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Drug Class Update: BPH Drugs

Date of Review: August 2023

Date of Last Review: July 2016
Dates of Literature Search: 04/01/2016 - 04/10/2023

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
The purpose of this review is to evaluate the literature for new high-quality evidence for the use of medications to treat benign prostatic hyperplasia (BPH) and provide an approval route for unfunded conditions that will be covered under the Early and Periodic Screening, Diagnostic and Treatment (EPSDT) program. The Early and Periodic Screening, Diagnostic and Treatment program may allow for treatment of some conditions not normally covered under the Oregon Health Plan (OHP) fee-for-service (FFS) program, for people under 21 years old who are enrolled in Medicaid.

Plain Language Summary:
- This review was done to identify and evaluate new research for the classes of drugs used to treat benign prostatic hyperplasia. Benign prostatic hyperplasia is a condition in men that results in an increase in size of their prostate, which may cause bothersome symptoms. These medications may sometimes be used to treat other conditions of the urinary tract.
- A high-quality review done by Cochrane Database for Systematic Reviews found that one of these classes, called phosphodiesterase inhibitors, was more helpful than a sugar pill (placebo) at improving urinary symptoms, such as having to urinate at night and urinate often. Combination therapy with phosphodiesterase inhibitors and other drugs used to treat benign prostatic hyperplasia was not much better than a phosphodiesterase inhibitor alone at improving symptoms and combination therapy was associated with more side effects.
- A second review done by Cochrane Database for Systematic Reviews found that the drug silodosin was more effective than placebo at improving symptoms related to benign prostatic hyperplasia. Silodosin was found to have similar efficacy to other medications called tamsulosin and alfuzosin. Silodosin was found to have more side effects than the other medications.
- There is a small amount of data, from a research done by Cochrane Database for Systematic Reviews, that a class of drugs called alpha-blockers may help to increase the number of children that pass their kidney stones (small blockages in the kidney). Alpha-blockers were effective at helping to break up kidney stones in adults, who were also receiving a treatment called shock wave lithotripsy (a type of ultrasound treatment).
- A review of treatments used for chronic prostatitis and chronic pelvic pain syndrome in men found that the drug finasteride did help to reduce symptoms in this population. The Oregon Health Plan does not pay for medications to treat chronic prostatitis and chronic pain syndrome.
- A recent guideline by the American Urological Association supports the medications that we are recommending to help patients with benign prostatic hyperplasia.

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- The Drug Use Research and Management Group recommends no changes be made to the current medication policy that is in place for the treatment of benign prostatic hyperplasia for patients that have fee-for-service medical coverage.

Research Questions:

1. Is there new comparative evidence evaluating treatments for BPH?
2. Is there new comparative harms data for BPH treatments (e.g., hypotension, sexual side effects, withdrawals due to adverse events, severe adverse events)?
3. Are there certain sub-populations (based on age, gender, ethnicity, or comorbidities) in which certain treatments for BPH are more effective or cause less harm?

Conclusions:

- There are five new systematic reviews, one new guideline, one new formulation, and six new safety warnings included in this review.
- A review for the use of phosphodiesterase inhibitors (PDEIs) for the treatment of lower urinary tract symptoms (LUTS) related to BPH was done by Cochrane in 2018.[1] There is low-quality evidence that PDEIs may improve urinary symptoms slightly better than placebo based on the International Prostate Symptom Score (IPSS) (mean difference [MD] -1.89; 95% confidence interval [CI], -2.27 to -1.5).[1] The minimal clinically significant difference (MCID) for IPSS is a change of more than 3 points. There was not a substantial clinical benefit to combination therapy of PDEIs plus alpha-blockers (AB) or PDEIs plus 5-alpha reductase inhibitors (5-ARIs).
- A 2017 Cochrane review evaluated the use of silodosin in men with LUTS due to BPH.[2] Silodosin was more effective at reducing symptoms than placebo based on IPSS scores (MD -2.65; 95% CI, -3.23 to -2.08) (low-quality evidence). In active treatment comparisons, silodosin was not clinically or statistically more effective than tamsulosin or alfuzosin; however, the incidence of sexual adverse effects was higher.
- The off-label use of AB has been studied for removal of renal and urinary tract stones in children and adults. Evidence is limited and of low quality (detailed below), preventing strong conclusions of efficacy.
- There is low-quality evidence from a Cochrane review that AB may be helpful in increasing the stone-free rate in children with small urinary tract stones (RR 1.34; 95% CI, 1.16 to 1.54) when compared to placebo.[3]
- A Cochrane review evaluated the use of AB in adult patients undergoing shock wave lithotripsy for renal or ureteral stones, which demonstrated increased stone clearance more than usual care (RR 1.16; 95% CI, 1.09 to 1.23) (low-quality evidence).[4]
- A Cochrane review found the use of 5-ARIs (e.g., finasteride) to reduce symptoms of chronic prostatitis (CP)/chronic pelvic pain syndrome (CPPS) more than placebo based on moderate quality of evidence (MD -4.6; 95% CI, -5.43 to -3.77).[5] Alpha-blockers may decrease symptoms but evidence was graded as very low quality.
- An updated 2021 guideline from the American Urological Association (AUA) supports current policy.[6]

Recommendations:

- No changes to the preferred drug list (PDL) are recommended based on review of current evidence.
- Update the prior authorization (PA) criteria in **Appendix 4** and remove the renewal criteria.
- No PDL changes were recommended after evaluation of costs in executive session.

Summary of Prior Reviews and Current Policy:

- A literature scan in July 2016 resulted in no changes to the PDL.

- There is evidence that therapies for BPH all significantly improve the International Prostate Symptom Score (IPSS) compared to placebo by -3.69 to -7.06 points.
- Preferred therapies are listed in **Appendix 1** and all non-preferred products are subject to PA criteria, which are presented in **Appendix 4**.

Background:
Benign prostatic hyperplasia (BPH), also called benign prostatic obstruction (BPO), is a common condition with an incidence that increases as men age. Prostate size usually begins to increase in men around 40-45 years of age with an incidence of approximately 80% at the age of 80.[6] Benign prostatic hyperplasia is a result of increases in glandular epithelial tissue, smooth muscle, and connective tissue in the prostatic transition zone.[7] Increased frequency of urination, nocturia, hesitancy, urgency, and weak urinary stream are LUTS associated with BPH.[8] Treatment includes lifestyle modifications (e.g., limiting fluid intake, weight control), medical and surgical options. In some men, if BPH is untreated it may result in rising post-void residuals, bladder stones, and recurrent urinary tract infections.

Drug classes used for the treatment of BPH are AB, 5-ARI and PDEIs. Alpha-blockers (e.g., alfuzosin, doxazosin, silodosin, tamsulosin, tamsulosin extended release [ER] and terazosin) are considered first line therapy for most male patients and help to relieve symptoms within days. They have been used off-label in women for kidney stones and lower urinary tract infections. Trial data suggest that the AB class help to reduce IPSS, a measure of prostate symptoms, by 30-40% as well as increase urinary flow rate.[9] Non-selective AB, such as alfuzosin, are less likely to cause erectile dysfunction (ED) compared to selective AB. Alpha-blockers are associated with orthostatic hypotension and some formulations need titration. There is also the potential for AB to cause intraoperative floppy iris syndrome (IFIS), iris trauma and posterior capsule rupture during cataract surgery, and patients should be informed of this risk. Alpha-blockers have demonstrated similar efficacy and if a patient does not receive benefit from one AB, given at an appropriate dose, then it is unlikely that subsequent AB will provide benefit.[6] Phosphodiesterase inhibitors (e.g., tadalafil – only PDEI approved for BPH) are recommended for men with BPH symptoms and concomitant erectile dysfunction (ED).[8] There is no evidence that PDEIs are superior to AB and there is no data to support combination therapy with AB and PDEIs. Anticholinergics are recommended for men with predominately bladder storage LUTS due to BPH. Patients that don't respond to AB or anticholinergic monotherapy may be offered combination therapy with both medications. Beta-3 agonists (e.g. mirabegron), as monotherapy or in combination with AB, may also be considered in patients with storage symptoms despite AB treatment.[8]

Five-alpha reductase inhibitors (e.g., finasteride, dutasteride), are used to prevent progression of BPH symptoms but do not have a role in the acute symptom management of BPH. Five-alpha reductase inhibitors are recommended for prostates larger than 35 g and a treatment duration of 6 to 12 months is needed to reduce prostate size. Improvement in IPSS ranges from 15 to 30% and decreases in prostate volume range from 18 to 28% with the use of 5-ARIs.[9] Treatment with 5-ARIs are used on an ongoing basis to prevent symptom relapse and reduce the need for surgical intervention. Combination therapy with AB and 5-ARIs are used to decrease urinary symptoms and reduce prostate size. Common adverse reactions are reduced libido, ED and ejaculation disorders.

The IPSS is a validated tool used to determine disease severity and LUTS, as well as response to treatments. It is comprised of up to 35 points based on 7 questions, with higher scores indicative of greater symptoms. Symptom severity can be classified by the scores: 0-7 mild; 8-19 moderate; 20-35 severe.[8] Clinically important differences include the percentage achieving a MCID, such as a 30-50% reduction in score from baseline, or achieving a change in IPSS score of 3 points or more following treatment.[6] The IPSS also has a quality of life assessment in which the MCID is defined as >1 point.[6] Another validated tool is the degree of urinary bother and is measured by the Benign Prostatic Hyperplasia Impact Index (BPHII) assessed by scores ranging from 0-13 with higher scores related to a higher degree of bother.[6] A MCID for BPHII has not been determined.

There were less than 200 patients in the Oregon Medicaid fee-for-service (FFS) population who took a medication for BPH in the last quarter of 2022.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
Cochrane – Phosphodiesterase Inhibitors for Lower Tract Symptoms Consistent with Benign Prostatic Hyperplasia
A 2018 Cochrane review evaluated the literature to compare the use of PDEIs versus placebo or active therapy (e.g., ABs and 5-ARIs) in men with LUTS due to BPH.[1] Sixteen trials were included lasting 4 to 12 weeks. Drug classes studied were the following: PDEI versus 5-ARI; PDEI + 5-ARI versus PDEI alone; PDEI + AB + 5-ARI versus AB + 5-ARI; PDEI versus 5-ARI; PDEI + 5-ARI vs. PDEI alone; PDEI + AB + 5-ARI versus AB + 5-ARI.[1] Drugs included in the analysis are tadalafil, sildenafil and vardenafil. The primary outcome of interest was urinary symptoms (measured by the IPSS-total score and BPHI score).

Results for the comparisons of PDEIs to placebo and active controls are displayed in **Table 2**.[1] There is low-quality evidence that PDEIs are more effective than placebo based on small reduction in symptoms; however, changes in IPSS scores were not considered clinically meaningful. There is no evidence of superior efficacy of PDEIs compared to alpha-blockers.[1] There is no evidence of a benefit of combination therapy on reduction of symptoms.

Table 2. Summary of Results for the Use of PDEIs compared to Placebo and Active Controls[1]

Outcome	Results	Quality of Evidence	Comments
PDEI vs. Placebo			
IPSS-total score	MD -1.89 (95% CI, -2.27 to -1.5)	Low	There is low quality evidence that PDEIs are more effective than placebo
BPHII	MD -0.52 (95% CI, -0.71 to -0.33)	Low	
Adverse Events	RR 1.42 (95% CI, 1.21 to 1.67)	Low	
PDEI vs. alpha-blockers			
IPSS-total score	MD 0.22 (95% CI, -0.49 to 0.93)	Moderate	No clinical difference in symptoms between PDEIs and alpha-blockers was demonstrated
BPHII score	MD 0.03 (95% CI, -1.1 to 1.16)	Low	
Adverse events	RR 1.35 (95% CI, 0.80 to 2.30)	Low	
PDEI plus alpha-blockers compared to alpha-blockers alone			
IPSS-total score	MD -2.56 (95% CI, -3.92 to -1.19)	Low	

Adverse Events	RR 2.81 (95% CI, 1.53 to 5.17)	Moderate	A small improvement in symptoms was demonstrated with combination therapy; however there were an increased risk of adverse events
PDEI plus alpha-blockers compared to PDEI alone			
IPSS-total score	MD -2.4 (95% CI, -6.47 to 1.67)	Low	A small improvement in symptoms was demonstrated with combination therapy; however, it was not statistically or clinically different from PDEI use alone
PDEI plus 5-ARI compared to 5-ARI alone (short-term: up to 12 weeks)			
IPSS-total score	MD -1.4 (95% CI, -2.24 to -0.56)	Moderate	A small improvement in symptoms was demonstrated with combination therapy but difference was not clinically significant
PDEI plus 5-ARI compared to 5-ARI alone (long-term: 26 weeks)			
IPSS-total score	MD -1.0 (95% CI, -1.83 to -0.17)	Moderate	A small improvement in symptoms was demonstrated with combination therapy but difference was not clinically significant
Adverse Events	RR 1.07 (95% CI, 0.84 to 1.36)	Low	
Abbreviations: 5-ARI = 5-alpha reductase inhibitors; BPH = benign prostatic hyperplasia; BPHII = Benign Prostatic Hyperplasia Impact Index; CI = confidence intervals; IPSS = International Prostate Symptom Score; LUTS = lower urinary tract symptoms; MD = mean difference; PDEI = phosphodiesterase inhibitors; RR = relative risk			

There is a lack of data beyond 12 weeks for the use of PDEIs in BPH, despite it being a chronic condition. Additionally, there was a lack of high-quality comparative evidence for PDEIs versus active therapy.

<u>Cochrane – Silodosin for the Treatment of Lower Urinary Tract Symptoms in Men with Benign Prostatic Hyperplasia</u>

Cochrane evaluated the use of silodosin for treating LUTS in men with BPH.[2] Silodosin was compared to placebo and active treatments (e.g., tamsulosin and alfuzosin). Nineteen studies, ranging from 4 weeks to 3 months, were identified enrolling 4295 participants. Men enrolled in the trials were a mean age of 66.5 years with an IPSS of 19.1 (indicative of moderate symptoms).[2] Due to lack of allocation concealment, problems with blinding and high amounts of imprecision the quality of the evidence was considered moderate to low. The primary outcome was symptom control, assessed by the IPPS score.

Silodosin was compared to placebo in four studies. There was low quality evidence that silodosin was more effective at reducing symptoms than placebo based on IPSS scores (MD -2.65; 95% CI, -3.23 to -2.08).[2] Quality of life was not clinically improved with the use of silodosin compared to placebo with IPSS-QoL scores of a mean difference of -0.42 lower (-0.71 to -0.13) (moderate quality of evidence) (scores ranged from 0-6 with 0 being best: no symptoms and 6 being worst: terrible). Silodosin use on the incidence of cardiovascular (CV) events is not clear due to very low quality of evidence and non-significant findings (RR 1.28; 95% CI, 0.67 to 2.45).[2] There is moderate quality of evidence that the use of silodosin was associated with a higher number of sexual adverse events (RR 26.07; 95% CI 12.36 to 54.97).[2]

In people that have LUTS due to BPH, silodosin was compared to tamsulosin and there was no statistical or clinical differences between groups based on IPSS scores (MD -0.04; 95% CI, -1.31 to 1.24).[2] For the outcomes of quality of life, treatment withdrawal due to any reason and CV events were not different between groups. There is moderate strength of evidence that sexual adverse events were higher with silodosin compared to tamsulosin (RR 6.05; 95% CI 3.55 to 10.31).[2]

There is low quality evidence that silodosin increases IPSS scores more than alfuzosin in men with LUTS due to BPH (MD 3.83; 95% CI, 0.12 to 7.54; 1 study).[2] Quality of life scores were similar with silodosin and alfuzosin based on the IPSS-QoL (MD 0.14; 95% CI, -0.46 to 0.74) (moderate quality of evidence). Cardiovascular adverse events were not significantly different compared to alfuzosin (RR 0.67; 95% CI, 0.36 to 1.24). Sexual adverse events were higher with silodosin compared to alfuzosin based on moderate strength of evidence (770 more per 1000).

Cochrane – Medical and Surgical Interventions for the Treatment of Urinary Stones in Children

A Cochrane review evaluated management techniques for urinary tract stones of the kidney or ureter in children.[3] Surgical and medical therapies were evaluated. Six RCTs (n=335) examined the efficacy of AB, compared to placebo, in the management of urinary stones with or without analgesics. Studies included the use of doxazosin, tamsulosin, or silodosin. The mean ages of the participants ranged from 20.3 months to 11.1 years and stone size in those treated medically was 2-12 mm.[3]

There was low quality evidence that AB increased the stone-free rate (e.g. passage of stones in children presenting with urinary stones), in study follow-up at up to 4 weeks when compared to placebo (RR 1.34; 95% CI, 1.16 to 1.54).[3] Secondary procedures for residual fragments were less with AB compared to placebo, 141 fewer per 1000 children treated. (very low quality evidence; 1 RCT).

Conclusions are limited by evidence only a few trials enrolling a small number of patients. Evidence was also downgraded due to indirectness and imprecision of study findings.

Cochrane – Alpha-blockers after Shock Wave Lithotripsy for Renal or Ureteral Stones in Adults

A 2020 Cochrane review evaluated the evidence for the use of AB as adjuvant medical expulsive therapy to usual care (e.g., oral or intravenous hydration, NSAIDs, pain medication, and antibiotics if needed) and placebo or usual care alone in adult patients with renal and ureteral stones.[4] There were 40 trials that met inclusion criteria which involved 4793 patients; four of which were placebo controlled. Stone size ranged from 7.1 mm to 13.2 mm.[4] Four ABs were studied: tamsulosin, silodosin, terazosin and alfuzosin. The primary outcome of interest was stone clearance.

Evidence from 36 RCTs found adjuvant AB, in patients undergoing shock wave lithotripsy, increased stone clearance more than usual care (RR 1.16; 95% CI, 1.09 to 1.23) (low quality evidence).[4] Alpha-blockers are often given after lithotripsy to promote stone passage. This finding equates to a stone clearance rate of 69.3% in the control group and 80.4% in the AB group. There is low quality evidence that auxiliary treatment was less or the same in those treated with AB compared to usual care (RR 0.67; 95% CI, 0.45 to 1.00).[4] Major adverse events were lower with AB compared to standard of care with 103 fewer events per 1000 adults treated (low quality evidence). Most adverse events were related to rehospitalizations or emergency room visits. Stone clearance time was shorter with AB compared to standard of care (3.74 fewer days; low quality of evidence).[4]

Quality of evidence is limited as 31 of the 40 trials were open-label, which may increase the risk of bias. Less than half of the studies provided allocation details; therefore, randomization details were deemed unclear. Due to the open-label design of many of the trials, the risk of detection bias was high since the outcome of stone clearance was a subjective finding determined by the investigator.

Cochrane – Pharmacological Interventions for Treating chronic Prostatitis/Chronic Pelvic Pain Syndrome

A 2019 review from Cochrane evaluated the efficacy and safety of using medications, specifically AB and 5-ARIs as it pertains to this review, in men with CP/CPPS.[5] Twenty-six studies were identified for these two classes of drugs (n=2238). Terazosin, doxazocin, phenoxybenzamine, tamsulosin, alfuzosin, and silodosin were the AB studied and 5-ARIs included finasteride. Follow-up ranged from 6 weeks to 6 months.[5] All studies were placebo-controlled.

Alpha-blockers compared to placebo were studied in 24 RCTs. Prostatitis symptoms, based on the NIH-CPSI score, were lower with the use of AB compared to placebo or no intervention in studies lasting up to 6 months; however, the decrease in symptoms was not considered clinically significant (MD -5.01; 95% CI, -7.41 to -2.61) (very low quality of evidence).[5] The NIH-CPSI scores range from 0 to 43, with lower scores indicating more benefit. A clinically significant decrease is 6 points or 25% reduction.[5] The number of patients considered responders (e.g., those with 25% or 6-point reduction) was not different between groups (RR 1.23; 95% CI, 0.94 to 1.61) (very low-quality of evidence).[5] There was low quality evidence that there were more adverse reactions (e.g., postural hypotension, and dizziness) in those treated with AB compared to placebo. Sexual dysfunction was higher with AB but not statistically significant based on moderate evidence (MD 0.26; 95% CI, -1.13 to 1.65).[5]

Finasteride was compared to placebo in two, outpatient studies in men with CP/CPPS. Moderate quality evidence demonstrated a reduction in prostatitis symptoms, based on the NIH-CPSI, with finasteride more than placebo (MD -4.6; 95% CI, -5.43 to -3.77).[5] The difference is not considered clinically meaningful. There was low quality evidence that the number of responders was not different between groups (RR 0.87; 95% CI, 0.33 to 2.30).[5] Adverse events occurred in 21 fewer per 1000 patients taking finasteride compared to placebo.[5]

The main limitations to the evidence in this review were the small number of studies and short duration of follow-up. Issues with study methodology contributed to downgrading of the evidence.

After review, 12 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[10–21]

New Guidelines:

American Urological Association – Management of Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia

In 2021 the AUA updated guidance on the management of LUTS in men with BPH.[6] Guideline methods were clearly defined and the evidence was evaluated and graded. Recommendation ranged from expert opinion to strong recommendation, based on the quality of the evidence. Some of the guideline authors did have conflicts of interest that were clearly outlined. Recommendations pertaining to medical treatment of BPH will be discussed.

- Alpha-blockers are recommended for patients with bothersome moderate to severe LUTS/BPH that is bothersome (Moderate recommendation based on Grade A evidence).[6]
- Choice of AB should be determined based on comorbidities (e.g., ejaculatory dysfunction, changes in blood pressure) (Moderate recommendation based on Grade A evidence).[6]
- Alpha-blockers may also be used in patients with acute urinary retention (AUR) related to BPH prior to a voiding trial (Moderate recommendation based on Grade B evidence). Patients should be warned of the risk of IFIS with the use of AB.

- The use of 5-ARIs are recommended in patients with LUTS/BPH with prostatic enlargement (prostate volume > 30 cc on imaging, a prostate specific antigen [PSA] of > 1.5 ng/dL or palpable prostate enlargement in digital rectal exam).[6] (Moderate recommendation based on Grade B evidence).
- The use of 5-ARIs, alone or with AB, are recommended to prevent the progression of LUTS/BPH (Strong recommendation based on Grade A evidence).[6]
- Patients should be advised of the risk of sexual side effects and low risk of prostate cancer associated with 5-ARI therapy. (Moderate recommendation based on Grade C evidence).
- Tadalafil could be considered a treatment option in patients with LUTS/BPH, irrespective of ED (Moderate recommendation based on Grade B evidence).[6]
- Combination therapy with an AB and 5-ARI should only be considered in patients with LUTS due to prostatic enlargement (Strong recommendation based on Grade A evidence).[6]
- Tadalafil in combination with AB should not be offered in patients with LUTS/BPH because there is no advantages in symptoms improvement over monotherapy with either agent alone (Moderate recommendation based on Grade C evidence).

Guidelines for Clinical Context:

EAU – Non-neurogenic Male Lower Urinary Tract Symptoms (LUTS), including Benign Prostatic Obstruction (BPO)

An updated 2023 guideline by the European Association of Urology (EAU) was recently published and included recommendations for the treatment of LUTS in men.[9] A systematic review of the literature was completed and conflicts of interest were disclosed; however, links to this information were disabled so this information could not be critically evaluated. Therefore, recommendations from the EAU will be considered for clinical context. The evidence was graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence. Evidence ranges from 1a to 5, with 1a being systematic reviews of RCTs with low heterogeneity and 5 being expert opinion.[9]

The use of AB are recommended to for men with moderate-to-severe LUTS to reduce urinary symptoms and increase peak urinary flow rate when compared to placebo (Strong recommendation, 1a level of evidence).[9] Five-alpha reductase inhibitors improve symptoms and decrease prostate volume and are recommended for men with moderate-to-severe LUTS and an increased risk of disease progression (e.g., prostate volume >40 mL) (Strong recommendation, 1b level of evidence).[9]

After review, one guideline was excluded due to poor quality.[22]

New Formulations or Indications:

Finasteride and Tadalafil (ENTADFI) – In December of 2021 a new combination product was approved for the treatment of BPH up to 26 weeks in men with an enlarged prostate.[23] The combination contains previously approved medications, finasteride 5 mg, a 5-ARI and tadalafil 5 mg, a PDE5 inhibitor. Finasteride/tadalafil should be taken once daily for up to 26 weeks. Finasteride/tadalafil was compared to placebo/finasteride in one double-blind, parallel-design study lasting 26 weeks. Changes in the primary endpoint, symptoms based on the IPSS, at 12 weeks were a -3.8 for placebo/finasteride compared to -5.5 for finasteride/tadalafil (MD -1.4; p=0.001).[23]

New FDA Safety Alerts:

Table 1. Description of new FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Silodosin[24]	RAPAFLO	December 2020	Use in specific populations	Silodosin is not indicated for females.
Dutasteride[25]	AVODART	January 2020	Warnings and Precautions	Potential risk to male fetus if drug is handled by female who is pregnant. If there is contact with a leaky capsule, hands should be washed immediately.
Tadalafil[26]	CIALIS	February 2018	Use in specific populations	Tadalafil is not indicated for use in females or pediatric patients.
Tadalafil[26]	CIALIS	May 2017	Warnings and Precautions	Reports of sudden loss of vision in one or both eyes have been reported with tadalafil. This could be a sign of non-arteritic anterior ischemic optic neuropathy (NAION). Tadalafil should be discontinued and seek care if vision loss occurs.
Dutasteride/tamsulosin[27]	JALYN	December 2020	Contraindications	The combination product is contraindicated in females who are pregnant. Capsules should not be handled by females who are pregnant.
Tamsulosin[28]	FLOMAX	January 2019	Use in specific populations	Tamsulosin is not indicated for use in women.

Randomized Controlled Trials:

A total of 130 citations were manually reviewed from the initial literature search. After further review, all randomized controlled trials were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

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25. Advodart (dutasteride) [prescribing information]. Research Triangle Park, NC. GlaxoSmithKline. January 2020.

26. Cialis (tadalafil) [prescribing information]. Indianapolis, IN. Lilly USA, LLC. February 2018.

27. Jalyn (dutasteride/tamsulosin) [prescribing information]. Research Triangle Park, NC. GlaxoSmithKline. December 2020.

28. Flomax (tamsulosin) [prescribing information]. Ridgefield, CT. Boehringer Ingelheim Pharmaceuticals, Inc. December 2018.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
terazosin HCl	TERAZOSIN HCL	CAPSULE	Y
doxazosin mesylate	CARDURA	TABLET	Y
doxazosin mesylate	DOXAZOSIN MESYLATE	TABLET	Y
finasteride	FINASTERIDE	TABLET	Y
finasteride	PROSCAR	TABLET	Y
tamsulosin HCl	FLOMAX	CAPSULE	Y
tamsulosin HCl	TAMSULOSIN HCL	CAPSULE	Y
tadalafil	CIALIS	TABLET	N
tadalafil	TADALAFIL	TABLET	N
doxazosin mesylate	CARDURA XL	TAB ER 24	N
alfuzosin HCl	ALFUZOSIN HCL ER	TAB ER 24H	N
dutasteride	AVODART	CAPSULE	N
dutasteride	DUTASTERIDE	CAPSULE	N
silodosin	RAPAFLO	CAPSULE	N
silodosin	SILODOSIN	CAPSULE	N
dutasteride/tamsulosin HCl	DUTASTERIDE-TAMSULOSIN	CPMP 24HR	N
dutasteride/tamsulosin HCl	JALYN	CPMP 24HR	N

Appendix 2: Medline Search Strategy
Database(s): **Ovid MEDLINE(R) ALL** 1946 to April 07, 2023
Search Strategy:

#	Searches	Results
1	tamulosin.mp.	4

2	terazocin.mp.	4
3	doxazocin.mp.	14
4	finasteride.mp. or Finasteride/	3579
5	tadalafil.mp. or Tadalafil/	2658
6	alfuzosin.mp.	634
7	dutasteride.mp. or Dutasteride/	1164
8	silodosin.mp.	483
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	7813
10	limit 9 to (english language and humans and yr="2016 -Current")	1432
11	limit 10 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	130

Appendix 3: Key Inclusion Criteria

Population	Men with benign prostatic hyperplasia (BPH)
Intervention	Phosphodiesterase inhibitors, alpha-blockers, 5-alpha reductase inhibitors
Comparator	Placebo or other active therapy
Outcomes	Reduction in urinary symptoms
Setting	Outpatient

Appendix 4: Prior Authorization Criteria

Benign Prostatic Hypertrophy (BPH) Medications

Goal(s):

- BPH with urinary obstruction is an OHP-funded treatment. BPH without obstruction is not a funded diagnosis.
- Restrict use for male pattern baldness and erectile dysfunction, which are not OHP-covered conditions.
- Allow case-by-case review for members covered under the EPSDT program for unfunded diagnoses.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Will the prescriber consider switching to a preferred product? Message: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #3
3. Is the request for an alpha-1 blocker?	**Yes:** Go to #4	**No:** Go to #6
4. Does the patient have a diagnosis related to functional and mechanical disorders of the genitourinary system including bladder outlet obstruction?	**Yes:** Go to #5	**No:** Go to #6

Approval Criteria		
5. Has the patient tried and not tolerated or not obtained the desired treatment effect on a 2-month trial of a preferred alpha-1 blocker?	**Yes:** Approve an alpha-1 blocker for up to 12 months	**No:** Pass to RPh. Deny until patient has tried and failed a covered alternative
6. Does the patient have a diagnosis of benign prostatic hyperplasia (BPH) or enlarged prostate with obstruction?	**Yes:** Approve for up to 12 months	**No:** Go to #7
7. Does the patient have a diagnosis of unspecified urinary obstruction or BPH without obstruction?	**Yes:** Current age ≥ 21 years: Pass to RPh. Deny; not funded by the OHP Current age < 21 years: Go to #8 "Not Funded" section.	**No:** Pass to RPh. Go to #8

8. RPh Only: All other conditions need to be evaluated to see if diagnosis is funded:

   Funded: covered diagnoses related to prostate may be approved for 1 year.
   Not Funded:
   - Unfunded diagnoses for patients <21 years of age should be reviewed for medical appropriateness/necessity under the EPSDT program
     - Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc.)?
     - Is the request for a preferred product OR has the patient failed to have benefit with, or have contraindications or intolerance to, at least 2 preferred products?
     - If patient qualifies for EPSDT benefit and clinic provides supporting literature, approve for up to 12 months.
   - Unfunded diagnoses for ≥21 years of age should be denied (not funded by the OHP).

   Not Covered: Cosmetic and uncovered diagnoses (e.g., hair growth, erectile dysfunction) should be denied (not covered by the OHP).
   - Alpha-1 blockers and 5-alpha reductase inhibitors may be used concurrently for BPH up to 1 year. Alpha-1 blockers may be discontinued once prostate is reduced to normal size.
   - If urine retention (obstructive), ask for more specific diagnosis.

P&T Review: *8/23 (KS); 7/16; 11/12; 9/10; 3/10; 5/08; 2/06*
Implementation: *9/1/23; 8/16, 2/21/13; 1/1/11; 4/20/10; 5/22/08; 7/1/06; 9/30/05*