights the disparities in therapeutic effectiveness and the unexplained failure of alpha-blockers in some cases. Additionally, the article assesses pharmacodynamic characteristics, therapeutic indications, efficacy, tolerability, and safety of this class of drugs. Moreover, this synthesis provides a basis to develop patterns and adjunctive therapy to better understand the limitations of LUTS contemporary treatments.

2. Discussion

2.1. Pharmacology of Alpha-Blockers

a-Mechanism of Action

Alpha-blockers function as a receptor inhibitor for several alpha-adrenergic binding sites [10]. Notably, alpha adrenergic receptors belong to the G-protein receptor superfamily, which includes two subtypes known as alpha and beta. They comprise various structurally related isoforms like alpha 1, alpha-2, beta-1, beta-2, and beta-3 [11]. Thereby, alpha-blockers antagonistically target alpha-1 and alpha-2 either alone, or both together.

There are three types of alpha-1 receptors that differ according to their location: alpha-1a, alpha-1b, and alpha-1d. These receptors are mostly found in the smooth muscle of the urogenital tract, vascular smooth muscle, and the bladder. Their selectivity varies depending on the receptor subtype [10]. Moreover, alpha-1 receptors, especially alpha-1-ADR, are present in the epithelium of the prostate [11]. These receptors mediate smooth muscle contraction by increasing the intracellular calcium level through the G-protein coupled receptor, stimulating phospholipase C, and the production of second messengers following the attachment of epinephrine and norepinephrine [12]. By antagonizing this pathway, alpha-blockers induce smooth muscle relaxation within the urogenital tract, improving urinary flow dynamics and reducing the severity of bothersome lower urinary tract symptoms[11]. Therefore, alpha-blockers remain fundamental in treating BPH with moderate-to-severe LUTS [13].

On the other hand, alpha-2 blockers suppress the vasoconstrictive mechanism of norepinephrine by blocking the stimulation of post-synaptic receptors triggered by catecholamine. This mechanism leads to

a decrease in blood pressure secondary to the decrease in the peripheral vascular resistance [14]. Unlike alpha-1 blockers, alpha-2 blockers involvement and use in urologic conditions remains limited.

b-Classification of Alpha-Blockers

Alpha blockers are classified as selective or non-selective. A subclass referred to as alpha-1A selective blockers has been identified among the selective group. Tamsulosin and silodosin which are used to treat benign prostatic hyperplasia, show high selectivity and affinity for alpha-1A-adrenergic receptors that act by reducing blood pressure [10]. Also, naftopidil presents threefold higher affinity for alpha-1D receptors compared to alpha-1A receptors and it is known for relieving both storage and voiding LUTS related to BPH[10].

On the other hand, non-selective alpha blockers are used to treat hypertension due to their ability to reduce the vascular resistance of the peripheral arterioles and increase venous capacitance, thus controlling blood pressure. Doxazosin, terazosin, and alfuzosin are nonselective alpha-1 blockers employed in the treatment of bladder neck obstruction [10]. In addition, phenoxybenzamine and phentolamine, are indicated for pre-surgical pheochromocytoma-related hypertension and urgent hypertension, respectively, along with other non-selective alpha blockers [14]. However, those agents are not recommended as unique treatments, but rather as an adjunctive therapy for high blood pressure [10].

Table 1 - Classification and Mechanism of Action of Alpha Blockers

Type	Drug(s)	Target Receptor	Effect
Non-selective	Doxazosin, Terazosin	α1A, α1B, α1D	Relax smooth muscle, lower blood pressure
Selective α1-Blockers	Tamsulosin, Silodosin	α1A	Target prostate and bladder neck, reduce LUTS
Selective α1B-Blockers	Prazosin, Doxazosin	α1B	Primarily reduce blood pressure
Selective α1D-Blockers	Alfuzosin, Naftodipil	α1D	Control bladder contraction

c-Pharmacokinetics and Pharmacodynamics

Among the non-selective alpha1 blockers, doxazosin (1-16 mg) which is administered orally once daily, presents a bioavailability of 65% and a half-life of 19-22 hours [14]. However, terazosin (1-20 mg) demonstrates a higher oral bioavailability reaching 90% and a half-life of 12 hours [14]. Alfuzosin, which is taken orally at 10 mg once daily, shows a bioavailability of 49% and an elimination half-life of 10 hours. [15]. Importantly, alfuzosin antagonizes alpha1-adrenergic receptors in prostatic smooth muscle, alleviating LUTS associated with benign prostatic hyperplasia.

Alfuzosin is primarily metabolized in the liver by the CYP3A4 enzyme, with 11% eliminated unchanged in urine [15]. In contrast, prazosin, demonstrates a rapid onset of action and a short half-life (2.5–4 hours), with an oral bioavailability ranging from 44% to 69% when taken two to three times daily at doses of 2–20 mg [14].

As a selective alpha-1A blocker, silodosin inhibits epinephrine and norepinephrine from binding to their receptors, consequently relaxing the bladder neck and prostatic smooth muscle and improving urinary flow. The drug presents an oral bioavailability of 32%, with a terminal half-life of 13 hours. When administered with food, silodosin's maximum plasma concentration (Cmax) decreases by 18–43%. Potentially, a toxic intermediate can be generated by CYP3A4 through the partial hepatic metabolism. [12].

Tamsulosin shows similar selectivity for alpha-1A and alpha-1D, with a high bioavailability reaching 100%, and a half-life of 16.3 hours. [15]. Naftopidil is mainly prescribed in Japan to treat BPH due to its minimal side effects; however, evaluation of its impact in other populations remains unclear.

2.2. Urologic Clinical Indications of Alpha-Blockers

Several indications and recommendations suggest the beneficial use of alpha-blockers in urology. BPH, a urological age-related enlargement of the prostate gland, is one of the indications to prescribe alpha-blockers for better symptomatic management[16]. Additionally, alpha-blockers are used in ureteric stones for medical expulsive therapy (MET). Kidney stones (nephrolithiasis) affect young adults, reporting colic pain, nausea, and emesis. Therefore, alpha-blockers are also recommended for these patients to facilitate the passage of distal stones measuring less than 10 mm [17]. The effectiveness of alpha-blockers in MET has been proven by 6 trials with a total of 563 patients receiving the placebo and silodosin (8mg) for 2-8 weeks. Results show that silodosin has notably increased the stone

expulsion rate (SER), sparing surgical intervention [18]. Also, four studies have been conducted on a total of 474 patients taking silodosin showing that this drug has reduced the stone expulsion time (SET) defined as the amount of time it takes to expel the stone [18]. Other investigations contrarily reported that in MET, the phosphodiesterase inhibitors (PDEIs) tadalafil, is more efficient in increasing SER compared to tamsulosin [17]. Regarding the efficacy and safety , a meta-analysis is conducted [19] proving that alpha-adrenergic blockers are safe to use although some mild side effects such as dizziness and retrograde ejaculation presented.

Furthermore, alpha-adrenergic antagonists are prescribed to patients with chronic prostatitis (CP)/ chronic pelvic pain syndrome (CPPS) and those undergoing a Trans-perineal Prostate Biopsy (TPB) (20,21). Most men presented with symptoms related to prostatitis which is the inflammation of the prostate gland. Studies have revealed that CP/CPPS, a category of prostatitis, can be treated with alpha-1- blockers especially silodosin that blocks their respective receptors in the central and peripheral nervous system improving the pressure applied by the bladder during urination. It has been recommended by the European Association of Urology (EAU) for patients with less than one year of CP/CPPS[21]. In addition, alpha-blocker drugs have been employed in TPB which is a technique commonly used to diagnose prostate cancer and involves inserting a needle through the perineum to take a sample biopsy. This procedure can cause complications such as inflammation and edema leading to the obstruction of the urethra. Thus, alpha blockers such as Tamsulosin are used to prevent acute urinary retention by relaxing the smooth muscles lining the prostate and urethra, enhancing urinary flow and counteracting the obstructive effects of swelling. The benefits of using alpha blockers with TPB have been demonstrated in a systemic review conducted by Loeb et al. It evaluates 24 studies analyzing the rate of AUR after TPB. The findings reveal a decrease of AUR with alpha blockers given before, during and after this procedure (1.6 and 8.8%) compared to 20.6% AUR where no alpha-blockers were employed [20].

Commonly, these agents are used in the management of LUTS in men with BPH, with the prostate enlarging and obstructing urine flow. EAU and American Urological Association (AUA) have urged patients with LUTS to take a combination therapy of PDEIs and alpha-blockers. This recommendation was backed-up by thirteen studies that compared the use of PDEIs in monotherapy and in combination therapy with alpha blockers where it has been shown that the dual therapy presented more improvement of the symptoms as opposed to the solo therapy [22]. This progress was seen in both IPSS total and IPSS QoL (quality of life) scores. Concerning the safety of this hybrid therapy, all studies reported that it is generally safe, although mild side-effects such as headache, dizziness and muscle pain were observed and well-tolerated [22]. Nonetheless, it has been noted that long-term use of alpha-adrenergic blockers such as tamsulosin may cause intraoperative floppy iris syndrome (IFIS) where the dilator muscle of the iris shrinks [23].

Moreover, alpha blockers are effective in perioperative urological care. Many patients experience urologic complications, commonly postoperative urinary retention (POUR), a condition in which the patient is unable to urinate even with a full bladder. A meta-analysis presented evidence that prophylactic tamsulosin aids in preventing this condition [24]. In this review, 394 out of 2221 patients developed POUR. However, analysis by groups showed that only 14.2% of patients receiving tamsulosin presented with POUR compared to 21.3% of those not receiving it, proving that POUR is consistently lower in patients treated with this alpha blocker. Nevertheless, patients who took this medication have experienced more side effects such as dizziness and IFIS [24]. Furthermore, prescribing tamsulosin before ureteroscopy, a technique used to treat urolithiasis, proved to be beneficial. Notably, tamsulosin inhibits ureteral smooth muscle contraction, resulting in relaxation of the ureteral opening, facilitating stone passage and decreasing postoperative symptoms such as fever and pain[25].

2.3. Efficacy and Comparative Studies

a- Monotherapy vs. Combination Therapy

• Alpha-Blocker Monotherapy

One of the earliest large scale RCTs conducted on these agents, specifically terazosin, showed a significant decrease in the Boyarsky score (score used before the creation of the IPSS) compared to placebo groups. [26] The PREDICT trial demonstrated that doxazosin once daily resulted in a mean reduction of 6.6 points in IPSS and an increase of 4.0 mL/s in Qmax over a 12-month period. [27]

Furthermore, a 2015 network meta-analysis by Yuan et al. (124 RCTs, n=58548) assessed α-blockers, 5-alpha reductase inhibitors (5-ARIs), phosphodiesterase-5 inhibitors (PDE5-Is), muscarinic receptor antagonists (MRAs), and placebo. The findings indicated that α-blockers, particularly doxazosin and terazosin, were the most effective in reducing IPSS and improving Qmax. Specifically, doxazosin showed a mean difference in IPSS of -3.67 and an increase in Qmax of 1.95 mL/s, and Terazosin demonstrated an IPSS MD of -3.37 and a Qmax increase of 1.21 mL/s, both compared to placebo. [28]

A more recent network meta-analysis by Yoosuf et al. (2024) from 22 RCTs on 3,371 patients, aimed to evaluate the comparative efficacy and safety profiles of various monotherapies, used in the treatment of LUTS secondary to BPH. The results confirmed that tamsulosin 0.4 mg, had the highest probability of improving key clinical outcomes compared to other monotherapies, such as IPSS, Qmax, and PVR. In addition, Doxazosin 8mg was associated with the greatest improvement in QoL. [29] Alpha blocker monotherapy remains the first-line therapy for bothersome LUTS in men, especially in cases of low progression and small prostate volume. Although monotherapy showed efficacy in symptomatic management, these agents alone did not prove to be effective in disease progression and risk of BPH-related surgery.

• 5-Alpha Reductase Inhibitors (5-ARIs)

The Proscar Long-Term Efficacy and Safety Study (PLESS) was a pivotal randomized, double-blind, placebo-controlled trial that evaluated the effect of finasteride in men with symptomatic BPH over 4 years. It demonstrated that finasteride 5mg reduced the risk of AUR by 57% and the risk for BPH-related surgery by 55%, while having a modest improvement for Qmax and IPSS [30]. The Enlarged Prostate International Comparator Study (EPICS) was a randomized, double-blind trial comparing the efficacy and safety of dutasteride and finasteride in men with symptomatic BPH. The study found that both medications reduced prostate volume by 25%, decreased serum PSA by 50%, improved Qmax and IPSS, and also prevented disease progression significantly [31].

A recent meta-analysis of RCTs on 23395 patients by *Kim et al. (2018)* also assessed the primary outcomes and the adverse events of 5-ARI monotherapy. It showed a modest improvement of IPSS and Qmax, respectively, by 1.93 pts and 1.2 mL/s, a significant reduction in prostate volume (6.02mL), and a serum PSA decrease (mean 0.68 ng/mL) compared to placebo. The risk of adverse events, including sexually related complications, was high, but generally tolerable. [32]

• Phosphodiesterase-5 Inhibitors

Tadalafil 5 mg daily has been approved for the treatment of LUTS secondary to BPH based on its dual benefit in alleviating urinary symptoms and erectile dysfunction (ED). Although changes in PVR were found to be generally minimal, several placebo-controlled trials demonstrated statistically significant reductions in IPSS (mean decrease of 6.3 points) and modest improvements in Qmax (1.6 mL/s)[33]

Further supporting these findings, Sebastianelli et al. (2019) conducted a prospective observational trial assessing tadalafil 5 mg, and found that PDE5-i monotherapy can be considered a primary treatment option for patients with LUTS/BPH and ED, highlighting its excellent tolerability, safety, and effectiveness profile, both alone and in combination with tamsulosin. [34]

Recent reviews further confirmed that PDE5is can be used as standalone agents or in combination with alpha blockers for enhanced symptom relief. While the magnitude of improvement in flow parameters is smaller than with a combination, the impact on QoL and ED makes these agents a valuable option in appropriately selected patients. [35]

• Combination of Alpha-blockers and 5-ARIs

The combination of a 5-ARI to an alpha-blocker is one of the most well-established strategies for treating moderate-to-severe LUTS in BPH. The MTOPS (Medical Therapy of Prostatic Symptoms) trial, was a pivotal study that compared the use of alpha-blockers, 5-ARIs, and their combination in men with BPH. Results demonstrated that their combination significantly improved both symptom scores and peak urinary flow rates when compared to either agent alone. Specifically, combination therapy reduced the risk of AUR and the need for surgical intervention by 66% compared to placebo, whereas doxazosin and finasteride monotherapies reduced the risk by 39% and 34%, respectively. [36]

Furthermore, in the CombAT (Combination of

Avodart and Tamsulosin) trial, the combination of dutasteride and tamsulosin also showed a reduction of symptoms compared to either monotherapy, over a 4-year observation. Specifically, the combination therapy group experienced a mean IPSS reduction of 6.3 points, compared to 3.8 points with tamsulosin and 5.3 points with dutasteride and an increase in Qmax of 2.4 mL/s, compared to 0.7 mL/s with tamsulosin and 2.0 mL/s with dutasteride. In addition, combination therapy significantly reduced the risk of AUR and BPH-related surgery compared to tamsulosin monotherapy. [37] As expected, dual therapy was associated with higher incidence of sexual effects, such as decreased libido, ejaculation disorders, and ED. Nevertheless, its effectiveness in preventing disease progression has proven better results on the long term in patients with moderate-severe BPH with enlarged prostates. [38] A recent systematic review on the Asian male population by Lee et al. (2024) also showed that combination therapy led to great improvements in both storage and voiding. On the other hand, IPSS maximal improvement was observed after 6 months, which highlights 5-ARIs time-dependent effects. It also detected higher risk of sexual dysfunction, that were also acceptable and manageable. [39]

• Combination of Alpha-Blockers and PDE5 Inhibitors

The combination of alpha-blockers and PDE5i is considered very effective for patients who suffer from both BPH and erectile dysfunction (ED). An analysis by Yan et al. (2014) assessed the efficacy of PDE5 inhibitors alone or in combination with alpha-blockers for treating ED and LUTS due to BPH. It demonstrated that the combination therapy significantly improved IIEF (International Index of Erectile Function-Erectile Function), IPSS, and Qmax values compared to PDE5 inhibitor monotherapy. [40] Ma et al. (2020) conducted a network meta-analysis analyzing 7 RCTs on 531 participants. The findings indicated that the combination of sildenafil (25 mg daily) with tamsulosin (0.4 mg daily) was most effective in improving the IIEF scores. Additionally, their combination showed the greatest improvement in Qmax, while being ranked highest in safety outcomes, suggesting it as a well-tolerated treatment option for BPH-LUTS with or without ED. [41] Another meta-analysis by Chen et al. (2021) also concluded that combination therapy was superior in improving LUTS severity. Although PDE5 inhibitors had slightly higher incidence of adverse events, such as headache, dyspepsia, and back pain, the combination therapy was generally well-tolerated, offering a clinically meaningful advantage over monotherapy for men with LUTS/BPH, particularly when ED coexists. [42]

• Combination of Alpha-blockers and Anticholinergics

Patients with BPH and concomitant overactive bladder symptoms such as urgency, frequency, and nocturia; alpha-blockers combined with anticholinergics showed significant benefits. In a randomized, double-blind trial, men treated with tamsulosin combined with extended-release oxybutynin (10 mg) experienced significantly greater improvements in IPSS compared to those receiving tamsulosin with placebo after 8 and 12 weeks of treatment. While the combination of alpha-blockers and antimuscarinics is generally well-tolerated, caution is advised in patients with high PVR due to potential increased risk of AUR. However, the incidence of post-void residual (PVR) volumes exceeding 300 mL was low and not statistically significant between groups. [43]

Furthermore, a comprehensive analysis of 15 randomized studies involving 4,556 patients demonstrated that the addition of antimuscarinics to alpha-blockers significantly improved urgency and frequency episodes, IPSS, and storage sub-scores compared to alpha-blocker monotherapy. Moreover, the addition of antimuscarinics had little effect on urinary function while adverse events were acceptably low. [44] On another hand, a Cochrane systematic review by Pang et al. (2021), including 23 RCTs encompassing 6,285 men aged 40 years and older with moderate to severe LUTS (IPSS $\geq$ 8) over a period of 12 weeks to 12 months, revealed that combination therapy is associated with little or uncertain effects on urologic symptom scores compared to placebo, alpha-blockers, or anticholinergics monotherapy. However, it may result in an improvement in QoL compared to anticholinergics monotherapy. [45]

b- Comparative Effectiveness of Different Alpha-Blockers

There is no doubt that alpha blockers are the cornerstone for treating LUTS and stone medical expulsive treatment. As previously mentioned, among monotherapies, tamsulosin 0.4 mg had the highest probability of improving key clinical outcomes compared to other monotherapies, such as IPSS, Qmax and PVR. On another note, Doxazosin 8mg ranked

first in QoL improvement. [29] A systematic review and network meta-analysis by Yong Nam Gwon et al. (2023), compared the effects of different alpha-blocker regimens on AUR and the success rate of trial without catheter (TWOC). Specifically, the combination of alfuzosin and tamsulosin offered the highest efficacy, followed by tamsulosin, silodosin, alfuzosin, and doxazosin alone. [46]

For stone medical expulsive therapy, particularly sized 5-10mm, silodosin was found to be more effective than tamsulosin in facilitating expulsion while also offering the benefits of shorter time (mean -2.55 days) and reduced pain episodes (-0.3). [47] Another study also reported the highest stone expulsion rate and stone expulsion time with silodosin, with no differences in complication rates between silodosin and tamsulosin.[48] Finally, Sharma et al. (2022) ranked the three commonly used alpha blockers for stone expulsive therapy as silodosin, alfuzosin, and tamsulosin respectively in both stone expulsive rate (Surface Under the Cumulative Ranking Curve of 94.8%, 58.8% and 46.2%) and stone expulsion time (90.4%, 64.9%, 44.5%) compared to placebo. [49] Kwon et al. further expanded the studies by targeting alpha blockers' effect on ureteral stent-related discomfort using Ureteric Stent Symptoms Questionnaire (USSQ), focusing on Urinary Symptom Score (USS) and Body Pain Score (BPS). Alfuzosin and tamsulosin efficacy was statistically the same for both scores, with tamsulosin having a higher rank probability. [50]

Tamsulosin, being highly selective for the α1A-adrenoceptor subtype, effectively targets the prostate and bladder neck while minimizing cardiovascular effects. Its most commonly reported adverse events include mild dizziness, orthostatic hypotension, and ED, although the latter tends to be less frequent than with silodosin. Silodosin, which has an even higher affinity for the α1A receptor, has demonstrated superior efficacy in stone expulsion and storage symptom relief, but is consistently associated with a higher rate of retrograde ejaculation, reported in up to 28% of patients in some trials [47], [5]. Alfuzosin, which is less selective for α1A, shows fewer sexual side effects but greater incidence of dizziness, hypotension, and fatigue, particularly in elderly patients. This was highlighted in the post-marketing surveillance study by Visingardi et al. (2024), concluding that tamsulosin showed the most favorable safety data. [51] Finally, doxazosin and terazosin, the least selective agents, are associated with the highest rates of systemic hypotension, syncope, and orthostatic dizziness, making them less suitable for older adults or those with cardiovascular comorbidities.

Patients' adherence to alpha blockers monotherapy for LUTS is an important factor in recurrence symptoms or progression of disease. In fact, in a study by Cindolo et al. (2015), patients on monotherapy had an adherence rate of 35% at 1year and 15% at 5 years. In addition, patients on combination therapy (AB + 5-ARIs) had even lower adherence rates with 3% at 5 years. [52] Among all alpha-blockers, tamsulosin is generally associated with better adherence, likely due to its milder side effects, once-daily dosing and strong physician familiarity. In contrast, silodosin has higher chances of discontinuation due to bothersome retrograde ejaculation in sexually active men. In addition, alfuzosin, often favored in patients with concerns about sexual function, may still face discontinuation due to cardiovascular side effects, especially in elderly or poly-medicated population. If patients were to take combination therapy, fixed-dose combinations (FDCs) offered advantages in terms of patient adherence and convenience. In fact, FDC reduces pill burden and simplify treatment regimens, while also being cost effective. [53] The study by Eisen et al. (2020) also support this idea and found that patients on the FDC had significantly higher adherence rates, with 41.8% remaining persistent at 12 months compared to 41.0% in the free-combination group. Moreover, a higher proportion of FDC-treated patients achieved a medication possession ratio (MPR) ≥ 0.80, indicating better adherence. [54]

2.4. Real World Data vs. Randomized Controlled Trials

While RCTs remain the gold standard for evaluating the efficacy and safety of pharmacologic therapies in BPH, they often take place under controlled environments that may not fully reflect real-world clinical practice. Most RCT evaluating alpha-blocker monotherapy have consistently demonstrated significant improvements, however, these trials frequently exclude older adults with multiple comorbidities, polypharmacy, or poor adherence potential. Consequently, their external validity may be limited when applied to the real-world data, where the population is more broad and

heterogenous. In fact, Real-world observational studies provide valuable insights into treatment effectiveness in routine clinical settings. A study by Cindolo et al. reported that the 1-year adherence for alpha blocker monotherapy rate was 29% among patients exposed to at least 6 months. Patients on combination therapy had a higher discontinuation rate in the first 2 years compared to those on monotherapy. This demonstrated that discontinuation of drug treatment was an independent risk factor for hospitalization for BPH management and surgical intervention, regardless of the therapeutic group. [55]

Another systematic review conducted in 2019 on 1081 patients found that discontinuing alpha-blocker monotherapy led to a worsening of symptoms compared to continuing therapy, with up to 49% of patients restarting treatment after discontinuation. Even though adverse effect did not change with discontinuation, this study highlights the importance of adherence in managing BPH symptoms effectively, which is underscored in most studies. [56] These two findings are examples of discrepancies between real world data and RCT. This emphasizes the need to consider both sources when in need to make clinical decisions. Indeed, while RCTs show the benefits of these therapies under ideal conditions, real world data offer insights on treatments performance in everyday clinical practice, accounting for factors such as patient adherence and tolerability.

2.5. Why Do Patients Fail Alpha-Blocker Therapy

Despite their widespread use and proven efficacy in improving LUTS, some patients fail alpha-blocker monotherapy over time. Failure can be attributed to different causes: insufficient symptom relief, intolerance to adverse effects, and progression of underlying pathophysiology not addressed by alpha-blocker use alone. Symptomatic non-responders constitute a notable subset of patients. Despite the fact that clinical trials report a considerable improvement of IPSS and Q_{max}, approximately 20–30% of patients experience inadequate clinical improvement [37]. This failure may reflect non-obstructive etiologies of LUTS, such as unrecognized detrusor underactivity, poor bladder compliance, overactive bladder or nocturnal polyuria. Additionally, as demonstrated in the MTOPS trial, alpha blocker monotherapy has no significant effect on in reducing the long-term risk of AUR or need for surgery, especially in patients with larger prostate volume or elevated serum PSA levels, needing initial combination therapy. [36] On another note, disease progression despite initial symptom control can also occur. Over time, patients may develop worsening bladder outlet obstruction, bladder decompensation, or complications such as recurrent infections or bladder stones, necessitating escalation to combination therapy or surgical management. [36]

Another major cause of treatment discontinuation is intolerance to side effects. Selective alpha blockers can cause ejaculatory dysfunction (18–28%); a cause of premature cessation, particularly in sexually active younger men. On the other hand, non-selective alpha-blockers, have side effects that can significantly impair QoL, such as orthostatic hypotension (up to 15%), dizziness (10–12%), asthenia, and nasal congestion.[57] Lastly, behavioral and psychosocial factors also contribute to discontinuation. Patient expectations influence perceived treatment failure. Inadequate patient education regarding the onset of action, realistic goals, and non-curative nature of alpha-blockers can lead to early dropout.

In summary, failure of alpha-blocker therapy is multifactorial and highlights the importance of individualized treatment selection, baseline risk stratification (serum PSA, prostate size), and ongoing patients' evaluation of both symptomatic response and disease progression. Finally, as the general management continues to evolve, tailoring therapy to each patient needs and preferences is most likely going to ensure that treatment strategies are both effective and meet discussed expectations. [58]

2.6. Safety and Adverse Effects

a-Common Side Effects and Tolerability

Generally, the pharmacological class of alpha-blockers shows good tolerability, however, their safety profiles vary between compounds. Commonly encountered adverse events include hypotension, dizziness, headache, and, remarkably, sexual dysfunction (ejaculatory disorders). For instance, non-uniform dosage of tamsulosin can cause plasma levels to fluctuate, raising the probability of adverse reactions namely altered voice, headaches, nasal congestion, palpitations, and postural hypotension [3]. Population subgroup assessment showed that tamsulosin may increase the susceptibility of side effects relative to

placebo. However, this doesn't apply for silodosin and doxazosin. [59]

In the case of sexually active men, 70% become non-compliant as soon as the drug disturbs sexual function. In particular, 90% of men taking tamsulosin 0.8mg suffered from decreased ejaculate volume, and one third of them experienced anejaculation [1]. In contrast, some drugs with high urological selectivity such as alfuzosin, showed a diminished amplitude of sexual adverse reactions (consequent non-adherence ranged from 5.8% to 11.8%, which is close to placebo) [60]. In addition, silodosin increases the incidence of retrograde ejaculation, but in an adjustable manner, hence the higher adherence to this latter [61,62]. Other side effects could include orthostatic hypotension, dizziness, headache [63].

Table 2 - Common Side Effects and Safety Profile of Alpha Blockers

Alpha Blocker	*Common Side Effects*	*Severity*	*Management/Recommendation*
Tamsulosin	Retrograde ejaculation, dizziness	Mild to Moderate	Monitor for sexual dysfunction, adjust dose as necessary
Silodosin	Retrograde ejaculation, dizziness	Moderate	Consider alternative if ejaculatory dysfunction is severe
Doxazosin	Orthostatic hypotension, fatigue, dizziness	Severe in elderly	Avoid in patients with cardiovascular issues, monitor blood pressure
Alfuzosin	Dizziness, fatigue, orthostatic hypotension	Moderate	Use with caution in elderly, monitor blood pressure

b-Drug Interactions

On another note, drug interactions are a crucial factor of the safety record of alpha-blockers. In particular, alfuzosin, combined with antihypertensive medications, antimuscarinic agents, or phosphodiesterase type 5 inhibitors (PDE5-Is) indicates a favorable safety profile with low occurrence of adverse reactions. In the ALF-ONE study involving over 6,500 patients, none of the factors (age, cardiovascular concomitant diseases, antihypertensive combination drugs) disrupted the safety of alfuzosin 10mg. The most common side effect was dizziness(4.8%), but hypotension was uncommon (0.7%) [60].

Also, safety of alfuzosin was not compromised in patients with BPH and hypertension (taken alone or in combination with antihypertensive therapy), in contrast, the drug treated high systolic and diastolic blood pressure in patients with uncontrolled hypertension. Moreover, the combination of alfuzosin with PDE5-Is, such as tadalafil or sildenafil, reported enhancements in urinary and sexual symptoms without amplifying the occurrence of side effects [2,60]. However, despite the positive effect of combination therapies of PDE5-Is with alpha blockers, they have the potential to increase the risk of symptomatic hypotension, headache, and dizziness [63].

c-Longterm Safety Considerations

Extended safety evaluations highlight the generally mild cardiovascular risk associated with many alpha-blockers, particularly the newer and more selective types. Alfuzosin, for example, has a safe cardiovascular profile: a study proved the minor cardiovascular involvement of this drug with a 10mg does not modifying neither blood pressure nor heart rate [60]. The improved receptor selectivity of drugs such as tamsulosin and silodosin minimizes cardiovascular risks, making them suitable for inclusion in comprehensive antihypertensive treatment plans. As previously employed as antihypertensive drugs given their ability to counter sympathetic overactivity, alpha blockers are still used as supportive therapies in patients with resistant hypertension or chronic kidney disease (their effect on the renin-angiotensin-aldosterone system is neglectable) [63,64]. Also, the possible effect of alpha blockers on metabolism should be considered when talking about long term concerns since, a correlation between these drugs and the onset of either diabetes or congestive heart failure is proposed by epidemiologic studies[63]

Concerning ophthalmic risk factors, silodosin and tamsulosin could be responsible for floppy iris syndrome (IFIS) during cataract surgery, the latter exhibiting higher incidence; a disparity resulting from tamsulosin's potent suppression of iris dilator muscle activity. Consequently, it is recommended to evaluate patients of cataract surgeries prior to treatment, considering non selective alpha blockers as alternatives [64]. Recent studies have brought into question the role of alpha-

blockers in prostate cancer detection and management. After cytotoxic properties in quinazoline compounds were identified, retrospective data indicate a potentially reduced risk of prostate cancer among long-term users. Nevertheless, clinical evidence remains insufficient, emphasizing the necessity of further comprehensive studies to clarify the role of alpha-blockers in prostate cancer treatment [5,65].

2.7. Emerging Trends

Physicians initially use α blockers for treating lower urinary tract symptoms (LUTS) caused by benign prostatic hyperplasia (PBH). This medication works on reducing the muscle tone by inhibiting the effects of norepinephrine on the smooth muscle in the prostate and bladder neck [66]. Another important treatment of BPH is the use of 5-α-reductase inhibitors (5-ARI), dutasteride and finasteride, which work by suppressing 5 α reductase enzyme, responsible for the conversion of testosterone into dihydrotestosterone (DHT) contributing to the growth of the prostate. Therefore, low levels of DHT may lead to shrinkage of the prostate reducing the risk of BPH [67].

A meta-analysis study demonstrate that silodosin decreases the expulsion time, limits the analgesic requirement, and exhibits higher selectivity for α1A-adrenergic receptors compared to tamsulosin hydrochloride, naftopidil or prazosin hydrochloride [68]. In case of ureteral stones, the size of the stone and its location play a crucial role in the spontaneous stone passage and the success of medical expulsive therapy. Larger stones are less likely to pass on their own as compared to smaller ones. Nonetheless, the usage of silodosin substantially raise the stone-free rate (SFR) to 62% for 5-10 mm stones as compared to just 26% with water [68]. Despite having retrograde ejaculation as the most commonly reported side effect, this medication is considered superior to other α blockers for the treatment of ureteral stones. Similarly, another meta-analysis evaluates the benefits of α adrenergic blockers in the treatment of ureteral stones for pediatric patients. α blockers like doxazosin, tamsulosin, and silodosin reduce the expulsion time by 5.18 days and increase the rate by 1.42 times regardless of the age of the children and the size of the stone [69]. Furthermore, a large RCT highlights the effectiveness of silodosin by randomly assigning 167 children into two groups, one receiving tamsulosin and the other group silodosin alone, and measuring their stone expulsion rate and time. As a result, silodosin demonstrates a higher statistical significance, an increased expulsion rate ($p = 0.04$) and a shorter expulsion time ($p < 0.001$) [69]. Therefore, children taking silodosin pass their stone more quickly than those taking tamsulosin.

Alternatively, α blockers are used in the treatment of stent related discomfort (SRD). Ureteral stents are commonly used tools placed inside the ureter in order to keep the passage open. Despite their ability to alleviate urinary tract obstructions, approximately 88% of patients struggle with stent related discomfort (SRD) after placing them, and 70% may need analgesics to relief the pain and the discomfort [70]. According to several systematic reviews, α blockers significantly reduce USS (Urological Symptom Scores) and BPS (Benign Prostatic Symptoms) with tamsulosin being ranked the highest and alfuzosin the second [70].

Moreover, muscarinic receptor antagonists play a pivotal role in reducing the urge to urinate as well as the frequency of urination by blocking muscarinic receptors (M3 subtype) found on the detrusor muscle of the bladder. By this, they prevent the effect of acetylcholine which contributes to urinary bladder contraction [67]. These antagonists can play a synergistic role when combined with alpha blockers by significantly improving the quality of life in patients dealing with voiding and storage symptoms of BPH [67]. Muscarinic receptors antagonists are not direct alternative for α blockers. However, they are often used in patients with storage symptoms.

2.8. Combination Therapies

Despite the fact that α blockers are primarily used for the treatment of most conditions like LUTS/BPH, stent related discomfort (SRD), and ureteral stones, adjunctive therapies may have significant advantages over monotherapies. They improve international Prostate Symptom Score (IPSS), quality of life (QoL), and also lead to symptomatic relief [71].

Phosphodiesterase-5-inhibitors (PDE5i) including sildenafil, tadalafil, vardenafil and avanafil, are the first line treatment for erectile dysfunction (ED) due to their widely studied safety, tolerability and efficacy. These medications allow sufficient blood inflow into the corpus cavernosum by inhibiting the action of phosphodiesterase [66] .Studies suggest a combination therapy of PDE5i with α blocker for patients with

severe symptoms of LUTS/BPH or for those who do not achieve an effective symptomatic control (66,67). Despite having multiple studies reporting mild and moderate adverse effects associated with this combination therapy, such as a decrease in diastolic pressure and an increase in the heart rate, these changes are not clinically significant [66] . By using their own mechanism each, PDE5i with α blockers improve IPSS from 1.3 to 8.5 points, and IPSS quality of life (QoL) from 0.15 to 1.5 points, thus, relieving the patient from LUTS/PBH symptoms [66]. Additionally, clinical trials related to BPH such as COMBAT and CONDUCT suggest the combination of 5-ARI with α blockers for patients with a large prostate and also severe symptoms of LUTS [67]. Findings also points to the treatment with Mirabegron which is a β-3 agonist that targets the function of the bladder instead of the size of the prostate [67]. It activates the β adrenergic receptors which are significantly expressed on the detrusor muscle of the bladder causing relaxation of the muscle during the storage phase of micturition. In this way, the agent helps the bladder to hold more urine, and a dose of 50 mg is the safest because a dose of 100 mg is attributed to a high blood pressure and cardiac arrhythmias [67]. Also, β-3 agonist Mirabegron can be combined with PDE5i for patients who started initially with PDE5i alone, and are dealing with OAB symptoms (overactive bladder symptoms)[66].

Published trials reveal co-administration of an α blockers with anticholinergics for patients with LUTS/BPH unresponsive to α blockers alone. After conducting three studies involving 1218 members randomly assigned into groups; some taking a combination therapy and others anticholinergics alone, findings reveal that this dual approach is associated little or no effect on the symptoms of the patients[72] .Analysis illustrate a relative risk higher than 1 (RR=1.26%), thus indicating a 26% higher risk of developing adverse effects as compared to the control group. Additionally, a wide confidence interval (0.81 to 1.95) provides no statistical significance [72].

Table 3 - Summary of the Combination Pharmacotherapies in the Management of LUTS/BPH, Indications, and Clinical Outcomes

Combination Therapies	Clinical Indications	Clinical Outcome
PDE5i with α-blockers	Severe Symptoms of LUTS/BPH	Improvement of PSS and QoL
5-ARI with α-blockers	Enlarged prostate and Severe Symptoms	Reduction of BPH Progression Risk
Mirabegron with PDE5i	Overactive Bladder Symptoms	Improved Urinary Symptoms & Bladder Storage Function
Hexanic extract of serenoa repens (HESr) with α-blockers	Sexual Dysfunction and Inflammatory Symptoms.	Improvement of PSS and QoL
Anticholinergics with α-blockers	Benign Prostatic Hyperplasia	Increased Incidence of Adverse Effects

Furthermore, another therapeutic approach commonly used by French general practitioners is a combination of α blockers with hexanic extract of serenoa repens (HESr) for the management of LUTS/BPH. [71]. Serenoa Repens, called saw palmetto, is a well-known plant with anti-androgenic properties that reduces 5-α-reductase enzymes improving overall IPSS and QoL [67]. Also, RCT shows that it possesses anti-inflammatory properties after significantly improving the severity of prostatic inflammation in 97 patients following a 6 months treatment with HESr (320 mg/day) [71]. An Italian study involving 186 patients indicates greater improvement in the total IPSS, 6.43 points in patients receiving a combination therapy of silodosin with HESr as compared to 3.21 points in those receiving a monotherapy of silodosin [71]. Another dual approach shows that tamsulosin with HESr leads to higher IPSS score (7.2 points) and a better quality of life ($p<0.02$) with less ejaculatory disturbances in a group of 709 patients [71].

Phytotherapy belongs to the field of alternative medicine, in which they create drugs based on plants extracts. In vitro studies recommend the usage of herbal medicine as well as dietary supplements for the treatment of BPH [67]. Many plants demonstrate anti-oxidant and anti-inflammatory properties like curcuma, pygeum africanum (prunus), palmitoylethanomadide and epilobium, and some show anti-proliferative effects like uritca dioica that binds on the membrane receptors of the prostate preventing its growth [67]. Lastly,

Cernitin is a pollen extract able to manage symptoms of patients with BPH. It reduces the tension in smooth muscles of the urethra in order to improve the flow of urine, and also promotes programmed cell death in prostatic tissues facilitating its shrinkage [67].

2.9. Cost-Effectiveness and Health-Economic Considerations

Cost-effectiveness and health-economic considerations are important factors influencing the use of α-blockers in the management of BPH and LUTS. As first-line agents, α-blockers are generally available as generic formulations, making them relatively affordable and accessible compared with newer pharmacologic options. Their rapid onset of symptom relief may reduce the need for early surgical intervention, thereby potentially lowering overall healthcare costs. However, long-term therapy, particularly when combined with other agents such as 5-α reductase inhibitors or phosphodiesterase-5 inhibitors, may increase cumulative treatment costs and affect patient adherence. Indirect costs related to adverse effects, treatment discontinuation, and follow-up visits should also be considered. Consequently, individualized treatment strategies that account for symptom severity, patient comorbidities, expected duration of therapy, and economic burden are essential to optimizing both clinical outcomes and cost-effectiveness in real-world practice.

3. Conclusion

This review focuses on the role of α-blockers in urological practice, especially benign prostatic hyperplasia, ureteric stones, and chronic pelvic pain syndromes. From a clinical standpoint, α blockers should be considered first-line agents for symptom control in BPH and selected cases of ureteric stones and chronic pelvic pain syndromes. According to multiple clinical trials, α-blockers contribute to great efficacy in alleviating urinary symptoms, facilitating the passage of the stone, and improving overall quality of life.

Moreover, researchers recommend combination therapies when monotherapies are not satisfactory enough, particularly with α blockers and PDE5i, because these two medications may offer better outcomes than other drugs in patients with persistent lower urinary tract symptoms despite adequate monotherapy. Despite the benefits of these dual approaches, adverse effects like sexual dysfunction and hypotension still have to be considered, making it challenging for urologists to properly select the most suitable drug combination to treat the patients. Careful patient counseling, baseline cardiovascular assessment, and follow-up are therefore essential when initiating or escalating combination therapy. Additionally, the use of herbal medicine is prescribed for the management of BPH in some patients because some plants, mainly serenoa repens, exhibit a similar mode of action to α-blockers, although clinicians should remain aware of variability in efficacy and the limited strength of supporting evidence.

New strategies, including precision medicine and the innovation of novel drug formulations have the potential to make a positive impact; however, their effectiveness isn't fully proven. Besides, the introduction of β-3 agonist is a suitable alternative for patients unable to tolerate α blockers or unresponsive to them. This option may be particularly useful in patients with prominent storage symptoms or contraindications to α-adrenergic blockade. Regardless of the emergence of new medications and alternatives, α blockers remain one of the most pivotal foundational treatments in urology. Future trials must focus on prioritizing dual therapies, making more precise patient selection criteria, and establishing new biomarkers (molecules and genes) in the aim of monitoring patient's overall condition or predicting future outcomes, ultimately aiming to support more individualized and evidence-based treatment decisions in daily urological practice.

Authors Contributions

Conceptualization, J. J.; data curation, J. J.; writing–original draft preparation, A. B. J., J. J., E.K. C., S. T., B. B., A. L.; writing–review and editing (provided feedback on analyses, and critically reviewed the manuscript for important intellectual content), J. J., N. G.

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