The role of anticholinergics in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: a systematic review and meta-analysis

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CRD summary
The authors concluded that anticholinergics appear safe in men with lower urinary tract symptoms suggestive of benign prostatic hypertrophy, but more research is required to evaluate their efficacy. The authors’ cautious conclusions appear to reflect the evidence from a small number of studies, but the poor reporting of review methods means that the reliability of the conclusion is unclear.

Authors' objectives
To evaluate the safety and efficacy of anticholinergics in men with lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH).

Searching
MEDLINE, EMBASE and the Cochrane CENTRAL Register were searched from inception to February 2006; details of the search strategy were reported. In addition, the reference lists of relevant articles and conference proceedings (1997 to 2005) from four named societies were screened. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and observational studies were eligible for inclusion in the review. The mean duration of follow-up in studies used to assess adverse events was 12.2 weeks (range: 4 to 26).

Specific interventions included in the review
Studies that evaluated an anticholinergic drug were eligible for inclusion. Studies that evaluated terodiline, emepronium and antisotopine (all withdrawn) or parenterally administered anticholinergics drugs were excluded. The included studies evaluated anticholinergics (tolterodine, propiverine and flavoxate) with and without alpha-adrenoceptor antagonists or phytotherapeutic agents. Comparison groups were either alpha-blockers or placebo. Drug doses were reported.

Participants included in the review
Studies that included men aged over 18 years with documented evidence of BPH or bladder outlet obstruction (BOO) were eligible for inclusion. Studies of patients with neurogenic bladder, spinal cord injury, multiple sclerosis or cerebral infarction, patients using catheters, patients with previous reconstructive lower urinary tract or BOO surgery, or patients using alternative intervention action upon detruser were excluded. Most of the included studies defined BOO using urodynamic or clinical criteria; some used benign prostatic enlargement.

Outcomes assessed in the review
Inclusion criteria were not specified in terms of the interventions, but it was clear the review focused on the assessment of efficacy and safety. The review assessed maximal urinary flow rate, postvoid residual urine volume (PVR), volume at first contraction, maximum cystometric capacity, acute urinary retention, mean voided volume, quality of life (QoL) and adverse events.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The validity of the RCTs was assessed on the basis of method of randomisation, allocation concealment, blinding, baseline similarity of the treatment groups, similar treatment of groups, adequate reporting of attrition and intention-to-treat analysis. External validity was assessed using population and treatment characteristics. The validity of the
observational studies was assessed on the basis of study objective, definition of main outcomes, inclusion and exclusion criteria, patient characteristics and representativeness of sample. The authors did not state how the validity assessment was performed.

**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. For each study, mean values for reported outcome measures were presented for each treatment group, along with level of statistical significance of the treatment difference. The numbers of patients in each treatment group with the adverse event of interest were also presented for each study.

**Methods of synthesis**

**How were the studies combined?**
Studies were excluded from the analysis if they did not meet two or more quality criteria, the duration of follow-up was less than 1 month, or variances or errors were not reported. For RCTs meeting these criteria, pooled weighted mean differences (WMDs) with 95% confidence intervals (CIs) were calculated for efficacy outcomes of interest using an inverse-variance fixed-effect meta-analysis. For some outcomes the studies were combined in a narrative. Adverse event rates were calculated using data from RCTs and observational studies. Some analyses were repeated using a random-effects model.

**How were differences between studies investigated?**
Heterogeneity was not formally assessed. Forest plots were presented for some analyses.

**Results of the review**
Twenty studies (n=1,409) were included: 5 RCTs (n=703) and 15 case series (n=706).

The results of the systematic quality assessment were not reported.

**Effectiveness.**

None of the 5 RCTs reported a significant difference for maximal urinary flow rate. A pooled analysis of the 3 trials that compared anticholinergics combined with alpha-adrenoceptor antagonists to alpha-adrenoceptor antagonists alone found no significant difference between treatments (WMD 0.07 mL/second, 95% CI: -0.56, 0.71).

Compared with placebo, anticholinergics were associated with a significant increase in PVR (WMD 11.6 mL, 95% CI: 4.5, 18.6; 3 studies) and volume at first contraction (WMD 47.12 mL, 95% CI: 21.94, 72.30; 2 studies).

Two studies reported that anticholinergics were associated with a significant increase in maximal cystometric capacity. Only one of these studies was placebo-controlled.

Three of the 5 studies assessing mean voided volume reported that anticholinergics were associated with a significant increase in mean voided volume compared with control; the other 2 studies reported no significant difference between treatments.

Three studies assessed LUTS and reported no significant difference between anticholinergics and placebo. Only one of these studies was placebo-controlled.

One of the 3 studies assessing QoL reported a significant increase in QoL in patients receiving anticholinergics compared with control; another reported no significant difference between treatments and one reported no change in most patients taking anticholinergics.

**Adverse events** (11 studies, n=847).

The most commonly reported adverse event was dry mouth (15.9% with anticholinergics versus 3.7% with control). Most cases were mild; 2% (14 patients) withdrew due to dry mouth.
Acute urinary retention was uncommon and rates were similar between treatments (0.8% with anticholinergics versus 0.6% with control). Difficulty in micturition or a raised PVR was reported in 4.9% (24 patients) and resulted in the withdrawal of 14 patients. Other adverse events included gastrointestinal symptoms, dizziness and blurred vision. The authors stated that significant methodological flaws were found in 6 observational studies, so these were excluded from the review; a further three did not provide data on adverse events.

**Authors' conclusions**
Anticholinergics appear safe in men with LUTS suggestive of BPH, but more research is required to evaluate efficacy.

**CRD commentary**
The review addressed a clear question that was defined in terms of the participants, intervention and study design; inclusion criteria for the outcomes were not specifically defined. Several relevant sources were searched and attempts were made to minimise language and publication bias. The methods used to select studies, assess validity and extract the data were not described, so it is not known whether any efforts were made to reduce reviewer error and bias. Validity was assessed using specified criteria but the results of a systematic assessment were not fully reported for all studies, which makes it difficult to assess the quality of the data.

The authors did not explicitly define a priori which studies were to be included in the meta-analyses of efficacy, and it was not always clear why some studies were included in meta-analyses for some outcomes and not others. Not all studies used a placebo-control and this was not always highlighted in the reporting of the results. Forest plots allowed a visual inspection of heterogeneity although this was not assessed statistically. The analysis of adverse events was based on limited data (several studies did not report acute urinary retention or other urinary adverse events). The authors’ cautious conclusions appear to reflect the evidence from a small number of studies, but the lack of reporting of review methods means that the reliability of the conclusion is unclear.

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

**Practice:** The authors stated that before anticholinergic treatment is started, the PVR should be measured and patients should be warned about the risk of difficulty in micturition and advised to stop treatment if this occurs. Alpha-blockers should be continued if found to be beneficial.

**Research:** The authors stated the need for further studies evaluating anticholinergics for men with BPH with or without evidence of BOO or detrusor overactivity, and for men with high grades of BOO, and to determine at what level of PVR anticholinergic treatments are of benefit. Long-term follow-up may help to exclude the risk of acute urinary retention.

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