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Indian Health Service National Pharmacy and Therapeutics Committee Benign Prostatic Hyperplasia NPTC Formulary Brief August Meeting 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 trospium 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 ultrasonography[9].

The primary treatment goals are to reduce lower urinary tract symptoms (LUTS), improve prostate-related quality of life, and prevent or delay disease progression[1]. 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 year[2]. 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 management[6].

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 symptoms[5]. 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 on[6].

The 5-ARIs inhibit the enzyme responsible for conversion of testosterone to dihydrotestosterone. By blocking this enzyme, the prostrate decreases 20-25% in volume and prostate-specific antigen (PSA) blood levels by 50%. The 5-ARIs dramatically improve lower

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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 flow[6]. 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 not[8]. 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 placebo[8]. 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 placebo[1].

In 2015, the EAU published an algorithm for LUTS treatment in males.

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 BPH[7].

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.

For questions about 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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Indian Health Service
National Pharmacy and Therapeutics Committee
Deprescribing
NPTC Formulary Brief
August Meeting 2016

Background:
Benjamin Franklin reflected that "the best doctor gives the least medicines." Yet, trends in prescription drug use continue to rise among the U.S. population. According to data from the Centers for Disease Control and Prevention National Health and Nutrition Examination Survey, the percentage of US adults prescribed five or more medications rose from 8% to 15% from 2000 to 2012.[1] This trend is especially problematic among the elderly.

Discussion:
Inappropriate medication prescribing has been linked to a host of adverse health outcomes including medication non-adherence, falls in the elderly, functional decline, emergency department visits, hospitalization, and even death.[2] It is well-known that the risk of adverse drug events rises substantially with increasing numbers of concurrent medications.[3] Polypharmacy is commonly defined as the concomitant ingestion of four or more medications. Elderly patients are particularly susceptible to adverse drug effects and drug-drug interactions because of age-related changes in pharmacokinetics and pharmacodynamics. These include changes in absorption, volume of distribution, and drug clearance as well as changes to the physiologic response to medications.[4]

Among the many drivers of polypharmacy is the phenomenon of the "prescribing cascade." The prescribing cascade begins when an adverse drug reaction is misinterpreted as a new medical condition.[5] A new drug is prescribed, and the patient is placed at risk of developing additional adverse effects relating to this potentially unnecessary treatment.

Implementation of clinical practice guidelines has been an important factor in the rise of prescription drug use. Paradoxically, clinicians may fail to prescribe appropriate medications for patients already on many medications due to clinician concerns about adverse effects.[6] This is not the goal of efforts to reduce polypharmacy.

Many screening tools have been developed to reduce inappropriate prescribing, particularly among the elderly. These include the Medication Appropriateness Index[7], STOPP/START criteria[8], and the Beers criteria. The 2015 American Geriatrics Society Beers Criteria were published online and are readily available for review.[9] They include a variety of comprehensive drug list tables based on the Beers categories. Prominent examples of potentially inappropriate medications include classes such as anti-cholinergics, anti-thrombotics, cardiovascular agents, anti-depressants, and benzodiazepines. Recommendations are commonly made on the basis of drug-drug interactions as well as the nexus between a particular drug and clinical syndrome or a drug and a disease state.

The appropriateness of medication prescribing needs to be considered at every step in the spectrum of the pharmacologic management of disease. More focus is needed on the indications for medication withdrawal, also known as "de-prescribing" to bring balance to the prescribing continuum in medical practice.[10] This process requires a collaborative effort among patients, providers, and pharmacists.

Deprescribing is the active process of reducing or stopping inappropriate medication which is supervised by a healthcare professional with the goal to manage polypharmacy and improve health outcomes.[11] Common barriers to deprescribing include the inaccessibility of evidence-based deprescribing guidelines, the prevalence of single-disease treatment recommendations, the complexity of care provided by multiple prescribers, fear of adverse consequences, and both communication and time constraints.[12] There is also the phenomenon of "prescribing inertia," which is the tendency to automatically renew a medication even when the original indication is no longer present.[13]

Shared decision-making is important to the process of deprescribing. It requires an approach which engages the patient as a partner and takes into account their attitudes, beliefs, and choices following appropriate informed consent. Studies have found that up to 90% of elderly patients on 5 or more medications are willing to reduce their number of prescribed medications.[14]

A variety of systematic approaches to medication optimization have shown varying degrees of promise in published studies.[15] Provider education can address provider knowledge deficits, particularly in geriatric medicine. Computerized order entry and decision support tools can aide prescribing decisions. Pharmacist-led interventions add another layer of professional involvement to optimize care. Specialists with geriatric training, serving either as consultants or members of a multi-disciplinary care team, can enhance care planning. A combination of these approaches may be superior to a single intervention.

Findings:
Decisions about the process of deprescribing should be guided by a careful review of the patient's clinical conditions, overall health, and the list of active medications.[13] Deprescribing should target drugs that are no longer indicated, no longer appropriate, or are no longer aligned with treatment goals.

A recent article published in JAMA Internal Medicine outlined a protocol for deprescribing with five steps.[10] The first step is to ascertain all drugs that the patient is currently taking and the reasons for each one. Second is the consideration of the overall risk of drug-induced harm in individual patients to determine the required intensity of the deprescribing intervention. Third is an assessment of each drug in regard to its current or future benefit potential compared with current or future harm or burden potential. Drugs are then prioritized for discontinuation that have the lowest benefit-harm ratio and lowest likelihood of adverse withdrawal reactions or disease rebound syndromes. A discontinuation regimen is then implemented followed by monitoring for improvement in outcomes or onset of adverse effects.

Conclusions:
Clearly the problem of polypharmacy and the process of deprescribing are complex but there are some practical points to aid in reducing inappropriate prescribing.16 First, it is essential to periodically review patient medication regimens, especially among the higher-risk elderly population. Prescribing inertia should be avoided when there is no ongoing need for treatment. To eliminate the risk of a prescribing cascade, adverse drug effects should always be considered when assessing with a new symptom. Non-pharmacologic approaches to patient management should be entertained, when appropriate. Individual agents within a drug class should be assessed relative to the risk of adverse effects. Dose titration should target the desired treatment effect, using the lowest effective dose. Finally, advanced patient age should not be considered a contraindication to potentially beneficial medication.

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