Long-Term Care Updates

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Updated Guidance on the Medical Management of Benign Prostatic Hyperplasia

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Introduction

Benign prostatic hyperplasia (BPH) is prevalent among older men between the ages of 45 and 80 years.[1] BPH is defined as a benign enlargement of the prostate gland due to stromal and epithelial cell hyperplasia.[2] It anatomically compresses the urethra, causing increased bladder outlet resistance, resulting in lower urinary tract symptoms (LUTS) that can be bother-some and progressive. Behavioral and lifestyle modifications are generally considered first-line in the management of BPH but are often accompanied by medical management, consisting of alpha-adrenergic antagonists (alpha blockers), 5-alpha reductase inhibitors (5ARIs), phosphodiesterase 5 selective inhibitors (PDE5s), anticholinergics, and beta-3 agonists.[1] The American Urological Association (AUA) recently updated its clinical guideline on the management of LUTS secondary to BPH. The guideline primarily consists of BPH evaluation, medical management, and surgical management.

This newsletter will focus on the AUA's recently updated guideline on the effective evidence-based medical management of BPH and the associated LUTS.

AUA's LUTS/BPH Guidelines

Alpha Blockers

The AUA provides two moderate recommendations based on high certainty of evidence for alpha blocker therapy. First, alpha blockers should be one of the initial treatment medications for symptomatic, moderate to severe LUTS/BPH. Secondly, patient age, comorbidities, and adverse effects should be considered when selecting a specific alpha blocker (alfuzosin, doxazosin, silodosin, tamsulosin, or terazosin). Terazosin and doxazosin are non-specific alpha-1 receptor blockers approved for BPH and hypertension. Tamsulosin and silodosin are alpha-1a selective blockers, and they along with alfuzosin have a lower risk of causing orthostatic hypotension and syncope.[1]

The relatively equal efficacy of all the alpha blockers for LUTS/BPH in regard to International Prostate Symptom Score (IPSS) improvement has been demonstrated for over two decades by several randomized controlled trials, systematic reviews, and meta-analyses. This finding was most recently confirmed by one network meta-analysis that found that alpha blockers

increased IPSS by 4-7 points as compared to placebo. In terms of switching from one alpha blocker to another, patient characteristics and specific alpha blocker have not been shown to impact efficacy, so it is not advisable to switch from one alpha blocker to another unless patients cannot tolerate current alpha blocker therapy due to side effects.[1]

For patients already on antihypertensive medications or with orthostatic hypotension, an alpha-1a selective blocker is recommended for BPH treatment; however, these (tamsulosin and silodosin) are more likely to cause ejaculatory dysfunction which is a common reason for discontinuation amongst younger sexually active males. A clinical study by Hellstrom and Sikka demonstrated that tamsulosin significantly reduced ejaculate volume (-2.4 ± 0.17mL) compared to alfuzosin (+0.3 ± 0.18mL) or placebo. Thus, for younger sexually active men, selecting an alpha blocker with low risk for ejaculatory dysfunction is advisable (alfuzosin). Based on expert opinion, when considering initiation of alpha blocker therapy in patients interested in cataract surgery, the risks, such as intraoperative floppy iris syndrome (IFIS), associated with concomitant use of alpha blockers and cataract surgery should be relayed to patients, as delaying initiation of the alpha blocker to after surgery is recommended.[1]

5ARIs

Based on moderate certainty of evidence 5ARIs are moderately recommended as a monotherapy option for the treatment of LUTS/BPH in patients with prostate volume sizes >30cc on imaging, prostate specific antigen (PSA) levels >1.5ng/dL, or a palpable prostate enlargement on a digital rectal exam. 5ARIs, including finasteride and dutasteride, exert their effects through decreased prostate tissue proliferation and increased atrophy and apoptosis which results in the prostate shrinking by 15% to 25% by 6 months. Smaller prostate size can greatly contribute to improved LUTS, but due to 5ARIs' mechanism of action, they should be reserved for patients with enlarged prostates or elevated PSA levels.[1]

The AUA also strongly recommends, based on high certainty of evidence, 5ARIs (as monotherapy or in combination with alpha blockers) as an appropriate treatment option in the prevention of LUTS/BPH progression and in reducing the risk of urinary retention and need for surgical intervention. Studies have shown finasteride and dutasteride to be more effective than placebo in managing LUTS, preventing BPH in adequately enlarged prostates, and lowering the risk for surgical interventions. While finasteride and dutasteride have distinct pharmacological differences, the guideline does not recommend a specific one over the other. Therefore, the choice between which agent to initiate should be based on patient specific parameters. Additionally, the onset of action for both agents is delayed, especially when compared to alpha blockers, so patients should be educated on the potential for a slow onset of symptom resolution. Moreover, the AUA moderately recommends that patients also be educated on the risks associated with 5ARIs prior to initiation, including sexual side effects, physical side effects, and prostate cancer risks. Sexual side effects of 5ARIs observed in clinical trials include gynecomastia, decreased libido, erectile dysfunction, and ejaculation disorders, with finasteride showing a more pronounced decline in overall sexual function compared to dutasteride. Anecdotal reports suggest a risk of developing "post-finasteride syndrome" which includes sexual, physical, and psychological side effects that seem to persist after discontinuation of finasteride therapy. However, the quality of these specific reports remains controversial. Studies also suggest that 5ARI therapy may put patients at a higher risk of developing high grade prostate cancer. Sarkar et al obtained records for 80,875 men with stage I-IV prostate cancer across 15 years and found that PSA levels were significantly higher in men on 5ARIs compared to men who were not at time of biopsy (13.5ng/mL vs. 6.4ng/mL; $p<0.001$). Additionally, compared to men not on 5ARI therapy, men on 5ARIs were significantly more likely to have Gleason grades of ≥8, clinical stages ≥T3, and node positive metastatic cancer ($p<0.001$).[1]

PDE5s

Regardless of the presence of erectile dysfunction (ED), the AUA moderately recommends, based on moderate certainty of evidence, tadalafil 5mg daily be discussed as a treatment option for LUTS/BPH.[1] Although the exact mechanism of action of PDE5s in BPH is unclear, tadalafil selectively inhibits phosphodiesterase type 5, increasing cyclic guanosine monophosphate (cGMP) and causing smooth muscle relaxation.[3] Across ten studies (n=5,129), the mean change in IPSS was found to be -1.74 points in favor of tadalafil (tadalafil -5.4 points vs. controls -3.5 points), and while tadalafil resulted in no difference in IPSS as compared to placebo, the percentage of patients who experienced a ≥3 points change in IPSS revealed a relative effect (1.13-1.80). This implied that tadalafil likely increases the effect on IPSS compared to placebo and may be an appropriate BPH treatment option, especially in men with concomitant ED.[1]

Combination Therapy

The AUA also addresses the use of combination therapy, and strongly recommends a 5-ARI in combination with an alpha blocker be considered for patients with LUTS who have enlarged prostates (prostate volume >30cc on imaging or palpable prostate enlargement on digital rectal exam) or elevated PSA levels (>1.5ng/dL). This is based on high certainty of evidence which found that combination therapy resulted in significant reductions in some clinical progression parameters, such as acute urinary retention, need for invasive therapy, symptom rate, and flow rate, when compared to monotherapy in patients with average or below average sized prostates. Additionally, larger prostate sizes and PSA levels correlated with more pronounced positive responses to combination therapy. It is important to note, however, that combination therapy, unsurprisingly, comes with higher risks for side effects compared to monotherapies.[1]

Patients who experience moderate to severe bladder storage impairment (presenting similar to overactive bladder symptoms) may be offered additional therapy with anticholinergic agents or beta-3 agonists. Conditional recommendations based on low certainty of evidence state that anticholinergic agents may be offered as either monotherapy or in combination with alpha blockers, or beta-3 agonists may be offered in combination with alpha blockers, as treatment options to patients with moderate to severe predominate storage LUTS. Anticholinergics used in combination with alpha blockers have been extensively studied but mostly in short term trials (<12 weeks), and the variable results among these studies makes determining definitive benefits of anticholinergics difficult. Thus, due to the potential for increased side effects with anticholinergics, it would be advisable to consider them as add on therapy only after alpha blockers alone have proven inadequate and the benefits outweigh the risks for individual patients. A safety trial involving tolterodine 2mg in patients with obstruction and over-activity found it to be associated with mild increases in post-void residual (PVR), mild decreases in bladder contractility, and no issues with urinary retention. Therefore, the effects of tolterodine may be beneficial in targeting urinary frequency symptoms in patients with BPH; however, PVR should be monitored both prior to initiating therapy and at follow-up. Regarding beta-3 agonists, they have yet to show significant improvements in LUTS when administered as monotherapy, but combination with an agent such as mirabegron alongside an alpha blocker may result in symptom improvement. Although, extensive research is still needed on this specific drug class combination.[1]

Lastly, while tadalafil 5mg daily should be considered as a treatment option for LUTS/BPH, it should not be used in combination with alpha blockers due to lack of benefit. This is a moderate recommendation based on low certainty of evidence. Studies have not shown that the combination is more beneficial than either agent as monotherapy, and together they can have a worsened side effect profile.[1]

Natural Products

Dietary supplements make up most complementary and alternative medicine therapies used for BPH, usually extracts of plants (phytotherapy) used alone or in combination. Commonly used supplements include saw palmetto (most commonly used and studied), *Pygeum africanum* (extract of African plum tree), *Hypoxis rooperi* (South African star grass), *Secale cereale* (rye pollen), *Urtica dioica* (stinging nettle), and *Cucurbita pepo* (pumpkin seed), zinc, and selenium.[1,2] While the AUA's guideline does not provide a detailed discussion on the management of LUTS/BPH using natural products, they do state that while some supplements have been studied and marketed for BPH, overall study results, methods, and quality have varied. Therefore, their use is not currently advisable.[1]

Follow Up

After initiation of LUTS/BPH medication therapy, the AUA recommends, based on clinical principle, that patients receive a follow-up evaluation in 4-12 weeks to assess effectiveness (utilizing the IPSS) and tolerability. Some medications, such as alpha blockers, beta-3 agonists, PDE5s, and anticholinergics, have a faster onset, so following up at 4 weeks would be appropriate; whereas patients on 5ARIs may experience a delayed onset of symptom relief, so follow up at 12 weeks or later may be more appropriate. Finally, based on expert opinion, patients who fail to adequately respond to medical management, including those with persistent or non-improving symptoms or who encounter issues with tolerability, should consider alternative therapies. This may include switching drug classes entirely if no response is seen, adding on additional medications for partial responses, or surgical management.[1]

Conclusion

Medical management of LUTS/BPH requires many clinical considerations. Alpha blockers are recommended as initial medication agents, and the optimal outcome requires a careful selection of the specific alpha blocker, taking into consideration patients' comorbidities, associated side effects, and lifestyles. 5ARIs are recommended as monotherapy in patients with enlarged prostates or elevated PSA levels, as well as in combination with alpha blockers. It is important patients are counseled on the sexual and physical side effects and potential risk for high grade prostate cancer associated with 5ARIs. PDE5s, specifically tadalafil 5mg daily, is also recommended as a potential treatment option; however, it should not be used in combination with alpha blockers due to lack of evidence of benefit and increased side effect risk. Lastly, anticholinergics and beta-3 agonists can be considered alone (anticholinergics only) or in combination with alpha blockers when moderate to severe predominant storage LUTS is a primary concern. It is important pharmacists are aware of the recommended medications for the treatment of LUTS/BPH in order to better optimize patient medication regimens, improve outcomes, and minimize adverse events.

References

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