The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and meta-analysis

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CRD summary
This review concluded that antimuscarinics were efficacious, safe, well tolerated and improved health-related quality of life. The authors’ conclusion about safety and efficacy seemed reasonable and likely to be reliable, although it was unclear whether this was generalisable to all relevant populations. It was not possible to assess the reliability of their conclusions on health-related quality of life.

Authors’ objectives
To assess the efficacy of antimuscarinic treatments for overactive bladder and review the evidence on their tolerability, safety and impact on health-related quality of life.

Searching
MEDLINE, EMBASE, CINAHL and Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to October 2007 without language restrictions; search terms were not provided. Abstract books from several conferences were searched. Bibliographies of included papers and relevant reviews were scanned.

Study selection
Randomised controlled trials (RCTs) of UK-licensed oral and transdermal system patch antimuscarinics were eligible for inclusion provided duration was at least two weeks. Eligible comparators were placebo, another licensed antimuscarinic or a different formulation or dose of the same drug. Therapy that combined an antimuscarinic with non-pharmacological treatment was included provided the control group received the same non-pharmacological treatment. Eligible participants were adults with idiopathic overactive bladder, detrusor overactivity and urinary incontinence. Studies where more than 50% of patients had bladder outlet obstruction, benign prostatic hyperplasia or obstruction, benign prostatic enlargement or previous surgery for lower urinary tract disease were excluded. Studies of stress urinary incontinence and stress-predominant mixed urinary incontinence were excluded.

The included studies assessed darifenacin, fesoterodine, oxybutynin, propiverine, solifenacin, tolterodine and trospium. Doses of individual drugs were reported. Formulations were administered through immediate release, extended release and transdermal system patch. There were 15 different drug, dose and formulation categories for the efficacy analysis and 18 for tolerability. More than half of the trials had a placebo arm. Mean number of incontinence episodes per day at baseline ranged from 0.7 to 6.1. Mean age of participants ranged from 40 to 75 years across the studies (mean 58 years). Study duration ranged from two to 52 weeks.

Two reviewers independently screened studies for inclusion. Disagreements were resolved through discussion.

Assessment of study quality
The authors did not state that they formally assessed validity. Only RCTs that reported that patients and investigators were blinded to treatment allocation were considered in the efficacy analysis. Open label and blinded studies were included for the analysis of safety and tolerability.

Data extraction
Two reviewers independently extracted data. Discrepancies were resolved by a third reviewer. Data were extracted to calculate relative risks (RR) and 95% confidence intervals (CI) for dichotomous outcomes and mean difference (in change) and 95% CI for continuous outcomes.

Methods of synthesis
Studies were stratified by antimuscarinic treatment, then total daily dose and drug formulation (immediate release or extended release). Studies were pooled for each comparator (placebo or active comparator) and outcome using the
Mantel-Haenszel fixed-effect method. Where trials had more than two relevant arms, each paired comparison was treated as though it was from a separate trial.

Results of the review
Eighty-three RCTs were included, 10 of which were cross-over trials. The number of participants in trials ranged from 30 to 1,593; 20 trials had fewer than 100 patients and five trials had over 1,000.

Return to continence: There was a statistically significant benefit with antimuscarinics compared to placebo for most of the drug categories, although these were all based on single trials (data were available for 10 of the 15 categories). Relative risk for return to continence at end of treatment ranged from 1.3 to 3.5. No data were available on fesoterodine at any dose. There were no statistically significant differences between different antimuscarinics or doses.

Number of incontinence episodes per day: There was a statistically significant benefit with antimuscarinics compared to placebo for most of the drug categories; the number of trials in each pooling ranged from one to seven (data were available for 10 of the 15 categories). Pooled mean change in number of incontinence episodes ranged from 0.4 to 1.1 per day. No data were available on trospium chloride. Based on a single study, fesoterodine 8mg was more effective than tolterodine extended release 4mg.

Other outcomes: There was a statistically significant benefit with antimuscarinics compared to placebo for all or most drug categories for number of micturations per day (pooled effect ranged from 0.5 to 1.3 episodes), number of urgency episodes per day (pooled effect ranged from 0.64 to 1.56 episodes), volume voided per micturation (pooled effect ranged from 13mL to 40mL) and proportion with improved bladder condition (range from 1.49 in one trial to 1.51 in another). There was some evidence of differences between individual drugs and/or doses for all outcomes except improvement in bladder condition.

Tolerability and safety: There was a statistically significant higher risk of withdrawal due to adverse events with oxybutynin (immediate release 15mg and immediate release 7.5mg to 10mg), propiverine (extended release 20mg) and solifenacin (10mg) compared to placebo. There was evidence of some difference between individual drugs and/or doses. Most treatments had a higher risk of any adverse events than placebo (pooled RR ranged from 1.00 to 2.00), but not serious adverse events. The most common adverse events were dry mouth and pruritus.

Quality of life data was to be reported in a separate paper.

Authors’ conclusions
Antimuscarinics were efficacious, safe and well tolerated treatments that improved health-related quality of life. Profiles of each drug and dosage differed and should be considered when making treatment choices.

CRD commentary
There was a clearly defined review question with explicit inclusion and exclusion criteria. Some attempts were made to locate unpublished studies, although there remained a risk of reports of negative findings being missing. Studies were selected and data extracted in duplicate, which minimised the risk of error and bias. Study quality was taken into consideration in the synthesis by only including blinded studies in the efficacy synthesis. This seemed a reasonable approach, although other potential sources of bias (such as loss to follow-up) were not explored. It was unclear how missing data were dealt with in the meta-analysis and whether dichotomous data in particular were extracted and analysed on an intention-to-treat basis. It was unclear how cross-over trials were dealt with in the analysis.

The decision to subgroup by drug, dose and formulation was justified by the authors and seemed a reasonable way to address potential heterogeneity. However, as a result there were only single studies available for most of the subgroups. Other potential sources of heterogeneity, in particular differences in patient populations, were not explored. Given the large number of outcomes considered and the large number of subgroups or categories, there was a strong possibility of generating spurious positive effects. As a result, the findings in relation to individual subgroups should be interpreted with some caution. The authors’ overall conclusion about safety and efficacy seemed reasonable and likely to be reliable, but it was unclear whether this was generalisable to all relevant populations. Although none of the treatments was associated with adverse effects, dry mouth and pruritus were more frequently reported in the treatment group. It was not possible to assess the reliability of their conclusions on health-related quality of life, as the results were not
reported.

Three of the authors were employees of Pfizer.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that further research was required on populations at increased risk for central nervous system adverse events and in treatment-naive patients.

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