



# THERAPEUTICS INITIATIVE

Evidence Based Drug Therapy

## Drugs for Overactive Bladder Symptoms

Overactive Bladder Syndrome (OAB) refers to individuals with the following symptoms: urinary urgency, excessive urinary frequency, or urge incontinence.<sup>1</sup> These symptoms are not life threatening, but can cause embarrassment. Incontinence, the most problematic symptom, predominantly affects women and occurs in approximately one-third of those with OAB.<sup>2</sup> OAB is sometimes induced or exacerbated by drugs.<sup>3</sup>

### What are the goals of treatment?

- To prevent or reduce episodes of urinary urgency when access to a toilet is limited.
- To prevent or reduce episodes of incontinence (urinary leakage).

### Non-drug therapy

Two Cochrane systematic reviews have assessed the effect on urinary incontinence of bladder training (systematic gradual increase in time between voiding)<sup>4</sup> and pelvic floor muscle training.<sup>5</sup> The first review described only 2 small trials with insufficient data to answer the question. The second review reported that pelvic floor muscle training decreases the incidence of incontinence in women with stress and mixed stress and urge incontinence by 1.25 (0.9 -1.6) episodes per 24 hours.<sup>5</sup> One 8 week trial (n=197) compared behavioural therapy (pelvic floor muscle control + strategies for urgency) and biofeedback with oxybutynin.<sup>6</sup> Behavioural therapy decreased incontinence episodes by 0.4 (0.03-0.8) per 24 hours as compared with oxybutynin.<sup>5</sup>

### Drug therapy

Two drugs, oxybutynin and tolterodine, are indicated in Canada for symptomatic relief of OAB. Both block muscarinic acetylcholine receptors, inhibiting detrusor muscle contraction and bladder emptying. The most common adverse effects are due to the drugs' anticholinergic actions: dry mouth, constipation, urinary retention, impaired lens accommodation, disturbed thinking, and delirium. The risk of anticholinergic adverse effects is greater in the elderly and in patients with co-morbidities.

### Pharmacokinetics

**Oxybutynin:** There is extensive first-pass metabolism to an active metabolite, N-desethyloxybutynin, which has an apparent half-life of 4 hours for immediate release and 8 hours for sustained release formulations. Elimination is by hepatic metabolism CYP3A4.<sup>7</sup>



**Tolterodine:** Kinetics differ in extensive metabolizers (90% to 95% of Caucasians) versus poor metabolizers (5% to 10% of Caucasians). In extensive metabolizers most of the drug is converted by CYP2D6 to an active metabolite 5-hydroxymethyl tolterodine, apparent half-life 2-3 hours. In poor metabolizers tolterodine is the active form, which is eliminated by hepatic metabolism via CYP3A, apparent half-life 9 hours. At similar doses peak active drug concentrations are about 4 times higher in poor than in extensive metabolizers.<sup>8</sup>

### What does drug treatment achieve?

#### Benefit

A Cochrane systematic review of 32 short-term placebo-controlled trials ( $\leq 12$  weeks) found that 60% of people with OAB treated with an anticholinergic drug report cure or symptom improvement as compared with 45% treated with placebo, absolute risk reduction (ARR) 15%, number needed to treat (NNT) 6 to 7.<sup>1</sup> For incontinence the average benefit was 0.6 less leakage episodes per 24 hours. Sustained release (SR) oxybutynin has not been compared with placebo in any published trials. Transdermal oxybutynin did not reduce incontinence nor lead to greater perceived benefit vs. placebo in one 12 week trial (n=378).<sup>9</sup> In another 12 week trial (n=371) both transdermal oxybutynin and SR tolterodine on average led to 1 less leakage episode per day.<sup>10</sup>

#### Harm

The most common harm reported in the systematic review was dry mouth, drug 37% vs. placebo 15%; absolute risk increase (ARI) 22%, number needed to harm (NNH) 4 to 5.<sup>1</sup> In two recent trials not included in the Cochrane review, pooled total serious adverse events (SAEs) occurred more frequently



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with SR tolterodine, 2.9%, than placebo 0.2%, ARI 2.7% (1 - 4%), NNH 37.<sup>11,12</sup> One of these trials included an oxybutynin arm: 2.9% of patients on oxybutynin experienced SAEs vs. none on placebo.<sup>12</sup> SAEs included convulsions, falls, traffic accidents, bradycardia and anxiety.<sup>11</sup>

### Which formulation, drug or dose?

A recent Cochrane review of head-to-head trials of anticholinergic drugs found no difference in symptom improvement for transdermal vs. oral formulations, for immediate release vs. sustained release or for oxybutynin vs. tolterodine. Tolterodine 1 mg per day was as effective as 2 mg or 4 mg per day and caused less dry mouth. Dry mouth was less frequent with tolterodine, 31%, than oxybutynin, 47%.<sup>13</sup>

### Conclusions

- Oxybutynin and tolterodine (all forms) have not been tested in randomized controlled trials (RCTs) beyond 12 weeks nor in elderly patients or those with serious co-morbidities.
- Oral anticholinergic formulations and regimens are equivalent in benefit; evidence for transdermal oxybutynin is less clear.
- **Symptomatic benefit occurs in 60% of people with OAB treated with an anticholinergic drug versus 45% of people treated with placebo, ARR 15%, NNT 6 to 7.**
- **Anticholinergic side effects, particularly dry mouth, are frequent: ARI 22%, NNH 4 to 5.**
- The benefit of anticholinergic drugs (0.6 less leakage episodes per day) must be weighed against the harm (3% of patients treated for 12 weeks experienced a serious adverse event).

### References

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**Erratum:** Letter #56 *Drugs for Alzheimer's Disease April-Aug 2005* contained an error in the drug dose table. The daily dose for rivastigmine (Exelon) is 6-12 mg, cost \$2.56-\$5.12; the daily dose for galantamine (Reminyl) is 16-24 mg, cost \$2.64-\$5.28.

### Clinical implications

- The RCT evidence shows that oxybutynin and tolterodine have modest symptomatic benefit: 6 to 7 people must be treated for 1 to benefit more than placebo. There is evidence that behavioural therapies involving pelvic floor muscle training are at least as effective, with fewer adverse effects. Since 45% of people respond to placebo, 'placebo' remedies or watchful waiting will likely help about half.
- For those unable to obtain relief otherwise, the limited benefit of oxybutynin and tolterodine must be weighed against the adverse effects, including serious adverse events (hospitalizations). Doctors and pharmacists should warn patients that dry mouth is common and cognitive disturbance possible. Individual variability in drug elimination suggests that different people respond to different doses.
- For people wishing a therapeutic trial, start with 2.5 mg of generic oxybutynin and titrate up if needed. Individuals should set treatment goals and weigh their symptom relief against side effects. Very few people will require long-term 24 hour a day symptom relief; intermittent use may be better. Drug interactions due to inhibitors of CYP3A4 and CYP2D6 are possible. Ongoing clinical monitoring is needed.

**Table: Anticholinergic drugs for overactive bladder syndrome**

Drug and formulation	Daily Dose	Daily Cost
oxybutynin (generic)	2.5 mg/d - 10 mg BID	\$0.13 - \$1.06*
oxybutynin (Ditropan)	2.5 mg/d - 10 mg BID	\$0.23 - \$2.10*
SR oxybutynin (Ditropan LA)	5 - 20 mg/d	\$1.94 - \$3.89*
Transdermal oxybutynin (Oxytrol TM)	~3.9 mg/d (36 mg patch/3 - 4 days)	\$1.86 †
tolterodine (Detrol)	1 mg/d - 2 mg BID	\$0.97 - \$1.95*
SR tolterodine (Detrol LA)	4 mg/d	\$1.95*

\* Average daily cost calculated using 2005 PharmaCare data

† Price at local pharmacy

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The draft of this Therapeutics Letter was submitted for review to 40 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.