INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Benign Prostatic Disorders***
-November 2022-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) reviewed benign prostatic disorders at the Fall 2022 meeting. Benign prostatic hyperplasia (BPH) is one of the most common conditions in aging men and the most common cause of lower urinary tract symptoms (LUTS). Autopsy studies have observed a histological prevalence of 8%, 50%, and 80% in the 4th, 6th, and 9th decades of life, respectively.[1] Parallel to the development of BPH, LUTS increase in frequency and severity with age. While LUTS/BPH is rarely life threatening, the impact on quality of life is significant and should not be underestimated.[2] Following clinical review and analysis, the NPTC **made no modifications** to the National Core Formulary. Of note, during the same meeting, the NPTC did add tadalafil to the National Core Formulary for the clinical indication of erectile dysfunction, with the recognition of its additional role in the management of BPH.

Discussion:

Treatment is indicated for patients with symptomatic BPH. Typical manifestations of LUTS/BPH include storage symptoms (urinary frequency, urgency, nocturia, and incontinence) and voiding symptoms (slow urinary stream, urinary intermittency, and terminal dribbling). Treatment generally begins with lifestyle and behavioral interventions for mild symptoms, and progresses to include pharmacologic therapy for moderate to severe symptoms. Pharmacologic therapy offers both symptom improvement (alpha-adrenergic receptor blockers, phosphodiesterase type 5 inhibitors [PDE5-Is], beta-3 adrenergic agonists, and anticholinergics) and prevention of disease progression (5-alpha reductase inhibitors [5ARIs]). Saw Palmetto (*Serenoa Repens*) is an herbal remedy used in therapy as well, but has limited data to support its use.[3]

A contemporary review of the American Urological Association (AUA), European Association of Urology (EAU), and Canadian Urological Association (CAU) guidelines regarding BPH treatment concluded that alpha-blocker therapy remains first-line for patients with moderate to severe LUTS/BPH, with no preference given to one agent over another. All guidelines also endorse the use of 5-ARIs as monotherapy in symptomatic patients with demonstrated prostatic enlargement, with no preference given to one agent over another. The aforementioned guidelines also endorse the use of PDE5-Is as monotherapy, with or without erectile dysfunction, and suggest tadalafil or any “long acting-PDE5” inhibitor. Additionally, in patients with LUTS/BPH with predominately bladder storage symptoms, the guidelines support anticholinergic agents as monotherapy. Combination alpha-blocker with 5-ARI therapy is also universally supported in the guidelines, in patients with moderate to severe symptomatic LUTS/BPH with demonstrated prostatic enlargement, not controlled with monotherapy. Combination alpha-blocker with a beta-3 agonist or an anticholinergic is supported for moderate to severe symptomatic LUTS/BPH, if relief of storage symptoms is insufficient with monotherapy with either drug.[4,5,6]

In contrast to the above consensus recommendations, the guidelines do differ in a few areas. For combination treatment with alpha-blockers and PDE5-Is, the AUA discourages the combination, whereas the EAU offers it as a possible therapy option, and the CUA does not address it. For saw palmetto (*Serenoa Repens*), neither the AUA nor the CUA endorse its use, while the EAU allows it to be recommended for patients with LUTS who want to avoid potential adverse events, especially related to sexual dysfunction. For beta-3 agonist monotherapy, the EAU and CUA allow for its use, while the AUA does not endorse monotherapy use.[4,5,6]

A meta-analysis from 2020 compared daily tadalafil with tamsulosin for symptomatic LUTS/BPH patients. Tadalafil improved the International Prostate Symptom Score (IPSS) (SMD: 0.16, 95% CI: –1.42 to 1.73), revealing that it has a therapeutic effect on LUTS comparable to that of tamsulosin. Also, tadalafil was significantly better than tamsulosin in improving International Index of Erectile Function (IIEF) scores (WMD: 5.02, 95% CI 3.78 to 6.27, P<0.0001). The authors concluded that tadalafil has a similar therapeutic effect as tamsulosin in managing LUTS suggestive of BPH, and that tadalafil has the added benefit of significantly improving erectile function vs. tamsulosin, advising that it be a monotherapy option for patients suffering from both LUTS and ED.[7]

Four separate meta-analyses from 2018-2020 compared combination alpha-blocker therapy plus PDE5-Is vs. monotherapy with either class in men with LUTS/BPH. Of note, tadalafil was the most commonly used PDE5-I in trials. The aggregate data showed that combination therapy exhibited superior efficacy in treating BPH-related LUTS and ED compared to monotherapy with either class. The combination therapy did however generate a higher incidence of adverse events compared to monotherapy with either class. Ultimately, the combination provided small improvements in BPH/ LUTS treatment efficacy, but those improvements should be weighed against the increased incidence of adverse events.[8,9,10,11]

A 2020 meta-analysis evaluated *Serenoa Repens* monotherapy vs. tamsulosin monotherapy in patients with BPH/LUTS. Patients who received treatment with *Serenoa Repens* had the same effect in IPSS (MD of 0.63, 95% CI [−0.33, 1.59], p=0.20), Quality of Life (MD of 1.15, 95% CI [−1.51, 4.52], p=0.33), maximum urinary flow (MD of 0.27, 95% CI [−0.15, 0.68], p=0.21), post-void residual volume (MD of −4.27, 95% CI [−22.97, 14.44], p=0.65), and prostate specific antigen (MD of 0.46, 95% CI [−0.06, 0.97], p=0.08) compared with the tamsulosin group. The tamsulosin group had greater improvement in prostate volume compared with the *Serenoa Repens* group (MD of −0.29, 95% CI [−0.41, −0.17], p<0.00001). For ejaculation disorders (OR = 12.56; 95% CI [3.83, 41.18]; p<0.0001) and libido decrease (OR = 5.40; 95% CI [1.17, 24.87]; p=0.03) specifically, the results indicated that the tamsulosin group had a higher incidence than the *Serenoa repens* group. This study indicated that *Serenoa repens* had similar effect in treating BPH compared with tamsulosin in terms of IPSS, quality of life, and post-void residual volume. *Serenoa Repens* did not increase the risk of adverse drug events, especially with respect to ejaculation disorders and libido decrease.[12]

Findings:

Recommendations for medical therapy in the treatment of BPH/LUTS are relatively consistent among major U.S and international urological guidelines. Differences that exist include the utility of *Serenoa Repens*, with some guidelines allowing for its use and some discouraging it. Those that allow it have it designated as a weak recommendation only. Recent meta-analyses support use of *Serenoa Repens* in the subset of patients who are primarily looking to avoid sexual adverse events. However, education is warranted about the limited magnitude of benefit likely to be provided by *Serenoa Repens* therapy.

All guidelines recommend PDE5-Is as a monotherapy option, but differences arise in regard to its use as combination therapy with alpha-blockers. Multiple, recent meta-analyses point to a small benefit in BPH/LUTS treatment with combination therapy but that benefit must be weighed against the higher incidence of adverse drug events with the combination therapy.

Tadalafil is the only PDE5-I with an FDA-approved indication for BPH and subsequently is the most utilized of all PDE5-I agents for BPH/LUTS. Other PDE5-Is have shown benefit in BPH/LUTS but data is lacking for endorsement of these agents and more head-to-head studies are needed. Tadalafil is the most studied PDE5-I agent in BPH, has the most substantial outcomes data available, and is the most recommended PDE5-I by the guidelines. It is currently the best PDE5-I choice for use as a monotherapy option for BPH.

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.

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