Background:
The IHS National Pharmacy and Therapeutics Committee (NPTC) reviewed antimuscarinic medications and the beta-3 adrenergic agonist, mirabegron, for use in overactive bladder (OAB)/urge urinary incontinence at the February 2019 meeting. Treatment of OAB was last reviewed in May 2013 at which time oxybutynin and trospium were added to the National Core Formulary (NCF). As a result of this review, the NPTC added extended-release (ER) oxybutynin to the NCF and removed trospium.

Discussion:
OAB is a syndrome of several urinary symptoms that occurs in the absence of urinary tract infection of other obvious pathology. It is defined as urinary urgency accompanied by frequency and nocturia. It may or may not be accompanied by urge incontinence. OAB affects approximately 33 million Americans, but incidence is likely underreported as women take about 6 ½ years after symptoms begin before seeking help. Although OAB is not life-threatening, it does greatly impact quality of life.1-2

Treatment goals focus on decreasing the impact of symptoms on quality of life. Some patients may choose to not treat their symptoms at all. First line options include behavioral therapies. Oral pharmacologic agents are second line treatment options and were the focus of the discussion by the NPTC. The agents included in this review are as follows: oxybutynin (IR, ER, and transdermal gel), tolterodine (IR and ER), darifenacin, solifenacin, trospium (IR and ER), fesoterodine, and mirabegron. Third line treatments are reserved for those refractory to behavioral and pharmacologic therapy. These options are usually undertaken with specialty consultation and include intradetrusor onabotulinum toxin A therapy, peripheral tibial nerve stimulation, and sacral neuromodulation.

The American Urological Association (AUA) and the European Association of Urology (EAU) recommend conservative management with lifestyle and behavioral modifications as initial treatment course. Both organizations list oral antimuscarinic drugs as first line pharmacologic choice for treatment of OAB. Neither guideline states a preference for a specific antimuscarinic. Both guidelines recommend ER formulations be preferentially prescribed over IR formulations. The AUA also lists mirabegron as an option as does the EAU but states that patients need to be informed about the uncertainty of long-term side effects. Follow up should be early, within 30 days, and should assess compliance, efficacy, tolerability, and possible alternative treatments if the initial agent is not achieving desired results.3-4

The Agency for Healthcare Research and Quality published an updated systematic review on urinary incontinence in 2018. For the intent of this review, only the information related to urge urinary incontinence was assessed. For pharmacologic agents, only antimuscarinics were evaluated. A review of 16 studies focused on quality of life and found no differences in those comparing pharmacologic interventions with each other. Adverse events (AE) were evaluated showing 2.4% of 2583 women experienced serious adverse events, but most were undefined. In the 21 studies that reported AE, dry mouth was the most common with a slightly higher incidence with oxybutynin. Pharmacologic agents had a statistically significant higher rate of cure (OR 1.80, 95% CI: 1.29-2.52), improvement (OR 1.79, 95% CI: 1.18-2.7) and satisfaction (OR 2.6, 95% CI: 2.05-3.28) compared with placebo. Pharmacologic treatment was significantly less effective in improvement of symptoms versus behavioral therapy (OR 0.24, 95% CI: 0.09-0.62), but no differences were seen in cure rates, satisfaction or quality of life.5

The Cochrane Collaboration has performed several reviews of antimuscarinic agents. Their 2012 review evaluated anticholinergic drugs for OAB symptoms in adults. This was a meta-analysis of randomized controlled trials (RCTs) evaluating quality of life, patient observations, quantification of symptoms, and AEs while comparing one antimuscarinic agent with either a different drug, route of administration or dose. Authors concluded that ER formulations might be preferred over IR. There was little evidence about quality of life, cost, or long-term outcomes. Tolterodine IR might be preferred over oxybutynin IR for less dry mouth. Solifenacin might be preferred over tolterodine for improvement in leakage and urgency episodes in 24 hours. Fesoterodine might be preferred over tolterodine ER for quality of life.
improvement, frequency, and leakage and urgency episodes in 24 hours, though it had a higher risk of withdrawal (RR 1.45, 95% CI 1.07-1.98) and dry mouth (RR 1.80, 95% CI 1.58-2.05).8

Mirabegron, the only beta-3 adrenergic agonist available in the US, was compared with antimuscarinics as monotherapy or combination therapy in a 2018 systematic review and network meta-analysis of 64 RCTs. This review focused on tolerability and efficacy. Mirabegron was found to have comparable overall efficacy to commonly used antimuscarinics with better tolerability for dry mouth, urinary retention, and constipation. Thus, it is an alternative treatment option to antimuscarinics for OAB. The combination of mirabegron and solifenacin showed efficacy and may be an effective option for patients with an inadequate response to initial pharmacologic treatment.7-8

A 2015 meta-analysis by Reynolds et al. reviewed the comparative effectiveness of anticholinergic for OAB in women. This analysis was a repeat of an earlier study performed 5 years prior with double the number of included RCTs. The outcomes were the same, concluding that all medications were effective in improving OAB symptoms with no single agent definitively superior to the others. Extended release formulations reduced urge urinary incontinence episodes by 1.73 episodes per day (95% CI: 1.37-2.09) and reduced voids by 2.06 per day (95% CI: 1.66-2.46). Adverse events ranged from 9-92% of participants but contributed to less than 17% withdrawal from all studies. The most commonly reported AEs were dry mouth, constipation, and vision changes.9

Vouri et al. studied AEs and treatment discontinuations of antimuscarinics in older adults (>65 years). When compared to placebo (3.3%), there were significantly higher rates of constipation (10% for combined antimuscarinics) with darifenac (18%), solifenacin (15.4%), fesoterodine (8.5%) and tolterodine (4.8%) (I²=46.1%). Rates of dry mouth were significantly higher with tolterodine ER (6.1%), darifenac (23.8%), solifenacin (26%), and fesoterodine (29.4%) (25% for combined antimuscarinics) versus placebo (5.3%) (I²=73.9%). When compared head-to-head, oxybutynin IR had more overall treatment-related AEs and dry mouth versus solifenacin. Fesoterodine had more dry mouth versus tolterodine ER. Fesoterodine had more reported discontinuations due to AEs than placebo or tolterodine ER as well as more discontinuations due to dry mouth versus placebo. There were only four head-to-head studies included in this meta-analysis and all trials were limited to 12 weeks, so outcomes may not be generalizable to the outpatient setting.10

Findings/Conclusions:
Following review of the literature, the NPTC concluded that available evidence does not favor one antimuscarinic medication over the others. Because oxybutynin is already named on the NCF, the committee voted to add the extended-release formulation based on evidence that AEs may be lower with extended-release formulations of antimuscarinics. The NPTC’s decision to remove trospium from the NCF was based primarily on two factors, namely overall low utilization throughout IHS and a lack of available data that supports lower incidence of AEs with trospium versus other antimuscarinics.

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.

References: