A systematic review and meta-analysis of randomized controlled trials with antimuscarinic drugs for overactive bladder

CRD summary
This review concluded that extended release anticholinergic formulations were preferred to immediate release. Dose escalation may improve the efficacy of immediate release formulations, but lead to increased adverse events. More studies were needed to determine appropriate drug therapy for first-, second- and third-line treatments. This review had some important methodological limitations and the authors conclusions may not be reliable.

Authors' objectives
To evaluate efficacy and safety of different doses, formulations and route of administration of the available anticholinergic drugs.

Searching
MEDLINE, EMBASE and Web of Science were searched to August 2007. Food and Drug Administration (FDA) website was also searched. Significant studies cited in reference lists of selected papers were retrieved. Search terms used were reported.

Study selection
Randomised controlled trials that compared different doses, formulations and routes of administration of anticholinergic drugs were eligible for inclusion. Studies were required to include efficacy data and complications. Efficacy outcomes included changes in: daytime micturitions in 24 hours; night time micturitions in 24 hours; micturitions in 24 hours; volume voided per micturitions, urgency; episodes in 24 hours; urge urinary incontinence (UUI) episodes in 24 hours; incontinence episodes in 24 hours; pads used per 24 hours; and quality of life scores. Safety outcomes included: overall rates of adverse events; withdrawals due to adverse events; dry mouth rate; moderate-to-severe or severe dry mouth rate; constipation; acute urinary retention; vision abnormality; and headache. Studies that evaluated lower urinary tract storage symptoms in patients with bladder-outlet obstructions, neurogenic bladders, phase I studies and post-hoc analyses of RCTs were excluded.

Included studies evaluated different doses and formulations of oxybutynin, tolterodine, propiverine, trosapur, darifenacin, solifenacin and fesoterodine; most had a follow-up time between two and 12 weeks.

Three reviewers independently assessed eligibility.

Assessment of study quality
Study quality was assessed the Jadad scale (five-item scale to assess adequacy of randomisation, participant blinding, dropouts and withdrawals to a maximum score of 5).

The authors did not state how many reviewers performed the validity assessment.

Data extraction
Numbers of events in each group were used to derive relative risks (RR) and 95% confidence intervals (CI) for dichotomous outcomes. Continuous variables were reported as means (standard deviation).

Two reviewers independently extracted data from each study. Authors of included articles were contacted for missing or incomplete data.

Methods of synthesis
For dichotomous outcomes, the pooled relative risks and corresponding 95% CIs were calculated using a fixed-effect model where statistical heterogeneity was not present and a random-effects model where statistical heterogeneity was present. Weighted mean differences (WMD) and standard deviations were calculated for continuous outcomes. Heterogeneity was assessed using the $X^2$ test. Publication bias was assessed using funnel plots.

Most included studies did not present data in an appropriate format to allow meta-analyses; these data for individual studies were reported in tables.

Results of the review
Fifty RCTs and three pooled analyses were included in the review. Most included trials had a Jadad score of 3 or more.

Different doses and formulations of the same drug:

**Efficacy:** There were no significant differences between tolterodine immediate release 1mg and tolterodine immediate release 2mg for micturitions per 24 hours, volume voided per micturition and urge urinary incontinence episodes per 24 hours. With regard to adverse events, only dry mouth was significantly more frequent in those patients taking tolterodine immediate release 2mg (OR 0.52, 95% CI 1.037 to 0.72, p<0.0001).

Immediate release compared to extended release formulations: Oxybutynin and tolterodine were evaluated in immediate release and extended release formulations. Patients randomised to oxybutynin immediate release were significantly more likely to experience the occurrence of any adverse event (OR 1.90, 95% CI 1.03 to 3.51, p=0.04; three trials), dry mouth (OR 1.45, 95% CI 1.02 to 2.05, p=0.04; five trials). Withdrawals due to adverse events, headache, constipation and vision abnormality were similar for both formulations. Patients randomised to tolterodine extended release formulation experienced a lower number of micturitions per 24 hours (WMD 0.34, 95% CI 0.02 to 0.66, p=0.03; two trials) and a higher volume voided per micturition (WMD -9.12, 95% CI -14.13 to -4.12, p=0.0004; two trials), but a similar number of incontinence episodes and pad use per day as patients randomised to tolterodine immediate release formulation. Tolterodine extended release formulations had a significantly lower rate of dry mouth (OR 1.39, 95% CI 1.13 to 1.71, p=0.002; two trials), but a higher rate of headache (OR 0.53, 95% CI 0.34 to 0.81, p=0.004; two trials). Withdrawals due to adverse events and constipation were similar in both groups. Two trials compared propiverine hydrochloride immediate release and extended release formulations and showed similar rates of adverse events, dry mouth, constipation, headache and vision abnormality.

Comparisons of different drugs:

There was no difference in efficacy between oxybutynin 5mg and tolterodine 2mg. Adverse events were significantly more common in patients randomised to oxybutynin. Compared to most other study drugs oxybutynin was similarly effective, but tended to show higher rates of adverse effects.

One study showed that tolterodine was less efficacious compared to solifenacin; compared to most other study drugs, tolterodine was similarly effective and showed similar rates of adverse effects.

Different routes of administration:

Two trials reported outcomes for different routes of administration. Patients randomised to oral treatment were more likely to experience dry mouth and constipation. Patients randomised to transdermal administration were more likely to experience localised application side effects and withdrawal due to adverse events.

There was no evidence of publication bias (data not reported).

Authors' conclusions
Many of the available RCTs were of good methodological quality. Extended release formulations should be preferred to the immediate release formulations due to the more favorable profile of efficacy and adverse events. For immediate release formulations, dose escalation might yield some improvements in efficacy at the cost of a significant increase in the rate of adverse events. More clinical studies were needed to determine which of the available drugs should be used...
as first-, second- and third-line treatments.

CRD commentary
This review addressed a clear question in terms of inclusion criteria, study design and outcomes of interest. But, the authors did not appear to adhere to their own inclusion criteria as they included meta-analyses. A number of relevant electronic databases were searched and search terms were reported. It did not appear that attempts were made to identify unpublished studies. Language restrictions were unclear. Appropriate steps were taken to ensure review error and bias were minimised in the selection of studies and extraction of data; it was unclear whether similar steps were taken for the assessment of validity. Although the quality of included studies was assessed, the authors did not appear to consider validity in interpreting results as RCTs were included regardless of their Jadad score. Results were pooled appropriately using meta-analysis. Heterogeneity was assessed, but results were reported in forest plots for adverse events only; no results were reported for efficacy. Overall this review had some important methodological limitations. It is unclear whether the author's conclusions are reliable.

Implications of the review for practice and research

Practice: The authors stated several treatment options for first- and second-line treatments, but pointed out that clear evidence-based decisions were limited because further evaluation was needed and further RCTs were ongoing. The implications for practice were discussed in the review.

Research: The authors stated that more clinical studies were needed to determine which of the available drugs should be used as first-, second- and third-line treatments.

Funding
None. Several authors had previously been consultants or investigators for manufacturers.

Bibliographic details

PubMedID
18632201

DOI
10.1016/j.eururo.2008.06.080

Original Paper URL
http://www.europeanurology.com/article/S0302-2838(08)00802-6/abstract

Indexing Status
Subject indexing assigned by NLM

MeSH
Benzhydryl Compounds /therapeutic use; Cresols /therapeutic use; Humans; Mandelic Acids /therapeutic use; Muscarinic Antagonists /therapeutic use; Phenylpropanolamine /therapeutic use; Randomized Controlled Trials as Topic; Tolterodine Tartrate; Urinary Bladder, Overactive /drug therapy

AccessionNumber
12009100807

Date bibliographic record published
31/03/2009

Date abstract record published
17/02/2010
Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.