

Anticholinergics for Overactive Bladder

Evidence, Clinical Issues and Comparisons

March 2008



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Recent Guidelines:

- Canadian Urological¹:
Can J Urol. 2006;13(3):3127-38
- NICE (UK) 2006²:
www.nice.org.uk/nicemedia/pdf/CG40fullguideline.pdf

Systematic Reviews:

- Cochrane: Hay-Smith J et al. Which anticholinergics drug for overactive bladder symptoms in adults. *Cochrane Systematic Reviews* 2005, Issue 3.³
- Oregon 2005⁴:
www.ohsu.edu/drugeffectiveness/reports/documents/OAB%20Final%20Report%20Update%203.pdf
- CEDAC (CDR) Canada,⁵
Darifenacin 2006⁵, Solifenacin 2007⁶, Trospium 2006⁷ www.cadth.ca

Review Articles:

- Ouslander. *NEJM* 2004;350:786-99⁸

Patient Resource:

- www.continence-fdn.ca

Highlights:

- 1) When initiating oxybutynin, start at 2.5mg and titrate up as needed and tolerated. PRN dosing as opposed to round-the-clock dosing is useful in some.
- 2) Long-acting oxybutynin **Ditropan XL**, **Uromax** and tolterodine **Detrol LA** are more convenient and somewhat better tolerated but cost more. {**Uromax** 10mg/day \$52 may offer cost advantage for long-acting formulation.}
- 3) All anticholinergics can worsen cognitive impairment in the elderly and those with dementia.
- 4) Theoretical advantages of new anticholinergics (darifenacin, solifenacin and trospium) have not yet translated into proven clinical benefits.

RxFiles UI Chart: http://www.rxfiles.ca/chartUI/utaen_trospium.pdf

Overactive Bladder – Background

- Overactive bladder (OAB) is also known as urge incontinence and occurs when there is an inability to delay voiding when an urge is perceived.
- OAB is differentiated from stress urinary incontinence (SUI) which is associated with a loss of urine secondary to intra-abdominal pressure such as occurs with coughing, sneezing and exercise.⁹
- Anticholinergics (ACs) are useful drugs for treating OAB, however their use is limited by the side effects of dry mouth and constipation.

Are non-drug treatment options effective?

- Bladder training (a gradual time lengthening between voids) or urge suppression may be useful in OAB, especially in addition to ACs.¹⁰
- Pelvic floor muscle training (PFMT)/**Kegels**, which is 1st line in SUI is less useful in OAB.^{11,12}
- { Other (e.g. ↓ caffeine, ↓ smoking; pessaries if prolapse/SUI) see chart }

Do any ACs cause less dry mouth?

- **Extended release formulations** of oxybutynin or tolterodine reduce risk of dry mouth versus regular formulations (NNT ≥14).⁴
- **Tolterodine** may cause less dry mouth than oxybutynin. {e.g. tolterodine 2mg BID caused less dry mouth than oxybutynin 5mg BID (NNT=4)}⁴.
- Options for relief of dry mouth include trying the oxybutynin patch formulation **OXYTROL**¹³ and non-drug options such as over-the-counter **saliva substitutes** (e.g. **Oral Balance Gel**). See also chart.

Considerations for choosing and using anticholinergic drugs in OAB?

- No ACs are more effective than oxybutynin^{3,4}
- Oxybutynin immediate release (IR) **DITROPAN** is the lowest cost AC & often suitable for initial therapy. **HS** dosing is suitable if night time is primary concern. It may also be useful “PRN” for those who only desire coverage for daily outings.
- Some patients will benefit from alternate ACs such as long acting tolterodine **DETROL LA**, which in some cases may be better tolerated or offer a more convenient dosing schedule.^{1,2,3,4,8}
- ACs may be started at low doses and titrated up to minimize side effects and identify lowest effective dose. Sample **low starting doses** are as follows:

- ♦ oxybutynin **DITROPAN** 2.5mg po BID-TID \$14-16
- ♦ oxybutynin XL **DITROPAN XL** 5mg po daily \$84 ✕ ⊗
- ♦ tolterodine LA **DETROL LA** 2mg po daily \$74 ✕ ⊗

- Special caution should be used for the elderly who are especially sensitive to side effects from ACs. Some with dementia or cognitive impairment may not tolerate ACs at all. If using an AC in the elderly, start at the lowest dose, titrate up and reassess for effectiveness and adverse effects. Remember that many drugs contribute to the total **anticholinergic load** (e.g. antidepressants, antipsychotics).¹⁴
- ACs should not be used with acetylcholinesterase inhibitors (e.g. **ARICEPT**, **REMINYL**, **EXELON**) given their opposing mechanisms.²³

Oxybutynin (Oxy) vs Tolterodine (Tol)

- A Cochrane systematic review found³:
 - ♦ no statistically significant differences for patient perceived improvement, leakage episodes or voids in 24hrs
 - ♦ less dry mouth and withdrawal due to adverse events with tolterodine
- The OPERA trial compared **Oxy ER 10mg daily** vs **Tolt ER 4mg daily** for 12 weeks in females with severe symptoms.¹⁵ Oxy ER was somewhat more effective (no urinary incontinence 23% vs 16.8%; NNT=16) but also caused more dry mouth (Any dry mouth: 29.7% vs 22.3%, NNH=13; Mod-severe dry mouth: 7.4 vs 5.0%, NS).

Newer anticholinergics

- Three new AC drugs (solifenacin, darifenacin and trospium) have been recently marketed. These offer minimal therapeutic advantage over long-acting forms of oxybutynin and tolterodine based on limited trials; however select patients may benefit.
- Theoretically these drugs may have more specificity for bladder M3 receptors and less penetration of the blood brain barrier. Some preliminary data has been favourable; however clinically important advantages have not yet been conclusively demonstrated.^{3,4,5,6,7,16,17}

Drug	Systematic Review Considerations
Solifenacin VESICARE 5-10mg po daily \$64	♦ Sol vs Tolt ^{3 RCTs} ; 4-12 weeks (18,19,20) ♦ ↓ incontinence episodes (0.59/day) ^{1 RCT} , ↓ urgency episodes (0.43-1.02/day) ^{2 RCTs} clinical significance uncertain ♦ ↑ constipation in all trials, (overall AEP ^{DC} similar or ↑) ♦ CDR: suggests not for formulary listing ⁶
Darifenacin ENABLEX 7.5mg po daily \$64	♦ Dar vs Oxy ^{2 RCTs} ; Dar vs Tolt ^{1 RCT} (21,22) ♦ no difference in efficacy; possible ↓ CNS SEs ♦ ↑ constipation vs Tolt & Oxy ^{IR} ; ↓ dry mouth vs Oxy ^{IR} ♦ CDR: suggests not for formulary listing; lack of CNS data in elderly where needed most ⁵
Trospium TROSEC 20mg po BID \$57 (or 20mg hs for night)	♦ Tro vs Oxy ^{3 RCTs} ; Tro vs Tolt ^{1 RCT} ♦ equal efficacy to Oxy ♦ ↓ dry mouth vs Oxy but not Tolt; (↑ constipation) ♦ CDR: suggests listing as per tolterodine for those who may not tolerate oxybutynin IR. ⁷

CDR=Common Drug Review (Canada); CNS=central nervous system
NNT=number needed to treat to benefit one; NNH=number needed to treat to cause harm one; Oxy=oxybutynin; RCT=randomized controlled trial;
Sol=solifenacin; Tolt=tolterodine; Tro=trospium

References – RxFiles Newsletter

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Acknowledgements: Contributors & Reviewers: Dr. A. Epp (SHR Obs/Gyne), Dr. C. Jabs (ROHR Obs/Gyne), Dr. S. Gonor (SHR-Urol), Dr. L. Rudachak (SHR-Rehab), Dr. R. Li Pi Shan (SHR-Rehab), Dr. J. Yelland (Parkridge LTC), S. Knezacek (Pharmacist, Parkridge LTC), Juliet Sarjeant (SHR-Physio), Eliza Meggs (RN, NCA, Nurse Continence Advisor; Saskatoon), Ann Burton (SHR-RN-Specialist, Parkridge Centre) & the RxFiles Advisory Committee.

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