INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Urinary Incontinence***
-April 2023-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a disease state review of urinary incontinence (UI). The NPTC last reviewed medications for overactive bladder (OAB) in 2019 with the addition of oxybutynin, extended-release (ER) formulation to the National Core Formulary (NCF) and removal of trospium from the NCF due to insufficient efficacy data. This 2023 updated review of UI includes treatment of stress urinary incontinence (SUI) and urge urinary incontinence (UUI) covering duloxetine (for SUI only), topical estrogens, botulinum toxin (BT), the antimuscarinic drug class, and the beta-3 adrenergic agonist class. Following clinical review and analysis, the NPTC voted to **ADD "any beta-3 adrenergic agonist" to the National Core Formulary.**

Discussion:

Urinary incontinence is defined in both men and women as an involuntary leakage of urine. Urine retention requires functional lower urinary tract, pelvic and neurologic components and intact pelvic floor muscle and connective tissue support. UI can be classified by pathophysiology: UUI or OAB is caused by uninhibited detrusor muscle contraction due to impaired sensory pathways at the bladder, spinal cord or cortical level. Stress UI is caused by impaired bladder and urethral support and impaired urethral closure[1]. Prevalence of UI in women in the United States increases with age, with estimates as high as 70% in women >60 years old[2]. Prevalence in Alaska Native/American Indian (AI/AN), while poorly documented in the literature, seems to be similar to the general population[3,4]. Risk factors for development of urinary incontinence include increasing age, obesity, parity and mode of birth (women), family history, ethnicity, medical comorbidities, diet, smoking and prostate procedures (men)[2,5]. In men, rates as high as 21% in patients >65 years old have been reported and confers a higher risk of institutionalization[5]. UI has been associated with a 20% increased risk of death in nursing home residents, and represents an important cause of functional decline and caregiver burden[2,5]. Causes of UUI in men include bladder outlet obstruction from benign prostatic hyperplasia (BPH), and SUI is primarily due to prostate surgery, spinal cord injury or other neurologic conditions which affect sphincter function[5]. Diagnosis is largely based on history and symptoms, voiding diaries and comprehensive medication reconciliations, although urodynamic studies can be helpful in classification[2,5]. Primary treatment goals include improvement in quality of life and urinary retention. Symptom management (protective garments, wicking catheters), modification of lifestyle (weight loss, reduction of alcohol and caffeine, treatment of constipation, smoking cessation), pelvic floor strengthening (Kegel exercises, pelvic floor PT, vaginal weighted cones, biofeedback), and bladder training are first-line interventions[2,5]. Second-line interventions include topical estrogen for peri/post-menopausal women (for all UI), duloxetine, pessaries, and surgical intervention for SUI, and beta-3 adrenergic agonists (B3 agonists) and anti-muscarinic agents for UUI/OAB[2,6]. Third line therapy for UUI/OAB include BT, percutaneous/transcutaneous tibial nerve stimulation, and sacral neuromodulation[6,15].

Topical estrogen is considered first-line for peri and post-menopausal women for treatment of both SUI and UUI/OAB[2,6]. Topical estrogen has moderate efficacy for treatment of UI, with primary mechanism likely in improvement of vaginal atrophy[7]. Meta-analyses examining the safety of topical estrogen demonstrated no significant differences in stroke, invasive breast cancer, colorectal cancer, endometrial cancer, PE/DVT, coronary heart disease (CHD), and fracture between users and non-users. In patients with an intact uterus, risk of CHD, fracture, all-cause mortality, were lower in users than in nonusers (HR 0.68, 95% CI: 0.55-0.86)[8]. Systemic estrogen has been widely proven to worsen all UI and should not be initiated for this issue[7]. Topical estrogen is safe and moderately effective treatment for UI in peri/post-menopausal women and should be initiated when appropriate. **Topical estrogen is on the IHS NCF.**

Duloxetine is a serotonin (5-HT)/norepinephrine (NE) reuptake inhibitor which is thought to modulate reuptake inhibition of 5-HT and NE at the motor nucleus of the urethral and anal sphincters[9]. Its use is off-label for the treatment of SUI in men and women, and considered second-line therapy by most guidelines in patients who are not surgical candidates[10,11]. For treatment of female SUI, a 2005 meta-analysis showed that duloxetine, alone and in combination with pelvic floor training, significantly reduced ($p<0.05$) in median incontinence episode frequency (57% vs 35% pelvic floor training alone; 29% no treatment), however a separate meta-analysis showed similar efficacy but reported a NNH of 7[12,13]. In men, duloxetine has shown improvement in early return of continence after prostate surgery (78% vs. 52%) compared to placebo, as well as improvements in subjective urine leaking (63.6% vs. 39.1%) compared with placebo, however side effects caused a 21% discontinuation[14]. Duloxetine may be considered for SUI treatment with appropriate counseling of potential side effects and efficacy of alternative therapies. **Duloxetine is on the IHS NCF.**

BT is a neurotoxin produced by *Clostridium botulinum* and is injected intravesicularly via cystoscopy for treatment of OAB/UUI[2]. It is highly effective for treatment of UUI/OAB compared to other first- and second-line therapies with meta-analysis data for onabotulinum toxin A associated with a ≥50% decrease in urinary incontinence episodes compared to 'all other licensed treatments'[14]. Despite its efficacy, BT is considered 3rd line for UUI/OAB due to the invasive nature of administration and was **not considered for addition to the IHS NCF due to limited use in primary care settings**.

Antimuscarinic agents have long been a first-line pharmacologic agent for treatment of OAB/UUI. All antimuscarinic agents are contraindicated in gastric retention, untreated narrow angle closure glaucoma, and supraventricular tachycardia. All antimuscarinics exert peripheral anticholinergic effects (e.g., dry mouth, constipation, tachycardia, palpitations) and have additive side effects with other medications that have anticholinergic effects[2]. Medications included in this class are darifenacin, fesoterodine, solifenacin, tolterodine, trospium, and oxybutynin. Antimuscarinic efficacy for OAB/UUI has been reviewed by the NPTC, most recently in 2019, with conclusions that antimuscarinics are relatively effective and safe for the treatment of OAB/UUI and that ER formulations showed better data for efficacy and tolerability. In 2019, oxybutynin ER was added to the NCF and trospium was removed for lack of efficacy. Efficacy data for antimuscarinics for the treatment of UUI/OAB were thoroughly reviewed in the 2019 Formulary Brief and will not be additionally covered here. During the current review, utilization data revealed that oxybutynin IR still holds majority market share for IHS facilities that obtain medications via the IHS Pharmaceutical Prime Vendor. Thus, an important target of this brief is to highlight that **ER formulations are better tolerated and more efficacious for treatment of OAB/UUI and should be used preferentially over IR formulations for the treatment of this condition**.

Since the 2019 review, data has emerged suggesting that cumulative exposure to antimuscarinics may be associated with increased rates of dementia and Alzheimer disease spurring the Society for Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) to state that “Chronic use (>3 months) of OAB anticholinergic medications is likely associated with an increased risk of new-onset dementia. Short-term (<4 weeks) use of most OAB anticholinergic medications is likely safe in most individuals” [2,17]. Two notable case-controlled trials, one of all anticholinergic medications and one specifically studying the antimuscarinic agents for OAB have shown an increase in the rates of dementia in people with exposure to these medications[18,19]. The nested-case controlled trial by Motto et al. included 11,392 patients ≥66 years old with dementia and an exposure to OAB antimuscarinics in the 6-12 months preceding dementia diagnosis and 29,881 age matched controls without dementia and found that compared with mirabegron, solifenacin (OR 1.34; 95% CI 1.11-1.60), darifenacin (OR 1.49; 95% CI 1.19-1.86), tolterodine (OR 1.21; 95% CI 1.02-1.45), and fesoterodine (OR 1.39; 95% CI 1.14-1.71) were associated with increased odds of incident dementia compared with receipt of mirabegron;, oxybutynin and trospium did not have this association[14]. A prior case-controlled trial had found that all antimuscarinics for OAB treatment were associated with an increased risk of dementia with an adjusted OR of 1.18 (95% CI 1.13-1.23, p<0.01)[15]. The same study found that exposure to an anticholinergic medication with high anticholinergic activity (all OAB meds fall into this category) 15-20 years before a diagnosis of dementia was significantly associated with greater dementia incidence with an odds ratio of 1.17 (95% CI: 1.10 to 1.24)[15]. Current recommendations by the American Urologic Association and European Association of Urology (EUA) include antimuscarinics for the treatment of OAB/UUI. The EUA states “long-term antimuscarinic treatment should be used with caution in elderly patients especially those who are at risk of, or have, cognitive dysfunction” in the 2022 guidelines[11,22].

B3 agonists are the newest class of OAB/UUI drugs with FDA approval of mirabegron in 2012 and vibegron in 2020. Mechanism of action is thought to be via activation of B3 receptors and relaxation of the detrusor muscle. Notable side effects for mirabegron include risk of exacerbation of uncontrolled hypertension (Canadian labeling lists severe uncontrolled HTN ≥180/110 as a contraindication), angioedema, and bladder flow obstruction[23]. Vibegron has fewer documented contraindications and side effects, most notably bladder flow obstruction[24]. Mirabegron can be used in children, while vibegron can be used in pregnancy and without caution in hypertension[23,24]. Mirabegron efficacy data is comparable to that of antimuscarinics. Data from the PILAR trials (industry-sponsored, placebo-controlled RCTs) demonstrated statistically significant improvement in incontinence episodes as well as low rates of serious adverse events (AEs)[25-27]. A pre-planned analysis using Montreal Cognitive Assessment (MoCA) evaluation for mild cognitive impairment (MCI) showed no statistically significant change in the adjusted mean MoCA total score with mirabegron versus placebo[28]. Efficacy in children was shown to be similar to solifenacin while frequency of AEs was lower[29]. Phase IV/post marketing trials have shown significantly improved OAB-q symptom bother scale scores and patient perception of bladder condition (p<0.05)[25]. Persistence with mirabegron was significantly better than with solifenacin and oxybutynin IR or ER (39% compared to 35%), (HR 1.22; 95% CI: 1.01-1.47; p=0.037), 17% (HR 1.83; 95% CI: 1.41-2.40; p<0.001) and 14% (HR 2.16; 95% CI: 1.76-2.65; p<0.001) respectively and had the highest persistence rate (30%) at 12 months of all the antimuscarinic agents (13.8–21.0% all comers)[25]. Vibegron has not been compared head-to-head with mirabegron, however, a recent U.S. Department of Defense review determined that B3 agonists have a high degree of interchangeability based on indirect comparisons although there may be benefit to vibegron given no evidence of clinically significant effects on blood pressure. Current guidelines recommend antimuscarinics or B3 agonists equally in treatment of OAB/UUI for patients who have failed conservative therapy with a strong rating and high level of evidence[11,22].

Currently, the U.S. Department of Veterans Affairs allows use of mirabegron after prior authorization, with criteria for use (updated 2021) for patients with a diagnosis of OAB/UUI including documented history of mental status changes with anticholinergic medication, failure or intolerable side effects after 12-week trial with either 2 formulary antimuscarinics, or 1 formulary and 1 nonformulary antimuscarinics, or diagnosis of Alzheimer’s disease, other dementia, cognitive impairment, gastric retention, xerostomia, uncontrolled narrow-angle glaucoma, or other condition for which an anticholinergic drug is contraindicated or could be harmful[30].

Findings:

Overall conclusions for this 2023 review of treatment for Urinary Incontinence:

- Topical estrogen is a low risk, first-line treatment for all UI classifications in peri/post-menopausal woman
- Duloxetine is the only pharmacologic treatment with significant data supporting treatment of SUI in men and women and appropriate counselling for potential harm is recommended prior to initiation
- Botulinum toxin is a useful third-line treatment but outside the scope of most IHS facilities at this time
- Anti-muscarinic agents are efficacious for treatment of UUI/OAB as determined in prior reviews by this committee and ER formulations are recommended over IR formulations
- Recent data correlates an increased risk of dementia with the long-term use of antimuscarinic agents
- No RCT has been performed to determine dementia causality of anticholinergic medications used for OAB/UUI
- AI/AN patients are high risk for multiple conditions that increase the risk of mild cognitive impairment and dementia
- Mirabegron is an effective medication to treat OAB/UUI and is recommended by guidelines with similar strength as antimuscarinic agents
- Efficacy of mirabegron is similar to antimuscarinic agents with better tolerability, persistence, safety profiles, and without a signal for increased dementia risk
- Vibegron has similar efficacy to mirabegron with a more limited side effect profile, however given its recent FDA approval, phase IV/real-world data is lacking

Currently, topical estrogen, duloxetine and oxybutynin IR and ER are agents on the IHS NCF that can be used for treatment of UI. ER formulations of antimuscarinic agents are better tolerated and more efficacious for treatment of OAB/UUI and should be used preferentially over IR formulations for the treatment of this condition. The IHS NPTC voted to ADD “any beta-3 adrenergic agonist” to the National Core Formulary.

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