



Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: Benign Prostatic Hyperplasia
-August 2016-



Background:

The IHS National Pharmacy and Therapeutics Committee (NPTC) reviewed pharmacotherapeutic management of benign prostatic hyperplasia (BPH) at the August 2016 meeting. Presently, doxazosin, finasteride, oxybutynin, tamsulosin and tiroprium reside on the National Core Formulary. The analysis included clinical and utilization/procurement data of BPH medications. **This review did not lead to any formulary modification**; however, it was felt that a formulary brief would be beneficial to IHS clinicians.

Discussion:

BPH develops as a strictly age-related phenomenon in nearly all men, starting at approximately 40 years of age. It is the fourth most common diagnosis in men after age 50 and, in the community setting, the prevalence of diagnosed BPH is 13.5%³. One study discovered prostate growth rate of 1.6% annually as measured by transurethral ultrasonography⁹.

The primary treatment goals are to reduce lower urinary tract symptoms (LUTS), improve prostate-related quality of life, and prevent or delay disease progression¹. In many other conditions the focus is on treating aggressively at the beginning and throughout the lifespan of the patient, whereas in BPH a “watchful waiting” approach can often be initiated. In one study, approximately 85% of men with mild LUTS were stable on watchful waiting at one year². Medications approved for BPH include alpha-1 blockers (AB), 5-alpha reductase inhibitors (5-ARI) and phosphodiesterase type 5 inhibitors (PDE5-I). Since mechanisms of action differ considerably between these classes, they can be used synergistically. Prostate size does impact medication choices for BPH management⁶.

Alpha-1 blockers work by inhibiting receptors in prostatic stromal and bladder neck tissues. This blockade reduces the sympathetic tone-induced urethral stricture causing BPH symptoms⁵. These agents significantly improve symptom scores (both irritative and obstructive symptoms), quality of life (QoL), and urinary flow rates but do not reduce the risk of acute urinary retention (AUR) or the need for surgery later on⁶.

The 5-ARIs inhibit the enzyme responsible for conversion of testosterone to dihydrotestosterone. By blocking this enzyme, the prostate decreases 20-25% in volume and prostate-specific antigen (PSA) blood levels by 50%. The 5-ARIs dramatically improve lower urinary tract symptoms (LUTS) symptoms, improve urinary flow rate, and reduce the risk of AUR. Because they reduce prostate size, they also reduce the need for BPH-related surgery.

The PDE5-Is are well recognized for their ability to treat erectile dysfunction, but also improve LUTS in BPH by increasing nitric oxide in genitourinary tract tissues. This results in calcium-dependent relaxation of endothelial smooth muscles and increased blood flow⁶. Although PDE5Is affect the smooth muscles of the prostate and bladder, their precise mechanism for reducing BPH symptoms is unknown.

Findings:

Several studies of significance laid the foundation for the current BPH treatment guidelines. In 2006, the TIME study evaluated the efficacy of tolterodine and tamsulosin. The combination of tolterodine and tamsulosin was found to be effective at reducing urgency episodes, the number of micturitions and nocturia and the International Prostate Symptom Score (IPSS) however tolterodine monotherapy was not⁸. In 2007, the SATURN study evaluated the combination of tamsulosin and solifenacin versus tamsulosin alone and placebo. Combination therapy did not result in significant improvement in IPSS but did improve micturition frequency and voided volume compared to tamsulosin alone. In 2011, the NEPTUNE trial demonstrated that combination solifenacin and tamsulosin OCAS (oral controlled absorption system) significantly improving storage and voiding symptoms, including QoL parameters over placebo⁸. Lastly, the EPICS trial compared dutasteride and finasteride for the treatment of BPH

symptoms. This 12-month RCT demonstrated that both agents are similarly effective in reducing prostate volume while improving LUTS with similar rates of adverse drug events.

MTOPS (1998) and ComBAT (2009) were two, large long-term studies that demonstrated superiority of combination therapy (ABs and 5-ARIs) over monotherapy in preventing symptomatic progression, risk of AUR and BPH-related surgery. These studies lead to the American Urological Association (AUA) and European Association of Urology (EAU) recommendations for combination therapy in patients with moderate-severe symptoms and/or at high risk of progression to prostate enlargement (>40ml, high PSA levels and advanced age). In general, these studies support the use of combination therapy when symptoms become refractory with monotherapy but do not suggest when combination therapy should be started.

In 2016, the Agency for Healthcare Research and Quality (AHRQ) conducted a comparative effectiveness review on BPH medications for LUTS. AHRQ concluded the following:

- Compared to placebo, newer drugs or drug combinations (silodosin, solifenacin/AB combination, and tadalafil) demonstrated improved clinical efficacy in LUTS, however they do not offer any clinical advantage over traditional AB treatment.
- Silodosin was more effective for LUTS than placebo but no more effective than the traditional AB therapy. It was also associated with an increased rate of ADEs.
- The three anticholinergic agents (tolterodine, solifenacin and fesoterodine), when combined with an AB, offered no additional benefits in the treatment of LUTS versus AB monotherapy.
- There is insufficient evidence for the use of mirabegron (beta-3 agonist) or its use in combination with an AB compared to AB monotherapy. However, these studies did demonstrate a decrease in urgency episodes and micturition frequency versus placebo¹.

In 2015, the EAU published an algorithm for LUTS treatment in males. See algorithm (page 137) [here](#).

There has been increased interest in the past few years for using PDE5-Is for BPH. A 2012 European study evaluated PDE5-Is in LUTS and compared tadalafil 5 mg daily, tamsulosin 0.4mg daily and placebo. Researchers used IPSS as a primary measure while secondary measures included the BPH Impact Index (BII) and the International Index of Erectile Function-Erectile Function (IIEF-EF) domain. Changes from baseline were statistically significant for both medications, with tadalafil reducing the IPSS by -2.1 (p=0.001) and tamsulosin by -1.5 (p=0.023). The BII was also significant for both medications compared to placebo, -0.8 for tadalafil (p=0.003) and -0.6 for tamsulosin (p=0.026). Of note, the IPSS QoL index showed significant improvement with tadalafil (p=0.02) but not with tamsulosin⁷. Both tadalafil and tamsulosin experienced statistically significant improvements in Qmax as well as increases in average flow rate. Differences in the treatment groups versus placebo were not statistically significant for volume voided or bladder capacity. There were no significant differences in ADEs between the treatment groups and placebo. Common ADEs for tadalafil were headache and nasopharyngitis while those receiving tamsulosin most commonly reported headache and dizziness.

In conclusion, tadalafil 5 mg daily for 12 weeks resulted in clinically meaningful improvements in LUTS similar to tamsulosin 0.4 mg daily. Also, tadalafil (but not tamsulosin) improved LUTS QoL, global impressions of BPH symptom impact, BPH treatment satisfaction, and improved erectile function for those men with ED. A major limitation to this study was that it was underpowered to compare individual medications to each other. This was the first international study however to demonstrate that PDE5-Is are similarly effective to ABs in treatment of BPH⁷.

Conclusions:

There are several important points to consider since that last NPTC review of BPH treatment in 2011.

1. The new AB silodosin demonstrated similar effectiveness to tamsulosin in improving short-term LUTS.
2. Traditional ABs (doxazosin, tamsulosin) remain the drug of choice for patients initiating therapy.
3. Tolterodine, solifenacin/AB combination and AB monotherapy have all been shown to be similarly effective for short-term LUTS, whereas oxybutynin and trospium have not.

4. Dutasteride and finasteride are similarly effective in reducing prostate volume and improving Qmax and LUTS at 12 months.
5. Finally, tadalafil improved short-term LUTS versus placebo and, when compared to tamsulosin, was similarly effective in treating short-term LUTS following 3 months of treatment.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the [NPTC website](#).

References:

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