



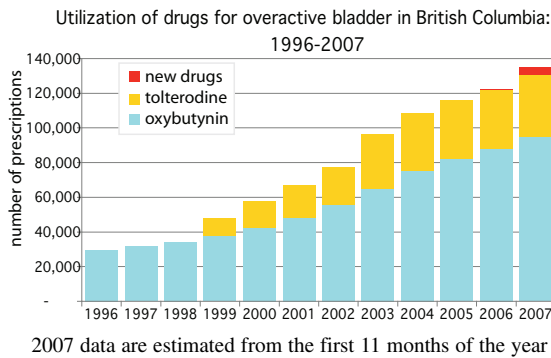
# THERAPEUTICS INITIATIVE

Evidence Based Drug Therapy

## Is newer better? New drugs for treatment of overactive bladder

In this Letter we update the prescription drug treatments for overactive bladder, previously reviewed in Letter #57 (Sep-Dec 2005). At that time we concluded that oxybutynin and tolterodine have modest symptomatic benefit: 6 to 7 people must be treated for one to benefit more than placebo. This limited benefit must be weighed against the anticholinergic adverse effects, including serious adverse events (hospitalizations).

The current Letter summarizes the Common Drug Review (CDR) reports on three drugs newly available in Canada for the treatment of overactive bladder (darifenacin, solifenacin and trospium). The prescription of drugs in this class increased from 1996 to the present in British Columbia (see figure).



### Darifenacin (Enablex<sup>®</sup>) Solifenacin (Vesicare<sup>®</sup>) Trospium (Trosec<sup>®</sup>)

**Approved Indication:** For use in the treatment of overactive bladder with symptoms of urgency with or without urge incontinence, usually with frequency and nocturia.<sup>1</sup>

**Mechanism of action:** Darifenacin, solifenacin and trospium are acetylcholine receptor antagonists, which relax bladder smooth muscle and inhibit involuntary detrusor muscle contractions.

Table 1: Pharmacokinetics<sup>1</sup>

	Darifenacin	Solifenacin	Trospium
Absorption	> 98%	90%	< 10% fatty meal reduces absorption by 70-80% compared to fasting
Half-life	12.8 to 18.7 hours	45-68 hours	20 hours
Metabolism	CYP 2D6 and CYP 3A4	mostly CYP 3A4	ester hydrolysis and conjugation
Renal excretion of unchanged drug	3%	< 15%	60% active tubular secretion in urine



### Evidence of Benefits and Harms

#### Darifenacin

Five RCTs compared darifenacin (3.75 - 30mg/day) with placebo. Two RCTs compared darifenacin (2.5mg TID - 30mg/day) with oxybutynin (2.5 - 5mg TID) and one RCT compared darifenacin (15mg/day) with tolterodine (2 mg BID). The RCTs varied in duration from 1 - 12 weeks. Four of five placebo controlled trials reported a statistically significant reduction in the median number of incontinence episodes with darifenacin (1.4 to 4.3 fewer episodes/week vs placebo). Three reported a statistically significant reduction in median voiding frequency with darifenacin (0.7 to 0.9 fewer episodes/day vs placebo). RCTs comparing darifenacin with oxybutynin or tolterodine demonstrated no difference in efficacy.

As for other anti-cholinergic drugs, darifenacin significantly increased dry mouth and constipation compared with placebo. It increased the incidence of constipation compared with tolterodine, but decreased the incidence of dry mouth compared with oxybutynin.

#### Solifenacin

Three (4 - 12 week) RCTs compared solifenacin (2.5 - 10 mg/day) with tolterodine (2 - 4mg BID). Two (4 - 12 week) RCTs compared solifenacin (2.5 - 10mg/day) with placebo. One active comparator



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RCT found statistically significantly fewer episodes of incontinence (mean reduction of 0.49 episodes/day for solifenacin vs tolterodine) and improvements in quality of life as measured by perception of bladder condition scale (mean difference 0.18 points on a total score of 6 points favouring solifenacin over tolterodine). The other two RCTs found a statistically significant difference only for urgency episodes (0.43 to 1.02 fewer episodes/day), favouring solifenacin over tolterodine. However, in all three RCTs solifenacin increased the incidence of constipation as compared with tolterodine.

#### Trospium

There were 12 RCTs of trospium (8 of trospium 10 - 40mg BID vs placebo, 3 of trospium 20mg BID vs oxybutynin 5mg BID and one of trospium 20mg BID vs placebo and tolterodine 2mg BID). Nine RCTs were of 2 - 4 weeks duration, and seven used urodynamic outcome measures. The Common Drug Review focused on two 12-week placebo controlled RCTs and one 52-week RCT comparing trospium 20mg BID with oxybutynin 5mg BID, all of which reported clinical outcome measures. Trospium was superior to placebo and equivalent to oxybutynin as assessed by the episodes of urge incontinence and voids per day. In the two placebo-controlled RCTs, trospium reduced daily voids by 2.4 - 3/day (from a baseline of 13/day), compared with a reduction of 0.6-1.8/day with placebo. Trospium significantly increased dry mouth and constipation, compared with placebo. At the above doses, trospium decreased incidence of dry mouth compared with oxybutynin, but not compared with tolterodine.

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.

#### Recommendations of the Canadian Expert Drug Advisory Committee (CEDAC) of the CDR

##### Darifenacin: Do not list

- “CEDAC recommends that darifenacin not be listed.”
- “There is insufficient evidence in support of an advantage of darifenacin over ... other agents [oxybutynin, tolterodine or trospium].”<sup>2</sup>

##### Solifenacin: Do not list

- “CEDAC recommends that solifenacin not be listed.”
- “There is insufficient evidence that solifenacin provides clinically important differences in outcomes compared to less expensive alternatives.”
- “Overactive bladder is most commonly observed in older populations, who are most susceptible to anticholinergic adverse effects. The long serum half-life (approximately 60 hours) and accumulation of solifenacin in patients with chronic kidney disease, increases the possibility of prolonged adverse drug events, especially in patients with impaired renal function.”<sup>3</sup>

##### Trospium chloride: List with criteria/condition

- “CEDAC recommends that trospium be listed for patients who cannot tolerate immediate-release oxybutynin and in a similar manner as drug plans list tolterodine.”<sup>4</sup>

#### General Concerns of CEDAC:

**The CEDAC committee had concerns about the increase in number of anticholinergic agents available to treat overactive bladder disorder, the increased use of these agents and the risk to benefit ratio, especially in elderly patients.** The committee recommended that the drug plans consider a drug class review of the effectiveness, safety and cost-effectiveness of these agents.

#### Conclusions

Based on the CDR systematic reviews, the three new drugs to treat overactive bladder syndrome are more expensive than oxybutynin with little or no therapeutic advantage in efficacy or adverse effects.

**Table 2: Dose, Cost and Funding status of drugs for overactive bladder syndrome in BC**

Drug	Brand Name	Daily Dose	Daily Drug Cost (\$)*	BC Funding status
oxybutynin	generic	2.5 mg/d - 10 mg BID	0.12 - 1.04	Full benefit
oxybutynin SR	Ditropan XL	5 - 20 mg daily	2.27 - 4.53	Special authority
oxybutynin transdermal	Oxytrol TM	3.9 mg/day patch for 3 - 4 days	1.64 - 2.18	Special authority
tolterodine	Detrol	1 mg/d - 2 mg BID	0.97 - 1.95	Special authority
tolterodine SR	Detrol LA	2 - 4 mg daily	1.95	Special authority
darifenacin	Enablex	7.5 - 15 mg daily	1.69	No coverage
solifenacin	Vesicare	5 - 10 mg daily	1.76	No coverage
trospium	Trosec	20 mg/d - 20 mg BID	0.80 - 1.60	No coverage

\* Median cost was calculated using PharmaNet data from October 2006 to October 2007.

#### References

1. Product Monographs for darifenacin, solifenacin succinate and trospium chloride. e-CPS on line, accessed October 2007.
2. CEDAC. Darifenacin Final Recommendation and Reasons for Recommendation. Common Drug Review, October 19, 2006. [http://www.cadth.ca/media/cdr/complete/cdr\\_complete\\_Enablex\\_Oct-19-06.pdf](http://www.cadth.ca/media/cdr/complete/cdr_complete_Enablex_Oct-19-06.pdf) accessed October 2007
3. CEDAC. Solifenacin Final Recommendation on Reconsideration and Reasons for Recommendation. Common Drug Review, January 24, 2007. [http://www.cadth.ca/media/cdr/complete/cdr\\_complete\\_Vesicare\\_Jan-24-2007.pdf](http://www.cadth.ca/media/cdr/complete/cdr_complete_Vesicare_Jan-24-2007.pdf) accessed October 2007
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