

THERAPEUTICS INITIATIVE

Evidence Based Drug Therapy

Are claims for newer drugs for overactive bladder warranted?

Two previous Therapeutics Letters on drugs for overactive bladder (OAB) concluded that the antimuscarinic drugs (oxybutynin, tolterodine, darifenacin, solifenacin and trospium) had limited short-term potential symptomatic benefit (NNT = 7) and significant risk of adverse effects (NNH = 5).^{1,2} This Letter compares drugs to one another, including newer drugs introduced since 2007, when our most recent Letter on this topic was published.²

Background

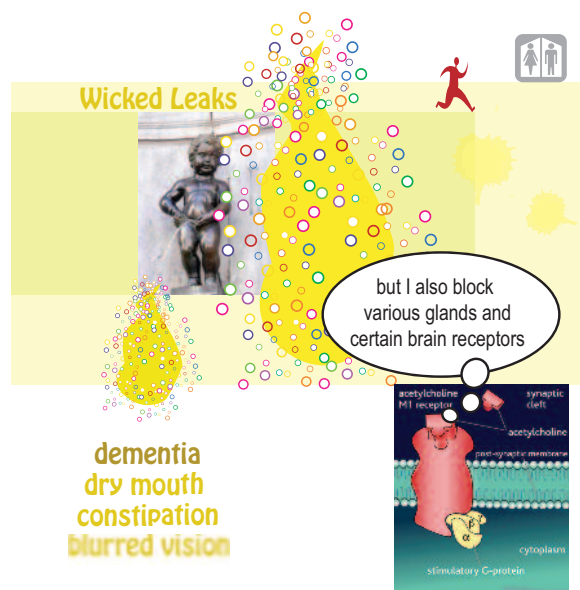
OAB refers to symptoms of urinary urgency, with or without incontinence or increased micturition frequency.^{3,4} This definition, standardized in 2002, shifted the emphasis from incontinence to urgency (the sudden strong urge to urinate) and widened the population to which these drugs were marketed. An independent population-based study in Finland (n=3727; age 18-79) reported an age-standardized OAB prevalence of 9.3% of women and 6.5% of men. However, if only those with incontinence are included, the prevalence drops to 2.4% of women and 0.7% of men.⁵

Treatment goals are to reduce distressing symptoms and improve quality of life. Reduction of incontinence is a key aim as it can affect quality of life more than urgency or frequency.⁶ Non-drug treatments should be tried first as patients may benefit from lifestyle changes or bladder training, without any adverse effect.^{2,7-9}

Antimuscarinics competitively block muscarinic cholinergic (acetylcholine) receptors. No drug is entirely selective for the muscarinic receptor types in the bladder, which are also distributed elsewhere in the body. All drugs exert dose-limiting anticholinergic adverse effects at these and other muscarinic receptor types. Drugs in this class can be broadly divided into short-acting, immediate-release (IR) and longer-acting or extended-release (ER) formulations.

Antimuscarinic Drug Class Review

We conducted a systematic review of direct comparator randomized controlled trials (RCTs) of antimuscarinic drugs in OAB, using Cochrane review methods. For infrequent harms, including cognitive effects in the elderly, we also reviewed RCTs in people without OAB, placebo-controlled RCTs, and non-randomized



studies. Outcomes were considered in a hierarchy based on importance to the patient: mortality, serious adverse events including cognitive impairment and urinary retention, quality of life, patient-reported improvement, withdrawals due to adverse effects, urgency incontinence, nocturia, and anticholinergic effects such as dry mouth, constipation or blurred vision.

Results: We identified two recent systematic reviews^{6,10} and 35 direct, active comparator RCTs in patients with OAB, mostly of ≤ 12 weeks duration. Most (22 RCTs) compared oxybutynin IR with other formulations of oxybutynin, tolterodine (IR or ER), darifenacin, solifenacin or trospium IR.

Efficacy differences were small and of doubtful clinical relevance. For example, condition-specific quality of life did not differ or differences were below the threshold for clinical relevance, and incontinence episodes did not differ, or differed by 0.2-0.6 episodes/day. Differences between drugs in pharmacokinetics, metabolism, drug-drug interactions, bladder selectivity, and propensity to cross the blood brain barrier were not reflected in clinically meaningful differences.

Adverse event reporting was often inadequate and trials were under-powered to analyse serious adverse events. In general, ER formulations led to less dry mouth than IR, and the highest observed rates were with oxybutynin IR. However, many trials used higher doses of oxybutynin IR than of comparators.

The trials shared many methodological shortcomings, including non-equivalent dose comparisons, poor harms ascertainment, selective outcome



reporting, poor methods reporting, and publication bias. Reported outcomes often failed to reflect the full patient experience.

Are 3 recently approved drugs for OAB better than older drugs?

Fesoterodine fumarate (Toviaz®)

Fesoterodine is closely related to tolterodine as it is hydrolyzed after absorption to tolterodine's active metabolite.¹¹ Three head-to-head RCTs compared fesoterodine with tolterodine ER.¹²⁻¹⁴ In one trial, fesoterodine 4 mg/day (n=272) and tolterodine ER 4 mg/day (n=290) did not differ.¹² In the three trials comparing fesoterodine 8 mg/day (n=1927) with tolterodine ER 4 mg/day (n=1947), 7% more patients on fesoterodine reported improvement or 'cure' on a 3-day bladder diary. Patients experienced ~ 1 fewer urgency incontinence episode per 4 days, 1 fewer urgency episode per 3 days, and 1 fewer nocturia episode per 11 days. These modest differences failed to outweigh the increased harm: 10% more patients on fesoterodine had adverse events, 2% more withdrew due to adverse effects and 1% more had serious adverse events. This is consistent with a stronger anticholinergic effect from fesoterodine 8 mg/day vs. tolterodine ER 4 mg/day (e.g., non-equivalent doses).

Oxybutynin chloride gel (Gelnique®)

Topical oxybutynin formulations avoid first pass metabolism in the intestine and liver and reduce peak plasma concentrations of oxybutynin and its active metabolite N-desethyloxybutynin, hypothesized to be associated with dry mouth.¹⁵ However, there are no comparative trials of benefits or harm of oxybutynin gel vs. alternatives in patients with OAB. As with other transdermal formulations, the gel's adverse effects include application site reactions.¹⁶

Mirabegron (Myrbetriq™)

Mirabegron is a recently approved, relatively selective β_3 -adrenoceptor agonist.¹⁷ Stimulation of the β_3 -adrenoceptor relaxes the bladder smooth muscle during the storage phase, increasing bladder capacity.¹⁷ Dose-dependent increases in blood pressure, heart rate and QT prolongation with higher doses led to a recommended usual dose of 25 mg/day in Canada.¹⁸ Effectiveness vs. placebo is similar to antimuscarinic drugs.¹⁸

References

1. Therapeutics Initiative. *Drugs for overactive bladder symptoms*. Therapeutics Letter Sept-Dec 2005; 57:1-2.
2. Therapeutics Initiative. *Is newer better? New drugs for treatment of overactive bladder*. Therapeutics Letter Sept-Oct 2007; 66:1-2.
3. Abrams P, Cardozo L, Fall M et al. *The standardization of terminology of lower urinary tract function: report of the Standardization Sub-committee of the International Continence Society*. *Neurourol Urodyn* 2002; 21(2):167-178.
4. Haylen BT, de Ridder D, Freeman RM et al. *An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction*. *Neurourol Urodyn* 2004; 29(1):4-20.

Five RCTs comparing mirabegron (mostly 50 mg/day) with solifenacin or tolterodine ER showed no significant differences.¹⁹⁻²⁴ In one RCT, tolterodine ER reduced incontinence slightly more than mirabegron.^{18,25} In another RCT, mirabegron did slightly worse than solifenacin (failure to demonstrate 'non-inferiority').²⁶

Rates of serious adverse events, total adverse events, and withdrawals due to adverse events were similar for mirabegron and tolterodine or solifenacin.¹⁸ Mirabegron led to less dry mouth but not to fewer adverse events in total.

Antimuscarinic drugs and cognition

Most direct comparator RCTs did not actively assess cognition and were under-powered for infrequent serious cognitive adverse events; one poor-quality RCT showed no difference in cognition between oxybutynin IR and oxybutynin ER.²⁷

An additional 15 RCTs assessed cognitive effects, mainly in healthy volunteers and/or vs. placebo. Assessed outcomes included recall on computerized cognitive tests and Mini Mental Status Evaluation. None of the RCTs allowed a conclusion of different cognitive effects with any specific antimuscarinic vs. another. No RCT assessed cognition with chronic use of antimuscarinic drugs.

A recently published, population-based cohort study in people \geq age 65 (n=3434, mean follow-up 7.8 years) assessed risk of new onset dementia following long-term cumulative exposure to anticholinergic drugs (10% OAB drugs).²⁸ Exposure equivalent to oxybutynin 5 mg daily for >3 years was associated with an increased risk of dementia compared with no exposure: adjusted hazard ratio (HR) 1.54 (95% CI 1.21 to 1.96). These findings are consistent with two shorter-term cohort studies^{29,30} and a recent systematic review.³¹

Conclusions

- All drugs for overactive bladder have limited short-term potential benefit and appreciable risk of adverse effects.
- There is insufficient evidence that benefits of long-term treatment outweigh harm for any overactive bladder drug.
- Claims of superiority for any antimuscarinic drug (including fesoterodine and oxybutynin chloride gel) over the others are **not** warranted due to methodological shortcomings of available RCTs.
- Mirabegron is a poor alternative due to its lack of an efficacy advantage and cardiac risks.
- **Recent observational studies suggest that all long-term anticholinergic drugs increase risk of dementia.**

5. Tikkinen KA, Tammela TL, Rissanen A et al. *Is the prevalence of overactive bladder overestimated? A population-based study in Finland*. *PLOS ONE* 2(2) 2007; e195. doi:10.1371/journal.pone.0000195.
6. Shamlivan T, Wyman J, Kane RL. *Nonsurgical Treatments for Urinary Incontinence in Adult Women: Diagnosis and Comparative Effectiveness*. Comparative Effectiveness Review No. 36. (Prepared by the University of Minnesota Evidence-based Practice Center under Contract No. HHS 290-2007-10064-1.) AHRQ Publication No. 11(12)-EHC074- EF. Rockville, MD. Agency for Healthcare Research and Quality. April 2012

For a complete list of references go to: www.ti.ubc.ca/letter93

Additional references for Therapeutics Letter 93

References

- Bettez M, Tu le M, Carlson K, Corcos J et al. 2012 Update: *Guidelines for adult urinary incontinence collaborative consensus document for the Canadian Urological Association*. Can Urol Assoc J 2012; 6(5):354-363.
- Gormley EA, Lightner DJ, Burgio KL et al. *Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline 2014*. www.auanet.org/common/pdf/education/clinical-guidance/Overactive-Bladder.pdf
- Rai BP, Cody JD, Alhasso A, Stewart L. *Anticholinergic drugs versus non-drug active therapies for non-neurogenic overactive bladder syndrome in adults*. Cochrane Database of Systematic Reviews 2012, Issue 12. Art. No.: CD003193. DOI: 10.1002/14651858.CD003193.pub4.
- Madhuvrata P, Cody JD, Ellis G et al. *Which anticholinergic drug for overactive bladder symptoms in adults*. Cochrane Database of Systematic Reviews 2012, Issue 1. Art. No.: CD005429. DOI: 10.1002/14651858.CD005429.pub2.
- Pfizer Canada Inc. *Fesoterodine fumarate (Toviaz™) Extended-release tablets 4 mg, 8 mg, Product Monograph*. Date of revision: February 12, 2015. Available at: <http://webprod5.hc-sc.gc.ca/dpd-bdpp/info.do?code=86587&lang=eng>. Last accessed April 6, 2015.
- Chapple C, van Kerrebroeck P, Tubaro A et al. *Clinical efficacy, safety and tolerability of once-daily fesoterodine in subjects with overactive bladder*. [Erratum appears in Eur Urol. 2008 Jun;53(6):1319]. Eur Urol 2007; 52(4):1204-1212.
- Herschorn S, Swift S, Guan Z et al. *Comparison of fesoterodine and tolterodine extended release for the treatment of overactive bladder: a head-to-head placebo-controlled trial*. BJU Int 2010; 105(1):58-66.
- Kaplan SA, Schneider T, Foote JE et al. *Superior efficacy of fesoterodine over tolterodine extended release with rapid onset: a prospective, head-to-head, placebo-controlled trial*. BJU Int 2010; 107(9):1432-1440.
- Actavis Specialty Pharmaceuticals Co. *Oxybutynin Gel (Gelnique®) 100 mg oxybutynin chloride per gram of topical gel, Product Monograph*. Date of preparation: April 22, 2015. Available at: <http://webprod5.hc-sc.gc.ca/dpd-bdpp/info.do?code=85101&lang=eng>. Last accessed April 6, 2015.
- US Food and Drug Administration (FDA) Center for Drug Evaluation and Research. Application number 22-204. *Gelnique (oxybutynin chloride) 10% gel*. Summary Review. Approval date 1/27/2009. Available at: www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022204s000SumR.pdf. Last accessed April 6, 2015.
- Astellas Canada Pharma Inc. *Mirabegron (Myrbetriq™) Extended-release tablets 25 mg and 50 mg, Product Monograph*. Date of Preparation March 4, 2013. Available at: <http://webprod5.hc-sc.gc.ca/dpd-bdpp/info.do?code=88770&lang=eng>. Last accessed April 6, 2015.
- Common Drug Review. *CDEC Final Recommendation: Mirabegron (Myrbetriq – Astellas Pharma Canada Inc); Indication: overactive bladder*. Nov 12, 2014. Available at: https://www.cadth.ca/sites/default/files/cdr/complete/cdr_complete_SR0363_Myrbetriq_nov14_2014.pdf. Last accessed April 6, 2015.
- Chapple CR, Dvorak V, Radziszewski P et al. *Dragon Investigator Group. A phase II dose-ranging study of mirabegron in patients with overactive bladder*. Int Urogynecol J Pelvic Floor Dysfunct 2013; 24(9):1447-1458.
- Khullar V, Amarenco G, Angulo J et al. *Efficacy and tolerability of mirabegron, a β_3 -adrenoceptor agonist, in patients with overactive bladder: results from a randomized European-Australian phase 3 trial*. Eur Urol 2013; 63(2):283-295.
- Kuo HC, Lee KS, Na Y et al. *Results of a randomized, double-blind, parallel-group, placebo- and active-controlled, multicenter study of mirabegron, a β_3 -adrenoceptor agonist, in patients with overactive bladder in Asia*. NeuroUrol Urodyn 2014; DOI 10.1002/nau.22645.
- Yamaguchi O, Marui E, Kakizaki H et al. *Phase III, randomized, double-blind, placebo-controlled study of the β_3 -adrenoceptor agonist mirabegron, 50 mg once daily, in Japanese patients with overactive bladder*. BJU Int 2014; 113(6):951-960.
- Abrams P, Kelleher C, Staskin D et al. *Combination treatment with mirabegron and solifenacin in patients with overactive bladder: efficacy and safety result from a randomized, double-blind, dose-ranging, phase 2 study (Symphony)*. Eur Urol 2015; 67(3):577-588.
- Edwards SJ, Karner C, Trevor N et al. *Mirabegron for the treatment of symptoms associated with overactive bladder*. BMJ-TAG, London, 2013. Available at: <https://www.nice.org.uk/guidance/ta290/documents/overactive-bladder-mirabegron-evidence-review-group-report2>. [Erratum: http://www.nets.nihr.ac.uk/_data/assets/pdf_file/0007/82618/ERGErr-11-138-01.pdf] Last accessed April 6, 2015.
- Chapple CR, Kaplan SA, Mitcheson D et al. *Randomized double-blind, active-controlled phase 3 study to assess 12-month safety and efficacy of mirabegron, a β_3 -adrenoceptor agonist, in overactive bladder*. Eur Urol 2013; 63(2):296-305.
- Astellas Pharma Europe Inc. *A double-blind, randomized, parallel group, multi-centre study to evaluate the efficacy and safety of mirabegron compared to solifenacin in subjects with overactive bladder (OAB) treated with antimuscarinics and dissatisfied due to lack of efficacy. Synopsis*. Available at: <http://www.clinicaltrials.jp/user/display/file/178-EC-001%20synopsis.pdf?fileId=1045>. Last accessed April 6, 2015.
- Minassian VA, Ross S, Sumabat O et al. *Randomized trial of oxybutynin extended versus immediate release for women ages 65 and older with overactive bladder: lessons learned from conducting a trial*. J Obstet Gynecol Can 2007; 29(9):726-732.
- Gray SL, Anderson ML, Dublin S et al. *Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study*. JAMA Intern Med 2015; 175(3): 401-407. DOI:10.1001/jamainternmed.2014.7663.
- Carriere I, Fourrier-Reglat A, Dartigues JF et al. *Drugs with anticholinergic properties, cognitive decline, and dementia in an elderly general population: the 3-city study*. Arch Intern Med 2009; 169(14):1317-1324.
- Jessen F, Kaduszkiewicz H, Daerr M et al. *Anticholinergic drug use and risk for dementia: target for dementia prevention*. Eur Arch Psychiatry Clin Neurosci 2010; 260 Suppl 2: S111-S115.
- Ruxton K, Woodman RJ, Mangoni A. *Drugs with anticholinergic effects and cognitive impairment, falls and all-cause mortality in older adults: a systematic review and meta-analysis*. Br J Clin Pharmacol 2015; DOI: 10.1111/bcp.12617.