Effectiveness of anticholinergic drugs compared with placebo in the treatment of overactive bladder: systematic review

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ELPS

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Abstract

Objective To determine the effectiveness of anticholinergic drugs for the treatment of overactive bladder syndrome.

Design Systematic review of randomised controlled trials.

Data sources Published papers and abstracts.

Study selection Randomised controlled trials with anticholinergic drug treatment in one arm and placebo in another.

Data extraction Primary outcomes of interest were patient perceived cure or improvement in symptoms, differences in number of incontinent episodes and number of voids in 24 hours, and side effects. Secondary outcomes of interest were urodynamic measures of bladder function (volume at first contraction, maximum cystometric capacity, and residual volume) and adverse events.

Data synthesis 32 trials were included, totalling 6800 participants. Most trials were described as double blind but were variable in other aspects of quality. At the end of treatment, cure or improvement (relative risk 1.41, 95% confidence interval 1.29 to 1.54), differences in incontinent episodes in 24 hours (estimated mean difference 0.6, 0.4 to 0.8), number of voids in 24 hours (0.6, 0.4 to 0.8), maximum cystometric capacity (54 ml, 43 ml to 66 ml), and volume at first contraction (52 ml, 37 ml to 67 ml), were significantly in favour of anticholinergics ($P < 0.0001$ for all). Anticholinergics were associated with significantly higher residual volumes (4 ml, 1 ml to 7 ml; $P=0.02$) and an increased rate of dry mouth (relative risk 2.56, 2.24 to 2.92; $P < 0.0001$). Sensitivity analysis, although affected by small numbers of studies, showed little likelihood of an effect of age, sex, diagnosis, or choice of drug.

Conclusions Although statistically significant, the differences between anticholinergic drugs and placebo were small, apart from the increased rate of dry mouth in patients receiving active treatment. For many of the outcomes studied, the observed difference between anticholinergics and placebo may be of questionable clinical significance. None of these studies provided data on long term outcome.

Introduction

Symptoms of overactive bladder comprise urgency (sudden and compelling desire to pass urine, which is difficult to defer), urge urinary incontinence (involuntary leakage of urine with the feeling of urgency), and frequency (voiding more than seven times a day), or nocturia (waking to void more than once at night).

Around one sixth of adults aged 18 years and over reported symptoms of an overactive bladder.[1 2] One third of people with overactive bladder have urge urinary incontinence. The prevalence of symptoms of overactive bladder increases with age.[1–5] In people with neurological conditions, such as multiple sclerosis, urinary dysfunction seems to be more common than in people who are neurologically unimpaired.[6]

Frequency and urgency can be just as bothersome as leakage, and overall the effects of overactive bladder symptoms on quality of life are profound.[1 7] Many affected people do not seek help from professionals.[1 5]

The two main treatment options for overactive bladder syndrome are bladder retraining and anticholinergic drugs. By blocking the parasympathetic pathway anticholinergics abolish or reduce the severity of detrusor muscle contraction. The drugs often cause side effects such as dry mouth or eyes, constipation, and, more rarely, headache or nausea. Uncertainty still exists as to the effectiveness of anticholinergics. Despite these uncertainties, anticholinergics are increasingly being used in both primary care and secondary care for the treatment of overactive bladder, and this has considerable implications for resources.[8] We conducted a systematic review of anticholinergic drug treatment compared with placebo therapy in the treatment of overactive bladder reported in randomised controlled trials.[9]

Methods

Relevant trials were identified from the Cochrane Incontinence Group's specialised register of controlled trials.[10] In addition, cited references from the included trials were searched. The date of the last search was January 2002. We included all randomised controlled trials on men and women with a diagnosis of overactive bladder based on symptoms or a urodynamic diagnosis of detrusor overactivity (idio-

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BMJ 2003;326:841–4

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Details of studies and references appear on bmj.com

Study	Anticholinergic No of participants	Mean (SD)	Placebo No of participants	Mean (SD)	Weighted mean difference (95% CI fixed)	Weight (%)	Weighted mean difference (95% CI fixed)
Leakage episodes in 24 hours							
No of leakage episodes							
Burgio 1998[w37]	65	0.81 (1.40)	62	1.20 (1.70)		9.8	-0.39 (0.93 to 0.15)
Subtotal (95% CI)	65		62			9.8	-0.39 (0.93 to 0.15)
Test for heterogeneity: χ^2=0.00, df=0, P=1.00							
Test for overall effect: z=1.41, P=0.16							
Change in leakage episodes							
Abrams 1998[w34]	180	-1.50 (3.20)	40	-0.90 (1.50)		6.7	-0.60 (-1.26 to 0.06)
Dorschner 2000[w41]	49	-0.60 (1.70)	49	-0.10 (0.70)		10.9	-0.50 (-1.01 to 0.01)
Drutz 1999[w42]	99	-1.70 (1.90)	33	-1.00 (2.20)		4.1	-0.70 (-1.54 to 0.14)
Jacquetin 2001[w46]	157	-1.20 (2.00)	39	-0.40 (1.90)		6.4	-0.80 (-1.47 to -0.13)
Millard 1999[w53]	226	-1.70 (2.70)	55	-1.30 (2.50)		5.2	-0.40 (-1.15 to 0.35)
Rentzhog 1998[w55]	54	-0.98 (1.47)	10	-0.40 (0.80)		7.2	-0.58 (-1.21 to 0.05)
Van Kerrebroeck 1998[w62]	60	-1.59 (3.10)	16	-1.90 (2.20)		1.6	0.31 (-1.02 to 1.64)
Van Kerrebroeck 2001[w63]	1021	-1.60 (2.50)	507	-0.99 (2.20)		48.1	-0.61 (-0.86 to -0.36)
Subtotal (95% CI)	1846		749			90.2	-0.58 (-0.76 to -0.40)
Test for heterogeneity: χ^2=2.58, df=7, P=0.92							
Test for overall effect: z=6.37, P<0.0001							
Total (95% CI)	1911		811			100.0	-0.56 (0.93 to 0.15)
Test for heterogeneity: χ^2=3.01, df=8, P=0.93							
Test for overall effect: z=6.49, P<0.0001							
Micturitions in 24 hours							
Abrams 1998[w34]	235	-2.50 (3.30)	56	-1.60 (3.60)		5.1	-0.90 (-1.93 to 0.13)
Dorschner 2000[w41]	49	-2.10 (3.10)	49	-0.60 (2.50)		4.4	-1.50 (-2.62 to -0.38)
Drutz 1999[w42]	111	-2.00 (2.40)	36	-1.10 (2.90)		5.0	-0.90 (-1.95 to 0.15)
Jacquetin 2001[w46]	157	-1.40 (3.60)	39	-1.20 (2.70)		5.3	-0.20 (-1.22 to 0.82)
Millard 1999[w53]	252	-2.30 (2.60)	64	-1.40 (2.30)		12.9	-0.90 (-1.55 to -0.25)
Rentzhog 1998[w55]	54	-1.80 (2.50)	10	-0.30 (1.40)		4.5	-1.50 (-2.59 to -0.41)
Van Kerrebroeck 1998[w62]	60	-0.01 (1.80)	16	-0.10 (1.00)		12.1	0.09 (-0.58 to 0.76)
Van Kerrebroeck 2001[w63]	1021	-1.70 (3.40)	507	-1.20 (2.90)		50.7	-0.50 (-0.83 to -0.17)
Subtotal (95% CI)	1939		777			100.0	-0.59 (-0.83 to -0.36)
Test for heterogeneity: χ^2=11.60, df=7, P=0.11							
Test for overall effect: z=4.99, P<0.0001							

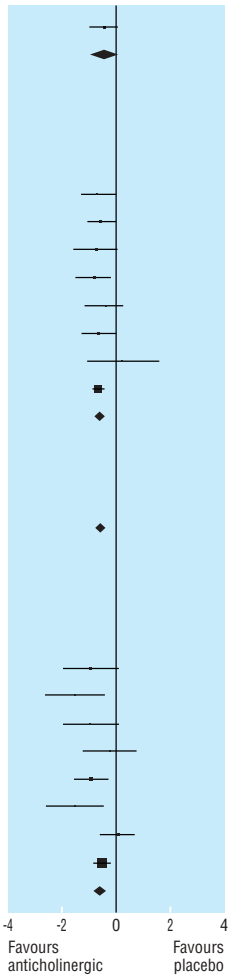

Fig 1 Effect of anticholinergics compared with placebo on number of leakages in 24 hours and number of micturitions in 24 hours

pathic or neurogenic), provided one arm of the study used an anticholinergic and another used placebo. Non-English language papers were translated.

Primary outcomes of interest were patient's observations of cure or improvement in symptoms, number of leakages, and number of voids. Secondary outcomes were urodynamic measures (volume at first contraction, maximum cystometric capacity, residual volume) and adverse events. Quality of life and economic outcomes were also considered. Methodological quality was assessed by considering the adequacy of random allocation and concealment, description of dropouts and withdrawals, analysis by intention to treat, and blinding during treatment and at outcome assessment.

Data were combined with a fixed effects model using relative risk for dichotomous outcomes and weighted mean differences for continuous outcomes. We planned a priori sensitivity analyses to investigate the effects of age, sex, severity of symptoms, cause of overactive bladder symptoms (idiopathic *v* neurogenic), and type of drug. Data plots were examined for evidence of heterogeneity, and a formal test of heterogeneity was used. Where heterogeneity was observed an explanation was sought.

Results

We identified 64 potential trials of which 32 were eligible for analysis.[w33–w64] The 32 trials recruited a total of 6800 participants (1529 men and 3938 women; some trials did not report sex). Of these, 3866 (57%) participants were randomised to receive anticholinergic drugs and 1743 (26%) were randomised to receive placebo. Three trials did not report the numbers randomised to each group, and three studies only reported the numbers after excluding the dropouts. Sample sizes ranged from 20 to 1529, with a median of 155.

Details of the 32 included trials are provided on bmj.com. Inclusion and exclusion criteria were unclear for some. Most trials included people with overactive bladder, regardless of sex, but some were restricted to those with urge urinary incontinence, some to women only, and one to men with bladder outlet obstruction.

Trials compared the following active treatments with placebo: tolterodine (12 trials), oxybutynin chloride (10 trials), trospium chloride (eight trials), propiverine (five trials), emepronium bromide (one trial), and propantheline (one trial). Six trials compared two different anticholinergics with placebo (tolterodine and oxybutynin, oxybutynin and trospium chloride, tolterodine and trospium chloride, oxybutynin and propiverine, oxybutynin and propantheline). In four trials drugs were given by intravesical administration, and in all the remaining trials drugs were taken orally. In the trials of oral drugs, length of treatment ranged from 12 days to 12 weeks. Outcome was measured at the end or shortly after the end of the treatment period in all trials.

The trials were more explanatory than pragmatic.[11] Outcome was generally measured at the end of treatment, and there was a focus on urodynamic measures. Due to deficiencies in data reporting (for example, point estimate without measure of variation), many trials contributed limited data to the review.

Methodological quality of included studies

The method of group allocation was rarely described, although all trials but one were said to be double blind. Although double blinding should adequately conceal group allocation, this is not guaranteed.[12] Only one trial specifically stated that outcome assessors were blind to group allocation. In some studies the code was broken on completion of the study, but only a few specified that this was after the analysis.

In 13 trials the evaluation of treatment efficacy was conducted on intention to treat principles, and seven trials specifically stated that a per protocol analysis was used to assess efficacy of treatment.

The description of withdrawals or dropouts was not adequate in eight trials. No dropouts occurred in the trials using single intravesical or oral doses of drug, and in nine trials the dropout rate was 10% or less. In the remainder, dropout rates ranged from 12% to 21%.

Those receiving active treatment were more likely to be subjectively improved (relative risk 1.41, 95% confidence interval 1.29 to 1.54). Those taking an anticholinergic had about one leakage episode less in 48 hours than those taking placebo (estimated mean difference for reduction in number of leakage episodes in 24 hours 0.6, 0.4 to 0.8; fig 1). Those taking an anticholinergic had about one less micturition in 48 hours than those taking placebo (estimated mean difference for reduction number of micturitions in 24 hours 0.6, 0.4 to 0.8; fig 1). No significant heterogeneity was found in these results.

A larger increase in maximum cystometric capacity occurred in those receiving active treatment (estimated mean difference 54 ml, 43 ml to 66 ml). Significant heterogeneity was observed (P=0.027). When the data from Froehlich et al, in which participants received treatment by intravesical administration, was removed from the pooled analysis, there was an improvement in maximum cystometric capacity in favour of the drug group (49 ml, 38 ml to 61 ml), and the test for heterogeneity was no longer significant (P=0.51). Volume at first contraction increased more in the drug group than in the placebo group (52 ml, 38 ml to 67 ml).

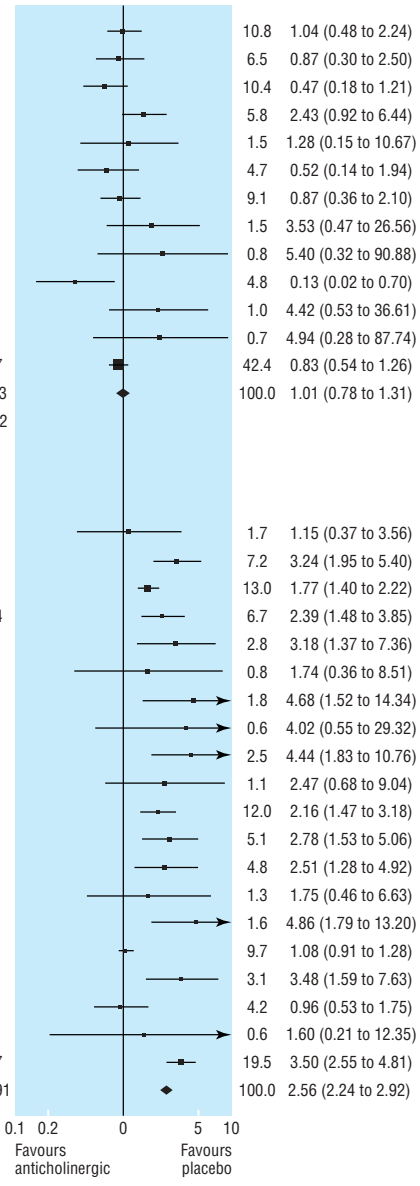

Fig 2 Effect of anticholinergics compared with placebo on withdrawal owing to side effects and dry mouth

On average, residual volume was 4 ml greater in the drug group (4 ml, 1 ml to 7 ml), but significant heterogeneity was observed (P<0.0001). When the data from Froehlich et al were excluded from the pooled analysis, those receiving active treatment had an increase in residual volume compared with those receiving placebo (3.5 ml, 0.1 ml to 6.8 ml), and the test for heterogeneity was no longer significant (P=0.14).

No significant difference was found in the number of withdrawals due to adverse events between drug and placebo groups (relative risk 1.01, 0.78 to 1.31), but there was significant heterogeneity (P=0.08; fig 2). Excluding the data from Rentzhog et al, a dose ranging study of tolterodine, did not change the finding of the pooled analysis much (1.05, 0.81 to 1.38), but the test for heterogeneity was no longer significant (P=0.24).

Dry mouth was the most frequently reported side effect, and data on this were available from 20 trials (relative risk 2.56, 2.24 to 2.92; fig 2). Significant heterogeneity was observed in this comparison ($P<0.0001$). Two trials, in elderly patients, had high rates of dry mouth in the placebo arm, perhaps as a consequence of polypharmacy. When these two trials were excluded from the pooled analysis, the risk of dry mouth was nearly three times greater (2.88, 2.46 to 3.36), and the test of heterogeneity was no longer significant (P=0.11). Despite clinical heterogeneity of the included trials (for example, sample populations and type of drug), sensitivity analyses did not show any differences in the results for age, sex, diagnosis (neurogenic or idiopathic detrusor overactivity), or type of drug.

Discussion

Anticholinergic drug therapy caused small but significant improvements in cure and improvement of symptoms of overactive bladder, number of leakage episodes a day, number of voids a day, and urodynamic measures when compared with placebo. The risk of dry mouth was increased, but residual volume was not. Most people experienced a large improvement, but this was true for the placebo groups as well as for the treated groups. Despite the emergence of numerous disease specific quality of life tests pertaining to incontinence in the1980s, these were seldom employed.

The included studies were explanatory rather than pragmatic, with limited follow up and a focus on surrogate outcomes. Because of this, and the small differences shown, the clinical relevance of the differences we found is uncertain. However, it is clear that anticholinergics have positive effects. Therefore we believe that the use of placebo arms in trials with anticholinergic drugs for the treatment of overactive bladder should be restricted to short term explanatory studies for the purpose of facilitating the licensing of new drugs in this class.

The observed difference in treatment effect between active drug and placebo was of lesser magnitude than expected from clinical experience. Many people treated for overactive bladder receive anticholinergic drugs and instruction in bladder retraining simultaneously. In contrast, most of the studies cited here did not provide any formal bladder retraining, and in many trials people who had undergone bladder retraining were excluded.

To date there has been no pragmatic comparison of anticholinergic drugs with bladder retraining, the main alternative for conservative management of overactive bladder syndrome. A Cochrane systematic review shows that the effects of bladder retraining compared with placebo may be similar to the differences found here.[13] A comparison of these two treatments, and their effectiveness when combined, should be undertaken.

We thank Birgit Moehrer for help with assessment of trials published in German, Italian, and Flemish, Fernanda Teixeira for help with trials published in Spanish, and Lief Rentzhog and Wolfgang Dorschner for providing unpublished data.

Contributors: See bmj.com

Funding: JH-S was funded by the Health Research Council of New Zealand. GE was partly funded by an internal research grant from the University of Otago.

What is already known on this topic

Anticholinergics are the first line medical treatment for overactive bladder

The effectiveness of these drugs is unclear

What this study adds

Anticholinergics produce significant improvements in overactive bladder symptoms compared with placebo

The benefits are, however, of limited clinical significance

Competing interests: GE was the study coordinator for one of the centres in a multicentre and multinational trial included in the review. KM is a coauthor of one included study and the primary author of a cross over study that was excluded from the review, has been reimbursed by two pharmaceutical companies for speaking at symposiums, and has been reimbursed for staff costs and consulting costs.

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(Accepted 20 February 2003)

Endpiece

Two of the same

God and the doctor we alike adore But only when in danger, not before;
The danger o'er, both are alike requited, God is forgotten, and the Doctor slighted.

Submitted by John Owen, English epigrammatist (1563-1622)

Fred Charatan,
retired geriatric physician, Florida