Papers

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

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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). Urodynamic manifestations include a reduced maximum cystometric capacity (the bladder volume at which the person feels they can no longer delay micturition) and detrusor contractions that cannot be voluntarily inhibited. If a relevant neurological condition coexists then the term neurogenic detrusor overactivity is used, otherwise the disorder is called idiopathic detrusor overactivity.

Symptoms of an overactive bladder are common in adults in the community. Around one sixth of both 16 776 randomly selected adults aged 40 years or over in six European countries and 5204 adults aged 18 years and over in the United States reported symptoms of an overactive bladder.[1] [2] One third of people with overactive bladder have urge urinary incontinence. Several large population studies have reported that 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. None of the currently available drugs selectively targets the M_2 or M_3 muscarinic receptors of the bladder. As a result the drugs often cause side effects by affecting muscarinic receptors elsewhere, resulting in dry mouth or eyes, constipation, and, more rarely, headache or nausea. The number of anticholinergic drugs available is increasing. However, uncertainty still exists as to their effectiveness, which ones are best, and which is the optimal route of administration. The relative benefits

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Details of studies and references appear on bmj.com

of anticholinergics in different patient groups (for example, elderly patients, men compared with women) remains unclear. 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.

Methods

Our study was carried out under the auspices of the Cochrane Incontinence Group.[9] Relevant trials were identified from the group's specialised register of controlled trials, which is described in the Cochrane Library.[10] This register is made up from the results of searches of databases and hand searches of relevant conference proceedings. In addition, the 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 (either idiopathic or neurogenic), provided one arm of the study used an anticholinergic and another used placebo. Two of the authors independently screened the studies for eligibility. Non-English language papers were translated. Many studies were associated with more than one publication, but we have referenced only the principal publication.

The group of direct antimuscarinic drugs included emepronium bromide, emepronium carrageenate, darifenacin, dicyclomine chloride, oxybutynin chloride, propantheline bromide, propiverine, tolterodine, and trospium chloride. Terodiline was excluded because it has been withdrawn from the market. We also excluded other drugs with less direct anticholinergic effects—for example, smooth muscle relaxants (flavoxate hydrochloride, calcium channel blockers, potassium channel openers, β adrenoceptor agonists, α adrenoceptor antagonists, and prostaglandin synthetase inhibitors) and tricyclic antidepressants.

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 independently abstracted by at least two reviewers and cross checked. Where data were collected but were not reported, or were reported in a form not suitable for inclusion in the formal analysis, further clarification was sought from trialists.

Data analysis

In trials with two or more active (anticholinergic drug) treatment arms, the data from the active treatments were combined for comparison with placebo. Included trial data were processed as described in the *Cochrane Collaboration Handbook* using the Metaview 4.1 program.[11] Data were combined with a fixed effects model using relative risk for dichotomous outcomes and weighted mean differences for continuous outcomes. Some studies reported outcomes at the end of treatment, and some reported changes from baseline. These results are reported separately, but were combined into the pooled overall estimate.

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. Funnel plots were examined for evidence of small sample bias.

Results

We identified 64 potential trials. Thirteen reports were excluded: three were analyses of more than one study with no individual study data,[w1–w3] five were in elderly patients with no evidence that they had overactive bladders,[w4–w8] in one the placebo arm was not randomised,[w9] two were not comparisons of suitable anticholinergic drugs with placebo,[w10 w11] and two did not report suitable outcomes.[w12 w13] We excluded 19 cross over trials as data were presented in a manner that was unsuitable for analysis.[12 w14–w32] The remaining 32 trials were analysed.[w33–w64] Some trials had multiple publications (maximum 13).[w63] 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,[w39 w40 w59] and three studies only reported the numbers after excluding the dropouts.[w33 w41 w48] Sample sizes ranged from 20 to 1529, with a median of 155.[w54 w63]

Details of the 32 included trials appear on bmj.com. Inclusion and exclusion criteria were unclear for some of the trials. 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.[w35]

Trials compared the following active treatments with placebo: tolterodine (12 trials),[w33–w35 w42 w46 w47 w49 w52–w55 w62 w63] oxybutynin chloride (10 trials),[w34 w37 w42–w44 w50 w51 w58 w60 w64] trospium chloride (eight trials),[w36 w38 w39 w44 w48 w49 w46 w61] propiverine (five trials),[w41 w45 w51 w57 w59] emepronium bromide (one trial),[w44] and propantheline (one trial).[w60] 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).[w34 w42 w44 w49 w51 w60] In four trials drugs were given by intravesical administration, and in all the remaining trials drugs were taken orally.[w43 w44 w50 w54] In the trials of oral drugs, length of treatment ranged from 12 days to 12 weeks.[w34 w42 w43 w53 w63] 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.[13] 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.[w44] Although double blinding should adequately conceal group allocation, this is not guaranteed.[14] Only one trial specifically stated that outcome assessors were blind to group allocation.[w37] In some studies the code was broken on completion of the study, but only a few specified that this was after the analysis.

Baseline comparability of the groups was not mentioned in seven studies.[w39 w44 w45 w48-w50 w64] The remaining 25 trials stated that the groups were comparable at baseline, although three studies did not provide supporting data.[w35 w38 w59] In 13 trials the evaluation of treatment efficacy was conducted on intention to treat principles,[w34 w37 w38 w44 w46 w48 w51-w54 w58 w63 w64] and seven trials

specifically stated that a per protocol analysis was used to assess efficacy of treatment.[w33 w36 w41 w42 w49 w61 w62]

The description of withdrawals or dropouts was not adequate in eight trials.[w33 w38 w39 w45 w48 w49 w59 w62] No

Study	Anticholinergic	Placebo	Relative risk (95% CI fixed)	Weight (%)	Relative risk (95% CI fixed)
Abrams 1998[w34]	117/236	27/57		10.9	1.05 (0.77 to 1.42)
Burgio 1998[w37]	45/55	34/52		8.8	1.25 (0.99 to 1.58)
Dorschner 2000[w41]	43/49	26/49		6.5	1.65 (1.25 to 2.20)
Halaska 1994[w45]	34/38	18/38		4.5	1.89 (1.33 to 2.69)
Millard 1999[w53]	126/252	24/64		9.6	1.33 (0.95 to 1.87)
Obrink 1978[w54]	8/10	2/10		0.5	4.00 (1.11 to 14.35)
Szonyi 1995[w58]	22/28	16/29		4.0	1.42 (0.97 to 2.08)
Van Kerrebroeck 2001[w63]	313/514	218/508		55.1	1.42 (1.26 to 1.60)
Total (95% CI)	708/1182	365/807		100.0	1.41 (1.29 to 1.54)

Test for heterogeneity: χ^2=11.26, df=7, P=0.13
Test for overall effect: z=7.52, P<0.0001

0.1 0.2 1 5 10
Favours placebo — Favours anticholinergic

Fig 1 Effect of anticholinergics compared with placebo on patient perception of cure or improvement in symptoms of overactive bladder

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							

-4 -2 0 2 4
Favours anticholinergic — Favours placebo

Fig 2 Effect of anticholinergics compared with placebo on number of leakages in 24 hours and number of micturitions in 24 hours

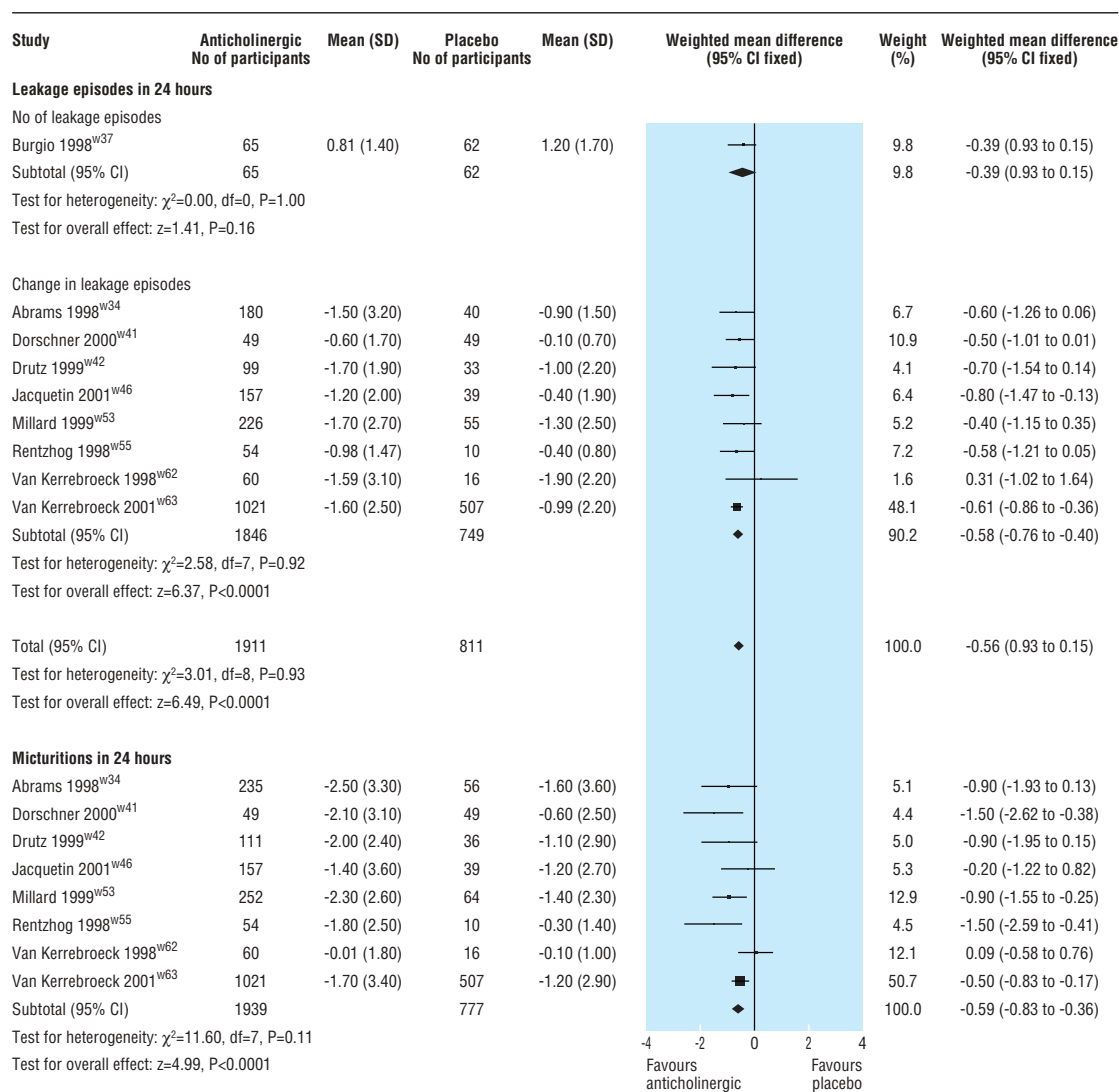| Study	Anticholinergic No of participants	Mean (SD)	Placebo No of participants	Mean (SD)	Weighted mean difference (95% CI fixed)	Weight (%)	Weighted mean difference (95% CI fixed)
Maximum cystometric capacity							
Maximum cystometric capacity							
Cardozo 2000[w38]	104	356.20 (182.10)	103	335.60 (164.70)		5.7	20.60 (-26.69 to 67.89)
Stohrer 1999[w57]	52	366.00 (143.00)	50	289.00 (163.00)		3.6	77.00 (17.40 to 136.60)
Subtotal (95% CI)	156		153			9.3	42.39 (5.35 to 79.44)
Test for heterogeneity: χ^2=2.11, df=1, P=0.15							
Test for overall effect: z=2.24, P=0.02							
Change in maximum cystometric capacity							
Abrams 1998[w33]	52	72.00 (125.00)	15	7.00 (5.00)		11.0	65.00 (30.93 to 99.07)
Alloussi 1998[w36]	99	79.10 (103.10)	48	5.20 (99.20)		10.7	73.90 (39.26 to 108.54)
Froehlich 1998[w44]	42	125.40 (115.10)	21	-9.10 (69.94)		6.1	134.50 (88.60 to 180.40)
Jonas 1997[w47]	197	31.00 (117.00)	44	4.00 (104.00)		10.6	27.00 (-7.80 to 61.80)
Junemann 1999[w48]	112	78.05 (84.87)	58	24.71 (89.91)		16.3	53.34 (25.37 to 81.31)
Madersbacher 1999[w51]	247	92.00 (107.00)	63	52.00 (92.00)		18.4	40.00 (13.65 to 66.35)
Rentzhog 1998[w55]	54	27.30 (130.00)	10	-17.00 (125.00)		1.8	44.30 (-40.58 to 129.18)
Thuroff 1991[w60]	117	65.70 (121.40)	52	22.50 (116.10)		8.6	43.20 (4.73 to 81.67)
Ulshofer 2001[w61]	22	82.30 (101.85)	17	-4.10 (100.30)		3.1	86.40 (22.49 to 150.31)
Van Kerrebroeck 1998[w62]	60	68.00 (133.00)	16	43.00 (92.00)		4.0	25.00 (-31.26 to 81.26)
Subtotal (95% CI)	1002		344			90.7	55.57 (43.69 to 67.44)
Test for heterogeneity: χ^2=19.18, df=9, P=0.024							
Test for overall effect: z=9.17, P<0.0001							
Total (95% CI)	1158		497			100.0	54.34 (43.03 to 65.65)
Test for heterogeneity: χ^2=21.73, df=11, P=0.027							
Test for overall effect: z=9.42, P<0.0001							
Volume at first contraction							
Volume at first contraction							
Cardozo 2000[w38]	102	298.60 (194.80)	103	255.70 (177.30)		8.4	42.90 (-8.11 to 93.91)
Stohrer 1999[w57]	52	224.00 (111.00)	50	159.00 (107.00)		12.2	65.00 (22.69 to 107.31)
Subtotal (95% CI)	154		153			20.7	55.99 (23.43 to 88.56)
Test for heterogeneity: χ^2=0.43, df=1, P=0.51							
Test for overall effect: z=3.37, P=0.0008							
Change in volume at first contraction							
Abrams 1998[w33]	52	62.00 (119.00)	15	14.00 (42.00)		14.6	48.00 (9.30 to 86.70)
Alloussi 1998[w36]	98	97.70 (123.50)	48	42.70 (89.90)		17.6	55.00 (19.72 to 90.28)
Jonas 1997[w47]	197	78.00 (144.00)	44	40.00 (134.00)		11.1	38.00 (-6.41 to 82.41)
Junemann 1999[w48]	112	124.54 (143.60)	58	60.21 (123.28)		12.8	64.33 (22.93 to 105.73)
Rentzhog 1998[w55]	54	69.60 (142.40)	10	-23.00 (103.00)		4.0	92.60 (18.32 to 166.88)
Thuroff 1991[w60]	117	32.60 (162.70)	52	-9.70 (128.40)		10.5	42.30 (-3.39 to 87.99)
Van Kerrebroeck 1998[w62]	60	79.00 (116.00)	16	40.00 (83.00)		8.7	39.00 (-11.16 to 89.16)
Subtotal (95% CI)	690		243			79.3	51.28 (34.65 to 67.90)
Test for heterogeneity: χ^2=2.36, df=6, P=0.88							
Test for overall effect: z=6.05, P<0.0001							
Total (95% CI)	844		396			100	52.25 (37.45 to 67.06)
Test for heterogeneity: χ^2=2.85, df=8, P=0.94							
Test for overall effect: z=6.92, P<0.0001							

-100 -50 0 50 100
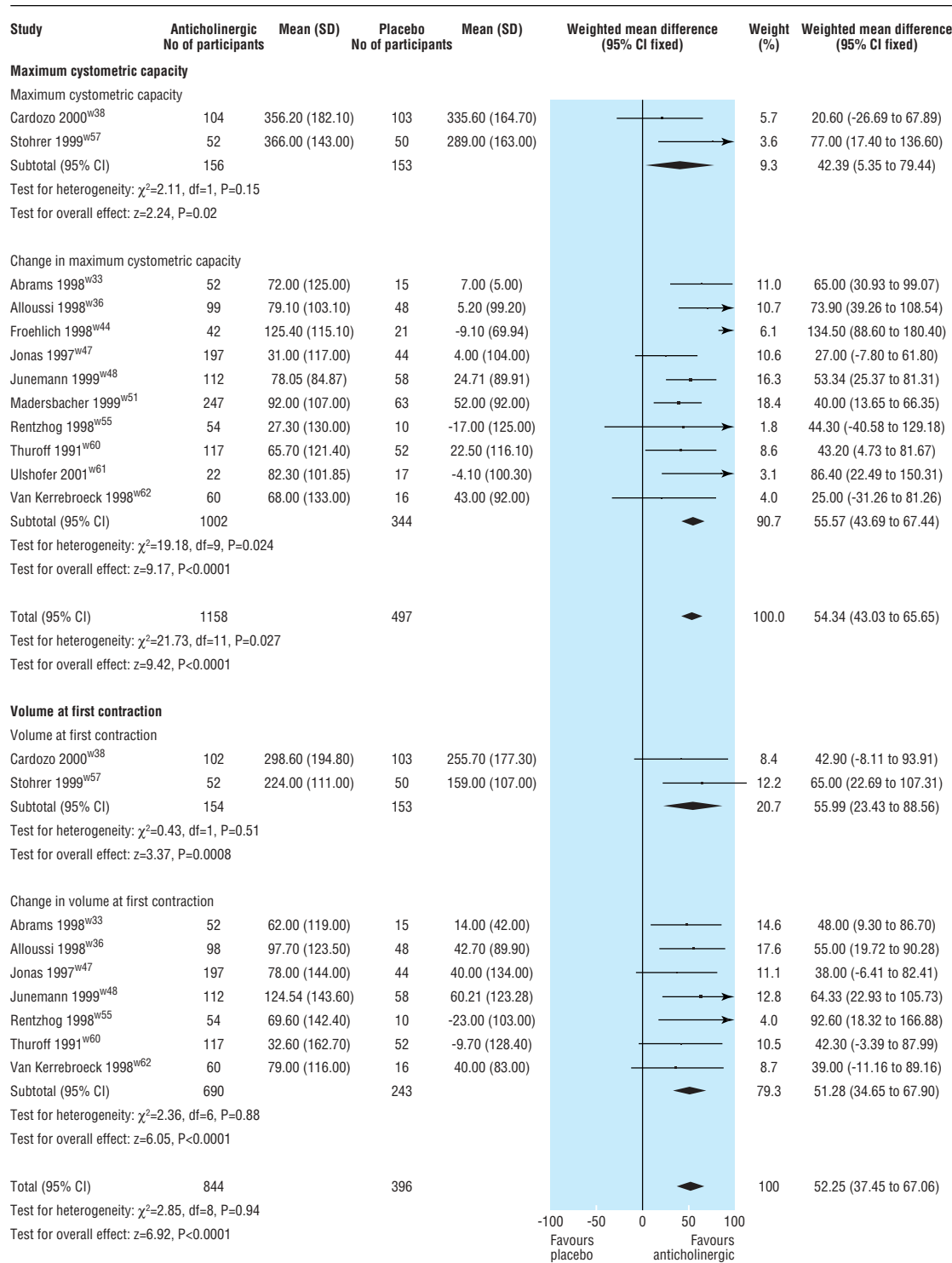Favours placebo — Favours anticholinergic

Fig 3 Effect of anticholinergics compared with placebo on maximum cystometric capacity and bladder volume at first contraction

dropouts occurred in the trials using single intravesical or oral doses of drug,[w43 w44 w50 w54 w64] and in nine trials the dropout rate was 10% or less.[w41 w46 w47 w50 w52 w53 w56 w57 w60] In the remainder, dropout rates ranged from 12% to 21%.[w42 w43 w51 w58 w63]

The primary, or only, reference for seven of the 32 included trials was a conference abstract, and none of these were interim reports of continuing studies.[w33, w35 w39 w48-w50 w59] Eight trials reported the patient's perception of cure or improvement in symptoms (fig 1).[w34 w37 w41 w45 w53 w54 w58 w63] Those receiving active treatment were more likely to be subjectively improved (relative risk 1.41, 95% confidence interval 1.29 to 1.54). Nine trials reported on post-treatment leakage episodes in 24 hours (fig 2).[w34 w37 w41 w42 w46 w53 w55 w62 w63] 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
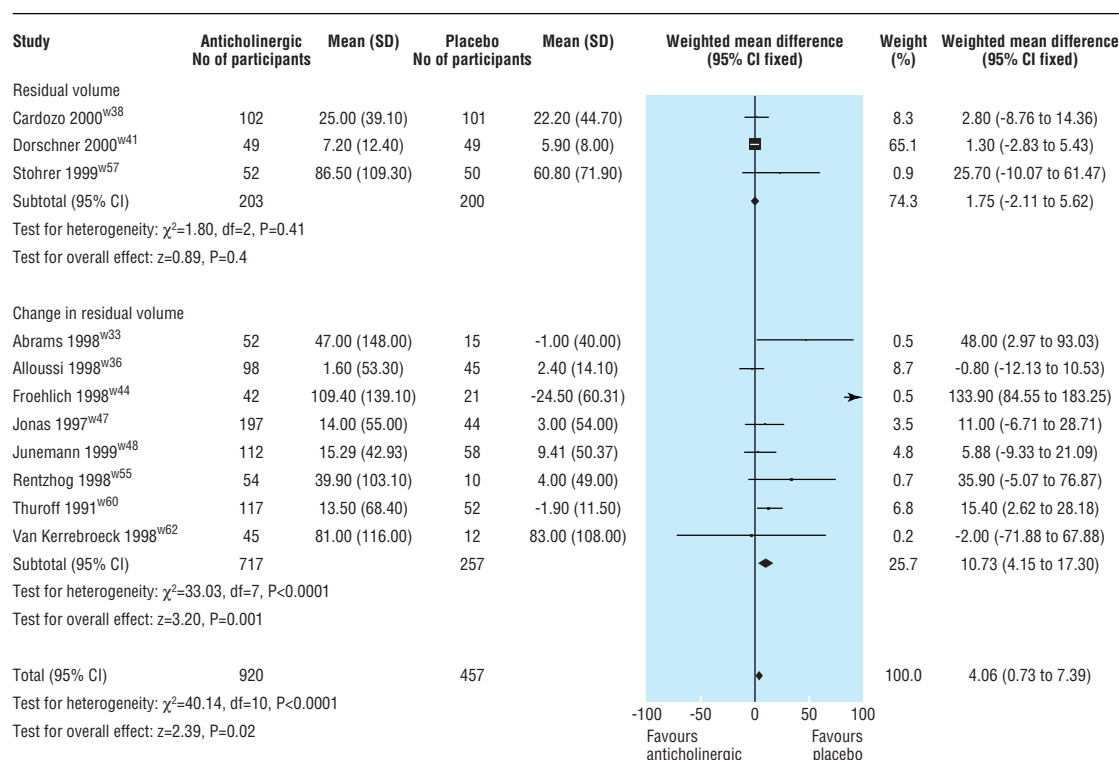
Study	Anticholinergic No of participants	Mean (SD)	Placebo No of participants	Mean (SD)	Weighted mean difference (95% CI fixed)	Weight (%)	Weighted mean difference (95% CI fixed)
Residual volume							
Cardozo 2000[w38]	102	25.00 (39.10)	101	22.20 (44.70)		8.3	2.80 (-8.76 to 14.36)
Dorschner 2000[w41]	49	7.20 (12.40)	49	5.90 (8.00)		65.1	1.30 (-2.83 to 5.43)
Stohrer 1999[w57]	52	86.50 (109.30)	50	60.80 (71.90)		0.9	25.70 (-10.07 to 61.47)
Subtotal (95% CI)	203		200			74.3	1.75 (-2.11 to 5.62)
Test for heterogeneity: χ^2=1.80, df=2, P=0.41							
Test for overall effect: z=0.89, P=0.4							
Change in residual volume							
Abrams 1998[w33]	52	47.00 (148.00)	15	-1.00 (40.00)		0.5	48.00 (2.97 to 93.03)
Alloussi 1998[w36]	98	1.60 (53.30)	45	2.40 (14.10)		8.7	-0.80 (-12.13 to 10.53)
Froehlich 1998[w44]	42	109.40 (139.10)	21	-24.50 (60.31)		0.5	133.90 (84.55 to 183.25)
Jonas 1997[w47]	197	14.00 (55.00)	44	3.00 (54.00)		3.5	11.00 (-6.71 to 28.71)
Junemann 1999[w48]	112	15.29 (42.93)	58	9.41 (50.37)		4.8	5.88 (-9.33 to 21.09)
Rentzhog 1998[w55]	54	39.90 (103.10)	10	4.00 (49.00)		0.7	35.90 (-5.07 to 76.87)
Thuroff 1991[w60]	117	13.50 (68.40)	52	-1.90 (11.50)		6.8	15.40 (2.62 to 28.18)
Van Kerrebroeck 1998[w62]	45	81.00 (116.00)	12	83.00 (108.00)		0.2	-2.00 (-71.88 to 67.88)
Subtotal (95% CI)	717		257			25.7	10.73 (4.15 to 17.30)
Test for heterogeneity: χ^2=33.03, df=7, P<0.0001							
Test for overall effect: z=3.20, P=0.001							
Total (95% CI)	920		457			100.0	4.06 (0.73 to 7.39)
Test for heterogeneity: χ^2=40.14, df=10, P<0.0001							
Test for overall effect: z=2.39, P=0.02							

-100   -50   0   50   100

Favours anticholinergic   Favours placebo

Fig 4 Effect of anticholinergics compared with placebo on residual urinary volume

leakage episodes in 24 hours 0.6, 0.4 to 0.8). Eight trials reported on the number of micturitions in 24 hours (fig 2).[w34 w41 w42 w46 w53 w55 w62 w63] 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). No significant heterogeneity was found in these results.

Twelve trials reported either maximum cystometric capacity after treatment or change in maximum cystometric capacity after treatment (fig 3).[w33-w38 w44-w57 w60-w62] 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).[w44]

Nine trials reported either volume at first contraction after treatment or change in volume at first contraction after treatment (fig 3).[w33 w36 w38 w47 w48,S55 w57 w60 w62] Volume at first contraction increased more in the drug group than in the placebo group (52 ml, 38 ml to 67 ml).

Residual volume after treatment or change in residual volume after treatment was reported by 11 trials (fig 4).[w33,S36 w38 w44 w47 w48 w51 w55 w57 w60 w62] 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).[w56]

Thirteen trials reported the number of people withdrawing owing to adverse events (fig 5).[w34-w36 w42 w46 w47 w51-w63] 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). Excluding the data from Rentzhog et al, a dose ranging study of tolterodine, did not change the finding of the pooled analysis very much (1.05, 0.81 to 1.38), but the test for heterogeneity was no longer significant (P=0.24).[w55]

Dry mouth was the most frequently reported side effect, and data on this were available from 20 trials (fig 5).[w33 w34 w37 w38 w42 w43 w46 w47 w49-w53 w55 w57 w58 w60-w63] The risk of dry mouth was two and a half times greater in the drug group (relative risk 2.56, 2.24 to 2.92). 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.[w37 w58] 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. Changing to a random effects model to get the pooled estimate did not change the results much or change the interpretation. The quality of the trials was uniform in the elements that have been shown to be most related
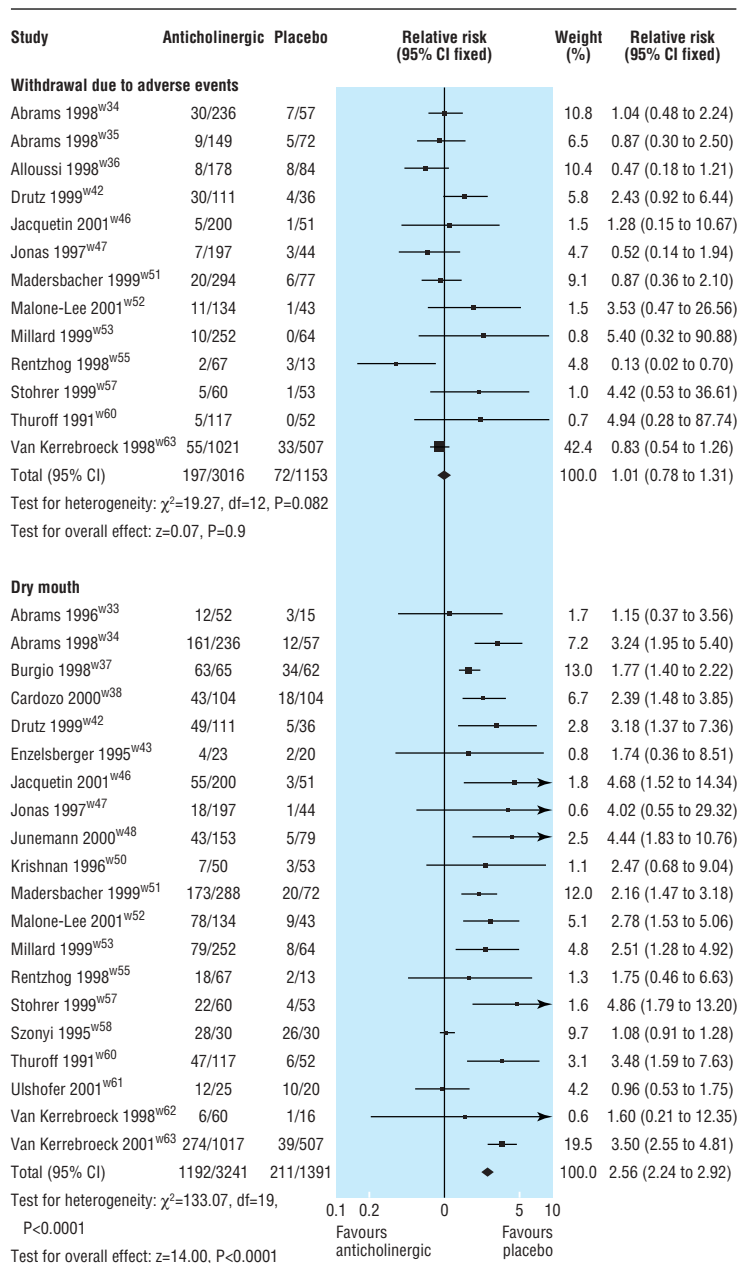
Study	Anticholinergic	Placebo	Relative risk (95% CI fixed)	Weight (%)	Relative risk (95% CI fixed)
Withdrawal due to adverse events					
Abrams 1998[w34]	30/236	7/57		10.8	1.04 (0.48 to 2.24)
Abrams 1998[w35]	9/149	5/72		6.5	0.87 (0.30 to 2.50)
Alloussi 1998[w36]	8/178	8/84		10.4	0.47 (0.18 to 1.21)
Drutz 1999[w42]	30/111	4/36		5.8	2.43 (0.92 to 6.44)
Jacquetin 2001[w46]	5/200	1/51		1.5	1.28 (0.15 to 10.67)
Jonas 1997[w47]	7/197	3/44		4.7	0.52 (0.14 to 1.94)
Madersbacher 1999[w51]	20/294	6/77		9.1	0.87 (0.36 to 2.10)
Malone-Lee 2001[w52]	11/134	1/43		1.5	3.53 (0.47 to 26.56)
Millard 1999[w53]	10/252	0/64		0.8	5.40 (0.32 to 90.88)
Rentzhog 1998[w55]	2/67	3/13		4.8	0.13 (0.02 to 0.70)
Stohrer 1999[w57]	5/60	1/53		1.0	4.42 (0.53 to 36.61)
Thuroff 1991[w60]	5/117	0/52		0.7	4.94 (0.28 to 87.74)
Van Kerrebroeck 1998[w63]	55/1021	33/507		42.4	0.83 (0.54 to 1.26)
Total (95% CI)	197/3016	72/1153		100.0	1.01 (0.78 to 1.31)
Test for heterogeneity: χ²=19.27, df=12, P=0.082					
Test for overall effect: z=0.07, P=0.9					
Dry mouth					
Abrams 1996[w33]	12/52	3/15		1.7	1.15 (0.37 to 3.56)
Abrams 1998[w34]	161/236	12/57		7.2	3.24 (1.95 to 5.40)
Burgio 1998[w37]	63/65	34/62		13.0	1.77 (1.40 to 2.22)
Cardozo 2000[w38]	43/104	18/104		6.7	2.39 (1.48 to 3.85)
Drutz 1999[w42]	49/111	5/36		2.8	3.18 (1.37 to 7.36)
Enzelsberger 1995[w43]	4/23	2/20		0.8	1.74 (0.36 to 8.51)
Jacquetin 2001[w46]	55/200	3/51		1.8	4.68 (1.52 to 14.34)
Jonas 1997[w47]	18/197	1/44		0.6	4.02 (0.55 to 29.32)
Junemann 2000[w48]	43/153	5/79		2.5	4.44 (1.83 to 10.76)
Krishnan 1996[w50]	7/50	3/53		1.1	2.47 (0.68 to 9.04)
Madersbacher 1999[w51]	173/288	20/72		12.0	2.16 (1.47 to 3.18)
Malone-Lee 2001[w52]	78/134	9/43		5.1	2.78 (1.53 to 5.06)
Millard 1999[w53]	79/252	8/64		4.8	2.51 (1.28 to 4.92)
Rentzhog 1998[w55]	18/67	2/13		1.3	1.75 (0.46 to 6.63)
Stohrer 1999[w57]	22/60	4/53		1.6	4.86 (1.79 to 13.20)
Szonyi 1995[w58]	28/30	26/30		9.7	1.08 (0.91 to 1.28)
Thuroff 1991[w60]	47/117	6/52		3.1	3.48 (1.59 to 7.63)
Ulshofer 2001[w61]	12/25	10/20		4.2	0.96 (0.53 to 1.75)
Van Kerrebroeck 1998[w62]	6/60	1/16		0.6	1.60 (0.21 to 12.35)
Van Kerrebroeck 2001[w63]	274/1017	39/507		19.5	3.50 (2.55 to 4.81)
Total (95% CI)	1192/3241	211/1391		100.0	2.56 (2.24 to 2.92)
Test for heterogeneity: χ²=133.07, df=19, P<0.0001					
Test for overall effect: z=14.00, P<0.0001					

0.1 0.2   0   5   10
Favours anticholinergic   Favours placebo

Fig 5 Effect of anticholinergics compared with placebo on withdrawal owing to side effects and dry mouth

to bias—that is, hiding the group allocation and blinding, so sensitivity analysis on the basis of study quality was not done. Few trials reported quality of life measures, and none reported an economic analysis.

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 incon-

tinence in the 1980s, these were seldom employed. The effect of repeated completion of bladder diaries could not be ascertained, but may have had a bladder retraining effect in both groups.

Many of the included studies did not report outcomes that were used in this systematic review, even though these are recommended by of the International Continence Society.[15] In addition many results were reported in a manner that rendered them unsuitable for combination with others—for example, no measure of variation was given. These omissions could have created bias, but the lack of heterogeneity would suggest that this is unlikely.

New drugs are currently being developed for the treatment of overactive bladder, as are new formulations (for example, extended release forms) and new routes of administration, such as the skin patch. These may have larger effects or have fewer side effects than is currently the case, but such possible benefits cannot be judged from our systematic review.

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.

Two small trials that compared intravesical administration of anticholinergic or placebo did seem to have more pronounced effects than trials using oral administration. Rates of cure or improvement in symptoms seemed to be increased, there was a greater increase in maximum cystometric capacity but also a greater increase in residual urine after anticholinergic therapy. These differences might be due to chance, the difference in route of administration, or some difference in the study populations.[w44 w54]

Many studies showed that trials sponsored by drug companies have more favourable outcomes than those with independent funding.[16 17] Twelve of the 32 trials declared the support of a pharmaceutical company.[w34 w38 w40-w42 w46 w55 w58 w60-w63] This support ranged from the supply of active and placebo tablets through to full funding and data analysis. None of the remaining trials made any statement about the absence or presence of company involvement, except that one trial was funded by a grant from a health research body.[w37]

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 conservative management of overactive bladder syndrome. A Cochrane systematic review shows that the effects of bladder retraining compared

<table>
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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

</td></tr>
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with placebo may be similar to the differences found here.[18] A comparison of these two treatments, and their effectiveness when combined, should be undertaken.

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