Received: 27 July 2018 | Revised: 7 September 2018 | Accepted: 21 October 2018
DOI: 10.1002/nau.23893



REVIEW ARTICLE

WILEY Neurourology Urodynamics ICS SUFU

# Which anticholinergic is best for people with overactive bladders? A network meta-analysis

**Peter Herbison**[1] | **Joanne E McKenzie**[2]

[1] Department of Preventive and Social Medicine, Dunedin School of Medicine, University of Otago, Otago, New Zealand

[2] School of Public Health and Preventive Medicine, Monash University, level 6, The Alfred Centre, Melbourne, Victoria, Australia

**Correspondence**
Peter Herbison, Department of Preventive and Social Medicine, Dunedin School of Medicine, University of Otago, 45 Domain Road Bannockburn 9384, New Zealand.
Email: peter.herbison@otago.ac.nz

**Funding information**
Health Research Council of New Zealand, Grant number: 12/256

**Aim:** To carry out a network meta-analysis of randomised controlled trials (RCTs) of anticholinergic drug treatment for people with overactive bladders.

**Methods:** Comprehensive searches for relevant RCTs were carried out starting with RCTs included in previous systematic reviews with the last search in February 2017. Searches included terms for the anticholinergic drugs tolterodine, oxybutynin, trospium, propiverine, solifenacin, darifenacin, imidafenacin, and fesoterodine. Data was extracted from the systematic reviews or reports of studies for cure or improvement, voids per 24 hr, leakage episodes per 24 hr and dry mouth. Data was analysed using frequentist network meta-analysis.

**Results:** 128 studies were found. There was no clearly best treatment for cure or improvement. The differences between treatments for voids and leakages were small and unlikely to be of clinical importance. Transdermally delivered oxybutynin was clearly the best treatment for dry mouth but was still worse than placebo.

**Conclusions:** All the anticholinergic drugs were better than placebo but apart from dry mouth were similar in effect. Transdermal oxybutynin caused less dry mouth than the other treatments, so may be worth considering as the first treatment.

**KEYWORDS**
anticholinergics, antimuscarinics, network meta-analysis, overactive bladder

## 1 | INTRODUCTION

Over Active Bladder (OAB) is defined as urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection (UTI) or other obvious pathology. It affects about 17% of the adult population, men and women equally.[1] In about half of the women and a third of the men, urine leaks before they can make it to a toilet.[1] Over active bladder greatly affects peoples' quality of life.[2]

Anticholinergic (antimuscarinic) drugs are the current mainstay of medical treatment. The effect of anticholinergics is modest, preventing only one leakage and one void every second day.[3] These drugs also have side effects, which occur because the drugs are not selective for the muscarinic receptors in the bladder, so also affect functioning of the saliva glands, the gut, and other smooth muscle. Further, most anticholinergics can easily cross the blood brain barrier potentially causing cognitive problems. The impact on the saliva glands appears to be the most problematic, resulting in dry mouth, which can be unpleasant. Many of the drugs have different formulations such as immediate release and extended release. The extended release is intended to reduce peak concentrations in the blood and thus reduce side effects.

John Heesakkers led the peer-review process as the Associate Editor responsible for the paper.

  

This combination of modest effectiveness and important side effects mean that many do not persist in taking these drugs.[4,5] However, to date, systematic reviews have only investigated the effects of the different drugs and different formulations treated as the same treatment,[3,6] and not the effects of different anticholinergic drugs and their formulations. Estimation of the latter may reveal useful differences between the drugs. We therefore undertook a network meta-analysis to compare and rank anticholinergic drugs and their formulations for the treatment of symptoms of overactive bladder.

## 2 | METHODS

### 2.1 | Search strategy

All randomized trials included in two Cochrane systematic reviews formed the initial set of trials. These reviews examined the effects of anticholinergics versus placebo[3] and comparisons of different anticholinergics.[6] The searches in these reviews were updated for this study. Search terms included the individual drug names, and the words anticholinergic and antimuscarinic. A typical search is given in Appendix 1. The last search was carried out in February 2017.

### 2.2 | Eligibility criteria

To be included a study had to be a parallel randomized trial comparing an anticholinergic drug with placebo or another anticholinergic drug. The included anticholinergic drugs were tolterodine, oxybutynin, trospium, propiverine, solifenacin, darifenacin, imidafenacin, and fesoterodine. Tolterodine was split into immediate release (IR) and extended release (ER) and oxybutynin was split into IR, ER and transdermal (either patch or gel). Trials of another treatment alone versus that treatment plus an anticholinergic were included since the effect of the anticholinergic drug could be estimated. Participants had to be adults with overactive bladders. There were no restrictions on the sex of the participants, the cause of the OAB (if reported) or language. Multi-arm studies were allowed.

### 2.3 | Outcomes

To be considered for inclusion in this study, the trials must have included at least one of the following outcomes: the number of leakage episodes; the number of voids per day; cure or improvement; and dry mouth. Leakages and voids were collected with a urinary diary. Some trials reported the number of leakages in all participants and sometimes only in those who were incontinent at baseline. Cure or improvement was measured variously across the trials, using measures such as dry on urinary diary, asking whether cured or improved, or asking whether they got benefit from treatment. We considered any of these measurement scales a measure of the domain "cure or improvement." Outcomes used were recorded at the end of the treatment period.

### 2.4 | Study selection and data extraction

Studies included in the Cochrane reviews were independently screened for inclusion by two authors of the review with disagreements resolved by a third author. The abstract for each retrieved publication that had not been previously screened for the two Cochrane reviews, was assessed for potential inclusion against the eligibility criteria by one author of this study. Full text of potentially eligible studies was retrieved and assessed for inclusion. This resulted in 38 additional studies

Data for trials included in the Cochrane reviews was extracted from those reviews, and checked against the published article. Data was extracted by one of the authors from the additional included trials using prepared forms. For some trials, summary statistics were read from graphs, which were printed as large as possible and then distances measured. In other trials, while summary statistics were not reported for individual arms, enough information was reported to allow the calculation of the difference between treatments and its standard error. If there were multiple arms with the same drug at different doses, we combined across arms, but only if the doses were those recommended for clinical use.

### 2.5 | Assessment of risk of bias in included trials

The risk of bias was taken from the Cochrane reviews were possible. For the additional 38 trials risk of bias assessment was carried out by one author, using the Cochrane Risk of Bias tool.[7] This tool rates the risk of bias as high, unclear or low for the six dimensions sequence generation, allocation concealment, blinding, withdrawals, selective outcome reporting and other risk of bias.

### 2.6 | Analysis

Pairwise comparisons of all treatments that were compared directly were carried out using random effects meta-analysis.[8] The odds ratio was used as the effect metric for the binary outcomes, and the mean difference for the continuous outcomes. We fitted a contrast-based network meta-analysis (NMA) model in a frequentist framework for each outcome.[9,10] These models provide differences between each of the treatments, combining direct and indirect evidence. Direct evidence is when two or more treatments are compared in RCTs. Indirect evidence of the difference between two

treatments is gained when each has a common comparator, for example, there is indirect evidence on the difference between treatment A and treatment C from trials comparing A and B and others comparing B and C. The NMA models were fitted using the suite of network packages in Stata v13.[10] These assumed that the between-trial heterogeneity variance of the treatment effects was the same for every treatment comparison. A ranking for the treatments was produced for each outcome.[11] There may be problems where the direct and indirect evidence gives different results, and this is called inconsistency. Models were run both with and without the consistency assumption,[12–14] to test for inconsistency. The network meta-analyses were rerun excluding the studies with participants who had bladder outlet obstruction or benign prostate hyperplasia (BOO/BPH).

## 3 | RESULTS

### 3.1 | Results of the search

The multiple searches resulted in 134 trials. Two of these trials included participants with spinal cord injuries, and three with neurological causes (such as multiple sclerosis). These five trials did not meet the eligibility criteria, and so were excluded from this study. One trial compared different doses of the same drug, so was excluded. One study was a dose ranging study with eight arms, four with placebo and different doses of solifenacin, and four with an alpha blocker and the same doses of solifenacin (van Kerrebroeck [included study 110]). Thus this trial provided two valid comparisons of placebo versus solifenacin so was treated as two trials. This resulted in 128 included trials with 58 335 participants (Included refs 1-128 in supplement). An arm with an oxybutynin eluting vaginal ring was included in the transdermal group.

Characteristics of the 128 included studies are given in Table 1. Twenty studies (16%) allowed doses to be increased or decreased during the trial. The most common length of treatment was 12 weeks (81/129, 63%). Twenty-one were shorter than 12 weeks and four were longer, including three at 1 year. Two studies continued until people were on their optimum dose so did not have a fixed length of treatment. Of the 16 trials in men with BOO/BPH, 4 did not use alpha blockers and the other 12 had alpha blockers in both arms.

**TABLE 1** Characteristics of the studies

| Characteristic | Number | Percent |
|---|---|---|
| Number of studies | 129 | |
| 2 Arm | 111 | 86 |
| 3 Arm | 18 | 14 |
| Treatments | | |
| Placebo | 99 | 77 |
| Oxybutynin IR | 25 | 19 |
| Oxybutynin ER | 11 | 9 |
| Oxybutynin transdermal | 7 | 5 |
| Tolterodine IR | 28 | 22 |
| Tolterodine ER | 22 | 17 |
| Solifenacin | 25 | 19 |
| Trospium | 11 | 9 |
| Propiverine | 14 | 11 |
| Fesoterodine | 17 | 13 |
| Darifenacin | 6 | 5 |
| Imidafenacin | 7 | 5 |
| Indication | | |
| OAB | 72 | 56 |
| UUI | 41 | 32 |
| BOO/BPH | 16 | 12 |
| Sex (excluding BOO/BPH) | 113 | |
| Female only | 18 | 16 |
| Male and Female | 95 | 84 |
| Type of dosage | | |
| Fixed | 109 | 84 |
| Titrated | 20 | 16 |
| Length of treatment | | |
| ≦4 weeks | 22 | 17 |
| 4-11 weeks | 20 | 15 |
| 12 weeks | 81 | 63 |
| >12 weeks | 3 | 2 |
| Withdrawals | 119 | |
| ≦10% | 49 | 41 |
| >10 to ≦20% | 56 | 47 |
| >20% | 14 | 12 |
| Conflicts of interest | | |
| Industry funding | 97 | 75 |
| Conflicts stated | 66 | 51 |
| No statement | 23 | 18 |
| Stated that no conflicts | 2 | 2 |

### 3.2 | Risk of bias

The risk of bias (RoB) assessment is illustrated in supplementary Figure S1. No study had a high RoB for either sequence generation or allocation concealment although for many trials the reporting did not allow a distinction between low and unclear RoB. Many studies simply reported that they were double blind, but this description is ambiguous and does not ensure a low RoB for performance or detection. All of the outcomes were patient reported. The only domain with a large proportion of high RoB was "other" as many of the studies were industry funded and Thirty-nine studies

(30%) included a urinary diary so should have been able to report the number of voids and leakages, but either didn't, or reported them in such a way that they could not be included in a meta-analysis (eg, no measure of variation).

### 3.3 | Cure or improvement

Cure or improvement was reported in 44 of the 128 trials (Supplementary Figure S2). All of the treatments except for imidafenacin were more effective than placebo (Table 2). Fesoterodine was more effective than transdermal oxybutynin and tolterodine ER, while transdermal oxybutynin was less effective than oxybutynin IR, as was tolterodine ER. Darifenacin was ranked the best treatment for this outcome with a 40.1% chance of being best, followed by tolterodine IR and oxybutynin ER both on 13.1% (Supplementary Table S1).

### 3.4 | Leakages episodes

The results for leakage episodes were available from 65 of the 128 studies (Supplementary Figure S3). None of the darifenacin trials reported this outcome in a usable way. All drugs, apart from oxybutynin ER and trospium, were more effective than placebo, and there were no statistically significant differences between the different drugs (Table 3). Further, all of the differences were small, with the largest difference equating to one fewer leakage episode every five or so days. Fesoterodine was ranked first among the treatments but with only a 17.2% probability of being first, followed by transdermal oxybutynin on 15.1%, imidafenacin on 14.1%, oxybutynin IR on 13.6% and tolterodine ER on 12.9% (Supplementary Table S1).

### 3.5 | Voids

Usable data was available for 68 trials for voids (Supplementary Figure S4). Apart from oxybutynin ER and darifenacin, all drugs were better than placebo (Table 4). Imidafenacin was more effective than all other drugs apart from transdermal oxybutinin, solifenacin and trospium. Again most differences were small, and apart from those with imidafenacin, were equivalent to at most one fewer void every 4 or 5 days. Imidafenacin was a clear first in the rankings with a 76.1% probability of being the best (Supplementary Table S1).

### 3.6 | Dry mouth

One hundred and fifteen of the trials reported results for this outcome (Supplementary Figure S5). All of the drugs were worse than placebo, with the smallest difference being for transdermal oxybutynin (odds ratio 1.96, 95% confidence interval 1.28-3.02) (Table 5). There were differences between drugs with, for example oxybutynin IR being associated with more dry mouth than all the other drugs. Propiverine, fesoterodine and darifenacin were also often associated with more dry mouth than the others. Examination of the ranks after excluding placebo from the analysis, placed transdermal oxybutynin as by far the top ranked treatment in terms of having a lesser risk of dry mouth (97.4% chance of being best) (Supplementary Table S1).

### 3.7 | Inconsistency and OAB only

The direct comparisons (using only results from RCTs that direct compare treatments) are presented in Supplementary Tables S2-5. Many of these results are based on only one comparison. While many treatments have not been compared the results are consistent with the NMA results. When the NMA was restricted to those studies that had OAB or UUI as the inclusion criteria (ie, excluding BOO/BPH) there were only minor changes in the estimates of the relative treatment effects (results not shown).

## 4 | DISCUSSION

### 4.1 | Principal findings

This study finds that all the anticholinergic drugs have similar effects on voids and leakages. There were differences in the other outcomes with darifenacin being the best for the outcome cure or improvement and transdermal oxybutynin clearly the best for dry mouth. Importantly, our analysis identified that none of drugs were clearly superior over the four outcomes examined.

For voids and leakages all drugs are more effective than placebo at the end of the treatment period, albeit that the differences are small. There is little difference between the drugs in terms of the number of voids and the number of leakage episodes. Most differences were less than one fewer void or leakage every 4 or 5 days. The ranking for best treatment was different for the two outcomes with no clear best treatment for leakages, and imidafenacin the best for voids.

Most drugs had similar results for cure or improvement. All drugs apart from imidafenacin were better than placebo. Darifenacin was ranked highest, followed equally by oxybutynin ER and tolterodine IR and then by trospium but the probabilities of being the best were similar with no clearly best drug. For dry mouth all treatments were worse than placebo, but there were considerable differences between the treatments, with transdermal oxybutynin having the least risk of dry mouth.

### 4.2 | Comparison with previous research

This study confirms two findings from previous research on the effectiveness of anticholinergic drug treatment of OAB.[3,6,15,16] Traditional pairwise meta-analyses that use

**TABLE 2** Odds ratios and their 95% confidence intervals of differences between treatments from the network meta-analysis of cure or improvement

| | Placebo | Oxybutynin IR | Oxybutynin ER | Oxybutynin transdermal | Tolterodine IR | Tolterodine ER | Solifenacin | Trospium | Propiverine | Fesoterodine | Darifenacin | Imidafenacin |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | | **2.20** | **2.02** | **1.48** | **2.23** | **1.42** | **1.84** | **1.93** | **1.87** | **2.10** | **2.37** | 1.43 |
| | | **1.69,2.88** | **1.25,3.26** | **1.12,1.97** | **1.67,2.98** | **1.22,1.65** | **1.39,2.43** | **1.13,3.29** | **1.44,2.42** | **1.72,2.57** | **1.12,5.03** | 0.62,3.29 |
| Oxybutynin IR | **0.45** | | 0.92 | **0.67** | 1.01 | **0.65** | 0.83 | 0.88 | 0.85 | 0.95 | 1.08 | 0.65 |
| | **0.35,0.59** | | 0.56,1.51 | **0.47,0.97** | 0.76,1.35 | **0.48,0.86** | 0.57,1.21 | 0.49,1.58 | 0.61,1.18 | 0.69,1.33 | 0.48,2.39 | 0.28,1.53 |
| Oxybutynin ER | **0.50** | 1.09 | | 0.73 | 1.10 | 0.70 | 0.91 | 0.95 | 0.92 | 1.04 | 1.17 | 0.71 |
| | **0.31,0.80** | 0.66,1.79 | | 0.42,1.27 | 0.65,1.89 | 0.44,1.12 | 0.53,1.56 | 0.47,1.95 | 0.54,1.58 | 0.62,1.73 | 0.48,2.86 | 0.27,1.84 |
| Oxybutynin transdermal | **0.68** | **1.49** | 1.36 | | **1.51** | 0.96 | 1.24 | 1.30 | 1.26 | **1.42** | 1.60 | 0.97 |
| | **0.51,0.89** | **1.03,2.15** | 0.79,2.36 | | **1.02,2.22** | 0.70,1.31 | 0.84,1.82 | 0.71,2.38 | 0.90,1.77 | **1.00,2.01** | 0.71,3.58 | 0.41,2.28 |
| Tolterodine IR | **0.45** | 0.99 | 0.91 | **0.66** | | 0.64 | 0.82 | 0.86 | 0.84 | 0.94 | 1.06 | 0.64 |
| | **0.34,0.60** | 0.74,1.32 | 0.53,1.55 | **0.45,0.98** | | 0.46,0.87 | 0.56,1.21 | 0.48,1.56 | 0.60,1.16 | 0.66,1.33 | 0.47,2.38 | 0.27,1.51 |
| Tolterdine ER | **0.70** | **1.55** | 1.42 | 1.04 | **1.57** | | 1.29 | 1.36 | 1.32 | **1.48** | 1.67 | 1.01 |
| | **0.61,0.82** | **1.16,2.07** | 0.89,2.27 | 0.76,1.42 | **1.15,2.15** | | 0.96,1.73 | 0.78,2.36 | 0.98,1.76 | **1.18,1.86** | 0.77,3.59 | 0.43,2.34 |
| Solifenacin | **0.54** | 1.20 | 1.10 | 0.81 | 1.22 | 0.77 | | 1.05 | 1.02 | 1.14 | 1.29 | 0.78 |
| | **0.41,0.72** | 0.83,1.74 | 0.64,1.89 | 0.55,1.19 | 0.83,1.79 | 0.58,1.04 | | 0.58,1.92 | 0.73,1.43 | 0.81,1.61 | 0.58,2.88 | 0.33,1.83 |
| Trospium | **0.52** | 1.14 | 1.05 | 0.77 | 1.16 | 0.74 | 0.95 | | 0.97 | 1.09 | 1.23 | 0.74 |
| | **0.30,0.88** | 0.63,2.06 | 0.51,2.14 | 0.42,1.41 | 0.64,2.09 | 0.42,1.28 | 0.52,1.74 | | 0.54,1.75 | 0.62,1.93 | 0.49,3.09 | 0.23,1.99 |
| Propiverine | **0.53** | 1.18 | 1.08 | 0.79 | 1.19 | 0.76 | 0.98 | 1.03 | | 1.12 | 1.27 | 0.77 |
| | **0.41,0.69** | 0.85,1.64 | 0.63,1.85 | 0.56,1.11 | 0.86,1.65 | 0.57,1.02 | 0.70,1.38 | 0.57,1.86 | | 0.81,1.56 | 0.57,2.81 | 0.35,1.69 |
| Fesoterodine | **0.48** | 1.05 | 0.96 | **0.71** | 1.06 | **0.68** | 0.87 | 0.92 | 0.89 | | 1.13 | 0.68 |
| | **0.39,0.58** | 0.75,1.46 | 0.58,1.60 | **0.50,1.00** | 0.75,1.51 | **0.54,0.85** | 0.62,1.23 | 0.52,1.62 | 0.64,1.23 | | 0.52,2.46 | 0.29,1.60 |
| Darifenacin | **0.42** | 0.93 | 0.85 | 0.63 | 0.94 | 0.60 | 0.77 | 0.81 | 0.79 | 0.89 | | 0.60 |
| | **0.20,0.89** | 0.42,2.07 | 0.35,2.08 | 0.28,2.40 | 0.42,2.11 | 0.28,1.29 | 0.35,1.73 | 0.32,2.05 | 0.36,1.75 | 0.41,1.93 | | 0.20,1.86 |
| Imidafenacin | 0.70 | 1.54 | 1.41 | 1.03 | 1.56 | 0.99 | 1.28 | 1.35 | 1.30 | 1.47 | 1.65 | |
| | 0.30,1.61 | 0.65,3.61 | 0.54,3.66 | 0.44,2.44 | 0.66,3.66 | 0.43,2.30 | 0.54,3.02 | 0.50,3.61 | 0.59,2.87 | 0.62,3.45 | 0.54,5.07 | |

An odds ratio in a particular cell reflects the contrast between the drug in the column to the drug in the row.

**TABLE 3** Mean differences and their 95% confidence intervals between treatments from the network meta-analysis in leakages episodes per day

| | Placebo | Oxybutynin IR | Oxybutynin ER | Oxybutynin transdermal | Tolterodine IR | Tolterodine ER | Solifenacin | Trospium | Propiverine | Fesoterodine | Imidafenacin |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | | **−0.52** | −0.36 | **−0.52** | **−0.46** | **−0.56** | **−0.41** | −0.32 | **−0.47** | **−0.58** | **−0.49** |
| | | **−0.90,−0.14** | −0.95,0.23 | **−0.94,−0.10** | **−0.78,−0.13** | **−0.84,−0.28** | **−0.71, −0.11** | −0.89,0.26 | **−0.82, −0.13** | **−0.89,−0.26** | **−0.95,−0.04** |
| Oxybutynin IR | | | 0.16 | 0.01 | 0.07 | −0.03 | 0.11 | 0.21 | 0.05 | −0.05 | 0.03 |
| | | | −0.40,0.73 | −0.49,0.50 | −0.28,0.41 | −0.49,0.43 | −0.34,0.57 | −0.38,0.79 | −0.43,0.53 | −0.54,0.44 | −0.55,0.61 |
| Oxybutynin ER | | | | −0.16 | −0.10 | −0.20 | −0.05 | 0.04 | −0.11 | −0.21 | −0.13 |
| | | | | −0.85,0.54 | −0.66,0.47 | −0.85,0.45 | −0.69,0.59 | −0.74,0.82 | −0.78,0.55 | −0.89,0.45 | −0.87,0.61 |
| Oxybutynin transdermal | | | | | 0.06 | −0.04 | 0.11 | 0.20 | 0.05 | −0.05 | 0.02 |
| | | | | | −0.44,0.56 | −0.53,0.45 | −0.39,0.61 | −0.49,0.89 | −0.46,0.55 | −0.58,0.47 | −0.58,0.63 |
| Tolterodine IR | | | | | | −0.10 | 0.05 | 0.14 | −0.02 | −0.12 | −0.04 |
| | | | | | | −0.52,0.32 | −0.35,0.44 | −0.48,0.75 | −0.45,0.41 | −0.57,0.33 | −0.58,0.51 |
| Tolterdine ER | | | | | | | 0.15 | 0.24 | 0.08 | −0.02 | 0.06 |
| | | | | | | | −0.21,0.51 | −0.40,0.87 | −0.35,0.52 | −0.39,0.35 | −0.46,0.58 |
| Solifenacin | | | | | | | | 0.09 | −0.06 | −0.17 | −0.08 |
| | | | | | | | | −0.55,0.72 | −0.49,0.37 | −0.59,0.26 | −0.62,0.45 |
| Trospium | | | | | | | | | −0.15 | −0.26 | −0.17 |
| | | | | | | | | | −0.82,0.51 | −0.91,0.40 | −0.90,0.55 |
| Propiverine | | | | | | | | | | −0.10 | −0.02 |
| | | | | | | | | | | −0.56,0.35 | −0.49,0.45 |
| Fesoterodine | | | | | | | | | | | 0.08 |
| | | | | | | | | | | | −0.41,0.58 |

A minus figure means the drug in the column has fewer leakage episodes than the drug in the row.

**TABLE 4** Mean differences and their 95% confidence intervals between treatments from the network meta-analysis in voids per day

| | Placebo | Oxybutynin IR | Oxybutynin ER | Oxybutynin transdermal | Tolterodine IR | Tolterodine ER | Solifenacin | Trospium | Propiverine | Fesoterodine | Darifenacin | Imidafenacin |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | | **−0.57** | −0.41 | **−0.61** | **−0.63** | **−0.56** | **−0.81** | **−0.84** | **−0.65** | **−0.65** | −0.74 | **−1.22** |
| | | **−0.95,−0.18** | −0.99,0.17 | **−1.10,−0.12** | **−0.93.−0.34** | **−0.81,−0.31** | **−1.06, −0.56** | **−1.28, −0.40** | **−0.99, −0.31** | **−0.91,−0.40** | −1.49,0.01 | **−1.65,−0.80** |
| Oxybutynin IR | | | 0.16 | −0.04 | −0.07 | 0.01 | −0.24 | −0.27 | −0.08 | −0.09 | −0.17 | **−0.66** |
| | | | −0.36,0.68 | −0.66,0.57 | −0.38,0.24 | −0.44,0.46 | −0.67,0.19 | −0.20,0.74 | −0.56,0.40 | −0.54,0.37 | −1.00,0.65 | **−1.22,−0.10** |
| Oxybutynin ER | | | | −0.20 | −0.23 | −0.15 | −0.40 | −0.43 | −0.24 | −0.24 | −0.33 | **−0.82** |
| | | | | −0.95,0.56 | −0.74,0.29 | −0.78,0.48 | −1.01,0.21 | −1.10,0.23 | −0.89,0.41 | −0.88,0.39 | −1.27,0.60 | **−1.53,−0.11** |
| Oxybutynin transdermal | | | | | −0.03 | 0.05 | −0.20 | −0.23 | −0.04 | −0.04 | −0.13 | −0.62 |
| | | | | | −0.59,0.54 | −0.49,0.58 | −0.74,0.34 | −0.87,0.42 | −0.59,0.51 | −0.59,0.50 | −1.02,0.76 | −1.24,0.01 |
| Tolterodine IR | | | | | | 0.08 | −0.18 | −0.21 | −0.01 | −0.02 | −0.11 | **−0.59** |
| | | | | | | −0.31,0.46 | −0.52,0.17 | −0.67,0.26 | −0.42,0.39 | −0.41,0.37 | −0.89,0.68 | **−1.09,−0.09** |
| Tolterdine ER | | | | | | | −0.25 | −0.28 | −0.09 | −0.09 | −0.18 | **−0.67** |
| | | | | | | | −0.56,0.06 | −0.78,0.22 | −0.51,0.32 | −0.41,0.22 | −0.95,0.59 | **−1.15,−0.18** |
| Solifenacin | | | | | | | | −0.03 | 0.16 | 0.16 | 0.07 | −0.41 |
| | | | | | | | | −0.52,0.46 | −0.24,0.56 | −0.19,0.50 | −0.64,0.77 | −0.90,0.07 |
| Trospium | | | | | | | | | 0.19 | 0.19 | 0.10 | −0.38 |
| | | | | | | | | | −0.35,0.73 | −0.32,0.69 | −0.76,0.96 | −0.99,0.22 |
| Propiverine | | | | | | | | | | −0.003 | −0.09 | **−0.57** |
| | | | | | | | | | | −0.41,0.41 | −0.72,0.90 | **−1.01,−0.14** |
| Fesoterodine | | | | | | | | | | | −0.09 | **−0.57** |
| | | | | | | | | | | | −0.88,0.70 | **−1.02,−0.12** |
| Darifenacin | | | | | | | | | | | | −0.48 |
| | | | | | | | | | | | | −1.34,0.37 |

A minus figure means the drug in the column has fewer voids than the drug in the row.

**TABLE 5** Odds ratios and their 95% confidence intervals for differences from the network meta-analysis between treatments for dry mouth

| | Placebo | Oxybutynin IR | Oxybutynin ER | Oxybutynin transdermal | Tolterodine IR | Tolterodine ER | Solifenacin | Trospium | Propiverine | Fesoterodine | Darifenacin | Imidafenacin |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | | **9.51** | **4.28** | **1.96** | **3.72** | **2.93** | **4.08** | **3.71** | **4.76** | **5.64** | **5.50** | **3.70** |
| | | **7.60,11.91** | **3.10,5.91** | **1.28,3.02** | **3.03,4.56** | **2.41,3.57** | **3.30,5.06** | **2.78,4.94** | **3.63,6.24** | **4.62,6.88** | **3.90,7.74** | **2.53,5.39** |
| Oxybutynin IR | **0.11** | | **0.45** | **0.21** | **0.39** | **0.31** | **0.43** | **0.39** | **0.50** | **0.59** | **0.58** | **0.39** |
| | **0.08,0.13** | | **0.33,0.62** | **0.13,0.33** | **0.31,0.49** | **0.23,0.41** | **0.32,0.57** | **0.28,0.53** | **0.36,0.69** | **0.44,0.80** | **0.39,0.86** | **0.25,0.60** |
| Oxybutynin ER | **0.23** | **2.22** | | **0.46** | 0.87 | **0.69** | 0.95 | 0.87 | 1.11 | 1.32 | 1.28 | 0.86 |
| | **0.17,0.32** | **1.62,3.06** | | **0.27,0.78** | 0.62,1.22 | **0.48,0.97** | 0.66,1.39 | 0.58,1.30 | 0.74,1.67 | 0.91,1.91 | 0.81,2.04 | 0.53,1.41 |
| Oxybutynin transdermal | **0.51** | **4.85** | **2.18** | | **1.89** | 1.49 | **2.08** | **1.89** | **2.43** | **2.87** | **2.80** | **1.88** |
| | **0.33,0.78** | **3.04,7.72** | **1.29,3.69** | | **1.19,3.01** | 0.94,2.37 | **1.30,3.33** | **1.13,3.15** | **1.53,3.85** | **1.79,4.60** | **1.62,4.85** | **1.08,3.28** |
| Tolterodine IR | **0.27** | **2.56** | 1.15 | **0.53** | | 0.79 | 1.10 | 1.00 | 1.28 | **1.52** | **1.48** | 0.99 |
| | **0.22,0.33** | **2.03,3.23** | 0.82,1.61 | **0.33,0.84** | | 0.60,1.03 | 0.84,1.43 | 0.72,1.38 | 0.94,1.74 | **1.15,2.01** | **1.01,2.16** | 0.66,1.51 |
| Tolterdine ER | **0.34** | **3.24** | **1.46** | 0.67 | 1.27 | | **1.39** | 1.26 | **1.62** | **1.92** | **1.87** | 1.26 |
| | **0.28,0.42** | **2.46,4.28** | **1.03,2.07** | 0.42,1.06 | 0.97,1.66 | | **1.06,1.82** | 0.90,1.78 | **1.17,2.24** | **1.50,2.47** | **1.27,2.77** | 0.83,1.91 |
| Solifenacin | **0.24** | **2.33** | 1.05 | **0.48** | 0.91 | **0.72** | | 0.91 | 1.17 | **1.38** | 1.35 | 0.90 |
| | **0.20,0.30** | **1.75,3.10** | 0.72,1.52 | **0.30,0.77** | 0.70,1.18 | **0.55,0.94** | | 0.64,1.29 | 0.85,1.59 | **1.04,1.83** | 0.91,1.99 | 0.60,1.36 |
| Trospium | **0.27** | **2.57** | 1.15 | **0.53** | 1.00 | 0.79 | 1.10 | | 1.28 | **1.52** | 1.48 | 1.00 |
| | **0.20,0.36** | **1.88,3.51** | 0.77,1.74 | **0.32,0.88** | 0.73,1.38 | 0.56,1.11 | 0.78,1.56 | | 0.87,1.89 | **1.07,2.15** | 0.95,2.31 | 0.62,1.59 |
| Propiverine | **0.21** | **2.00** | 0.90 | **0.41** | 0.78 | **0.62** | 0.86 | 0.78 | | 1.18 | 1.15 | 0.78 |
| | **0.16,0.28** | **1.45,2.76** | 0.60,1.35 | **0.26,0.65** | 0.57,1.06 | **0.45,0.85** | 0.63,1.17 | 0.53,1.14 | | 0.85,1.65 | 0.75,1.78 | 0.52,1.15 |
| Fesoterodine | **0.18** | **1.69** | 0.76 | **0.35** | **0.66** | **0.52** | **0.72** | **0.66** | 0.84 | | 0.97 | **0.65** |
| | **0.15,0.22** | **1.26,2.27** | 0.52,1.10 | **0.22,0.56** | **0.50,0.87** | **0.41,0.67** | **0.55,0.96** | **0.46,0.93** | 0.61,1.17 | | 0.66,1.45 | **0.44,0.98** |
| Darifenacin | **0.18** | **1.73** | 0.78 | **0.36** | **0.68** | **0.53** | 0.74 | 0.67 | 0.87 | 1.03 | | 0.67 |
| | **0.13,0.26** | **1.16,2.58** | 0.49,1.24 | **0.21,0.62** | **0.46,0.99** | **0.36,0.79** | 0.50,1.10 | 0.43,1.05 | 0.56,1.33 | 0.69,1.52 | | 0.41,1.11 |
| Imidafenacin | **0.27** | **2.58** | 1.16 | **0.53** | 1.01 | 0.79 | 1.11 | 1.00 | 1.29 | **1.53** | 1.49 | |
| | **0.19,0.39** | **1.68,3.95** | 0.71,1.89 | **0.30,0.93** | 0.66,1.52 | 0.52,1.21 | 0.74,1.66 | 0.63,1.60 | 0.87,1.91 | **1.02,2.29** | 0.90,2.47 | |

Numbers over 1 mean that the drug in the column is associated with more dry mouth than the drug in the row

only direct comparisons are able to only make limited claims. However, from reviews that have included only pairwise meta-analyses,[3,6] it is clear that all of the drugs are more effective than placebo, and that extended release formulations have fewer side effects than immediate release versions

Previous network meta-analyses have used fewer studies and included fewer people.[15,16] Kessler et al concentrated on a wide range of adverse events and found that darifenacin, fesoterodine, transdermal oxybutynin, propiverine, solifenacin, tolterodine, and trospium had similar rates of adverse effects,[16] with only oral oxybutynin having higher rates. This did not distinguish between immediate and extended release versions, and did not include propiverine and imidafenacin.

Buser et al found that trospium chloride, transdermal and fesoterodine had the best efficacy for six outcomes: perception of cure or improvement, urgency episodes per 24 h, leakage episodes per 24 h, urgency incontinence episodes per 24 h, micturitions per 24 h, and nocturia episodes per 24 h.[15] Combining efficacy and adverse event outcomes, higher dosages of orally administered oxybutynin and propiverine had the least favorable profiles. This review separated treatments by drug and dose, resulting in 37 different treatments.

### 4.3 | Strengths and limitations

There is considerable variation in the risk of bias of the included studies. Many are not reported well enough to say the risk of bias was high or low, so there are a lot of domains with unclear risks of bias. Many studies have unclear risk of bias for allocation concealment, and many were funded by industry and had conflicts of interest among the authors. A higher risk of bias is associated with an exaggeration in the differences between treatments. Most of the differences found in this study are not large, apart from for dry mouth, so the risk of bias is unlikely to have a marked effect on the results.

The results for cure or improvement should be treated with caution. The ways of measuring this varied considerably, from no leakage on videourodynamic testing to the participants stating that they were better, or did not want further treatment. Other outcomes, such as urgency episodes and urgency incontinence may be important but few studies measured these.

It is possible that people with more severe OAB could benefit more from treatment. This would cause a problem if the studies including more severely affected people were preferentially treated with particular drugs, but the numbers were too small to see if this was the case.

Each of the drugs is treated as though it is independent of the others. This may not be true as, for example, oxybutynin is treated as three different treatments with immediate release, extended release and transdermal patches and gel separated. This may result in the standard errors being smaller than they should be. Different doses of the drugs are combined. Looking at the differences in dose is difficult as many of the studies have flexible dosing regimens, as would be used in normal clinical practice, and some other studies started with a lower dose and then everyone got an increased dose.

Network meta-analysis assumes that the populations of people included in the studies are similar. The inclusion criteria of the trials included in this analysis are similar apart from some only including males with prostate problems. The sensitivity analysis excluding those studies did not lead to different conclusions.

These results only apply at the end of the treatment period. While it is likely that the effects continue if the treatments continue to be used, many people give up taking anticholinergic drugs as the balance of side effects and efficacy may not be favorable.[4,5]

## 5 | CONCLUSIONS

The effects of anticholinergics for the treatment of OAB on incontinence episodes and voids per day were clinically similar. Darifenacin had the highest probability of being best for cure and improvement, but this was only 40%, indicating the drug was not clearly superior. Transdermal or gel oxybutynin was the best treatment for avoiding dry mouth with the probability of being best of 95%. However, the odds of having dry mouth were still twice as large as with placebo (OR 1.96, 95%CI 1.28-3.02). But as other outcomes were similar, and dry mouth is the main reason people give up taking these drugs, transdermal administration may be a good way to start treatment.

## ACKNOWLEDGMENTS

This study was funded in part by grant 12/256 from the Health Research Council of New Zealand. They had no role apart from providing funding. This review has been registered in PROSPERO (CRD42014010114).

## ORCID

*Peter Herbison* http://orcid.org/0000-0002-5684-024X

## REFERENCES

1. Milsom I, Abrams P, Cardozo L, Roberts RG, Thuroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BJU Int*. 2001;87:760–766.
2. Schultz SE, Kopec JA. Impact of chronic conditions. *Health Rep*. 2003;14:41–53.
3. Sexton CC, Notte SM, Maroulis C, et al. Persistence and adherence in the treatment of overactive bladder syndrome with anticholinergic therapy: a systematic review of the literature. *Int J Clin Pract*. 2011;65:567–585.

4. Veenboer PW, Bosch JL. Long-term adherence to antimuscarinic therapy in everyday practice: a systematic review. *J Urol*. 2014;191:1003–1008.
5. Madhuvrata P, Cody JD, Ellis G, Herbison GP, Hay-Smith EJ. Which anticholinergic drug for overactive bladder symptoms in adults. *Cochrane Database Syst Rev*. 2012;1:CD005429.
6. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
7. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188.
8. Salanti G. Indirect and mixed-treatment comparison, network, or multiple treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods*. 2012;3:80–97.
9. White IR. Network meta-analysis. *Stata J*. 2015;15:951–985.
10. White IR. Multivariate random-effects meta-regression: updates to mvmeta. *Stata J*. 2011;11:255–270.
11. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med*. 2010;29:932–944.
12. Higgins JPT, Jackson D, Barrett JL, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Methods*. 2012;3:98–110.
13. White IR, Barrett JK, Jackson D, Higgins JPT. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Res Synth Methods*. 2012;3:111–125.
14. Buser N, Ivic S, Kessler TM, Kessels AGH, Bachmann LM. Efficacy and adverse events of antimuscarinics for treating overactive bladder: network meta-analyses. *Eur Urol*. 2012;62:1040–1060.
15. Kessler TM, Bachmann LM, Minder C, et al. Adverse event assessment of antimuscarinics for treating overactive bladder: a network meta-analytic approach. *PLoS ONE*. 2011;6:e16718.

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**How to cite this article:** Herbison P, McKenzie JE. Which anticholinergic is best for people with overactive bladders? A network meta-analysis. *Neurourology and Urodynamics*. 2018;1–10. https://doi.org/10.1002/nau.23893

## APPENDIX 1: EXAMPLE SEARCH STRATEGY

Searches were run at various stages during the project. This is one example.

Databases to which the following strategy (or an adaption) was applied: EBM Reviews – Cochrane Central Register of Controlled Trials <January 2017>, Ovid MEDLINE(R) <1996 to Present with Daily Update>, Embase <1974 to 2017 January>

Search Strategy for Ovid:

---

1 imidafenacin.mp. [mp=ti, ot, ab, sh, hw, kw, nm, kf, px, rx, an, ui, tn, dm, mf, dv] (204)
2 anticholinergic.mp. [mp=ti, ot, ab, sh, hw, kw, nm, kf, px, rx, an, ui, tn, dm, mf, dv] (20235)
3 antimuscarinic.mp. [mp=ti, ot, ab, sh, hw, kw, nm, kf, px, rx, an, ui, tn, dm, mf, dv] (4041
4 cholinergic agonists/ (10753)
5 muscarinic agonists/ (6466)
6 2 or 4 (30732)
7 3 or 5 (10431)
8 solifenacin.mp. [mp=ti, ot, ab, sh, hw, kw, nm, kf, px, rx, an, ui, tn, dm, mf, dv] (2023)
9 tolterodine.mp. [mp=ti, ot, ab, sh, hw, kw, nm, kf, px, rx, an, ui, tn, dm, mf, dv] (4345)
10 trospium.mp. [mp=ti, ot, ab, sh, hw, kw, nm, kf, px, rx, an, ui, tn, dm, mf, dv] (1578)
11 oxybutynin.mp. [mp=ti, ot, ab, sh, hw, kw, nm, kf, px, rx, an, ui, tn, dm, mf, dv] (6288)
12 darifenacin.mp. [mp=ti, ot, ab, sh, hw, kw, nm, kf, px, rx, an, ui, tn, dm, mf, dv] (1494)
13 propiverine.mp. [mp=ti, ot, ab, sh, hw, kw, nm, kf, px, rx, an, ui, tn, dm, mf, dv] (1681)
14 fesoterodine.mp. [mp=ti, ot, ab, sh, hw, kw, nm, kf, px, rx, an, ui, tn, dm, mf, dv] (845)
15 1 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (48760)
16 copd.mp. or Pulmonary Disease, Chronic Obstructive/ (119506)
17 15 not 16 (46928)
Then restricted to randomised controlled trials