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Review Article

Recent advances in medical management of benign prostatic hyperplasia: narrative review

Dipika K. Wanve[1]*, Tanisha Mote[2], Nitinkumar S. Doshi[1], Kunal Khobragade[1]

[1]Mankind Pharma Ltd., Navi Mumbai, Maharashtra, India
[2]Sant Gajanan Maharaj College of Pharmacy, Mahagaon, Gadhinglaj, Maharashtra, India

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***Correspondence:**
Dr. Dipika K. Wanve,
E-mail: dipikawanve@gmail.com

ABSTRACT

Benign prostatic hyperplasia (BPH) is a prevalent condition in aging men, commonly linked with lower urinary tract symptoms (LUTS) such as frequency, urgency, nocturia, and weak urinary stream, all of which significantly impact quality of life. Pharmacological therapy remains the first-line management, yet conventional agents like alpha-1 blockers and 5-alpha reductase inhibitors (5-ARIs) often face challenges due to poor adherence, sexual side effects, and suboptimal symptom control. Given the progressive nature of BPH and its increasing prevalence in the elderly worldwide, including India, there is a need for more effective and better-tolerated treatment options. A comprehensive literature review was performed using PubMed, Cochrane Library, Wiley Online Library, Google Scholar, and ClinicalTrials.gov. Studies published between 2020 and 2025 were included to capture recent therapeutic innovations. References from selected articles were also cross-examined to ensure completeness. Pharmacological advances: While α-blockers and 5-ARIs remain standard, they inadequately target BPH's multifactorial pathophysiology involving inflammation, hormonal imbalance, and increased smooth muscle tone. Emerging therapies include phosphodiesterase-5 (PDE-5) inhibitors, which relax prostate and bladder smooth muscle, improving both LUTS and erectile function; β3-adrenoceptor agonists for bladder storage symptoms; and gonadotropin-releasing hormone antagonists that reduce prostate volume without hormonal flare. Additionally, COX-2 inhibitors show promise in managing inflammation-driven LUTS such as nocturia. BPH represents a complex age-related condition beyond prostate enlargement. Although traditional therapies offer benefit, newer agents-targeting hormonal, inflammatory, and metabolic pathways-expand treatment options. Future care will rely on personalized, minimally invasive, and biologically informed strategies to enhance efficacy, safety, and patient quality of life.

Keywords: LUTS, BPH, Treatment, Pharmacotherapy, Immunotherapy, Gene therapy

INTRODUCTION

Benign prostatic hyperplasia (BPH), defined by non-malignant enlargement of the prostate, is among the most prevalent urological disorders affecting aging men worldwide. As the world's aging population, the incidence and public health impact of BPH are rising, substantially burdening healthcare systems and diminishing patient quality of life.[1] Clinically, BPH commonly manifests as LUTS including urinary frequency, urgency, nocturia, and weak stream which adversely affect not only urological function but also sexual and psychological wellbeing.[2]

Pharmacological treatment remains the backbone of BPH management, particularly for patients with mild to moderate symptoms, providing minimum alternative to surgery. However, conventional therapy like alpha-1 adrenergic blockers and 5-ARIs are often hampered by adherence issues, side effects (e.g., ejaculatory dysfunction, gynecomastia), and a generalized, non-individualized approach that overlooks crucial patient-

specific factors-such as prostate size, symptom profile, and baseline sexual health.[3]

Recent advances in BPH pathophysiology, molecular biology, and symptom phenotyping have led to the invention of novel pharmacological treatments. Among them are alpha-blockers, innovative combination regimens, and newly characterized side-effect profiles to enable more individualized therapy.[4] Heightened recognition of risks-such as intraoperative floppy iris syndrome and cardiovascular events-has reinforced the need for precision medicine. Emerging treatments now encompass luteinizing hormone-releasing hormone (LHRH) antagonists, anti-inflammatories, receptor-specific agents, non-hormonal treatment, and immunotherapies, Phytochemical therapies, each targeting underlying mechanisms to offer better-tolerated, long-term symptom control.[5]

Additionally, minimally invasive gene-based approaches, β3-adrenergic agonists, selective androgen receptor modulators (SARMs), mast cell stabilizers, and continuous investigation into genetic and epigenetic biomarkers are redefining the treatment condition and promoting a transition towards personalized medicine.[6] This narrative review summarizes the latest pharmacologic advances for BPH focusing on efficacy, safety, and real-world practice underscoring a shift toward individualized, mechanism-based remedies aimed to improving outcomes and quality of life.

GLOBAL AND INDIAN PREVALENCE AND BURDEN

The prevalence of BPH substantially increases with age, affecting about 8% of men aged 30-39, 50% of men aged 50-59, and up to 80% of men aged 80-89.2 According to the global burden of disease 2019 study, the highest number of BPH cases occurs in men aged 65-69, with the highest age-specific prevalence observed in men aged 75-79.7 Although BPH cases are rising, its global age-adjusted prevalence stayed stable at around 2,380 per 100,000 in 2019. The burden varies widely-India shows a much higher impact at 3,480 per 100,000 compared to the global average of 48.9 DALYs 8. In India, BPH cases nearly doubled from 9.55 million in 2000 to 18.2 million in 2019-a 90.9% surge-reflecting its strong link to aging, especially in men over 50.9.

NATURAL HISTORY AND DISEASE PROGRESSION

BPH is a chronic, progressive condition marked by non-malignant proliferation of glandular and stromal elements in the prostate's transition zone, causing prostate enlargement and LUTS in aging men. Its natural history ranges from microscopic histologic changes beginning as early as the third decade to significant urinary obstruction and complications that affect quality of life and may require surgery. Identifying its causes, risk factors, complex pathophysiology, and progression is necessary for efficient management. BPH is multifactorial and strongly age-related, affecting up to 88% of men by their 80s, caused by changes in hormones especially in dihydrotestosterone and estrogen that promote cellular proliferation and urethral compression. Genetic predisposition, taking for up to 70% of cases, along with metabolic multiple health condition namely obesity, diabetes, and cardiovascular disease, further increase risk, likely through inflammatory and hormonal pathways.[10]

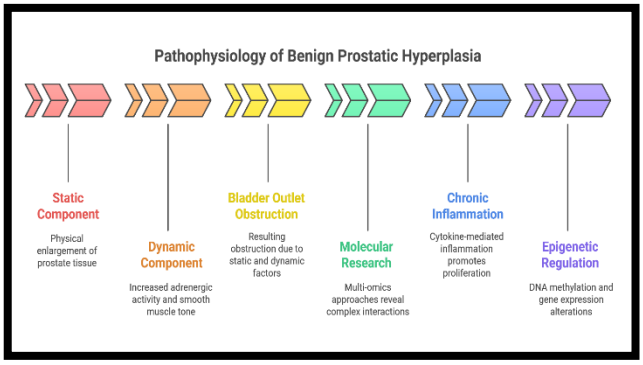

Figure 1: Pathophysiology of BPH.

The pathophysiology of BPH involves both static factors (prostate tissue enlargement) and dynamic factors (increased smooth muscle tone), leading to bladder outlet obstruction.[11] Chronic inflammation, immune cell infiltration, and epigenetic changes (altered gene expression, DNA methylation) further drive disease progression.[12] Age-related bladder changes, such as vascular remodelling and detrusor muscle dysfunction, also contribute to LUTS. Histological studies show that chronic bladder ischemia from vascular remodelling leads to detrusor atrophy, fibrosis, and impaired nerve signalling. Although the bladder initially compensates with muscle hypertrophy, long-term obstruction and aging cause decompensation and worsening LUTS.[13]

Progressive BPH can result in complications including acute urinary retention, recurrent UTIs, bladder stones, bladder wall thickening, impaired detrusor contractility, and even upper tract damage (hydronephrosis, renal insufficiency). It also increases the risk of prostate and bladder cancers, requiring vigilant screening.

Current therapies such as α-blockers and 5-α reductase inhibitors improve symptoms and slow progression modestly, but many patients face persistent symptoms, treatment failure, or side effects. Surgical options (TURP, aquablation) help resistant cases but carry risks and are not curative.[14] Emerging therapies, such as LHRH antagonists targeting NF-κB and IGF-1 pathways, may address underlying mechanisms. Combining such precision hormone-based treatments with existing approaches could improve outcomes and reduce invasive interventions as populations age.[15]

TRADITIONAL PHARMACOLOGICAL THERAPIES

Alpha-1 adrenergic blockers are foundational for BPH symptom management, rapidly relieving LUTS by relaxing prostate and bladder neck smooth muscle. Uroselective agents like Tamsulosin and silodosin minimize cardiovascular side effects but can cause ejaculatory dysfunction. Alfuzosin, with high prostatic concentration, offers a favourable safety profile and fewer sexual side effects, suitable even for cardiovascular patients or those on antihypertensive therapy.[16]

Five-ARIs like Finasteride and Dutasteride reduce prostate volume and slow disease progression by blocking testosterone conversion to dihydrotestosterone. Although onset is gradual, taking months, large trials such as MTOPS and REDUCE confirm their effectiveness in lowering acute urinary retention risk and surgical intervention rates while delaying symptom progression.[17,18]

Phosphodiesterase type 5 inhibitors (PDE5i), with Tadalafil as the only approved agent for BPH and LUTS, show promise beyond traditional therapies. Next-generation PDE5i with better pharmacokinetics, uroselectivity, and extended-release forms aim to optimize delivery, reduce side effects, and improve adherence, enhancing smooth muscle relaxation and pelvic blood flow to improve voiding and storage symptoms without affecting sexual function.[3]

Muscarinic receptor antagonists (MRAs) manage storage-related LUTS in BPH by blocking bladder M3 receptors, reducing involuntary detrusor contractions. Common MRAs-oxybutynin, solifeacin, tolterodine-improve symptoms, especially combined with alpha-blockers in patients with smaller prostates/lower PSA. Side effects like dry mouth and rare urinary retention, mainly in older adults, may limit use. Newer MRAs and modified-release forms are being developed to enhance safety and tolerability.[19]

Beta-3 adrenergic agonists like Mirabegron improve storage-predominant LUTS in BPH by relaxing detrusor muscle via β3-adrenoceptor activation. When added to alpha-1 blockers, they reduce urgency and storage symptoms, as shown in the MATCH study. Mirabegron is well tolerated in older adults with minimal blood pressure impact and low urinary retention risk.

Table 1: Traditional pharmacological therapies.[20]

Drug (dose)	Regulatory approval (FDA) [link]	Class and indications	Mechanism of action	Common side effects
Tamsulosin 0.4 mg OD	FDA-approved for BPH; generic versions available (PR Newswire, FDA access data)	α_1-Blocker for BPH	Selectively blocks α_1 receptors in prostate/bladder neck to improve urine flow	Dizziness, ejaculatory dysfunction, orthostatic hypotension
Silodosin 8 mg OD	FDA-approved (Rapaflo, Oct 8 2008) (FDA access data, Harvard health)	α_{1a}-Blocker for BPH	Highly selective α_{1a} blocker; relaxes prostatic and urethral smooth muscle	Retrograde ejaculation, nasal congestion, dizziness
Dutasteride 0.5 mg OD	FDA-approved for BPH 2001 (FDA access data, MedPath)	Dual 5-α reductase inhibitor for BPH	Inhibits type I and II 5-α reductase → reduces DHT	Sexual dysfunction, breast tenderness, decreased PSA
Tadalafil 5 mg OD	FDA-approved for BPH (since Oct 6 2011) and ED (Drugs.com, NCBI)	PDE-5 inhibitor for BPH and ED	Enhances smooth muscle relaxation via PDE-5 inhibition	Headache, flushing, dyspepsia
Sildenafil 50-100 mg PRN	FDA-approved for ED (Viagra since Mar 27 1998); not approved for BPH (FDA access data, history)	PDE-5 inhibitor for ED; investigational in BPH	Improves pelvic blood flow and detrusor relaxation	Visual disturbances, flushing, hypotension
Oxybutynin 5 mg BID/TID	FDA-approved (oral since 1975) for OAB (Wikipedia, FDA access data)	Antimuscarinic for OAB (used in BPH with OAB)	Non-selective muscarinic blocker; reduces detrusor contractions	Dry mouth, constipation, blurred vision
Solifenacin 5-10 mg OD	FDA-approved (VesiCare since Nov 19 2004) (FDA access data)	M_3 Antagonist for OAB (used in BPH with OAB)	Selectively blocks M_3 receptors to reduce bladder overactivity	Dry mouth, constipation, QT prolongation
Mirabegron 25-50 mg OD	FDA-approved (Myrbetriq since Jun 28 2012) (FDA access data, NCBI)	β_3-Agonist for OAB (used in BPH with OAB)	Activates β_3 receptors to relax detrusor during bladder filling	Hypertension, nasopharyngitis, headache

ADVANCES IN COMBINATION PHARMACOTHERAPY

Combination pharmacotherapy with alpha-blockers and 5-ARIs enhances BPH management by targeting Dynamic (smooth muscle tone) and static (prostate volume). It provides components of disease superior long-term symptom relief, improves quality of life, reduces disease progression and delays surgery, especially in moderate to severe cases with larger prostates.[25]

Common regimens include tamsulosin plus dutasteride and silodosin plus dutasteride. Tamsulosin blocks alpha-1A and α-1D receptors, while silodosin selectively targets α-1A, reducing hypotension risk. Both improve urinary symptoms and slow progression, with silodosin plus Dutasteride potentially offering better tolerability.[21,22]

Table 2: Combination therapies for LUTS associated with BPH.

Combination therapy	Clinical benefits
Alpha-blockers (AB) + 5ARIs	Demonstrates marked reduction in disease progression, improved urinary flow, and better symptom relief. Outperforms monotherapy in several clinical trials.[27-32]
AB + anticholinergics (Ach)	Helps manage urgency and frequency in patients with persistent symptoms. More effective than single-agent therapy, though may lead to more side effects.
AB + beta-3 agonists (B3AA)	Certain studies report improvement in overactive bladder symptoms when combined with alpha-blockers, though overall evidence remains limited.
AB + PDE5 inhibitors (PDE5i)	Shows enhancement in both urinary and sexual functions. However, concerns remain about long-term adherence and sustained benefits.
AB + 5ARIs + anticholinergics	Provides symptom control in severe or treatment-resistant cases. However, increased likelihood of side effects limits routine use.
5ARIs + PDE5i	May offer improvements in LUTS and erectile function, although adherence issues could affect treatment success.
PDE5i + Ach	Some benefit seen in overactive bladder and LUTS management, but supporting evidence is scarce.
B3AA + PDE5i	Preliminary data suggest symptom relief, though further research is necessary to confirm effectiveness.

*AB: Alpha-blockers (e.g., Tamsulosin, doxazosin, alfuzosin, silodosin) (e.g., Finasteride, dutasteride), Ach: Anticholinergics (e.g., Solifeacin, oxybutynin), PDE5i: Phosphodiesterase-5 inhibitors (e.g., Tadalafil, sildenafil), B3AA: Beta-3 adrenergic agonists (e.g., Mirabegron).

NEED FOR ADVANCEMENT

BPH poses increasing clinical challenges due to its high prevalence in aging men and the complex genetic, molecular, and immune factors driving its pathogenesis. Although pharmacologic and minimally invasive therapies provide relief, but they often fail to stop disease progression, especially in patients with comorbidities or high genetic risk.[23]

Recent multi-omics research reveals that BPH results from a network of genomic, transcriptomic, and metabolic dysregulation, with immune activation and chronic inflammation playing key roles in prostate enlargement and symptom progression. Genetic predisposition accounts for 40-70% of cases, highlighting the disease's heritability and the limitations of current treatments, which mostly address symptoms rather than root causes. In this context, gene therapy offers a promising shift by targeting molecular drivers such as BTN3A2, C4A, DNA methylation sites, and IL-17–mediated inflammation.[24]

Advances in gene editing and transfer technologies suggest the potential for disease modification rather than symptom control, positioning gene therapy as a vital future approach particularly for patients with strong genetic susceptibility or those unresponsive to conventional treatments.[25]

NOVEL DIAGNOSTIC BIOMARKER IN BPH

Recent advances in BPH research have identified novel diagnostic biomarkers via integrated genomic, immune, and molecular analyses. Genes such as CHRDL1, NEFH, TAGLN, and SYNM are upregulated in BPH but downregulated in prostate cancer, aiding differentiation and correlating with immune response. Machine learning highlights DACH1, CACNA1D (upregulated), and STARD13, RUNDC3B (downregulated) as markers linked to immune infiltration. GSTP1 methylation and transglutaminases (TG4, TG2) serve as effective, non-invasive diagnostic and progression biomarkers. These insights enhance diagnostic precision and support personalized, immune-targeted therapies focusing on autoimmune inflammation and TNF-α pathways.[26]

NOVEL PHARMACOLOGICAL APPROACH IN BPH AND LUTS

TNF antagonist

TNF-antagonists are emerging as novel therapies for BPH, especially in patients with inflammatory or

autoimmune conditions. Evidence from large cohorts and animal models shows TNF-antagonists reduce BPH incidence and prostate growth by decreasing epithelial proliferation, macrophage infiltration, inflammation, and NFκB signaling. Unlike broad anti-inflammatories like methotrexate or NSAIDs, TNF blockers uniquely lower BPH risk and prostate inflammation, suggesting targeted cytokine inhibition offers stronger disease modification. Clinical trials on agents like adalimumab in non-autoimmune BPH highlight their potential in resistant cases.[27,28]

LHRH antagonists

LHRH antagonists such as Cetrorelix, Leuprolide, Degarelix**,** Teverelix are primarily used in prostate cancer treatment due to their ability to suppress testosterone production via the GnRH pathway. By blocking LHRH receptors in prostatic tissue, these agents can also reduce prostate volume and relieve obstructive urinary symptoms, making them a potential option in BPH management. Beyond hormonal suppression, they may promote apoptosis or inhibit cellular proliferation through mechanisms like plasminogen activator inhibition.[29]

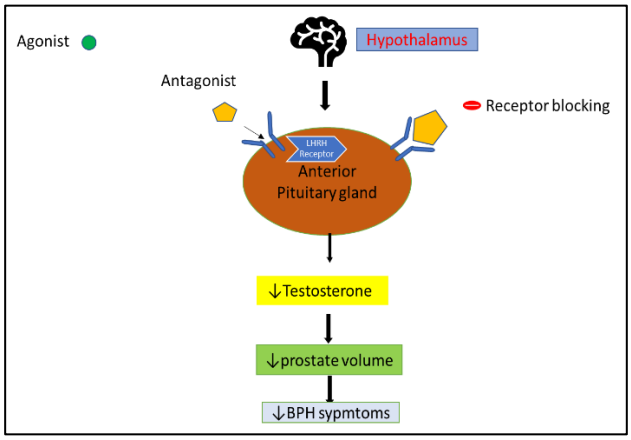

Figure 2: Mechanism of LHRH antagonists.

Cetrorelix

Cetrorelix suppress prostatic overgrowth, inflammation and reduces cellular proliferation without causing systemic testosterone depletion. Unlike conventional hormonal agents that induce long-term androgen suppression and related sexual side effects, Cetrorelix achieves only transient reductions in testosterone, allowing symptom relief while preserving hormonal balance. Clinical trials have shown improvements in IPSS, Qmax, QoL, and prostate volume, with a Phase III study reporting a 5.6-point IPSS reduction over 26 weeks, though some studies failed to reach statistical significance. These findings highlight its promise as a testosterone-sparing hormonal option, although its routine use in BPH remains investigational pending further large-scale evidence.[30]

Leuprolide

By suppressing androgen production, Leuprolide can significantly reduce prostate volume and improve urinary flow and symptoms. Clinical trials show Leuprolide can significantly benefit men with BPH. In Eri et al n=55), 3.75 mg IM Leuprolide every 28 days for 24 weeks reduced PSA by 87% and PAP by 39%, with significant symptom improvement. Another randomized, placebo-controlled study (n=50) found a 34.5% reduction in prostate size and a 32-54% increase in urinary flow rate, though some patients had flushing and decreased sexual function. In a larger adjunct therapy RCT (n=77), adding Leuprolide to standard therapy gave a better symptom score reduction (2.5 vs. 1.5 IPSS) than standard alone, with side effects similar to standard treatment. A small daily dosing cohort (n=15) reported a 40-46% reduction in prostate size, symptom benefit for all, but some experienced decreased potency and flushing.[31]

Teverelix

Teverelix, by suppressing luteinizing hormone and testosterone without the androgen surge seen with GnRH antagonists, offers efficacy and safety benefits. In a phase 2 randomized trial of treatment-naïve men over 50, subcutaneous Teverelix reduced IPSS scores by 6.3 points at week 16, with 44% reporting early symptom improvement by week 2 and 83% by week 12. It also decreased prostate volume by 11% in four weeks, improved urinary flow, and enhanced quality of life, maintaining a favorable safety profile. Teverelix is thus a fast-acting, testosterone-sparing option, especially for patients at risk of urinary retention or intolerant to conventional therapies, though long-term data are needed.[31]

GnRH antagonist

Degarelix

Degarelix GnRH antagonist has been investigated for prostate cancer (PCa) patients, including those who failed prior LHRH antagonist therapy. In salvage settings, PSA response rates were modest (16.7% and 33.3%), with limited 12-month progression-free survival (8.8% and 8.3%), though it was well tolerated, mainly causing injection-site reactions. However, as first-line therapy, Degarelix demonstrated superior disease control and faster androgen suppression compared to LHRH antagonists in phase III trials. While its benefit is limited in refractory PCa or BPH-related PSA elevation, Degarelix offers a favorable safety profile and potential advantages if introduced early in treatment.[32]

Nonsteroidal anti-inflammatory drugs

NSAIDs like Celecoxib and Loxoprofen have been explored for their potential role in managing BPH-related symptoms, particularly nocturia, due to their anti-

inflammatory effects. It inhibits COX 2 enzymes which leads to decrease prostaglandin production. This helps to reduce prostate edema and it improves urinary flow.[33]

Celecoxib cyclooxygenase-2 (COX-2) inhibitor

Celecoxib in animal studies found to lowers prostate weight, enhances epithelial apoptosis (TUNEL assay), and decreases COX-2 and mast cell density. In a randomized, double-blind, placebo-controlled trial involving 80 men with BPH and frequent night time urination, celecoxib 100 mg taken nightly for one month significantly reduced nocturnal voids-from an average of 5.2 to 2.5 and improved IPSS scores without major side effects. Smaller studies combining celecoxib with alpha-blockers like Doxazosin or terazosin have reported additional benefits, including PSA reduction and decreased prostate volume.[34]

Loxoprofen-nonselective nonsteroidal anti-inflammatory drug

In a study of 78 BPH patients with at least two nocturia episodes, loxoprofen (60 mg at bedtime) plus standard therapy significantly reduced nocturia at 3 months compared to controls (-1.5 vs. -1.1 episodes; p=0.034), though benefits waned at 6 and 12 months. Adverse effects such as gastric discomfort and leg edema occurred in 22.5%, indicating short-term efficacy but caution with prolonged use due to safety concerns.

Immunotherapy

GV1001 (Tertomotide)

GV1001 (tertomotide), an injectable telomerase-based vaccine initially developed for cancer immunotherapy, is being investigated as a novel treatment for BPH. In a Phase II randomized trial of 161 men with moderate-to-severe LUTS, biweekly GV1001 injections (0.4 or 0.56 mg) led to significantly greater IPSS reductions at 13 weeks compared to placebo (-7.2 and -6.8 vs. -3.5) and meaningful prostate volume reductions at 16 weeks across all treatment groups. GV1001 was well tolerated, with no increase in adverse events versus placebo. These results highlight GV1001's potential as an immunomodulatory BPH therapy, though further studies are needed to confirm long-term efficacy and optimal dosing.[35]

Collectively, such novel therapies represent a shift toward targeted, less invasive BPH treatments aimed at improving outcomes while minimizing systemic side effects, underscoring the need for larger, well-controlled trials to validate their safety and effectiveness.

Afala (Anti -prostate specific antigen antibody)

Afala (Afalaza or Athaliah) is an oral antibody-based therapy targeting prostate-specific antigen (PSA) for treating BPH and chronic prostatitis. In a phase III trial with 249 men, daily Afala (12 mg twice daily) significantly improved IPSS and Qmax over 12 months versus placebo without major adverse events. A comparative study with 186 patients showed Afala's efficacy was comparable to Serenoa repens extract in improving IPSS, quality of life, urinary flow rates, and reducing prostate volume and residual urine. A 12-month observational study of 30 patients also confirmed symptom, QoL, and urinary improvements with no safety concerns. These results indicate Afala is a safe, well-tolerated, non-hormonal oral option for mild to moderate BPH symptom.[36]

Gene therapy

URO-902 (BK channel-based gene therapy)

URO-902 is an emerging gene therapy. It uses naked plasmid DNA encoding the α-subunit of the BKCa channel, which regulates smooth muscle excitability.[37] Initially studied in overactive bladder patients, URO-902 significantly reduced urinary frequency and urgency after a single intradetrusor injection, showing excellent tolerability in phase II a trial.[38] By enhancing BK channel expression in smooth muscle cells, it stabilizes membrane potential and reduces intracellular calcium influx, suppressing involuntary contractions. Though not yet tested in BPH, its rationale is supported by shared smooth muscle overactivity in bladder and prostate. Intraprostatic delivery may reduce prostatic tone and relieve obstruction, offering a potentially long-lasting, non-hormonal therapy. Growing interest in URO-902 for BPH focuses on optimizing delivery, dosing, and durability of effects. Its development reflects a broader shift toward biologic and gene-based interventions in urology.[38]

PRX-302 (Topsalysin: PSA-activated proaerolysin)

PRX-302 is a novel intraprostatic injectable therapy for BPH. It is a genetically engineered bacterial protoxin activated by prostate-specific antigen (PSA) abundant in prostatic tissue. Once injected, PSA activates PRX-302, inducing targeted apoptosis in prostate cells, reducing tissue volume, and relieving LUTS without affecting systemic hormones or surrounding organs. Clinical trials show promising results a phase I/II study in 33 men reported 60–64% IPSS improvement sustained for 12 months without sexual side effects, while a phase IIb trial with 92 participants confirmed durable symptom relief and improved peak urinary flow after a single injection targeting 20% of the prostate, with only mild transient local side effects. Erectile and ejaculatory functions remained intact. As PRX-302 advances through Phase III trials, it may become a minimally invasive, effective alternative to conventional BPH treatments. Despite mixed European data on intraprostatic injections, PRX-302 is among the most advanced injection therapies approaching regulatory approval.[39]

NX-1207 (Pro-apoptotic protein injection)

NX-1207 is an investigational, single-session, office-based intraprostatic injection therapy. It reduces prostate volume and improves LUTS without affecting systemic hormones like PSA or testosterone. Phase I/II U.S. trials demonstrated significant symptom improvement (IPSS/AUASI reduction of 9-11 points) and prostate shrinkage (4.6–6.8 mL), outperforming Finasteride, with no sexual side effects or systemic exposure. Long-term data showed durable effects, with over half of patients avoiding further BPH treatments for up to five years. However, recent European trials yielded inconsistent results, raising efficacy concerns. Ongoing phase III studies aim to confirm effectiveness and refine patient selection. If successful, NX-1207 may provide a convenient, non-hormonal, minimally invasive alternative to surgery or chronic medication for BPH.[40]

Table 3: Gene therapy.

Drug name	Route of administration	Mechanism of action	Clinical status
URO-902 (5000-10,000 µg/injection)	Intradetrusor/prostatic injection	BK channel gene upregulation	Phase IIa in OAB; BPH application experimental
PRX-302 (0.6-3.0 ml of 0.6–3 µg/mL)	Intraprostatic injection	PSA-activated pore-forming toxin	Phase IIb positive; phase III ongoing
NX-1207 (2.5 mg or 5 mg per injection)	TRUS-guided intraprostatic injection	Local apoptosis via proprietary peptide	Phase II strong; mixed phase III results

Selective androgen receptor modulator

Selective androgen receptor modulators offer anabolic benefits of androgens while minimizing effects on androgen-sensitive tissues like the prostate. Unlike testosterone, SARMs are nonsteroidal and do not convert to DHT or estrogen, metabolites linked to prostate enlargement.[41] Their tissue-selective action provides full anabolic activity in muscle and bone but only partial activity in the prostate, making them ideal for hypogonadal men with BPH who risk adverse effects from traditional androgen therapy.

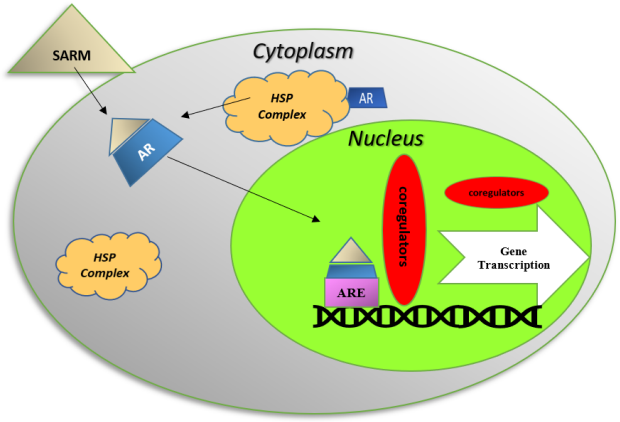

Figure 3: Mechanism of action of SARM.
*SARM-selective androgen receptor modulators, AR-androgen receptor, HSP-heat shock potential, ARE-androgen receptor modulators.[41]

OPK-88004 (LY-2452473) (Selective androgen receptor modulator)

OPK-88004 is an oral SARM offering a novel treatment for hypogonadal men with BPH, especially those contraindicated for testosterone therapy. Preclinical studies show it reduces prostate weight, potentially controlling androgen-driven growth while preserving muscle and metabolic health.[41] A phase II trial in men with BPH-related LUTS assessed safety, symptom relief, and prostate volume changes at 15 and 25 mg doses over 16 weeks, though results are pending. Another placebo-controlled trial in testosterone-deficient men post-prostatectomy showed OPK-88004 increased lean mass and reduced fat without raising PSA or causing erythrocytosis. With its prostate-sparing and anabolic benefits, OPK-88004 is promising for hypogonadal men with BPH needing anabolic support, warranting further BPH-focused studies.[41]

BMS-564,929 (Selective androgen receptor modulator)

BMS-564,929, a selective androgen receptor modulator by Bristol-Myers Squibb, shows 160-fold greater anabolic activity in muscle versus prostate, reducing prostate stimulation risk. Initially for muscle wasting, it has potential in BPH management. Pharmacokinetics indicate safety, but clinical trials on BPH outcomes are still needed.

Oxytocin receptor antagonist

Epelsiban (GSK 557,296 B)

Epelsiban was well tolerated in a phase 2 trial for premature ejaculation but showed no significant improvement in intravaginal ejaculatory latency time. Its potential in BPH arises from oxytocin receptor overexpression in hyperplastic prostate tissue, which promotes stromal and epithelial proliferation and increases smooth muscle tone.[42]

By blocking these receptors, Epelsiban may reduce smooth muscle contractions and limit prostatic growth. Preclinical studies in aged prostate models support its efficacy, making Epelsiban a novel, non-hormonal BPH therapy with potentially fewer side effects like sexual

dysfunction or hypotension compared to the conventional treatments.[42]

Anti-allergic/antifibrotic agent

Tranilast

A mast cell stabilizer and TGF-β pathway inhibitor approved in the 1980s for the asthma. Its anti-inflammatory and anti-fibrotic properties have recently sparked interest for BPH, especially in cases of prostate enlargement driven by chronic inflammation and fibrotic remodelling.

Preclinical studies in BPH animal models show that oral Tranilast significantly suppresses mast cell activation, inhibits TGF-β–driven endothelial-to-mesenchymal transition, and reduces prostate volume all without major side effects by targeting the inflammation-fibrosis axis, Tranilast may offer a novel, non-hormonal approach to managing BPH symptoms and limiting prostate growth.[43]

β₃-adrenergic agonist

Vibegron (GEMTESA®)

Vibegron is a selective β3-adrenergic receptor agonist that relaxes the detrusor muscle during bladder filling, increasing bladder capacity and reducing storage LUTS with BPH.[44] It improves these symptoms without impairing bladder emptying, a critical factor in BPH management. Clinical trials including the phase III COURAGE and EMPOWUR studies demonstrated that adding Vibegron to standard BPH therapy significantly reduces urgency episodes, micturition frequency, nocturia, and urge urinary incontinence, with sustained benefits up to 40 weeks.[44]

Vibegron also showed better tolerability and a favorable safety profile compared to Tolterodine and does not inhibit CYP2D6, minimizing drug interaction risks in older adults. Approved by the FDA for overactive bladder (OAB) in 2020, its indication was extended in 2024 to include OAB symptoms in men receiving BPH pharmacotherapy. Its once-daily dosing and minimal side effects make Vibegron a promising adjunct for men with persistent storage symptoms despite standard treatments.[44]

Angiotensin-converting enzyme inhibitors

Renin–angiotensin system inhibitors, including Enalapril, losartan, and Telmisartan, have shown promise as cost-effective adjuncts in BPH by promoting apoptosis and preserving prostate structure in animal models. Mostafa et al found captopril (100 mg/kg) reduced prostate weight, PAP, and PSA, enhancing apoptosis via p53, Bax, caspase-3, and lowering PCNA and Bcl-2.[45,46]

Progestogens

Progestogenic agents such as allylestrenol and chlormadinone acetate (CMA) are used mainly in Japan to treat BPH-related LUTS by exerting antiandrogenic effects that reduce prostate size. Allylestrenol lowers serum testosterone by about 40%, improving IPSS by 5 points. CMA (50 mg twice daily for 16 weeks) reduces prostate volume by 5.3 mL, increases peak urinary flow (Qmax) by 2.4 mL/s, and in men with LUTS and erectile dysfunction, improves IPSS, Qmax, quality of life, decreases prostate size by 25%, and lowers PSA by 50%. Etonogestrel (150-300 µg) shows promise in reducing testosterone and prostate volume, alleviating LUTS, and potentially preventing acute urinary retention and surgery, while avoiding the typical hypogonadal effects.[49,50]

Onabotulinumtoxin A (BoNT-A)

Onabotulinumtoxin A (BoNT-A), used for neuromuscular disorders and overactive bladder, has been explored for BPH by inhibiting acetylcholine release and relaxing prostate smooth muscle. Single-arm studies reported improvements in AUA symptom scores and peak urinary flow. A phase II trial with 380 men showed symptom and flow benefits across doses (100-300 U). Another study observed improved sperm parameters post-injection. However, a 2014 phase II trial found no significant IPSS changes versus placebo, while a separate trial showed BoNT-A reduced prostate volume more than Tamsulosin, indicating mixed efficacy.[51,52]

Table 4: Emerging therapies for BPH.[24]

Drugs	Drug class	Indication	Trial status	Mechanism of action
Cetrorelix	GnRH antagonist	BPH,	Phase III (2006-2011)	Inhibits LH/FSH → lowers testosterone and prostate volume
Leuprolide	LHRH antagonist	BPH	Phase III (1990s-2000s)	Suppresses testosterone via LHRH inhibition
Degarelix	GnRH antagonist	BPH, LUTS	Phase II (2008-2012)	Blocks GnRH receptors → rapid suppression of LH and testosterone
Teverelix	GnRH antagonist	BPH, prostate cancer, contraception	Phase II (2021-ongoing)	Selective GnRH blockade → reduces LH/testosterone without initial flare
NSAIDs	Non-steroidal anti-inflammatory drugs	BPH, pain relief	Phase IV (2005-present)	Inhibits COX enzymes→reduces prostatic inflammation

Continued.

Drugs	Drug class	Indication	Trial status	Mechanism of action
GV1001 (Tertomotide)	Telomerase peptide/ vaccine	BPH, prostate cancer	Phase II (2018-ongoing)	Anti-fibrotic; immune-mediated targeting of telomerase-positive and androgen-driven cells
Afala	Homeopathic anti-PSA agent	BPH, chronic prostatitis	Phase III (2008-2014)	Anti-PSA antibodies → modulate PSA and improve prostate function
URO-902	BK channel gene therapy	BPH	Phase III (2022-ongoing)	Upregulates BK channels→ relaxes prostatic/bladder smooth muscle
PRX-302 (Topsalysin)	PSA-activated cytotoxin	BPH, prostate cancer	Phase III 2016-ongoing)	Activates in PSA-rich cells → selective prostate cell death
NX-1207	Proapoptotic agent	BPH	Phase III (2012-2014)	Induces localized apoptosis → preserves testosterone and PSA levels
OPK-88004	SARM	BPH (under study)	Awaiting phase II (post-2020)	Promotes muscle growth with minimal prostate stimulation
BMS-564,929	SARM	(Preclinical BPH interest)	Preclinical (2005-2008)	Selective anabolic effects → minimal prostate stimulation
Tranilast	TGF-β inhibitor/ antifibrotic	BPH (preclinical)	Preclinical (2009-2012)	Blocks fibrotic pathways → prevents tissue remodeling
Vibegron	β_3-Adrenergic receptor agonist	BPH-associated LUTS (storage symptoms)	Phase III (COURAGE) (2021-2023)	Relaxes bladder detrusor → improves urinary storage symptoms
Allylestrenol and CMA	Progestogens/ anti-androgens	BPH, LUTS	Phase III (2008-2014)	Inhibit androgen action → shrink prostate
Onabotul-inumtoxin A	Neurotoxin	BPH, overactive bladder (OAB)	Phase II-IV (2006-2019)	Inhibits acetylcholine → relaxes prostatic smooth muscle

Table 5: Newer phytochemical approaches in BPH.[82]

Name	Common name	Source	Mechanism of action
Serenoa repens	Saw palmetto	Palm fruit	5-α-reductase inhibition; anti-inflammatory
Pygeum africanum	African plum bark	Tree bark	Anti-androgen; apoptosis; anti-inflammatory
Cucurbita pepo	Pumpkin seed oil	Pumpkin seeds	DHT inhibition; anti-inflammatory; muscle relaxation
Urtica dioica	Stinging nettle	Plant roots	5-α-reductase inhibition; anti-inflammatory
Epilobium angustifolium	Willow herb	Aerial parts	Anti-androgen; anti-inflammatory
Hypoxis hemerocallidea	African potato	Tuber	COX inhibition; β-sitosterol
Pinus pinaster	Maritime pine	Twigs/resin	Contains β-sitosterol
Solanum lycopersicum	Tomato (lycopene)	Fruit	5-α-reductase inhibition; promotes apoptosis
Roystonea regia	Royal palm	Fruit	5-α-reductase inhibition; smooth muscle relaxation
Secale cereale	Rye pollen	Pollen	5-α-reductase inhibition; sphincter relaxation; α-blocker
Linum usitatissimum	Flaxseed oil	Flax seeds	5-α-reductase inhibition; anti-inflammatory
Isoflavones	Soy isoflavones	Soy products	Estrogen receptor-mediated apoptosis

NEWER PHYTOCHEMICAL APPROACHES IN BPH

Phytotherapy offers a promising alternative for managing LUTS in BPH, with plant-based agents such as *Serenoa repens*, *Pygeum africanum*, and *Cucurbita pepo* demonstrating mechanisms like 5-alpha-reductase inhibition, anti-inflammatory action, and hormonal modulation. Although clinical trials report only modest efficacy, these treatments are generally well tolerated with minimal side effects.

Despite their global use, phytochemicals are not currently included in standard treatment guidelines due to limited high-quality evidence. Nonetheless, they remain a convenient option for select patients and represent an evolving area of interest in BPH therapy.[53]

NOVEL GENE-BASED PHARMACOLOGICAL AND MULTI-OMICS APPROACH IN BPH

Recent multi-omics studies have significantly advanced the understanding of BPH, highlighting new genetic and immune-related targets for diagnosis and therapy. Large-

scale genomic analyses identified BTN3A2 and C4A as key genes associated with BPH in both blood and prostate tissue. Epigenetic data revealed that the cg14345882-BTN3A2-BPH axis, involving altered DNA methylation, may regulate BTN3A2 and affect disease susceptibility. BTN3A2, expressed in various T cell subsets, likely promotes BPH by enhancing inflammatory pathways such as γδ T cell activation and IL-17 elevation, leading to immune dysregulation and prostate tissue remodeling. C4A, part of the complement system, contributes via immune complex activation. Further, transcriptome-wide studies and Mendelian randomization identified 30 potential drug targets, including PTGES3, targeted by gedunin, although cardiovascular safety requires assessment. Links to circulating metabolites and immune biomarkers underscore the metabolic-immune interplay in BPH. These integrative findings support novel, non-invasive diagnostic models and personalized, immune-targeted approaches, though broader population studies and in vivo validation remain needed.[25]

PERSONALISED AND PATIENT-CENTERED PHARMACOLOGIC STRATEGIES

Personalized treatment is essential in managing BPH due to significant variability in symptoms and clinical features among patients. Treatment plans are tailored based on dominant LUTS, prostate size, PSA levels, sexual health, and comorbidities. For men with mainly voiding symptoms, alpha-blockers such as Tamsulosin provide rapid relief and are typically first-line therapy.[52] Those with bothersome storage symptoms like urgency, frequency, or nocturia may benefit from adding mirabegron or antimuscarinics, especially when overactive bladder is suspected. In cases of considerable prostate enlargement (usually >30-80 cc) and elevated PSA, 5-ARIs like Finasteride or Dutasteride are effective in slowing progression, with combination therapy alongside alpha-blockers giving superior symptom control versus monotherapy.[54]

Maintaining sexual function is critical; some treatments, notably 5-ARIs and alpha-blockers like silodosin, may cause side effects including reduced libido, ejaculatory dysfunction, and erectile dysfunction.[3] Thus, evaluating baseline sexual health using validated tools like the IIEF or MSHQ before beginning therapy is recommended. Low-dose Tadalafil (5 mg daily) can address both erectile dysfunction and LUTS without compromising sexual function.[54]

Emerging pharmacogenomics research indicates about 25% of patients poorly respond to 5-ARIs, with genetic variants such as SNP rs61767072 in the SRD5A2 gene associated with non-response, while other gene variants like NOS3 show no effect. These insights enable gene-guided treatment planning to optimize personalized care and reduce ineffective therapies.[55]

CONCLUSION

BPH is more than just prostate enlargement it involves complex changes in the lower urinary tract that impact daily life for many aging men. While medications like alpha-blockers and 5-ARIs remain the most common choices, side effects such as sexual dysfunction often limit long-term use. Newer options, including PDE5 inhibitors, hormone-targeting agents, and anti-inflammatory drugs, are expanding the treatment landscape and offering hope to those who don't respond well to traditional therapies Phytochemical therapies, derived from plant-based compounds, are also gaining attention for their potential to relieve symptoms with fewer adverse effects.As research advances, there's growing interest in personalized and minimally invasive approaches, such as gene-based treatments and therapies tailored to individual symptom patterns and biological markers. However, long-term effectiveness, safety, and affordability remain key concerns. Continued innovation and a deeper understanding of BPH will be essential to improve symptom control, preserve quality of life, and meet the needs of a growing aging population.

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