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# Emerging drugs for the treatment of benign prostatic hyperplasia: a 2023 update

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**Abstract**

**Introduction:** Benign prostatic hyperplasia (BPH) is condition that affects over 50% of men as they enter their fifth decade of life, often leading to lower urinary tract symptoms (LUTS). Primary treatment options include alpha blockers, 5-alpha reductase inhibitors, and phosphodiesterase-5 inhibitors. However, these medications can have some side effects, and there is a noticeable dearth of information addressing the long-term use of these medications. Thus, the exploration of all treatment modalities helps ensure patients receive personalized and effective care. Consequently, the primary objective of this review is to identify potential emerging medications for the treatment of BPH.

**Areas covered:** We conducted an extensive review of articles discussing pharmacotherapy for BPH spanning the last 15 years. Our information gathering process involved Scopus, PubMed-MEDLINE, Cochrane, Wiley Online Library Google Scholar, ClinicalTrials.gov, and the PharmaProjects database. This approach ensures that readers gain an in-depth knowledge of the existing therapeutic agents as well as promising avenues for managing BPH.

**Expert opinion:** BPH treatment targets a patient's specific constellation of symptoms. Therefore, a broad knowledge base encompassing various treatment options is paramount in ensuring optimal treatment. Looking forward, the emphasis on personalization promises to reshape the landscape of BPH treatment and improve patient outcomes.

**Keywords:** Benign Prostatic Hyperplasia (BPH); Lower Urinary Tract Symptoms (LUTS); Bladder outlet obstruction (BOO); alpha blockers; pde5 inhibitor; 5-alpha-reductase inhibitor

## 1. Background:

Benign prostatic hyperplasia (BPH) stands as a prevalent condition primarily affecting aging males, necessitating a clear definition before delving into its medical therapies [1]. As men approach their fifties, more than half of them will develop BPH, and a significant portion of these individuals will experience lower urinary tract symptoms (LUTS) attributed to BPH [2–4].LUTS can significantly impede one's storage (incontinence, nocturia, frequency) and voiding (retention, weak stream) ability, resulting in a diminished quality of life (QoL) [5]. The aging population has led and will continue to lead to a steady increase in the prevalence and incidence of LUTS secondary to BPH [6].

A multicenter observational study involving over 800 males aged 50–80 years evaluated lifestyle factors, prostate-related variables, and symptom severity [7]. The study revealed a strong association between the severity of symptoms, as assessed by the AUA-SS (American Urological Association Symptom Score), and decreased QoL. Furthermore, the impact of BPH extends beyond the patient; surveys of couples in which the male partner had BPH demonstrated that the female partners experienced various morbidities, including sleep disturbance, disruption to social life, and increased psychological burden, with the severity of the patient's symptoms correlating with the degree of morbidity in the partner [8,9]. Given the significant burden posed by BPH, this review aims to scrutinize existing medical therapies for LUTS/BPH and explore emerging drugs currently under investigation.

## 2. Medical Need:

Assessing a patient with LUTS secondary to BPH requires a comprehensive evaluation that considers various factors. The initial assessment encompasses a thorough history and physical examination, taking into account the patient's age, comorbidities, risk of disease progression, available treatment options, QoL, and sexual activity.

For instance, metabolic syndrome, which includes conditions such as hypertension and central obesity, has emerged as a significant influence on BPH progression [10]. Studies have shown that men with metabolic syndrome tend to have larger prostates, with specific factors like low levels of high-density lipoprotein (HDL) associated with even larger prostate sizes and higher annual BPH growth rates [11]. Conditions like diabetes mellitus, hypertension, obesity, low HDL cholesterol, and high fasting insulin levels have all been linked to increased prostate growth rates, although the AUA-SS did not show significant differences between patients with or without metabolic syndrome [11,12]. Moreover, men with LUTS tend to have higher glycosylated hemoglobin levels and unfavorable lipid profiles, further underscoring the connection between metabolic factors and BPH progression [13,14].

Questionnaires, such as the AUA-SS, are valuable tools for tracking symptoms over time. Treatment decisions are often influenced by symptom severity, with watchful waiting recommended for patients with mild symptoms (AUA-SS $\leq$7) and minimal bother. Watchful waiting entails lifestyle modifications, including counseling about the condition's relation to prostate volume and behavioral changes such as fluid intake management and dietary

adjustments [15]. However, symptoms may worsen over time, necessitating further intervention.

When symptoms significantly impact a patient's QoL, medications are prescribed to alleviate and prevent symptom exacerbation. The primary goal of this treatment option is to enhance the patient's QoL, recognizing that most patients will experience the progression of LUTS symptoms over time.

## 3. Methodology

A systematic literature search was conducted using Scopus, PubMed-MEDLINE, Cochrane, Wiley Online Library Google Scholar, ClinicalTrials.gov, and the PharmaProjects database including studies and reviews published between January 2007 and December 2022. This 15-year interval was chosen given the recent plethora of new modalities that have entered the BPH armamentarium, many of which have been marketed as appropriate for older and high-risk patients. The following database search words were used either individually or in conjunction: “BPH”, “LUTS”, “treatment”, “pharmacotherapy”, and “drug”. References of included articles were also investigated.

## 4. Existing treatments

Pharmacotherapy is a popular option for LUTS treatment, most often utilizing alpha-blockers and 5 alpha reductase inhibitors. Phosphodiesters 5 inhibitors, a slightly more recent treatment, are also effective. Selected existing treatments are outlined in Table 1.

### 4.1. Alpha blockers

Bladder outlet obstruction (BOO) is in part a function of the interactions between smooth muscle factors and the tissue of the prostate. Medical therapy targets these components by blocking alpha-adrenergic receptors in the prostatic stromal smooth muscle. The primary alpha blockers used for treating men with lower LUTS include alfuzosin, tamsulosin, and silodosin, although the use of older drugs like terazosin and doxazosin is seen as well.

Tamsulosin has modest selectivity for α1A over α1B adrenergic receptors, while silodosin shows a 162:1 selectivity for α1A compared to α1B receptors[16]. Benefits such as increased urinary flow rate and bladder capacity, and reduced detrusor overactivity are usually observed within 3–4 days and can last for over a year [15,17,18]. Furthermore, a recent a meta-analysis found that alpha blockers may have some benefit in acute urinary retention secondary to BPH in increasing the trial without a catheter (TWOC) success rate. Alfuzosin, silodosin, tamsulosin, and alfuzosin plus tamsulosin all lead to a higher TWOC rate, while doxazosin did not [5].

However, there are some drawbacks to this class of medications. Recent work by Lusty et al. examining over 175,000 men found an increased risk of cardiac failure with exposure to α-blockers (HR = 1.22; 95% CI 1.18 – 1.26)[19]. Another study by Bumbia et al. found that alpha-blockers are less effective with higher grades of intra-vesicular intrusion [20]. Studies have also ejaculation issues as a common side effect [21]. Duan et al., in a study of US Medicare records from 2006 – 2012 found that Tamsulosin may lead to an increased risk of dementia compared

both to placebo and other alpha blockers, with higher doses leading to an increased risk [22]. However, a retrospective study did not find any significant correlation between BPH drugs and the risk of dementia [23].

### 4.2. 5-ARI reductase inhibitors

Steroid 5-α-reductase inhibitors (5ARIs), block the conversion of testosterone to dihydrotestosterone (DHT) in the prostate. These inhibitors, most commonly finasteride and dutasteride, come in two isoenzyme forms: the prostatic type-1, and type-2, found dermally and hepatically [24]. Benefits are observed 4–6 weeks post-treatment, with maximum effects at 3–6 months [15].

Finasteride affects only type-1 isoenzymes, while dutasteride affects both types. In men with prostates over 40 mL, these drugs can reduce prostate size by 16–19% [25]. Multiple studies have found clinical efficacy is reached within 6–12 weeks [26,27], and long-term durability extends up to 5 years [28].

A study by O'Leary et al. evaluated dutasteride compared to placebo in men with BPH, finding a 28.5% reduction in prostate volume compared to 1.8% placebo reduction after 1 month [25]. In another study by Debruyne et al., they found after 4 years prostate volume was decreased by 27% [29,30]. More recent studies have further investigated this class of medication. A 2023 study debunked the previously held belief that finasteride increases the risk of high-grade prostate cancer [31]. Furthermore, a recent meta-analysis of nearly 95,000 men found that 5-

ARIs did not lead to any increased risk of heart failure, myocardial infarction, stroke, or cardiovascular death [32]. In contrast, Lusty et al found a slightly increased risk of cardiac failure in patients on 5-ARIs [19], and Ayodele et al. found a slightly increased right of idiopathic VTE [33].

While these medications effectively increase the free flow of urine, they are not without adverse effects. Many men suffer from sexual function issues, primarily erectile dysfunction, ejaculatory problem, and a decrease in libido [31,34]. Additionally, a study by Garcia-Argibay et al. found a significant association between either finasteride or dutasteride use over four years and depression, although no association was found with dementia or Alzheimer disease [35]. Jeong et al. found that discontinuing 5ARIs led to the recurrence of prostatic symptoms, suggesting that patients with severe symptoms or larger prostates should continue 5ARI therapy indefinitely [36].

### 4.3. PDE 5 inhibitors

One of the primary regulators of prostatic smooth muscle contractility is the nitric oxide–cGMP pathway. Phosphodiesterase type 5 (PDE5) inhibitors, such as tadalafil, vardenafil, and sildenafil, have been employed for both erectile dysfunction and LUTS/BPH. In addition to relaxing prostatic smooth muscle tone, these drugs may inhibit stromal cell proliferation and modulate autonomic nervous system activity [37,38]. Studies on uroflowmetry parameters have yielded mixed results [39]. A meta-analysis showed improvements in AUA-SS and IIEF scores but not in Qmax [40].

Tadalafil has been studied in phase II–III trials, showing no significant change in Qmax or voiding efficiency at 6 and 12 weeks [30]. However, it did improve obstructive subscores assessed by the IPSS at those timepoints [41]. Vignozzi et al. found that tadalafil and vardenafil reduced IL-8 secretions, an inflammatory marker in prostatic tissue [42]. A recent study by Zahir et al. found that while both sildenafil and tadalafil both led to decreased PVR and improved IPSS and IPSS-QOL scores, sildenafil led to a significantly greater decrease in PVR and increase in IPSS-QOL [43].

### 4.4. Anticholinergics

As symptoms of bladder outlet obstruction (BOO) escalate, patients may experience increased urinary frequency and urgency, often leading to overactive bladder (OAB). Anticholinergic medications, such as oxybutynin, solifenacin, and tolterodine, can provide relief by antagonizing muscarinic receptors that modulate detrusor contractility. These medications result in reduced smooth muscle tone and symptom relief. Oxybutynin works through competitive acetylcholine antagonism at postganglionic muscarinic receptors. Solifenacin has high selectivity for M3 muscarinic receptors, while tolterodine is more selective for the bladder over salivary glands. However, these drugs have limitations, including dry mouth, constipation, increased dementia risk, and increased fall risk, particularly in the elderly [44].

### 4.5. β-3 agonist

Mirabegron (Myrbetriq®/Betmiga®) is a selective β-3 adrenergic receptor agonist approved for treating urgency, urinary incontinence, and frequency symptoms due to overactive bladder (OAB). It is also recommended for men with lower urinary tract symptoms (LUTS) secondary to BPH with OAB [45]. Clinical trials have shown its safety, efficacy, and tolerability [46,47]. Mirabegron targets the beta-3 adrenergic receptor on the urinary smooth muscle resulting in the relaxation of the detrusor muscle and thereforereducing detrusor overactivity and other urothelial functions [48].

A study by Nitti et al. found a significant decrease in urinary frequency and urgency at 3 months, most pronounced in men on 50 mg of mirabegron [49]. Another study by Takahashi et al. found an improvement in OABSS and IPSS-QoL measurements at 12 weeks [50]. Another study found that Mirabegron led to fewer adverse events than antimuscarinic therapy [51].

## 5. Combination therapy

### 5.1. Alpha blocker with 5ARIs

The Medical Therapy of Prostatic Symptoms (MTOPS) trial demonstrated the efficacy of combination therapy using alpha-blockers and 5ARIs over monotherapy [52]. Over 4.5 years, 3,047 men underwent a three-arm double-blind study of either placebo, doxazosin, finasteride, and combination therapy. Combination therapy significantly reduced acute urinary retention (AUR) risk and invasive therapy need compared to placebo or monotherapy[1].

The Combination of Avodart and Tamsulosin (CombAT) trial further supported the efficacy of combination therapy, which, compared to either monotherapy, showed significantly increased reductions in voiding and storage symptoms [53]. However, in the combination group, drug-related adverse events were elevated [54]. Another review of six studies by Zitoun et al. found that combination therapy showed a significant improvement in IPSS, QoL, PUF, and clinical progression [55]. However, a recent study by Lusty et al. also found a slightly increased risk of cardiac failure for patients on a combination of alpha blockers with 5ARIs (HR 1.09; 95% CI 1.02 – 1.17)[19].

### 5.2. Alpha blockers and PDE 5 inhibitors

Combination therapy involving alpha-blockers and PDE5 inhibitors has been increasingly used for treating men with LUTS and erectile dysfunction (ED).

Kaplan et al. found that combination therapy with 25 mg sildenafil and 10 mg alfuzosin led to greater improvements in AUA-SS and IIEF scores compared to monotherapy [56]. Roehrborn et al. evaluated the effects of varying doses of tadalafil and found some subjective improvement but no significant changes in Qmax [57]. Stief et al. and Dmochowski et al. also reported improvements in AUA-SS scores but no changes in urodynamic parameters [58,59]. In contrast, Tuncel et al. found that tamsulosin and sildenafil combination therapy was not superior to monotherapy [60].

### 5.3. Alpha blockers with anticholinergics

In the Tolterodine and Tamsulosin in Men with LUTS including OAB: Evaluation of Efficacy and Safety (TIMES) trial by Kaplan et al., the use of antimuscarinic agent alone or in combination with an α-blocker was evaluated in men with LUTS including OAB [61]. 879 men were randomized to one of 4 potential arms: placebo, 4 mg of tolterodine ER, 0.4 mg of tamsulosin, or both medications for 12 weeks. When compared to placebo, patients on combination therapy showed significant improvement in AUA-SS, QoL, urge incontinence, urgency, nocturia, and micturition's per night. There were minimal adverse effects, similar rates of AUR requiring catheterrization across all groups, and no statistically significant differences in either Qmax or PVR.

Athanasopoulos et al. found in patients with BOO and detrusor instability that tamsulosin and tolterodine combination therapy of tamsulosin and significantly improved QoL scores and bladder capacity compared to tamsulosin alone [62]. Additionally, there was a decreased maximum unstable contraction pressure and increased volume at the first unstable contraction. More recently, Cho et al. investigated the combination therapy of alfuzosin and imidafenacin versus monotherapy of alfuzosin in men with LUTS and storage symptoms [63]. While both groups showed improvement, patients on combination therapy showed significant improvement in urgency, frequency, micturition number per 24 hours, AUA-SS QOL, and patient perception of intensity of urgency scale (PPIUS) score.

### 5.4. Alpha blockers and beta-3 agonists

In a study by Ichihara et al. of 76 patients, the effectiveness of 50 mg of mirabegron plus 0.2 mg of tamsulosin was compared to tamsulosin alone in patients with LUTS secondary to BPH and

OAB. The primary endpoint of this 8-week trial was the change in the overactive bladder symptom score (OABSS) [64]. The combination therapy group showed a significant change in OABSS compared to the monotherapy group (2.21 vs. 0.87, $p = 0.012$). Additionally, at the 8-week follow-up, the combination group exhibited the most substantial improvements in symptom scores for daytime frequency, urinary urgency, American Urological Association Symptom Score (AUA-SS), and quality of life (QoL) compared to the monotherapy group.

### 5.5. Antimuscarinics and 5 ARIs

In a trial of 51 men by Chung et al., the safety and efficacy of dutasteride and tolterodine extended-release were assessed in patients with OAB and LUTS compared to those taking just dutasteride [65]. This open-label trial involved patients with OAB and prostate sizes exceeding 30 grams who received an additional 4 mg of extended-release tolterodine over a 3-month study period. The group treated with tolterodine experienced a significant reduction in 24-hour micturition frequency by over 3 episodes, a 19% reduction in OAB episodes, and a 71% reduction in severe OAB episodes, along with a reduction of 1 nighttime void per night. AUA-SS scores decreased from 19.3 to 14.3 in patients receiving dutasteride monotherapy and to 7.1 in those on combination therapy ($p < 0.001$). Moreover, storage symptoms decreased from 98 to 4.5, and there was a decrease of 0.2 mL/sec in maximum flow rate (Qmax), while post-void residual (PVR) increased by 4.2 mL. Importantly, no patients experienced urinary retention, and reported side effects were minimal.

Additionally, MacDiarmid et al. conducted a 420 patient study examining the combination of extended-release oxybutynin with tamsulosin in LUTS reduction [66]. All patients took 0.4 mg

of tamsulosin daily and were randomized to receive either placebo or 10 mg of oxybutynin daily for 12 weeks. The combination therapy resulted in significantly greater improvement in the International Prostate Symptom Score (IPSS) compared to tamsulosin alone at 8 and 12 weeks of treatment. Notably, a significant decrease in PVR was observed in the combination therapy group at weeks 4, 8, and 12. The occurrence of adverse events was similar in both groups.

### 5.6 Antimuscarinic plus beta-3 agonists

The BEDSIDE study by Drake et al. in 2174 patients looked at the efficacy of solifenacin 5 or 10 mg vs. 5 mg solifenacin plus 50 mg mirabegron, where the mirabegron was started if an inadequate response was noted on solifenacin alone at week 4 [67]. At 12 weeks, significant improvements in daily incontinence (-0.26 or 18% per day) and micturition events (-0.45 per day), were seen with the combination versus monotherapy. In the opposite vein, the MILAI II trial in Japan initially treated patients with 50 mg mirabegron and had persistence of OAB symptoms[68]. These patients were randomized to receive solifenacin 5 mg, propiverine 20 mg, imidafenacin 0.2 mg, or tolterodine ER 4 mg for at least one year. While 80% of patients experienced a mild treatment-emergent adverse event (dry mouth, nasopharyngitis, and constipation were most common), significant improvements were seen in OABSS scores, including in symptom severity and quality of life, from week 12 onward. Further analysis showed a decrease in incontinence episodes and nocturia. The SYNERGY II trial looked at 1829 patients with “wet” OAB over 12 months whom were randomized to either solifenacin 5 mg, mirabegron 50 mg, or the combination of the two [69]. The combination was statistically significant to both monotherapy in terms of incontinence episodes per day, micturitions per day, OAB-q symptom bother and HRQoL scores, and TS-VAS scores.

### 5.7. 5 ARIs and PDE 5 inhibitors

Casabé et al., in a randomized, double blind, parallel study, assessed the use of tadalafil at 5 mg in combination with finasteride at 5 mg was evaluated in 695 men presenting with LUTS and sexual dysfunction symptoms [70]. 350 men received placebo and 345 men received combination therapy for 26 weeks. The assessment of safety and efficacy was carried out using the American Urological Association Symptom Score (AUA-SS) for LUTS and the International Index of Erectile Function (IIEF) for erectile QoL were observed at 4, 12, and 26 weeks (reductions of 4.0, 5.2, and 5.5, respectively). Additionally, IIEF scores favored the combination therapy over placebo ($p < 0.001$). This combination of tadalafil and finasteride not only provided early relief from LUTS symptoms but also showed improvements in erectile function in the studied group. Several meta-analyses have consistently demonstrated a significant benefit of this combination in alleviating LUTS. However, the effect on erectile dysfunction is unclear [71–73].

## 6. Market Review

The burden of LUTS secondary to BPH significantly impacts public health. Despite available medical and surgical therapy options, BPH continues to be associated with various complications, including urinary retention, AUR, urinary tract infections, and more. In a study spanning from 2007 to 2010 in California, an evaluation of 3.7 million US men seeking emergency services revealed a 25% incidence of urinary retention within this cohort, underscoring the potential for significant adverse effects [74,75]. While alpha blockers and 5-alpha reductase 5ARIs are considered the most effective treatments, their side effects can be

intolerable for some patients. Consequently, new drugs are in development, many utilizing different mechanisms of action [76]. The BPH treatment market is projected to reach a value of $14.1 billion USD by 2026, reflecting the growing importance of this field in the medical community, healthcare providers' pursuit of accurate information for patient treatment, and pharmaceutical companies' interest in rapid growth and development of new therapies [77].

## 7. Current Research Goals

Current research goals for BPH are not yet well-understood. Researchers are investigating both modifiable and non-modifiable risk factors in LUTS and BPH. Addressing these risk factors ought to have significant benefits in patient counseling and the development of more effective management strategies. While many current treatments primarily target voiding dysfunction, there is a growing focus on understanding the disease's origin and addressing modifiable factors. Age and the presence of dihydrotestosterone (DHT) in the system are among the crucial factors contributing to the development of BPH, making further research into future therapies critically important.

## 8. Scientific Rationale and Risk Factors

The progression of BPH is believed to be driven by the proliferation of stromal cells in the prostate and an impairment of apoptosis. Various growth factors and the influence of testosterone play a role in this process. Testosterone, produced by Leydig cells under the influence of luteinizing hormone (LH) and LH-releasing hormone (LHRH), is bound to sex hormone-binding globulin (SHBG) in the bloodstream [78]. Steroid-5-alpha-reductase 2 is an enzyme that converts testosterone into dihydrotestosterone (DHT), the primary androgen in the prostate, accounting

for 90% of total prostatic androgen [79,80]. As men age, DHT levels remain elevated, disrupting the balance between cell proliferation and cell death, ultimately leading to BPH [80–82]. DHT stimulates growth factors like epidermal growth factor (EGF), keratinocyte growth factor (KGF), and insulin-like growth factors (IGFs), which modulate cellular proliferation in the prostate. Additionally, DHT influences the expression of transforming growth factor-beta (TGF-beta), affecting the balance between cell proliferation and cell death, contributing to BPH development [82].

Prostatic tissue inflammation is another significant factor in BPH progression. Various metabolic syndromes, including obesity, diabetes, and dyslipidemia, have been linked to a proinflammatory response. These metabolic syndromes are associated with elevated levels of inflammatory cytokines such as CRP, IL-1, IL-6, and tumor necrosis factor (TNF-alpha) [83]. Obesity has been seen to increase the release of chemokines and macrophage infiltration into the prostate, propagating inflammation [83]. These inflammatory infiltrates are commonly found in resected prostatic tissue [84]. Elevated cytokine levels, specifically IL-6 and IL-8, are associated with metabolic syndrome and contribute to the inflammatory response [85]. Chronic inflammation has been linked to focal upregulation of cyclooxygenase 2 (COX-2) within the glandular epithelium, generating proinflammatory prostaglandins that drive prostate cell proliferation [85,86]. Studies have shown that patients with high-grade inflammation had higher AUA-SS scores, larger prostate volumes, and more severe symptoms compared to those with low-grade inflammation [84].

**9. Competitive environment**

Because of the high number of patients suffering with BPH, there is consistent development of new and exciting therapies. These treatments, whether medical or surgical, need to be fully characterized, in terms of their efficacy, safety, and adverse effects. More specifically, an examination of specific measures of symptom relief, side-effects, and complications are necessary for an understanding of these emerging treatments. For a list of compounds under investigation see Table 1.

## 10. Novel pharmacotherapies

### 10.1. Luteinizing hormone-releasing hormone (LHRH) antagonists

Luteinizing hormone-releasing hormone (LHRH) antagonists, including degarelix, teverelix, and cetrorelix, have found application in prostate cancer management. They achieve this by suppressing testosterone production through their influence on the gonadotropin-releasing hormone (GnRH) system. By interacting with the LHRH receptors in human prostate tissue, these antagonists effectively reduce prostate size, thereby alleviating urinary obstructive symptoms [89]. It is also thought that LHRH antagonists could inhibit cellular growth and division, either by increasing apoptosis or through plasminogen activor system inhibition [90]. A study on cetrorelix demonstrated its effectiveness in improving IPSS, QoL, Qmax, and reducing prostate volume [91]. However, while two phase III studies found no difference in IPSS on cetrorelix vs. placebo, one study found improvements in Qmax, QoL, and PVR [92]. A study of 528 patients from 2011 reported a 5.6-point reduction in IPSS from baseline with cetrorelix at 26 weeks [93].

Teverelix showed IPSS improvements up to 8 weeks after a single subcutaneous injection [76]. This led to the development of an open-label phase I study that demonstrated LH, FSH, and total-testosterone pharmacodynamic endpoints were more prolonged following intramuscular administration compared to subcutaneous administration. There has not been a study that looked at Teverelix affects in BPH; however, a recent phase II study is analyzing the effects of Teverelix in prostate cancer [94].

Degarelix completed a phase II open-label study for the treatment of LUTS/BPH, with a transient serum testosterone reduction to castration level (0.5 ng/ml). The trial was conducted with two doses of 32 and 64 mg at two-dosing regimens of one or two administrations separated by 14 days. Results showed no improvement from baseline after 42 days of treatment (NCT00527488). Another trial recently completed evaluated degarelix at 10, 20 and, 30 mg in comparison to placebo. The mean change in IPSS when comparing placebo to 30 mg was 4.46 and 5.88, respectively, although this was not statistically significant (NCT00947882).

### 10.2. Nonsteroidal anti-inflammatory drugs (NSAIDs)

Nonsteroidal anti-inflammatory drugs (NSAIDs), such as celocoxib and loxoprofen, have been studied for BPH prevention and nocturia treatment due to their anti-inflammatory properties. A meta-analysis of three randomized control trials involving 183 patients showed that NSAIDs improved IPSS by 2.89 points compared to placebo and reduced peak urine flow by 0.89 mL/s [95]. Some studies suggest NSAID use may increase the risk of developing BPH, while others

found no increased risk [96–99]. More research is needed to evaluate NSAID efficacy in treating LUTS in BPH.

### 10.3. NX-1207

NX-1207 is a proapoptotic agent that is injected into an inflamed prostate without anesthesia or catheterization. A prospective randomized study in men with LUTS/BPH revealed improved symptoms three months after NX-1207 treatment compared to finasteride [100]. Two Phase III trials in the USA have been completed, evaluating the safety and efficacy of NX-1207 for BPH treatment. While they did not meet their primary efficacy endpoints, safety and efficacy were sustained (NCT00945490 and NCT01438775), with results pending. Recently, there has been a phase III evaluation of a re-injection of NX-1207 for BPH; however, the results are still pending (NCT01846793).

### 10.4. PRX302 (Topsalysin)

PRX302 (topsalysin) is a prostate PSA-activated modified recombinant protein that causes cell membrane pore formation and localized apoptosis. Phase I and II trials showed good tolerability in BPH patients [113]. Phase I involved urethral injection, while Phase II used prostate volume-dependent deposits. These treatments improved IPSS scores by 8–10 points for up to 1 year.

The Phase IIb TRIUMPH study demonstrated a significant IPSS improvement at 3 months, with an average 8–9 point reduction at 12 months [114]. PRX302 also increased Qmax by about 3 mL/sec and was well-tolerated with no drug-related side effects over 12 months. The subsequent

Phase III international trial (PLUS-1) involved administering as a single transrectal intraprostatic injection to 479 patients. Results showed a significant 7.6-point IPSS improvement from baseline compared to placebo. Toxicity was mild and transient, mainly associated with initial injection symptoms (NCT01966614). Another trial found a 9.1-point IPSS change in PRX302 versus 5.8 in placebo, with a significant Qmax increase of 3.13 versus 1.31 in placebo [115].

**10.5. Afala**

Afala, also known as Afalaza or Athaliah, is an anti-prostate specific antigen antibody developed by Materia Medica Holding for BPH and chronic prostatitis. Materia Medica Holding had a phase III clinical trial evaluating the safety and efficacy of afalaza in patients with symptoms of BPH (NTC01716104). The results of this trial was published by Pushkar et al[119]. They investigated 249 patients aged 45-60 with BPH/LUTS, prostate volume >30 cc, PVR < 100 ml, Qmax from 10-15 ml/s, and serum PSA <4 ng/ml. Patients were randomized to the Afala 12 mg twice daily or placebo for 12 months. Significant improvements in IPSS were noted as 1, 3, 6, and 12 months with Afala vs the placebo (-3.7 vs. -2.9 at 12 months respectively). Qmax also increased significantly at 1, 6, and 12 months vs. placebo (+2.5 vs. +1.4 ml/s at 12 months respectively). There were no significant differences in adverse events between the two groups, and 75% of AE were unrealted to medication.

Savel'eva et al. ran a trial of 186 patients with BPH comparing the use of afala to *Serenoa repens* extract[120]. Partipants were 40-75 with an IPSS of 8-20, prostate volume >25 cc, PVR < 150 ml, Qmax from 5-15 ml/s, and serum PSA <4 ng/ml. Patients took Afala 12 mg twice daily or 320 mg SRE. Significant improvements in IPSS and QoL were seen at 4, 8, 12, and 16 weeks of

therapy for both treatments compared to baseline (14.7 vs 8.2 for IPSS at 16 weeks Afala, 3.7 vs 1.7 for QoL at 16 weeks Afala). Furthermore, significant improvements in Qmax and average flow rate were seen in at 4, 7, 12, and 16 weeks of each therapy vs. baseline (10.2 and 6.5 ml/s vs 14.1 and 9.0 ml/s for maximum and average flow rate at 16 weeks of Afala). At 16 weeks, significant reduction in prostate volume and residual urine volume was seen for both therapies vs. baseline (44.6 vs 41.9 cc for Afala). However, there were no significant differnces between the two therapies in any category. Gudkov followed 30 patients treated with Afala for 12 months with PSA < 4 ng/ml and total IPSS <7 or >18[121]. Patients received 2 tablets twice a day (24 mg daily) for 7 months. Significant improvements in IPSS (14.5 vs 8.2), QoL (4.8 vs. 2.5), Qmax (8.2 vs 13.8), and PVR (156 vs. 70.2) were seen at 12 months. There were no significant differences in adverse events between groups.

**10.6. GV1001 (Tertomotide)**

GV1001, also known as tertomotide, is an injectable vaccine targeting telomerase peptides which activates T-cells to kill cancer cells under development by VaxOnco. While originally under investigation for cancer treatment, a clinical trial was launched to determine its effectiveness and safety for benign prostatic hyperplasia (NCT02955892). The results were published in a study by Moon et al. evaluating the safety and efficacy of three dosing schemes of GV1001 in 161 patients over 50 with an IPSS ≥13, prostate volume ≥30 cc, PVR ≤200 ml, and Qmax from 5-15 ml/s[122]. Patients were randomly assigned to 1) 0.4 mg with a 2 week injection interval, 2) 0.56 mg with a 2 week injection interval, 3) 0.56 with a 4 week injection interval, or 4) placebo. Injections were given through 12 weeks, and follow-up was conducting through 16 weeks. At week 13, a statistically significant change in IPSS was seen for the two groups on 2 week

injection intervals compared to placebo (−3.5 for control vs −7.2 and −6.8 for groups 1 and 2, respectively). At 16 weeks, there was significant reduction in prostate gland volume at week 16 vs control in all treatment groups (0.8 for control vs −4.6, −2.5, and −4.2 mL for groups 1-3 respectively). There were no significant differences in adverse events between groups.

### 10.7. Angiotensin converting enzyme inhibitors

For the better part of 20 years, researchers have been investigating if renin-angiotensin system (RAS) inhibitors have any positive effects on BPH. If such effects were found, RAS inhibitors would represent another cheap treatment that many patients already use. Previously, it has been reported that enalapril, losartan, and telmisartan can guard against testosterone-induced BPH by inducing apoptosis in rats while preserving the histoarchitecture of the prostate[123,124]. A recent study by Mostafa et al looked at the effects on 100 mg/kg of capropril on testosterone-induced BPH in rats with promising results. They found significant decreases in prostate weight, PAP, and PSA levels compared to the BPH group. Specifically, they saw that captopril leads to significantly increased p53 and Bax mRNA expression, Bcl-2 mRNA levels, and caspase-3 activity, while exhibiting suppression of the prolifering cell nuclear antigen (PCNA)[78].

### 10.8. Progestogens

Allylestrenol and chlormadinone acetate (CMA) are progestogens used mainly in Japan to treat LUTS/BPH by exerting antiandrogenic actions leading to prostatic atrophy. Allylestrenol reduces testosterone by 40%, resulting in an average five point improvement on IPSS. At 50 mg taken orally twice daily for 16 weeks, CMA led to an average prostate volume reduction of 5.3 mL and an improvement in maximum flow rate of 2.4 mL/sec [110]. In a study by Fujimoto et

al., CMA was administered to 114 patients with LUTS and erectile dysfunction (ED) for 16 weeks, resulting in improvements in IPSS, Qmax, and QoL, with a 25% reduction in prostate volume at week 16, and a reduction of PSA by 50% [111].

Oral etonogestrel, at 150 and 300 µg doses, reduces testosterone levels, decreases prostate size, and alleviates LUTS without hypogonadal side effects. It is considered safe and effective, providing a rapid onset preventing clinical progression, acute urinary retention (AUR), and the need for surgery [112].

**10.9. Onabotulinumtoxin A**

Botulinum toxin A (BoNT-A) is utilized to treat upper limb spasticity, strabismus, and detrusor overactivity. Its mechanism involves inhibiting acetylcholine release at neuromuscular junctions, potentially inducing prostate relaxation and enhancing LUTS/BPH. Several single-arm trials have demonstrated the benefits of Botox for men with BPH when administered via two routes: transrectally or transperineally [101]. In a randomized double-blind phase II study, 380 men received placebo or onabotulinumtoxin A either transperineally or transrectally with either 100, 200, and 300 U [102]. All patients showed significant AUA-SS and Qmax improvement. Another trial (NCT00894517) found BoNT-A improved sperm count, ejaculatory volume, and motility [103]. However, a 2014 phase II trial using 200 U BoNT-A in the lateral prostatic lobes showed no difference in the change from baseline in the total IPSS at week 12 compared to placebo (NCT01107392). In another phase II randomized study (NCT01589263), the BoNT-A group had a significantly smaller prostate volume (26.79) compared to the tamsulosin group (32.33) at the study's conclusion.

## 11 Phytotherapy and Supplements

### 11.1 *Serenoa Repens*

*Serenoa repens* extract (SPE), also called saw palmetto extract, has been shown to improve daytime frequency, nocturia, and IPSS. These treatments have no effect on PSA, urinary flow rates, or residual volumes. The 11 site, 357 men CAMUS had participants receive to 320, 640, or 960mg of SPE or placebo [104]. The study aimed to assess the impact on AUA-SS. SPE, at varying doses, showed no difference compared to a placebo. However, a recent systematic review of 27 studies found that hexanoic SPE extract had similar efficacy to 5-alpha-reductase inhibitors and tamsulosin [105]. Moreover, based on a review of 58 different studies, an international panel of urology experts issued a consensus statement recommending SPE as a treatment option for men with mild-to-moderate BPH/LUTS[106]. More research needs to be done to elucidate the specific effects and efficacy of SPE.

### 11.2. Equol

Equol, an isoflavone found in soybeans, inhibitors prostate hormones, akin to 5ARIs. A 115 patient 2017 study evaluated 10, 50, or 150 mg against placebo [107]. Prostate volume significantly decreased in the 10 mg group at 4 weeks compared to baseline. The 150 mg group showed the most improvement in Qmax, suggesting that S-equol may be effective in enhancing flow rate and reducing prostate size in men with BPH.

Phytoestrogens, like soy isoflavones, possess nonsteroidal estrogenic properties, induce cellular apoptosis, and exert antioxidant effects. In a randomized placebo-controlled pilot study with 176

BPH participants, 40 mg of isoflavones were administered daily. While the isoflavone was well tolerated, only minimal benefit over placebo to IPSS and Qmax were noted [108].

### 11.3. Pomegranate

Pomegranate contains polyphenolic compounds that are believed to have antioxidant, anti-inflammatory, and proapoptotic properties. Pomegranate juice is rich in anthocyanins, ellagic acid derivatives, and hydrolysable tannins, including punicalagins. The vesicles obtained from pomegranate juice are packed with antioxidants, potentially playing a role in the observed therapeutic benefits against BPH. In fact, a recent trial of pomegranate-juice derived nanovescicles were found to induce apoptosis in BPH1 cells in rats [109]. Thus, a phase I placebo-controlled trial of the effects of pomegranate on LUTS was started the results have not been published (NCT00381108).

### 11.4 Carotenoids

Carotenoids, a nutritional supplement or botanical drug used to alleviate lower LUTS, typically consist of a carrier and a lycopene, phytoene, or phytofluene component [87]. While two open-label phase III studies on the long-term safety and efficacy of multi-carotenoids were completed, no results have been posted (NCT01002274 and NCT01002222). However, a phase II study showed IPSS improvement with use of a multi-carotenoids composition. In contrast, Holton et al. found no significant association between carotene and lycopene consumption and male LUTS progression [88].

### 11.5. Vitamin D3 (calcitriol) analogs

Elocalcitol, a synthetic vitamin D3 receptor, inhibits human BPH cell growth, reduces androgen signaling without systemic impact, induces apoptosis, causes prostatic atrophy, and effectively curbs IL8-dependent BPH stromal cell proliferation and inflammation [116]. Colli et al., evaluated BXL628 against placebo in 119 patients. They found prostate volume increased by 4.32 cc with placebo and decreased 2.90 cc with BXL628 [116].

A phase IIb study in men with BPH demonstrated that 150 µg/d of elocalcitol optimized improvement in Qmax and IPSS and reduction in prostate volume compared to placebo [117]. However, in another study, there was no change in bladder volume in OAB patients after 4 weeks of Elocalcitol change in bladder volume in patients with overactive bladders following 4 weeks of treatment [118].

**9. Potential Development Issues**

While there have been significant advancements in the pharmacotherapy options for treating LUTS secondary to BPH, it is difficult to determine the effectiveness of these medications due to the prevalence of side effects. For example, alpha-blockers may cause dizziness and low blood pressure, while 5ARIs can lead to sexual dysfunction. This limits the choices available to patients and highlights the need for therapies with improved tolerability profiles. While some clinical trials have identified potential drug targets, many of these have not materialized into widely adopted treatments. Moreover, the incomplete understanding of the etiology of LUTS and BPH complicates treatment strategies, posing a challenge to researchers trying to develop targeted therapies that address the root causes of these conditions. Simply put, research delving

deeper into the pathophysiology is needed to identify novel drug targets with minimal side effects.

## 10. Conclusion

BPH is a complex condition that extends beyond just prostatic disease. It involves various pathophysiological factors in the lower urinary tract. There is a wide array of medical treatments available, and healthcare professionals must carefully select the most suitable drug or drugs for individual patients. With the aging population, the number of symptomatic patients seeking relief is on the rise. As of now, alpha-blockers and 5ARIs are the most commonly prescribed medical treatments due to their tolerability, despite potential side effects. PDE5 inhibitors are also gaining traction in patients who struggle with said side effects. New treatment options have shown promise in clinical trials, offering relief to patients. However, these treatments often lack the durability, cost-effectiveness, and side-effect profiles of traditional medications.

Future research in basic science is crucial to gain a deeper understanding of existing treatment options and expand the pharmacological arsenal for men with LUTS secondary to BPH. This comprehensive strategy aims to enhance IPSS and Qmax while minimizing adverse effects. Developing therapies with improved long-term efficacy, reduced side effects, and affordability is essential to meet the evolving healthcare needs of aging populations. By addressing these challenges, we can provide better care and improved quality of life for individuals with LUTS and BPH.

## 11. Expert opinion

The landscape of BPH treatment is on the verge of significant transformation, with several novel drugs currently in clinical trials that hold the potential to become viable treatment options. While some of these innovative therapies are exploring established therapeutic pathways, others are venturing into new and uncharted territory. It is imperative that these emerging frontiers are thoroughly studied to deepen our understanding of BPH's etiology and potentially reshape the course of its progression.

One crucial aspect of this evolving field is the emphasis on basic science research. Investing in fundamental research is essential for unraveling the intricate pathogenesis of BPH. By delving into the underlying molecular and cellular mechanisms, we can gain invaluable insights that may lead to the development of more targeted and effective medications. BPH is not a one-size-fits-all condition; it involves a complex interplay of various factors, necessitating drugs that can target these diverse components.

Another aspect of BPH treatment that continues to gain popularity is using a multi-drug regimen. As the number of treatments increases, and as those treatments become more mechanistically specific with smaller side effect profiles, the appeal of using multiple medications with complimentary effects will only increase. This will allow physicians to carefully tailor medications to maximize patient quality of life.

However, despite the promising potential of these new treatments, there are challenges that need to be addressed. Many therapies that have demonstrated efficacy in laboratory settings have

struggled to replicate the same success in clinical trials. This disconnect can be attributed to various factors, including financial constraints, practicality issues, and unforeseen complications. For instance, the use of rho-kinase inhibitors, which have shown promise in vitro, faces practical hurdles in translating their benefits to clinical settings [125].

Over the next several years, we anticipate the emergence of new drugs that could offer durable and effective treatment options for BPH. To realize this potential, it is crucial for all stakeholders involved in the process to collaborate seamlessly. This collective effort should involve researchers dedicated to exploring new avenues of treatment, pharmaceutical companies committed to developing these therapies, government bodies providing support and regulation, and physicians at the forefront of patient care.

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B Chughtai is a consultant for Olympus and Boston Scientific.

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Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.


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**PDE5 inhibition may lead to tissue perfusion. Furthermore, it modulates autonomic nervous system activity. Lastly, it has been known to inhibit the prostatic inflammatory process. These all help to improve voiding symptoms in men.

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**Table 1:** Description of currently used and emerging drugs used to treat BPH

| Compound/Class | Company | Indication | Stage of development | Mechanism of action |
|---|---|---|---|---|
| **Current Treatments** | | | | |
| **Tamsulosin** | Multiple | BPH | Active Use | α-adrenoreceptor antagonist |
| **Silodosin** | | | | |
| **Alfuzosin** | | | | |
| **Finasteride** | Multiple | BPH, androgenetic alopecia | Active Use | 5-α-reductase inhibitors |
| **Dutasteride** | Multiple | BPH | Active Use | |
| **Tadalafil** | Multiple | BPH, erectile dysfunction | Active Use | Phosphodiesterase type 5 inhibitors |
| **Vardenafil** | | | | |
| **Sildenafil** | | | | |
| **Oxybutynin** | Multiple | Overactive bladder, detrusor overactivity, BPH | Active Use | Competitive acetylcholine antagonism at postganglionic muscarinic receptors |
| **Solifenacin** | | | Active Use | Inhibition of M3 acetylcholine muscarinic receptors |
| **Tolterodine** | | | Active Use | Inhibition of muscarinic acetylcholine receptors |
| **Mirabegron** | Astellas Pharma US | **Overactive bladder, detrusor overactivity, incontinence, BPH** | Active Use | β-3 adrenergic receptor agonist |
| **Emerging Treatments** | | | | |
| ***Novel Pharmacotherapy*** | | | | |
| | | | | |
| **Degarelix** | Ferring Pharmaceuticals | BPH/LUTS | Phase II | LHRH antagonist |
| **Teverelix** | Ardana Pharmaceuticals | BPH, prostate cancer and contraception | Phase II | |
| **Cetrorelix** | AEterna Zentaris | BPH | Phase III | |
| **Nonsteroidal anti-inflammatory** | Samsung Medical Center | BPH, relief from pain | Phase IV | Anti-inflammatory properties |

| | | | | |
|---|---|---|---|---|
| **drugs (NSAIDs)** | | | | |
| **NX-1207** | Nymox Corporation | BPH | Phase III | Proapoptotic agent |
| **PRX302 (Topsalysin)** | Sophiris Bio Corp | BPH, prostate Cancer | Phase III | Causes localized cell death of PSA-forming cells |
| **Afala** | Materia Medica Holding | BPH, chronic prostatitis | Phase III | Anti-PSA antibody |
| **GV1001 (Tertomotide)** | VaxOnco | BPH, Prostate Cancer | Phase II | T cell activation towards cancer cells |
| **Angiotensin converting enzyme inhibitors** | N/A | BPH | N/A | Increased p53 & Bax mRNA expression, Bcl-2 mRNA levels, and caspase-3 activity |
| **Etonogestrel** | Merck Sharp and Dohme Corp. | BPH/LUTS and contraceptive | Phase IIb | Progestogen |
| **Allylestrenol and chlormadinone acetate (CMA)** | N/A | BPH/LUTS | Phase III | |
| **Onabotulinumtoxin A** | Allergan | BPH, OAB | Phase II–IV | Blocks acetylcholine release at the neuromuscular junction and induces relaxation of the prostate, Neurotoxin |
| ***Phytotherapy and Supplements*** | | | | |
| **Serenoa repens (Saw palmetto)** | Kaiser Permanente | Urological | Phase III | Antiandrogenic effects and inhibition of binding of DHT |
| **Equol** | Ausio Pharmaceuticals, LLC | BPH | Phase II | Isoflavones inhibit hormones in prostate |
| **Pomegranate Tablet** | Jarrow Pharmaceuticals/Pomegranate Health | BPH/LUTS | Phase I | Antioxidant, anti-inflammatory, and proapoptotic properties |
| **Carotenoids (Lycopene)** | N/A | Prostate Cancer, BPH, nutritional | Phase III | Prevents proliferation of prostatic tissue |

| | | | | |
|---|---|---|---|---|
| | | health | | |
| **Vitamine D3 (calcitriol) analogs** | Bioxell Spa. | LUTS/BPH | Phase IIb | Vitamin D3 Agonist |