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Oral anticholinergic drugs versus placebo or no treatment for managing overactive bladder syndrome in adults (Review)

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[Intervention Review]

Oral anticholinergic drugs versus placebo or no treatment for managing overactive bladder syndrome in adults

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ABSTRACT

Background

Around 16% of adults have symptoms of overactive bladder (OAB; urgency with frequency and/or urge incontinence), with prevalence increasing with age. Anticholinergic drugs are commonly used to treat this condition.

This is an update of a Cochrane Review first published in 2002 and last updated in 2006.

Objectives

To assess the effects of anticholinergic drugs compared with placebo or no treatment for treating overactive bladder syndrome in adults.

Search methods

We searched the Cochrane Incontinence Specialised Register, which contains trials identified from the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, MEDLINE In-Process, MEDLINE Epub Ahead of Print, ClinicalTrials.gov, WHO ICTRP and handsearching of journals and conference proceedings (searched 14 January 2020), and the reference lists of relevant articles. We updated this search on 3 May 2022, but these results have not yet been fully incorporated.

Selection criteria

We included randomised or quasi-randomised trials in adults with overactive bladder syndrome that compared an anticholinergic drug alone with placebo treatment.

Data collection and analysis

Two review authors independently assessed eligibility and extracted data from the included studies, including an assessment of the risk of bias. We assessed the certainty of the body of evidence using the GRADE approach. We processed data as described in the *Cochrane Handbook for Systematic Reviews of Interventions*.

Main results

We included 104 studies, 71 of which were new or updated for this version of the review. Although 12 studies did not report the number of participants, there were 47,106 people in the remainder of the included studies. The majority of the studies had insufficient information to

allow judgement of risk of bias and we judged them to be unclear for all domains. Nine anticholinergic drugs were included in these studies: darifenacin; fesoterodine; imidafenacin; oxybutynin; propantheline; propiverine; solifenacin; tolterodine and trospium. No studies were found that compared anticholinergic drugs to no treatment.

At the end of the treatment period, anticholinergics may slightly increase condition-specific quality of life (mean difference (MD) 4.41 lower, 95% confidence interval (CI) 5.28 lower to 3.54 lower (scale range -100 to 0); 12 studies, 6804 participants; low-certainty evidence). Anticholinergics are probably better than placebo in terms of patient perception of cure or improvement (risk ratio (RR) 1.38, 95% CI 1.15 to 1.66; 9 studies, 8457 participants; moderate-certainty evidence), and the mean number of urgency episodes per 24-hour period (MD 0.85 lower, 95% CI 1.03 lower to 0.67 lower; 23 studies, 16,875 participants; moderate-certainty evidence).

Compared to placebo, anticholinergics may result in an increase in dry mouth adverse events (RR 3.50, 95% CI 3.26 to 3.75; 66 studies, 38,368 participants; low-certainty evidence), and may result in an increased risk of urinary retention (RR 3.52, 95% CI 2.04 to 6.08; 17 studies, 7862 participants; low-certainty evidence). Taking anticholinergics may be more likely to lead to participants withdrawing from the studies due to adverse events (RR 1.37, 95% CI 1.21 to 1.56; 61 studies, 36,943 participants; low-certainty evidence). However, taking anticholinergics probably reduces the mean number of micturitions per 24-hour period compared to placebo (MD 0.85 lower, 95% CI 0.98 lower to 0.73 lower; 30 studies, 19,395 participants; moderate-certainty evidence).

Authors' conclusions

The use of anticholinergic drugs by people with overactive bladder syndrome results in important but modest improvements in symptoms compared with placebo treatment. In addition, recent studies suggest that this is generally associated with only modest improvement in quality of life. Adverse effects were higher with all anticholinergics compared with placebo. Withdrawals due to adverse effects were also higher for all anticholinergics except tolterodine. It is not known whether any benefits of anticholinergics are sustained during long-term treatment or after treatment stops.

PLAIN LANGUAGE SUMMARY

Effectiveness of anticholinergic drugs for treating people with overactive bladder syndrome

Review question

We wanted to see whether a group of drugs, called anticholinergics, made a difference to adults who had an overactive bladder (OAB) syndrome when compared to a placebo (fake) treatment. We collected and analysed all relevant studies to answer this question.

Background

Overactive bladder syndrome is a common problem, especially as people get older. It means that you may suddenly feel the need to go to the toilet (called an 'urgency episode'), or suddenly leak a bit of urine. Overactive bladder is caused by your bladder muscle losing control unexpectedly. It is sometimes called 'irritable bladder', 'detrusor overactivity', 'urge incontinence' or 'urgency-frequency syndrome'.

Anticholinergic drugs are often given to people who have overactive bladder. They work by relaxing the muscles and can help some of the symptoms of overactive bladder, such as leakage or needing to go to the toilet at short notice.

How up-to-date is this review?

We studied evidence that was available up until 14 January 2020. We updated this search on 3 May 2022, but these results have not yet been fully incorporated into the review.

Study characteristics

We included 104 studies in this review. Seventy-one of these were new or had been updated since the last time this review was published in 2006.

Twelve of these studies did not report how many people were included in their research. In total across the rest of the studies, 29,682 people were given an anticholinergic drug compared to 17,424 people who were given a placebo. The smallest study was made up of 18 people while the largest had 2334 participants. Most of the studies we included in the review lasted for 12 weeks. One study investigated symptoms only in men, while nine looked at symptoms in women. The rest of the studies included both men and women.

We only included studies that used anticholinergic drugs taken by mouth, and only at dosages that doctors normally prescribe to patients. Across the studies, nine different anticholinergic drugs were included: darifenacin; fesoterodine; imidafenacin; oxybutynin; propantheline; propiverine; solifenacin; tolterodine and trospium.

Study funding sources

Seventy studies included in this review were funded by the companies that make and sell the drugs.

Key results

We found that people who take an anticholinergic drug for overactive bladder may feel a positive change in their quality of life. Also, our results show that more patients will probably perceive an improvement or cure of their symptoms of overactive bladder when compared to those who take the placebo treatment.

Taking an anticholinergic drug probably results in a small reduction in the number of urgency episodes and the number of times people with overactive bladder go to the toilet in one day.

Twenty-two people in every 100 given an anticholinergic drug felt they had a dry mouth as a side effect of the drug, compared to 6 in 100 taking placebo. Taking anticholinergics may therefore increase the risk of having a dry mouth. Anticholinergics may also result in an increased risk of urinary retention: fewer than 2 in every 100 people felt they were unable to completely empty their bladder after taking an anticholinergic drug in comparison to fewer than 0.5 in every 100 people after taking placebo.

Authors' conclusions

We found that anticholinergic drugs could result in small but important changes to a person's quality of life and their overactive bladder symptoms, however it is unclear if these changes can be sustained over a long period of time.

SUMMARY OF FINDINGS

Summary of findings 1. Anticholinergics compared to placebo for overactive bladder syndrome in adults

Anticholinergics compared to placebo for overactive bladder syndrome in adults

Patient or population: adults with overactive bladder syndrome
Setting: hospital
Intervention: anticholinergics
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Certainty of the evidence (GRADE)	No of participants (studies)	Comments
	Without anticholinergics	With anticholinergics				
Mean change from baseline in condition-specific quality of life Scale from: -100 to 0	—	—	MD 4.41 lower (5.28 lower to 3.54 lower)	⊕⊕⊖⊖ LOW[1,2]	6804 (12 RCTs)	—
Patient perception of cure or improvement	424 per 1000	161 more per 1000 (from 64 more to 280 more)	RR 1.38 (1.15 to 1.66)	⊕⊕⊕⊖ MODERATE[1]	8457 (9 RCTs)	—
Mean number of urgency episodes per 24 hours	The mean number of urgency episodes per 24 hours in placebo groups ranged from 1.8 to 10.61	—	MD 0.85 lower (1.03 lower to 0.67 lower)	⊕⊕⊕⊖ MODERATE[1]	16,875 (23 RCTs)	—
Adverse events: dry mouth	63 per 1000	158 more per 1000 (from 143 more to 174 more)	RR 3.50 (3.26 to 3.75)	⊕⊕⊖⊖ LOW[3]	38,368 (66 RCTs)	—
Adverse events:urinary retention	3 per 1000	9 more per 1000 (from 4 more to 18 more)	RR 3.52 (2.04 to 6.08)	⊕⊕⊖⊖ LOW[1,4]	7862 (17 RCTs)	—
Withdrawal due to adverse events	34 per 1000	13 more per 1000 (from 7 more to 19 more)	RR 1.37 (1.21 to 1.56)	⊕⊕⊖⊖ LOW[3,5]	36,943 (61 RCTs)	—
Mean number of micturitions per 24 hours	The mean number of micturitions per 24 hours in	—	MD 0.85 lower	⊕⊕⊕⊖ MODERATE[1]	19,395 (30 RCTs)	—

	placebo groups ranged from 8.6 to 11.69	(0.98 lower to 0.73 lower)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Downgraded one level for serious risk of bias: most of the domains were unclear.
[2]Downgraded one level for serious publication bias: strongly suspected as the plot does not resemble a symmetrical funnel, i.e. smaller studies without significant results were likely to remain unpublished.
[3]Downgraded two levels for very serious risk of bias: the majority of the domains were unclear or high risk.
[4]Downgraded one level for serious imprecision: low number of events reported.

BACKGROUND

This is an update of a Cochrane Review first published in 2002 (Hay-Smith 2002) and last updated in 2006 (Nabi 2006).

For a glossary of plain language medical terms, please see Appendix 1.

Description of the condition

Overactive bladder (OAB) is one of several clinical syndromes under the wider umbrella term of lower urinary tract syndromes (LUTS, European Association of Urology 2021). According to the International Continence Society (ICS), “overactive bladder syndrome (OAB) is defined as urinary urgency, usually with urinary frequency and nocturia, with or without urgency urinary incontinence" (ICS 2018). To be called overactive bladder syndrome, the symptoms above should not be caused by metabolic problems such as diabetes mellitus, or problems with the urinary tract such as urinary tract infection. People with neurological causes of overactive bladder symptoms, such as Parkinson’s disease, are not excluded from the diagnosis. There remains some debate on whether the above definition is useful as overactive bladder is not necessarily the same disease process in every patient, but rather a collection of symptoms that could be bothersome caused by one of many possible disease processes (Lee 2013). Nonetheless, the term overactive bladder has been commonly used in the literature and we will continue to use this terminology within this systematic review.

For the purposes of this Cochrane Review, urgency is defined as the sudden and compelling desire to pass urine, which is difficult to defer. Sometimes there is involuntary leakage of urine with the feeling of urgency, which is called urgency urinary incontinence (UUI). Frequency is the complaint of needing to void often during the day or at night. In clinical practice, a person who voids more than eight times in 24 hours is considered to have frequency. If a person wakes more than once at night to void, this is called nocturia.

Frequency, urgency, UUI or a combination of these symptoms are a common problem amongst adults living in the community. These symptoms of overactive bladder can be bothersome and have marked effects on quality of life (Johnston 2019). A global systematic review of the prevalence of UUI identified ranges from 1.5% to 36.4% (Milsom 2014). Al Edwan and colleagues, reporting on overactive bladder prevalence in North Africa and the Middle East, found that approximately 50% of women aged 40 years or over had symptoms suggestive of overactive bladder and over 90% of these had symptoms of urinary incontinence. They found that 74% of these women had never had treatment for their overactive bladder symptoms (Al Edwan 2020).

While overactive bladder is often managed in the primary care setting several barriers, including embarrassment, poor communication and low patient adherence, contribute to the under treatment of patients with burdensome urinary symptoms (Filipetto 2014).

Description of the intervention

Overactive bladder is a nonspecific storage symptom complex with poorly defined pathophysiology and may indeed result from multiple potential pathophysiological mechanisms (Peyronnet 2019). One proposed factor is myogenic in nature, relating to spontaneous contraction of the detrusor smooth muscle (Meng 2012).

The two main treatment options for overactive bladder syndrome are conservative management (e.g. bladder training (Wallace 2004), electrical stimulation (Stewart 2016)), pharmacology (e.g. botulinum toxin injections (Duthie 2011)), or a combination of both. The mainstay of pharmacological treatment at present is anticholinergic medication and this review is one of several Cochrane Reviews investigating the effects of anticholinergic drugs. Alongside this review, which compares orally administered drugs to placebo or no treatment, other Cochrane Reviews have focused on whether different anticholinergic drugs have different effects (Madhuvrata 2012); whether anticholinergic drugs are better than active non-drug therapies (Rai 2012); and whether anticholinergic drugs are better than other available drug treatments (Roxburgh 2007).

At present, anticholinergic drugs are prescribed to be taken by mouth (the focus of investigation in this review), by intravesical injection or by transdermal skin patches with different dosage requirements depending on route of administration and the pharmaceutical properties of the drug. Imidafenacin, for example, has a range of accepted oral dosage between 0.1 mg and 0.2 mg twice daily, while propantheline has a therapeutic dosage range of 15 mg three times a day up to a maximum of 120 mg per day. Further details on the individual drugs investigated in this Cochrane Review can be found in the Types of interventions section.

How the intervention might work

Anticholinergics work by blocking the muscarinic M3 receptors located on the bladder smooth muscle and as a result these muscles are relaxed. Muscarinic receptors are also found in other parts of the body (e.g. the gut, salivary glands and tear ducts). Due to the mode of action of the drug, this can lead to adverse effects. Commonly reported adverse effects include dry mouth, constipation, dyspepsia, abdominal pain, urinary retention, urinary tract infection, dry eyes, blurred vision, headache and dizziness.

Why it is important to do this review

In part due to the uncertainty around the pathophysiology or pathophysiologies of overactive bladder, there remains uncertainty as to whether orally administered anticholinergics are effective. Despite these uncertainties, anticholinergics are increasingly being used in primary and secondary care settings for the treatment of overactive bladder and this has considerable resource implications (e.g. Tang 2013).

OBJECTIVES

To assess the effects of anticholinergic drugs compared with placebo or no treatment for treating overactive bladder syndrome in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised or quasi-randomised controlled trials of anticholinergic drugs versus placebo or no treatment for treating overactive bladder syndrome. We excluded cluster-randomised trials and cross-over trials. This was because it was felt that direct comparisons of treatments in individually randomised trials would provide the strongest evidence to address this question.

Types of participants

We included studies of all adult men and women (aged 18 years and above) with a symptomatic diagnosis of overactive bladder syndrome, a urodynamic diagnosis of detrusor overactivity (either idiopathic or neurogenic), or both.

Types of interventions

We included studies where at least one arm of the study used an anticholinergic drug and one other arm was placebo or no treatment. This comparison was used for the summary of findings table.

To be included, the drug had to be a muscarinic antagonist (anticholinergic) given by mouth for the purpose of decreasing symptoms of overactive bladder. The group of drugs included darifenacin, fesoterodine, imidafenacin, oxybutynin, propantheline, propiverine, solifenacin, tolterodine and trospium.

We focused on the standard therapeutic dosage ranges for adults in Europe and the UK. These areas follows:

- Darifenacin: initially 7.5 mg once daily, increased if necessary to 15 mg after 2 weeks.
- Fesoterodine: 4 mg once daily, increased if necessary up to 8 mg once daily.
- Imidafenacin: 0.1 mg twice daily, after breakfast and supper. The dosage may be increased if necessary to 0.2 mg twice daily.
- Oxybutynin: For adults: initially 5 mg two to three times daily, increased if necessary up to 5 mg four times daily. For elderly patients: initially 2.5 mg to 3 mg twice daily, increased if tolerated to 5 mg twice daily, adjusted according to response.
- Propantheline: 15 mg three times a day, dose to be taken at least one hour before food and 30 mg, dose to be taken at bedtime; maximum 120 mg per day.
- Propiverine: Immediate-release medicines: 15 mg one to two times a day, increased if necessary up to 15 mg three times a day. Modified-release capsules: 30 mg once daily.
- Solifenacin: 5 mg once daily, increased to 10 mg once daily if necessary.
- Tolterodine: Immediate-release medicines: 2 mg twice daily, reduced if not tolerated to 1 mg twice daily. Modified-release capsules: 4 mg once daily.
- Trospium: Immediate-release medicines 20 mg twice daily, to be taken before food. Modified-release medicines – adult - 60 mg once daily.

We excluded terodiline, an anticholinergic drug previously used in the treatment of overactive bladder, because it has been withdrawn from the market due to cardiovascular toxicities it can trigger. We also excluded emepronium as it is not recommended for use in clinical practice.

We excluded trials of intravesical anticholinergic medication administration in this version of the review. We also excluded trials of other drugs with less direct anticholinergic effects (e.g. smooth muscle relaxants, flavoxate hydrochloride, calcium channel blockers, potassium channel openers, beta-adrenoceptor agonists, alpha-adrenoceptor antagonists, prostaglandin synthetase inhibitors and tricyclic antidepressants).

Types of outcome measures

Primary outcomes

- Mean change from baseline in condition-specific quality of life (e.g. measured using the OAB-Q-SF or King's Health Questionnaire).
- Perception of cure or improvement (patient-reported using a validated instrument, e.g. the Patient Perception of Bladder Condition (PPBC). The PPBC was used as the primary tool for meta-analysis).
- Mean number of urinary urgency episodes per 24 hours (patient-reported, e.g. by patient diary).

Secondary outcomes

- Number of people experiencing one or more adverse effects (i.e. dry mouth, constipation, nausea, dyspepsia/indigestion, abdominal pain, urinary retention/high residual volume, urinary tract infection (UTI), dry eyes, blurred vision, headache, dizziness, flu-like symptoms/fatigue, nasopharyngitis/sore throat, insomnia).
- Number of withdrawals due to adverse events.
- Mean number of micturitions per 24 hours.

Timing of outcome assessment

All primary and secondary outcomes were measured post-intervention.

Main outcomes for summary of findings table

We included the following seven outcomes in the summary of findings table:

- Mean change from baseline in condition-specific quality of life (e.g. measured using the OAB-Q-SF or King's Health Questionnaire).
- Perception of cure or improvement (patient-reported, using a validated instrument, e.g. the PPBC).
- Number of urinary urgency episodes per 24 hours at the end of treatment.
- Adverse effects: dry mouth.
- Adverse effects: urinary retention.
- Number of withdrawals due to adverse events.
- Mean number of micturitions per 24 hours at the end of treatment.

In terms of adverse effects, it was not possible to include all of those investigated in the summary of findings table so we selected the most commonly reported (dry mouth) and the most invasive to treat (urinary retention) to include as being of most use to patients

and clinicians (however, full details of the adverse events occurring are reported in the results).

Search methods for identification of studies

We did not impose any language or other limits on any of the searches described below.

Electronic searches

We identified relevant trials from the Cochrane Incontinence Specialised Register. For more details of the search methods used to build the Specialised Register, please see the Group's web pages. To summarise, the Register contains trials identified from the Cochrane Central Register of Controlled Trials (CENTRAL) (on CRS Web), MEDLINE (on Ovid), MEDLINE In-Process (on Ovid), MEDLINE Epub Ahead of Print (on Ovid), MEDLINE Daily, ClinicalTrials.gov, World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (WHO ICTRP), and handsearching of journals and conference proceedings. Many of the trials in the Cochrane Incontinence Specialised Register are also contained in CENTRAL.

The date of the search of the Specialised Register for this review was: 14 January 2020. We performed a further updated search on 3 May 2022 the results of which have been added to Studies awaiting classification but have not been fully incorporated into the review.

The terms used to search the Cochrane Incontinence Specialised Register and additional information about the content are given in Appendix 2.

Searching other resources

We checked the reference lists of identified trials and other relevant articles.

Data collection and analysis

We conducted data collection and analysis in accordance with methods specified in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019).

Selection of studies

Two review authors (EBM and AS) independently screened the list of titles and abstracts, retrieved the full-text articles of potentially relevant trials and assessed them for eligibility. We resolved any disagreement through discussion or by involving a third party (MS).

Data extraction and management

At least two review authors (EBM, AS, MS) independently abstracted and cross-checked data using a pre-piloted form. Any disagreements between the two review authors were resolved by consulting a third review author (either EBM, AS or MS depending on who was not involved in the original data extraction process). Where data were collected but were not reported, or were reported in a form not suitable for inclusion in the formal analysis, we sought further clarification from the trialists. We performed all data entry using Review Manager software (Review Manager 2014). For condition-specific quality of life measures, on some instruments a lower score represents a higher quality of life. However, for other instruments a lower score represents a lower quality of life. Where necessary to aid meta-analysis, all quality of life scores were reinterpreted so that a lower score represented a higher quality of life. This was completed in reference to the instruments score range and assuming all scores were cardinal measures.

Assessment of risk of bias in included studies

Two review authors (from EBM, AS, MS) independently assessed the risk of bias of the included trials using Cochrane's risk of bias assessment tool (Higgins 2011). We assessed the following domains: random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants or personnel (performance bias); blinding of outcome assessment (detection bias); completeness of outcome data (attrition bias); selective reporting (reporting bias); and other potential sources of bias. We resolved any differences in opinion by discussion. Where disagreement persisted, we consulted a third party (from either EBM, AS or MS depending on who was not involved in the original assessment).

Measures of treatment effect

Where appropriate, we undertook meta-analyses. For categorical outcomes, we related the numbers reporting an outcome to the numbers at risk in each group to derive a risk ratio (RR) and their corresponding 95% confidence intervals (CIs). For continuous variables, we used means and standard deviations (SDs) to derive a mean difference (MD) and their corresponding 95% CIs.

Unit of analysis issues

The primary analysis was per participant randomised. For multi-arm studies, with binary outcomes, we combined two or more active (anticholinergic drug) treatment arms for comparison to placebo in the meta-analyses.

For combining two or more anticholinergics in the same study for continuous outcomes, we used this formula for standard deviation: SD=sqrt(SD^2/number in first group+SD^2/number in second group). The mean is the same as the mean is in group 1*(num in this group 1/number in groups 1 and 2) + mean in group 2*num in group 2/num in groups 1 and 2).

To split the continuous outcomes, we split the number of participants in the groups and left the mean and SD as they were.

Dealing with missing data

As far as possible, we analysed data on an intention-to-treat (ITT) basis, meaning that the analysis of participants was according to the groups to which they were originally randomised. However, if data were missing, we used the numbers as reported by the trialists.

In terms of postintervention data for the outcomes 'mean number of micturitions per 24 hours' and 'urgency episodes per 24 hours', when the mean data were reported as baseline and change from baseline, we added the mean change from baseline to baseline data to get the postintervention score. SDs could not be recalculated because the correlation was not reported, therefore we borrowed them from the study in the same meta-analysis with the largest reported post-intervention SD.

Assessment of heterogeneity

We assessed heterogeneity between studies through visual inspection of plots of the data, the Chi^2 test for heterogeneity and the I^2 statistic (Higgins 2019). We used the thresholds for

interpretation of the I^2 statistic as defined by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). The interpretations are:

- 0% to 40%: might not be important;
- 40% to 60%: may represent moderate heterogeneity;
- 60% to 90%: may represent substantial heterogeneity; and
- 90% to 100%: considerable heterogeneity.

The threshold for whether the source of heterogeneity warranted exploration in a meta-analysis was 40%, i.e. there was evidence of moderate heterogeneity between studies.

Assessment of reporting biases

We used funnel plots for detecting publication bias when there were more than 10 studies in a meta-analysis.

Data synthesis

We used a fixed-effect model to calculate the pooled RRs, MDs and their 95% CIs unless there was substantial heterogeneity in which case we used a random-effects model. In studies where different doses of the same drug were compared against placebo, we used what is considered to be the therapeutic dose in the UK or EU. In studies with two or more active (anticholinergic drug) treatment arms, we combined the data from the active treatments where possible for comparison with placebo, if it was clinically appropriate to do so. For the outcomes on urgency episodes and micturitions, we used postintervention data rather than the change from baseline.

Subgroup analysis and investigation of heterogeneity

We stratified data by the type of anticholinergic received by participants in meta-analyses to investigate heterogeneity. In order to investigate differences in how people respond to anticholinergics, we had also planned other subgroup analyses based on age, sex, severity of symptoms and cause of overactive bladder symptoms (i.e. idiopathic versus neurogenic). Data were not reported in a useable form to conduct subgroup analyses and therefore these analyses were not undertaken.

We conducted the analysis for subgroup differences by stratifying each outcome by drug. The results of tests for subgroup differences were based on the I^2 value. We further explored the tests for subgroup differences indicating an I^2 value higher than 40% by deselecting drugs based on the overlapping CIs and effect sizes, and interpreted accordingly.

Sensitivity analysis

Had data allowed, we would have performed sensitivity analyses to determine the effects of including or excluding studies at an overall high risk of bias.

Summary of findings and assessment of the certainty of the evidence

We prepared a summary of findings table using the GRADEpro software for the main comparison pre-stated in Types of interventions (GRADEpro GDT).

We used the GRADE approach to assess the certainty of evidence related to the 'Main outcomes for summary of findings table' as listed in the Types of outcome measures (Schünemann 2019). We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias). We justified all decisions to downgrade the certainty of studies using footnotes.

RESULTS

Description of studies

Results of the search

In this update we included 104 studies, 71 of which were new to the review or updated for this iteration (Abrams 2013; Baert 1995; Bray 2018; Cardozo 2008a; Chapple 2004c; Chapple 2007a; Chapple 2007b; Chapple 2013; Chapple 2014; Chu 2009; Chua 2018; De Ridder 2012; Dmochowski 2008; Dmochowski 2010; DuBeau 2014; Elbaset 2019; EUCTR2004-001116-31-ES; EUCTR2004-002143-27-AT; EUCTR2007-004126-24-CZ; Geller 2013; Gotoh 2011; Griebenow 1994; Hajebrahimi 2014; Herschorn 2008; Herschorn 2009a; Herschorn 2017a; Herschorn 2017b; Hill 2005; Homma 2008; Homma 2009; Huang 2012; Junemann 2006; Kaplan 2011; Kaplan 2014; Karram 2009; Khullar 2013; Kosilov 2014a; Kosilov 2015a; Kosilov 2015b; Kreder 2002; Kuo 2015; Lackner 2011; Lee 2006; Luis 2018; Mitcheson 2019; Nitti 2005; Nitti 2007; Olshansky 2006; Oreskovic 2012; Orri 2014; Resnick 2006; Robinson 2013; Rogers 2008; Romanzi 2005; Rudy 2006; Staskin 2004; Staskin 2007; Staskin 2019; Steers 2004; Takayasu 1990; Van Kerrebroeck 2001; Vardy 2009; Wagg 2013a; Weiss 2013; Yamaguchi 2007; Yamaguchi 2012; Yamaguchi 2014; Yonguc 2019; Yoshida 2018; Zesiewicz 2015; Zinner 2006).

We screened the 1161 records identified by the literature search and obtained 495 full-text articles for further assessment. A total of 218 reports of 104 studies met the inclusion criteria and are now included in the review. Additionally, five studies are ongoing and 14 studies are awaiting classification. We excluded 262 reports of 203 studies. The flow of literature through the assessment process is shown in the PRISMA diagram (Figure 1) (covering from the inception of the review to the current version).

Figure 1. PRISMA study flow diagram (covering searches from inception to this current version of the review)

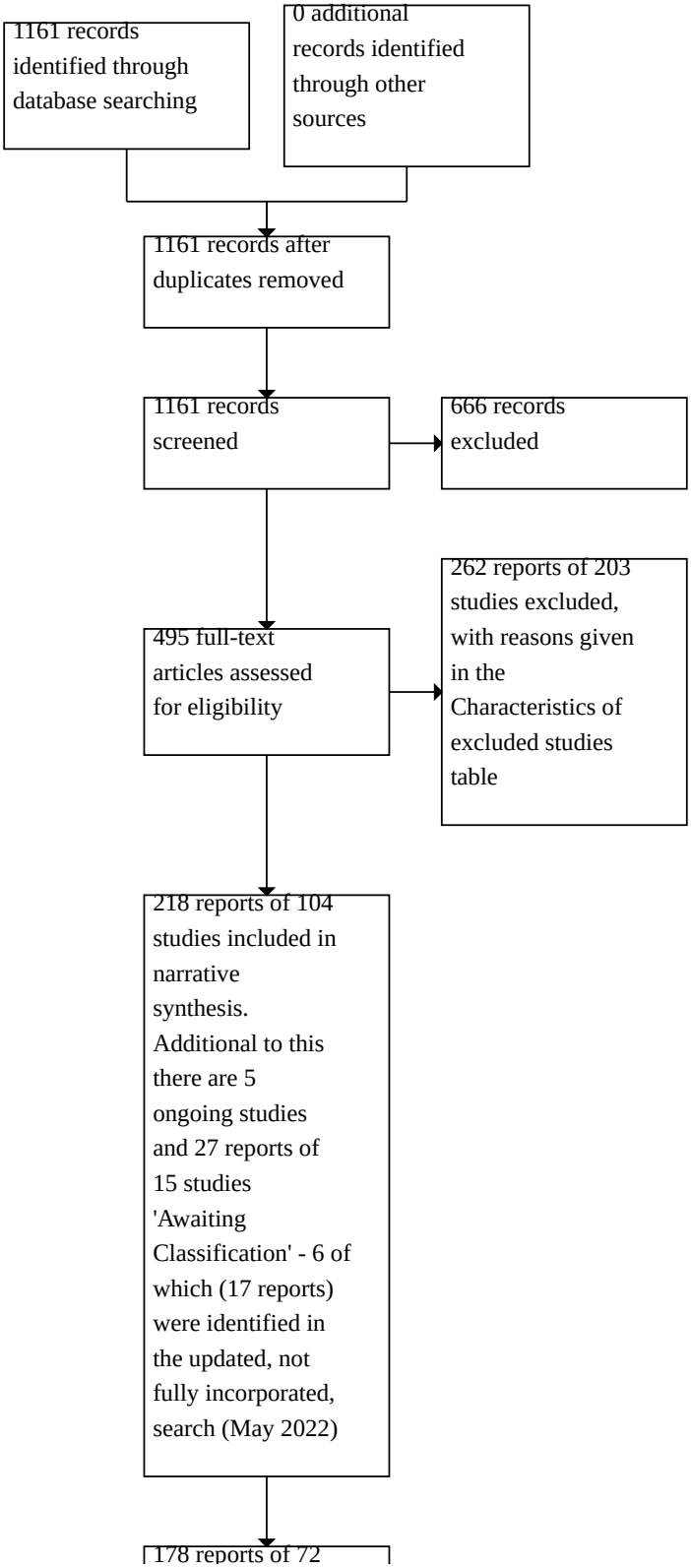
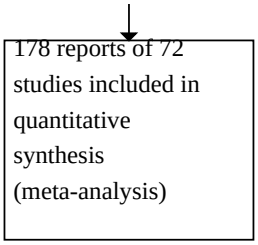


Figure 1. (Continued)



A further updated search on 3 May 2022 produced 70 records, which we screened for eligibility for this review. A total of 17 reports of six studies met the inclusion criteria but were not fully incorporated into the review (Chuang 2021; Frankel 2022; JapicCTI-152936; Kim 2022; Son 2021; Wagg 2020); these studies have been added to Studies awaiting classification.

Included studies

Further details of the studies can be found in the Characteristics of included studies.

A total of 29,682 participants received an anticholinergic drug compared to 17,424 participants who received a placebo. No studies were identified that compared an anticholinergic drug to no treatment. Twelve studies did not report group numbers (Assassa 2010; Chaliha 1998; EUCTR2004-001116-31-ES; EUCTR2007-004126-24-CZ; Hajebrahimi 2014; Hajebrahimi 2015; Kosilov 2014a; Kreder 2002; NCT00553657; Resnick 2006; Robinson 2013; Tago 1990). One study was ended by the pharmaceutical company before any participants were recruited (EUCTR2004-002143-27-AT).

One study was published in Japanese (Takayasu 1990), and one in Russian (Kosilov 2014a). We abstracted all information and data from the original papers.

Design

The studies were all randomised controlled trials (RCTs).

Sample sizes

Sample sizes ranged from 18 (Orri 2014) to 2334 (Kaplan 2011).

Setting

Forty-six trials stated that they were multinational (Abrams 1998; Abrams 2013; Alloussi 1998; Cardozo 2000; Cardozo 2004a; Cardozo 2008a; Chapple 2004a; Chapple 2004b; Chapple 2004c; Chapple 2007a; Chapple 2007b; Chapple 2013; Chapple 2014; De Ridder 2012; Drutz 1999; EUCTR2007-004126-24-CZ; EUCTR2004-001116-31-ES; EUCTR2004-002143-27-AT; Haab 2004; Herschorn 2008; Herschorn 2009a; Herschorn 2017a; Herschorn 2017b; Hill 2005; Homma 2003; Jacquetin 2001; Jonas 1997; Junemann 2000; Junemann 2006; Kaplan 2011; Kaplan 2014; Khullar 2004; Khullar 2013; Kreder 2002; Kuo 2015; Landis 2004; Malone-Lee 2001; Mitcheson 2019; Rentzhog 1998; Robinson 2013; Rovner 2005; Staskin 2019; Van Kerrebroeck 1998; Van Kerrebroeck 2001; Wagg 2013a; Zinner 2002). The total number of settings in a study ranged from two (Cardozo 2000; Drutz 1999; Homma 2003; Jacquetin 2001; Rentzhog 1998) to 42 countries (Herschorn 2017a).

Thirty-seven trials were conducted in single countries (Bray 2018; Burgio 1998; Chua 2018; Dmochowski 2008; Dmochowski 2010; DuBeau 2014; Elbaset 2019; Geller 2013; Gotoh 2011; Hajebrahimi 2014; Hajebrahimi 2015; Homma 2008; Homma 2009; Huang 2012; Kosilov 2014a; Kosilov 2015a; Kosilov 2015b; Lackner 2011; Lee 2006; Luis 2018; Assassa 2010; NCT00553657; Nitti 2005; Nitti 2007; Orri 2014; Resnick 2006; Rogers 2008; Rudy 2006; Staskin 2007; Vardy 2009; Weiss 2013; Yamaguchi 2007; Yamaguchi 2012; Yamaguchi 2014; Yoshida 2018; Zesiewicz 2015; Zinner 2004).

Twenty-two studies did not report details of the setting (Abrams 1996; Abrams 2001; Baert 1995; Chaliha 1998; Chapple 2001; Chu 2009; Dorschner 2000; Griebenow 1994; Halaska 1994; Luis 2018; Madersbacher 1999; Millard 1999; Olshansky 2006; Romanzi 2005; Steers 2004; Stohrer 1991; Stohrer 1999; Tago 1990; Thuroff 1991; Ulshofer 2001; Yonguc 2019; Zinner 2006).

Participants

The inclusion or exclusion criteria, or both, were not always well described in the studies. A common exclusion criterion was evidence of voiding dysfunction or bladder outlet obstruction, although in one study inclusion was restricted to men with symptoms of bladder overactivity and bladder outlet obstruction (Abrams 2001). Further details on study inclusion and exclusion criteria can be found in the Characteristics of included studies.

Types of symptoms

People who had symptoms consistent with overactive bladder syndrome were included in 77 studies (Abrams 1998; Abrams 2001; Abrams 2013; Baert 1995; Bray 2018; Burgio 1998; Cardozo 2000; Cardozo 2008a; Chapple 2004a; Chapple 2007a; Chapple 2007b; Chapple 2013; Chapple 2014; Chu 2009; Chua 2018; Dmochowski 2008; Dmochowski 2010; DuBeau 2014; EUCTR2004-001116-31-ES; EUCTR2004-002143-27-AT; EUCTR2007-004126-24-CZ; Geller 2013; Gotoh 2011; Griebenow 1994; Haab 2004; Hajebrahimi 2014; Hajebrahimi 2015; Halaska 1994; Herschorn 2008; Herschorn 2009a; Herschorn 2017a; Herschorn 2017b; Hill 2005; Homma 2003; Homma 2008; Homma 2009; Huang 2012; Junemann 2006; Kaplan 2011; Kaplan 2014; Karram 2009; Khullar 2004; Khullar 2013; Kosilov 2015a; Kosilov 2015b; Kreder 2002; Kuo 2015; Lackner 2011; Landis 2004; Lee 2006; Luis 2018; Malone-Lee 2001; Mitcheson 2019; NCT00553657; Nitti 2005; Nitti 2007; Olshansky 2006; Oreskovic 2012; Orri 2014; Resnick 2006; Rogers 2008; Rovner 2005; Rudy 2006; Staskin 2007; Staskin 2019; Steers 2004; Takayasu 1990; Ulshofer 2001; Vardy 2009; Wagg 2013a; Weiss 2013; Yamaguchi

2007; Yamaguchi 2012; Yamaguchi 2014; Yoshida 2018; Zinner 2002; Zinner 2006).

Seven studies restricted participation to those with neurogenic detrusor overactivity, urodynamically confirmed or not (Abrams 1996; De Ridder 2012; Stohrer 1991; Stohrer 1999; Tago 1990; Yonguc 2019; Zesiewicz 2015). Five studies included people with either idiopathic or neurogenic problems (Chapple 2004b; Chapple 2004c; Drutz 1999; Thuroff 1991; Van Kerrebroeck 2001).

Five studies did not report their inclusion criteria in a way that enabled us to judge the type of symptoms (Chapple 2001; Dorschner 2000; Kosilov 2014a; Romanzi 2005; Staskin 2004).

Sex

The majority of the studies included both men and women. Nine studies presented data for women only (Burgio 1998; EUCTR2007-004126-24-CZ; Geller 2013; Huang 2012; Lackner 2011; Oreskovic 2012; Orri 2014; Robinson 2013; Rogers 2008). One study presented data for men only (Abrams 2001).

Age

The participants' age ranged from 21 to 93 years (Olshansky 2006). However, it was only one study that included such a wide range of participant ages (Olshansky 2006). There was only one more study that included participants aged younger than 30 (Stohrer 1999). No other studies that reported participants' ages included participants older than 90. Most other studies that reported participants' ages included participants in their 40s, 50s and 60s. Twenty studies did not report participants' ages (Abrams 1996; Abrams 2001; Baert 1995; Chaliha 1998; Chapple 2001; Chapple 2014; EUCTR2004-001116-31-ES; EUCTR2004-002143-27-AT; EUCTR2007-004126-24-CZ; Griebenow 1994; Hajebrahimi 2014; Halaska 1994; Junemann 2000; Kreder 2002; Rentzhog 1998; Resnick 2006; Romanzi 2005; Tago 1990; Takayasu 1990; Yamaguchi 2012).

Interventions

All of the included studies were placebo-controlled. No study made a comparison between an anticholinergic drug and no treatment. The studies compared the following active treatments with placebo (oral and immediate or extended release).

Darifenacin was the intervention in nine studies (Baert 1995; Chapple 2007b; Haab 2004; Hill 2005; Luis 2018; Olshansky 2006; Romanzi 2005; Steers 2004; Zinner 2006).

Fourteen studies assessed the effects of fesoterodine compared with placebo (Chapple 2004a; Chapple 2007a; Chapple 2014; Dmochowski 2010; DuBeau 2014; Herschorn 2009a; Huang 2012; Kaplan 2011; Kaplan 2014; Nitti 2005; Nitti 2007; Wagg 2013a; Weiss 2013; Yonguc 2019).

Imidafenacin was the intervention of interest in three studies (Homma 2008; Homma 2009; Yoshida 2018).

Nine studies investigated the effects of oxybutynin compared with placebo (Abrams 1998; Burgio 1998; Chapple 2001; Drutz 1999; Homma 2003; Lackner 2011; Assassa 2010; Resnick 2006; Thuroff 1991).

Propiverine was studied in 12 studies (Chapple 2001; Dorschner 2000; Gotoh 2011; Griebenow 1994; Halaska 1994; Junemann 2006; Lee 2006; Madersbacher 1999; Stohrer 1999; Tago 1990; Yamaguchi 2007; Yamaguchi 2014).

Solifenacin was the intervention of interest in 19 studies (Abrams 2013; Cardozo 2004a; Cardozo 2008a; Chapple 2004b; Chapple 2004c; Chu 2009; Chua 2018; De Ridder 2012; Elbaset 2019; Hajebrahimi 2015; Herschorn 2017a; Herschorn 2017b; Karram 2009; Kosilov 2015a; Oreskovic 2012; Robinson 2013; Vardy 2009; Yamaguchi 2007; Zesiewicz 2015).

Tolterodine was by far the most studied anticholinergic drug in the included studies, with 38 studies including this as the intervention (Abrams 1996; Abrams 1998; Abrams 2001; Bray 2018; Cardozo 2000; Chapple 2004c; Chapple 2013; Drutz 1999; EUCTR2004-001116-31-ES; EUCTR2004-002143-27-AT; EUCTR2007-004126-24-CZ; Hajebrahimi 2014; Herschorn 2008; Herschorn 2009a; Homma 2003; Jacquetin 2001; Jonas 1997; Junemann 2000; Kaplan 2011; Khullar 2004; Khullar 2013; Kreder 2002; Kuo 2015; Landis 2004; Malone-Lee 2001; Millard 1999; Mitcheson 2019; NCT00553657; Olshansky 2006; Orri 2014; Rentzhog 1998; Rogers 2008; Romanzi 2005; Staskin 2019; Van Kerrebroeck 1998; Van Kerrebroeck 2001; Yamaguchi 2012; Zinner 2002).

Only one study studied the effects of propantheline (Thuroff 1991).

Twenty-two studies compared different doses of the same anticholinergic medication (Abrams 1996; Abrams 2013; Cardozo 2004a; Chaliha 1998; Chapple 2004a; Chapple 2014; Haab 2004; Hill 2005; Homma 2008; Jacquetin 2001; Jonas 1997; Junemann 2006; Kosilov 2015b; Malone-Lee 2001; Millard 1999; Nitti 2005; Nitti 2007; Rentzhog 1998; Robinson 2013; Steers 2004; Van Kerrebroeck 1998; Van Kerrebroeck 2001). Of these, five studies included arms using dosages that were not considered therapeutic. These dosages were not combined for data extraction and analysis (Chaliha 1998; Homma 2008; Nitti 2005; Rentzhog 1998; Van Kerrebroeck 1998).

Eighteen studies investigated two or more different anticholinergic drugs in comparison to placebo (Abrams 1998; Chapple 2004b; Chapple 2004c; Chapple 2007a; De Ridder 2012; Drutz 1999; Herschorn 2009a; Homma 2003; Homma 2009; Junemann 2000; Kaplan 2011; Madersbacher 1999; Assassa 2010; Olshansky 2006; Romanzi 2005; Thuroff 1991; Yamaguchi 2007; Yamaguchi 2014).

In the majority of studies, intervention was preceded by run-in periods of varying lengths and treatment with co-medications was specifically an exclusion criterion. However, for 20 of the included studies this information was not reported (Burgio 1998; Chaliha 1998; Chapple 2004b; Dmochowski 2008; DuBeau 2014; Herschorn 2008; Homma 2003; Huang 2012; Karram 2009; Lee 2006; Rogers 2008; Romanzi 2005; Rudy 2006; Stohrer 1999; Tago 1990; Vardy 2009; Wagg 2013a; Zinner 2006).

In a majority of the studies, the length of the treatment was 12 weeks (Abrams 1998; Abrams 2001; Abrams 2013; Bray 2018; Cardozo 2004a; Chapple 2004a; Chapple 2004b; Chapple 2004c; Chapple 2007a; Chapple 2007b; Chu 2009; Chua 2018; Dmochowski 2008; Dmochowski 2010; Drutz 1999; DuBeau 2014; Elbaset 2019; Gotoh 2011; Haab 2004; Herschorn 2008; Herschorn 2009a; Herschorn 2017a; Herschorn 2017b; Hill 2005; Homma 2003; Homma 2008; Homma 2009; Huang 2012; Kaplan 2011; Kaplan

2014; Karram 2009; Khullar 2013; Kosilov 2015b; Kreder 2002; Kuo 2015; Landis 2004; Lee 2006; Luis 2018; Millard 1999; Nitti 2007; Olshansky 2006; Orri 2014; Robinson 2013; Rogers 2008; Romanzi 2005; Rovner 2005; Rudy 2006; Staskin 2004; Staskin 2007; Staskin 2019; Steers 2004; Van Kerrebroeck 2001; Vardy 2009; Wagg 2013a; Weiss 2013; Yamaguchi 2007; Yamaguchi 2012; Yamaguchi 2014; Zesiewicz 2015; Zinner 2002; Zinner 2004; Zinner 2006). The remainder of the studies chose shorter treatment periods of two to four weeks in duration (Abrams 1996; Abrams 1998; Burgio 1998; Cardozo 2000; Chaliha 1998; Chapple 2013; Chapple 2014; De Ridder 2012; Dorschner 2000; EUCTR2004-001116-31-ES; Geller 2013; Griebenow 1994; Hajebrahimi 2014; Halaska 1994; Jacquetin 2001; Jonas 1997; Junemann 2000; Junemann 2006; Lackner 2011; Madersbacher 1999; Malone-Lee 2001; Oreskovic 2012; Rentzhog 1998; Stohrer 1991; Stohrer 1999; Tago 1990; Takayasu 1990; Thuroff 1991; Ulshofer 2001; Van Kerrebroeck 1998; Yonguc 2019; Yoshida 2018). There were also three studies that lasted eight weeks (Khullar 2004; Mitcheson 2019; Nitti 2005), one that lasted six weeks (Kosilov 2015a) and one that lasted 16 weeks (Cardozo 2008a).

Outcomes

Overall, there was a lack of consistency in the types of outcome measures reported by trialists and a lack of consistency in the way data were reported. Due to deficiencies in data reporting (e.g. point estimates without any measure of variation), many studies contributed only limited data to the review. The lack of similarity in measures reduced the possibilities for combining results from individual studies.

Patient perception of cure or improvement

Patient observations were rarely reported and, in reading study reports, it does not appear that these data were often collected. Where patient perception was reported, this was variable in terms of the measures used, ranging from a simple "yes/no" question to the Patient Perception of Bladder Condition (PPBC) instrument. We chose to only include studies in the meta-analysis that used the PPBC as it has previously been validated (Chapple 2007b; Dmochowski 2010; DuBeau 2014; Herschorn 2008; Herschorn 2009a; Huang 2012; Kaplan 2011; Kaplan 2014; Wagg 2013a).

Quality of life

Measures of quality of life were reported in 25 studies. Eleven studies used the King's Health Questionnaire (KHQ) (Chapple 2004b; Chapple 2004c; Chapple 2007a; Homma 2003; Homma 2008; Homma 2009; Gotoh 2011; Junemann 2006; Khullar 2004; Yamaguchi 2007; Yamaguchi 2014). Fifteen studies used the overactive bladder questionnaire (OAB-q) (Chapple 2007b; Chapple 2014; Chua 2018 Dmochowski 2010; DuBeau 2014; Herschorn 2008; Herschorn 2009a; Huang 2012; Kaplan 2011; Kaplan 2014; Karram 2009; Rogers 2008; Vardy 2009; Wagg 2013a; Weiss 2013). One study used the Incontinence Impact Questionnaire (IIQ) (Zinner 2004). One trial used the Giessen Complaint Survey and Basle Subjective Wellbeing Study (Dorschner 2000). Chapple 2004b also reported on quality life using the Contilife score. Seven studies used several measures of quality of life: Incontinence Quality of Life (IQOL) (De Ridder 2012); OAB-q and KHQ (Dmochowski 2008; Staskin 2007); IIQ and Urogenital Distress Inventory (UDI) (Oreskovic 2012); S-Qol and Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ) (Rogers 2008); OAB-q, KHQ and International Consultation of Incontinence Questionnaire (ICIQ) (Zinner 2006).

Urgency episodes per 24 hours at the end of treatment

Forty-seven studies reported urgency episodes as an outcome. However, a total of 24 studies did not contribute to this analysis. Fifteen studies did not provide the data in a format sufficient to calculate the score at the end of treatment (Abrams 2013; Bray 2018; Chapple 2007b; Chapple 2013; Chu 2009; Halaska 1994; Herschorn 2008; Herschorn 2017a; Hill 2005; Landis 2004; Lee 2006; Mitcheson 2019; Robinson 2013; Staskin 2019; Steers 2004). Other reasons for not including studies in the meta-analysis were: change from baseline mean was calculated on a per-patient basis and expressed as percentage change (Cardozo 2004a); baseline data were considered after eight weeks of the study beginning (Cardozo 2008a); only severity of urgency was reported (Haab 2004; Zesiewicz 2015); only results one month after the end of treatment were shown (Kosilov 2015b); lack of time period indication for urgency episodes (Madersbacher 1999); results were not reported (NCT00553657); and urgency episodes were reported per week (Nitti 2005; Zinner 2006). Twenty-three RCTs were included in the meta-analysis for this outcome.

Adverse events

The following adverse events were noted in the studies: dry mouth; constipation; nausea; dyspepsia/indigestion; abdominal pain; urinary retention/high residual volume; urinary tract infection (UTI); dry eyes; blurred vision; headache; dizziness; flu-like symptoms/fatigue; nasopharyngitis/sore throat; and insomnia. Other adverse events that have previously been attributed to anticholinergics but not reported in any of the studies include: tachycardia/palpations; cognitive dysfunction; and memory loss.

Adverse events were the most commonly reported secondary outcome of interest with 57 studies reporting side effects. Three studies did not make it clear whether they recorded the occurrence of adverse events (Kosilov 2014a; Kosilov 2015a; Kosilov 2015b). Forty-five studies did not report the above adverse events as an outcome (Bray 2018; Chapple 2001; Chapple 2007b; Chapple 2014; Chua 2018; De Ridder 2012; Elbaset 2019; EUCTR2004-001116-31-ES; EUCTR2004-002143-27-AT; EUCTR2007-004126-24-CZ; Geller 2013; Griebenow 1994; Hajebrahimi 2014; Hajebrahimi 2015; Halaska 1994; Herschorn 2017a; Kaplan 2011; Kaplan 2014; Karram 2009; Khullar 2013; Kreder 2002; Kuo 2015; Lackner 2011; Luis 2018; Madersbacher 1999; Assassa 2010; Mitcheson 2019; NCT00553657; Olshansky 2006; Orri 2014; Resnick 2006; Robinson 2013; Rogers 2008; Staskin 2004; Staskin 2019; Takayasu 1990; Ulshofer 2001; Wagg 2013a; Weiss 2013; Yamaguchi 2012; Yonguc 2019; Yoshida 2018; Zesiewicz 2015; Zinner 2002; Zinner 2004).

Number of micturitions per 24 hours at the end of treatment

Fifty-eight studies reported micturitions as an outcome. Twenty-eight RCTs were not included in the meta-analysis for the following reasons. Twenty-six of them did not provide sufficient information to calculate end of treatment score (Abrams 1996; Abrams 1998; Bray 2018; Cardozo 2004a; Cardozo 2008a; Chapple 2004a; Chapple 2007b; Chapple 2013; Chu 2009; Haab 2004; Hill 2005; Homma 2003; Junemann 2000; Landis 2004; Malone-Lee 2001; Nitti 2005; Oreskovic 2012; Rentzhog 1998; Robinson 2013; Rovner 2005; Staskin 2019; Steers 2004; Thuroff 1991; Van Kerrebroeck 2001; Zinner 2004; Zinner 2006). Two studies did not report the results (EUCTR2007-004126-24-CZ; NCT00553657). Thirty RCTs were included in the meta-analysis for this outcome.

Excluded studies

We excluded a total of 203 studies. Reasons for exclusion are listed in the Characteristics of excluded studies.

Risk of bias in included studies

An overview of the risk of bias assessments is graphically represented in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

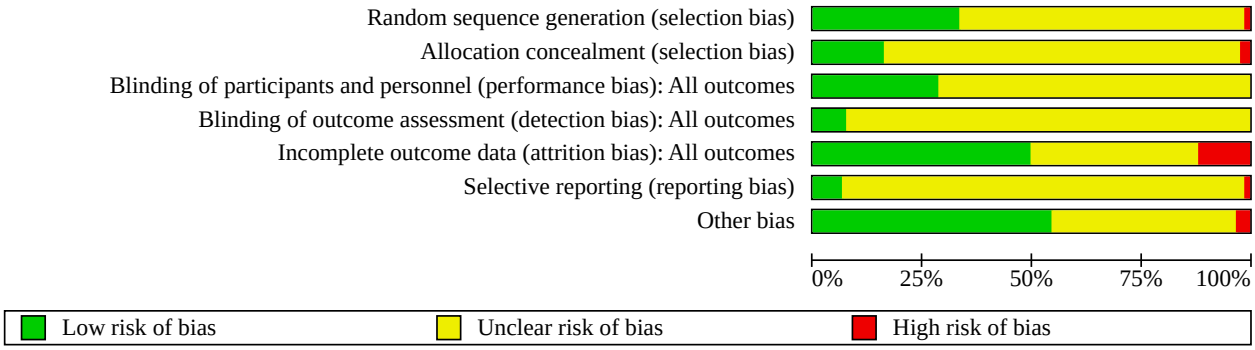


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

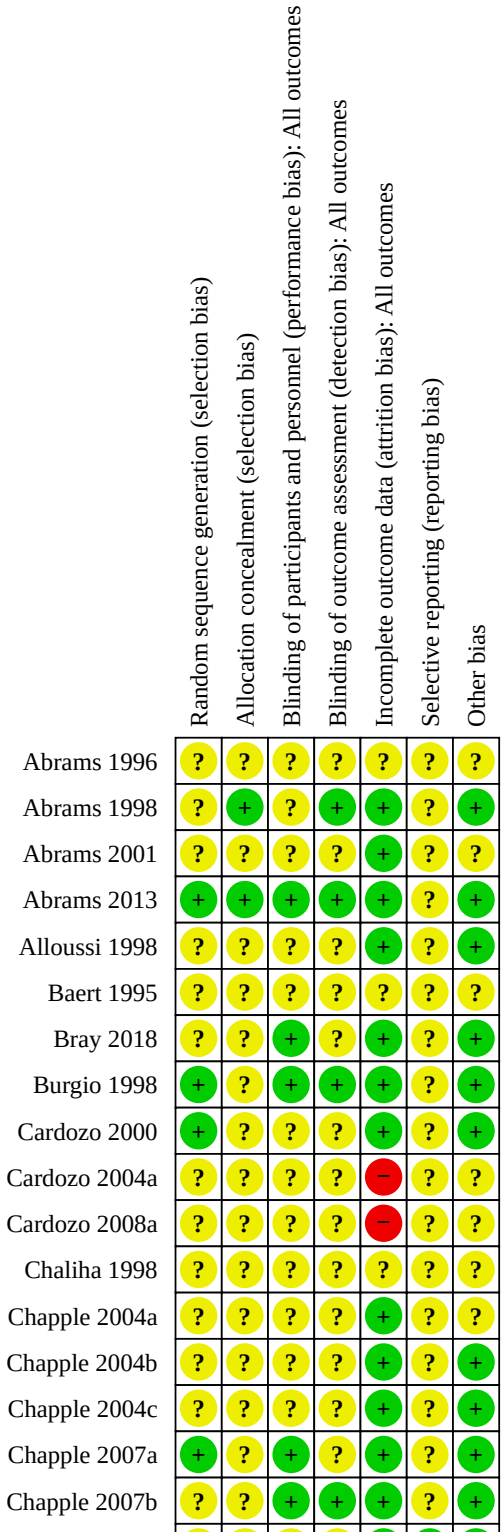


Figure 3. (Continued)

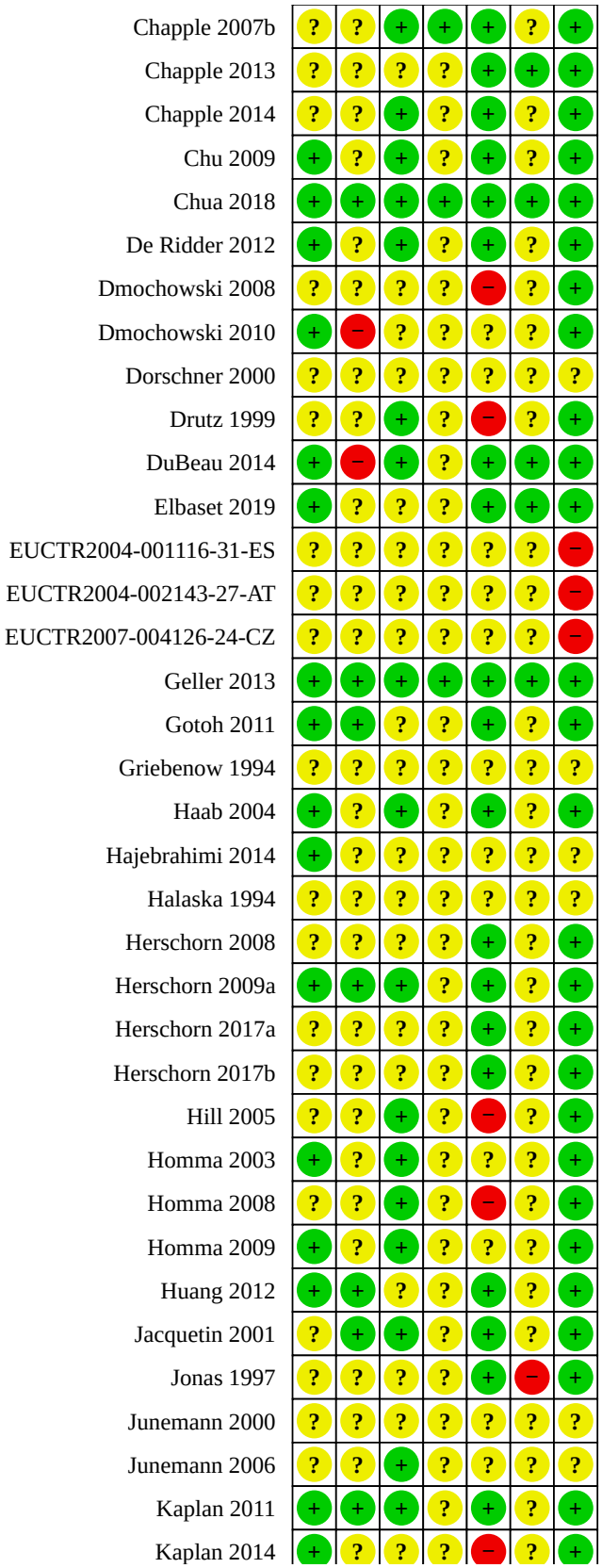


Figure 3. (Continued)

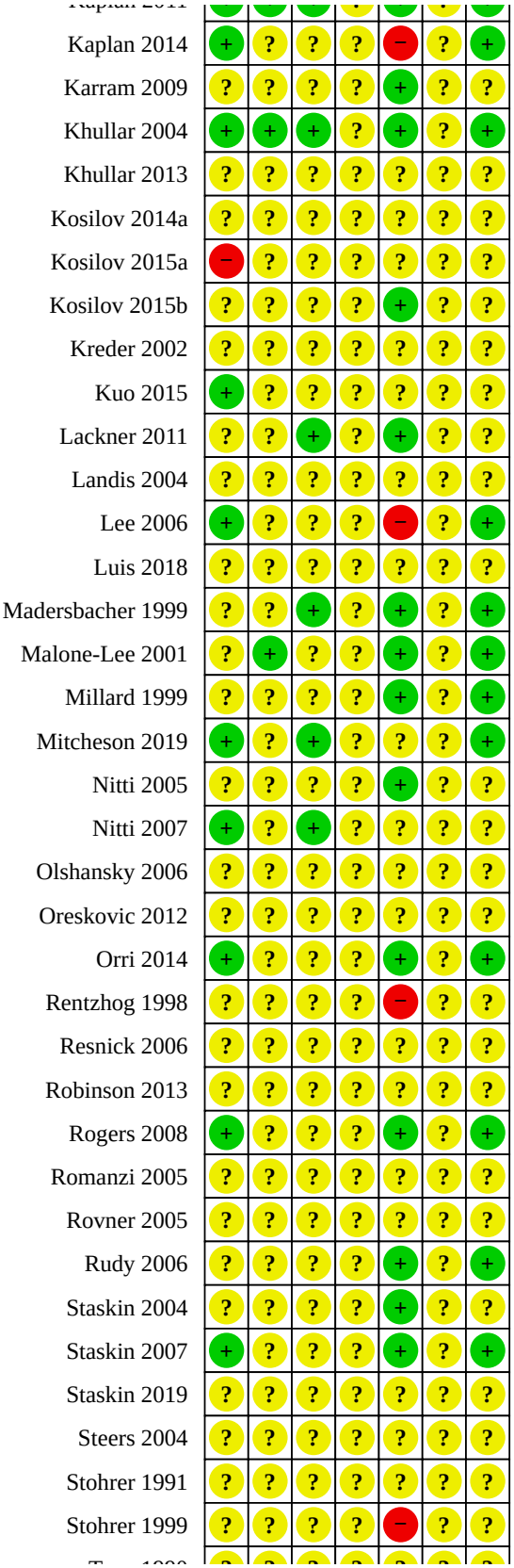
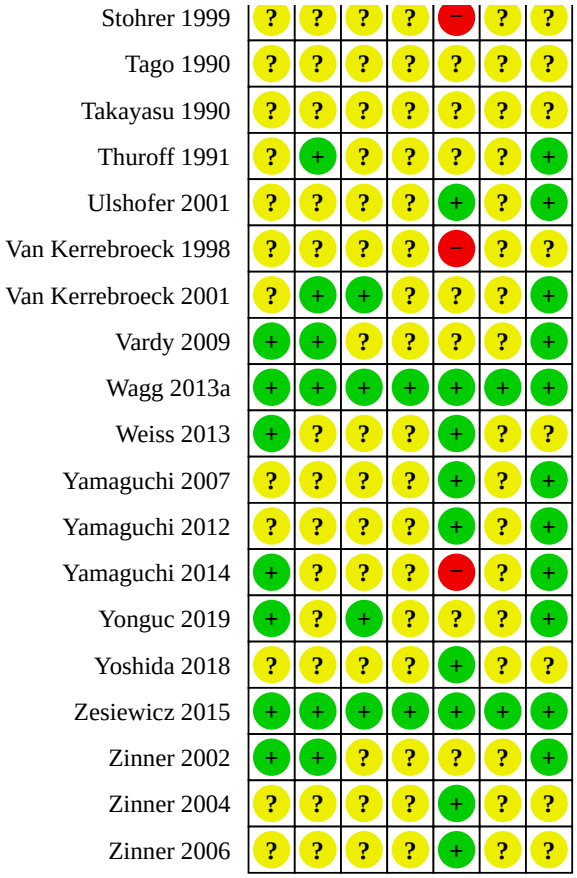


Figure 3. (Continued)



Allocation

Random sequence generation (selection bias)

Thirty-five studies provided sufficient information about the methods of random sequence generation and we judged them to be at low risk of bias (Abrams 2013; Burgio 1998; Cardozo 2000; Chapple 2007a; Chu 2009; Chua 2018; De Ridder 2012; Dmochowski 2010; DuBeau 2014; Elbaset 2019; Geller 2013; Gotoh 2011; Haab 2004; Hajebrahimi 2014; Herschorn 2009a; Homma 2003; Homma 2009; Huang 2012; Kaplan 2011; Kaplan 2014; Khullar 2004; Kuo 2015; Lee 2006; Mitcheson 2019; Nitti 2007; Orri 2014; Rogers 2008; Staskin 2007; Vardy 2009; Wagg 2013a; Weiss 2013; Yamaguchi 2014; Yonguc 2019; Zesiewicz 2015; Zinner 2002). We deemed one study to be at high risk of bias as it used a simple probability sampling technique (Kosilov 2015a). The remaining 68 studies did not provide enough details about the methods used in sequence generation and we therefore judged them to be unclear.

Allocation concealment (selection bias)

A total of 17 studies provided sufficient information to be sure there was adequate allocation concealment and we judged them to be at low risk of bias (Abrams 1998; Abrams 2013; Chua 2018; Geller 2013; Gotoh 2011; Herschorn 2009a; Huang 2012; Jacquetin 2001; Kaplan 2011; Khullar 2004; Malone-Lee 2001; Thuroff 1991; Van Kerrebroeck 2001; Vardy 2009; Wagg 2013a; Zesiewicz 2015; Zinner 2002). We judged two studies to be high risk of bias as "the randomisation schedule was generated, secured, distributed, and stored by Pfizer Global Clinical Data Services", the funder of the studies, raising concerns about independence (Dmochowski 2010; DuBeau 2014). We judged all the remaining studies to be at unclear risk of bias as they did not provide sufficient detail about allocation concealment.

Blinding

Blinding of participants and personnel (performance bias)

Blinding of participants and personnel was unclear in the majority of studies due to poor reporting of this aspect of the study. We did not judge any study to be at high risk. Thirty studies had a low risk of bias as they clearly documented their blinding process (Abrams 2013; Bray 2018; Burgio 1998; Chapple 2007b; Chapple 2014; Chu 2009; Chua 2018; De Ridder 2012; Drutz 1999; DuBeau 2014; Geller 2013 ; Haab 2004; Herschorn 2009a; Hill 2005; Homma 2003; Homma 2008; Homma 2009; Jacquetin 2001; Junemann 2006; Kaplan 2011; Khullar 2004; Madersbacher 1999; Mitcheson 2019; Lackner 2011; Nitti 2007; Van Kerrebroeck 2001; Wagg 2013a; Yonguc 2019; Zesiewicz 2015).

Blinding of outcome assessment (detection bias)

We considered blinding of outcome assessment to be adequate in nine studies, which we judged to be at low risk of bias (Abrams 1998; Abrams 2013; Burgio 1998; Chapple 2007b; Chua 2018; Geller 2013; Wagg 2013a; Zesiewicz 2015). The remaining studies did not provide enough information to enable us to make an assessment and so we judged these to be at unclear risk of bias for this domain.

Incomplete outcome data

We judged 12 studies to have inadequately reported outcome data and thus were at high risk of bias (Cardozo 2004a; Cardozo 2008a; Dmochowski 2008; Drutz 1999; Hill 2005; Homma 2008; Kaplan 2014; Lee 2006; Rentzhog 1998; Stohrer 1999; Van Kerrebroeck 1998; Yamaguchi 2014). In contrast, we judged 52 studies to be at low risk of bias as they adequately reported attrition (Abrams 1998; Abrams 2001; Abrams 2013; Alloussi 1998; Bray 2018; Burgio 1998; Cardozo 2000; Chapple 2004a; Chapple 2004b; Chapple 2004c; Chapple 2007a; Chapple 2007b; Chapple 2013; Chapple 2014; Chu 2009; Chua 2018; De Ridder 2012; DuBeau 2014; Elbaset 2019; Geller 2013; Gotoh 2011; Haab 2004; Herschorn 2008; Herschorn 2009a; Herschorn 2017a; Herschorn 2017b; Huang 2012; Jacquetin 2001; Jonas 1997; Kaplan 2011; Karram 2009; Khullar 2004; Kosilov 2015b; Lackner 2011; Madersbacher 1999; Malone-Lee 2001; Millard 1999; Nitti 2005; Orri 2014; Rogers 2008; Rudy 2006; Staskin 2004; Staskin 2007; Ulshofer 2001; Wagg 2013a; Weiss 2013; Yamaguchi 2007; Yamaguchi 2012; Yoshida 2018; Zesiewicz 2015; Zinner 2004; Zinner 2006). We judged the remainder to be at unclear risk as there was not enough information provided to make another judgement.

Selective reporting

Seven studies were at low risk of reporting bias because it was clear that the published reports included all expected outcomes (Chapple 2013; Chua 2018; DuBeau 2014; Elbaset 2019; Geller 2013; Wagg 2013a; Zesiewicz 2015). We judged one study to be at a high risk of bias in this domain (Jonas 1997). Jonas 1997 did not report three of the listed outcomes: empty resting pressure, full resting pressure and voided volume (5, 6, 11 on the list). The remaining studies were at an unclear risk of bias for this domain.

Other potential sources of bias

Three studies were at high risk of other bias as they were stopped prematurely by the drug company involved and no reasons were given for these stoppages (EUCTR2004-001116-31-ES; EUCTR2004-002143-27-AT; EUCTR2007-004126-24-CZ). We judged 57 studies to be at low risk of other bias (Abrams 1998; Abrams 2013; Alloussi 1998; Bray 2018; Burgio 1998; Cardozo 2000; Chapple 2004b; Chapple 2004c; Chapple 2007a; Chapple 2007b; Chapple 2013; Chapple 2014; Chu 2009; Chua 2018; De Ridder 2012; Dmochowski 2008; Dmochowski 2010; Drutz 1999; DuBeau 2014; Elbaset 2019; Geller 2013; Gotoh 2011; Haab 2004; Herschorn 2008; Herschorn 2009a; Herschorn 2017a; Herschorn 2017b; Hill 2005; Homma 2003; Homma 2008; Homma 2009; Huang 2012; Jacquetin 2001; Jonas 1997; Kaplan 2011; Kaplan 2014; Khullar 2004; Lee 2006; Madersbacher 1999; Malone-Lee 2001; Millard 1999; Mitcheson 2019; Orri 2014; Rogers 2008; Rudy 2006; Staskin 2007; Thuroff 1991; Ulshofer 2001; Van Kerrebroeck 2001; Vardy 2009; Wagg 2013a; Yamaguchi 2007; Yamaguchi 2012; Yamaguchi 2014; Yonguc 2019; Zesiewicz 2015; Zinner 2002).

Effects of interventions

See: **Summary of findings 1** Anticholinergics compared to placebo for overactive bladder syndrome in adults

Primary outcomes

Mean change from baseline in condition-specific quality of life

Twelve studies with a total of 6804 participants (3906 in the anticholinergic group and 2898 in the placebo group) contributed to the meta-analysis of this outcome (Chapple 2007b; Chua 2018; De Ridder 2012; DuBeau 2014; Herschorn 2008; Herschorn 2017a; Huang 2012; Junemann 2006; Kaplan 2014; Khullar 2013; Rogers 2008; Wagg 2013a). Eight of these studies used the King's Health Questionnaire (KHQ) while one used the total score of the Incontinence Quality of Life measure (IQoL) (De Ridder 2012), and three studies used Overactive Bladder Questionnaire (OAB-q) (Huang 2012; Kaplan 2014; Rogers 2008).

We used random-effects meta-analysis for this outcome due to high heterogeneity. As a reduction in score equals an improvement in quality of life for the instruments used in the studies that contributed to this meta-analysis, anticholinergic drugs may improve condition-specific quality of life compared to placebo (mean difference (MD) -4.41, 95% confidence interval (CI) -5.28 to -3.54; Analysis 1.1; Summary of findings 1; low-certainty evidence).

Eighteen studies could not be included in the meta-analysis because they reported different scales than OAB-q or KHQ (Chapple 2004b; Chapple 2013; Oreskovic 2012; Zinner 2004), did not provide overall quality of life score (Dmochowski 2010; Gotoh 2011; Homma 2003; Homma 2009; Khullar 2004; Yamaguchi 2007; Yamaguchi 2014), and/or did not report data necessary to conduct meta-analysis (such as standard deviation (SD) or standard error (SE)) (Chapple 2013; Chapple 2014; Gotoh 2011; Herschorn 2009a; Homma 2003; Homma 2009; Kaplan 2011; Karram 2009; Vardy 2009; Weiss 2013; Yamaguchi 2007; Yamaguchi 2014; Zinner 2006). For the studies that did not provide an overall quality of life score, we used the incontinence impact change from baseline score as it is considered the most appropriate. However, a brief interpretation of other domains is also provided. Please see Table 1 for quality of life results of the studies that could not be included in the meta-analysis.

All studies unequivocally reported improvement in quality of life compared to placebo, as illustrated in Table 1.

Patient perception of cure or improvement

Nine studies contributed to this outcome, with a total of 8457 participants (5367 in the anticholinergic group and 3090 in the placebo group) (Chapple 2007b; Dmochowski 2010; DuBeau 2014; Herschorn 2008; Herschorn 2009a; Huang 2012; Kaplan 2011; Kaplan 2014; Wagg 2013a).

Anticholinergic drugs probably lead to patients perceiving a greater sense of cure or improvement compared to placebo (risk ratio (RR) 1.38, 95% CI 1.15 to 1.66; P < 0.00001; Analysis 1.2; Summary of findings 1; moderate-certainty evidence).

There were 11 other studies that reported the patient perception of cure or improvement outcome but were not included in the meta-analysis due to lack of information or different scales or outcome measures used (Burgio 1998; De Ridder 2012; Geller 2013; Herschorn 2017a; Khullar 2004; Millard 1999; Rovner 2005; Takayasu 1990; Vardy 2009; Zesiewicz 2015). These studies are described in this section.

Only two studies presented the change from baseline result with the Patient Perception of Bladder Condition (PPBC) scale (De Ridder 2012; Herschorn 2017a). The results and interpretation of the results are shown in Table 2.

The remaining eight studies that were not included in either the meta-analysis or the table are included in the direction of effect plot (Table 3), since different outcome measures and scales were used across the studies. We ranked the studies by risk of bias rating (those with more risk of bias domains rated as 'low' were closer the top, and those with fewer were closer to the bottom). All of the studies reported improvement with anticholinergic drugs compared with placebo. Nonetheless, since the exact calculation of the overall improvement cannot be estimated, the result should be interpreted with caution.

Mean number of urgency episodes per 24 hours at the end of treatment

Twenty-three studies reported this outcome with a total of 16,875 participants (10,951 in the anticholinergic group and 5924 in the placebo group) (Chapple 2004b; Chapple 2007a; Chua 2018; Dmochowski 2010; DuBeau 2014; Gotoh 2011; Herschorn 2009a; Homma 2008; Homma 2009; Junemann 2006; Kaplan 2011; Kaplan 2014; Karram 2009; Kuo 2015; Nitti 2007; Oreskovic 2012, Vardy 2009; Wagg 2013a; Yamaguchi 2007; Yamaguchi 2012; Yamaguchi 2014; Yonguc 2019; Yoshida 2018).

Anticholinergic drugs probably lead to a slight reduction in urgency episodes per 24 hours at the end of treatment compared to placebo (MD -0.85, 95% CI -1.03 to -0.67; P < 0.00001; Analysis 1.3; Summary of findings 1; moderate-certainty evidence).

Secondary outcomes

Adverse events: dry mouth

Sixty-six studies reported this outcome with total of 38,368 participants (24,523 in the anticholinergic group and 13,845 in the placebo group) (Abrams 1996; Abrams 1998; Abrams 2013; Burgio 1998; Cardozo 2000; Cardozo 2004a; Cardozo 2008a; Chapple 2004a; Chapple 2004b; Chapple 2004c; Chapple 2007a; Chapple 2007b; Chapple 2014; Chu 2009; Chua 2018; Dmochowski 2008; Dmochowski 2010; Drutz 1999; DuBeau 2014; Elbaset 2019; Gotoh 2011; Haab 2004; Herschorn 2008; Herschorn 2009a; Herschorn 2017a; Hill 2005; Homma 2003; Homma 2008; Homma 2009; Jacquetin 2001; Jonas 1997; Junemann 2000; Junemann 2006; Kaplan 2011; Kaplan 2014; Karram 2009; Khullar 2004; Kosilov 2015a; Kosilov 2015b; Kuo 2015; Lee 2006; Madersbacher 1999; Malone-Lee 2001; Millard 1999; Mitcheson 2019; Nitti 2005; Nitti 2007; Rentzhog 1998; Rogers 2008; Rovner 2005; Rudy 2006; Staskin 2007; Steers 2004; Stohrer 1999; Thuroff 1991; Van Kerrebroeck 1998; Van Kerrebroeck 2001; Vardy 2009; Wagg 2013a; Weiss 2013; Yamaguchi 2007; Yamaguchi 2014; Yoshida 2018; Zinner 2002; Zinner 2004; Zinner 2006).

Anticholinergic drugs may result in an increase in dry mouth compared to placebo (RR 3.50, 95% CI 3.26 to 3.75; P < 0.00001; Analysis 1.4; Summary of findings 1; low-certainty evidence).

The I^2 value for subgroup differences for this outcome is 50.7%. When tolterodine was removed from the analyses, the I^2 value for subgroup differences was 19.2%. Additionally, without tolterodine the results changed to favour placebo more (RR 3.75, 95% CI 3.44 to 4.07). Hence, tolterodine might be better tolerated in terms of dry mouth compared to other drugs included in the review.

Adverse events: urinary retention

Seventeen included studies reported this outcome, with a total 7862 participants (4614 in the anticholinergics group and 3248 in the placebo group) (Abrams 2001; Burgio 1998; Chapple 2004b; Chu 2009; DuBeau 2014; Gotoh 2011; Herschorn 2017a; Homma 2003; Khullar 2004; Kosilov 2015a; Kosilov 2015b; Lee 2006; Nitti 2007; Rentzhog 1998; Staskin 2007; Van Kerrebroeck 1998; Zinner 2002). Anticholinergic drugs may lead to an increased risk of urinary retention compared to placebo (RR 3.52, 95% CI 2.04 to 6.08; P < 0.00001; Analysis 1.5; Summary of findings 1; low-certainty evidence).

Adverse events: abdominal pain

Fifteen studies have been included in the analysis for abdominal pain, with a total of 8195 participants (5587 in the anticholinergic group, 2608 in the placebo group) (Chapple 2004a; DuBeau 2014; Hill 2005; Homma 2003; Homma 2009; Jacquetin 2001; Junemann 2006; Khullar 2004; Kosilov 2015a; Malone-Lee 2001; Nitti 2005; Staskin 2007; Van Kerrebroeck 1998; Van Kerrebroeck 2001; Zinner 2004). The risk of having abdominal pain is 67% higher in anticholinergics group compared to the placebo group (RR 1.67, 95% CI 1.20 to 2.33; P = 0.003; Analysis 1.6).

Adverse events: blurred vision

Thirty-two RCTs reported on blurred vision and were included in the analysis, with a total of 18,639 participants (12,437 in the anticholinergic group and 6202 in the placebo group) (Abrams 2013; Alloussi 1998; Burgio 1998; Cardozo 2004a; Cardozo 2008a; Chapple 2004b; Chapple 2004c; Chu 2009; Chua 2018; DuBeau 2014; Gotoh 2011; Herschorn 2017a; Hill 2005; Homma 2003; Homma 2008; Homma 2009; Jonas 1997; Junemann 2006; Karram 2009; Khullar 2004; Kosilov 2015a; Madersbacher 1999; Malone-Lee 2001; Nitti 2005; Rentzhog 1998; Staskin 2007; Thuroff 1991; Van Kerrebroeck 1998; Van Kerrebroeck 2001; Vardy 2009; Yamaguchi 2007; Zinner 2002). Participants taking anticholinergic drugs are 58% more likely to experience blurred vision adverse event than participants in the placebo group (RR 1.58, 95% CI 1.26 to 1.99; P < 0.0001; Analysis 1.7).

Adverse events: constipation

Fifty-three studies were included in the analysis that reported on constipation, with a total of 37,317 participants (24,756 in the anticholinergic group and 12,561 in the placebo group) (Abrams 2013; Burgio 1998; Cardozo 2004a; Cardozo 2008a; Chapple 2004a; Chapple 2004b; Chapple 2004c; Chapple 2007a; Chapple 2007b; Chapple 2014; Chua 2018; Dmochowski 2008; Dmochowski 2010; DuBeau 2014; Gotoh 2011; Haab 2004; Herschorn 2008; Herschorn 2009a; Herschorn 2017a; Hill 2005; Homma 2003; Homma 2008; Homma 2009; Jacquetin 2001; Jonas 1997; Junemann 2006; Kaplan 2011; Kaplan 2014; Karram 2009; Khullar 2004; Kuo 2015; Lee 2006; Malone-Lee 2001; Mitcheson 2019; Nitti 2005; Nitti 2007; Rentzhog 1998; Rogers 2008; Rovner 2005; Rudy 2006; Staskin 2007; Steers 2004; Thuroff 1991; Van Kerrebroeck 2001; Vardy 2009; Wagg 2013a; Weiss 2013; Yamaguchi 2007; Yamaguchi 2014; Yoshida 2018; Zinner 2002; Zinner 2004; Zinner 2006). The risk of having constipation for those taking anticholinergics is more than two times higher than for those taking placebo (RR 2.03, 95% CI 1.78 to 2.31; P < 0.000001; Analysis 1.8).

The I^2 value for subgroup differences for this outcome is 76.5%. When tolterodine and oxybutynin were deselected, the I^2 value

lowered to 0%. When tolterodine and oxybutynin are added to the analyses, the risk of constipation from using anticholinergics is slightly lowered (RR 2.03, 95% CI 1.78 to 2.31), while without them it may be greater (RR 2.39, 95% CI 2.10 to 2.72). Constipation might therefore be better tolerated when taking tolterodine and oxybutynin than other anticholinergics included in the review.

Adverse events: cough

Six studies that reported cough were included in the analysis, with a total of 3853 participants (2091 in the anticholinergic group and 1762 in the placebo group) (Dmochowski 2010; DuBeau 2014; Nitti 2005; Nitti 2007; Rudy 2006; Wagg 2013a). The estimate implies that participants in the anticholinergic group have a 157% increased risk of cough compared to the placebo group (RR 2.57, 95% CI 1.39 to 4.77; P = 0.03; Analysis 1.9).

Adverse events: dizziness

Twenty-three studies were included in the analysis for dizziness, with a total of 12,444 participants (7709 in the anticholinergic group and 4735 in the placebo group) (Abrams 2013; Cardozo 2000; Chapple 2007a; Chu 2009; Chua 2018; DuBeau 2014; Herschorn 2008; Homma 2003; Homma 2008; Junemann 2006; Karram 2009; Khullar 2004; Kosilov 2015a; Kuo 2015; Lee 2006; Malone-Lee 2001; Mitcheson 2019; Nitti 2005; Rovner 2005; Thuroff 1991; Van Kerrebroeck 2001; Wagg 2013a; Zinner 2002). The result suggests that the anticholinergic group participants are 37% more at risk of experiencing dizziness compared to the participants in the placebo group (RR 1.37, CI 95% 1.09 to 1.74; P = 0.008; Analysis 1.10).

Adverse events: dry eyes

Nine studies were included in the analysis for dry eyes, with a total of 6897 participants (4177 in the anticholinergic group, 2720 in the placebo group) (Chapple 2007a; Dmochowski 2010; DuBeau 2014; Mitcheson 2019; Nitti 2005; Nitti 2007; Staskin 2007; Van Kerrebroeck 2001; Vardy 2009). The estimate implies that there is an 86% greater risk that taking anticholinergics will result in dry eyes compared to placebo (RR 1.86, 95% CI 1.23 to 2.83; P = 0.004; Analysis 1.11).

The I^2 value for subgroup differences for this outcome is 43.8%. When tolterodine was deselected, the I^2 value decreased to 0%. With tolterodine, a slight reduction in the risk of dry eyes with anticholinergics was noted (RR 1.86, 95% CI 1.23 to 2.83), whereas there was an increase with tolterodine removed from the analysis (RR 2.90, 95% CI 1.57 to 5.36). This suggests the risk of dry eyes might be reduced when taking tolterodine when compared to other anticholinergics included in this review.

Adverse events: dyspepsia/indigestion

Twenty-two studies with a total of 12,699 participants (7827 in the anticholinergic group and 4872 in the placebo group) reported dyspepsia/indigestion as an adverse event and were included in the analysis (Abrams 1998; Abrams 2013; Chapple 2004a; Chapple 2004b; Chu 2009; DuBeau 2014; Haab 2004; Herschorn 2017a; Hill 2005; Homma 2003; Homma 2008; Junemann 2006; Khullar 2004; Malone-Lee 2001; Nitti 2005; Rovner 2005; Staskin 2007; Van Kerrebroeck 2001; Vardy 2009; Wagg 2013a; Zinner 2002; Zinner 2006). The result suggests that patients taking anticholinergics are 2.24 times more likely to experience dyspepsia/indigestion than those taking placebo (RR 2.24, 95% CI 1.70 to 2.94; P < 0.00001; Analysis 1.12).

The I^2 value for subgroup differences for this outcome is 44.5%. After investigating sensitivity and deselecting tolterodine, the I^2 value reduced to 0%. When tolterodine was added to the analyses, risk of dyspepsia/indigestion with anticholinergics reduced (RR 2.24, 95% CI 1.70 to 2.94), but without tolterodine the risk increased (RR 3.24, 95% CI 2.20 to 4.77). Thus, tolterodine might present less of a risk for dyspepsia/indigestion compared to other anticholinergics included in the review.

Adverse events: flu-like symptoms/fatigue

Thirteen studies were included in the analysis for flu-like symptoms/ fatigue, with a total of 8674 participants (5344 in the anticholinergic group and 3330 in the placebo group) (Abrams 2013; Chapple 2004a; Chapple 2007a; Dmochowski 2010; DuBeau 2014; Herschorn 2008; Hill 2005; Karram 2009; Nitti 2005; Thuroff 1991; Van Kerrebroeck 2001; Vardy 2009; Wagg 2013a). There was no evidence of a difference in the risk of experiencing flu-like symptoms/fatigue but the confidence interval is wide enough to include differences favouring either anticholinergics or placebo (RR 1.19, 95% CI 0.89 to 1.59; P = 0.23; Analysis 1.13).

Adverse events: headache

Forty-one studies were included in the analysis for headache, with a total of 25,568 participants (16,482 in the anticholinergic group and 9086 in the placebo group) (Abrams 2013; Cardozo 2000; Chapple 2004a; Chapple 2004b; Chapple 2007a; Chu 2009; Chua 2018; Dmochowski 2008; Dmochowski 2010; DuBeau 2014; Haab 2004; Herschorn 2008; Herschorn 2009a; Hill 2005; Homma 2003; Homma 2008; Homma 2009; Jacquetin 2001; Jonas 1997; Junemann 2006; Kaplan 2011; Karram 2009; Khullar 2004; Lee 2006; Malone-Lee 2001; Mitcheson 2019; Nitti 2005; Nitti 2007; Rogers 2008; Rovner 2005; Rudy 2006; Staskin 2007; Steers 2004; Thuroff 1991; Van Kerrebroeck 2001; Vardy 2009; Wagg 2013a; Weiss 2013; Zinner 2002; Zinner 2004; Zinner 2006). The result implies that anticholinergics increase the risk of experiencing headache by 20% compared against placebo (RR 1.20, 95% CI 1.05 to 1.36; P = 0.007; Analysis 1.14).

Adverse events: insomnia (inability to sleep)

Five studies reported and were included in the analysis for this outcome, with a total of 4391 participants (2440 in the anticholinergic group and 1951 in the placebo group) (Dmochowski 2010; DuBeau 2014; Rogers 2008; Van Kerrebroeck 2001; Zinner 2002). There was no evidence of a difference in the risk of experiencing insomnia but the confidence interval is wide enough to include a slight reduction or a large increase in the risk of insomnia with anticholinergics compared with placebo (RR 1.39, 95% CI 0.83 to 2.32; P = 0.21; Analysis 1.15).

Adverse events: nasopharyngitis/sore throat

Seventeen studies were included in the analysis for this outcome, with a total of 9833 participants (5744 in the anticholinergic group, 4089 in the placebo group) (Abrams 2013; Chapple 2007a; Chu 2009; DuBeau 2014; Herschorn 2008; Hill 2005; Homma 2008; Homma 2009; Karram 2009; Kuo 2015; Mitcheson 2019; Nitti 2005; Nitti 2007; Rogers 2008; Rudy 2006; Wagg 2013a; Yoshida 2018). The result suggests that the risk of experiencing nasopharyngitis/sore throat

is 24% lower in the anticholinergic group than in the placebo group (RR 0.76, 95% CI 0.63 to 0.93; P = 0.006; Analysis 1.16).

The I^2 value for subgroup difference for this outcome is 44.2%. However, there are only two subgroups, fesoterodine and tolterodine, and thus subgroup differences cannot be explored between the two. From the analysis, it appears that two studies (Zinner 2002; Van Kerrebroeck 2001), out of the five studies included in the analysis (Dmochowski 2010; DuBeau 2014; Zinner 2002; Rogers 2008; Van Kerrebroeck 2001), show the opposite direction of effect from the rest of the studies, which could explain the subgroup differences.

Adverse events: nausea

Twenty-three studies reported on nausea, with a total of 13,605 participants (8432 in the anticholinergic group, 5173 in the placebo group) (Abrams 1998; Chapple 2004a; Chapple 2007a; Chu 2009; DuBeau 2014; Homma 2008; Junemann 2006; Karram 2009; Khullar 2004; Kosilov 2015a; Madersbacher 1999; Malone-Lee 2001; Mitcheson 2019; Nitti 2005; Nitti 2007; Staskin 2007; Thuroff 1991; Van Kerrebroeck 1998; Van Kerrebroeck 2001; Vardy 2009; Wagg 2013a; Zinner 2002; Zinner 2006). There was no evidence of a difference in the risk of experiencing nausea but the confidence interval is wide enough to include differences favouring either anticholinergics or placebo (RR 0.99, 95% CI 0.79 to 1.23; P = 0.91; Analysis 1.17).

Adverse events: pruritus/erythema

Three studies reported on pruritus/erythema, with a total of 981 participants (539 in the anticholinergic group, 442 in the placebo group) (DuBeau 2014; Kosilov 2015a; Kosilov 2015b). There was no evidence of a difference in the risk of experiencing pruritus/erythema but the confidence interval is very wide and include differences favouring either anticholinergics or placebo (RR 2.06, 95% CI 0.44 to 9.55; P = 0.36; Analysis 1.18).

Adverse events: urinary tract infection (UTI)

Twenty-two studies assessed UTI, with a total of 17,541 participants (11,389 in the anticholinergic group and 6152 in the placebo group) (Abrams 2013; Chapple 2014; Chu 2009; Chua 2018; DuBeau 2014; Herschorn 2009a; Herschorn 2017a; Hill 2005; Jonas 1997; Kaplan 2011; Karram 2009; Khullar 2004; Mitcheson 2019; Nitti 2005; Nitti 2007; Rogers 2008; Rudy 2006; Staskin 2007; Van Kerrebroeck 2001; Wagg 2013a; Zinner 2002; Zinner 2006). The result suggests that there is a similar or higher risk of UTI with anticholinergics compared with placebo (RR 1.23, 95% CI 1.02 to 1.48; P = 0.03; Analysis 1.19).

Number of withdrawals due to adverse events

Sixty-one RCTs reported the number of withdrawals due to adverse events with a total of 36,943 participants (23,889 in the anticholinergic group and 13,054 in the placebo group) (Abrams 1998; Abrams 2001; Abrams 2013; Alloussi 1998; Cardozo 2004a; Cardozo 2008a; Chapple 2004a; Chapple 2004b; Chapple 2004c; Chapple 2007a; Chapple 2007b; Chapple 2014; Chu 2009; Chua 2018; Dmochowski 2008; Dmochowski 2010; Drutz 1999; DuBeau 2014; Geller 2013; Gotoh 2011; Haab 2004; Herschorn 2008; Herschorn 2009a; Herschorn 2017a; Hill 2005; Homma 2008; Homma 2009; Huang 2012; Jacquetin 2001; Jonas 1997; Junemann 2006; Kaplan 2011; Kaplan 2014; Karram 2009; Khullar 2004; Kosilov 2015a; Kosilov 2015b; Kuo 2015; Lee 2006; Madersbacher 1999; Malone-Lee 2001; Millard 1999; Nitti 2005; Nitti 2007; Oreskovic 2012; Rentzhog 1998; Rogers 2008; Rudy 2006; Staskin 2007; Steers 2004; Stohrer 1999; Thuroff 1991; Van Kerrebroeck 2001; Vardy 2009; Wagg 2013a; Weiss 2013; Yamaguchi 2007; Yamaguchi 2014; Yoshida 2018; Zinner 2004; Zinner 2006). Participants in the anticholinergic group may be more likely to withdraw due to adverse events than those in the placebo group (RR 1.37, 95% CI 1.21 to 1.56; P < 000001; Analysis 1.20; Summary of findings 1; low-certainty evidence).

The I^2 value for subgroup differences for this outcome is 42.7%. After investigating sensitivity, and deselecting tolterodine, the I^2 value was reduced to 0%. With tolterodine, the risk of withdrawal due to adverse events due to anticholinergics was lowered (RR 1.37, 95% CI 1.21 to 1.56), while without tolterodine the risk may be increased (RR 1.52, 95% CI 1.33 to 1.72). Thus, tolterodine might be better tolerated overall compared to other drugs included in the review.

Number of micturitions per 24 hours at the end of treatment

Thirty studies reported the number of micturitions per 24 hours at the end of treatment with a total of 19,395 participants (12,294 in the anticholinergics group and 7101 in the placebo group) (Chapple 2004b; Chapple 2004c; Chapple 2007a; Chua 2018; Dmochowski 2010; Drutz 1999; DuBeau 2014; Gotoh 2011; Herschorn 2009a; Herschorn 2017a; Homma 2008; Homma 2009; Jacquetin 2001; Junemann 2006; Kaplan 2011; Kaplan 2014; Karram 2009; Khullar 2004; Kuo 2015; Nitti 2007; Orri 2014; Rogers 2008; Vardy 2009; Wagg 2013a; Yamaguchi 2012; Yamaguchi 2014; Yonguc 2019; Yoshida 2018; Zesiewicz 2015; Zinner 2002).

Anticholinergic drugs probably lead to a slight reduction in the number of micturitions per 24 hours compared to placebo (MD -0.85, 95% CI -0.98 to -0.73; P < 0.00001; Analysis 1.21; Summary of findings 1; moderate-certainty evidence).

Publication bias

After inspection of the funnel plots, we suspected publication bias for the 'condition-specific quality of life' outcome only as the plot does not resemble a symmetrical funnel, i.e. smaller studies without significant results were likely to remain unpublished (see Figure 4). We did not identify publication bias for any other outcomes (studies appear to be scattered symmetrically around the funnel plots) (Figure 5; Figure 6; Figure 7; Figure 8; Figure 9).

Figure 4.

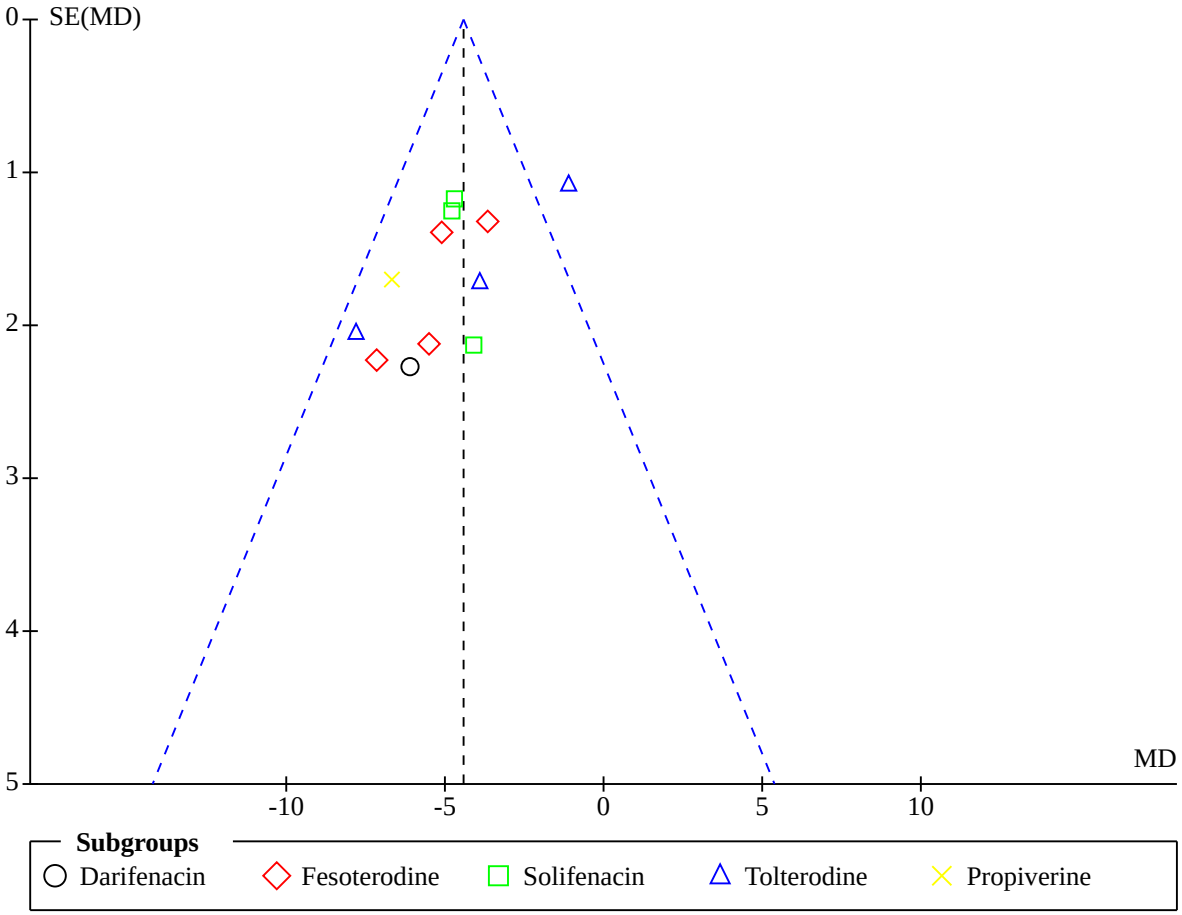


Figure 5.

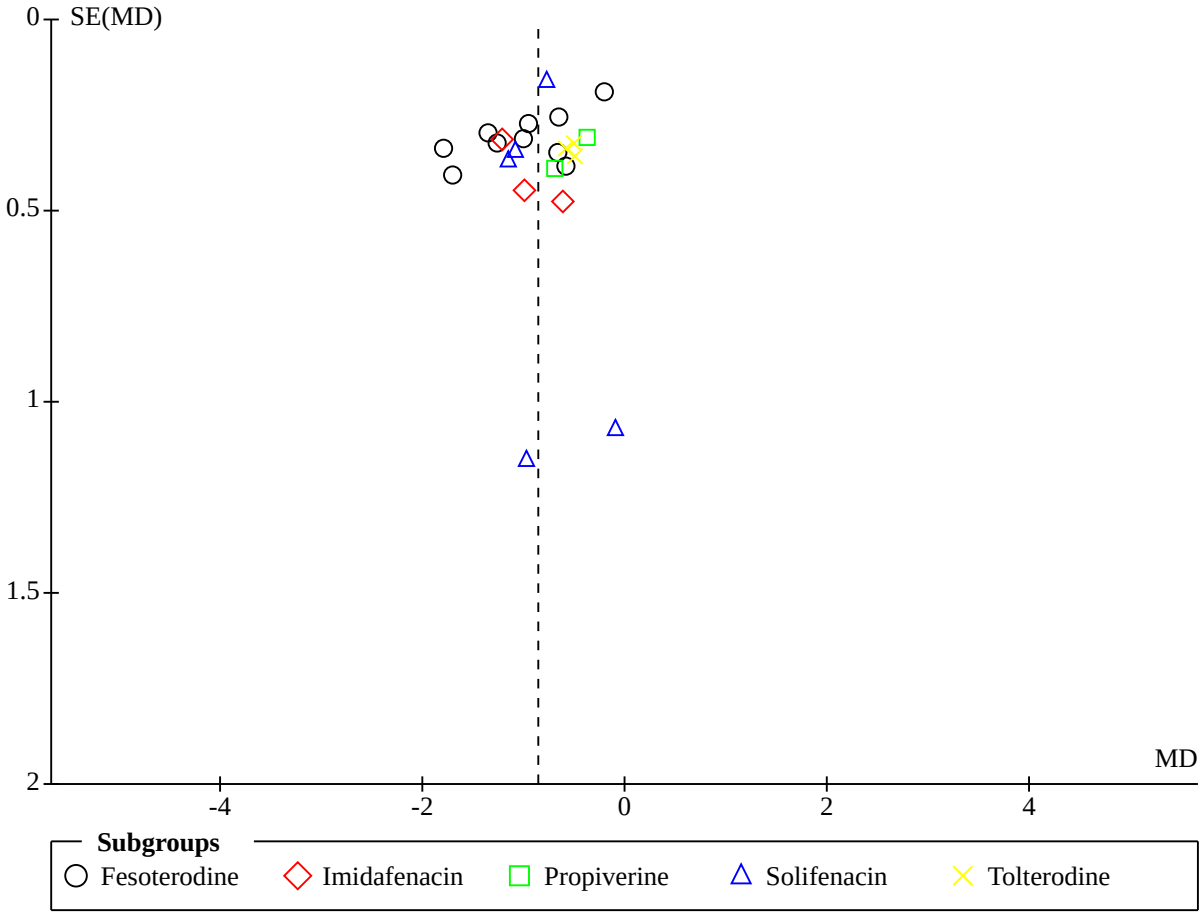


Figure 6.

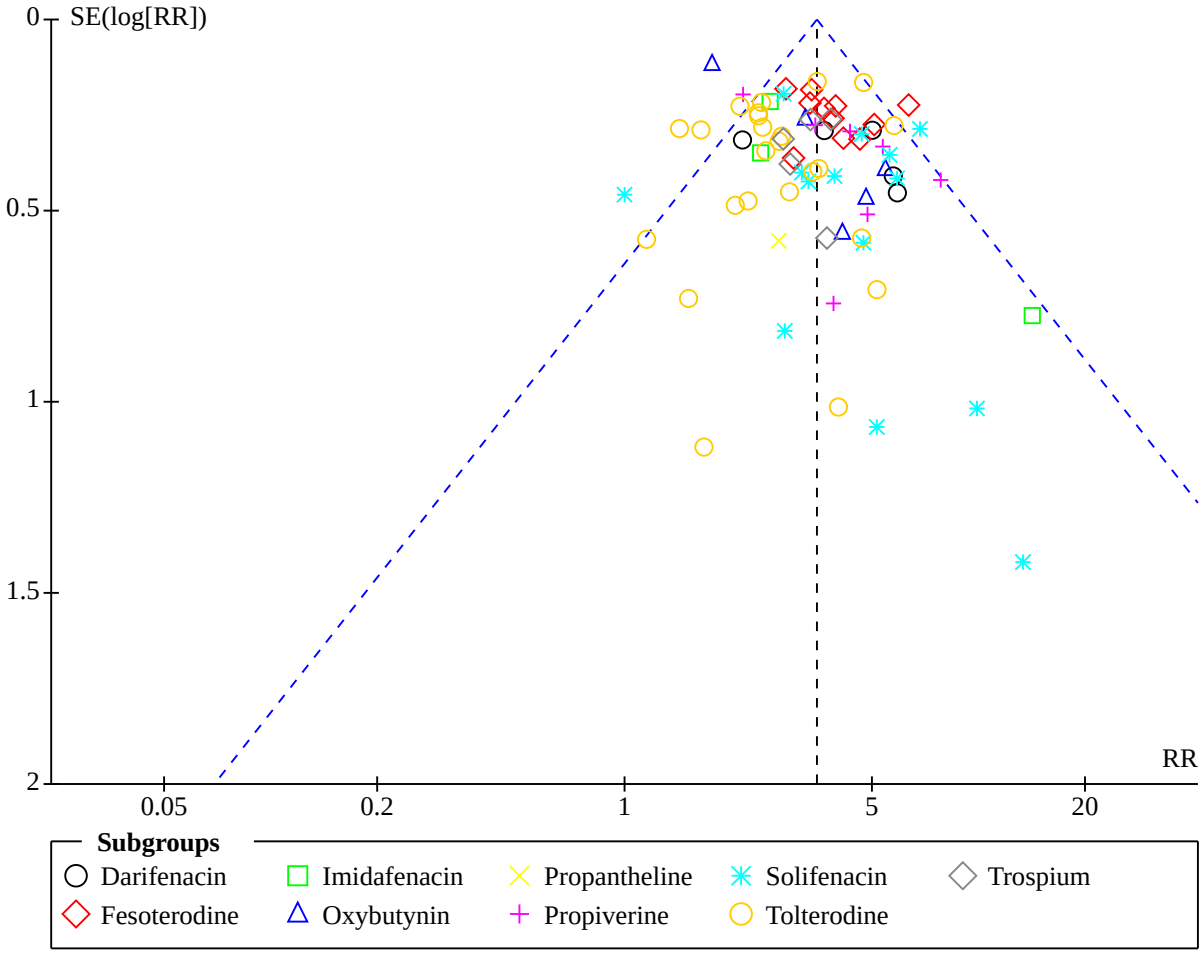


Figure 7.

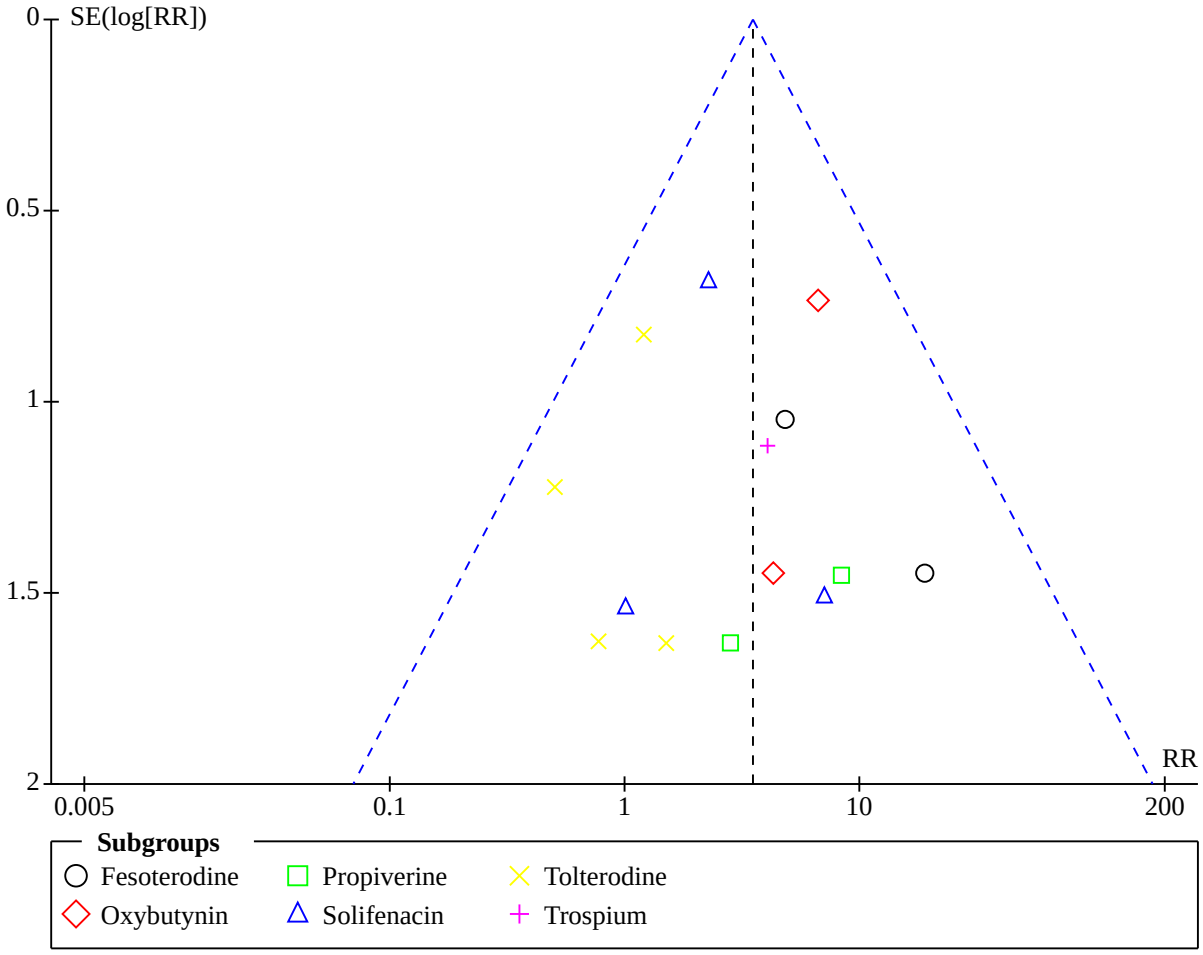


Figure 8.

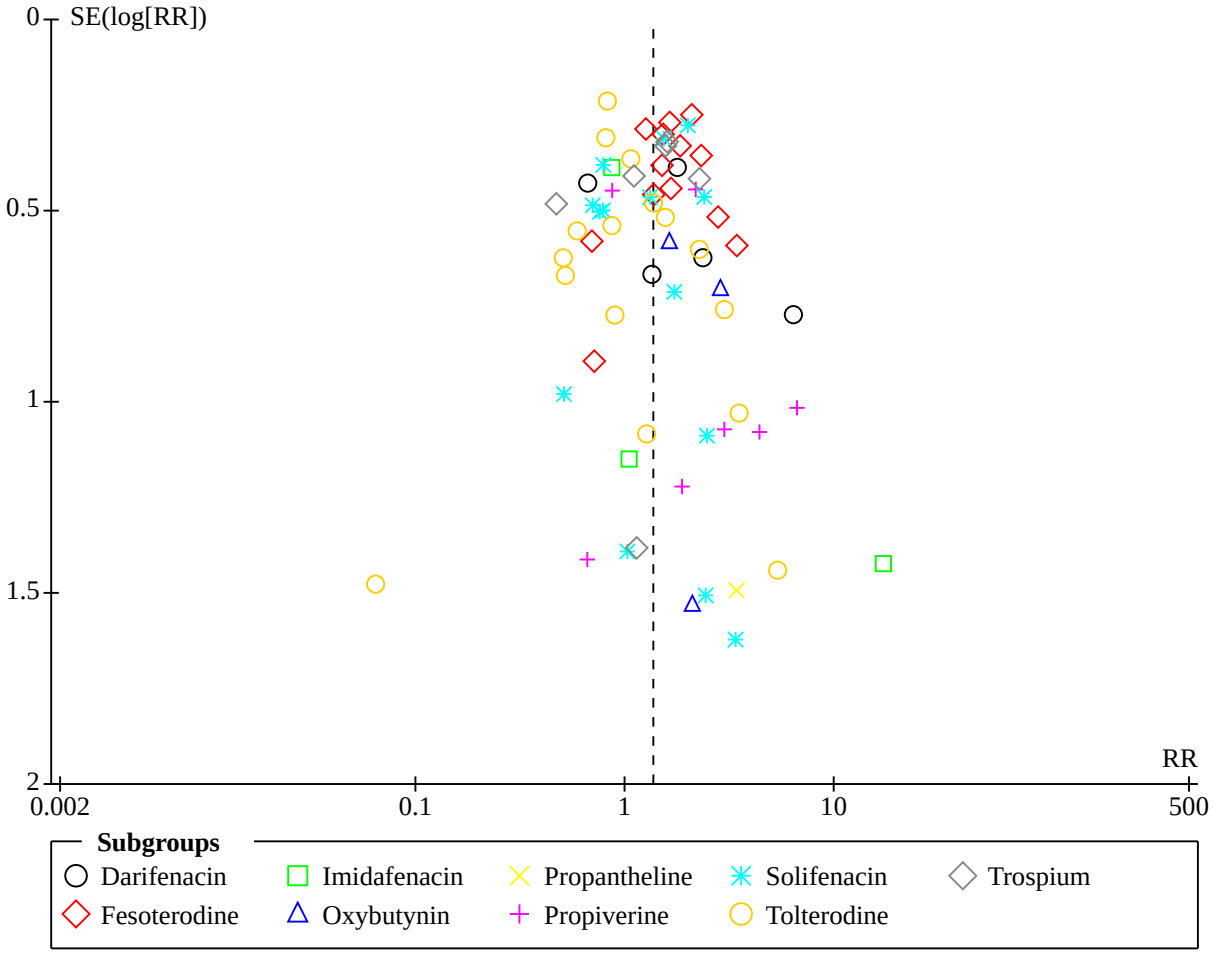
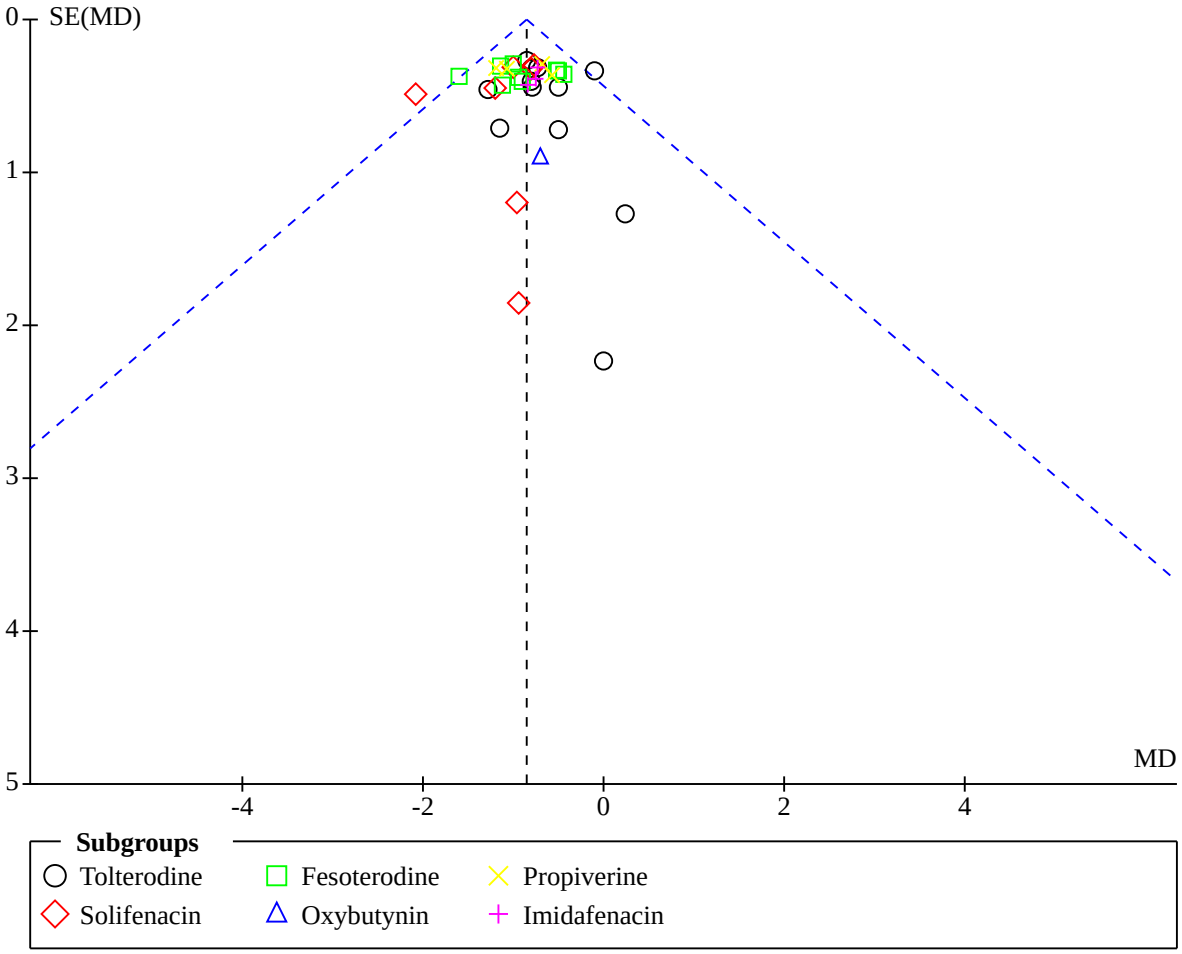


Figure 9.



DISCUSSION

This review is an update of one of a series of Cochrane Reviews of drug therapy for overactive bladder syndrome and should be viewed in that context. Other reviews have considered whether different anticholinergic drugs have different effects (Madhuvrata 2012); whether anticholinergic drugs are better than other active (non-drug) therapies (Rai 2012); and whether anticholinergic drugs are better than other drug treatments (Roxburgh 2007). This review shows that while anticholinergic drugs are more effective than placebo, and well tolerated by patients with an improvement in condition-specific quality of life, the effects on these outcomes are minimal. Thus, the risk of adverse events needs to be considered before administering anticholinergic drugs.

Summary of main results

An overview of the main outcomes can be found in Summary of findings 1.

There was moderate-certainty evidence that at the end of the treatment period anticholinergics probably performed more effectively than placebo in terms of patient perception of cure or improvement, the mean number of urgency episodes per 24-hour period and the mean number of micturitions per 24-hour period.

There was low-certainty evidence that at the end of the treatment period anticholinergics may slightly increase quality of life. However, low-certainty evidence also suggested that taking anticholinergic drugs may result in an increase in dry mouth and urinary retention adverse events, and may be slightly more likely to lead participants to withdraw due to adverse events.

Overall completeness and applicability of evidence

There are now a substantial number of studies included in this review, which appear to maintain the conclusions in previous iterations of this review. However, we assessed the majority of the risk of bias domains for these studies as being 'unclear'. In addition, there was some variation in the outcomes reported within studies and in how the same outcomes were measured across studies.

We chose not to report urodynamic data as there has been little correlation between such findings and clinical outcome (Kopp Kallner 2019). The emphasis on urodynamic measures in the literature should be re-evaluated with more focus on patient experience and socioeconomic factors. Increasingly, trials are selecting outcomes relating to patient satisfaction and acceptability of treatment, which is to be welcomed as these are important factors in the choice of management. Data from these trials have, however, shown modest effect sizes compared to

placebo (e.g. DuBeau 2014). No studies identified for inclusion in this review investigated any socioeconomic variables (e.g. income, education status).

None of the included studies reported results for those with frequency and/or urgency alone (OAB-dry) separately to those with urgency urinary incontinence (OAB-wet). As such, it was not possible to assess differences by type of overactive bladder. Similarly, the only possible subgroup analysis by sex was for withdrawal due to adverse events. It was not possible to investigate potential differences between the sexes for the majority of outcomes.

Quality of the evidence

We assessed the methodological limitations in the design, conduct or reporting of the studies included in this systematic review using the published reports of the studies and we were therefore reliant on the quality of reporting. Overall, the reporting of many studies was inadequate with many not reporting demographic details such as the age, sex or concurrent medications of the participants. This may be important as age and polypharmacy are independent predictors of dry mouth, the main adverse side effect of anticholinergics. Data were not available in some studies for many of the prespecified outcomes of this systematic review.

We assessed risk of bias using the Cochrane risk of bias tool. Many studies did not report methods and outcomes sufficiently enough to permit any judgement other than unclear risk. This was most noticeable in the selective outcome reporting domain, where only eight out of the 104 included studies provided enough information to allow judgement to take place. We judged one study to be at high risk of bias for this domain (Jonas 1997), while we judged seven to be at low risk (Chapple 2013; Chua 2018; DuBeau 2014; Elbaset 2019; Geller 2013; Wagg 2013a; Zesiewicz 2015). In terms of allocation concealment there is a risk of conflict of interest, albeit many industry-funded trials have to meet strict regulatory standards. Industry-funded trials can introduce publication bias and lead to a different interpretation of the results (Roseman 2012). However, it is worth mentioning that conflicts of interest do not necessarily cause biased results, but create a risk (Savović 2018). Our decision to rate ‘allocation concealment’ as high risk of bias in the studies that involved conflict of interest was based on the fact that the randomisation schedule was generated, secured, distributed and stored by Pfizer Global Clinical Data Services, and that no more information was provided regarding this domain. This therefore means that people involved in the allocation concealment process might have known the sequence. However, there were only two studies affected by this rationale and rating (Dmochowski 2010; DuBeau 2014).

We assessed the certainty of the evidence using GRADE. We judged the certainty of the evidence to be low for four outcomes (condition-specific quality of life, dry mouth, urinary retention and withdrawals due to adverse events). We judged the evidence for all the remaining main outcomes to be of moderate certainty. The most common reason for downgrading was study design, though imprecision was also a factor in the downgrading of both the urinary retention and withdrawal due to adverse events outcomes.

One of the limitations of the review is that many studies do not contribute to the meta-analyses. Those that do may or may not be a biased selection of the population of primary trials. We combined data from primary trials recruiting on different criteria or using different drugs in various doses. These factors may influence the estimates of effect in this review. However, the effects appear generally consistent across the included studies that did contribute data. On the few occasions where heterogeneity was observed it proved difficult to explore the reasons. The best way to address these concerns would be to perform an individual patient data meta-analysis. Many more studies would then contribute to the analysis. In addition, the effect of confounders (such as age, cause of overactive bladder) could be investigated. We also included propantheline, which is not usually used clinically any more. However, it was included in the original review and therefore we did not exclude it in this update. Finally, patient perspective would have been advantageous for this review. However, the original review was conducted a long time ago, before such procedures were common.

In general, many of the included studies had the characteristics of explanatory rather than pragmatic trials. Explanatory trials, also known as efficacy trials, address the question 'can this therapy work?' Efficacy studies tend to have strict inclusion and exclusion criteria, a comparison of therapy versus placebo and short-term outcomes. They measure surrogate rather than patient-centred outcomes (for example, urodynamics rather than quality of life) and take place in centres of clinical excellence. Their results are commonly used to support applications for drug regulatory approval. In contrast, pragmatic trials, also known as effectiveness trials, address the question 'does this therapy work?'. Effectiveness studies are characterised by large, more heterogeneous samples, comparisons with standard care, less restrictive inclusion/exclusion criteria and long-term patient-centred outcomes (Roland 1998). Their results inform the choice of management in everyday clinical settings.

All the included studies were of short duration and measured outcomes at the end of treatment. Therefore, outcomes were measured when the effects of treatment were likely to be at their maximum. Anticholinergics are unlikely to cure overactive bladder syndrome fully and are only likely to work while the patient is still taking them, so the long-term effects of continuing treatment are of most clinical interest. Some trials have continued with open-label follow-up. The interpretation of these studies is difficult, not only because of the use of active treatment by those originally allocated placebo but also because of the number of overlapping pooled analyses published, based on different numbers of primary studies. In a follow-up of a single study, it was found that 71% of patients completed 12 months of open-label follow-up on extended-release tolterodine (Van Kerrebroeck 2001). In contrast, Lawrence 2000 audited a pharmaceutical database in the USA and reported that less than a third of people continued to fill out prescriptions for either immediate-release tolterodine or immediate-release oxybutynin six months after the first prescription, although the use of oxybutynin was discontinued faster than tolterodine. This may represent the differences between people prescribed anticholinergics in a trial versus in a more typical care setting.

Pharmaceutical companies are continuing to develop anticholinergic drugs. It is worth noting that the majority of the trialists declared pharmaceutical company support (see the Characteristics of included studies). This support ranged from the supply of active and placebo tablets (in blinded packaging)

through to full funding, data analysis, writing up and publication of the results. Some of the remaining studies did not make any statement about the absence or presence of company involvement. One study was funded by grants from health research bodies (Burgio 1998). In other settings, meta-analyses comparing findings from drug company-funded studies with non-drug company-funded trials have found that the outcomes of company-funded studies are more favourable to the new treatment, although this is not always the case (Lexchin 2003; Naci 2014). In general in this review, the trials supported by companies were well reported and appeared to be of better methodological quality. However, while they examined issues of efficacy and safety, clinical and cost-effectiveness outcomes were often overlooked.

This review provides evidence of efficacy and of the likelihood of adverse effects, particularly dry mouth. Some studies suggest that the positive effects are translated into improved quality of life while medication continues, at least to a modest level. However, there is very little evidence about the long-term effects of anticholinergic medication. This applies to fixed-length courses of treatment and to continued treatment for an indefinite period of time, both during treatment and after it has stopped. Addressing these issues requires a shift in the research agenda to more pragmatic trial designs.

Potential biases in the review process

One potential source of bias may have been introduced while selecting outcomes for the summary of findings table. As data from all the previously included studies from the original review were already entered within RevMan, there is a possibility that the review authors' judgement for selecting the outcomes for the summary of findings table might have been influenced by the data that were already entered. However, in order to reduce the risk of potential bias in the review process, we followed the methods detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Despite our best efforts, not all relevant literature may have been identified and therefore the included studies may be a biased selection based on what was available. Furthermore, although we attempted to conduct a comprehensive search for studies, the fact that six studies identified in the most recent searches have not yet been incorporated may be a source of potential bias.

Agreements and disagreements with other studies or reviews

We identified several different systematic reviews that investigated the use of anticholinergics in the treatment of overactive bladder syndrome (Chapple 2005b; Chapple 2008a; Haeusler 2002; Harvey 2001; Hartmann 2009a; Kessler 2011a; McDonagh 2009; Oefelein 2011; Reynolds 2015; Shamliyan 2012). The majority of these reviews were limited to placebo-controlled studies. While the inclusion criteria of this review allowed for studies that had a no treatment control arm, no studies were identified where that was the case.

Most of the other reviews reached similar conclusions to this Cochrane Review, namely that while anticholinergic drugs are more effective than placebo, and well tolerated by patients with an improvement in condition-specific quality of life, the effects on these outcomes are minimal. They also identify no real differences among the different anticholinergics studied, with the exception of dry mouth.

Similar to the another Cochrane Review (Madhuvrata 2012), Kessler identifies 10 mg or more of oxybutynin taken orally as presenting the highest risk of dry mouth (Kessler 2011a), whereas our review finds the risk to be greater with solifenacin. This could be a consequence of more studies choosing to include solifenacin as an interventional drug in more recent years.

Two further meta-analyses of tolterodine versus placebo have been published (Appell 1997; Larsson 1999). However, neither of these publications provides an adequate systematic review of the available trials comparing anticholinergic drugs with placebo. Neither publication reports the objectives of the systematic review, a search strategy, inclusion and exclusion criteria for trials, or the methods of data extraction and analysis. It appears that these meta-analyses combine the results of pharmaceutical company-funded phase II (Larsson 1999), or phase III (Appell 1997), trials of tolterodine versus placebo.

In summary, while most of the reviews align with our conclusions in suggesting that anticholinergics are better than placebo, the effect is modest and may not be of clinical benefit to patients with overactive bladder. Ultimately, the choice must be left to the patient to decide whether their symptoms are sufficiently relieved and whether the side effects are tolerable for the level of improvement achieved.

AUTHORS' CONCLUSIONS

Implications for practice

The administration of anticholinergic drugs for overactive bladder syndrome results in differences compared to placebo medication. Those receiving anticholinergic therapy were more likely to perceive cure or improvement of symptoms, and a reduction in leakage and urgency episodes and voids (fewer than one per day). Evidence from more recently reported studies also indicates modestly improved quality of life. However, there was also a marked placebo response. When counselling those with overactive bladder syndrome, these benefits need to be balanced with the risk of side effects, such as dry mouth. Depending on the type of medication being offered, the risk of dry mouth may be increased by three times.

The only long-term follow-up comes from open-label studies, with anticholinergic therapy offered to all study participants regardless of their original allocation to active or placebo treatment. The short duration of most studies and the lack of long-term follow-up gives us little information about the long-term effects and acceptability of anticholinergic therapy.

Cost-effectiveness was also not addressed by any of the studies identified for inclusion in this review.

Although over 100 studies were identified for this review, most of the evidence assessed in our summary of findings table was of low to moderate certainty. The certainty in the evidence base could be increased by study authors reporting their methods in more detail. Finally, the six studies that are currently awaiting classification may alter the conclusions of this review once assessed.

Implications for research

Anticholinergics can help some people with overactive bladder syndrome with their quality of life, though it may be necessary to find the best one for each individual. To allow the results of trials to be considered together most usefully, any future research into overactive bladder syndrome should incorporate standardised, validated outcomes and quality of life measures that are relevant to those with overactive bladder syndrome. Furthermore, the patient perspective on outcomes and measures also needs to be considered so that trials are more relevant. Particular attention needs to be paid to the patient perception of change and satisfaction with outcome, quality of life and economic outcomes. The emphasis on reporting urodynamic measures needs to be redressed. Clearly reporting the methods of group allocation and the reasons for withdrawal from the studies would reduce the risk of bias and potentially identify issues with the study methodology. Outcome assessors should be blinded to group allocation and this should be more clearly reported in studies to further reduce the risk of bias.

As anticholinergic drugs are not intended to be curative, sustained success is likely to depend on people continuing to take them. Trials are needed to assess the long-term usefulness of these drugs. The most commonly prescribed anticholinergics have now been compared with placebo in a number of trials and have been found to be effective, albeit with adverse effects. In our view, placebo-controlled trials should be confined to testing the short-term efficacy and safety of any new anticholinergic therapies. Longer trial durations may provide new insights into the long-term effectiveness of these therapies and provide data on the duration of adverse effects and the longevity of effects on patient quality of life. However, as most of the available anticholinergics are effective, new drugs might be better compared to existing first-line treatments including both existing anticholinergics and bladder training.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abrams 1996

Study characteristics	
Methods	**Study design:** RCT, placebo-controlled, parallel design, phase II **Study dates:** not reported
Participants	**Setting:** multicentre **Country:** not reported **Age:** not reported **Sex:** not reported **Inclusion criteria:** objective signs of neurological disease and urinary frequency or incontinence and urodynamically proven detrusor hyperreflexia **Exclusion criteria:** treatment within preceding 14 days with other anticholinergic drugs
Interventions	**Group I (n = 15):** placebo **Group II (n = 14):** tolterodine 1 mg twice a day

Abrams 1996 *(Continued)*

	Group III (n = 16): tolterodine 2 mg twice a day **Group IV (n = 10):** tolterodine 4 mg twice a day, but not relevant to the review **Group V (n = 12):** tolterodine 0.5 mg twice a day, but not relevant to the review 14-day treatment period 2-week run-in
Outcomes	Number of leakage episodes, frequency of micturition, volume voided Urodynamic parameters Adverse events Laboratory tests ECG Blood pressure
Study funding sources	Not reported
Notes	Abstract Dose reduction permitted within first week Dropouts not stated Incomplete subjective data No follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	States double-blind but blinding is not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, no prespecified outcomes
Other bias	Unclear risk	Insufficient information

Abrams 1998

Study characteristics

Methods	**Study design:** RCT:placebo-controlled, parallel design, phase III

Abrams 1998 *(Continued)*

	Dates study conducted: July 1995 to July 1996
Participants	**Setting:** multicentre **Country:** multinational (UK, Republic of Ireland, Sweden) **Age (mean, range):** placebo: 58 (26 to 78); tolterodine: 55 (19 to 80); oxybutynin: 58 (21 to 80) **Sex:** 222 females and 71 males **Inclusion criteria:** at least 18 years old with urodynamically confirmed OAB, increased frequency of micturition (at least 8/24 hours), UI (at least 1/24 hours) and/or urgency **Exclusion criteria:** clinically significant SI, detrusor hyperreflexia, hepatic, renal or haematological disorders, symptomatic or recurrent UTI, BOO, bladder training or electrostimulation therapy, indwelling catheter or self-catheterisation, pregnant or breastfeeding or women not using reliable contraception
Interventions	**Group I (n = 57):** placebo **Group II (n = 118):** tolterodine 2 mg twice a day **Group III (n = 118):** oxybutynin 5 mg three times a day 12-week treatment period; 1-week run-in
Outcomes	Symptom questionnaire (6-point rating severity scale) Number of leakage episodes, frequency of micturition, volume voided Adverse events Laboratory tests Blood pressure
Study funding sources	Company support declared
Notes	Dose reduction to prevent withdrawal Two week follow-up 37 dropouts (Group I: 7; Group II: 10; Group III: 20)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised 2:2:1, method not stated
Allocation concealment (selection bias)	Low risk	Quote: "Each patient took two physically indistinguishable tablets"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information if personnel blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Patient-reported micturition variables and subjective assessment, therefore the outcome measuring is not likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts clearly explained
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, no prespecified outcomes

Abrams 1998 *(Continued)*

Other bias	Low risk	The study appears to be free of other sources of bias

Abrams 2001

Study characteristics	
Methods	**Study design:** RCT: placebo-controlled, parallel design. Randomised 2:1. **Dates study conducted:** not reported
Participants	**Setting:** multicentre **Country:** multinational **Age:** not reported **Sex:** men only **Inclusion criteria:** men over 40 years with urodynamically verified overactive bladder and mild, moderate or severe BOO **Exclusion criteria:** concurrent treatment with 5 alpha-reductase inhibitors or alpha-adrenergic antagonists, baseline postvoid residual > 40% maximum cystometric capacity, prior prostate or bladder surgery
Interventions	**Group I (n = 149):** tolterodine 2 mg twice a day **Group II (n = 72):** placebo 12-week treatment period
Outcomes	Urodynamic parameters Adverse events
Study funding sources	Not reported
Notes	Abstract 28 dropouts (Group I: 16; Group II: 12) No follow-up

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised 2:1, method not stated
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind but blinding is not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking of assessors not stated

Abrams 2001 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data balanced across the groups, reasons for dropouts reported
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, no pre-specified outcomes
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Abrams 2013

Study characteristics	
Methods	**Study design:** phase II, placebo- and monotherapy-controlled, dose-ranging, 12-week trial **Dates study conducted:** from March 2011 to June 2012
Participants	**Setting:** multicentre **Country:** 20 countries (Belarus; Belgium; Czechia; Denmark; Finland; France; Germany; Hungary; Italy; Netherlands; Norway; Poland; Portugal; Romania; Russia; Slovakia; Spain; Sweden; Ukraine; United Kingdom) **Age (mean):** placebo: 54.7; Soli 5 mg: 54.1; Soli 10 mg: 55 **Sex:** placebo: 53 (66.3%) female; solifenacin 5 mg: 100 (66.7%) female; solifenacin 10 mg: 52 (68.4%) female **Inclusion criteria:** "≥18 years with symptoms of OAB for ≥3 months..." "with ≥8 micturitions per 24 h and ≥3 urgency episodes per 72 h (with/without incontinence)..." **Exclusion criteria:** at visit 1/screening: participant is breastfeeding, pregnant or intends to become pregnant during the study. The pregnancy test at screening must be negative in women of childbearing potential; female participants of childbearing potential not using a highly effective method of birth control during the study and for 30 days after final study drug administration; male participants (unless surgically sterile) with female spouses/partners who are of childbearing potential, not using a barrier method of contraception during the study and for 30 days after the final study drug administration. In addition, female partners of male participants of childbearing potential should also use a highly effective method of birth control during the study and for 30 days after the final study drug administration; significant PVR volume (> 150 mL); significant stress incontinence or mixed stress/urgency incontinence where stress is the predominant factor as determined by the investigator; neurological cause for detrusor overactivity; indwelling catheter or practices intermittent self-catheterisation; diabetic neuropathy; chronic inflammation such as interstitial cystitis, bladder stones, previous pelvic radiation therapy or previous or current malignant disease of the pelvic organs; previous lower urinary tract or pelvic floor surgery except cystoscopy; intravesical treatment in the past 12 months with e.g. botulinum toxin, resiniferatoxin, capsaicin; uncontrolled narrow angle glaucoma, urinary or gastric retention, severe ulcerative colitis or Crohn's disease, toxic megacolon, myasthenia gravis or any other condition which makes the use of anticholinergics contraindicated; clinically significant cardiovascular or cerebrovascular diseases within 6 months prior to screening such as myocardial infarction, uncontrolled angina, significant ventricular arrhythmias, heart failure and stroke; receiving current non-drug treatment including electro-stimulation therapy (with the exception of a bladder training program or pelvic floor exercises which started more than 30 days prior to screening; using medications intended to treat OAB or prohibited medications; known or suspected hypersensitivity to solifenacin succinate, mirabegron or any of their excipients; significant neurological disease or defect affecting bladder function (e.g. neurogenic bladder, systemic or central neurological disease such as multiple sclerosis and Parkinson's disease); severe hypertension which is defined as a sitting average systolic blood pressure >= 180 mmHg and/or an average diastolic blood pressure >=110 mmHg.

Abrams 2013 *(Continued)*

Interventions	**Group I (n = 150):** solifenacin 5 mg **Group II (n = 76):** solifenacin 10 mg **Group III (n = 80):** placebo **Group IV (n = 76):** mirabegron 25 mg, but not relevant to this review **Group V (n = 77):** mirabegron 50 mg, but not relevant to this review **Group VI (n = 77):** solifenacin 2.5 mg, but not relevant to this review **Group VII (n = 146):** solifenacin 2.5 mg + mirabegron 25 mg, but not relevant to this review **Group VIII (n = 147):** solifenacin 2.5 mg + mirabegron 50 mg, but not relevant to this review **Group IX (n = 141):** solifenacin 5 mg + mirabegron 25 mg, but not relevant to this review **Group X (n = 150):** solifenacin 5 mg + mirabegron 50 mg, but not relevant to this review **Group XI (n = 78):** solifenacin 10 mg + mirabegron 25 mg, but not relevant to this review **Group XII (n = 80):** solifenacin 10 mg + mirabegron 50 mg, but not relevant to this review 12-week treatment period
Outcomes	**Primary outcome:** change from baseline to end of treatment (EOT) in mean volume voided per micturition (MVV) **Secondary outcomes:** change from baseline to EOT in micturition frequency and incontinence episode frequency per 24 hours Change from baseline to EOT in number of urgency episodes (grade 3 and/or 4) per 24 hours on the Patient Perception of Intensity of Urgency Scale (PPIUS) Change from baseline to EOT in Symptom Bother and Health Related Quality of Life (HRQoL) scores, assessed by the Overactive Bladder Questionnaire (OAB-q) Change from baseline to EOT in patient treatment satisfaction on visual analogue scale (TS-VAS) Safety assessments included frequency of treatment-emergent adverse events (TEAEs), systolic/diastolic blood pressure, pulse rate, laboratory tests, ECG and post-void residual volume
Study funding sources	Astellas
Notes	NCT01340027 Study known as SYMPHONY 12 groups in total: 6 monotherapies and 6 combination therapies

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eligible patients were randomised to 1 of the 12 treatments arms in a 2:2:2:2:2:1:1:1:1:1:1:1 ratio using a centrally co-ordinated Interactive Recognition Technologies system
Allocation concealment (selection bias)	Low risk	All medication kits contained preprinted medication numbers. The medication number of the kit dispensed to each patient was noted in the electronic case report form

Abrams 2013 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Neither patient nor other study personnel was made aware of the treatment given to any patient unless a medical emergency necessitated such disclosure
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Neither patient nor other study personnel was made aware of the treatment given to any patient unless a medical emergency necessitated such disclosure
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient data accounted for
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Low risk	The study appears to be free of other sources of bias

Alloussi 1998

Study characteristics	
Methods	**Study design:** RCT: placebo-controlled, parallel design. Randomised 2:1. **Dates study conducted:** February 1996 to November 1997
Participants	**Number of participants:** 309 male and female patients **Setting:** multicentre (46) **Country:** multinational (Germany, Russia, Bulgaria) **Age (mean, SD):** trospium 56.9 (16.22) years; placebo: 56 (15.67) **Sex:** trospium 30% male; placebo: 3.2% male **Inclusion criteria:** at least 18 years old with written, informed consent, confirmed DO by medical history and urodynamics, for mixed incontinence, motor component to be dominant and accompanied by at least one unstable contraction at minimum 10 cm H_2O with simultaneous urge or urge incontinence. Maximum cystometric capacity < 350 mL. **Exclusion criteria:** pregnant or breastfeeding women, urological or gynaecological surgeries < 3 months previous, neurogenic detrusor hyperactivity, exclusive stress incontinence, closed-angle glaucoma, untreated tachycardiac dysrhythmia, gastrointestinal stenoses, myasthenia gravis, UTI, allergies and/or intolerance towards atropine, oxybutynin, trospium chloride, or tablet adjuvants. Patients treated with anticholinergics, tri- or tetracyclic antidepressants, calcium antagonists started > 3 months before study, or beta-sympathomimetics within 7 days before first urodynamic measurement, antihistamines, amantadine, quinidine and disopyramide disallowed.
Interventions	**Group I (n = 210):** trospium chloride 20 mg twice a day **Group II (n = 99):** placebo 3-week treatment period; 7-day run-in
Outcomes	Assessment of patient improvement Micturition diaries for 2 days during study Urodynamic parameters Adverse events Laboratory tests

Alloussi 1998 *(Continued)*

Study funding sources	Not reported
Notes	47 dropouts (Group I: 32; Group II: 15) No follow-up Micturition diaries done inconsistently and only a few available at end of study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised 2:1, method not stated
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking of assessors not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data balanced across the groups, reasons for dropouts reported
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, no prespecified outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Baert 1995

Study characteristics	
Methods	**Design:** RCT, double-blind **Dates study conducted:** not reported
Participants	**Setting:** not reported **Country:** not reported **Age:** not reported **Sex:** not reported **Inclusion criteria:** not reported **Exclusion criteria:** not reported
Interventions	**Group I (n = 35):** darifenacin 5 mg 3 times a day **Group II (n = 10):** placebo

Baert 1995 *(Continued)*

	Patients separated into 2 subgroups 1 (n = 29): those who demonstrated unstable contractions at baseline and 2 (n = 16) who did not. These groups were randomised separately such that each of the patients in group 2 received active treatment for each one who received placebo.
Outcomes	**Primary outcomes:** primary cystometric variables were volume at first unstable contraction, maximum cystometric capacity, maximum amplitude of unstable contraction, and frequency of unstable contractions Secondary cystometric variables were: peak free flow rate, initial residual volume and maximum detrusor pressure during voiding Symptom variables were assessed by recording incontinent episodes per week, volume passed per void, total voidings per day and frequency and severity of urgency **Secondary outcomes:** adverse events
Study funding sources	Not specified
Notes	Abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not enough information in abstract
Allocation concealment (selection bias)	Unclear risk	Not enough information in abstract
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not enough information in abstract
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not enough information in abstract
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not enough information in abstract
Selective reporting (reporting bias)	Unclear risk	Not enough information in abstract
Other bias	Unclear risk	Not enough information in abstract

Bray 2018

Study characteristics

Methods	**Study design:** double-blind, randomised placebo-controlled with a parallel design, followed by 12 weeks open-label **Dates study conducted:** November 2004 to August 2006

Bray 2018 *(Continued)*

Participants	**Setting:** 11 centres **Country:** UK **Age (mean, SD):** tolterodine 47 (11.4); placebo 47 (11.5) **Sex:** 100% female **Inclusion criteria:** women aged 18 years or over; OAB symptoms for at least 6 months prior to entering the study; BWT of at least 5 mm and post-micturition volume of less than 50 mL at screening **Exclusion criteria:** taking an anticholinergic drug or receiving any treatment for OAB; significant SUI; experiencing or with history of UTI
Interventions	**Group I (n = 31):** tolterodine extended-release 4 mg once daily **Group II (n = 34):** placebo 12 week
Outcomes	**Primary outcome:** bladder wall thickness **Secondary outcomes:** change from baseline to week 12 in micturition diary variables (number of micturitions, UUI episodes and urgency episodes per 24 hours, and change in mean volume voided per micturition)
Study funding sources	Pfizer
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Eligible women were randomised using a centrally controlled computer-based system at the baseline visit in a ratio of 1:1
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind; outcome assessment blinding description in paper
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for, ITT analysis
Selective reporting (reporting bias)	Unclear risk	Reports that ITT and PP analyses were carried out but PP not reported
Other bias	Low risk	The study appears to be free of other sources of bias

Burgio 1998

Study characteristics	
Methods	**Study design:** RCT: placebo-controlled, parallel design **Dates study conducted:** 1 July 1989 to 30 August 1995
Participants	**Number of participants:** 197 female patients **Age (mean, SD):** 67.7 (7.5) **Sex:** only female participants **Inclusion criteria:** community-dwelling, ambulatory and at least 55 years of age. Urge incontinence at least twice per week and for at least 3 months. Urge incontinence to be the predominant pattern (number of urge accidents to exceed number of stress accidents). Urodynamic evidence of bladder dysfunction. **Exclusion criteria:** continual leakage, postvoid residual > 200 mL, uterine prolapse, narrow-angle glaucoma, unstable angina, decompensated congestive heart failure, history of malignant arrhythmias, or impaired mental status (MMSE score < 20)
Interventions	**Group I (n = 67):** oxybutynin 2.5 to 5 mg 3 times a day **Group II (n = 65):** placebo **Group III (n = 65):** pelvic floor muscle training/behavioural training with or without biofeedback, but not relevant to the review 8-week treatment period
Outcomes	Patient satisfaction and perceptions of treatment Leakage episodes Adverse events
Study funding sources	Support from health research grant declared
Notes	Dose reduction allowed to prevent withdrawal 28 dropouts (Group I: 4; Group II: 12; Group III: 12) No follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were stratified by type (urge, mixed) and whether incontinence mild, moderate or severe. Randomisation was then performed within each stratum using computer-generated random numbers using block of 6 to avoid inequity in group size.
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Oxybutynin and placebo were dispensed in identical capsules"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessor masked: "a research assistant, blinded to treatment group, scored bladder diaries and managed the data"

Burgio 1998 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The analysis was based on intention to treat and thus included all subjects. When subjects did not complete treatment, calculation of improvement was based on the most recent bladder diaries"
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Cardozo 2000

Study characteristics	
Methods	**Study design:** RCT: placebo-controlled, parallel design, phase III **Dates study conducted:** 1995 to 1997
Participants	**Number of participants:** 208 male and female patients **Setting:** multicentre (16) **Country:** multinational (UK and Poland) **Age (mean, SD):** trospium: 46.3 (13.86), placebo: 7.0 (13.53) (must be a mistake for the placebo group) **Sex:** trospium: 33% male; placebo: 43% male **Inclusion criteria:** 18 to 70 years old, normal body weight, vital signs and age-appropriate ECG findings; confirmed DI **Exclusion criteria:** SI confirmed by medical history, closed-angle glaucoma, tachydysrhythmias, mechanical stenoses of the gastrointestinal tract or urinary outlet obstruction, myasthenia gravis, allergies, and other severe diseases. Concomitant treatment with other anticholinergics, antidepressants, alpha-blockers and beta-sympathomimetics not allowed.
Interventions	**Group I (n = 104):** trospium chloride 20 mg twice a day **Group II (n = 104):** placebo 3-week treatment period 7 day run-in
Outcomes	4-point score for improvement 4-point scale for medication acceptability Urodynamic parameters Adverse events Laboratory tests ECG Physical examination, vital signs
Study funding sources	Company support declared
Notes	Dropouts not stated No follow-up ITT and PP analyses Mean age for placebo group reported as 7; unclear of correct age
Risk of bias	

Cardozo 2000 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Each patient was assigned in chronological order to one of the randomization numbers using a computer-generated randomization list"
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking of assessors not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Accounted for attrition and groups reasonably balanced, ITT
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Cardozo 2004a

Study characteristics	
Methods	**Study design:** RCT: placebo-controlled, parallel design, phase III **Dates study conducted:** not reported
Participants	**Setting:** multicentre **Country:** not reported **Age (mean, SD):** solifenacin 10 mg: 55.9 (14.2); solifenacin 5 mg: 55.4 (13.8); placebo: 56.1 (13.3) **Sex:** solifenacin 10 mg: female 238 (82.1%); solifenacin 5 mg female: 237 (82.9%); Placebo: female: 227 (80.8%) **Inclusion criteria:** more than 18 years old, average urinary frequency of more than 8 or more times in 24 hours and at least 3 episodes of urgency and/or 3 episodes of urinary incontinence during 3-day micturition diary. Normal body weight, vital signs and age-appropriate ECG findings. Confirmed DI. **Exclusion criteria:** neurogenic bladder, outlet obstruction, urinary retention, bladder stone, stress Incontinence, UTI interstitial cystitis, pelvic radiation, diabetic neuropathy, use of concomitant anticholinergics
Interventions	**Group I (n = 286):** solifenacin 5 mg **Group II (n = 290):** solifenacin 10 mg **Group III (n = 281):** placebo 12-week treatment period 2 week run-in
Outcomes	**Primary outcomes:** change in baseline in mean number of micturition per 24 hours

Cardozo 2004a *(Continued)*

	Secondary outcomes: change from baseline in mean number of urgency episodes, nocturia, urge incontinence and volume voided per micturition Safety assessment Adverse events Laboratory tests ECG Blood pressure
Study funding sources	Not reported
Notes	Primary reasons for discontinuation mentioned Loss to follow-up mentioned Power calculation done, quality of life reported subsequently

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking of assessors not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition not explained and not clear whether groups were similar in terms of attrition; PP analysis
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Unclear risk	Insufficient information

Cardozo 2008a

Study characteristics

Methods	**Study design:** RCT: placebo-controlled, parallel design **Dates study conducted:** April 2004 to October 2005
Participants	**Setting:** multicentre (105 centres) **Country:** 14 European countries **Age (mean):** solifenacin 5/10 mg: 57.7 years; placebo: 57.9 **Sex:** solifenacin 5/10 mg: 89.1% female; placebo: 85.7% female

Cardozo 2008a *(Continued)*

	Inclusion criteria: male or female aged ≥ 18 years with symptoms of OAB for more than 3 months and 3 or more episodes of urgency with or without incontinence in the last 3 days **Exclusion criteria:** clinically significant BOO, postvoid residual volume > 200 mL, evidence of UTI, bladder stones, chronic interstitial cystitis, previous irradiation, malignant disease, child bearing potential, pregnancy, lactation, contraindication for use of anticholinergic medication
Interventions	**Group I (n = 641):** solifenacin 5/10 mg per oral once daily **Group II (n = 224):** placebo 16-week treatment period 2-week run-in
Outcomes	**Primary outcomes:** mean change from baseline to endpoint in the number of episodes of severe urgency with or without urgency incontinence per 24 hours, defined as grade 3 and 4 on the 5 point PPIUS **Secondary outcomes:** change from baseline in the mean number of total urgency episodes per 24 hours (PPIUS 1-4), number of incontinence episodes per 24 hours and micturition frequency per 24 hours Change in patient perception of bladder condition (PPBC) score and the use of VAS to measure urgency bother and treatment satisfaction Efficacy assessed at 0, 1, 8, 12, 16 weeks Adverse events and postvoid residual volume at 8 and 16 weeks
Study funding sources	Study undertaken with a research grant from Astellas Pharma Europe Ltd.
Notes	Dropouts: Group I: 67/641; Group II: 30/224

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States randomised but insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blinded but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Large number of dropouts; not clear in which group; groups already unbalanced
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Unclear risk	Insufficient information

Chaliha 1998

Study characteristics	
Methods	**Study design:** RCT: placebo-controlled, parallel design **Dates study conducted:** not reported
Participants	76 participants completed the trial **Setting:** multicentre **Country:** not reported **Age:** not reported **Sex:** not reported **Inclusion criteria:** low compliance bladder, urodynamically confirmed DO **Exclusion criteria:** not reported
Interventions	**Group I:** trospium chloride 20 mg twice a day **Group II:** placebo **Group III:** trospium chloride 10 mg twice a day, but not relevant to the review **Group IV:** trospium chloride 40 mg twice a day, but not relevant to the review 76 participants in total 21-day treatment period Numbers in each arm are not reported
Outcomes	Tolerability score Urodynamic parameters Adverse events Biochemical analyses
Study funding sources	Not reported
Notes	Abstract Numbers for each group not stated Dropouts not stated Data not in useable form for this review

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind but blinding not stated

Chaliha 1998 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking of assessors not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts not stated
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Chapple 2004a

Study characteristics	
Methods	**Study design:** randomised, placebo-controlled, dose-ranging phase II trial **Dates study conducted:** October 2001 to December 2002
Participants	**Setting:** multicentre **Country:** Europe, Israel, South Africa **Number of participants:** 728 patients randomised **Age (mean, range):** 56 (18 to 79) years **Sex:** 16% male **Inclusion criteria:** men and women with symptoms of OAB for at least 6 months, aged between 18 and 78 years. Participants were required to have had an urodynamic assessment demonstrating detrusor overactivity within 12 months prior to enrolment.
Interventions	**Group I (n = 183):** placebo **Group II (n = 186):** fesoterodine 4 mg once daily **Group III (n = 173):** fesoterodine 8 mg once daily **Group IV (n = 186):** fesoterodine 12 mg once daily, but not relevant to the review 1-week placebo run-in period 12-week treatment period
Outcomes	**Primary outcomes:** change in average number of micturitions per 24 hours, change in average number of urge incontinence episodes per week **Secondary outcomes:** change in micturitions during day time, nocturia, average voided volume per micturition, urgency episodes per week, severity of urgency using a 4-grade scale, participant's evaluation of bother and participant's assessment of treatment efficacy Adverse events Lab tests, vitals (blood pressure and heart rate), ECG and residual volume
Study funding sources	Not reported

Chapple 2004a *(Continued)*

Notes	Abstract The primary analysis set for this study were the full analysis set Data obtained from clinicalstudyresults.org; obtained unpublished data from Pfizer 119 dropouts (Group I: 21, Group II: 29, Group III: 30 and Group IV: 39)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States randomised, no other description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Unclear risk	Insufficient information

Chapple 2004b

Study characteristics

Methods	**Study design:** RCT: placebo-controlled, parallel design, phase II **Dates study conducted:** not reported
Participants	**Setting:** multicentre **Country:** 9 European countries **Age (mean):** 57 years **Sex:** 40% male **Inclusion criteria:** age between 18 to 80 years; idiopathic DI; > 8 voids/24 hours for 3 days; 3 episodes of incontinence or urgency during 3 days of micturition diary **Exclusion criteria:** neurogenic bladder, outlet obstruction, urinary retention, bladder stone, stress incontinence, UTI interstitial cystitis, pelvic radiation, diabetic neuropathy, use of concomitant anticholinergics
Interventions	**Group I (n = 37):** solifenacin 5 mg

Chapple 2004b *(Continued)*

	Group II (n = 33): solifenacin 10 mg **Group III (n = 36):** placebo **Group IV (n = 37):** tolterodine 2 mg twice a day **Group V (n = 40):** solifenacin 2.5 mg, but not relevant to the review **Group VI (n = 34):** solifenacin 20 mg, but not relevant to the review 225 male and female patients in total 12-week treatment period 2-week run-in
Outcomes	Change in baseline mean number of micturitions per 24 hours, change from baseline in mean number of urgency episodes, change in urge incontinence and volume voided per micturition Total sum score of Contilife domains and overall Contilife score Adverse events Laboratory tests ECG Blood pressure
Study funding sources	Not given
Notes	Loss to follow-up or failure to complete study (Group I: 5; Group II: 3, Group III: 7, Group IV: 7; Group V: 6; and Group VI: 5)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking of assessors not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Clearly described attrition and groups balanced
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Chapple 2004c

Study characteristics

Chapple 2004c *(Continued)*

Methods	**Study design:** RCT: placebo-controlled, parallel design, phase IIIa **Dates study conducted**: not reported
Participants	**Setting:** multicentre (81 sites internationally) **Country:** international **Age (mean, SD):** solifenacin 5 mg 58.1 (13.4); solifenacin 10 mg 57.2 (13.4); tolterodine 56.9 (12.8); placebo: 57.8 (13.7) **Sex:** solifenacin 5 mg: 27.1% male; solifenacin 10 mg: 28.8% male; tolterodine: 20% male; placebo: 23.7% male **Inclusion criteria:** age more than 18 years; DI more than 3 months; > 8 voids per 24 hours for 3 days; 5 to 50 episodes of incontinence or urgency during 1 week, urgency 1 episode per 24 hours **Exclusion criteria:** bladder outlet obstruction symptoms stabilised over 6 months, pregnancy, post-void residual > 200 mL; contraindications to anticholinergics, hypersensitivity to drug
Interventions	**Group I (n = 266):** solifenacin 5 mg **Group II (n = 264):** solifenacin 10 mg **Group III (n = 250):** tolterodine 2 mg twice a day **Group IV (n = 253):** placebo 12-week treatment period 2-week run-in
Outcomes	**Primary outcome:** efficacy of solifenacin 5 mg and 10 mg once daily in patients with OAB **Secondary outcomes:** safety and tolerability of solifenacin, and to compare the efficacy and safety of solifenacin with tolterodine 2 mg twice daily Adverse events Laboratory tests ECG Blood pressure
Study funding sources	Yamanouchi Pharmaceutical Co.
Notes	Women committed to use of contraceptives during pregnancy were recruited Bladder training not allowed during study, concomitant use of drugs modifying liver enzymes not permitted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking of assessors not stated

Chapple 2004c *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Clearly described attrition and groups balanced
Selective reporting (reporting bias)	Unclear risk	Protocol is not available
Other bias	Low risk	The study appears to be free of other sources of bias

Chapple 2007a

Study characteristics	
Methods	**Study design:** RCT: placebo-controlled, parallel design **Dates study conducted:** not reported
Participants	**Setting:** multicentre (150 sites) **Country:** Belgium, Bulgaria, Czech Republic, Estonia, France, Germany, Hungary, Italy, the Netherlands, Poland, Romania, Russia, Spain, Sweden, Ukraine, the UK, South Africa, Australia and New Zealand **Number of participants:** 1135 male and female patients were randomised. 1132 received study medication **Age (mean, SD):** placebo: 56.0 (13.7); tolterodine: 57.7 (14.6); fesoterodine 4 mg: 57.1 (13.2); fesoterodine 8 mg 55.6 (14.1) **Sex:** placebo: 19% male, tolterodine 4 mg: 22% male, fesoterodine 4 mg 19% male; fesoterodine 8 mg: 19% male **Inclusion criteria:** history of OAB with urinary urgency for > 6 months. At least 18 years of age with ≥ 8 micturitions per 24 hours and either > 6 urgency episodes or ≥ 3 UUI episodes per 24 hours (in a 3-day diary) **Exclusion criteria:** lower urinary tract pathology (e.g. stress urinary incontinence, bladder stones, interstitial cystitis, urothelial tumours), pelvic prolapse of grade 3 or higher, clinically relevant bladder outlet obstruction, polyuria (> 3 L per 24 hours) symptomatic or recurrent urinary tract infection or postvoid residual urine volume > 100 mL. Participants who were currently receiving treatment, were treated within 2 weeks of screening visit with antimuscarinic agents, were treated within the past 4 weeks with electrostimulation for bladder training or had an active urinary tract infection or underlying neurological disease responsible for their OAB were not included. Cardiac arrhythmia and/or unstable angina or QTcB interval > 500 mL were not included.
Interventions	**Group I (n = 283):** placebo **Group II (n = 290):** tolterodine ER 4 mg/day **Group III (n = 272):** fesoterodine 4 mg/day **Group IV (n = 287):** fesoterodine 8 mg/day 2 weeks placebo run-in period Treatment for 12 weeks
Outcomes	Micturitions per 24 hours UUI/24 hours

Chapple 2007a *(Continued)*

	Treatment response (4-category treatment scale) Mean volume voided per micturition Daytime micturitions per 24 hours, nocturnal micturitions, urgency episodes per 24 hours Continent days per week Adverse events ECG Lab parameters
Study funding sources	Company support declared
Notes	ITT population: 1132 full analysis set 1:1:1 randomisation ITT analysis 147 dropouts (Group I: 33, Group II: 37, Group III: 41, Group IV: 36) No follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Computer-generated schedule anticipating a balancing of treatments across countries and sites"
Allocation concealment (selection bias)	Unclear risk	Only says "subjects were randomised 1:1:1:1", no further detail given regarding allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind, double dummy" Comment: the preparations come in two different forms, capsule and tablet, so to ensure blinding, each patient receives both a tablet and a capsule as part of intervention. In the treatment arm one would be placebo and in the placebo arm both would be placebo.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Clearly described attrition and balanced groups
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, no prespecified outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Chapple 2007b

Study characteristics

Chapple 2007b *(Continued)*

Methods	**Study design:** RCT: placebo-controlled, parallel design **Dates study conducted:** not reported
Participants	**Setting:** multicentre (73 centres) **Country:** Germany, Hungary, Poland, South Africa, Sweden, UK, USA **Number of participants:** 400 male and female patients were randomised **Age (mean, SD):** darifenacin 72 (5); placebo 73 (5) years **Sex:** darifenacin: 22.6% male; placebo 24.8% **Inclusion criteria:** men and women aged ≥ 65 years with symptoms of OAB including an average of ≥ 1 urge urinary incontinence episode/day and ≥ 10 micturitions/day **Exclusion criteria:** treatment with drugs known to affect urinary bladder function or external urethral sphincter (e.g. duloxetine), a total daily urine volume > 3000 mL, mean volume voided per micturition > 300 mL. Clinically significant stress urinary incontinence or bladder outlet obstruction and post-void residual volume > 100 mL as assessed by ultrasound. Women with stage 3 or 4 pelvic organ prolapse were excluded. Bladder retraining or received electrical stimulation therapy within 3 months of screening. Serious UTI, clinically significant congenital or acquired disorder of the urinary tract.
Interventions	**Group I (n = 133):** placebo **Group II (n = 266):** darifenacin 7.5 mg/day per oral, after 2 weeks dose increase to 15 mg/day permitted 1-week placebo run-in period Treatment for 12 weeks
Outcomes	**Primary outcome:** median change from baseline in mean urgency urinary incontinence episodes (UUIE)/week **Secondary outcomes:** median change from baseline in mean micturition/day, median change from baseline in mean urgency episodes/day,median change from baseline in mean pads used/week, median change from baseline in mean nocturnal voids/week, responder rate (percentage of patients achieving ≥ 30%, ≥ 50%, ≥ 70% or ≥ 90% reduction from baseline in mean UUIE/week, 3 dry days, 7 dry days. 7-day diary for baseline and week 12, 3-day diary for week 1, 2 and 6 OAB-q, PPBC, patient and physician assessment of treatment benefit (no, yes - a little, yes – very much)
Study funding sources	Study funded by Novartis Pharmaceuticals Inc.
Notes	38 dropouts (Group I: 16, Group II: 22) Similar numbers discontinued in both groups (placebo 12.7% and darifenacin 7.5/15 mg 8.3%). Reasons for discontinuation similar. ITT principle and last observation carried forward for missing values

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States randomised, no other description

Chapple 2007b *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding was achieved by the use of identical packaging, schedule of administration, labelling, appearance and odours of study drugs
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Patients, investigators, persons performing assessments and data analysis remained blinded to the identity of treatment from the time of randomisation until database lock
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar numbers discontinued in both groups (placebo 12.7% and darifenacin 7.5/15 mg 8.3%). Reasons for discontinuation similar.
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Chapple 2013

Study characteristics	
Methods	**Study design:** multinational, multicentre, randomised, double-blind, double-dummy, parallel-group placebo- and active - controlled phase II study **Dates study conducted:** not reported
Participants	**Setting:** multinational **Country:** not reported **Age (mean, SD):** tolterodine: 56.6 (12.8); placebo: 57.1 (12.9) **Sex:** tolterodine: 69 (81.2%) female; placebo: 151 (91%) female **Inclusion criteria:** men and women ≥ 18 years of age experiencing symptoms of OAB for ≥ 3 months with frequency of micturition on average ≥ 8 times per 24 hours and at least 3 episodes of urgency (grade 3 or 4) with or without incontinence during a 3-day micturition diary period at baseline **Exclusion criteria:** clinically significant bladder outflow obstruction; significant PVR ≥ 200 mL; incontinence where stress was the predominant factor; indwelling catheters or intermittent self-catheterisation; diabetic neuropathy; symptomatic UTI, interstitial cystitis, bladder stones, previous pelvic radiation therapy or previous or current malignant disease of the pelvic organs; contraindications for anticholinergics; non-drug treatment including electro-stimulation therapy (although bladder training or pelvic floor exercise programmes that had started > 1 month prior to the start of the study could be continued); use of other urinary incontinence medications; known or suspected hypersensitivity to tolterodine, other anticholinergics, mirabegron, lactose or any excipients; clinically significant cardiovascular (including ECG abnormalities) or cerebrovascular disease; or any other condition making the patient unsuitable for the study as deemed by the investigator
Interventions	**Group I (n = 85):** tolterodine ER 4 mg once daily **Group II (n = 166):** placebo Treatment period 4 weeks

Chapple 2013 *(Continued)*

Outcomes	**Primary outcome:** change from baseline to end-of-treatment in the mean number of micturitions per 24 hours **Secondary outcomes:** changes in mean volume voided per micturition, mean number of urinary incontinence, urgency urinary incontinence, and urgency episodes per 24 hours, severity of urgency, number of nocturia episodes, changes in ICIQ-OAB and ICIQOABqol symptom scores, and in patients' perception of treatment benefit, safety endpoints were incidence and severity of AEs, and changes from baseline to end of treatment in vital signs, laboratory tests, ECG parameters and PVR
Study funding sources	Astellas
Notes	NCT00337090 Results posted on JAPIC at: http://www.clinicaltrials.jp/user/ctrDetail_e.jsp?resultId=657 (accessed 22 February 2016)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Describes participants as being randomised but no further details of methods
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported although study described as double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported although study described as double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	All withdrawals and data sets used clearly described
Selective reporting (reporting bias)	Low risk	All expected variables reported
Other bias	Low risk	The study appears to be free of other sources of bias

Chapple 2014

Study characteristics

Methods	**Study design:** randomised double-blind RCT **Dates study conducted:** May 2011 to November 2012
Participants	**Setting:** multicentre (241 centres) **Country:** multinational **Age:** not reported

Chapple 2014 *(Continued)*

	Sex: 81% female **Inclusion criteria:** ≥ 18 years, with OAB symptoms ≥ 6months, ≥ 8 micturitions and ≥ 2 and ≤ 15 UUI episodes/24 hours on baseline diary, at least moderate bladder-related problems on the PPBC; able to complete micturition diaries and study-related questionnaires and comply with study procedures. Females of childbearing potential who were heterosexually active were required to use an adequate form of contraception **Exclusion criteria:** females who were pregnant, nursing or intended to become pregnant during the trial or 3 months after were not eligible. Other exclusion criteria were: contraindication for fesoterodine, condition that may affect bladder function, including predominant SUI, significant POP, clinically significant BOO (evidenced by previous history of acute urinary retention requiring catheterisation, use of indwelling catheter, or intermittent self-catheterisation, urodynamic evidence of obstruction, severe voiding symptoms included previously measured PVR ≥ 200 mL) not being appropriately managed, neurological conditions known or suspected of influencing bladder function, current or recurrent UTI, treatment with other anticholinergic medications within 2 to 3 weeks of screening, new or unstable use of certain medications including diuretics, a-blockers, tricyclics and oestrogens, treatment with potent CYP3A4 inhibitors within 2 weeks of screening, CYP3A4 inducers within 30 days of screening, botox within 6 months of screening, or initiation of electrostimulation, bladder training or PFMT within 4 weeks of screening
Interventions	**Group I (n = 790):** fesoterodine 4 mg once daily orally **Group II (n = 779):** fesoterodine 8 mg once daily orally **Group III (n = 386):** placebo 12-week study period
Outcomes	**Primary outcome:** change from baseline to week 12 in UUI episodes/24 hours **Secondary outcomes:** not reported
Study funding sources	Study supported by Pfizer
Notes	Efficacy analysis is based on FAS Last observation carried forward principle used for missing values Withdrawals due to adverse events: Group I 27/790, Group II 45/779, Group III 14/386

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients randomised 2:2:1 but no further details given
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind; medications and placebo were identical in appearance to preserve blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information

Chapple 2014 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts are explained and the methods for managing missing data were clearly described
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Low risk	The study appears to be free of other sources of bias

Chu 2009

Study characteristics	
Methods	**Study design:** RCT, parallel design **Dates study conducted:** February 2001 and October 2001
Participants	**Setting:** multicentre (33 centres) **Country:** United States **Age (mean, SD):** solifenacin 59 (14) years; placebo 58 (13) years **Sex:** solifenacin 20% male; 16.6% male **Inclusion criteria:** men and women aged ≥ 18 years of with diagnosis of OAB made by an investigator based on symptoms (urinary frequency, urgency or urge incontinence). Patients had to have recorded a mean of ≥ 8 micturitions per 24 hours plus a mean of ≥ 1 incontinence episode per 24 hours and/or a mean of ≥ 1 urgency episode per 24 hours during the screening period. **Exclusion criteria:** stress urinary incontinence or mixed urinary incontinence in which stress was predominant, a neurologic cause of detrusor overactivity, urinary retention, grade III/IV prolapse with cystocele, and recurrent or active urinary tract infection. Patients with abnormal findings on 12-lead ECG or abnormal lab findings were excluded.
Interventions	**Group I (n = 340):** solifenacin 10 mg once daily orally **Group II (n = 332):** placebo 12-week study period
Outcomes	**Primary outcome:** change from baseline in the mean number of micturitions per 24 hours at week 12 **Secondary outcome:** change from baseline in the mean number of urgency, incontinence, nocturnal voiding and nocturia per 24 hours Adverse events, physical examinations, vital signs, ECG and laboratory evaluation Postvoid residual was measured by bladder scan at screening and week 12
Study funding sources	Study supported by Astellas Pharma Inc, Tokyo, Japan
Notes	Last observation carried forward principle used for missing values Standard error converted to standard deviation for the purpose of the review
Risk of bias	

Chu 2009 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	States 1:1 randomisation, performed at centre level. SAS Institute Inc., Cray, North Carolina was used to generate the randomisation code.
Allocation concealment (selection bias)	Unclear risk	No information of how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Drug and placebo in identical blister packs and had identical appearance
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals and the reasons for withdrawals were similar (solifenacin: 70/340, placebo: 58/332)
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Chua 2018

Study characteristics	
Methods	**Study design:** RCT, double-blind, double dummy, placebo-controlled **Dates study conducted:** October 2010 to August 2014
Participants	**Setting:** single centre **Country:** Philippines **Age (mean, SD):** placebo 53.9 (12.14); solifenacin 57.2 (9.36) **Sex:** 9 (28%) male **Inclusion criteria:** 18 to 79 years old, ambulatory, OAB ≥ 3 months, average ≥ 8 micturitions/24 hours and ≥ 1 urgency episode with/without incontinence/24 hours as documented in 3-day micturition diary, participants bothered by symptoms as reflected by OAB-questionnaire **Exclusion criteria:** patients unwilling to be involved with frequent follow-ups as per study protocol, refused consent, conditions that were contraindicated to take either gabapentin or solifenacin, diagnosed cases of acute of chronic UTI, bladder stones, SUI or MUI, BPH, obstructive sleep apnoea, diabetes mellitus, history of interstitial cystitis, painful bladder syndrome, chronic pelvic pain, neurogenic bladder diseases or patients taking OAB related medications that could not be stopped for a duration of less than 8 weeks before study start
Interventions	**Group I (n = 31):** solifenacin 5 mg (can be increased to 10 mg) **Group II (n = 32):** placebo

Chua 2018 *(Continued)*

	12-week study period
Outcomes	OABq Mean change urge incontinence
Study funding sources	Primarily by Medical Center Research & Biotech division. Pfizer Urology Asia partially supported by providing the gabapentin, additional funds for the solifenacin and additional lab tests of the patients enrolled.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Assignment based on serial numbers made according to a computer-generated stratified blocking randomisation program
Allocation concealment (selection bias)	Low risk	The randomisation and allocation schedule of the patient was concealed in an envelope. The information was secured and stored in the data monitor section of the clinical trial centre where the trial was being conducted.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding included the outcome assessors, the patients and the investigators
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding included the outcome assessors, the patients and the investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts are explained and the methods for managing missing data were clearly described
Selective reporting (reporting bias)	Low risk	All expected data are reported
Other bias	Low risk	The study appears to be free of other sources of bias

De Ridder 2012

Study characteristics

Methods	**Study design:** randomised trial, parallel design **Dates study conducted:** not reported
Participants	**Setting:** multicentre (45 sites) **Country:** not reported **Age (mean, SD):** 43.7 (11.9) **Sex:** 95 (50.3%) male, 94 (49.7%) female

De Ridder 2012 *(Continued)*

	Inclusion criteria: patients with neurogenic detrusor overactivity, male or female, aged 18 to 65 years, had MS (expanded disability status scale ≤ 8) or SCI (partial or complete lesions) with stable NDO ≥ 6 months. **Exclusion criteria:** not reported in abstract, patients with NDO due to Parkinson's disease or other neurological conditions or with max bladder capacity ≥ 400 mL
Interventions	**Group I (n = 48):** solifenacin 5 mg once daily orally **Group II (n = 51):** solifenacin 10 mg daily orally **Group III (n = 47):** oxybutynin 15 mg daily **Group IV (n = 43):** placebo 2-week run-in period 4-week study period
Outcomes	**Primary outcome:** change from baseline in max cystometric capacity at week 4 **Secondary outcomes:** patient-reported improvement, QoL
Study funding sources	Study supported by Astellas Pharma Europe
Notes	Efficacy analysis is based on FAS Withdrawals due to adverse events

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized 1:1:1:1 using a central computerised randomisation scheme, prepared by third party
Allocation concealment (selection bias)	Unclear risk	No information of how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States double-blind: each patient took an identical regimen of 2 tablets and 3 capsules in the same time pattern each day to ensure blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, no prespecified outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Dmochowski 2008

Study characteristics	
Methods	**Study design:** RCT: placebo-controlled, parallel design **Dates study conducted:** September 2005 to June 2006
Participants	**Setting:** multicentre (62 centres) **Country:** USA **Age (mean, SE):** placebo 59.8 (0.5); trospium 60.4 (0.54) years **Sex:** trospium 16.3% male; placebo 14% male **Inclusion criteria:** participants aged 18 years or older with OAB of 6 months or longer duration with symptoms of urinary frequency (a mean of 10 or more toilet voids per day), urgency (1 or more episodes of severe urgency associated with toilet void) and UUI (a mean of 1 or more UUI episodes per day) **Exclusion criteria:** total voided volumes greater than 3000 mL/day or mean voided/void greater than 250 mL, individuals with predominantly stress or overflow incontinence. Neurogenic bladder, indwelling or intermittent catheterisation, significant renal disease, uninvestigated haematuria or urinary tract infection during screening, history of more than 3 urinary tract infection in previous 12 months, significant urinary retention, cancer, interstitial cystitis, prostate specific antigen level greater than 4 ng/mL, prostate cancer or chronic prostatitis
Interventions	**Group I (n = 284):** placebo **Group II (n = 280):** trospium chloride extended release 60 mg once daily per oral Placebo run-in: not reported Treatment for 12 weeks
Outcomes	Change in mean number of toilet voids per day Change in mean number of UUI episodes per day Urgency severity Mean volume voided/void Dry rate (no UUI during diary collection period) OAB - symptom composite score Adverse events, vital signs, lab tests, physical examination, compliance Responder or normalisation rate – participants with a mean of 8 or fewer toilet voids per day with no UUI episodes during 3-day diary collection period Questionnaires used: 3-day bladder diary, Indevus Urgency Severity Scale (IUSS) OAB symptom composite score (OAB-SCS), OAB-q
Study funding sources	Study funded by Espirit and Indevus Pharmaceuticals Inc.
Notes	26 dropouts (Group I: 8, Group II: 18) Last observation carried forward for missing values Standard error converted to standard deviation
Risk of bias	

Dmochowski 2008 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States randomised, no other description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blinded, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Groups unbalanced after withdrawal (more attrition in intervention group); reasons for withdrawals not specified
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Dmochowski 2010

Study characteristics	
Methods	**Study design:** RCT: placebo-controlled, parallel design **Dates study conducted:** August 2007 to April 2008
Participants	**Number of participants:** 896 male and female patients were randomised **Setting:** multicentre **Country:** USA **Age (mean):** 59.9 years **Sex:** 89.7% women **Inclusion criteria:** men and women aged ≥ 18 years with symptoms of OAB for > 3 months before screening, recorded a mean micturition of ≥ 8 micturitions per 24 hours and ≥ 3 urgency episodes per 24 hours and rated their bladder condition at baseline causing at least some moderate problems using PPBC **Exclusion criteria:** history of acute urinary retention requiring catheterisation, severe voiding difficulty, stress urinary incontinence, significant pelvic organ prolapse or lower urinary tract surgery within preceding 6 months, hepatic or renal disease, neurologic disease that significantly affected bladder function, treatment with OAB medication or potent CYP3A4 inhibitor within 2 weeks, men on 5-alpha reductase inhibitors and any contraindication to fesoterodine
Interventions	**Group I (n = 448):** placebo

Dmochowski 2010 *(Continued)*

	Group II (n = 448): fesoterodine 4 mg once daily per oral, could choose to increase to 8 mg at the end of 2 weeks Placebo run-in for 2 weeks Treatment for 12 weeks
Outcomes	Change from baseline in the mean number of micturitions per 24 hours Bladder diary variables Quality of life using OAB-q Proportion of patients reporting improvement on PPBC and Urgency Perception Scale (UPS); PPBC: ≥ 2-point improvement, 1 point improvement, no change or deterioration from baseline UPS: improvement, no change, deterioration) Percentage change for bladder diary variables Adverse events, BP and heart rate
Study funding sources	Study funded by Pfizer
Notes	116 dropouts (Group I: 60, Group II: 56) Last observation carried forward for missing values; ITT principle used Standard error converted to standard deviation OAB-q data, urgency episodes and UUI episodes per 24 hours were not useable as reported as least square mean change with no standard deviation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation implemented using central system accessed by phone or internet that generated single participant identification and randomisation numbers
Allocation concealment (selection bias)	High risk	The randomisation schedule was generated, secured, distributed and stored by Pfizer Global Clinical Data Services
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blinded, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout rates similar between groups but reasons not stated
Selective reporting (reporting bias)	Unclear risk	Not enough information
Other bias	Low risk	The study appears to be free of other sources of bias

Dorschner 2000

Study characteristics	
Methods	**Study design:** RCT: placebo-controlled, parallel design **Dates study conducted:** not reported
Participants	**Setting:** multicentre **Country:** multinational (2) **Age (mean):** 67 years **Sex:** propiverine: female 40; placebo: female 37 **Inclusion criteria:** over 60 years of age; > 7 micturitions/24 hours, > 0 incontinence episodes/24 hours, < 300 mL volume/micturition **Exclusion criteria:** acute UTIs, bladder emptying disorders, residual urine > 20% voided volume, micturition volume > 300 mL. Renal insufficiency, concomitant medication interfering with the study drug, clinically relevant variations in laboratory parameters prior to study. Patients suffering from serious, life-threatening cardiovascular diseases
Interventions	**Group I (n = 49):** placebo **Group II (n = 49):** propiverine 15 mg 3 times a day 4 week treatment period 2 week run-in
Outcomes	Urge score (Gaudenz) Number of leakage episodes, frequency of micturition, bladder volume Quality of Life (Giessen Complaint Survey and Basle Subjective Wellbeing Study) Uroflow Residuals Adverse events ECG (standard and 24-hour long-term) Laboratory tests
Study funding sources	The study was supported by an educational grant provided by Apogepha
Notes	9 dropouts (group not stated) No follow-up

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking of assessors not stated

Dorschner 2000 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	9 dropouts (group not stated)
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Drutz 1999

Study characteristics	
Methods	**Study design:** RCT, placebo and comparator controlled, parallel design **Dates study conducted:** not reported
Participants	**Setting:** multicentre (25 sites) **Country:** multinational (2) **Age (mean):** 64 years **Sex**: 22.7% male **Inclusion criteria:** at least 18 years old, understood and signed informed consent. Females to be post menopausal, surgically sterile or using adequate contraception. Cystometric evidence of detrusor overactivity plus urinary frequency (at least 8/day) and either UI (at least 1/24 hours) and/or urgency. **Exclusion criteria:** clinically evaluated stress incontinence, hepatic or renal disease, diseases that made patient unsuitable for study, recurrent UTI, interstitial cystitis, uninvestigated haematuria or haematuria secondary to malignant disease, indwelling catheter or intermittent catheterisation, treatment with any investigational drug in 2 months pre entry, previous treatment with tolterodine, electrostimulation or bladder training within 14 days of entry, treatment with any anticholinergic drug or urge incontinence drug within 14 days, unstable dosage of any treatment with anticholinergic, adverse effects or initiation of such treatment during study, previously serious adverse effects on oxybutynin, average total voided/24 hours > 3000 mL, clinically significant voiding difficulty with risk of urinary retention (residual volume > 200 mL or flow rate < 10 mL/s)
Interventions	**Group I (n = 56):** placebo **Group II (n = 109):** tolterodine 2 mg twice a day **Group III (n = 112):** oxybutynin 5 mg 3 times a day 12-week treatment period
Outcomes	Number of leakage episodes, frequency of micturition and volume voided Adverse events Laboratory tests Blood pressure
Study funding sources	Supported by Pharmacia and Upjohn
Notes	Dose reduction permitted within first 2 weeks only as alternative to withdrawal 57 dropouts (Group I: 8, Group II: 14, Group III: 35) 36% placebo, 36% tolterodine and 63% oxybutynin patients were excluded from the analysis No follow-up Randomised 1:2:2. Double-blind. PP analysis
Risk of bias	

Drutz 1999 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy method
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking of assessors not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Differential dropouts, PP analysis
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

DuBeau 2014

Study characteristics	
Methods	**Study design:** RCT, double-blind, placebo-controlled, parallel-group trial **Dates study conducted:** September 2009 to May 2011
Participants	**Setting:** multicentre (108 sites) **Country:** USA **Age (mean):** 75 years **Sex:** not reported **Inclusion criteria:** men and women aged ≥ 65 years of with history of OAB for ≥ 3 months, some moderate problems on patient perception of bladder control, and on average ≥ 2 urge incontinence episodes/day; ≥ 8 micturitions/day **Exclusion criteria:** any condition contraindicating the use of fesoterodine, hepatic disease or liver enzymes greater than 2 times upper limit if normal, clinically significant renal disease, neurological condition that may affect bladder function, advanced malignancy, clinically significant bladder outlet obstruction, PVR greater than 200 mL, women with stress urinary incontinence, recurrent urinary tract infection, MMSE score less than 20, behaviour intervention or electrical stimulation within 8 weeks, patients receiving anticholinergics/antispasmodic drugs or those with anticholinergic effects
Interventions	**Group I (n = 281):** fesoterodine 4 mg, could be increased to 8 mg once daily orally at 4 weeks **Group II (n = 281):** placebo

DuBeau 2014 *(Continued)*

	12-week study period
Outcomes	**Primary outcome:** change from baseline in urge urinary incontinence at week 12 **Secondary outcomes:** change from baseline in the number of micturitions per day, and urgency episodes per day PPBC and Urgency Perception Scale Change in QoL evaluated by OAB-q questionnaire Urinary diary activity assessment, questionnaire to evaluate QoL at week 0, 4 and 12 Adverse events, vital signs and PVR
Study funding sources	Study supported by Pfizer
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised randomisation system, generated, secured and distributed by Pfizer Global Clinical Data Services
Allocation concealment (selection bias)	High risk	The randomisation schedule was generated, secured, distributed, and stored, by Pfizer Global Clinical Data Services
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts are explained and the methods for managing missing data were clearly described
Selective reporting (reporting bias)	Low risk	All prespecified outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Elbaset 2019

Study characteristics

Methods	**Study design:** RCT **Dates study conducted:** May 2016 to October 2018
Participants	**Setting:** single centre **Country:** Egypt

Elbaset 2019 *(Continued)*

	Age (mean, SD): solifenacin 10 mg 32.7 (10.6), placebo 32.9 (10.0) **Sex:** 16 male, 84 female **Inclusion criteria:** patients with refractory idiopathic OAB diagnosed both clinically and urodynamically. All patients showed initial failure of 10 mg of solifenacin for 3 months, after which they were managed by intravesical injections of 100 IU of BTX-A (botox) **Exclusion criteria:** use of another anticholinergic drug, age < 18 years, neurogenic DO, active UTI evidenced by positive urine culture, previous solifenacin intolerability and the development of urine retention after botox injections
Interventions	**Group I (n = 50):** solifenacin 10 mg **Group II (n = 50):** placebo for 12 weeks + 6 weeks solifenacin 10 mg 12 + 6-week study period
Outcomes	**Primary outcomes:** assessment of efficacy of anticholinergic treatment after the effects of botox faded based on the total OABSS after 12 weeks of follow-up **Secondary outcomes:** urodynamic parameters after 12 weeks of treatment Tertiary objectives included assessment of risk factors of anticholinergic failure. Complications were recorded after re-treatment with solifenacin in both groups. QoL changes from baseline were assessed using I-Qol.
Study funding sources	Not reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised into the study group and control group on a 1:1 basis with a computer-generated program in blocks of random lengths
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts are explained and the methods for managing missing data were clearly described
Selective reporting (reporting bias)	Low risk	All expected data are reported
Other bias	Low risk	The study appears to be free of other sources of bias

EUCTR2004-001116-31-ES

Study characteristics	
Methods	**Study design:** RCT, double-blind, parallel-group confirmatory phase III study **Dates study conducted:** trial registered 17 November 2004, trial status prematurely ended 21 December 2004
Participants	**Setting:** multicentre **Country:** not reported **Age:** not reported **Sex:** not reported **Inclusion criteria:** outpatients, age 18 to 80 years, premenopausal female patients: adequate contraception, urge urinary incontinence for a duration of at least 6 months confirmed by medical history and documented in the patient's file. Presence of: a minimum of 1 episode of the feeling of urgency (strong desire to micturate) and at least one of the following: a minimum of 8 micturitions/24 hours, on average; a minimum of 1 incontinence episode/24 hours, on average, during 7 days prior to the randomisation visit, normal basic urinalysis, negative urine culture **Exclusion criteria:** evidence of MUI with prevailing obstructive component or stress component, treatment currently or within the last week with any a-adrenergic agonists or antagonists, lower tract pathology potentially responsible for incontinence known from medical history for the last 3 months, UTI defined in terms of clinical signs and symptoms, with/without microbiological confirmation within 2 weeks prior to randomisation, any obstructive condition affecting the urethra or clinically significant prostatic disease requiring therapy, mechanical obstructive uropathy known from medical history and/or shown by residual urine volume > 200 mL at screening and/or randomisation, polyuria (> 2500 mL/24 hours known from medical history and confirmed during run-in, increased frequency and/or nocturia only due to renal or cardiac insufficiency known from medical history, neurological disease influencing bladder function, urogenital surgery previously, known allergy/hypersensitivity to any components of the study medication or structurally related drugs, pregnancy or lactation period, respiratory/renal/gastrointestinal/haematological/endocrine/psychiatric or any other disease/condition that in the opinion of the investigator, could affect the evaluation of the study medication, myasthenia gravis, untreated narrow angle glaucoma, clinically significant heart disease, severe or malignant hypertension, uncontrolled mild or moderate hypertension, uncontrolled diabetes, previous participation in this study, participation in another study of an investigational drug currently or within the last 30 days, chronic alcohol or drug abuse within the last 6 months, any condition which in the opinion of the investigator can jeopardise or would compromise the participant's ability to participate in this study.
Interventions	**Group I:** tolterodine 2 mg twice a day **Group II:** placebo 3 weeks + 3 days single blind run-in
Outcomes	**Primary outcomes:** number of incontinence episodes (per 24 hours, change from baseline to end of study) **Secondary outcomes:** responder rate; percentage of patients with improvement of one point or more of the six point Likert scale
Study funding sources	Laboratorios Dr. Esteve S.A.
Notes	Sample size is not reported Trial registration
Risk of bias	

EUCTR2004-001116-31-ES *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information; trial registration
Selective reporting (reporting bias)	Unclear risk	Insufficient information; trial registration
Other bias	High risk	Trial ended prematurely with no apparent reasons

EUCTR2004-002143-27-AT

Study characteristics	
Methods	**Study design:** double-blind, stratified, randomised, parallel, placebo-controlled **Dates study conducted:** different dates depending on country: AT (completed), DK (prematurely ended), SE (completed) and DE (ongoing)
Participants	**Setting:** multicentre **Country:** multinational **Age:** not reported **Sex:** not reported **Inclusion criteria:** female outpatient ≥ 18 years, predominant UUI without predominant SUI for 3 consecutive months prior to visit, predominant UUI defined as at least 7UUI episodes and at least twice as many UUI as SUI episodes recorded on the SUI questionnaire at visit 1 AND by at least 7 UI episodes per week on the screening diary completed prior to visit 2, at least 10 voids per 24 hours on screening diary prior to visit 2, an urine output of less than 3000 mL/24 hours as measured and recording on a screening frequency volume chart prior to visit 2, a negative cough stress test with a bladder volume of at least 150 mL, is ambulatory and able to use a toilet independently and without difficulty, has a PVR volume ≤ 100 mL within 15 minutes of a spontaneous void at visit 1 documented either by ultrasound or catheterisation, has no language or cognitive barriers, agrees to comply with the requirements of the protocol, and has signed written informed consent, has responded appropriately to all screening questions at visit 1. **Exclusion criteria:** premenopausal women who are pregnant, been pregnant in the last 6 months, currently breastfeeding or have not resumed normal menstruation for 3 months due to breastfeeding, of child-bearing potential and are not practicing acceptable methods of birth control; had continence

EUCTR2004-002143-27-AT *(Continued)*

	surgery, or received bladder neck bulking agent therapy including collagen injections for incontinence within 6 months prior to randomisation; has a current diagnosis ureteric, bladder, urethral or rectal fistula, uncorrected congenital abnormality leading to urinary incontinence, voiding difficulty, including significant hesitancy or history of retention, has POP with protrusion of any vaginal segment greater than 1 cm beyond the hymen; had any major surgery within 3 months prior to randomisation; currently has or has a history of invasive urogenital cancer; history of mania/bipolar disorder; judged clinically to be at suicidal risk identified as a score of 2 or greater of q9 BDI-II; active seizure disorder; unstable diabetes mellitus; known neurologic lesions or conditions or local lesions (for example bladder stones, tumours) that could cause bladder overactivity; uncontrolled narrow angle glaucoma or a risk of acute narrow angle glaucoma; currently has or history of ulcerative colitis or toxic mega colon; history of severe allergies requiring emergency medical treatment or multiple adverse drug reactions; risk of increased bleeding or full anticoagulation; MAOIs, SSRIs, SNRIs, tricyclics or any other excluded medication intake within 14 days prior to randomisation; on a medication regimen, including diuretics, where dose and/or frequency have not been stable for at least 12 weeks prior to randomisation; taken any medication for UI within 1 month prior to randomisation; currently uses any anti-incontinence device including tampons used to prevent incontinence, vaginal pessaries for prolapse or incontinence; had any nonpharmacologic intervention for incontinence or prolapse within 3 months of randomisation; known active substance abuse disorder within the 5 years prior to randomisation or reports regular consumption of 21 or more units of alcohol per week; any active cardiac ischaemic condition, including myocardial infarction within 6 months prior to randomisation; uncontrolled or poorly controlled hypertension; a symptomatic arrhythmia despite antiarrhythmic medication, uncontrolled angina, or a significant abnormality on ECG; acute liver injury or severe cirrhosis (Child-Pugh Class C); hepatic dysfunction as defined by the following laboratory parameters: a. SGPT (ALT) or SGOT (AST) greater than or equal to 3 times upper limit of normal (ULN) or b. Bilirubin greater than or equal to 1.5 times ULN; a positive urine culture (> 100,000 cfu/mL) at Visit 1, or a history of 4 or more urinary tract infections (UTIs) in the preceding year as determined by the clinical investigator; known severe renal impairment as defined by creatinine clearance < 30mL/min; known hypersensitivity to duloxetine, tolterodine or any of its inactive ingredients.
Interventions	**Group I:** tolterodine tartrate (XL) 4 mg once daily **Group II:** placebo **Group III:** duloxetine hydrochloride (40 mg twice a day), but not relevant to this review Sample size is not reported
Outcomes	**Primary outcomes:** reduction in the number of incontinence episodes per week; patient's global perception of treatment effect **Secondary outcomes:** to compare the effects of duloxetine with those of placebo on bladder function as measured by other parameters derived from the patient completed 1-week urinary diary; to compare the effects of duloxetine with those of placebo on Patient Reported Outcomes (PRO) as measured by validated quality of life scales and symptom scores; to compare the effects of tolterodine, 4 mg once daily with those of placebo, utilising all the efficacy measures outlined above for duloxetine, including the primary endpoints; to compare the safety of duloxetine and tolterodine with that of placebo; to collect data for a future integrated analysis of two pivotal trials (1208.15 and 1208.16) on the efficacy of duloxetine compared with tolterodine during acute treatment measured by the mean change in IEF from baseline to endpoint
Study funding sources	Boehringer Ingelheim Austria GmbH
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information

EUCTR2004-002143-27-AT *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information; trial registration
Selective reporting (reporting bias)	Unclear risk	Insufficient information; trial registration
Other bias	High risk	Trial discontinued; reasons unclear but company state not safety or clinical issue

EUCTR2007-004126-24-CZ

Study characteristics	
Methods	**Study design:** placebo-controlled randomised, dose-ranging, double-blind study **Dates study conducted:** November 2007 to February 2009
Participants	**Setting:** multicentre **Country:** multinational **Age:** not reported **Sex:** not reported **Inclusion criteria:** females ≥ 18 years and ≤ 75 years of age with diagnosis of OAB with symptoms of UUI and frequency (≥ 1 urgency episode/day, ≥ 8 micturitions/day, ≥ 5 UUI episodes/week), which could be associated with nocturia, but without bladder pain **Exclusion criteria:** SUI or MUI where stress incontinence is the predominant component based on prior history; OAB/UUI due to cause other than detrusor overactivity; urinary retention or other evidence of poor detrusor function; pain during voiding or bladder pain without voiding; history of radiation cystitis or history of pelvic irradiation; history of interstitial cystitis or bladder related pain syndrome(s); PVR > 30 mL (?typo 300?); current UTI or frequent UTI (i.e. ≥ 5 UTIs per year); concomitant use of medication(s) that are CYP3A substrate(s) with narrow therapeutic range, or potent inhibitor(s) of a CYP450 isoenzyme 3A4, or any treatment with this/these medications within the 4 weeks prior to the study
Interventions	**Group I:** tolterodine 4 mg **Group II:** placebo Overall: n = 345 Sample size is not reported for individual groups

EUCTR2007-004126-24-CZ *(Continued)*

Outcomes	**Primary outcomes:** change from baseline in the number of micturitions per 24 hours **Secondary outcomes:** to compare the effects of duloxetine with those of placebo on bladder function as measured by other parameters derived from the patient completed 1-week urinary diary To compare the effects of duloxetine with those of placebo on Patient Reported Outcomes (PRO) as measured by validated quality of life scales and symptom scores To compare the effects of tolterodine, 4 mg once daily, with those of placebo, utilising all the efficacy measures outlined above for duloxetine, including the primary endpoints To compare the safety of duloxetine and tolterodine with that of placebo To collect data for a future integrated analysis of two pivotal trials (1208.15 and 1208.16) on the efficacy of duloxetine compared with tolterodine during acute treatment measured by the mean change in IEF from baseline to endpoint
Study funding sources	Sanofi
Notes	Trial registration No useable information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information; trial registration
Selective reporting (reporting bias)	Unclear risk	Insufficient information; trial registration
Other bias	High risk	Trial stopped early, which was decided by the company; it was not related to any safety issue or any clinical problem

Geller 2013

Study characteristics

Methods	**Study design:** RCT: double-blind, placebo-controlled trial

Geller 2013 *(Continued)*

	Dates study conducted: April 2013 to April 2015
Participants	**Setting:** single centre **Country:** USA **Age (mean, SD):** trospium: 66.7 (10.1); placebo: 68.9 (10.9) **Sex:** only female **Inclusion criteria:** women 50 years or older, a diagnosis of OAB (International Continence Society definition), English literacy, ability to swallow oral medication, and cognitive ability to give consent **Exclusion criteria:** active diagnoses of dementia, depression, delirium, urinary retention, gastric retention, severe decreased gastrointestinal motility conditions, uncontrolled narrow-angle glaucoma, myasthenia gravis, current anticholinergic use, current cholinesterase use and a diagnosis of renal impairment (creatinine clearance ≤ 30 mL/min) based on medical record review and participant interview at the time of enrollment
Interventions	**Group I (n = 21):** 60 mg trospium chloride ER **Group II (n = 25):** placebo Trial duration 4 weeks 2-week washout period
Outcomes	**Primary outcome:** the difference in HVLT-R total score at week 4 between the trospium group and placebo group **Secondary outcome:** OAB symptoms assessed with the OAB-q and the PPBC
Study funding sources	American Urogynecologic Society Research Foundation Award
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed with computer-generated number blocks of 6
Allocation concealment (selection bias)	Low risk	Group assignment numbers were placed in sequential, opaque envelopes and were opened after screening and enrollment were completed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded by IDS
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The IDS controlled all aspects of medication management including drug blinding, randomisation, packaging and dispensing to the clinic sites. The medication was stored on-site in a locked cabinet and maintained by the research team.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All withdrawals accounted for

Geller 2013 *(Continued)*

Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

Gotoh 2011

Study characteristics	
Methods	**Study design:** RCT: placebo-controlled, parallel design **Dates study conducted:** November 2007 to June 2008
Participants	**Setting:** multicentre (58 centres) **Country:** Japan **Age (mean):** 57.65 years **Sex:** 62.2% male **Inclusion criteria:** male and female outpatients ≥ 20 years old with OAB symptoms for at least 12 weeks. Patients with ≥ 8 micturitions/24 hours as an essential condition and ≥ 1 urgency incontinence episodes/24 hours or ≥ urgency episodes/24 hours were included **Exclusion criteria:** apparent stress urinary incontinence, polyuria with a daily volume ≥ 3000 mL or post-void residual volume ≥ 100 mL. Patients who had lower urinary tract obstruction, received alpha1-blocker treatment for benign prostatic hyperplasia (BPH), or underwent prostatectomy were also excluded
Interventions	**Group I (n = 274):** placebo **Group II (n = 291):** propiverine 20 mg once daily per oral Placebo run-in for 2 weeks Treatment for 12 weeks
Outcomes	Change in the number of micturitions/24 hours from baseline Change in the number of urgency and urgency incontinence episodes/24 hours Urine volume/micturition Number of nocturia episodes Changes from baseline in the overactive bladder symptom score (OABSS) QoL using KHQ Adverse events ECG Blood pressure and pulse rate
Study funding sources	Study supported by a grant from Taiho Pharmaceuticals, Tokyo, Japan
Notes	37 dropouts (Group I: 17, Group II: 20)

Gotoh 2011 *(Continued)*

	Last observation carried forward for missing values; ITT principle used

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block allocation consisting of 4 patients per set used
Allocation concealment (selection bias)	Low risk	States allocation sequence was concealed from investigators
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts and reasons for dropouts similar
Selective reporting (reporting bias)	Unclear risk	Not enough information
Other bias	Low risk	The study appears to be free of other sources of bias

Griebenow 1994

Study characteristics	
Methods	**Study design:** RCT: double-blind, placebo-controlled, parallel trial **Dates study conducted:** not reported
Participants	**Setting:** not reported **Country:** not reported **Age:** not reported **Sex:** not reported **Inclusion criteria:** 60 years or older, no severe heart disease, no change of electrolytes, urgency or urge incontinence **Exclusion criteria:** not reported
Interventions	**Group I (n = 47):** propiverine 15 mg 3 times a day **Group II (n = 46):** placebo Trial duration 4 weeks plus 2-week placebo run-in
Outcomes	Cardiac dysrhythmia

Griebenow 1994 *(Continued)*

Study funding sources	Not reported
Notes	Abstract only No usable data on any outcomes of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Haab 2004

Study characteristics

Methods	**Study design:** RCT, placebo-controlled, parallel design **Dates study conducted:** not reported
Participants	**Setting:** multicentre (57 sites) **Country:** international **Age (mean):** darifenacin 3.75 mg 56.7; darifenacin 7.5 mg 57.7; darifenacin 15mg: 56.6; placebo: 56.5 **Sex**: darifenacin 3.75 mg: 16.9% male; darifenacin 7.5 mg: 16.1% male, darifenacin 15 mg: 13.0% male; placebo: 15.8% male **Inclusion criteria:** 18 to 88 years, OAB symptoms for more than 6 months, urge incontinence 0 to 5 episodes/week, ability to fill up micturition charts **Exclusion criteria:** contraindications to anticholinergic; stress incontinence; BOO with residual more than 200 mL; hypersensitivity to medications
Interventions	**Group I (n = 164):** placebo

Haab 2004 *(Continued)*

	Group II (n = 53): darifenacin 3.75 mg 3 times a day **Group III (n = 229):** darifenacin 7.5 mg **Group IV (n = 115):** darifenacin 15 mg 12-week treatment period 2-week run-in
Outcomes	**Primary outcome:** number of incontinence episodes per week **Secondary outcomes:** frequency of micturition, frequency of urgency, nocturnal awakening, incontinence episodes resulting in change of pads, volume voided Adverse events Laboratory tests Blood pressure
Study funding sources	Pfizer Inc.
Notes	8 patients reported side effects (Group I: 1; Group II: 6; Group IV: 1). One patient had serious av heart block Data reported in median with no SD Power calculation present

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Complete blocks of participant numbers and medication packs were issued to each recruiting centre
Allocation concealment (selection bias)	Unclear risk	No information of how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy method
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts similar
Selective reporting (reporting bias)	Unclear risk	Not enough information
Other bias	Low risk	The study appears to be free of other sources of bias

Hajebrahimi 2014

Study characteristics

Methods	**Study design:** triple-blind, randomised controlled trial **Dates study conducted:** not reported

Hajebrahimi 2014 *(Continued)*

Participants	**Setting:** not reported **Country:** not reported **Age:** not reported **Sex:** female only **Inclusion criteria:** premenopausal women with diagnosis of OAB syndrome **Exclusion criteria:** not reported
Interventions	**Group I:** tolterodine 4 mg daily **Group II:** placebo Tadalafil 10 mg group, but not relevant to our review Total number of participants = 90 Individual numbers of participants in each group not reported Trial duration 4 weeks
Outcomes	**Primary outcome:** symptom severity pre- and post-treatment by ICIQ-OAB **Secondary outcomes:** not reported
Study funding sources	Not reported
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised to 3 arms by computerised random blocks
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Reported as "triple blind", but no further information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Reported as "triple blind", but no further information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Halaska 1994

Study characteristics	
Methods	**Study design:** RCT: placebo-controlled, parallel-group **Dates study conducted:** not reported
Participants	**Setting:** not reported **Country:** not reported **Age:** not reported **Sex:** not reported **Inclusion criteria:** over 60 years old, with urgency or urge incontinence, micturition volume 100 to 300 mL, residual volume > 20% of micturition volume at visit 1 **Exclusion criteria:** not reported
Interventions	**Group I (n = 47):** placebo **Group II (n = 46):** propiverine 15 mg 3 times a day 28 day treatment period 14 day run-in
Outcomes	Number of leakage episodes, volume voided, urgency Uroflows, urological investigations, psychometric evaluations Laboratory tests Gaudenz questionnaire
Study funding sources	Not reported
Notes	Abstract No follow-up Dropouts not stated

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking of assessors not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts not stated

Halaska 1994 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Herschorn 2008

Study characteristics	
Methods	**Study design:** RCT: placebo-controlled, parallel design **Dates study conducted:** September 2004 to October 2005
Participants	**Setting:** multicentre (66 centres) **Country:** Canada, Denmark, Germany, Italy, Netherlands, Norway, Poland, Spain, Sweden, Turkey, and United Kingdom **Age (mean):** 57.5 years **Sex:** tolterodine: 28% male; placebo: 29% male **Inclusion criteria:** male and female aged ≥ 18 years of age and were required to have recorded a mean of ≥ 8 micturitions per 24 hours and ≥ 3 episodes of urgency or urgency incontinence in a 3–day bladder diary. OAB symptoms for ≥ 3 months and at least moderate bothersome OAB symptoms, as reported on the OAB Bother Rating Scale **Exclusion criteria:** participants were excluded from the study if they had received any drug used to treat UUI or OAB within 14 days before the study treatment period
Interventions	**Group I (n = 410):** tolterodine ER 4 mg per oral once daily **Group II (n = 207):** placebo 12-week treatment period
Outcomes	Change in the percentage of participants reporting improvement on the PPBC at week 12 Change from baseline in bladder diary variables Change from baseline on PPBC Change from baseline on the OAB-q at week 12 Adverse events Questionnaires used: PPBC (Patients Perception of Bladder Condition), 3-day bladder diary, OAB-q questionnaire
Study funding sources	Study undertaken with a research grant from Pfizer Inc.
Notes	Dropouts: Group I: 36/410; Group II: 22/207

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised but no description

Herschorn 2008 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts and reasons similar
Selective reporting (reporting bias)	Unclear risk	Not enough information
Other bias	Low risk	The study appears to be free of other sources of bias

Herschorn 2009a

Study characteristics	
Methods	**Study design:** RCT, parallel design (2:2:1) **Dates study conducted:** not reported
Participants	**Setting:** multicentre **Country:** not reported **Age (mean, SD):** tolterodine: 58.5 (13.2); fesoterodine: 57.8 (12.8); placebo: 58.4 (13.7) **Sex:** tolterodine: 564 (83%) female; fesoterodine: 558 (82%) female; placebo: 269 (81%) female **Inclusion criteria:** symptoms of OAB for more than 3 months before screening and mean of one or more UUI/24 hours and ≥ 8 voids/24 hours reported in 3-day bladder diary **Exclusion criteria:** significant hepatic or renal disease, lower genitourinary pathology or surgical treatment thereof responsible for voiding dysfunction, neurological conditions such as stroke, multiple sclerosis, spinal cord injury or Parkinson's disease, previous history of acute urinary retention requiring catheterisation, predominant stress incontinence, treatment with antimuscarinics within 2 weeks before screening
Interventions	**Group I (n = 334):** placebo **Group II (n = 684):** tolterodine ER 4 mg once daily **Group III (n = 679):** fesoterodine 8 mg once daily 12-week treatment period 2-week run-in period
Outcomes	UUI/24 hours, volume voided/void, voids/24 hours, nocturnal voids, urgency episodes/24 hours (5-point urgency sensation scale)

Herschorn 2009a *(Continued)*

	PPBC (Patients Perception of Bladder Condition) UPS (Urgency Perception Scale) OABq Adverse events All patients in the fesoterodine group started on 4 mg for 1 week followed by 8 mg for 11 weeks
Study funding sources	Company support declared
Notes	Efficacy was analysed using full-analysis set, which included randomised patients who took one or more dose of double-blind study drug and had one or more valid baseline or post-baseline efficacy 167 dropouts (Group I: 30; Group II: 56; Group III: 81) No follow-up Unadjusted data obtained from Pfizer; unadjusted end of treatment values used for analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation schedule was generated, secured and distributed, and stored, by Pfizer Global clinical data services
Allocation concealment (selection bias)	Low risk	Implemented using a centralised system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy - all patients receiving 1 capsule and 1 tablet daily in the morning. Neither the investigator nor the patient was aware of which treatment administered.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts - placebo: 30 (9%), tolterodine ER: 56 (8%), fesoterodine: 81 (12%) with similar reasons for missing data
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Herschorn 2017a

Study characteristics

Methods	**Study design:** randomised, double-blind, parallel-group, placebo- and active-controlled phase III study **Dates study conducted:** 5 November 2013 to 22 October 2015

Herschorn 2017a *(Continued)*

Participants	**Setting:** multicentre (435 sites) **Country:** multinational (32 countries) **Age (mean, SD):** 57.4 (13.4) **Sex:** 789 male, 2738 female **Inclusion criteria**: ≥ 18 years, symptoms of wet OAB (urgency, urinary frequency and UI) for ≥ 3 months; In MUI patients, UUI had to be the predominant factor as evidenced by diary data and determined by the investigator. Those who recorded on average ≥ 8 micturitions/24 hours, ≥ 1 urgency episode/24 hours (grade 3 or 4 on Patient Perception of Intensity of Urgency Scale) and ≥ 3 UI episodes over the 7-day micturition diary were eligible for randomisation. **Exclusion criteria:** clinically significant bladder flow obstruction at risk of urinary retention; PVR > 150 mL; significant stress incontinence or MUI where stress was the predominant factor, as determined by the investigator; neurological cause for detrusor overactivity; indwelling catheter/practicing intermittent self-catheterisation; chronic inflammation e.g. bladder pain syndrome/interstitial cystitis; intravesical treatment in the past 12 months e.g. botox; uncontrolled narrow angle glaucoma, urinary or gastric retention, severe ulcerative colitis or Crohn's disease, toxic megacolon, myasthenia gravis or any contraindications to anticholinergics; clinically significant cardiovascular or cerebrovascular disease; average QTcF interval > 450 msec for males or > 470 msec for females based on triplicate EECGs completed at screening or at risk of QT prolongation; clinically significant abnormal 12 lead ECG; severe hypertension (sitting average systolic BP ≥ 180 mmHg and/or average diastolic BP ≥ 110 mmHg; Moderate-to-severe hepatic impairment (Child-Pugh class B or C); severe renal impairment (estimated glomerular filtration rate < 30 mL/min/1.73 m^2); current or previous malignant disease of the pelvis; receiving current non-drug treatment for OAB including electrostimulation therapy (with the exception of a bladder training programme or pelvic floor exercises which started > 30 days before screening); using medications intended to treat OAB or other prohibited medications; known or suspected hypersensitivity to solifenacin, mirabegron or any of their excipients; investigational therapy within 28 days or 5 half-lives, whichever was longer, before screening; current/history of alcohol and/or drug abuse; any condition which, in the investigator's opinion makes the participant unsuitable for study participation; employee of Astellas Group or third parties associated with the study or the clinical study site team. At randomisation: evidence of a UTI (urine culture containing > 100,000 cfu/mL) as assessed in the screening visit samples. The patient could be re-screened after successful treatment of the UTI confirmed by a dipstick negative for nitrite); average total daily urine volume > 3000 mL as recorded in the micturition diary; serum creatinine > 150 micromol/L, AST and/or ALT > 2 x UKLN or GGT > 3 x ULN or total bilirubin > 2 ULN as assessed in screening visit samples.
Interventions	**Group I (n = 423):** solifenacin 5 mg/day **Group II (n = 429):** placebo 4 other treatment arms (combined or monotherapy of mirabegron) but not relevant 4-week run-in, 12 weeks + 2-week washout
Outcomes	**Primary outcomes:** change from baseline to end of treatment in the mean number of UI episodes/24 hours and micturitions/24 hours, assessed using a 7-day electronic micturition diary **Secondary outcomes:** change from baseline to EOT in the MVV/micturition and PROs including change from baseline to end of treatment in OAB-q symptom bother score; HRQoL total score, Patient Perception of Bladder Condition (PPBC), Treatment Satisfaction Visual Analogue Scale (TS-VAS) and responder analyses. Change from baseline at weeks 4, 8, 12 and EOT in: mean number of UI episodes/24 hours, micturitions/24 hours, urgency episodes 24 hours, UUI episodes/24 hours and nocturia episodes/24 hours; the percentages of responders achieving zero UI episodes/24 hours at EOT in the last 7 days prior to each visit, micturition frequency normalisation (< 8 episodes/24 hours) at weeks 4, 8, 12 and EOT, and the number of UUI episodes and nocturia episodes in the 7-day diary
Study funding sources	Astellas

Herschorn 2017a *(Continued)*

Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation to double blind treatment in a 2:2:1:1:1:1 ratio
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Reported as "double blind" but no further details given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participant data accounted for
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Low risk	The study appears to be free of other sources of bias

Herschorn 2017b

Study characteristics

Methods	**Study design:** RCT **Dates study conducted:** March 2013 to March 2015
Participants	**Setting:** Multicentre (58 sites) **Country:** North America and Europe **Age (mean, SD):** 62.0 (12.3) years **Sex:** 13.5% male **Inclusion criteria:** adults with symptoms of OAB for 6 or more months, 2 or more UUI episodes/day without more than 1 UUI free day for 3 days, 8 or more micturitions per day and inadequate response and/or intolerance to anticholinergic and willing to use CIC if needed **Exclusion criteria:** OAB due to neurological reason, predominance of stress UI, previous and/or current soli therapy, previous and/or current botox therapy for any urological condition or any condition within 12 weeks of randomisation and any treatments for OAB within 7 days of start of screening
Interventions	**Group I (n = 151)**: solifenacin 5 mg **Group II (n = 60)**: placebo

Herschorn 2017b *(Continued)*

	Group III (n = 145): onabotulinum toxin A 100u, but not relevant to this review 12-week treatment
Outcomes	**Primary outcomes:** mean change from baseline in number of UI episodes/day and proportion of patients with 100% reduction in UI at week 12 **Secondary outcomes:** % change in UI, changes from baseline in micturition and nocturia episodes, KHQ role limitations and social limitations domains, proportion of patients with 50% or greater and 75% or greater UI reduction with a positive response (improvement or great improvement in urinary symptoms) on TBS and in those with a change from baseline of the MID or greater (-5 points) on the KHQ domains, AE
Study funding sources	Not reported
Notes	Patients could increase to 10 mg solifenacin

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Eligible for randomisation to double-blind treatment in a 2:2:1:1:1:1 ratio
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Reported as "double blind" but no further details given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participant data appear accounted for
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Hill 2005

Study characteristics

Methods	**Study design:** RCT: placebo-controlled, parallel design **Dates study conducted:** not reported
Participants	**Setting:** multicentre (62 European centres) **Country:** multinational (Belgium, Denmark, Israel, Norway, Poland, Sweden, the Netherlands, UK)

Hill 2005 *(Continued)*

	Age (mean): darifenacin 7.5: 56.1 years; darifenacin 15: 55.1 years; darifenacin 30: 54.0; placebo: 53.7 years **Sex:** darifenacin 7.5: 12% male; darifenacin 15: 14%; darifenacin 30: 13.9%; placebo: 17.4% **Inclusion criteria:** male and female patients ≥ 18 years with urge incontinence (at least 10 episodes over 14 days), high micturition frequency (mean of at least 8 voids per day) and urinary urgency (at least once per day) **Exclusion criteria:** clinically significant stress incontinence, BOO or post-void residual volume greater than 200 mL. Local pathology that could cause urinary symptoms, urogenital surgery within previous 6 months or cystoscopy in the previous 30 days were excluded. Patients with indwelling catheter, CISC, significant systemic disease were excluded. Patients intending to start bladder training programme during the study or contraindication to antimuscarinic therapy were not permitted to enter the study. Pregnant and lactating women were excluded.
Interventions	**Group I (n = 108):** darifenacin 7.5 mg once daily **Group II (n = 107):** darifenacin 15 mg once daily **Group III (n = 109):** placebo **Group IV (n = 115):** darifenacin 30 mg once daily, but not relevant to the review 2-week single-blind placebo run-in period 12-week treatment period
Outcomes	**Primary outcome:** number of incontinence episodes per week **Secondary outcomes:** number of micturition and urgency episodes per day, bladder capacity, severity of each episode of urgency (using 100 mm visual analogue scale), number of significant leaks per week and number of OAB related nocturnal awakenings Adverse events, lab tests, ECG, BP and heart rate
Study funding sources	Funded by Pfizer
Notes	50 dropouts (Group I: 9; Group II: 14; Group III: 19; Group IV: 8) Fixed dose

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	1:1:1:1 randomisation in blocks of 8 but no methods described
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States "double blind", double-dummy technique used to maintain blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description

Hill 2005 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Missing outcome data not balanced across the groups (7.5 mg: 8% versus 15 mg: 14% versus 30 mg: 19% versus placebo: 8%)
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Homma 2003

Study characteristics	
Methods	**Study design:** RCT: placebo-controlled, parallel design **Dates study conducted:** not reported
Participants	**Setting:** multicentre (69 sites) **Country:** Japan and Korea **Age (mean, SD):** 58.4 (14.0) **Sex:** tolterodine: 32% male; oxybutynin: 27% male; placebo: 31% male **Inclusion criteria:** > 20 years. Urinary frequency more than 8 times in 24 hours. Urge incontinence 5 times in a week, symptoms of overactive bladder more than 6 months **Exclusion criteria:** stress urinary incontinence, urinary volume of more than 3 L, average volume per void of more than 200 mL, significant hepatic and renal insufficiency. Pregnant women.
Interventions	**Group I (n = 122):** placebo **Group II (n = 239):** tolterodine ER 4 mg **Group III (n = 244):** oxybutynin IR 3 mg 12 weeks treatment period 1 to 2 weeks washout/run-in period
Outcomes	Number of leakage episodes, frequency of micturition, volume voided Adverse events Patient quality of life Laboratory tests Blood pressure Compliance by pill count
Study funding sources	Supported by a grant from Pharmacia Corporation
Notes	Quality of life reported in a separate publication

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised in 2:2:1 ratio using the method of random permuted blocks
Allocation concealment (selection bias)	Unclear risk	Not stated

Homma 2003 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Modified double-dummy technique matching placebos for both drugs provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts not reported
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Homma 2008

Study characteristics	
Methods	**Study design:** RCT: parallel design, placebo-controlled dose-finding study **Dates study conducted:** not reported
Participants	**Setting:** multicentre (64 centres) **Country:** Japan **Number of participants:** 401 male and female patients randomised **Age (mean, SD):** imidafenacin 0.1: 62.5 (13.0) years; imidafenacin 0.2: 64.5 (13.5) years; imidafenacin 0.3: 63.6 (12.9) years; placebo: 61.9 (11.8) years **Sex:** imidafenacin 0.1: 25.3% male; imidafenacin 0.2: 32.3% male; imidafenacin 0.5: 34.2% male; placebo: 27.4% male **Inclusion criteria:** men and women ≥ 20 years with OAB symptoms. Urinary incontinence (≥ 5 episodes/week), frequency of micturition (≥ 8 voids/day) and urgency (≥ 1 episode/day) **Exclusion criteria:** post-void residual ≥ 100 mL, genuine stress incontinence, bladder cancer, bladder stones or symptomatic urinary tract infections, indwelling or intermittent urethral catheterisation and benefiting from electrostimulation therapy or bladder training in the 3 months prior to the run-in period. Concomitant treatment with anticholinergic drugs and cholinergic drugs was not permitted during the study.
Interventions	**Group I (n = 101):** placebo **Group II (n = 100):** imidafenacin 0.2 mg/day **Group III (n = 99):** imidafenacin 0.1 mg/day, but not relevant to the review **Group IV (n = 101):** imidafenacin 0.5 mg/day, but not relevant to the review 2-week single-blind run-in period 12-week treatment period

Homma 2008 *(Continued)*

Outcomes	**Primary outcome:** percentage change in the number of incontinence episodes per week from baseline **Secondary outcome:** percentage change from the baseline in the number of urgency incontinence episodes per week, and urgency episodes per day, change from baseline in the number of micturitions per day and urine volume voided per micturition. Severity of urgency (4-point scale - no urgency, mild, moderate and severe) QoL - KHQ Adverse events, withdrawals due to adverse events Lab tests, ECG, post-void residual volume, vital signs All outcomes assessed at baseline and every 4 weeks other than QoL assessed at baseline and at 12 weeks
Study funding sources	Supported by a grant from Ono Pharmaceutical Co. and Kyorin Pharmaceutical Co.
Notes	Efficacy analysis was the per protocol set 45 withdrawals (Group I: 7 (17.1%); Group II: 6 (5.9%); Group III: 7 (7.0%); Group IV: 25 (24.8%))

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States randomised, no other description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States double-blind, double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts were dissimilar between the groups (Group I: 7 (17.1%); Group II: 6 (5.9%); Group III: 7 (7.0%); Group IV: 25 (24.8%)
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Homma 2009

Study characteristics

Methods	**Study design:** RCT: placebo and active comparator controlled, parallel design, phase III trial **Dates study conducted:** not reported

Homma 2009 *(Continued)*

Participants	**Setting:** multicentre (158 centres) **Country:** Japan **Age (mean, SD):** imidafenacin: 57.7 (12.7) years; propiverine: 59.8 (11.9) years; placebo: 58.0 (13.5) years **Sex:** imidafenacin: 12.6% male; propiverine: 15.7%; placebo: 12.6% **Inclusion criteria:** men and women > 20 years with OAB symptoms. Urinary incontinence (≥ 5 episodes/week), frequency of micturition (≥ 8 voids/day) and urgency (≥ 1 episode/day) **Exclusion criteria:** post-void residual > 100 mL, genuine stress incontinence, bladder cancer, bladder stones or symptomatic urinary tract infections, indwelling or intermittent urethral catheterisation and benefiting from electrostimulation therapy or bladder training in the 3 months prior to the run-in period. Concomitant treatment with anticholinergic drugs and cholinergic drugs, oestrogens, phenothiazine drug, monoamine oxidase inhibitors was not permitted during the study. Presence of disease contraindicating the use of antimuscarinic medication, polyuria, pregnant or nursing women were also ineligible.
Interventions	**Group I (n = 147):** placebo **Group II (n = 324):** imidafenacin 0.1 mg twice a day **Group III (n = 310):** propiverine 20 mg once daily 2-week placebo run-in period 12-week treatment period
Outcomes	**Primary outcome:** incontinence episodes per week **Secondary outcomes:** number urgency incontinence episodes per week, and urgency episodes per day, number of micturitions per day and urine volume voided per micturition. Severity of urgency QoL - KHQ (assessed at baseline and at 12 weeks) Adverse events Lab tests, ECG, post-void residual volume, vital sign All outcomes other than QoL assessed once every 4 weeks
Study funding sources	Company support declared
Notes	70 dropouts (Group I: 16 (10.9%); Group II: 23 (7.1%); Group III: 31 (10%)) Full analysis set was used for efficacy analysis Per protocol set used to carry out non-inferiority analysis using last observation carried forward for any missing 12-week values

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised using the methods of random permuted blocks
Allocation concealment (selection bias)	Unclear risk	Insufficient information

Homma 2009 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy technique
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts were similar between groups (Group I: 16 (10.9%); Group II: 23 (7.1%); Group III: 31 (10%)), reasons for withdrawals not reported
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Huang 2012

Study characteristics	
Methods	**Study design:** RCT, parallel design **Dates study conducted:** not reported
Participants	**Setting:** 13 clinical sites **Country:** United States **Age (mean, SD):** 56 (14) **Sex:** female 100% **Inclusion criteria:** participants were ambulatory women who were ≥ 18 years old. Women who reported clinically frequent incontinence during preliminary telephone screening (i.e. ≥ 7 incontinence episodes per week in the past 3 months) were invited to come to an in-person visit to complete the 3 IQ on paper to self-diagnose incontinence. Those who self-diagnosed incontinence on 3IQ (i.e. those who indicated that they had incontinence that occurred most often when they had the urge or the feeling that they needed to empty bladder but could not get to the toilet fast enough) were eligible to continue. Therefore the study population consisted of women who indicated that they had either isolated urgency incontinence or mixed incontinence that was predominantly with urgency. **Exclusion criteria:** self-reported complex medical histories that automatically would request a specialist evaluation for incontinence, such as anti-continence surgery in the past 5 years, other pelvic surgery in the past 6 months, > 3 urinary tract infection in the past year, lower urinary tract or rectal fistula, interstitial cystitis, symptomatic pelvic organ prolapse, urogenital cancer or radiation, congenital abnormality that leads to incontinence or major neurological disorder. Urinary or gastric retention, uncontrolled narrow angle glaucoma, myasthenia gravis, severe ulcerative colitis, clinically significant hepatic or renal disease, toxic mega colon, potent CYP3A4 inhibitor treatment in the last 2 weeks or pregnancy or nursing.
Interventions	**Group I (n = 322):** flexible dose fesoterodine 4 to 8 mg orally **Group II (n = 323):** placebo 12-week treatment period

Huang 2012 *(Continued)*

Outcomes	**Primary outcome:** self-reported urgency incontinence episodes per day **Secondary outcomes:** change in incontinence frequency, diurnal and nocturnal voiding frequency and frequency of voiding episodes that are associated with at least a moderate or severe sensation of urgency. Improvement in scores on validated questionnaires that assess the self-reported impact of women's bladder symptoms like Overactive Bladder Questionnaire and Patients Perception of Bladder Condition Adverse events Post-void residual volume
Study funding sources	Study funded by Pfizer Inc.
Notes	Last observation carried forward

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by computer permuted blocks of 2 to 4 without stratification for clinical site
Allocation concealment (selection bias)	Low risk	Active and placebo tablets were prepared by the UCSF pharmacy where they were labelled by a pharmacist with randomisation numbers and distributed to clinical sites
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	States participants, clinical personnel and statistical staff were masked to treatment assignment, but methods not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar attrition between groups
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Low risk	The study appears to be free of other sources of bias

Jacquetin 2001

Study characteristics

Methods	**Study design:** RCT: placebo-controlled, parallel-group, phase III **Dates study conducted:** not reported
Participants	**Setting:** multicentre **Country:** multinational (4)

Jacquetin 2001 *(Continued)*

	Age (mean): placebo: 56 years; tolterodine 1 mg: 53 years; tolterodine 2 mg: 58 years **Sex:** placebo: 19% male; tolterodine 1 mg: 11.6% male; tolterodine 2 mg: 18.4% male **Inclusion criteria:** over 18 years old with urodynamically verified detrusor overactivity, symptoms of urinary frequency and either urge incontinence or urgency or both. **Exclusion criteria:** SI, hepatic or renal disease, symptomatic or recurrent UTI, interstitial cystitis, haematuria, clinically significant voiding difficulty, patients receiving bladder training, electrostimulation, or having an indwelling catheter or intermittent catheterisation; pregnant or breastfeeding women or women of childbearing age who were not using reliable contraception
Interventions	**Group I (n = 51):** placebo **Group II (n = 97):** tolterodine 1 mg twice a day **Group III (n = 103):** tolterodine 2 mg twice a day 4-week treatment period 2-week run-in
Outcomes	Number of leakage episodes, frequency of micturition, volume voided Adverse events Laboratory tests Blood pressure Compliance by pill count
Study funding sources	Company support declared
Notes	6 dropouts (Group I: 1; Group II: 3; Group III: 2) 2-week follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Low risk	Physically indistinguishable tablets were given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Physically indistinguishable tablets were given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking of assessors not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts similar
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Jonas 1997

Study characteristics	
Methods	**Study design:** RCT: placebo-controlled, parallel design **Dates study conducted:** not reported
Participants	**Number of participants:** 242 patients (male and female) **Setting:** multicentre (58) **Country:** multinational (3) **Age (mean):** 58 years **Sex:** 24.7% male **Inclusion criteria:** at least 18 years old with detrusor overactivity and evidence of frequency in combination with UI, urinary urgency or both. **Exclusion criteria:** significant stress incontinence, hepatic or renal disease, any condition contraindicating anticholinergic therapy, recurrent UTIs, interstitial cystitis, uninvestigated haematuria or clinically significant voiding difficulty with risk of urinary retention. Patients on any anticholinergic treatment or using an indwelling catheter or who had electrostimulation or bladder training in the 14 days prior to inclusion visit.
Interventions	**Group I (n = 44):** placebo **Group II (n = 99):** tolterodine 1 mg twice a day **Group III (n = 99):** tolterodine 2 mg twice a day 4-week treatment period 2-week run-in
Outcomes	Urodynamic parameters Adverse events Laboratory tests Blood pressure
Study funding sources	Not reported
Notes	10 dropouts (Group I: 3; Group II: 4; Group III: 3) No follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking of assessors not stated

Jonas 1997 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts similar, ITT
Selective reporting (reporting bias)	High risk	Extensively reported 4, summarised others but have not reported 3 of the listed outcomes - empty resting pressure, full resting pressure, voided volume (5, 6, 11 on the list)
Other bias	Low risk	The study appears to be free of other sources of bias

Junemann 2000

Study characteristics	
Methods	**Study design:** RCT: placebo-controlled, parallel design **Dates study conducted:** from May 1996 to May 1999
Participants	**Setting:** multicentre **Country:** multinational (3) **Age:** not reported **Sex:** not reported **Inclusion criteria:** urge syndrome (motor urge, sensory urge and combined motor urge and stress incontinence) verified by urodynamics **Exclusion criteria:** not reported
Interventions	**Group I (n = 76):** trospium chloride 2 x 20 mg daily **Group II (n = 77):** tolterodine 2 x 2 mg daily **Group III (n=79):** placebo 3-week treatment period 10-day run-in
Outcomes	Frequency of micturition Adverse events Laboratory tests Physical examinations
Study funding sources	Not reported
Notes	Abstract Dropouts not stated No follow-up ITT analysis

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated

Junemann 2000 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Junemann 2006

Study characteristics	
Methods	**Study design:** RCT: parallel design, placebo-controlled, phase III/IV **Dates study conducted:** December 2001 to August 2003
Participants	**Setting:** multicentre (98 European centres) **Country:** multinational (Bulgaria, Spain, Ukraine, Romania, Austria and France) **Age (mean):** 56.1 years **Sex:** 10.5% males **Inclusion criteria:** male (104) and female (884) patients ≥ 18 years with at least 2 incontinence episodes within 3 days, and at least 10 micturitions within 24 hours **Exclusion criteria:** stress incontinence, intermittent catheterisation, neurogenic detrusor under and overactivity, post-void residual of > 100 mL, acute urinary tract infection, electrostimulation therapy, bladder training if performed within 4 weeks before run-in period of the study, anomalies of the lower genitourinary tract, pre-existing medical contraindications for anticholinergics, cardiac insuffiencey, multiple sclerosis, evidence of severe renal, hepatic or metabolic disorders, history of drug or alcohol abuse, concomitant medication known to interfere with study medication, pregnant or breastfeeding
Interventions	**Group I (n = 395):** propiverine IR 15 mg twice a day **Group II (n = 391):** propiverine ER 30 mg once daily **Group III (n = 202):** placebo Run-in period of 7 days Treatment period of 32 days
Outcomes	Incontinence episodes/24 hours

Junemann 2006 *(Continued)*

	Number of micturition/24 hours, urge episodes/24 hours, volume of micturition, QoL, efficacy evaluation by the patient and investigator (very good, good, moderate, insufficient or no statement) Adverse events Lab tests ECG - QT intervals BP, pulse rate
Study funding sources	Study funded by Apogepha
Notes	Results of PP population reported, states results of ITT population were similar 60 dropouts: Group I: 26; Group II: 23; Group III: 11

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States randomised, but no description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States "double blind double dummy"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reasons for withdrawal not stated but number of withdrawals similar between groups (Group I: 26; Group II: 23)
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Unclear risk	Insufficient information

Kaplan 2011

Study characteristics

Methods	**Study design:** randomised, placebo-controlled, parallel-group trial (2:2:1 ratio) **Dates study conducted:** from February 2009 to October 2009
Participants	**Setting:** multicentre (210 centres) **Country:** North America, South America, Europe, Asia and Africa **Age (mean, SD):** tolterodine 58.1 (13.8); fesoterodine: 57.9 (13.5); placebo 59.5 (13.2)

Kaplan 2011 *(Continued)*

	Sex: tolterodine: 818 (84%) female; fesoterodine: 816 (85%) female; placebo: 410 (86%) **Inclusion criteria:** men and women (≥ 18 years) self-reported OAB symptoms for ≥ 3 months and had a mean of at least one UUI episode and ≥ 8 micturitions per 24 hours in 3-day bladder diaries at baseline **Exclusion criteria:** clinically significant hepatic or renal disease, voiding dysfunction, neurological condition (stroke, multiple sclerosis, spinal cord injury or Parkinson's disease), history of acute urinary retention requiring catheterisation, predominant stress urinary incontinence, antimuscarinics within 2 weeks before screening or electrostimulation, bladder retraining or pelvic floor exercises. Female participants who were pregnant, nursing or of child-bearing potential.
Interventions	**Group I (n = 930):** fesoterodine 8 mg once daily **Group II (n = 942):** tolterodine ER 4 mg once daily **Group III (n = 462):** placebo 2-week placebo run-in period 12-week treatment period All participants in fesoterodine group received 4 mg for first week followed by fesoterodine 8 mg for next 11 weeks
Outcomes	3-day voiding diary at baseline, 1, 4 and 12 weeks UUI episodes, micturitions, nocturnal micturitions, urgency episodes, severe urgency episodes and frequency - urgency sum per 24 hours, 3-day diary dry rate and MVV per micturition PPBC, UPS - urgency perception score (5 point - 1 = no urgency, 2 = mild urgency, 3 = moderate urgency, 4 = severe urgency and 5 = UUI) at baseline, 1, 4 and 12 weeks OAB-q at baseline and 12 weeks
Study funding sources	Study funded by Pfizer Inc.
Notes	Efficacy analysis based on FAS Missing data were imputed by last observation carried forward principle 233 dropouts (Group I: 10%; Group II: 9%; Group III: 10%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation schedule with a block size of 5 was implemented, generated, secured, distributed and stored by Pfizer
Allocation concealment (selection bias)	Low risk	Secured, distributed and stored by Pfizer clinical data services
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated

Kaplan 2011 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts 88/973 in fesoterodine group, 88/973 in tolterodine group and 47/478 in placebo group. Both dropouts and reasons for dropout similar across groups.
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Kaplan 2014

Study characteristics	
Methods	**Study design:** RCT, parallel design **Dates study conducted:** from May 2011 to May 2012
Participants	**Setting:** multicentre (156 sites) **Country:** multinational (15 countries in Europe, North America, Asia and Africa) **Age (mean, SD):** placebo 58.2 (13.2); fesoterodine 57.3 (13.4) years **Sex:** ~16% male in each treatment group **Inclusion criteria:** men and women aged ≥ 18 years of with history of OAB for ≥ 6 months, some moderate problems on patient perception of bladder control, and on average ≥ 2 urge incontinence episodes/day; ≥ 8 micturitions/day **Exclusion criteria:** women with stress urinary incontinence marked cystocele or pelvic organ prolapse, patients receiving anticholinergics/antispasmodic drugs or those with anticholinergic effects, cholinergic agonists, potent cytochrome P450 3A4 inhibitors. Contraindications to anticholinergic drugs, clinically significant bladder outlet obstruction, intention to start bladder training programme. Placebo: 58.2 (13.2), fesoterodine: 57.3 (13.4)
Interventions	**Group I (n = 308):** fesoterodine 4 mg for 1 week and 8 mg once daily orally from week 2 to 12 **Group II (n = 301):** placebo 2-week run-in period 12-week study period
Outcomes	**Primary outcomes:** change from baseline after the tolterodine ER 4 mg run-in to week 12 in the number of UUI episodes/24 hours **Secondary outcomes:** treatment differences in changes from baseline to week 4 in number of UUI episodes/24 hours, changes from baseline to weeks 4 and 12 in number of micturitions and urgency episodes/24 hours; responder rates (≥ 50% or ≥ 70% reductions in UUI episode frequency from eligibility prior to the run-in and from baseline at weeks 4 and 12; diary-dry rate at weeks 4 and 12 (percentage of participants with > 1 UUI episode on baseline diary and 0 UUI episodes on post-baseline diary); and changes from baseline to week 12 in PPBC, UPS and OAB-q scores
Study funding sources	Study supported by Pfizer
Notes	Efficacy analysis is based on FAS Last observation carried forward principle used for missing values

Kaplan 2014 *(Continued)*

	No useable data in the abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised 1:1 via a centralised system
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	High risk	Dissimilar numbers of dropouts (27% in fesoterodine group and 15% in placebo)
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Low risk	The study appears to be free of other sources of bias

Karram 2009

Study characteristics	
Methods	**Study design:** RCT, parallel design **Dates study conducted:** not reported
Participants	**Setting:** multicentre (61 centres) **Country:** USA **Age (mean):** 57.2 years **Sex:** 14.8% male **Inclusion criteria:** ambulatory men and women, age 18 or older with OAB symptoms defined as having at least 1 urgency episode/24 hours, with or without urge incontinence and accompanied by frequency at least 8 micturitions/24 hours, nocturia or both for at least 3 months **Exclusion criteria:** stress or mixed urinary incontinence where stress predominated. Urinary tract infection, chronic inflammation, bladder stones, clinically significant outflow obstruction or anticholinergic hypersensitivity.
Interventions	**Group I (n = 372):** solifenacin 5 mg once daily orally **Group II (n = 367):** placebo

Karram 2009 *(Continued)*

	At week 4 dose could be maintained at 5 mg or increased to 10 mg. At week 8 dose could be maintained, increased from 5 mg to 10 mg, or decreased from 10 mg to 5 mg. 12-week treatment period
Outcomes	Mean change from baseline to endpoint in the number of urgency episodes per 24 hours Change from baseline in average daily number of micturitions, urinary incontinence and nocturia episodes Median change from baseline in warning time Urgency severity assessed using IUSS (Indevus urgency severity scale) and UPS (Urgency Perception Scale) PPBC (Patient Perception of Bladder Condition) and HRQL using OAB-q 3-day bladder diary completed at week 0, 4, 8 and 12
Study funding sources	Study supported by Astellas Pharma US, Inc. and GlaxoSmithKline.
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States randomised, no other description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	States double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts 58/372 in solifenacin group and 64/367 in placebo group. Both dropouts and reasons for dropout similar across groups.
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Unclear risk	Insufficient information

Khullar 2004

Study characteristics

Methods	**Study design:** RCT: placebo-controlled, parallel design

Khullar 2004 *(Continued)*

	Dates study conducted (only screening reported): October 2000 to July 2001
Participants	**Setting:** multicentre (101 sites) **Country:** Europe **Age (mean, SD):** placebo: 57.4 (13.8) years; tolterodine: 58.6 (13.1) years **Inclusion criteria:** > 18 years of age; 8 micturition episodes/24 hours; 5 episodes of urge incontinence/week, urgency **Exclusion criteria:** stress incontinence; total urine volume > 3 L; renal pathology; UTI; bladder outflow obstruction; pregnancy; any contraindication to anticholinergics
Interventions	**Group I (n = 569):** tolterodine 4 mg **Group II (n = 285):** placebo 8-week treatment period 7-day run-in
Outcomes	Micturition diaries used to assess any change in urge incontinence episodes, micturition frequency Perceived bladder condition severity was rated using a validated 6-point rating scale (1, no problems; 2, very minor problems; 3, minor problems; 4, moderate problems; 5, severe problems; and 6, many severe problems) Tolerability assessed Adverse events Quality of life
Study funding sources	Funded by Pfizer Inc.
Notes	Analysis was performed on an ITT basis Power calculation done (80%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation provided by permuted blocks
Allocation concealment (selection bias)	Low risk	Trial drugs of identical appearance were prepackaged according to the randomisation list, and a multiple of the block size was distributed to each study centre
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial drugs of identical appearance were prepackaged according to the randomisation list, and a multiple of the block size was distributed to each study centre
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts and reasons stated
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Khullar 2013

Study characteristics	
Methods	**Study design:** RCT **Dates study conducted:** not reported
Participants	**Setting:** multicentre (189 sites) **Country:** multinational (Europe and Australia) **Age (mean, SD):** placebo: 59.3 (12.15); tolterodine: 59.1 (12.75) **Sex:** placebo: male 27.9%, female 72.1%; tolterodine: male 27.2%, female 78.2% **Inclusion criteria:** ≥ 18 years, OAB symptoms ≥ 3 months, based on a 3-day micturition diary, patients with ≥ 8 micturitions/24 hours and ≥ 3 urgency episodes/72 hours **Exclusion criteria:** stress incontinence or stress-predominant mixed incontinence at screening, or an average total daily urine volume > 3000 mL as recorded in a 3-day micturition diary period 1987 participants randomised: tolterodine (n = 495); placebo (n = 497); mirabegron 50 mg (n = 497) and mirabegron 100 mg (n = 498). "...men and women ≥18 yr of age with symptoms of OAB for 3 mo. Patients were selected for randomisation if they met all inclusion criteria including an average micturition frequency of eight or more times per 24-h period and at least three episodes of urgency, with or without incontinence, during a 3-d micturition diary period."
Interventions	**Group I (n = 495)**: tolterodine ER 4 mg once daily **Group II (n = 497):** placebo Two other groups: mirabegron 50 mg, mirabegron 100 mg, but not relevant Trial period: 12 week 2-week placebo run-in
Outcomes	**Primary outcome:** change from baseline to final visit in the mean number of incontinence episodes and micturitions per 24 hours **Secondary outcomes:** change from baseline to final visit in mean volume voided per micturition, changes from baseline to week 4 in mean number of incontinence episodes and micturitions per 24 hours, the percentage of responders at final visit (patients with 50% decrease from baseline in mean number of incontinence episodes per 24 hours), the percentage of responders with no incontinence episodes, OAB Questionnaire (OAB-q), the Patient Perception of Bladder Condition (PPBC), treatment Satisfaction-Visual Analog Scale (TS-VAS)
Study funding sources	Astellas
Notes	NCT00689104. Report of the SCORPIO trial.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Eligible patients were randomised (1:1:1:1)" Comment: no further details

Khullar 2013 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Kosilov 2014a

Study characteristics	
Methods	**Study design:** not reported **Dates study conducted:** not reported
Participants	**Setting:** not reported **Country:** not reported **Age (mean):** 67.1 years **Sex:** female only **Inclusion criteria:** not reported **Exclusion criteria:** not reported
Interventions	Patients were divided into 3 groups and were treated with 2 antimuscarinic drugs
Outcomes	Not reported in abstract
Study funding sources	Not reported in abstract
Notes	Abstract only in English, main article Russian

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information

Kosilov 2014a *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Kosilov 2015a

Study characteristics	
Methods	**Study design:** RCT **Dates study conducted:** not reported
Participants	**Setting:** single centre **Country:** Russia **Age (mean):** 71.2 years **Sex:** 143 female, 93 male **Inclusion criteria:** patients over 65, who suffer from severe symptoms of overactive bladder (the frequency of episodes of incontinence (EI) 3 or more per day) **Exclusion criteria:** chronic active diseases including hypertension and patients who suffer from intolerance to antimuscarinics and agonists of beta-3 adrenoreceptors
Interventions	**Group I (n = 52):** solifenacin 10 mg **Group II (n = 59):** placebo Group III: mirabegron 50 mg, but not relevant to the review Group IV: same doses of both drug simultaneously, but not relevant to the review 239 analysed Study duration 6 weeks
Outcomes	Not reported
Study funding sources	Not reported

Kosilov 2015a *(Continued)*

Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomisation was carried out with the use of simple probability sampling
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Patients were not aware of the pharmacological properties and names of the drugs they were taking but not clear whether personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clear how many withdrawals or how any missing data handled
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Kosilov 2015b

Study characteristics

Methods	**Study design:** RCT **Dates study conducted:** 1 March to 31 December 2012
Participants	**Setting:** single centre **Country:** Russia **Age (mean):** solifenacin 10 mg: 67.2; solifenacin 5 mg: 65.9; placebo: 65.1 **Sex:** 347 female (66.2%), 177 male (33.8%) **Inclusion criteria:** patients aged > 60 years who had been diagnosed with a UTI. All denied presence of OAB signs in medical history. At least 1 month after end of treatment and lab confirmation of UTI absence, each patient completed OAB-AT and uroflowmetry. All patients with OAB then continued in study. **Exclusion criteria:** not reported
Interventions	**Group I (n = 107):** 10 mg solifenacin **Group II (n = 99):** 5 mg solifenacin **Group III (n = 102):** placebo

Kosilov 2015b *(Continued)*

	Trial duration: 12 months
Outcomes	**Primary outcomes:** number of urgency episodes, incontinence episodes and episodes of daytime urination **Secondary outcomes:** comparison of the conditions of the LUT after treatment
Study funding sources	Not reported
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only states that patients "were selected using blinded random sampling" without further detail
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The report states "blinded" study but does not provide details of the process
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participant data accounted for
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Kreder 2002

Study characteristics

Methods	**Study design:** RCT, double-blind **Dates study conducted:** not reported
Participants	**Setting:** multicentre **Country:** multinational **Age:** not reported **Sex:** not reported **Inclusion criteria:** OAB

Kreder 2002 *(Continued)*

	Exclusion criteria: not reported
Interventions	**Group I:** tolterodine 4 mg **Group II:** placebo 1529 randomised Numbers of participants are not reported in individual groups 12-week study period
Outcomes	**Primary outcome**: efficacy and safety of tolterodine
Study funding sources	Not reported
Notes	Abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not enough information in abstract to assess
Allocation concealment (selection bias)	Unclear risk	Not enough information in abstract to assess
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not enough information in abstract to assess
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not enough information in abstract to assess
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not enough information in abstract to assess
Selective reporting (reporting bias)	Unclear risk	Not enough information in abstract to assess
Other bias	Unclear risk	Not enough information in abstract to assess

Kuo 2015

Study characteristics

Methods	**Study design**: RCT: double-blind, parallel-group, placebo and active controlled **Dates study conducted:** 21 December 2009 to 16 September 2011
Participants	**Setting:** multicentre **Country:** 67 sites across Taiwan, Korea, China and India

Kuo 2015 *(Continued)*

	Age (mean, SD): placebo: 55.3 (13.63); tolterodine: 53.9 (14.5) **Sex:** placebo: 98 male (30.3%), female 225 (69.7%); tolterodine: male 120 (36.0%) female 213 (64%) **Inclusion criteria:** legal minimum age (18 in China and India, 20 in Korea (and Taiwan at the time)), symptoms of OAB ≥ 3 months prior to initiation of run-in period; average of ≥ 8 micturitions/24 hours; average of ≥ 1 episode of urgency or urgency incontinence/24 hours, during 3 day micturition diary period **Exclusion criteria:** stress urinary incontinence as predominant symptom at screening; UTI, urinary stone, interstitial cystitis, history of recurrent UTI; confirmed PVR volume ≥ 100mL or clinically significant LUT obstructive disease; average total daily urine volume > 3000 mL as recorded in 3-day voiding diary period; uncontrolled hypertension (sitting systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 110 mmHG), pulse rate ≥ 110 BPM or < 50 BPM; indwelling catheter or practices intermittent self-catheterisation
Interventions	**Group I (n = 333):** tolterodine ER 4 mg **Group II (n = 323):** placebo Group III mirabegron 50 mg/day, but not relevant Total number of n analysed 994 12-week study period
Outcomes	**Primary outcome:** change from baseline to final visit in mean number of micturitions/24 hours **Secondary outcomes:** change from baseline to final visit in mean number of urgency episodes, and nocturia episodes/24 hours, and mean volume voided/micturition. Change from baseline to each study visit was also measured. Values basined from patients's 3-day micturition diary. Change from baseline to final visit in individual domains of KHQ
Study funding sources	Astellas Inc.
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was accomplished using a computer-generated randomisation scheme with stratification by site
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information

Kuo 2015 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Lackner 2011

Study characteristics	
Methods	**Study design:** RCT, double-blinded **Dates study conducted:** not reported
Participants	**Setting:** 12 skilled nursing homes in Minnesota **Country:** USA **Age (mean, SD):** oxybutynin: 89.2 (5.2) years; placebo: 88 (7.1) years **Sex:** female only **Inclusion criteria:** female nursing home residents 65 years or older with UUI and mild to severe cognitive impairment; post-void residual urine volume of less than 150 mL **Exclusion criteria:** males; people younger than 65; people without UUI or cognitive impairment; post-void residual urine volume of more than 150mL
Interventions	**Group I (n = 26):** 5 mg once daily oral extended-release oxybutynin **Group II (n=24):** placebo 4-week treatment
Outcomes	Urinary incontinence episodes, urinary frequency, total dryness, postvoid residual volume (mL)
Study funding sources	Not reported
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Authors mention that participants were stratified by Mini Mental Status Examination (MMSE) 12 score of 5 to 10 and 11 to 23 out of 30 possible points and then randomised to treatment with active drug or placebo; however the randomisation process is not described
Allocation concealment (selection bias)	Unclear risk	No information of how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States double-blind: the participants received identically appearing sham tablet of either placebo or oxybutynin
Blinding of outcome assessment (detection bias)	Unclear risk	No description

Lackner 2011 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers of dropouts are similar across both groups, reasons are stated
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, no prespecified outcomes
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Landis 2004

Study characteristics	
Methods	**Study design:** RCT: placebo-controlled, parallel design **Dates study conducted:** not reported
Participants	**Setting:** multicentre **Country:** multinational **Age (mean):** tolterodine: 60.57 years; placebo: 61.13 years **Sex:** tolterodine: 17.7% male; placebo: 18.9% **Inclusion criteria:** > 18 years, urinary frequency more than 8 times in 24 hours. Urge incontinence 5 times in a week. **Exclusion criteria:** lower urinary tract surgery in last 6 months, interstitial cystitis, urethral syndrome, painful bladder syndrome, overflow incontinence Total urinary volume of more than 3 L. Significant hepatic and renal insufficiency. Pregnant women.
Interventions	**Group I (n = 492):** tolterodine ER 4 mg once daily **Group II (n = 494):** placebo 12-week treatment period
Outcomes	Number of incontinence episodes per week, frequency of micturition, frequency of urgency, nocturnal awakening, incontinence episodes resulting in change of pads, volume voided Adverse events Laboratory tests Blood pressure
Study funding sources	Pharmacia Corporation, Alza Pharmaceuticals and Pharmaci
Notes	Data reported as median and hence unsuitable for meta-analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description

Landis 2004 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking of assessors not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts not reported
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Unclear risk	Insufficient information

Lee 2006

Study characteristics	
Methods	**Study design:** RCT, parallel design **Dates study conducted:** December 2003 to July 2004
Participants	**Setting:** multicentre (12 sites) **Country:** Korea **Age (mean):** 52.2 years **Sex:** 25.6% male **Inclusion criteria:** men and women ≥ 18 years with OAB symptoms for > 3 months. Patients were required to show an average frequency of ≥ 10 voids/24 hours and urgency of 2 or more episodes/24 hours defined as moderate to severe in IUSS (Indevus Urgency Severity Scale) **Exclusion criteria:** clinically significant stress urinary incontinence, genitourinary condition that could cause OAB symptoms, such as urinary tract infection and contraindications to the use of antimuscarinic drugs
Interventions	**Group I (n = 176):** propiverine 20 mg orally once daily **Group II (n = 88):** placebo 2-week washout period 12-week treatment period
Outcomes	Mean number of urgency events/24 hours Mean change and mean percentage changes from baseline to 12 weeks in patient perception of urgency, urgency severity/void, sum of urgency severity/24 hours, daytime and nocturnal voiding frequency/24 hours

Lee 2006 *(Continued)*

	Adverse events 3-day voiding diary completed at baseline, week 4 and week 12 and patient perception of urgency assessed using Urgency Perception Score
Study funding sources	Study funded by Cheil Pharmaceutical Co. Ltd., Seoul, Korea
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation list prepared by trial independent statistician using a random permuted block design
Allocation concealment (selection bias)	Unclear risk	Only says "in a strict consecutive order at the centre"; unclear method of allocation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	States double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing outcome data not balanced in numbers (propiverine: 46/176; placebo: 12/88)
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Luis 2018

Study characteristics

Methods	**Study design:** RCT, double-blind **Dates study conducted:** not reported
Participants	**Setting:** not reported **Country:** not reported **Age (mean, SD):** 59.0 (15.4) years **Sex:** female only **Inclusion criteria:** women with OAB **Exclusion criteria:** not reported
Interventions	**Group I (n = 36):** darifenacin 7.5 mg

Luis 2018 *(Continued)*

	Group II (n = 44): placebo 12-week treatment period
Outcomes	OAB-q, ICIQ-SF, KHQ, bladder diaries to quantify symptom control and QoL
Study funding sources	Abbot
Notes	Abstract only No useable data All participants underwent PFMT before being randomised

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised occult sequences
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Madersbacher 1999

Study characteristics

Methods	**Study design:** RCT: placebo-controlled, parallel design, randomised 2:2:1 **Dates study conducted:** not reported
Participants	**Setting:** multicentre (32) **Country:** multinational (2) **Age (mean):** propiverine: 49.6 years; oxybutynin: 50.3 years; placebo: 47.6 years **Sex:** propiverine: 6.1% male; oxybutynin: 6.6% male; placebo: 6.3% male

Madersbacher 1999 *(Continued)*

	Inclusion criteria: history of urgency or urge incontinence, maximum cystometric bladder capacity at least 300 mL, at least 18 years old and body weight at least 45 kg **Exclusion criteria:** detrusor hyperreflexia, postoperative (bladder) incontinence, intravesical obstruction, post-void residual urine > 15% maximum cystometric bladder capacity, acute UTIs, angina pectoris, glaucoma, megacolon, clinically relevant cardiac, renal or hepatic dysfunctions, tachy/dysrhythmias, frequency or nocturia due to heart or renal insufficiency, or overt cerebral sclerosis. Use of other spasmolytics or anticholinergics, beta-sympathomimetics, calcium antagonists, dopamine agonists, prolactin inhibitors, prostaglandin synthesis inhibitors, striated muscle relaxants or medication for Parkinsonism
Interventions	**Group I (n = 149):** propiverine 15 mg 3 times a day **Group II (n = 145):** oxybutynin 5 mg twice a day **Group III (n = 72):** placebo 4-week treatment period 7-day run-in
Outcomes	Frequency of urgency Urodynamic parameters Clinical symptoms and overall assessment documented by physicians Incontinence questionnaire (Gaudenz)
Study funding sources	Not reported
Notes	42 dropouts (Group I: 19; Group II: 16; Group III: 7) No follow-up ITT analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy method
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking of assessors not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis, dropouts similar
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Malone-Lee 2001

Study characteristics	
Methods	**Study design:** RCT: placebo-controlled, parallel design, randomised 3:3:2 **Dates study conducted:** not reported
Participants	**Setting:** multicentre (26) **Country:** multinational (3) **Age (mean):** 75 years **Sex:** 35% male **Inclusion criteria:** at least 65 years old with 8 or more voids per 24 hours and/or urge incontinence at least 1 per 24 hours **Exclusion criteria:** "standard"
Interventions	**Group I (n = 43):** placebo **Group II (n = 61):** tolterodine 1 mg twice a day **Group III (n = 73):** tolterodine 2 mg twice a day 4-week treatment period 14-day run-in
Outcomes	Number of leakage episodes, frequency of micturition, volume voided Adverse events Laboratory tests ECG Compliance by pill count
Study funding sources	Supported by Pharmacia & Upjohn AB, Sweden
Notes	12 dropouts (Group I: 1; Group II: 4; Group III: 7) ITT analysis 2-week follow-up for adverse events

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Low risk	All study medication was supplied as physically indistinguishable tablets
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking of assessors not stated
Incomplete outcome data (attrition bias)	Low risk	ITT analysis

Malone-Lee 2001 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Millard 1999

Study characteristics	
Methods	**Study design:** RCT: placebo-controlled, parallel design, phase III, randomised 1:2:2 **Dates study conducted:** not reported
Participants	**Setting:** multicentre **Country:** multinational (2) **Age (mean):** placebo: 60.5 years; tolterodine 1 mg: 60.1 years; tolterodine 2 mg: 60.2 years **Sex**: placebo: 34% male; tolterodine 1 mg: 22% male; tolterodine 2 mg: 23% male **Inclusion criteria:** at least 18 years old, with cystometrically proved detrusor overactivity (idiopathic or hyper-reflexia or contractions with an amplitude at least 10 cm H_2O); at least 8 voids/24 hours; at least 1 incontinent episode/24 hours and/or urinary urgency, premenopausal women required to use adequate contraception **Exclusion criteria:** SI (cough test), clinically significant voiding difficulty, recurrent UTIs, interstitial cystitis, uninvestigated haematuria or any bladder cancer, indwelling catheter or self-catheterisation, hepatic or renal disease, narrow angle glaucoma, electrostimulation or bladder training or anticholinergic drug initiated 14 days before or any time during study, unstable dose of any treatment with anticholinergic side effects, average total voided volume > 3000 mL/24 hours, treatment with any other investigational drug during or 2 months pre study
Interventions	**Group I (n = 64):** placebo **Group II (n = 123):** tolterodine 1 mg twice a day **Group III (n = 129):** tolterodine 2 mg twice a day 12-week treatment period 2-week run-in
Outcomes	Cured incontinence and complete cure Patient rating of bladder condition (6-point Likert) Leakage episodes Achievement of normal voiding frequency (< 8/day) Adverse events Laboratory tests ECG Blood pressure Compliance by pill count
Study funding sources	Supported by Pharmacia & Upjohn AB, Uppsala, Sweden
Notes	No dose reductions permitted 25 dropouts (Group I: 3; Group II: 7; Group III: 15) ITT analysis No follow-up

Millard 1999 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking of assessors not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for dropouts are clearly stated (due to adverse effects)
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Mitcheson 2019

Study characteristics	
Methods	**Study design:** RCT, double-blind, placebo- and active comparator-controlled parallel-group, 2-part superiority trial **Dates study conducted:** April 2011 to October 2013
Participants	**Setting:** multicentre **Country:** over 18 countries **Age (mean, SD):** 58.6 (9.3) years **Sex:** 89.7% female, 1395 (987 in part 1 and 408 in part 2) randomised; 1324 (936 in part 1, 388 in part 2) analysed; 10.3% male **Inclusion criteria:** patients were aged 40 to 75 years in part 1 and 18 to 75 years in part 2. Patients were required to have OAB for 3 months before screening, meet predefined OAB-wet or OAB-dry criteria, have a greater number of urge episodes than stress incontinence episodes, and have no clinically significant laboratory or ECG abnormalities **Exclusion criteria:** patients with LUTS pathology that could be responsible for urgency, frequency or incontinence (such as urolithiasis, interstitial cystitis, and benign prostatic hypertrophy); history of injury, surgery, or neurodegenerative diseases that could affect the lower urinary tract or its nerve supply; continual urine leakage (aware or unaware); surgery to correct stress urinary incontinence or prolapsed uterus within 6 months; elevated PVR; bladder training or electrostimulation within 2 week;

Mitcheson 2019 *(Continued)*

	haematuria or faecal incontinence; or requirement for indwelling catheter or intermittent catheterisation were excluded
Interventions	**Group I (n = 257):** tolterodine ER 4 mg **Group II (n = 205):** placebo Total number of participants: 1395 (987 in part 1 and 408 in part 2) Part 1: vibegron 3 mg, 15 mg, 50 mg or 100 mg, tolterodine ER 4 mg or placebo for 8 weeks, or V50/TER4 for 4 weeks then V50 for 4 weeks, part 2: V100/TER 4, V100, TER4 or placebo for 4 weeks
Outcomes	**Primary outcomes:** vibegron dose-related reduction in LSM daily number of micturitions in all patients at week 8 (part 1) **Secondary outcomes:** changes from baseline to week 4 in LKSM daily number of micturitions (part 2). Changes from baseline to week 8 (part 1) and week 4 (part 2) in LSM daily number of total incontinence and urge incontinence episodes (OAB wet only) and to week 8 (part 1) and week 4 (part 2) in LSM daily number of urgency episodes in all patients. Efficacy and safety were also evaluated in the 52-week extension of this trial. Exploratory endpoints included results of the KHQ.
Study funding sources	Merck Sharp & Dohme Corp.
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation using an interactive response technology system
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The trial was double-blinded using in-house blinding procedures; investigators/study staff, patients, and sponsor were all blinded to treatment assignments"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Investigators/study staff, patients and sponsor were all blinded to treatment assignments
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Low risk	The study appears to be free of other sources of bias

Nitti 2005

Study characteristics

Nitti 2005 *(Continued)*

Methods	**Study design:** randomised, placebo-controlled, dose-ranging phase II trial, parallel design **Dates study conducted:** 18 June 2002 to 30 July 2003
Participants	**Setting:** multicentre (28 centres) **Country:** USA **Age (mean):** placebo: 56.9 years; fesoterodine 4 mg: 53.9 years; fesoterodine 8 mg: 55.2 years fesoterodine 12 mg (irrelevant dose): 57.5 years **Sex:** placebo: 19% male, fesoterodine 4 mg: 14% male, fesoterodine 8 mg: 11% male, fesoterodine 12 mg: 8% male **Inclusion criteria:** male and female patients aged 18 to 78 with ≥ 8 micturitions/24 hours and ≥ 2 urge incontinence episodes/week with or without baseline urodynamic evidence of detrusor overactivity **Exclusion criteria:** not reported
Interventions	**Group I (n = 43):** placebo **Group II (n = 44):** fesoterodine 4 mg once daily **Group III (n = 47):** fesoterodine 8 mg once daily **Group IV (n = 39):** fesoterodine 12 mg once daily, but not relevant 173 patients randomised 1-week placebo run-in period 8-week treatment period
Outcomes	Micturitions/24 hours Urge incontinence episodes/week Voided volume per micturition Urgency episodes/week Nocturia Severity of urgency using 4-grade scale (1 = none, 2 = mild, 3 = moderate, 4 = severe) Bother score using 2 domains of KHQ: role limitation and sleep/energy Adverse events, vital signs, ECG, lab values and residual urine volume
Study funding sources	Study funded by Pfizer
Notes	Abstract, data from Pfizer Inc. Both FAS and PPS analysed Last observation carried forward 32 dropouts (Group I: 8; Group II: 7; Group III: 9; Group IV: 8)

Risk of bias

Bias	Authors' judgement	Support for judgement

Nitti 2005 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	States randomised, no description. Participants stratified into 2 strata depending on the outcome of urodynamic assessment.
Allocation concealment (selection bias)	Unclear risk	No information, but blinding not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	No differential dropout (Group I: 8; Group II: 7; Group III: 9; Group IV: 8) and reasons for dropout similar. Missing data imputed by last observation carried forward method.
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Nitti 2007

Study characteristics	
Methods	**Study design:** RCT, placebo-controlled, parallel design **Dates study conducted:** 30 October 2003 to 10 February 2005
Participants	**Setting:** multicentre (83 centres) **Country:** United States **Age (mean):** placebo: 59 years; fesoterodine 4 mg: 59 years; fesoterodine 8 mg: 59 years **Sex:** placebo: 26% male; fesoterodine 4 mg: 24% male; fesoterodine 8 mg: 22% **Inclusion criteria:** men and women 18 years or older with OAB syndrome for 6 months or greater, including urinary frequency (8 micturitions or greater per 24 hours) and urinary urgency (6 episodes or greater during 3 day diary) or UUI (3 episodes or greater during the 3-day diary period) **Exclusion criteria:** significant stress incontinence, urolithiasis, interstitial cystitis or urothelial tumours, pelvic organ prolapse grade 3 or greater, clinically relevant bladder outlet obstruction, PVR volume greater than 100 mL, polyuria (greater than 3 L/24 hours), symptomatic or recurrent urinary tract infections, current treatment with antimuscarinic agents, neurogenic cause of OAB, clinically relevant arrhythmia, unstable angina or a corrected QT interval of greater than 500 milliseconds or current treatment or treatment within the last 4 weeks with electrostimulation or bladder training
Interventions	**Group I (n = 274):** placebo **Group II (n = 283):** fesoterodine 4 mg per day **Group III (n = 279):** fesoterodine 8 mg per day 2-week placebo run-in, 12-week treatment period

Nitti 2007 *(Continued)*

	2-, 8- and 12-week follow-up
Outcomes	Number of micturitions per 24 hours Number of urgency incontinence episodes per 24 hours Treatment response (yes/no - variable derived from 4-point treatment benefit scale) Mean voided volume per micturition Number of continent days Number of urgency episodes per 24 hours Treatment response (self-administered treatment benefit scale) Adverse events ECG Post-void residual urine volume Lab parameters
Study funding sources	Supported by Schwarz and Pfizer, financial/other relationship with pharma
Notes	Full analysis set Missing responses imputed via last observation carried forward Dropouts: placebo: 41 (15%); fesoterodine 4 mg: 58 (20.5%); fesoterodine 8 mg: 56 (20.1%) Least square mean change reported for micturitions/24 hours, UUI episodes/24 hours and urgency episodes/24 hours - so not useable. Unadjusted data obtained from the authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule stratified by site
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Low risk	States "double blind", placebo tablets were identical to 4 mg and 8 mg fesoterodine tablets
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of dropouts similar between groups (placebo: 41 (15%); fesoterodine 4 mg: 58 (20.5%); fesoterodine 8 mg: 56 (20.1%)) but reasons for dropouts not reported
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes

Nitti 2007 *(Continued)*

Other bias	Unclear risk	Insufficient information

Olshansky 2006

Study characteristics	
Methods	**Study design:** RCT, double-blind **Dates study conducted:** not reported
Participants	**Setting:** not reported **Country:** not reported **Age (range):** 21 to 93 years **Sex:** 16% male **Inclusion criteria:** OAB for at least 6 months **Exclusion criteria:** not reported
Interventions	**Group I (n = 112):** darifenacin 15mg once daily **Group II (n = 223):** tolterodine immediate release 2 mg twice daily **Group III (n = 115):** placebo 12-week treatment Total number of participants 450
Outcomes	Cardiac effects of darifenacin and tolterodine. Cardiovascular safety included spontaneously reported adverse events, change in heart rate and change in blood pressure from baseline to last observation (irrelevant to this review).
Study funding sources	Novartis Pharma AG, Basel, Switzerland
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not enough information in the abstract
Allocation concealment (selection bias)	Unclear risk	Not enough information in the abstract
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not enough information in the abstract

Olshansky 2006 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not enough information in the abstract
Selective reporting (reporting bias)	Unclear risk	Not enough information in the abstract
Other bias	Unclear risk	Not enough information in the abstract

Oreskovic 2012

Study characteristics	
Methods	**Study design:** RCT, parallel design **Dates study conducted:** not reported
Participants	**Setting:** not reported **Country:** not reported **Age (mean):** solifenacin: 56.77 years; placebo: 57.03 years **Sex:** females only **Inclusion criteria:** symptoms of OAB for at least 6 months. Urge incontinence (no more than 50 episodes per week), frequency of micturition (at least 8 voids per 24 hours) and urgency (once per day) **Exclusion criteria:** contraindications for the use of anti-muscarinic drugs (e.g. uncontrolled narrow angle glaucoma, urinary or gastric retention), clinically significant stress urinary incontinence, clinically significant bladder outlet obstruction or post-void residual volume more than 200 mL, genitourinary condition that could cause urinary symptoms, recent urogenital surgery or hepatic disease
Interventions	**Group I (n = 77):** solifenacin 5 mg once daily orally **Group II (n = 80):** placebo 4-week treatment period 2-week run-in period
Outcomes	Mean change from baseline in micturition episodes, urgency, nocturia and incontinence episodes per 24 hours Adverse events
Study funding sources	Not reported
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description

Oreskovic 2012 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Method of concealment has not been described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No data
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals and reasons not reported
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Orri 2014

Study characteristics	
Methods	**Study design:** RCT, parallel design, web-based trial **Dates study conducted:** March 2011 to September 2012
Participants	**Setting:** single centre **Country:** USA **Age (mean):** tolterodine: 48.4 years; placebo: 46.2 years **Sex:** females only **Inclusion criteria:** residents of United States having access and ability to use computer with internet access, women aged > 21 years or older with OAB symptoms for more than 3 months, more than one UUI episode/day, 8 or more voids per day **Exclusion criteria:** women unable to complete e-diary. Contraindication for use of tolterodine, urinary retention, gastric retention, uncontrolled narrow angle glaucoma, toxic megacolon, myasthenia gravis, severe hepatic impairment, significant renal disease, polyuria > 3 L/day, recurrent UTI, haematuria, urogenital cancer, radiation of pelvis, bladder outlet obstruction, pregnant, nursing, or intending to become pregnant and predominant stress incontinence
Interventions	**Group I (n = 12):** tolterodine ER 4 mg/day **Group III (n = 6):** placebo 2-week run-in period 12-week study period
Outcomes	Change from baseline in mean number of micturitions/24 hours at week 12
Study funding sources	Pfizer Inc.

Orri 2014 *(Continued)*

Notes	Efficacy analysis was performed for FAS Withdrawals: Group I 1/12; Group III 0/6

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants "were randomized (2:1) via an interactive voice response/interactive web response system to double-blind treatment"
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals and reasons similar
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, the report is more about study design than outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Rentzhog 1998

Study characteristics

Methods	**Study design:** RCT: placebo-controlled, parallel design, phase II **Dates study conducted:** not reported
Participants	**Number of participants:** 81 male and female patients **Setting:** multicentre (17 sites) **Country:** multinational (Sweden and UK) **Age**: not reported **Sex:** 24% male **Inclusion criteria:** aged 18 to 75 years old with symptoms of urinary urgency, increased frequency and/or urge incontinence. Urodynamically confirmed detrusor instability. Insignificant bacteriuria and normal laboratory tests. No evidence of bladder outlet obstruction **Exclusion criteria:** stress incontinence or detrusor hyperreflexia, clinically significant cardiac, hepatic, renal or haematological disorders, patients with contraindications to antimuscarinic agents, pregnant or lactating women, women of childbearing age who were not using reliable contraception.
Interventions	**Group I (n = 13):** placebo

Rentzhog 1998 *(Continued)*

	Group II (n = 16): tolterodine 1 mg twice a day **Group III (n = 14):** tolterodine 2 mg twice a day **Group IV (n = 16):** tolterodine 4 mg twice a day, but not relevant to the review **Group V (n = 21):** tolterodine 0.5 mg twice a day, but not relevant to the review 2-week treatment period 3-week run-in
Outcomes	Symptomatic improvement (VAS) Number of leakage episodes, frequency of micturition Number of pads used Urodynamic parameters Adverse events ECG
Study funding sources	Company support declared
Notes	Dose reduction allowed to next lowest level 16 dropouts (Group I: 3; Group II: 4; Group III: 1; Group IV: 3; Group V: 5) PP analysis 2-week telephone follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking of assessors not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	PP analysis
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Resnick 2006

Study characteristics

Methods	**Study design:** RCT, double-blind, placebo-controlled trial

Resnick 2006 *(Continued)*

	Dates study conducted: 1 March 1996 to 31 March 2006
Participants	**Setting:** single site **Country:** USA **Age:** not reported **Sex:** female only **Inclusion criteria:** cognitively intact, community-dwelling persons at least 55 years old with urge incontinence at least every 2 days **Exclusion criteria:** significant stress incontinence; outlet obstruction; post-voiding residual urine > 300 mL; MMSE < 24/30; inability to go to the toilet independently; contraindication to antimuscarinic therapy; gastrointestinal obstruction; megacolon; severe liver or renal disease; uncontrolled hyperthyroidism; multiple sclerosis; anteroposterior resection; pelvic radiation; spinal cord disease resulting in para- or quadriplegia
Interventions	**Group I:** oxybutynin **Group II:** placebo No numbers of participants in individual groups Target sample size: 250 Trial duration not reported
Outcomes	**Primary outcomes:** percentage reduction in incontinence episodes on 4-day bladder diary **Secondary outcomes:** number of participants dry at end of study; subjective satisfaction
Study funding sources	NIHDDK
Notes	Trial registration No useable data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information

Resnick 2006 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Robinson 2013

Study characteristics	
Methods	**Study design:** RCT, parallel design **Dates study conducted:** not reported
Participants	**Setting:** multicentre **Country:** USA, Austria, Belgium, Bulgaria, Canada, Czech Republic, France, Germany, Hungary, Israel, Italy, Norway, Poland, Romania, Russian Federation, Slovakia, Spain, Sweden, Turkey, UK **Age (mean, SD):** 54.9 (13.1) **Sex:** women only **Inclusion criteria:** women with urodynamic diagnosis of detrusor overactivity **Exclusion criteria:** evidence of urinary tract infection, bladder outlet obstruction or urogenital prolapse (greater than grade II); history or diagnosis of specific urinary conditions, including urinary retention, stress urinary incontinence, or neurogenic DO; known hypersensitivity to study medications or their excipients; or any other clinical condition, diagnosis, symptomatology or ongoing investigation that, in the opinion of the investigator, contraindicated their participation
Interventions	**Group I (n = 182):** solifenacin 5 mg once daily orally **Group II (n = 175):** solifenacin 10 mg once daily orally **Group III (n = 186):** placebo 12-week study period
Outcomes	Bladder wall thickness Change from baseline in urinary incontinence at week 12 Change from baseline in the number of micturitions per day, and urgency episodes per day PPBC change in QoL evaluated by OAB-q questionnaire
Study funding sources	Study supported by Astellas Pharma
Notes	SHRINK study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description

Robinson 2013 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals and reasons for withdrawals not reported
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Rogers 2008

Study characteristics	
Methods	**Study design:** RCT, placebo-controlled, parallel design **Dates study conducted:** not reported
Participants	**Setting:** multicentre (54 outpatient sites) **Country:** United States **Age (mean, SD):** tolterodine: 49 (12) years; placebo: 47 (12) years **Sex:** female only **Inclusion criteria:** female patients aged ≥ 18 years with a mean of ≥ 8 micturitions, ≥ 0.6 UUI episodes, ≥ 3 OAB micturitions per 24 hours. Women also had to report some moderate problems on Patient Perception of Bladder Condition. Participants were to have had OAB symptoms for ≥ 3 months and to have been in a stable sexually active relationship with a male partner for > 6 months **Exclusion criteria:** women with ≥ stage 3 pelvic organ prolapsed, history of lower urinary tract surgery, life long sexual dysfunction unrelated to lifelong UUI or predominant stress UI were excluded
Interventions	**Group I (n = 211):** placebo **Group II (n = 202):** tolterodine ER 4 mg Study period 12 weeks
Outcomes	**Primary outcome:** change from baseline to week 12 in the number of UUI episodes per 24 hours **Secondary outcomes:** changes in total number of micturitions, change in number of OAB micturitions, frequency-urgency sum, incontinence pads use, questionnaire scores 5-day bladder diary, Urgency Sensation Scale (USS), sexual quality of life questionnaire-female (SQOL-F), Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ) and Hospital Anxiety and Depression scale (HAD)

Rogers 2008 *(Continued)*

Study funding sources	Study funded by Pfizer Inc.
Notes	Standard error converted to standard deviation Missing post-baseline data were imputed using the last observation carried forward method

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation schedule generated with a fixed block size of 4
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	States double-blind, but no description of blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced across the groups (tolterodine ER 4 mg: 19% versus placebo: 20%)
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Romanzi 2005

Study characteristics

Methods	**Study design:** RCT, placebo-controlled, 3-arm trial **Dates study conducted:** not reported
Participants	**Setting:** multicentre, 54 outpatient sites **Country:** United States **Age:** not reported **Sex:** not reported **Inclusion criteria:** no information in the abstract **Exclusion criteria:** no information in the abstract
Interventions	**Group I (n = 223):** tolterodine 2 mg **Group II (n = 112):** darifenacin 15 mg

Romanzi 2005 *(Continued)*

	Group III (n = 115): placebo
	12-week study period
Outcomes	Reduction in incontinence episodes
	Adverse events
	Outcomes assessed at 2, 6 and 12 weeks
Study funding sources	Not reported
Notes	Abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information in the abstract
Allocation concealment (selection bias)	Unclear risk	No information in the abstract
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated double-blinded, but no description of the blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information in the abstract
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information in the abstract
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Rovner 2005

Study characteristics

Methods	**Study design:** RCT
	Dates study conducted: not reported
Participants	**Setting:** multicentre (167 centres)
	Country: multinational (Australia, Europe and North America)
	Age (mean, SD): placebo 66 (14) years; tolterodine 66 (16) years
	Sex: male only

Rovner 2005 *(Continued)*

	Inclusion criteria: ≥ 18 years of age with symptoms of urinary frequency (≥ 8 micturitions/24 hours) and UUI (≥ 5 episodes/week) for ≥ 6 months **Exclusion criteria:** not reported
Interventions	**Group I (n = 77):** tolterodine ER 4 mg once daily **Group II: (n = 86):** placebo 12-week study period
Outcomes	Quote: "All micturitions and UUI episodes were recorded at the times they occurred. Patient perception of treatment benefit was evaluated at week 12 using a 2-step assessment and ordered categorical scale. Adverse events (AEs) were recorded throughout the study."
Study funding sources	Pfizer
Notes	Conference abstract Post hoc analysis Probably small subset of participants randomised as study was "performed at 167 centers in Australia, Europe, and North America."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Rudy 2006

Study characteristics

Methods	**Study design:** RCT, parallel design

Rudy 2006 *(Continued)*

	Dates study conducted: not reported
Participants	**Setting:** multicentre (52 sites) **Country:** United States **Age (mean, SE):** placebo 61.0 (0.7); trospium 61.1 (0.69) **Sex:** trospium: 18.8% male; placebo: 18.2% male **Inclusion criteria:** female and male patients of 18 years or older with overactive bladder symptoms for at least 6 months. Patients were required to have a minimal urinary frequency average of 10 or more toilet voids per day, symptoms of urgency and at least 7 urge urinary incontinence episodes per week. **Exclusion criteria:** patients with incontinence that was predominantly stress, insensate or overflow in nature were excluded. Those with neurogenic bladder disorders, significant renal disease, uninvestigated haematuria and urinary tract infection at washout or more than twice during the prior year. Patients with significant bladder outlet obstruction defined as post-void residual volume greater than 100 mL. Patients currently using any anticholinergic drug or other therapy for OAB within 21 days before randomisation. Those who had undergone bladder surgery with 6 months before randomisation and those with cancer or interstitial cystitis were excluded as were men with prostate-specific antigen level of 10 ng/mL or greater. Additional exclusion criteria were diuretic use, oestrogen therapy, and non-medical bladder therapy, pregnancy and contraindication to antimuscarinic therapy.
Interventions	**Group I (n = 329):** trospium chloride 20 mg twice daily per oral **Group II (n = 329):** placebo Washout 1 week 12-week study period
Outcomes	**Primary outcome:** change in the average number of toilet voids per 24 hours **Secondary outcomes:** change in the average urgency severity associated with toilet voids, volume voided per toilet void, number of urgency incontinence episodes, nocturnal symptoms and rate of improvement/response over time Degree of urgency was measured as the urgency severity using IUSS (Indevus Urgency Severity Scale) Quality of life measures Adverse events, clinical laboratory tests, vital signs and 12 lead electrocardiogram findings at baseline and the end of the study Urinary diary data were collected at weeks 1, 4 and 12 using a 7-day diary
Study funding sources	Study funded by Indevus Pharmaceuticals, Inc.
Notes	Patients who completed 12-week visit were eligible for open–label treatment phase for 6 months ITT principle Efficacy analysis performed using last observation carried forwards method Efficacy data not usable as standard deviation not reported

Risk of bias

Bias	Authors' judgement	Support for judgement

Rudy 2006 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	States 1:1 randomisation, no further description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT principle
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Staskin 2004

Study characteristics	
Methods	**Study design:** RCT, parallel, double-blind, placebo-controlled **Dates study conducted:** not reported
Participants	**Setting:** multicentre **Country:** US **Age (mean):** 61 years in both treatment groups **Sex:** trospium 81% females (n = 265, counted manually); placebo 82% females (n = 267, counted manually) **Inclusion criteria:** not reported **Exclusion criteria:** not reported
Interventions	**Group I (n = 327):** trospium chloride 20 mg twice daily per oral **Group II (n = 326):** placebo 12-week study period
Outcomes	**Primary outcomes:** sleepiness, which was assessed using SSS scale, visits were scheduled at baseline (predose) and at weeks 1, 4 and 12 during treatment period
Study funding sources	Not reported
Notes	—

Staskin 2004 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	States double-blind, but no description of how blinding was done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, insufficient information about pre-specified outcomes
Other bias	Unclear risk	Insufficient information

Staskin 2007

Study characteristics	
Methods	**Study design:** RCT, parallel design **Dates study conducted:** 29 August 2005 to 31 May 2006
Participants	**Setting:** multicentre (55 sites) **Country:** United States **Age (mean):** trospium: 59.5 years; placebo: 59.3 years **Sex:** trospium: 14.8% male; placebo: 15.5% male **Inclusion criteria:** men and women 18 years or older with symptoms of OAB for 6 months or greater. Symptoms of urgency, i.e. at least severe urgency severity rating per 3 days, as measured using a validated urgency severity scale. Minimum urinary frequency of 30 or greater toilet voids per 3 days with an average of 1 or greater UUI episode/day. Average total volume voided 3000 mL or less per day and 250 mL or less per void. **Exclusion criteria:** patients with incontinence that was predominantly stress, insensate or overflow in nature were excluded. Those with neurogenic bladder disorders, significant renal disease, uninvestigated haematuria and urinary tract infection at washout or more than 3 times during the previous year. Patients with significant bladder outlet obstruction defined as post-void residual volume greater than 100 mL. Those who had undergone bladder surgery with 6 months before randomisation and those with cancer or interstitial cystitis were excluded as were men with prostate-specific antigen level of 4

Staskin 2007 *(Continued)*

	ng/mL or greater. Additional exclusion criteria were diuretic use, and oestrogen therapy outside of a long-term stable programme.
Interventions	**Group I (n = 298):** trospium chloride extended-release 60 mg per oral once daily **Group II (n = 303):** placebo once daily per oral 7-day washout period 12-week study period Open-label extension for 9 months
Outcomes	**Primary outcome:** change in urinary frequency and in the daily frequency of urge urinary incontinence episodes **Secondary outcomes:** frequency of urge urinary incontinence episodes per week, urgency severity associated with each toilet voids as measured using Indevus Urgency Severity Scale, volume voided per void, daily frequency of urgency associated voids and complete responder rate or normalisation defined as average of 8 or less toilet voids and no urge urinary incontinence per day Adverse events, clinical laboratory tests, vital signs and 12 lead electrocardiogram findings at baseline and the end of the study Bladder diary data collected at baseline, week 1, 4 and 12
Study funding sources	Study supported by Esprit Pharma and Indevus Pharmaceuticals
Notes	ITT principle Efficacy analysis performed using last observation carried forwards method Standard error converted to standard deviation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was accomplished with an Interactive Voice Response System
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals and reasons for withdrawals are similar, ITT
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes

Staskin 2007 *(Continued)*

Other bias	Low risk	The study appears to be free of other sources of bias

Staskin 2019

Study characteristics	
Methods	**Study design:** RCT, double-blind, placebo and active comparator-controlled, phase III trial **Dates study conducted:** July 2018 to February 2019
Participants	**Setting:** multicentre **Country:** international **Age (mean):** ~60 years **Sex:** "with ~85% women and 15% men in each group" **Inclusion criteria:** 18 years with a history of OAB **Exclusion criteria:** patients were excluded if they had a daily average urine volume output of greater than 3000 mL
Interventions	**Group I (n = 431):** tolterodine tartrate ER **Group II (n = 540):** placebo Group III vibegron 75 mg daily, but not relevant 12-week study period Total number of participants: 1530 randomised; 1518 analysed
Outcomes	**Primary outcomes:** change from baseline to week 12 in the average daily number of micturitions was calculated for each patient. Change from baseline to week 12 in the average daily number of UUI episodes was calculated for each wet OAB patient. **Secondary outcomes:** change from baseline to week 12 in the average daily number of urgency episodes calculated for each patient; average volume voided per micturition calculated for each patient from all recorded volumes; and proportion of wet OAB patients with ≥ 75% reduction in the average daily number of UUI episodes
Study funding sources	Not reported
Notes	Abstract Trial registration

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information

Staskin 2019 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Steers 2004

Study characteristics	
Methods	**Study design:** RCT, parallel design **Dates study conducted:** not reported
Participants	**Setting:** multicentre **Country:** not reported **Age (mean):** darifenacin: 57.5 years; placebo: 68.6 years **Sex:** darifenacin: 35.3% male; placebo 16.5% male **Inclusion criteria:** men and women aged ≥ 18 years of age with OAB symptoms for more than 6 months **Exclusion criteria:** not reported
Interventions	**Group I (n = 268):** darifenacin controlled-release tablets once daily 7.5 mg per oral, dose increased to 15 mg after 2 weeks if required **Group II (n = 127):** matching placebo 2-week run-in period 12-week study period
Outcomes	**Primary efficacy:** reduction in the number of incontinence episodes/week at 12 weeks **Secondary efficacy:** micturition frequency/day, bladder capacity, frequency of urgency/day, severity of urgency Adverse events Clinical and lab tests and vital signs
Study funding sources	Not reported
Notes	Abstract

Steers 2004 *(Continued)*

	Data not in usable form as reported as median

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States randomised, no description in the abstract
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blinded, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals and reasons were not reported
Selective reporting (reporting bias)	Unclear risk	Lack of information - only abstract is available
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Stohrer 1991

Study characteristics

Methods	**Study design:** RCT: placebo-controlled, parallel design **Dates study conducted:** 1 October 1986 to 30 June 1987
Participants	**Setting:** multicentre (3) **Country:** not reported **Age (mean):** trospium: 32.3 years; placebo: 34.2 years **Sex:** trospium: 51% male; placebo 57% male **Inclusion criteria:** spinal cord injury with consecutive detrusor hyperreflexia **Exclusion criteria:** urinary infections, mechanical obstruction of lower urinary tract, congestive glaucoma, known allergy to atropine, N-butylscopolamine bromide or trospium chloride, tachyarrhythmias, renal, hepatic or cardiovascular insufficiency, body weight exceeding 90 kg, anticholinergic treatment within 14 days of study start
Interventions	**Group I (n = 29):** trospium chloride 20 mg twice a day **Group II (n = 32):** placebo 3-week treatment period 2-week run-in

Stohrer 1991 *(Continued)*

Outcomes	Urodynamic parameters Laboratory tests Adverse events
Study funding sources	Not reported
Notes	6 dropouts (Group I: 2; Group II: 4) No follow-up Data not in useable form for this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking of assessors not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts similar, reasons for dropout not stated
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Stohrer 1999

Study characteristics

Methods	**Study design:** RCT: placebo-controlled, parallel design **Dates study conducted:** not reported
Participants	**Setting:** multicentre **Age (mean, SD):** propiverine: 30.3 (11.7); placebo: 29.3 (10.9) **Sex:** propiverine: 61.6% male; placebo: 60.3% male **Inclusion criteria:** over 18 years old with detrusor hyperreflexia and suprasacral spinal cord injury **Exclusion criteria:** pregnancy, cardiac, hepatic and renal dysfunctions, intestinal and urogenital obstructions, narrow angle glaucoma, severe psychotics and acute urinary tract infections

Stohrer 1999 *(Continued)*

Interventions	**Group I (n = 60):** propiverine 15 mg 3 times a day **Group II (n = 53):** placebo 14-day treatment period
Outcomes	Patient assessment of improvement Micturition variables Urodynamic parameters Adverse events Laboratory tests Physician assessment of efficacy
Study funding sources	Not reported
Notes	11 dropouts (Group I: 8; Group II: 3) No follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No data
Allocation concealment (selection bias)	Unclear risk	No data
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking of assessors not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Differential dropouts, reasons for dropouts not reported
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Tago 1990

Study characteristics

Methods	**Study design:** RCT, double-blind, placebo-controlled, parallel design **Dates study conducted:** not reported
Participants	**Setting:** multicentre (41) **Country:** not reported

Tago 1990 *(Continued)*

	Age: not reported **Sex:** not reported **Inclusion criteria:** neurogenic bladder and unstable bladder with uninhibited detrusor contraction, pollakisuria and UI **Exclusion criteria:** not reported
Interventions	**Group I:** propiverine 20 mg once a day **Group II:** placebo 2-week treatment period Group numbers not reported 142 patients in total
Outcomes	Subjective symptoms, global improvement rating, global utility rating Urodynamic parameters Adverse events
Study funding sources	Not reported
Notes	Abstract Group numbers not reported Dropouts not reported Data not in useable form for this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking of assessors not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Group numbers not reported; dropouts not reported
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Takayasu 1990

Study characteristics	
Methods	**Study design**: not reported **Dates study conducted:** June 1988 May 1989
Participants	**Setting:** multicentre **Country:** Japan **Age**: not reported **Sex**: not reported **Inclusion criteria:** 60+, no severe heart disease, no change of electrolytes, urgency or urge incontinence **Exclusion criteria:** lower urinary tract obstruction, UTI, bladder neurosis, severe disease or glaucoma, drug allergy, heart kidney or liver disease, pregnant, lactating, doctor judged unqualified
Interventions	**Group I (n = 64):** propiverine 10 mg twice a day **Group II (n = 60):** placebo (placebo contains 0.5 mg propiverine but states inactive dose) 2-week study period
Outcomes	Subjective improvement in frequency Urinary incontinence and urgency Treatment efficacy Overall safety Patient's impression Overall efficacy
Study funding sources	Not reported
Notes	Translation from Japanese No useable data

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information

Takayasu 1990 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Thuroff 1991

Study characteristics	
Methods	**Study design:** RCT: placebo-controlled, parallel design **Dates study conducted:** not reported
Participants	**Setting:** multicentre **Country:** multinational (2) **Age (mean):** oxybutynin 48 years; propantheline 50.9 years; placebo 49.2 **Sex:** oxybutynin 59 females; propantheline 53 females; placebo 50 females **Inclusion criteria:** at least 15 years old with symptoms of frequency, urgency and/or incontinence. Cystometry findings related to either idiopathic (unstable detrusor) or neurogenic origins (detrusor hyperreflexia). **Exclusion criteria:** no drugs affecting lower urinary tract function to be taken. Antihypertensive medication allowed if regularly taken at consistent dosage. Minor tranquillisers allowed if taken for sleep only. Pregnancy, congestive heart failure, severe renal/liver disease, myasthenia gravis, unable to swallow/uncooperative patient, hiatal hernia/reflux oesophagitis, gastrointestinal tract obstruction, urinary tract obstruction, residual > 50 mL, untreated UTI, hyperreflexia without urge, lower urinary tract pathological conditions.
Interventions	**Group I (n = 63):** oxybutynin 5 mg 3 times a day **Group II (n = 54):** propantheline 15 mg 3 times a day **Group III (n = 52):** placebo 4-week treatment period 1-week run-in
Outcomes	Urinary symptoms (VAS) Frequency of micturition Urodynamic parameters Urine analysis Laboratory tests Adverse events
Study funding sources	Company support declared
Notes	15 dropouts (Group I: 4; Group II: 6; Group III: 5) No follow-up
Risk of bias	

Thuroff 1991 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Low risk	Drugs were packed in opaque plastic bottles
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking of assessors not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts similar, reasons for dropouts not stated
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Ulshofer 2001

Study characteristics	
Methods	**Study design:** RCT, double-blind **Dates study conducted:** not reported
Participants	**Setting:** multicentre **Country:** not reported **Age (mean):** trospium: 49.1 years; placebo: 53.9 years **Sex:** trospium: 9.1% male; placebo 5.9% male **Inclusion criteria:** aged between 18 and 75 years, cystometric bladder capacity of less than 300 mL, required to have an early primary urge to void < 60% capacity, involuntary loss of urine during the filling phase cystometry with detectable detrusor contraction (amplitude of intrinsic increase in pressure 15 cl H_2O after extrinsic or within provocations) **Exclusion criteria:** alcohol or drug abuse signs and symptoms of other forms of incontinence, bodyweight > 90 kg, myasthenia gravis, narrow angle glaucoma, urinary tract infection, pregnancy, psychiatric disease, pre, and/or co-medication with other antimuscarinic drugs, amantadine, tricyclic antidepressants, antihistamines, disopyramide and beta-adrenoreceptor agonists
Interventions	**Group I (n = 22):** trospium chloride 15 mg 3 times a day **Group II (n = 17):** placebo 28 days of treatment

Ulshofer 2001 *(Continued)*

Outcomes	Maximum bladder capacity (measured by means of cystomanometry) Adverse effects (patients were asked about dryness of mouth, increased heart rate, gastrointestinal disorders, sweat secretion problems and accommodation disturbances) Blood pressure, pulse rate, haematological and biochemical parameters were determined prior to and upon completion of treatment Compliance was assessed by pill counting
Study funding sources	Dr R. Pfeger GmbH (German pharmaceutical company)
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was carried out using blocks within each stratum, however authors do not provide details on how the blocks were generated
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts are stated - 3 in trospium chloride group and 4 in placebo, ITT
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, no pre-specified outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Van Kerrebroeck 1998

Study characteristics

Methods	**Study design:** randomised, placebo-controlled, parallel design **Dates study conducted:** January 1994 to August 1994
Participants	**Setting:** multicentre (14) **Country:** multinational (Austria, France, Germany, the Netherlands) **Age (mean):** 42 years **Sex:** 53.4% male

Van Kerrebroeck 1998 *(Continued)*

	Inclusion criteria: 18 to 75 years old with symptoms of urgency, increased frequency of micturition/self-catheterisation and/or urge incontinence. Urodynamically proven detrusor hyperreflexia. Insignificant bacteriuria and normal laboratory tests **Exclusion criteria:** stress incontinence, cardiac, hepatic, renal or haematological disorders, bladder outlet obstruction, poor general or mental health, contraindications to antimuscarinic agents and patients already receiving therapy for urinary incontinence. Pregnant or lactating women and women of childbearing age not using reliable contraception.
Interventions	**Group I (n = 19):** placebo **Group II (n = 16):** tolterodine 1 mg twice a day **Group III (n = 18):** tolterodine 2 mg twice a day **Group IV (n = 17):** tolterodine 4 mg twice a day, but not relevant to this review **Group V (n = 20):** tolterodine 0.5 mg twice a day, but not relevant to this review 2-week treatment period 1-week run-in preceded by 2-week washout if necessary
Outcomes	Subjective urinary symptoms (VAS) Number of leakage episodes, frequency of micturition, volume voided Urodynamic parameters Pad test Adverse events Laboratory tests Blood pressure ECG
Study funding sources	Company support declared
Notes	2-week telephone follow-up No dropouts Almost half of patients using self-catheterisation Dose reduction permitted PP analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking of assessors not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	PP analysis

Van Kerrebroeck 1998 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Van Kerrebroeck 2001

Study characteristics	
Methods	**Study design:** RCT: placebo-controlled, parallel design, randomised 1:1:1 **Dates study conducted:** not reported
Participants	**Number of participants:** 1529 male and female patients **Setting:** multicentre (167 sites) **Country:** multinational (4 Australasia, 89 Europe, 74 North America) **Age (mean):** tolterodine 4 mg: 60 years; tolterodine 2 mg: 60 years; placebo: 61 years **Sex:** tolterodine 4 mg: 21.5% male; tolterodine 2 mg: 25.9% male; placebo: 23.9% male **Inclusion criteria:** at least 18 years of age with urinary frequency (8 or more/24 hours), urge incontinence (at least 5/week) and symptoms of overactive bladder for at least 6 months **Exclusion criteria:** stress incontinence, total daily urine > 3000 mL, any contraindications to antimuscarinic treatment, significant hepatic or renal disease, symptomatic or recurrent UTI, interstitial cystitis, haematuria or BOO, current electrostimulation or bladder training therapy, indwelling catheter or intermittent self-catheterisation. Pregnant or breastfeeding women, and women of childbearing potential not using adequate contraception. Other treatments for overactive bladder are not allowed apart from oestrogen started > 2 months before randomisation. No treatment by any other investigational drug allowed.
Interventions	**Group I (n = 507):** tolterodine extended-release 4 mg once a day **Group II (n = 514):** tolterodine immediate-release 2 mg twice a day **Group III (n = 508):** placebo 12-week treatment period 1- to 2-week run-in
Outcomes	**Primary outcomes:** change in the number of incontinence episodes per week from baseline to week 12 **Secondary outcomes:** number of micturitions/24 hours; volume voided/micturition; number of pads used/24 hours; adverse events, clinical chemistry and haematologic variables
Study funding sources	Company support declared
Notes	No dose reductions permitted 187 dropouts (no group data) 1-week follow-up ITT analysis

Risk of bias

Bias	Authors' judgement	Support for judgement

Van Kerrebroeck 2001 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Low risk	Random permuted blocks were used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	A double-dummy drug packaging technique was used to maintain blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking of assessors not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Does not mention all the reasons for withdrawals (only adverse effects)
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Vardy 2009

Study characteristics	
Methods	**Study design:** RCT, parallel design, phase IV trial **Dates study conducted:** not reported
Participants	**Number of participants:** 768 randomised **Setting:** multicentre **Country:** USA **Age (mean, SD):** solifenacin: 59 (13) years; placebo: 60 (12) years **Sex:** solifenacin: 19% male; placebo: 16% male **Inclusion criteria:** eligible patients (age ≥ 18 years) were required to have overactive bladder symptoms for ≥ 3 months (≥ 8 micturitions and ≥ 1 urgency episode, with or without incontinence, per 24 hours). **Exclusion criteria:** significant stress or stress predominant mixed incontinence, recurrent urinary tract infection (UTI; ≥ 3 episodes within the past 3 months) or evidence of UTI at baseline, evidence of chronic urologic inflammation/interstitial cystitis or urinary/gastric retention. The use of concomitant medications was either prohibited (antimuscarinics, antispasmodics, tricyclic antidepressants and anti-Parkinsons agents) or restricted (tri- and tetracyclic antidepressants, antihistamines and antiemetics), for which patients were permitted to continue if they had been taking the drug on a long-term basis at a stable dose.
Interventions	**Group I (n = 386):** 5 mg solifenacin once daily orally for 4 weeks. At week 4 they could maintain or increase the dose to 10 mg. At week 8 patients taking 10 mg could maintain or decrease the dose to 5 mg. **Group II (n = 382):** placebo

Vardy 2009 *(Continued)*

	Washout 2 weeks 12-week study period
Outcomes	**Primary outcome:** symptom bother scale of the OAB-q **Secondary outcomes:** mean change in the urinary frequency, urgency, incontinence, and nocturia episodes. Health-related quality of life, patients perception of bladder related problems, work productivity, resource utilisation and sexual function. Brief physical examination, vital signs and adverse events At baseline, 4, 8 and 12 weeks after randomisation patients completed the OAB-q and 3-day bladder diaries. At baseline and week 12 patients completed the PPBC, Treatment Satisfaction Visual Analog Scale(TS-VAS), BSW measure, Work Productivity and Activity Impairment (WPAI) questionnaire, Medical Care Use Index (MCUI) and the gender-specific, International – Male/Female Sexual Matters association with Lower Urinary Tract Symptoms (ICIQ-M/FLUTSsex)
Study funding sources	Study supported by Astellas Pharma US Inc. and Glaxo-Smith-Kline
Notes	No useable data as standard deviations were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	1:1 randomisation using Astellas Interactive Randomisation System
Allocation concealment (selection bias)	Low risk	Interactive randomisation system
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals were similar but the reasons for withdrawals were not reported (solifenacin: 35/385; placebo: 48/381)
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Wagg 2013a

Study characteristics

Methods	**Study design:** RCT, parallel design **Dates study conducted:** not reported

Wagg 2013a *(Continued)*

Participants	**Setting:** multicentre (61 sites) **Country:** Austria, Belgium, Denmark, Finland, Germany, Israel, Italy, Norway, Portugal, Slovakia, Spain, Sweden, Switzerland, Turkey and the United Kingdom **Age (mean, SD):** non escalators: placebo (n = 116): 72.4 (5.8), fesoterodine (n = 152): 73.2 (5.9); escalators: placebo (n = 277): 72.9 (5.7), fesoterodine (n = 240): 72.2 (5.7) **Sex:** 418 females **Inclusion criteria:** men and women aged ≥ 65 years of with history of OAB for ≥ 3 months; ≥ 8 micturitions/day; ≥ 3 urgency episodes/day and on a 3-day bladder diary at baseline who self-reported at least some moderate problems on the Patient Perception of Bladder Condition questionnaire and had a MMSE score of 20 or greater and able to complete micturition diaries and study-related questionnaires and adhere to study procedures **Exclusion criteria:** hypersensitivity to the active substance or to peanuts, soya or any of the excipients, predominant stress incontinence, significant bladder outlet obstruction, previous history of acute urinary retention requiring catheterisation, severe voiding difficulties or active urinary tract infection, renal disease, multiple sclerosis or spinal cord injury, treatment with other antimuscarinics within 2 to 3 weeks before baseline, treatment with potent CYP3A4 inhibitor, or intermittent usage of diuretics or alpha blockers or initiation of treatment within 2 weeks of baseline
Interventions	**Group I (n = 392):** fesoterodine 4 mg once daily orally. Participants were allowed to increase to 8 mg at week 4 and 8. Participants who increased from 4 mg to 8 mg at week 4 could return to 4 mg dose at week 8 **Group II (n = 393):** placebo; a sham dose escalation and de-escalation was followed for participants randomised to placebo 12-week study period
Outcomes	**Primary outcome:** change from baseline in the urgency episodes per 24 hours **Secondary outcome:** change from baseline in the number of micturitions, urgency urinary incontinence episodes, severe urgency episodes, nocturnal micturitions and incontinence pads used per 24 hours Change in QoL evaluated by OAB-q questionnaire PPBC, Urgency Perception Scale (UPS) were completed at week 4, 8 and 12 OAB-Satisfaction questionnaire and Treatment Benefit Scale (TBS) were completed at week 12 MMSE was completed at week 12
Study funding sources	Study funded by Pfizer Inc.
Notes	Last observation carried forward principle used for missing values Outcomes were reported as 2 groups i.e. participants aged 65 to 75 years and older than 75 years Reported outcomes of both the groups were combined by the authors of the review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation occurred through a centralised system with 1:1 ratio of fesoterodine to placebo and of morning to evening dosing, according to age (75 or older versus under 75)

Wagg 2013a *(Continued)*

Allocation concealment (selection bias)	Low risk	Pfizer generated and secured the randomisation schedule
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Neither the investigators nor the participants were aware of the treatment identity"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Patient-reported outcomes were assessed via bladder diary etc. and participants were unaware of treatment identity
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar number of withdrawals (82 in anticholinergic group and 74 in placebo); ITT analysis used
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	No evidence of any sources of additional bias

Weiss 2013

Study characteristics	
Methods	**Study design:** RCT, double-blind, placebo-controlled trial **Dates study conducted:** August 2009 to September 2011
Participants	**Setting:** multicentre **Country:** USA **Mean age (SD, range):** fesoterodine: 58.0 (14.7, 21 to 92) years; placebo: 57.5 (14.0, 18 to 92) years **Sex (n, % women):** fesoterodine: 313/463 (67.6%); placebo: 312/474 (65.8%) **Inclusion criteria:** adults aged 18 years or older with self-reported OAB symptoms, including nocturnal urgency for more than 3 or more months before screening, and a mean of 8 or more micturitions per 24 hours, 3 or more urgency episodes per 24 hours and 2 to 8 nocturnal urgency episodes per 24 hours. **Exclusion criteria:** any contraindication for fesoterodine use, clinically significant hepatic or renal disease, treatment with potent CYP3A4 inhibitors, use of tricyclic antidepressants, oestrogens, diuretics, alpha blockers or 5-alpha reductase inhibitors, pregnancy or nursing, history/known diagnosis of sleep disorder, nocturia due to uncontrolled conditions other than OAB including hear failure, diabetes mellitus, diabetes insipidus or polyuria, history of acute retention or severe voiding difficulties, use of indwelling catheter or intermittent self-catheterisation, urinary tract infection or recurrent urinary tact infection (treated for urinary tract infection more than 3 times in the last year), initiation of electro stimulation, formal bladder training or pelvic exercise within 4 weeks of screening, prior use of study medication or treatment with antimuscarinics within 2 weeks of screening
Interventions	**Group I (n = 381):** fesoterodine flexible 4 mg to 8 mg orally per day **Group II (n = 400):** placebo Placebo run-in period 2 weeks Study period 12 weeks

Weiss 2013 *(Continued)*

Outcomes	**Primary outcomes:** mean number of micturition-related nocturnal urgency episodes per 24 hours **Secondary outcomes:** OAB-q symptom bother scale, HRQoL scale
Study funding sources	Study funded by Pfizer
Notes	Missing data imputed using last observation carried forward method

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised randomisation system (Impala). Randomisation schedule was generated, secured and stored by the sponsor.
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals accounted for
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, no pre-specified outcomes
Other bias	Unclear risk	Insufficient information

Yamaguchi 2007

Study characteristics

Methods	**Study design:** RCT; placebo-controlled, parallel design, phase III trial **Dates study conducted:** not reported
Participants	**Setting:** multicentre (155 centres) **Country:** Japan **Age (mean, SD):** solifenacin 5 mg: 60.4 (13.3) years; solifenacin 10 mg: 59.9 (13.0) years; propiverine: 59.6 (13.6) years; placebo: 60.8 (12.5) years **Sex:** solifenacin 5 mg: 17.0% male; solifenacin 10 mg: 14.3% male; propiverine: 16.4% male; placebo: 15.7% male **Inclusion criteria:** men and women aged > 20 years and with OAB reported for ≥ 6 months. Mean number of voids/24 hours of ≥ 8, ≥ 3 episodes of urgency and/or ≥ 3 episodes of urgency incontinence during a 3-day voiding diary period

Yamaguchi 2007 *(Continued)*

	Exclusion criteria: significant BOO an assessment based on measuring postvoid residual urine volume, PVR > 100 mL, BOO symptoms, urinary retention, demonstrable stress incontinence, bladder stones, UTI, interstitial cystitis, previous or current malignant disease of the pelvic organ and pelvic radiation. Patients were excluded if they were taking concomitant anticholinergic medications or had known hypersensitivity to anticholinergic medication or lactulose.
Interventions	**Group I (n = 405):** placebo **Group II (n = 398):** solifenacin 5 mg once daily **Group III (n = 381):** solifenacin 10 mg once daily **Group IV (n = 400):** propiverine 20 mg once daily 2-week placebo run-in period 12-week treatment period
Outcomes	**Primary outcome:** voids/24 hours **Secondary outcomes:** urgency/24 hours, incontinence/24/hours, urgency incontinence episodes per 24 hours, nocturia episodes and mean volume voided/void, QoL - KHQ Adverse events Lab tests Vital signs ECG Outcomes assessed at baseline, 4, 8 and 12 weeks
Study funding sources	This study was funded and sponsored by Astellas Pharma Inc (formerly Yamanouchi Pharmaceutical Co. Ltd, Tokyo, Japan). Editorial assistance was provided by Priya Venkatesan, Medicus International.
Notes	136 dropouts (Group I: 34; Group II: 34; Group III: 32; Group IV: 36) 1533 were eligible for efficacy assessment Imputation by carrying last observation was carried forward No follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States randomised, insufficient information
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated

Yamaguchi 2007 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals and reasons for withdrawals similar across groups (Group I: 34; Group II: 34; Group III: 32; Group IV: 36). Imputation by last observation carried forward.
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Yamaguchi 2012

Study characteristics	
Methods	**Study design:** RCT, double-blind, placebo- and active-controlled, phase III **Dates study conducted:** not reported
Participants	**Setting:** multicentre **Country:** Japan **Age:** not reported **Sex:** Group I (tolterodine): 82.6% female; Group II (placebo): 84.2% female **Inclusion criteria:** patients with micturitions/24 hours and urgency or urgency incontinence episode/24 hours **Exclusion criteria:** not reported
Interventions	**Group I (n = 378):** tolterodine 4 mg **Group II (n = 381):** placebo **Group III (n = 380):** mirabegron 50 mg, but not relevant to the review 12-week study period
Outcomes	**Primary outcomes:** change from baseline to end of treatment in mean number of micturition episodes/24 hours **Secondary outcomes:** change from baseline to end of treatment in mean number of urgency episodes/24 hours, urinary incontinence episodes/24 hours, urgency incontinence episodes/24 hours, and QoL domain scores on the King's Health Questionnaire
Study funding sources	Astellas
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information

Yamaguchi 2012 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	1139 randomised, 85 dropouts (similar across groups). Patients clearly documented for FAS and SAF sets.
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Low risk	The study appears to be free of other sources of bias

Yamaguchi 2014

Study characteristics	
Methods	**Study design:** RCT; placebo/active-controlled, parallel design **Dates study conducted:** 4 October 2010 to 23 May 2011
Participants	**Setting:** multicentre (112 centres) **Country:** Japan **Age (mean, SD):** oxybutynin: 55.4 (12.4) years; propiverine: 55.6 (12.5) years; placebo: 56.2 (13.2) years **Sex:** oxybutynin: 9.5% male; propiverine: 14.5% male; placebo: 7.8% male **Inclusion criteria:** men and women aged > 20 years and with OAB reported for ≥ 24 months. Mean number of voids/24 hours of ≥ 8, ≥ 1 episodes of urgency and/or ≥ 1 episodes of urgency incontinence during a 3-day voiding diary period. **Exclusion criteria:** genuine stress incontinence, another disease causing symptoms difficult to differentiate from those of OAB, any condition affecting urinary tract obstruction, post-void residual urine volume > 100 mL, clinically significant hepatic/renal impairment, malignancy, any skin condition that could be exacerbated by application of the study drug patches, extensive tattoos or nevi that interfered with patch application, history of frequent sunburn, and women who were pregnant, lactating, possibly or wished to become pregnant during the study period.
Interventions	**Group I (n = 381):** placebo **Group II (n = 576):** propiverine 20 mg once daily **Group III (n = 573):** oxybutynin patch 35 cm^2 (containing 73.5 mg of oxybutynin hydrochloride) once daily, but not relevant to this review 2-week placebo run-in period 12-week treatment period with 5 scheduled patient visits
Outcomes	Voids/24 hours Urgency/24 hours

Yamaguchi 2014 *(Continued)*

	Incontinence/24/hours Urgency incontinence episodes per 24 hours Nocturia episodes and mean volume voided/void QoL - KHQ Adverse events Lab tests Vital signs ECG Residual urine volume Outcomes assessed at baseline, 4, 8 and 12 weeks
Study funding sources	Company support declared
Notes	146 dropouts (Group I: 22; Group II: 42; Group III: 82) 1487 were eligible for efficacy assessment No follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using the method of random permuted blocks
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blinded, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawals and significantly higher withdrawals in the oxybutynin patch group due to adverse events (Group I: 22; Group II: 42; Group III: 82)
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Yonguc 2019

Study characteristics

Yonguc 2019 *(Continued)*

Methods	**Study design:** RCT, double-blind, placebo-controlled study with 4 week open-label extension **Dates study conducted:** May 2016 to May 2018
Participants	**Country:** not reported **Setting:** single institution **Age (mean, SD):** fesoterodine 65.7 (8.8); placebo 69.6 (9.2) **Sex:** 32 female; 31 male **Inclusion criteria:** PD patients, age ≥ 40, to be stable with constant dose of anti-parkinsonian drugs, modified Hoehn and Yahr scale score 1.0 to 4.0. United Kingdom Parkinson's Disease Society Brain Bank Criteria. Patients included in the study were on steady medication for PD symptoms for at least 90 days **Exclusion criteria:** history of prostate cancer, severe renal disease, major hepatic impairment, history of acute urinary retention, having a post-void residual urine more than 150 mL, and active medication with drugs which have anti-muscarinic and cognitive dysfunction side effects. The patients who have a history of severe constipation or untreated narrow angle glaucoma were also excluded
Interventions	**Group I (n = 32):** fesoterodine 4 mg daily **Group II: (n = 31):** placebo 4 weeks double-blind (treatment duration) + 1 week washout + 4 weeks open-label extension
Outcomes	**Primary outcomes:** daily mean number of micturitions **Secondary outcomes:** difference in the mean number of UUI, nocturia, UU as recorded by 3-day bladder diary, the mean change in the severity of incontinence measured by International Consultation on Incontinence Questionnaire-Short Form (ICIQ-sf), the mean change in OAB symptom scores measured by Over Active Bladder-Validated 8 (OAB-V8) questionnaire, incontinence quality of life (QoL) measured by SEAPI questionnaire and the cognitive functions were secondary outcome measures. The modified Hoehn and Yahr scale was used to describe the symptom progression of PD
Study funding sources	Not reported
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The researchers and participants were unaware of the content of the medication
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information

Yonguc 2019 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Low risk	The study appears to be free of other sources of bias

Yoshida 2018

Study characteristics	
Methods	**Study design:** RCT, 4-arm, parallel-group, placebo-controlled phase III study with 2-week placebo run-in **Dates study conducted:** July 2015 to June 2016
Participants	**Setting:** multicentre (109 centres) **Country:** Japan **Age (mean, SD):** imidafenacin 59.7 (12.4); placebo 58.9 (11.8) **Sex:** 1102 female, 122 male **Inclusion criteria:** receiving an adequate explanation for the study by the investigator, understanding the purpose of the study, wiling to participate in the study by his/her own free decision, written informed consent, and accepting by the investigator for participating in the study; male/female ≥ 20 years old; symptoms of OAB ≥ 6 months; willing and able to complete the micturition diary/questionnaires correctly, including record of volume of urine voided; ability to go to the bathroom without support; no clinically significant abnormal ECG **Exclusion criteria:** inappropriate decision as a study participant by the investigator; if female, is currently pregnant or breastfeeding, or expecting to conceive within the projected duration of the study; concurrent malignancy or history of cancer within the last 5 years prior to screening; systolic BP ≥ 160 mmHg, diastolic BP ≥ 100 mmHg or pulse ≥ 110 BPM measured when at rest; severe cardiac, liver, kidney or blood disorder; allergy, intolerance or history of a significant clinical or laboratory adverse experience associated with beta-adrenoreceptor agonists or anticholinergics; post-void residual urine volume (PVR) ≥ 100 mL
Interventions	**Group I (n = 117)** imidafenacin 0.1 mg twice a day **Group II (n = 369):** placebo Group III: vibegron 50 mg or 100 mg once a day, but not relevant Trial duration 12 weeks SAF: 1225, FAS: 1224
Outcomes	**Primary outcomes:** change in mean number of micturitions/day at week 12 from baseline **Secondary outcomes:** changes in baselines in OAB symptom variables (daily episodes of urgency, urgency incontinence, incontinence, nocturia and voided volume/micturition). Quality of life and safety were assessed.
Study funding sources	Kyorin Pharmaceutical Co. Ltd. and Kissei Pharmaceutical Co. Ltd.

Yoshida 2018 *(Continued)*

Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Blinding was carried out using the double-dummy method so participants were blinded, but not clear whether clinicians were
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Patient flow clearly documented through study
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, no pre-specified outcomes
Other bias	Unclear risk	Insufficient information

Zesiewicz 2015

Study characteristics

Methods	**Study design:** RCT, double-blind, placebo-controlled **Dates study conducted:** 2010 to 2013
Participants	**Setting:** multicentre (3 centres) **Country:** USA **Age (mean, SD):** solifenacin 67.6 (6.6); placebo 66.5 (9.3) **Sex:** solifenacin: 70% male; placebo 80% male **Inclusion criteria:** participants to be aged 40 to 80 years, have a stable dose of anti-PD medications 4 weeks prior to study entry, score 1.0 to 3.0 on the Modified Hoehn and Yahr scale, evidence of PSA ≤ 4 (males only) within the last 12 months, and have a bladder scan at screening documenting PVR ≤ 200 mL. PD as determined by the UK Parkinson's Disease Society Brain Bank Criteria for the diagnosis of Parkinson's disease. **Exclusion criteria:** history of prostate cancer or TURP (males only); severe renal disease, blood urea nitrogen (BUN) 50% greater than normal (normal BUN levels should be within a range of 5 to 20 mg/dL with creatinine between 0.7 and 1.4 mg/dL), major hepatic impairment (cirrhosis, viral hepatitis, non-alcoholic steatohepatitis, Wilson's disease or haemochromatosis), history of BOO or gastrointestinal obstructive disorders, history of narrow angle glaucoma, history of pelvic radiation, active UTI or history of chronic severe constipation. Additional exclusion criteria included: current treatment with ke-

Zesiewicz 2015 *(Continued)*

	toconazole, CYP3A4 inhibitors, certain contraindicated antiarrhythmics (flecainide, digoxin), antipsychotics, tricyclics, psychotropics, anticholinergics/antispasmodics, arylalkylamines, anti-androgens, antihypertensives. Participants who were currently taking selective serotonin-norepinephrine reuptake inhibitors, estrogens or acetylcholinesterase inhibitors were required to have a stable dose for 90 days prior to enrollment.
Interventions	**Group I (n = 10):** solifenacin succinate 5 mg to 10 mg daily **Group II (n = 13):** placebo 12-week trial 1-week washout between study and open-label 8-week open-label extension
Outcomes	**Primary outcomes:** change in mean number of micturitions/24-hour period as recorded on a 3-day bladder diary **Secondary outcomes:** change in mean number of urinary incontinence episodes, the mean number of nocturia episodes, urinary urgency as measured by the PPIUS, mean change in PPBC, PD QoL, IQoL, and clinical global impression
Study funding sources	Astellas Pharmaceuticals
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Using a computer generated randomization schedule, participants were randomized to receive solifenacin succinate or placebo...in a 1:1 ratio without blocking on stratification."
Allocation concealment (selection bias)	Low risk	Quote: "An unblinded team member who was not involved in patient enrollment or assessments labeled medication kits with study ID numbers according to the randomization schedule. Kits were dispersed to participants in sequential order and were identical in appearance other than ID number. Sealed emergency unblinding envelopes were available at each site in case required by adverse events"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All blinded team members and participants remained blinded until the open label phase."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All blinded team members and participants remained blinded until the open label phase."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Small sample size and no power calculation, however all participant flow through the study was accounted for
Selective reporting (reporting bias)	Low risk	All specified outcomes were reported

Zesiewicz 2015 *(Continued)*

Other bias	Low risk	While the study was financially sponsored by Astellas, the company had no role in randomisation, evaluation or analysis, nor were patients compensated for participation

Zinner 2002

Study characteristics	
Methods	**Study design:** RCT, placebo-controlled, parallel design **Dates study conducted:** not reported
Participants	**Setting:** multicentre (167 sites) **Country:** multinational (Australia, Canada, New Zealand, Europe, USA) **Age: younger than 65 years groups (mean, SD):** tolterodine: 51 (10.5) years; placebo: 51 (10) years **older than 65 years groups (mean, SD):** tolterodine: 74 (6) years; placebo 74 (6) years **Sex: younger than 65 years groups:** tolterodine: 12.9% male; placebo: 13.3% male; **older than 65 years groups:** tolterodine: 24.2% male; placebo: 26.9% male **Inclusion criteria:** > 18 years, urinary frequency more than 8/24 hours urge incontinence > 5 episodes/week OAB > 6 months, ability to fill up micturition charts **Exclusion criteria:** stress urinary incontinence, urine volume of more than 3 L, hepatic or renal failure, UTI, haematuria, interstitial cystitis, pregnancy
Interventions	**Group I (n = 507):** tolterodine 4 mg **Group II (n = 508):** placebo 12 week trial
Outcomes	Changes in micturition charts from baseline, incontinence episodes/week Mean number of micturition/24 hours, mean volume voided per micturition
Study funding sources	Not reported
Notes	Data reported as below 65 years and above 65 years

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Through the method of random permuted blocks, patients were randomized"
Allocation concealment (selection bias)	Low risk	Quote: "The randomization list was prepared by a trial-independent statistician using a computer software program and was kept secure until the database was locked and subsequently unblinded for analysis"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated

Zinner 2002 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts and reasons not stated
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Zinner 2004

Study characteristics	
Methods	**Study design:** RCT: placebo-controlled, parallel design **Dates study conducted:** not reported
Participants	**Setting:** multicentre (51 sites) **Country:** USA **Age (mean):** trospium: 63 years; placebo: 61.5 years **Sex:** trospium: 22.5% male; placebo: 28.7% years **Inclusion criteria:** cystometric evidence of detrusor instability; absent or minimal bladder suspension defect; max urinary flow above 15 mL/s; residual < 50 mL; MSU < 100,000 colonies/mL; no bladder stone or tumour by cystoscopy **Exclusion criteria:** severe heart failure or glaucoma. Neurological disease or detrusor sphincter dyssynergia. Drugs taken during study affecting autonomous nervous system or smooth muscles.
Interventions	**Group I (n = 262):** trospium 20 mg twice a day **Group II (n = 261):** placebo Trial duration 12 weeks 2-week washout
Outcomes	Change in number of micturition episodes in 24 hours, change in episodes of urge incontinence Efficacy and tolerability of drugs Urgency severity scale Incontinence impact questionnaires
Study funding sources	Financial interest and/or other relationship with Indevus, Lilly, Watson, Kyowa, Schwartz Pharma and Pfizer
Notes	Intention-to-treat analysis done No standard deviation given in outcome results

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information

Zinner 2004 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rate is identical between the groups, ITT analysis used
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Unclear risk	Insufficient information

Zinner 2006

Study characteristics	
Methods	**Study design:** RCT, parallel design **Dates study conducted:** not reported
Participants	**Setting:** multicentre trial conducted in the community setting **Age (mean):** darifenacin: 59.1 years; placebo: 59.1 years **Sex:** darifenacin: 13.6% male; placebo: 12.0% male **Inclusion criteria:** men and women aged ≥ 18 years of with history of OAB for ≥ 6 months and on average ≥ 1 urge incontinence episodes/day; ≥ 8 micturitions/day; ≥ 4 urgency episodes/day and mean warning time of ≤ 15 minutes during 12 consecutive hours. **Exclusion criteria:** women with stress urinary incontinence marked cystocoele or pelvic organ prolapse, patients receiving anticholinergics/antispasmodic drugs or those with anticholinergic effects, cholinergic agonists, potent cytochrome P450 3A4 inhibitors, opioids and drugs that cause significant constipation. Contraindications to anticholinergic drugs, clinically significant bladder outlet obstruction, intention to start bladder training programme and an indwelling catheter or intermittent self-catheterisation.
Interventions	**Group I (n = 216):** darifenacin controlled-release 15 mg once daily orally **Group II (n = 229):** placebo 12-week study period
Outcomes	**Primary outcome:** change from baseline in warning time at week 12 **Secondary outcomes:** change from baseline in the duration of warning time at weeks 2 and 6, number of urge incontinence episodes per week, median change from baseline in the number of micturitions per day, mean volume of urine per void and urgency episodes per week Change in QoL evaluated by OAB-q questionnaire at 6 and 12 weeks, Kings Health Questionnaire at week 12 Urinary diary activity assessment questionnaire to evaluate QoL at week 2, 6 and 12

Zinner 2006 *(Continued)*

	Adverse events, physical examinations, ECG and laboratory evaluation
Study funding sources	Study supported by Novartis Pharma AG
Notes	Last observation carried forward principle used for missing values No useable data as median change reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States 1:1 randomisation, no description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but blinding not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals and the reasons for withdrawals were similar (darifenacin: 29/216; placebo: 37/229)
Selective reporting (reporting bias)	Unclear risk	Protocol is not available, lack of information about the outcomes
Other bias	Unclear risk	Insufficient information

AE: adverse event
BP: blood pressure
BOO: bladder outlet obstruction
BPM: beats per minute
BWT: bladder wall thickness
cm: centimetre
CIC: clean intermittent catheterisation
DI: detrusor instability
DO: detrusor overactivity
ECG: electrocardiogram
EOT: end of treatment
ER: extended-release
FAS: full analysis set
H2O: water
HRQL: health-related quality of life
HVLT-R: Hopkins Verbal Learning Test-Revised
ICIQ: International Consultation of Incontinence Questionnaire
IEF: incontinence episode frequency
IIQ: Incontinence Impact Questionnaire
ITT: intention-to-treat
I-QoL: Incontinence Quality of Life questionnaire
IR: immediate-release
KHQ: King's Health Questionnaire

kg: kilogram
LUT: lower urinary tract
LSM: least square mean
mg: milligram
MID: minimally important difference
mL: millilitre
mL/s: millilitre per second
MMSE: Mini Mental State Exam
MS: multiple sclerosis
MVV: mean volume voided
MUI: mixed urinary incontinence
NDO: neurogenic detrusor overactivity
OAB: overactive bladder
OAB-q: overactive bladder questionnaire
PD: Parkinson's disease
PFMT: pelvic floor muscle training
POP: pelvic organ prolapse
PP: per protocol
PPBC: Patient Perception of Bladder Condition
PPIUS: Patient Perception of Intensity of Urgency Scale
PPS: per protocol population
PRO: patient-reported outcome
PVR: post-void residual
QoL: quality of life
RCT: randomised controlled trial
SAF: safety analysis population
SCI: spinal cord injury
SE: standard error
SF36: Standard Form 36
SI: stress incontinence
SSS: Symptom Severity Scale
SUI: stress urinary incontinence
TBS: Treatment Benefit Scale
TURP: transurethral resection of the prostate
UDI: Urogenital Distress Inventory
UI: urinary incontinence
UTI: urinary tract infection
UUI: urinary urge incontinence
VAS: visual analogue scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ablove 2017	Not OAB
Abrams 2005	Pooled analysis
Abrams 2008	Pooled analysis of 3 RCTs; trials not reported separately
Albala 2014	Not overactive bladder population
Andersen 1987	Irrelevant intervention drug
Appell 1997	A meta-analysis of 4 studies. Trials not reported separately. Not all trials placebo-controlled.
Arruda 2007	No placebo group
Assassa 2010	Not relevant intervention: bladder training + drug/placebo

Study	Reason for exclusion
Aydoğmuş 2014	No placebo group
Aziminekoo 2014	No placebo group
Azuri 2016	No placebo group
Bagger 1985	Cross-over trial
Bailey 2004	No placebo group
Batista 2015	No placebo group
Bawa 2016	Child population
Boaretto 2011	No placebo group
Bono 1982	Cross-over trial
Breuel 1993	Healthy participants
Brocklehurst 1972	A study in the elderly with no evidence presented that the participants had overactive bladders
Burgio 2007	No placebo group
Burgio 2010	No placebo group
Cardozo 2004b	Pooled analysis of 4 RCTs; 2 trials included in the review, other 2 trials not reported separately
Cardozo 2005	Intervention above therapeutic dosage
Cardozo 2006	Pooled analysis of 4 RCTs; 2 trials included in the review, other 2 trials not reported separately
Cartwright 2011	Wrong intervention: oxybutynin transdermal patch
Chapple 2004d	Pooled analysis of 3 RCTs; trials not reported separately
Chapple 2004e	Pooled analysis of 3 RCTs; trials not reported separately
Chapple 2005	A pooled analysis of 3 studies; trials not reported separately
Chapple 2006a	No placebo group
Chapple 2006b	Pooled analysis of 4 RCTs; 2 trials included in the review, other 2 trials not reported separately
Chartier-Kastler 2015	No placebo group
Chen 2008	No placebo group
Chen 2012a	No placebo group, combination therapy
Chen 2012b	No placebo group
Chen 2015	No placebo group
Cho 2013	No placebo group

Study	Reason for exclusion
Conde-Santos 2009	Not OAB population
Coombes 1996	Cross-over trial
Dash 2016	Not OAB population
Davila 2001	Oxybutynin dose is not within the range of therapeutic dose
Dede 2013	No placebo group
Dell'Atti 2015	No placebo group
Deng 2012	No placebo group
Di Stasi 2001	Cross-over trial
Dmochowski 2003	The drug is not in the range of the therapeutic dose
Dmochowski 2005	Wrong delivery
Dmochowski 2006	Cross-over trial, no placebo group
Dmochowski 2007	Pooled analysis of 2 RCTs, one of which includes non-OAB patients
Drake 2017	No placebo group
DuBeau 2009	No placebo group, wrong intervention
Eftekhar 2014	No placebo group
EUCTR2005-005546-39-BE	No placebo group
Ferreira 2010	No placebo group
Franzen 2010	No placebo group
Gerstenberg 1986	Terodiline has been withdrawn from therapeutic use worldwide
Ghanbari 2015	No placebo group
Gittelman 2003	Pooled analysis of 2 RCTs; trials not reported separately
Gittelman 2014	Wrong intervention - vaginal ring
Goode 2002	The drug is not in the range of the therapeutic dose
Griebling 2009	Pooled analysis of 5 RCTs; trials included in the pooled analysis not reported
Ha 2008	No placebo group
Haab 2011	Not OAB population
Hao 2012	No placebo group, not OAB population
Herberg 1997	No placebo arm, healthy participants

Study	Reason for exclusion
Herbison 2004	No placebo group
Herschorn 2003	No placebo group
Herschorn 2009b	No placebo group, not included drug, wrong study design
Homma 2006	Wrong intervention: transdermal patch
Hsiao 2011	Open-label, no placebo group
Hsiao 2019	No placebo group
Jafarabadi 2015	No placebo group
Jeong 2007	No placebo group
Jing 2012	No placebo group, combination therapy
Johnson 2012	Not OAB population
Johnson 2013	No placebo group
Junemann 1999	The drug is not in the range of the therapeutic dose
Kafri 2013	No placebo/no treatment group
Katoh 2019	No placebo group
Kay 2009	Healthy participants
Kim 2009a	No placebo group, combination therapy
Kim 2009b	No placebo group, not OAB population
Kim 2009c	Wrong comparison
Kim 2011	No placebo group
Kinjo 2015	No placebo group
Kirschner-Hermanns 1997	A study in the elderly with no evidence presented that the participants had OAB
Kobayashi 2009	No placebo group
Komesu 2018	No placebo, wrong intervention, wrong study design
Konstantinidis 2010a	No placebo group
Konstantinidis 2010b	No placebo group
Kosilov 2014b	Combination therapy
Kosilov 2014c	Combination therapy
Kosilov 2014d	Combination therapy

Study	Reason for exclusion
Kosilov 2018	Combination therapy
Kramer 1987	Cross-over trial
Kuipers 2002	Cross-over study
Kutub Uddin Awal 2018	No placebo group
Larsson 1999	A meta-analysis of 4 studies; trials not reported separately. Some studies published separately.
Lee 2009	Combination therapy, no placebo group
Lee 2013	Wrong intervention
Leng 2012	No placebo group
Liao 2012	No placebo group, wrong population
Madersbacher 2003	No placebo group, wrong intervention
Madersbacher 2005	No placebo group
Malhotra 2008	Wrong intervention, wrong study design
Malhotra 2010	Healthy participants
Malkoc 2012	No placebo group, combination therapy
Mangel 2012	No placebo group
Manjunatha 2014	No placebo group, open-label
Manriquez 2013	No placebo group
Massey 1986	Cross-over trial
Matsukawa 2016	No placebo group
Mattiasson 2001	No placebo group, combination therapy
Mattiasson 2008	No placebo group, combination therapy
Mazur 1994	No placebo group
McCreanor 1998	No placebo group
Mehnert 2009	Healthy participants
Meyhoff 1983	Cross-over trial
Millard 2003	No placebo group
Millard 2006	Pooled analysis of 3 RCTs; 3 trials reported separately and included in the review
Moisey 1980	Cross-over trial

Study	Reason for exclusion
Moore 1990	Cross-over trial
Murray 1984	Cross-over trial
Nardulli 2012	No placebo group
National Taiwan University Hospital 2015	No placebo group
NCT00189800	No placebo group
NCT00269750	No placebo group
NCT00338624	Combination therapy, wrong population
Nelken 2011	No placebo group
Nishii 2011	No placebo group
Nishizawa 2007	No placebo group
Norton 1994	Terodiline withdrawn from therapeutic use worldwide
Oh-Oka 2012	Wrong intervention, active placebo group
Ohba 2019	No placebo group, wrong population
Orhan 2015	Combination therapy, active placebo group
Osman 2003	No placebo group, wrong population
Ouslander 1995	A study in the elderly with no evidence presented that the participants had OAB
Park 2014	No placebo group
Paulson 1978	Wrong population
Payne 2007	Pooled analysis of Cardozo 2004a and Chapple 2004e. Both studies included in the review.
Pleil 2003	Efficacy trial with open lab extension but intervention drug not described
Pontari 2010	MRI imaging
Preyer 2007	No placebo group
Qiu 2002	Not within UK or EU therapeutic dosage range
Rackley 2006	37% non-OAB
Rana 2016	No placebo group
Reese 2005	Pooled analysis of 3 RCTs; trials not reported separately
Riva 1984	Cross-over trial

Study	Reason for exclusion
Robinson 1983	Emepronium bromide with flavoxate hydrochloride versus placebo; excluded as active therapy includes flavoxate
Rosario 1995a	Cross-over trial
Rosario 1995b	Cross-over trial
Rovner 2017	Combination therapy, active placebo group
Sand 2005	Open-label, wrong study design
Sand 2011	Pooled analysis
Sekeroglu 2016	Wrong comparator, wrong study design
SerranoBrambila 2000	Cross-over trial
Shim 2015	Active placebo group, not OAB population, combination therapy
Shimizu 2013	Active placebo group
Song 2006	Active placebo group
Srivastava 2019	Not OAB population
Staskin 2006	Pooled analysis of 4 RCTs; 2 trials included in the review, other 2 trials not reported separately
Staskin 2009a	Wrong intervention: gel
Staskin 2010	No placebo arm
Stohrer 2013	No placebo group
Szonyi 1995	Medication plus behavioural intervention
Tack 2012	Pooled data and a review
Tapp 1987	Terodiline has been withdrawn from therapeutic use worldwide
Tapp 1989	Terodiline has been withdrawn from therapeutic use worldwide
Tapp 1990	Cross-over trial
Terodiline 1993	Terodiline has been withdrawn from therapeutic use worldwide
Tseng 2007	No placebo group
Tubaro 2007	Pooled analysis of 2 RCTs; 2 trials not reported separately
Tubaro 2017	Pooled analysis of 5 phase III trials looking at tolterodine, mirabegron and placebo but no direct comparison of tolterodine and placebo
Vecchioli-Scaldazza 2016	No placebo group
Vecchioli-Scaldazza 2017	No placebo group, open-label

Study	Reason for exclusion
Viayna 2004	RCT. Healthy male volunteers with no mention of OAB symptoms or UI at baseline. Aim of study to evaluate safety and tolerability of an antimuscarinic.
Visco 2012	No placebo group
Wagg 2006	Pooled analysis of 4 RCTs; 3 of which are included in the review
Wagg 2013b	Cross-over trial
Walter 1982	Cross-over trial
Wang 2013	No placebo group
Wang 2019a	All groups were inclusive of onabotulinum toxin A injection
Wang 2019b	No placebo group
Wehnert 1989	Cross-over trial
Wehnert 1992	Cross-over trial
Wein 1978	Postoperative detrusor overactivity (after prostate surgery or bladder resection, men only)
Wein 1999	A meta-analysis of 2 studies; trials not reported separately
Wesnes 2008	Healthy participants
Whitehead 1967	A study in the elderly with no evidence presented that the participants had OAB
Williams 1981	A study in the elderly with no evidence presented that the participants had OAB
Wise 1992	Terodiline withdrawn from market, no placebo group
Xu 2013	No placebo group
Yang 1990	Cross-over trial, no drug of interest
Yangyun 2014	No placebo group
Yasui 2011	Not OAB population, combination therapy
Yokoyama 2009	No placebo group
Yokoyama 2013a	No placebo group
Yokoyama 2013b	Patients with nocturnal polyuria and nocturia included
Zaitsu 2011	No placebo group
Zeegers 1987	Cross-over trial
Zhang 2012	No placebo group
Zhu 2013	No placebo group

Study	Reason for exclusion
Zinner 2005	Cross-over trial
Zorzitto 1989	Cross-over trial

MRI: magnetic resonance imaging
OAB: overactive bladder
RCT: randomised controlled trial
UI: urinary incontinence

Characteristics of studies awaiting classification *[ordered by study ID]*

Chapple 2001

Methods	**Study design:** secondary analysis of 3 studies **Dates study conducted:** not reported
Participants	**Setting:** all included studies were multicentre **Country:** not reported **Age:** not reported **Sex:** not reported **Inclusion criteria:** not reported **Exclusion criteria:** not reported
Interventions	**Study I:** **Group I (n = 145)**: oxybutynin 5 mg twice a day **Group II (n = 149):** propiverine 15 mg 3 times a day **Group III (n = 72)**: placebo **Study II:** **Group I (n = 72):** propiverine 15 mg 3 times a day **Group II (n = 62):** placebo **Study III:** **Group I (n = 49):** propiverine 15 mg 3 times a day **Group II (n = 49)**: placebo 598 participants across all studies 14- or 28-day treatment period
Outcomes	**Primary outcome**: efficacy and tolerability of propiverine
Notes	Pooled analysis of 3 studies; 2 were included in this review, Madersbacher 1999 and Dorschner 2000. The third study is Dreikorn. This conference abstract is the only report of the Dreikorn study that is in the public domain.

Chuang 2021

Methods	**Study design:** RCT **Dates study conducted:** not reported
Participants	**Setting:** multicentre **Country:** Taiwan **Age:** 59 (SD not reported) **Sex:** 71 males, 42 females **Inclusion criteria:** male or female patients ≥ 20 years of age, with OAB symptoms for ≥ 3 months and had at least an average of one UUI or one urge symptom per 24 hours as recorded in the 3-day micturition diary **Exclusion criteria:** not reported
Interventions	**Group I (n = 73):** imidafenacin 0.1 mg twice a day **Group II (n = 39):** placebo
Outcomes	The primary efficacy outcome was the change in the mean number of micturitions per day. Secondary endpoints included mean changes from baseline in urgency episodes and urge incontinence episodes per day and mean volume voided per micturition.
Notes	Study identified from the top-up search; results of this study were not incorporated

DuBeau 2000

Methods	**Study design:** RCT
Participants	88 participants - older adults (mean age 71 years) with urodynamically diagnosed urgency urinary incontinence
Interventions	8-week oxybutynin versus placebo (allocated 3:2)
Outcomes	Urinary incontinence outcomes based on 72-hour voiding records and participant satisfaction measured using a 5-point Likert scale
Notes	Unclear if this study has been reported elsewhere

Frankel 2022

Methods	RCT
Participants	**Inclusion criteria:** adults with OAB wet (defined as an average of ≥ 8.0 micturitions and ≥ 1.0 UUI episodes per day in the 7-day voiding diary at baseline) or OAB dry (defined as an average of ≥ 8 micturitions, ≥ 3.0 urgency episodes, and < 1.0 UUI episode per day in the 7-day voiding diary at baseline) for ≥ 3 months before the screening visit **Exclusion criteria:** not reported
Interventions	**Group I (n=547):** vibegron 75 mg

Frankel 2022 *(Continued)*

	Group II (n=431): tolterodine 4 mg extended-release **Group III (n=540):** placebo
Outcomes	Micturitions, urgency episodes and UUI episodes
Notes	This trial is already included and incorporated in the review. The papers identified above were from the top-up search.

Govier 2010

Methods	**Setting:** multicentre (33 centres) **Country:** USA **Study design:** phase III, randomised, double-blind, placebo-controlled, parallel-group, pivotal trial
Participants	**Number of participants:** 634 randomised and received at least one dose of intervention or placebo **Inclusion criteria:** men and women aged 18 years or over, with OAB symptoms including urinary frequency, urgency or urgency incontinence were eligible to enter the 2-week screening phase. Patients kept micturition diaries for 3 days during the screening - those with mean 8 or more micturitions per 24 hours plus a mean of one or more incontinence episode per 24 hours and/or a mean of one or more urgency episode per 24 hours were eligible for inclusion into the randomised phase. **Exclusion criteria:** stress incontinence or mixed incontinence where stress was predominant; patients with a neurological cause of detrusor overactivity; urinary retention; grade III/IV prolapse with cystocele and recurrent or active urinary tract infection. Women of childbearing potential were required to have a negative serum pregnancy test at screening and to use a medically acceptable form of contraception during study participation.
Interventions	Group I: solifenacin 10 mg (n = 318) Group II: placebo (n = 316)
Outcomes	**Primary outcome**: change from baseline to week 12 (endpoint) in mean number of micturitions per 24 hours **Secondary outcomes**: change from baseline to endpoint in the mean number of incontinence, urgency, nocturnal voiding and nocturia episodes per 24 hours; mean volume voided per micturition; treatment-emergent adverse events
Notes	The primary paper for this trial was sourced after the cut-off time for inclusion so was not included in this review. It will be assessed for inclusion in a subsequent update.

Herschorn 1999

Methods	—
Participants	—
Interventions	—
Outcomes	—

Herschorn 1999 *(Continued)*

Notes	Link broken so cannot source, unclear which study this refers to. Note of funding for study.

Ibinaeva 2012

Methods	**Study design:** RCT, parallel design
Participants	**Number of participants:** 24 randomised **Inclusion criteria:** overactive bladder symptoms **Exclusion criteria:** not reported
Interventions	**Group I:** solifenacin 5 mg **Group II:** placebo
Outcomes	Not reported in abstract
Notes	The authors are aware that this study meets the inclusion criteria as the translation of this study has been obtained. However, it did not meet the authors' cut-off date for inclusion. Furthermore, the sample size of this study is small and thus is very unlikely to have an impact on the results.

JapicCTI-152936

Methods	—
Participants	—
Interventions	—
Outcomes	—
Notes	Translation needed

Kim 2022

Methods	RCT
Participants	**Inclusion criteria:** Main inclusion at screening (Visit 1): • Men and women 19 years or older with OAB symptoms for ≥ 3 months • Participant who is willing and able to complete the voiding diary correctly • Participant who is willing and able to provide informed consent indicating that they understand the purpose and procedures required for the study **Exclusion criteria:** Main exclusion at screening (Visit 1):

Kim 2022 *(Continued)*

	• Clinically significant stress urinary incontinence or mixed urinary incontinence where stress is the predominant factor • Participant who has injury or neurodegenerative disease, which is able to effect on lower urinary tract and nerves • Participant with diabetes insipidus, urinary stone, urinary tract infection, interstitial cystitis, recurrent urinary tract infection, pelvic organ prolapse or neurogenic bladder • Clinically significant benign prostatic hyperplasia at the discretion of the investigator • Had bladder or lower urinary tract surgery within 12 months from the screening visit • Medical history of malignant tumour in urinary system or pelvic organs • > 150 mL of post-void residual volume in the screening test
Interventions	**Group I**: DA-8010 placebo + solifenacin succinate placebo **Group II:** DA-8010 2.5 mg + solifenacin succinate placebo **Group III:** DA-8010 5 mg + solifenacin succinate placebo **Group IV:** DA-8010 placebo + solifenacin succinate 5 mg Estimated number of participants: 595
Outcomes	Primary outcome measures: • Change from baseline in the mean number of micturitions per 24 hours at 12 weeks (time frame: 12 weeks) • Change from baseline in the mean number of micturitions per 24 hours at 12 weeks Secondary outcome measures: • Change from baseline in the mean number of micturitions per 24 hours at 4 and 8 weeks (time frame: 4 and 8 weeks) • Change from baseline in the mean number of micturitions per 24 hours at 4 and 8 weeks • Change from baseline in the mean number of urinary urgency (Grade 2, 3, 4) per 24 hours at 4, 8 and 12 weeks (time frame: 4, 8 and 12 weeks) • Change from baseline in the mean number of urinary urgency (Grade 2, 3, 4) per 24 hours at 4, 8 and 12 weeks
Notes	Results are not reported; clinical trial registry; identified from the top-up search

Martin 2007

Methods	**Study design:** RCT
Participants	Planned to recruit 275 participants. Male or female outpatients ≥ 18 years of age with "Symptoms of OAB for a minimum of 3 consecutive months prior to study entry; severity of OAB (as defined by patient reported symptoms of frequency ≥ 8 micturition per 24 hours, urgency ≥ 3 episodes per 24 hours, and urinary urgency incontinence on average ≥ 1 per day), for a minimum of one month prior to study entry."
Interventions	"400 mg and 600 mg flupirtine (ELB245) given once daily for 12 weeks (8 + 4 weeks) versus placebo and versus 4 mg tolterodine given once daily in patients with incontinent overactive bladder (OAB)"
Outcomes	**Primary outcome:** "The change from baseline in the mean number of micturitions per 24 hours (based on a 3-day average)" **Secondary outcomes:** OAB-related measures, urgency measures, quality of life

Martin 2007 *(Continued)*

Notes	2 trial registrations for the same trial in different registries: • EudraCT Number: 2006-004854-26 • NCT00439192 **Trial status:** prematurely ended. Initial estimate of duration of trial was 9 months. **Date of the global end of the trial:** 3 Aug 2007 (no reasons given for premature ending) **Received ethics decision (favourable):** February 2007 **Sponsor's protocol code number:** ELB245201-06 Flupirtine maleate From ClinicalTrials.gov: study start date: February 2007; study completion date: August 2007 Results or a publication were not available

Osca-García 1997

Methods	—
Participants	—
Interventions	—
Outcomes	—
Notes	Translation needed

Pleil 2005

Methods	**Study design:** 3 international RCTs
Participants	Participants with overactive bladder syndrome (study 1 = 596; study 2 = 555; study 3 = 1177 participants)
Interventions	Three 12-week studies of tolterodine versus placebo
Outcomes	Health-related quality of life, benefit, satisfaction and willingness to continue
Notes	Data appear to be presented separately for 3 RCTs but not clear which studies these are. Clarification has been sought but the email was undeliverable.

Son 2021

Methods	RCT
Participants	**Inclusion criteria:** male and female patients aged ≥ 19 years with OAB symptoms (frequency, urgency, and/or urgency urinary incontinence) for ≥ 3 months **Exclusion criteria:** not reported

Son 2021 *(Continued)*

Interventions	**Group I (n = 77):** placebo **Group II (n = 76):** DA8010 2.5 mg **Group III (n = 77):** DA8010 5 mg **Group IV (n = 76):** solifenacin 5 mg
Outcomes	The primary endpoint was change from the baseline of mean 24-hour frequency at the end of treatment (12 weeks). The secondary endpoints included the mean 24-hour frequency at 4 and 8 weeks; number of overall incontinence episode/24 hours; number of urgency urinary incontinence episodes/24 hours; number of urgency episodes/24 hours; number of nocturia episode/24 hours; average voided volume; and maximum voided volume at 4, 8 and 12 weeks; Patient Perception of Bladder Condition (PPBC) scores at 4, 8 and 12 weeks; Overactive Bladder Questionnaire (OAB-q) scores at 4 and 12 weeks; and "benefit, satisfaction, and willingness to continue" (BSW) at 12 weeks.
Notes	Identified from the top-up search; results are not incorporated

Wagg 2020

Methods	—
Participants	—
Interventions	—
Outcomes	—
Notes	Identified from the top-up search. Unclear which studies are included in the analysis. No response from the authors.

HRQL: health-related quality of life
OAB: overactive bladder
OAB-q: OAB questionnaire
RCT: randomised controlled trial
SD: standard deviation
TER: tolterodine extended-release
UUI: urinary urge incontinence

Characteristics of ongoing studies *[ordered by study ID]*

Hajebrahimi 2015

Study name	Ocular effects of solifenacin succinate in women with narrow angle glaucoma and overactive bladder syndrome
Methods	**Study design:** RCT, double-blind, placebo-controlled **Dates study conducted:** expected recruitment start 22 June 2015, expected recruitment end date 22 December 2015
Participants	**Setting:** single-centre **Country:** Iran **Age:** not reported

Hajebrahimi 2015 *(Continued)*

	Sex: not reported **Inclusion criteria:** all women 18 years or older with narrow-angle glaucoma and symptoms of OAB (urinary frequency and urgency) **Exclusion criteria:** a history of ocular surgery; diabetes; severe refractive disorders; malignant glaucoma; a history of sensitivity to anticholinergics; symptoms of urinary obstruction; severe prolapse of pelvic floor
Interventions	**Group I:** solifenacin 5 mg **Group II:** placebo Sample size not reported Trial duration 4 weeks
Outcomes	**Primary outcomes:** changes in intraocular pressure at baseline, 1 week and 4 weeks after the beginning of the study according to Goldman applanation tonometry **Secondary outcomes:** change in the angle of the anterior chamber of the eye at baseline, 1 week and 4 week according to gonioscopy
Starting date	2015
Contact information	hajebrahimis@gmail.com
Notes	Author of this study advised that the study remains ongoing due to low recruitment (15 July 2021)

NCT00553657

Study name	The study to test the effect of standardization of fluid intake in female patients with overactive bladder
Methods	**Study design:** RCT, double-blind, placebo-controlled, parallel-group **Dates study conducted:** not reported
Participants	**Setting:** single-site **Country:** Australia **Age:** not reported **Sex:** female only **Inclusion criteria:** females aged 18 years or older with OAB symptoms as evidenced by daily episodes of urgency without incontinence, which may be associated with frequency or nocturia but without bladder pain. At least 8 micturitions per 24 hours period at screening **Exclusion criteria:** any abnormality identified on the screening examination or any other medical condition or circumstance making the patient unsuitable for participation in the study based on the Investigator's and Medical Monitor's assessment; any contraindication to Detrol LA or other anti-muscarinic medications; inability to consume 10 cc/kg of fluid within 30 minutes; regular alcohol consumption averaging 7 drinks/week for women (1 drink = 100 mL of wine or 285 mL of beer or 30 mL of hard liquor); positive urine drug or alcohol at screening at screening; average blood pressure measurements systolic ≥ 140 or diastolic ≥ 90 at screening; QTcB value ≥ 450 msec at screening; poorly controlled diabetes mellitus or hypertension, as evidenced by a change in medication within the 2 months prior to initiation of the study; history of urinary retention or gastric retention; known history of narrow-angle glaucoma; history of QT prolongation; known reduction in hepatic

NCT00553657 *(Continued)*

	or renal function; concomitant use of loop diuretics (e.g. furosemide); concomitant use of a medication that is a potent inhibitor of CYP3A4; Class IA or Class III antiarrhythmic medications; patient is unable and/or unwilling to adhere to lifestyle guidelines; For women of child-bearing potential, a positive serum β-hCG at screening or pre-dose, or an unwillingness to agree to adequate contraception from the time of screening until the completion of the study; positive for hepatitis C antibody, hepatitis B surface antigen or HIV at screening; presence of urinary tract infection within 4 weeks of screening; post-void residual volume of > 150 mL (bladder ultrasound).
Interventions	**Group I:** tolterodine (Detrol La) **Group II:** placebo Trial duration unclear Total number of participants 55 No sample sizes reported of individual groups
Outcomes	Variability in change from baseline in mean volume per void measured on 3 consecutive days; mean change from baseline in volume voided per void. Percent and actual change from baseline in maximum volume voided, number of micturitions, number of incontinence episodes, number of urgency episodes and time to first void on 3 consecutive days.
Starting date	2007
Contact information	Not available
Notes	Trial registration No useable information Attempted to contact authors but no contact detail could be identified

NCT03566134

Study name	A therapeutic exploratory clinical study of DA-8010 in patients with overactive bladder
Methods	**Study design:** randomised, therapeutic clinical study **Dates:** 10 July 2018 to 27 December 2019
Participants	**Country:** Korea **Enrollment:** 306 **Age:** 19 years or older **Sex:** men or women **Inclusion criteria:** men and women 19 years or older with OAB symptoms for 3 or more months; participant who is willing and able to complete the micturition diary correctly; participant who is willing and able to provide informed consent indicating that they understand the purpose and procedures required for the study **Exclusion criteria:** clinically significant stress urinary incontinence or mixed urinary incontinence where stress is the predominant factor; diagnosed with interstitial cystitis or bladder pain syndrome; clinically significant pelvic organ prolapse; participant who has neurologic status which is able to effect vesical function, such as multiple sclerosis, spinal injury or Parkinson's disease; med-

NCT03566134 *(Continued)*

	ical history of malignant tumour in urinary system or pelvic organs; clinically significant bladder outlet obstruction or more than 200 mL of post-void residual volume
Interventions	**Group I:** DA-8010 2.5 mg + solifenacin succinate placebo orally once per day **Group II**: DA-8010 5 mg + solifenacin succinate placebo orally once per day **Group III:** DA-8010 placebo + solifenacin succinate 5 mg orally once per day **Group IV:** DA-8010 placebo + solifenacin succinate placebo orally once per day
Outcomes	Change from baseline to week 12 in mean number of micturitions per 24 hours
Starting date	10 July 2018
Contact information	Dong-A ST Co. Ltd.
Notes	Recruitment has been completed

NCT03632772

Study name	Comparison of solifenacin and mirabegron in treatment of overactive bladder symptoms in men after TURP
Methods	**Study design**: prospective randomised trial **Dates:** 1 August 2018 to 31 July 2019
Participants	**Setting:** hospital clinic **Country:** Taiwan **Estimated enrollment:** 130 **Age:** 20 to 80 years according to inclusion criteria **Sex:** males only **Inclusion criteria:** male patients with benign prostate hyperplasia (BPH) and undergo transurethral prostatectomy (TURP) or transurethral incision of the prostate (TUIP); patients void smoothly after catheter removal; no active urinary tract infection; no gross haematuria or blood clot obstruction; patient or his care giver can complete voiding diary and report symptoms **Exclusion criteria:** patients have overt neurological diseases such as cerebrovascular disease, senile dementia or spinal cord injury; patients have severe medical disease and completely immobile; patients have post-void residual volume larger than 150 mL; patients do not have OAB after TURP
Interventions	**Group I:** solifenacin 5 mg once daily for 4 weeks **Group II:** mirabegron 50 mg once daily for 4 weeks **Group III:** no treatment
Outcomes	**Primary outcomes:** change in Urgency Severity Scale (USS) from baseline to 4 weeks after catheter removal and starting OAB medication **Secondary outcomes included:** the change in Overactive Bladder Symptom Score (OABSS) from baseline to 2 and 4 weeks; frequency episodes, urgency episodes, urgency urinary incontinence

NCT03632772 *(Continued)*	
	(UUI) episodes in the 3 day voiding diary; maximum flow rate (Qmax), voided volume, post-void residual volume (PVR), International Prostate Symptom Score (IPSS), Quality of Life Index (QoL-I)
Starting date	1 August 2018
Contact information	Hann-Chorng Kuo MD: hck@tzuchi.com.tw
Notes	—

NCT03817931	
Study name	Higher neural changes following anticholinergic, beta 3 agonist, or placebo in patients with overactive bladder
Methods	**Study design:** randomised, controlled pilot trial
Participants	**Setting:** urology clinic **Country:** USA **Estimated enrollment**: 30 **Age:** participants will be 50 to 90 years old as per the inclusion criteria **Sex:** women only as per the inclusion criteria **Inclusion criteria:** female patients of age 50 to 90 years old with OAB as defined by the ICS who report that symptoms cause moderate problems using the PPBC; English speaking and able to consent **Exclusion criteria:** males are excluded to eliminate prostate pathology and urethral strictures, as well as possible bias with gender differences on fMRI; participants with moderately severe or severe depression (screening score of 15 or more) on the Personal Health Questionnaire-9 (PHQ-9); participants with moderate to severe anxiety (screening score 25 - 30) on the Hamilton Anxiety Rating Scale (HAM-A); a screening score indicating below normal cognitive function at baseline (score of 25 or less) on the Montreal cognitive assessment; participants with neurologic disorders, dementia, prior cerebrovascular accident, neurogenic bladder or post-void residual greater than 250 mL; anticholinergics for OAB or beta 3 agonists use for treatment of OAB in the preceding 6 months prior to enrollment; pregnant or planning to become pregnant in the next 6 months, or current breastfeeding; the inability to undergo MRI
Interventions	**Group I:** solifenacin 5 mg tablet orally once daily for 30 days **Group II:** mirabegron 25 mg tablet orally once daily for 30 days **Group III:** placebo
Outcomes	**Primary outcomes:** functional connectivity on MRI, resting state blood oxygenation level dependent (BOLD) changes, diffusion tensor imaging
Starting date	5 August 2019
Contact information	Jill M Danford MD: highr077@gmail.com
Notes	**Sponsors:** Baylor Research Institute; The Methodist Hospital System; International Urogynecological Association

BOLD: blood oxygenation level dependent

BPH: benign prostate hyperplasia
fMRI: functional magnetic resonance imaging
HAM-A: Hamilton Anxiety Rating Scale
ICS: International Continence Society
IPSS: international prostate symptom score
mg: milligram
mL: millilitre
MRI: magnetic resonance imaging
OAB: overactive bladder
OABSS: overactive bladder symptom score
PHQ: Personal Health Questionnaire
PPBC: Patient Perception of Bladder Condition
PVR: post-void residual
Qmax: maximum flow rate
QoL-I: Quality of Life Index
TUIP: transurethral incision of the prostate
TURP: transurethral prostatectomy
USS: urgency severity scale
UUI: urgency urinary incontinence

DATA AND ANALYSES

Comparison 1. Anticholinergics versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Mean change from baseline in condition-specific quality of life	12	6804	Mean Difference (IV, Fixed, 95% CI)	-4.41 [-5.28, -3.54]
1.1.1 Darifenacin	1	399	Mean Difference (IV, Fixed, 95% CI)	-6.10 [-10.55, -1.65]
1.1.2 Fesoterodine	4	2475	Mean Difference (IV, Fixed, 95% CI)	-4.88 [-6.48, -3.29]
1.1.3 Solifenacin	3	1038	Mean Difference (IV, Fixed, 95% CI)	-4.65 [-6.20, -3.09]
1.1.4 Tolterodine	3	1918	Mean Difference (IV, Fixed, 95% CI)	-2.87 [-4.51, -1.24]
1.1.5 Propiverine	1	974	Mean Difference (IV, Fixed, 95% CI)	-6.67 [-10.00, -3.34]
1.2 Patient perception of cure or improvement	9	8457	Risk Ratio (M-H, Random, 95% CI)	1.38 [1.15, 1.66]
1.2.1 Tolterodine	3	2792	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.71, 2.36]
1.2.2 Darifenacin	1	361	Risk Ratio (M-H, Random, 95% CI)	1.52 [1.15, 2.01]
1.2.3 Fesoterodine	7	5304	Risk Ratio (M-H, Random, 95% CI)	1.37 [1.12, 1.68]
1.3 Mean number of urgency episodes per 24 hours	23	16875	Mean Difference (IV, Random, 95% CI)	-0.85 [-1.03, -0.67]
1.3.1 Fesoterodine	10	10007	Mean Difference (IV, Random, 95% CI)	-0.98 [-1.32, -0.64]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3.2 Imidafenacin	3	1440	Mean Difference (IV, Random, 95% CI)	-1.02 [-1.46, -0.58]
1.3.3 Propiverine	2	1486	Mean Difference (IV, Random, 95% CI)	-0.49 [-0.97, -0.02]
1.3.4 Solifenacin	5	1640	Mean Difference (IV, Random, 95% CI)	-0.86 [-1.12, -0.60]
1.3.5 Tolterodine	3	2302	Mean Difference (IV, Random, 95% CI)	-0.52 [-0.91, -0.14]
1.4 Adverse events: Dry mouth	66	38368	Risk Ratio (M-H, Fixed, 95% CI)	3.50 [3.26, 3.75]
1.4.1 Darifenacin	5	1836	Risk Ratio (M-H, Fixed, 95% CI)	4.15 [3.09, 5.57]
1.4.2 Fesoterodine	11	8200	Risk Ratio (M-H, Fixed, 95% CI)	3.92 [3.41, 4.52]
1.4.3 Imidafenacin	3	1459	Risk Ratio (M-H, Fixed, 95% CI)	2.80 [1.99, 3.95]
1.4.4 Oxybutynin	5	954	Risk Ratio (M-H, Fixed, 95% CI)	3.02 [2.37, 3.85]
1.4.5 Propantheline	1	80	Risk Ratio (M-H, Fixed, 95% CI)	2.73 [0.88, 8.49]
1.4.6 Propiverine	7	3741	Risk Ratio (M-H, Fixed, 95% CI)	3.79 [3.00, 4.78]
1.4.7 Solifenacin	14	7028	Risk Ratio (M-H, Fixed, 95% CI)	4.19 [3.42, 5.14]
1.4.8 Tolterodine	24	12649	Risk Ratio (M-H, Fixed, 95% CI)	3.02 [2.68, 3.41]
1.4.9 Trospium	5	2421	Risk Ratio (M-H, Fixed, 95% CI)	3.33 [2.52, 4.40]
1.5 Adverse events: Urinary retention/high residual volume	17	7862	Risk Ratio (M-H, Fixed, 95% CI)	3.52 [2.04, 6.08]
1.5.1 Fesoterodine	2	1394	Risk Ratio (M-H, Fixed, 95% CI)	8.66 [1.76, 42.65]
1.5.2 Oxybutynin	2	432	Risk Ratio (M-H, Fixed, 95% CI)	6.01 [1.67, 21.69]
1.5.3 Propiverine	2	786	Risk Ratio (M-H, Fixed, 95% CI)	5.91 [0.71, 49.48]
1.5.4 Solifenacin	5	2167	Risk Ratio (M-H, Fixed, 95% CI)	2.59 [0.86, 7.77]
1.5.5 Tolterodine	6	2482	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.31, 2.96]
1.5.6 Trospium	1	601	Risk Ratio (M-H, Fixed, 95% CI)	4.07 [0.46, 36.18]
1.6 Adverse events: Abdominal pain	15	8195	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [1.20, 2.33]
1.6.1 Darifenacin	1	324	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [0.23, 17.92]
1.6.2 Fesoterodine	3	1423	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.66, 2.34]
1.6.3 Imidafenacin	1	772	Risk Ratio (M-H, Fixed, 95% CI)	9.07 [0.55, 149.30]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.6.4 Oxybutynin	1	305	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.34, 6.53]
1.6.5 Propiverine	1	988	Risk Ratio (M-H, Fixed, 95% CI)	9.54 [0.58, 157.70]
1.6.6 Solifenacin	1	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.6.7 Tolterodine	6	3159	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.89, 2.27]
1.6.8 Trospium	2	1113	Risk Ratio (M-H, Fixed, 95% CI)	2.21 [0.77, 6.32]
1.7 Adverse events: Blurred vision	32	18639	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [1.26, 1.99]
1.7.1 Darifenacin	1	324	Risk Ratio (M-H, Fixed, 95% CI)	2.55 [0.12, 52.58]
1.7.2 Fesoterodine	2	695	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.05, 1.04]
1.7.3 Imidafenacin	2	973	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.49, 4.20]
1.7.4 Oxybutynin	3	521	Risk Ratio (M-H, Fixed, 95% CI)	1.92 [0.80, 4.60]
1.7.5 Propantheline	1	80	Risk Ratio (M-H, Fixed, 95% CI)	2.45 [0.12, 49.36]
1.7.6 Propiverine	4	2527	Risk Ratio (M-H, Fixed, 95% CI)	2.15 [1.29, 3.59]
1.7.7 Solifenacin	12	8435	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [1.06, 2.05]
1.7.8 Tolterodine	8	4221	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [0.90, 3.66]
1.7.9 Trospium	2	863	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.35, 4.00]
1.8 Adverse events: Constipation	53	37317	Risk Ratio (M-H, Random, 95% CI)	2.03 [1.78, 2.31]
1.8.1 Darifenacin	5	2118	Risk Ratio (M-H, Random, 95% CI)	2.59 [1.89, 3.55]
1.8.2 Fesoterodine	11	8450	Risk Ratio (M-H, Random, 95% CI)	2.30 [1.81, 2.92]
1.8.3 Imidafenacin	3	1459	Risk Ratio (M-H, Random, 95% CI)	1.75 [1.04, 2.93]
1.8.4 Oxybutynin	3	521	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.71, 1.63]
1.8.5 Propantheline	1	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.8.6 Propiverine	5	3907	Risk Ratio (M-H, Random, 95% CI)	2.93 [1.84, 4.67]
1.8.7 Solifenacin	10	7652	Risk Ratio (M-H, Random, 95% CI)	2.41 [1.70, 3.41]
1.8.8 Tolterodine	16	10804	Risk Ratio (M-H, Random, 95% CI)	1.34 [1.06, 1.70]
1.8.9 Trospium	4	2326	Risk Ratio (M-H, Random, 95% CI)	3.13 [1.75, 5.59]
1.9 Adverse events: Cough	6	3853	Odds Ratio (M-H, Fixed, 95% CI)	2.57 [1.39, 4.77]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.9.1 Fesoterodine	5	3195	Odds Ratio (M-H, Fixed, 95% CI)	2.17 [1.13, 4.18]
1.9.2 Trospium	1	658	Odds Ratio (M-H, Fixed, 95% CI)	8.17 [1.02, 65.73]
1.10 Adverse events: Dizziness	23	12444	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [1.09, 1.74]
1.10.1 Fesoterodine	4	2612	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.65, 1.93]
1.10.2 Imidafenacin	1	201	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.15, 7.03]
1.10.3 Oxybutynin	2	394	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.25, 5.62]
1.10.4 Propantheline	1	80	Risk Ratio (M-H, Fixed, 95% CI)	4.42 [0.25, 79.12]
1.10.5 Propiverine	2	1209	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.29, 4.57]
1.10.6 Solifenacin	5	1900	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.74, 2.44]
1.10.7 Tolterodine	10	6048	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [1.09, 2.01]
1.11 Adverse events: Dry eyes	9	6897	Risk Ratio (M-H, Fixed, 95% CI)	1.86 [1.23, 2.83]
1.11.1 Fesoterodine	5	3110	Risk Ratio (M-H, Fixed, 95% CI)	2.58 [1.31, 5.08]
1.11.2 Solifenacin	1	768	Risk Ratio (M-H, Fixed, 95% CI)	5.94 [0.72, 49.09]
1.11.3 Tolterodine	3	2418	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.61, 2.02]
1.11.4 Trospium	1	601	Risk Ratio (M-H, Fixed, 95% CI)	4.07 [0.46, 36.18]
1.12 Adverse events: Dyspepsia/indigestion	22	12699	Risk Ratio (M-H, Fixed, 95% CI)	2.24 [1.70, 2.94]
1.12.1 Darifenacin	3	1324	Risk Ratio (M-H, Fixed, 95% CI)	2.99 [1.53, 5.87]
1.12.2 Fesoterodine	4	2208	Risk Ratio (M-H, Fixed, 95% CI)	4.86 [1.90, 12.45]
1.12.3 Imidafenacin	1	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.12.4 Oxybutynin	2	451	Risk Ratio (M-H, Fixed, 95% CI)	2.85 [1.06, 7.67]
1.12.5 Propiverine	1	988	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [0.26, 16.34]
1.12.6 Solifenacin	5	2750	Risk Ratio (M-H, Fixed, 95% CI)	3.43 [1.53, 7.67]
1.12.7 Tolterodine	7	4176	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.90, 2.00]
1.12.8 Trospium	1	601	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [0.51, 8.06]
1.13 Adverse events: Flu-like symptoms/fatigue	13	8674	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.89, 1.59]

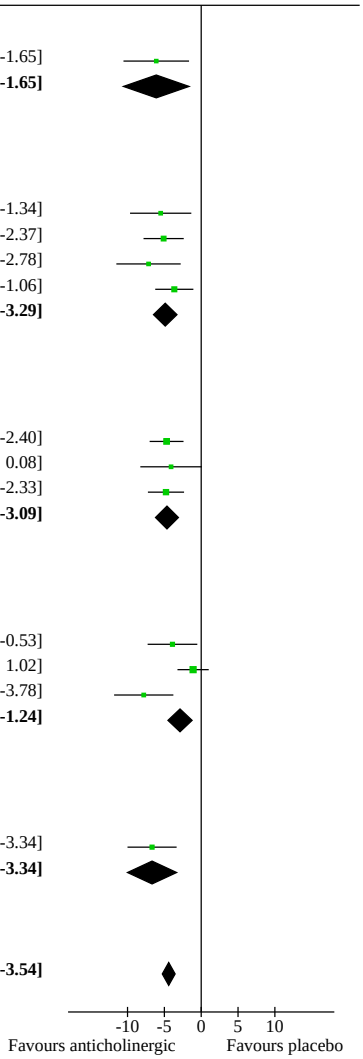
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.13.1 Darifenacin	1	324	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.15, 1.71]
1.13.2 Fesoterodine	6	3792	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.64, 1.38]
1.13.3 Oxybutynin	1	89	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.05, 30.10]
1.13.4 Propantheline	1	80	Risk Ratio (M-H, Fixed, 95% CI)	4.42 [0.25, 79.12]
1.13.5 Solifenacin	3	1822	Risk Ratio (M-H, Fixed, 95% CI)	2.19 [0.93, 5.16]
1.13.6 Tolterodine	3	2567	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [0.87, 3.13]
1.14 Adverse events: Headache	41	25568	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [1.05, 1.36]
1.14.1 Darifenacin	4	1719	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [1.01, 2.84]
1.14.2 Fesoterodine	10	7449	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.99, 1.58]
1.14.3 Imidafenacin	2	973	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.51, 3.10]
1.14.4 Oxybutynin	2	394	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.26, 2.12]
1.14.5 Propantheline	1	80	Risk Ratio (M-H, Fixed, 95% CI)	3.44 [0.18, 64.17]
1.14.6 Propiverine	2	1209	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [0.41, 5.88]
1.14.7 Solifenacin	6	2700	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.54, 1.20]
1.14.8 Tolterodine	15	8709	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.01, 1.56]
1.14.9 Trospium	4	2335	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.69, 1.60]
1.15 Adverse events: Insomnia (unable to sleep)	5	4391	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.83, 2.32]
1.15.1 Fesoterodine	3	2456	Risk Ratio (M-H, Fixed, 95% CI)	1.89 [0.93, 3.85]
1.15.2 Tolterodine	2	1935	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.43, 1.98]
1.16 Adverse events: Nasopharyngitis/sore throat	17	9833	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.63, 0.93]
1.16.1 Darifenacin	1	324	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.32, 2.26]
1.16.2 Fesoterodine	5	3013	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.59, 1.49]
1.16.3 Imidafenacin	3	1459	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.55, 1.00]
1.16.4 Solifenacin	3	1726	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.29, 0.91]
1.16.5 Tolterodine	5	2653	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.49, 1.16]
1.16.6 Trospium	1	658	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.50, 2.34]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.17 Adverse events: Nausea	23	13605	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.79, 1.23]
1.17.1 Darifenacin	1	439	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [0.56, 5.06]
1.17.2 Fesoterodine	6	3740	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.61, 1.40]
1.17.3 Imidafenacin	1	201	Risk Ratio (M-H, Fixed, 95% CI)	3.03 [0.12, 73.50]
1.17.4 Oxybutynin	2	235	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.24, 1.79]
1.17.5 Propantheline	1	80	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.25, 5.80]
1.17.6 Propiverine	2	1359	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.53, 2.34]
1.17.7 Solifenacin	4	2290	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.71, 1.90]
1.17.8 Tolterodine	8	4660	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.54, 1.26]
1.17.9 Trospium	1	601	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.26, 9.06]
1.18 Adverse events: Pruritus/erythema	3	981	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [0.44, 9.55]
1.18.1 Fesoterodine	1	562	Risk Ratio (M-H, Fixed, 95% CI)	5.00 [0.24, 103.68]
1.18.2 Solifenacin	2	419	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.19, 8.13]
1.19 Adverse events: Urinary tract infection (UTI)	22	17541	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [1.02, 1.48]
1.19.1 Darifenacin	2	763	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.66, 2.03]
1.19.2 Fesoterodine	7	6312	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.86, 1.87]
1.19.3 Solifenacin	5	2641	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.97, 2.05]
1.19.4 Tolterodine	8	6566	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.72, 1.36]
1.19.5 Trospium	2	1259	Risk Ratio (M-H, Fixed, 95% CI)	2.01 [0.98, 4.10]
1.20 Withdrawal due to adverse events	61	36943	Risk Ratio (M-H, Random, 95% CI)	1.37 [1.21, 1.56]
1.20.1 Darifenacin	5	1836	Risk Ratio (M-H, Random, 95% CI)	1.66 [0.84, 3.27]
1.20.2 Fesoterodine	13	11246	Risk Ratio (M-H, Random, 95% CI)	1.69 [1.39, 2.06]
1.20.3 Imidafenacin	3	1668	Risk Ratio (M-H, Random, 95% CI)	1.86 [0.29, 11.81]
1.20.4 Oxybutynin	3	376	Risk Ratio (M-H, Random, 95% CI)	2.06 [0.89, 4.80]
1.20.5 Propantheline	1	80	Risk Ratio (M-H, Random, 95% CI)	3.44 [0.18, 64.17]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.20.6 Propiverine	7	3858	Risk Ratio (M-H, Random, 95% CI)	1.74 [1.01, 3.01]
1.20.7 Solifenacin	14	7095	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.02, 1.71]
1.20.8 Tolterodine	16	8142	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.75, 1.25]
1.20.9 Trospium	6	2642	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.88, 1.99]
1.21 Mean number of micturitions per 24 hours	30	19395	Mean Difference (IV, Fixed, 95% CI)	-0.85 [-0.98, -0.73]
1.21.1 Tolterodine	12	6190	Mean Difference (IV, Fixed, 95% CI)	-0.71 [-0.95, -0.47]
1.21.2 Solifenacin	7	3109	Mean Difference (IV, Fixed, 95% CI)	-1.02 [-1.33, -0.72]
1.21.3 Fesoterodine	9	6201	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-1.12, -0.67]
1.21.4 Oxybutynin	1	59	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-2.47, 1.07]
1.21.5 Propiverine	4	2772	Mean Difference (IV, Fixed, 95% CI)	-0.89 [-1.20, -0.57]
1.21.6 Imidafenacin	3	1064	Mean Difference (IV, Fixed, 95% CI)	-0.76 [-1.18, -0.35]

Analysis 1.1. Comparison 1: Anticholinergics versus placebo, Outcome 1: Mean change from baseline in condition-specific quality of life

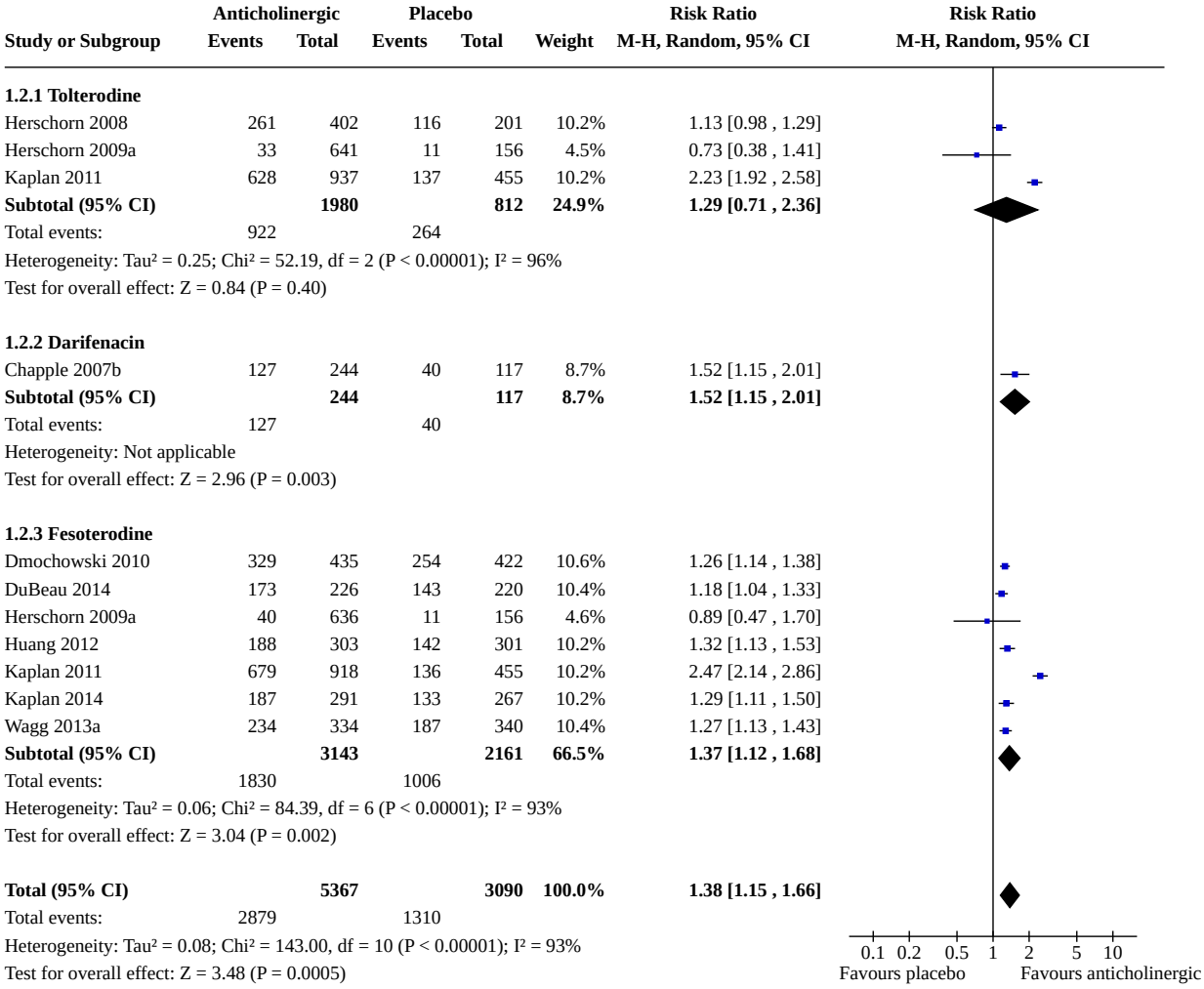
Study or Subgroup	Anticholinergic Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 Darifenacin								
Chapple 2007b	-22.9	21.38	266	-16.8	21.38	133	3.8%	-6.10 [-10.55 , -1.65]
Subtotal (95% CI)			**266**			**133**	**3.8%**	**-6.10 [-10.55 , -1.65]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.69 (P = 0.007)								
1.1.2 Fesoterodine								
DuBeau 2014	-23.1	25.1446	281	-17.6	25.1446	281	4.4%	-5.50 [-9.66 , -1.34]
Huang 2012	-17.1	17.6	303	-12	16.6	301	10.2%	-5.10 [-7.83 , -2.37]
Kaplan 2014	-21.55	26.381994	286	-14.4	25.980814	267	4.0%	-7.15 [-11.52 , -2.78]
Wagg 2013a	-13.2	17.5	374	-9.55	18.8	382	11.3%	-3.65 [-6.24 , -1.06]
Subtotal (95% CI)			**1244**			**1231**	**29.9%**	**-4.88 [-6.48 , -3.29]**
Heterogeneity: Chi² = 2.02, df = 3 (P = 0.57); I² = 0%								
Test for overall effect: Z = 6.01 (P < 0.00001)								
1.1.3 Solifenacin								
Chua 2018	-8.1	5.12	31	-3.4	4.12	32	14.3%	-4.70 [-7.00 , -2.40]
De Ridder 2012 (1)	-7.95	4.33	136	-3.86	13.26	40	4.4%	-4.09 [-8.26 , 0.08]
Herschorn 2017a	-20.15	17.7777	399	-15.37	17.6	400	12.6%	-4.78 [-7.23 , -2.33]
Subtotal (95% CI)			**566**			**472**	**31.3%**	**-4.65 [-6.20 , -3.09]**
Heterogeneity: Chi² = 0.08, df = 2 (P = 0.96); I² = 0%								
Test for overall effect: Z = 5.85 (P < 0.00001)								
1.1.4 Tolterodine								
Herschorn 2008	-19.2	20.049938	402	-15.3	19.848426	201	6.7%	-3.90 [-7.27 , -0.53]
Khullar 2013	-14.8	16.6932	470	-13.7	16.5289	473	16.9%	-1.10 [-3.22 , 1.02]
Rogers 2008	-29.5	20.291624	183	-21.7	19.246818	189	4.7%	-7.80 [-11.82 , -3.78]
Subtotal (95% CI)			**1055**			**863**	**28.2%**	**-2.87 [-4.51 , -1.24]**
Heterogeneity: Chi² = 8.81, df = 2 (P = 0.01); I² = 77%								
Test for overall effect: Z = 3.44 (P = 0.0006)								
1.1.5 Propiverine								
Junemann 2006	-19.82	21.86	775	-13.15	21.28	199	6.8%	-6.67 [-10.00 , -3.34]
Subtotal (95% CI)			**775**			**199**	**6.8%**	**-6.67 [-10.00 , -3.34]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.92 (P < 0.0001)								
Total (95% CI)			**3906**			**2898**	**100.0%**	**-4.41 [-5.28 , -3.54]**
Heterogeneity: Chi² = 17.02, df = 11 (P = 0.11); I² = 35%								
Test for overall effect: Z = 9.93 (P < 0.00001)								
Test for subgroup differences: Chi² = 6.12, df = 4 (P = 0.19), I² = 34.6%								



Footnotes

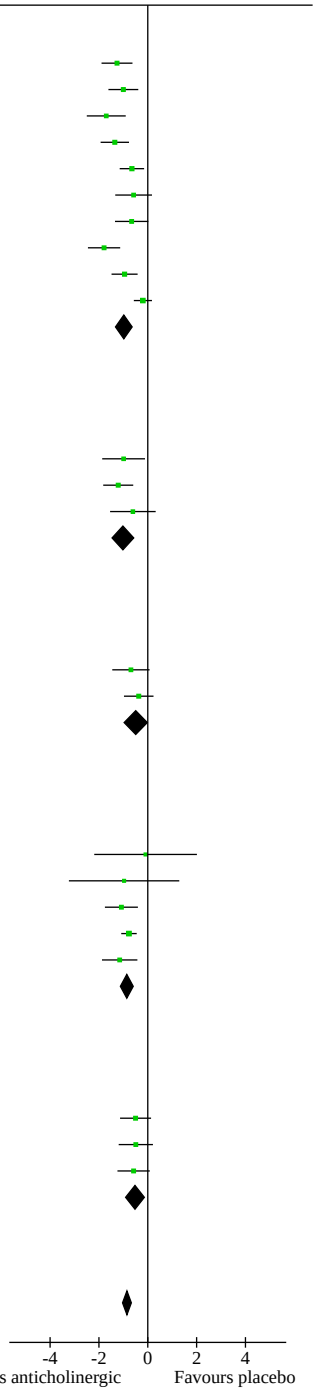
(1) IQoL total score

Analysis 1.2. Comparison 1: Anticholinergics versus placebo, Outcome 2: Patient perception of cure or improvement



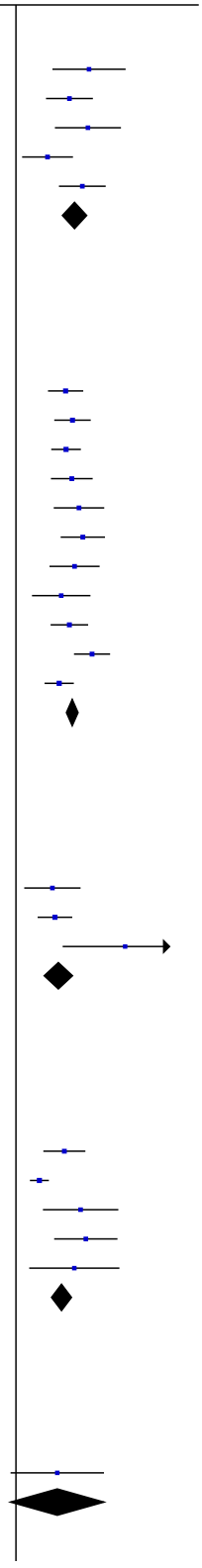
Analysis 1.3. Comparison 1: Anticholinergics versus placebo, Outcome 3: Mean number of urgency episodes per 24 hours

Study or Subgroup	Anticholinergic Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.3.1 Fesoterodine								
Chapple 2007a	9.07	4.4	823	10.33	4.75	279	4.7%	-1.26 [-1.89 , -0.63]
Dmochowski 2010	5.2	4.4	428	6.2	4.75	434	4.9%	-1.00 [-1.61 , -0.39]
DuBeau 2014	5.85	4.4	256	7.55	4.75	251	3.5%	-1.70 [-2.50 , -0.90]
Herschorn 2009a	6.01	4.4	1259	7.36	4.75	311	5.1%	-1.35 [-1.93 , -0.77]
Kaplan 2011	5.85	4.4	1848	6.5	4.75	413	6.0%	-0.65 [-1.15 , -0.15]
Kaplan 2014	7.89	4.4	292	8.47	4.75	279	3.8%	-0.58 [-1.33 , 0.17]
Nitti 2007	9.95	4.4	534	10.61	4.75	266	4.3%	-0.66 [-1.34 , 0.02]
Wagg 2013a	4.7	4.4	365	6.49	4.75	373	4.4%	-1.79 [-2.45 , -1.13]
Yamaguchi 2007	1.81	4.4	1138	2.76	4.75	395	5.6%	-0.95 [-1.48 , -0.42]
Yonguc 2019	1.6	0.8	32	1.8	0.7	31	7.5%	-0.20 [-0.57 , 0.17]
Subtotal (95% CI)			**6975**			**3032**	**49.7%**	**-0.98 [-1.32 , -0.64]**
Heterogeneity: Tau² = 0.21; Chi² = 30.16, df = 9 (P = 0.0004); I² = 70%								
Test for overall effect: Z = 5.64 (P < 0.00001)								
1.3.2 Imidafenacin								
Homma 2008	1.85	2.51	93	2.84	3.54	95	3.1%	-0.99 [-1.87 , -0.11]
Homma 2009	2.27	2.86	623	3.48	3.49	143	4.8%	-1.21 [-1.82 , -0.60]
Yoshida 2018	1.39	4.4	117	2	4.75	369	2.8%	-0.61 [-1.54 , 0.32]
Subtotal (95% CI)			**833**			**607**	**10.7%**	**-1.02 [-1.46 , -0.58]**
Heterogeneity: Tau² = 0.00; Chi² = 1.11, df = 2 (P = 0.57); I² = 0%								
Test for overall effect: Z = 4.51 (P < 0.00001)								
1.3.3 Propiverine								
Gotoh 2011	1.49	4.4	284	2.18	4.75	270	3.7%	-0.69 [-1.45 , 0.07]
Yamaguchi 2014	1.8	4.4	559	2.17	4.75	373	4.9%	-0.37 [-0.97 , 0.23]
Subtotal (95% CI)			**843**			**643**	**8.6%**	**-0.49 [-0.97 , -0.02]**
Heterogeneity: Tau² = 0.00; Chi² = 0.41, df = 1 (P = 0.52); I² = 0%								
Test for overall effect: Z = 2.04 (P = 0.04)								
1.3.4 Solifenacin								
Chapple 2004b	4.08	4.4	37	4.17	4.75	36	0.7%	-0.09 [-2.19 , 2.01]
Chua 2018	2.81	4.4	31	3.78	4.75	32	0.6%	-0.97 [-3.23 , 1.29]
Karram 2009	2.25	4.4	357	3.33	4.75	350	4.3%	-1.08 [-1.76 , -0.40]
Oreskovic 2012	5.77	1.33	77	6.54	0.5	80	8.2%	-0.77 [-1.09 , -0.45]
Vardy 2009	2.65	4.4	374	3.8	4.75	266	4.0%	-1.15 [-1.87 , -0.43]
Subtotal (95% CI)			**876**			**764**	**17.8%**	**-0.86 [-1.12 , -0.60]**
Heterogeneity: Tau² = 0.00; Chi² = 1.86, df = 4 (P = 0.76); I² = 0%								
Test for overall effect: Z = 6.41 (P < 0.00001)								
1.3.5 Tolterodine								
Junemann 2006	3.94	3.48	723	4.44	4.06	187	4.7%	-0.50 [-1.13 , 0.13]
Kuo 2015	3.09	4.4	333	3.58	4.75	323	4.1%	-0.49 [-1.19 , 0.21]
Yamaguchi 2012	2.47	4.4	368	3.05	4.75	368	4.4%	-0.58 [-1.24 , 0.08]
Subtotal (95% CI)			**1424**			**878**	**13.2%**	**-0.52 [-0.91 , -0.14]**
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 2 (P = 0.98); I² = 0%								
Test for overall effect: Z = 2.68 (P = 0.007)								
Total (95% CI)			**10951**			**5924**	**100.0%**	**-0.85 [-1.03 , -0.67]**
Heterogeneity: Tau² = 0.08; Chi² = 38.74, df = 22 (P = 0.02); I² = 43%								
Test for overall effect: Z = 9.30 (P < 0.00001)								
Test for subgroup differences: Chi² = 5.81, df = 4 (P = 0.21), I² = 31.1%								



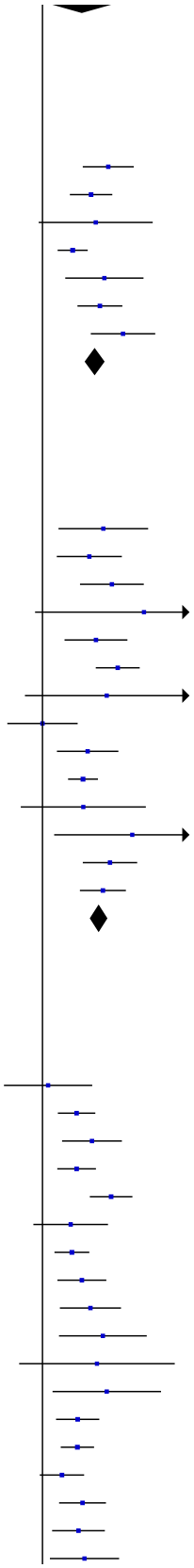
Analysis 1.4. Comparison 1: Anticholinergics versus placebo, Outcome 4: Adverse events: Dry mouth

Study or Subgroup	Anticholinergic Events	Anticholinergic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Darifenacin						
Chapple 2007b	59	266	5	133	0.6%	5.90 [2.43 , 14.35]
Haab 2004	36	115	14	164	1.1%	3.67 [2.07 , 6.48]
Hill 2005	68	215	6	109	0.8%	5.75 [2.58 , 12.82]
Steers 2004	50	268	11	127	1.4%	2.15 [1.16 , 3.99]
Zinner 2006	62	214	13	225	1.2%	5.01 [2.84 , 8.85]
Subtotal (95% CI)		**1078**		**758**	**5.1%**	**4.15 [3.09 , 5.57]**
Total events:	275		49			
Heterogeneity: Chi² = 6.17, df = 4 (P = 0.19); I² = 35%						
Test for overall effect: Z = 9.46 (P < 0.00001)						
1.4.2 Fesoterodine						
Chapple 2004a	199	545	20	183	2.8%	3.34 [2.18 , 5.13]
Chapple 2007a	156	559	20	283	2.5%	3.95 [2.54 , 6.15]
Dmochowski 2010	113	438	34	445	3.2%	3.38 [2.36 , 4.84]
DuBeau 2014	66	281	17	281	1.6%	3.88 [2.34 , 6.44]
Herschorn 2009a	188	679	10	167	1.5%	4.62 [2.50 , 8.54]
Kaplan 2011	265	960	13	239	2.0%	5.07 [2.96 , 8.70]
Kaplan 2014	51	308	12	301	1.1%	4.15 [2.26 , 7.63]
Nitti 2005	44	90	7	43	0.9%	3.00 [1.48 , 6.11]
Nitti 2007	144	561	19	271	2.4%	3.66 [2.32 , 5.78]
Wagg 2013a	133	392	21	393	2.0%	6.35 [4.10 , 9.84]
Weiss 2013	98	381	36	400	3.3%	2.86 [2.00 , 4.08]
Subtotal (95% CI)		**5194**		**3006**	**23.3%**	**3.92 [3.41 , 4.52]**
Total events:	1457		209			
Heterogeneity: Chi² = 10.72, df = 10 (P = 0.38); I² = 7%						
Test for overall effect: Z = 18.93 (P < 0.00001)						
1.4.3 Imidafenacin						
Homma 2008	24	100	10	101	0.9%	2.42 [1.22 , 4.80]
Homma 2009	223	627	20	145	3.1%	2.58 [1.69 , 3.93]
Yoshida 2018	9	117	2	369	0.1%	14.19 [3.11 , 64.76]
Subtotal (95% CI)		**844**		**615**	**4.1%**	**2.80 [1.99 , 3.95]**
Total events:	256		32			
Heterogeneity: Chi² = 4.71, df = 2 (P = 0.09); I² = 58%						
Test for overall effect: Z = 5.87 (P < 0.00001)						
1.4.4 Oxybutynin						
Abrams 1998	161	236	12	57	1.8%	3.24 [1.95 , 5.40]
Burgio 1998	63	65	34	62	3.3%	1.77 [1.40 , 2.22]
Drutz 1999	77	112	4	28	0.6%	4.81 [1.93 , 12.03]
Homma 2003	131	244	6	61	0.9%	5.46 [2.53 , 11.77]
Thuroff 1991	30	63	3	26	0.4%	4.13 [1.38 , 12.34]
Subtotal (95% CI)		**720**		**234**	**7.0%**	**3.02 [2.37 , 3.85]**
Total events:	462		59			
Heterogeneity: Chi² = 24.57, df = 4 (P < 0.0001); I² = 84%						
Test for overall effect: Z = 8.96 (P < 0.00001)						
1.4.5 Propantheline						
Thuroff 1991	17	54	3	26	0.4%	2.73 [0.88 , 8.49]
Subtotal (95% CI)		**54**		**26**	**0.4%**	**2.73 [0.88 , 8.49]**
Total events:	17		3			
Heterogeneity: Not applicable						



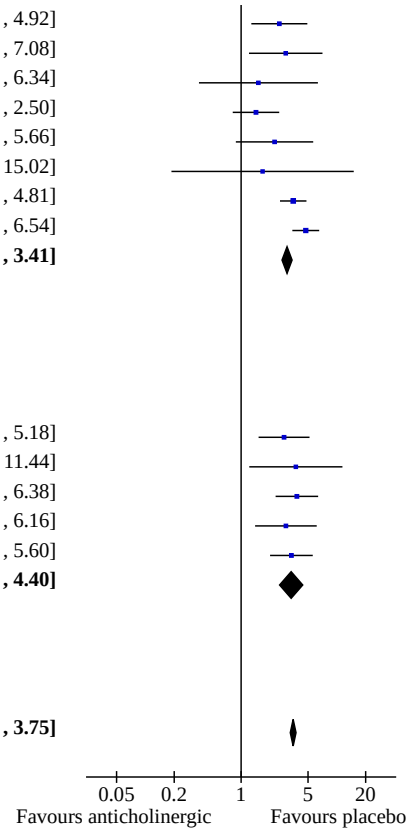
Analysis 1.4. (Continued)

Total events:	17		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.73 (P = 0.08)						
1.4.6 Propiverine						
Gotoh 2011	57	291	10	274	1.0%	5.37 [2.80 , 10.30]
Junemann 2006	175	786	13	202	1.9%	3.46 [2.01 , 5.95]
Lee 2006	14	142	2	79	0.2%	3.89 [0.91 , 16.70]
Madersbacher 1999	173	288	20	72	3.0%	2.16 [1.47 , 3.18]
Stohrer 1999	22	60	4	53	0.4%	4.86 [1.79 , 13.20]
Yamaguchi 2007	103	400	12	202	1.5%	4.33 [2.44 , 7.69]
Yamaguchi 2014	70	534	6	358	0.7%	7.82 [3.43 , 17.81]
Subtotal (95% CI)		**2501**		**1240**	**8.8%**	**3.79 [3.00 , 4.78]**
Total events:	614		67			
Heterogeneity: Chi² = 12.82, df = 6 (P = 0.05); I² = 53%						
Test for overall effect: Z = 11.19 (P < 0.00001)						
1.4.7 Solifenacin						
Abrams 2013	41	234	3	81	0.4%	4.73 [1.51 , 14.86]
Cardozo 2004a	23	299	7	301	0.7%	3.31 [1.44 , 7.59]
Cardozo 2008a	80	505	6	223	0.8%	5.89 [2.61 , 13.30]
Chapple 2004b	19	107	0	36	0.1%	13.36 [0.83 , 215.84]
Chapple 2004c	96	547	6	134	0.9%	3.92 [1.76 , 8.75]
Chu 2009	91	340	13	332	1.2%	6.84 [3.90 , 11.98]
Chua 2018	5	31	1	32	0.1%	5.16 [0.64 , 41.71]
Elbaset 2019	8	50	8	50	0.8%	1.00 [0.41 , 2.46]
Herschorn 2017a	25	423	8	429	0.7%	3.17 [1.45 , 6.95]
Karram 2009	89	357	31	350	3.0%	2.81 [1.92 , 4.12]
Kosilov 2015a	5	52	2	59	0.2%	2.84 [0.57 , 14.01]
Kosilov 2015b	20	206	1	102	0.1%	9.90 [1.35 , 72.76]
Vardy 2009	51	386	9	382	0.9%	5.61 [2.80 , 11.23]
Yamaguchi 2007	197	777	11	203	1.6%	4.68 [2.60 , 8.42]
Subtotal (95% CI)		**4314**		**2714**	**11.4%**	**4.19 [3.42 , 5.14]**
Total events:	750		106			
Heterogeneity: Chi² = 20.88, df = 13 (P = 0.08); I² = 38%						
Test for overall effect: Z = 13.74 (P < 0.00001)						
1.4.8 Tolterodine						
Abrams 1996	12	52	3	15	0.4%	1.15 [0.37 , 3.56]
Cardozo 2000	43	104	18	104	1.7%	2.39 [1.48 , 3.85]
Chapple 2004c	49	263	7	133	0.9%	3.54 [1.65 , 7.60]
Chapple 2007a	49	290	20	283	1.9%	2.39 [1.46 , 3.92]
Chapple 2014	305	1569	13	386	2.0%	5.77 [3.35 , 9.94]
Drutz 1999	32	109	4	28	0.6%	2.06 [0.79 , 5.33]
Herschorn 2008	89	408	21	204	2.6%	2.12 [1.36 , 3.31]
Herschorn 2009a	112	684	10	167	1.5%	2.73 [1.46 , 5.11]
Homma 2003	80	239	6	61	0.9%	3.40 [1.56 , 7.43]
Jacquetin 2001	55	200	3	51	0.5%	4.67 [1.52 , 14.34]
Jonas 1997	18	197	1	44	0.2%	4.02 [0.55 , 29.32]
Junemann 2000	21	63	2	31	0.3%	5.17 [1.29 , 20.64]
Kaplan 2011	130	973	13	239	2.0%	2.46 [1.41 , 4.27]
Khullar 2004	112	569	23	285	2.9%	2.44 [1.59 , 3.73]
Kuo 2015	30	371	18	366	1.7%	1.64 [0.93 , 2.90]
Malone-Lee 2001	78	134	9	43	1.3%	2.78 [1.53 , 5.06]
Millard 1999	79	252	8	64	1.2%	2.51 [1.28 , 4.92]
Mitcheson 2019	22	257	6	205	0.6%	2.92 [1.21 , 7.08]



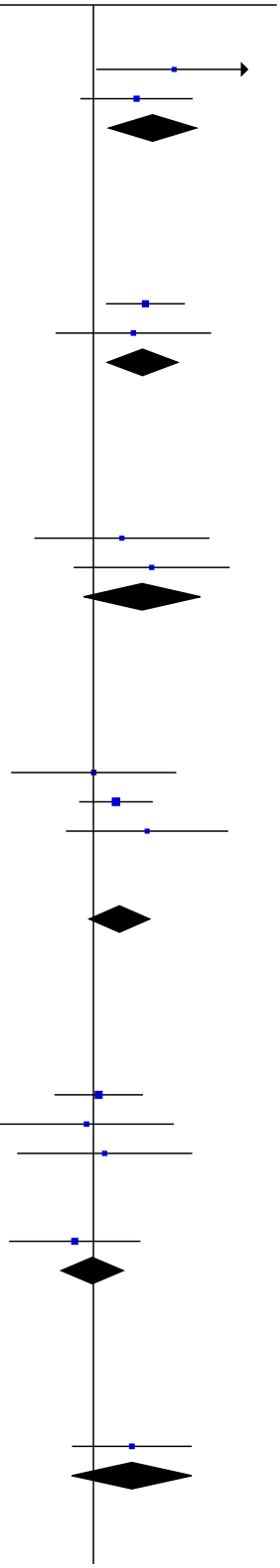
Analysis 1.4. (Continued)

Millard 1999	79	252	8	64	1.2%	2.51 [1.28 , 4.92]
Mitcheson 2019	22	257	6	205	0.6%	2.92 [1.21 , 7.08]
Rentzhog 1998	7	30	2	13	0.3%	1.52 [0.36 , 6.34]
Rogers 2008	26	201	19	210	1.8%	1.43 [0.82 , 2.50]
Rovner 2005	12	77	6	86	0.5%	2.23 [0.88 , 5.66]
Van Kerrebroeck 1998	3	34	1	19	0.1%	1.68 [0.19 , 15.02]
Van Kerrebroeck 2001	274	1017	39	507	4.9%	3.50 [2.55 , 4.81]
Zinner 2002	184	505	39	507	3.7%	4.74 [3.43 , 6.54]
Subtotal (95% CI)		**8598**		**4051**	**34.3%**	**3.02 [2.68 , 3.41]**
Total events:	1822		291			
Heterogeneity: Chi² = 37.73, df = 23 (P = 0.03); I² = 39%						
Test for overall effect: Z = 17.94 (P < 0.00001)						
1.4.9 Trospium						
Dmochowski 2008	36	280	13	284	1.2%	2.81 [1.52 , 5.18]
Junemann 2000	22	57	3	29	0.4%	3.73 [1.22 , 11.44]
Rudy 2006	65	329	17	329	1.6%	3.82 [2.29 , 6.38]
Staskin 2007	26	298	9	303	0.8%	2.94 [1.40 , 6.16]
Zinner 2004	57	256	17	256	1.6%	3.35 [2.01 , 5.60]
Subtotal (95% CI)		**1220**		**1201**	**5.6%**	**3.33 [2.52 , 4.40]**
Total events:	206		59			
Heterogeneity: Chi² = 0.73, df = 4 (P = 0.95); I² = 0%						
Test for overall effect: Z = 8.48 (P < 0.00001)						
Total (95% CI)		**24523**		**13845**	**100.0%**	**3.50 [3.26 , 3.75]**
Total events:	5859		875			
Heterogeneity: Chi² = 142.91, df = 74 (P < 0.00001); I² = 48%						
Test for overall effect: Z = 35.67 (P < 0.00001)						
Test for subgroup differences: Chi² = 16.23, df = 8 (P = 0.04), I² = 50.7%						



Analysis 1.5. Comparison 1: Anticholinergics versus placebo, Outcome 5: Adverse events: Urinary retention/high residual volume

Study or Subgroup	Anticholinergic Events	Anticholinergic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.1 Fesoterodine						
DuBeau 2014	9	281	0	281	2.9%	19.00 [1.11 , 324.88]
Nitti 2007	10	561	1	271	7.8%	4.83 [0.62 , 37.54]
Subtotal (95% CI)		**842**		**552**	**10.7%**	**8.66 [1.76 , 42.65]**
Total events:	19		1			
Heterogeneity: Chi² = 0.61, df = 1 (P = 0.44); I² = 0%						
Test for overall effect: Z = 2.65 (P = 0.008)						
1.5.2 Oxybutynin						
Burgio 1998	14	65	2	62	11.8%	6.68 [1.58 , 28.19]
Homma 2003	8	244	0	61	4.6%	4.30 [0.25 , 73.52]
Subtotal (95% CI)		**309**		**123**	**16.4%**	**6.01 [1.67 , 21.69]**
Total events:	22		2			
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%						
Test for overall effect: Z = 2.74 (P = 0.006)						
1.5.3 Propiverine						
Gotoh 2011	1	291	0	274	3.0%	2.83 [0.12 , 69.06]
Lee 2006	7	142	0	79	3.7%	8.39 [0.49 , 145.01]
Subtotal (95% CI)		**433**		**353**	**6.7%**	**5.91 [0.71 , 49.48]**
Total events:	8		0			
Heterogeneity: Chi² = 0.26, df = 1 (P = 0.61); I² = 0%						
Test for overall effect: Z = 1.64 (P = 0.10)						
1.5.4 Solifenacin						
Chapple 2004b	2	187	0	37	4.8%	1.01 [0.05 , 20.63]
Chu 2009	7	340	3	332	17.5%	2.28 [0.59 , 8.74]
Herschorn 2017a	3	423	0	429	2.9%	7.10 [0.37 , 137.02]
Kosilov 2015a	0	52	0	59		Not estimable
Kosilov 2015b	0	206	0	102		Not estimable
Subtotal (95% CI)		**1208**		**959**	**25.1%**	**2.59 [0.86 , 7.77]**
Total events:	12		3			
Heterogeneity: Chi² = 0.85, df = 2 (P = 0.65); I² = 0%						
Test for overall effect: Z = 1.69 (P = 0.09)						
1.5.5 Tolterodine						
Abrams 2001	5	149	2	72	15.5%	1.21 [0.24 , 6.08]
Homma 2003	1	239	0	61	4.6%	0.78 [0.03 , 18.79]
Khullar 2004	1	569	0	285	3.8%	1.51 [0.06 , 36.83]
Rentzhog 1998	0	30	0	13		Not estimable
Van Kerrebroeck 1998	0	34	0	19		Not estimable
Zinner 2002	1	503	2	508	11.5%	0.50 [0.05 , 5.55]
Subtotal (95% CI)		**1524**		**958**	**35.4%**	**0.96 [0.31 , 2.96]**
Total events:	8		4			
Heterogeneity: Chi² = 0.45, df = 3 (P = 0.93); I² = 0%						
Test for overall effect: Z = 0.08 (P = 0.94)						
1.5.6 Trospium						
Staskin 2007	4	298	1	303	5.7%	4.07 [0.46 , 36.18]
Subtotal (95% CI)		**298**		**303**	**5.7%**	**4.07 [0.46 , 36.18]**
Total events:	4		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.26 (P = 0.21)						

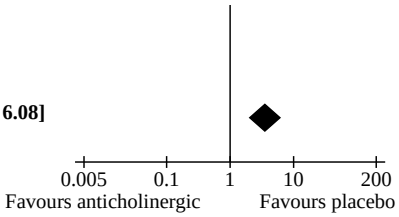


Analysis 1.5. (Continued)

Heterogeneity: Not applicable
Test for overall effect: Z = 1.26 (P = 0.21)

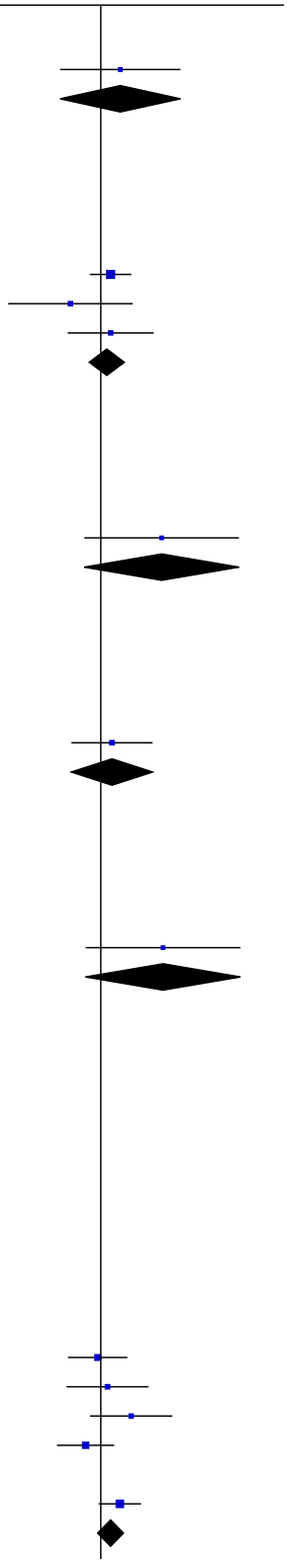
Total (95% CI)	**4614**	**3248**	**100.0%**	**3.52 [2.04 , 6.08]**	
Total events:	73	11			

Heterogeneity: Chi² = 9.24, df = 13 (P = 0.75); I² = 0%
Test for overall effect: Z = 4.52 (P < 0.00001)
Test for subgroup differences: Chi² = 7.29, df = 5 (P = 0.20), I² = 31.4%



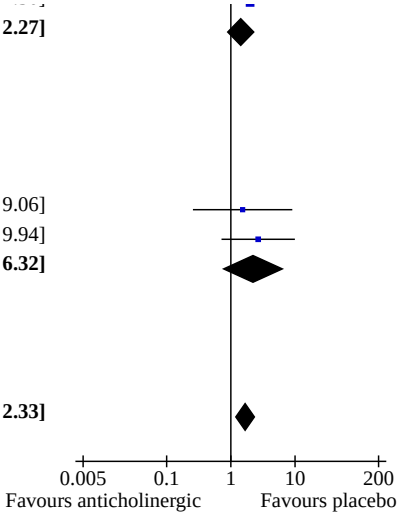
Analysis 1.6. Comparison 1: Anticholinergics versus placebo, Outcome 6: Adverse events: Abdominal pain

Study or Subgroup	Anticholinergic Events	Anticholinergic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.1 Darifenacin						
Hill 2005	4	215	1	109	2.2%	2.03 [0.23 , 17.92]
Subtotal (95% CI)		**215**		**109**	**2.2%**	**2.03 [0.23 , 17.92]**
Total events:	4		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
1.6.2 Fesoterodine						
Chapple 2004a	34	545	8	183	20.2%	1.43 [0.67 , 3.03]
DuBeau 2014	1	281	3	281	5.1%	0.33 [0.03 , 3.19]
Nitti 2005	6	90	2	43	4.6%	1.43 [0.30 , 6.81]
Subtotal (95% CI)		**916**		**507**	**29.8%**	**1.24 [0.66 , 2.34]**
Total events:	41		13			
Heterogeneity: Chi² = 1.47, df = 2 (P = 0.48); I² = 0%						
Test for overall effect: Z = 0.67 (P = 0.50)						
1.6.3 Imidafenacin						
Homma 2009	19	627	0	145	1.4%	9.07 [0.55 , 149.30]
Subtotal (95% CI)		**627**		**145**	**1.4%**	**9.07 [0.55 , 149.30]**
Total events:	19		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.54 (P = 0.12)						
1.6.4 Oxybutynin						
Homma 2003	12	244	2	61	5.4%	1.50 [0.34 , 6.53]
Subtotal (95% CI)		**244**		**61**	**5.4%**	**1.50 [0.34 , 6.53]**
Total events:	12		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						
1.6.5 Propiverine						
Junemann 2006	18	786	0	202	1.3%	9.54 [0.58 , 157.70]
Subtotal (95% CI)		**786**		**202**	**1.3%**	**9.54 [0.58 , 157.70]**
Total events:	18		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.58 (P = 0.11)						
1.6.6 Solifenacin						
Kosilov 2015a	0	52	0	59		Not estimable
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.6.7 Tolterodine						
Homma 2003	14	239	4	61	10.8%	0.89 [0.30 , 2.62]
Jacquetin 2001	10	200	2	51	5.4%	1.27 [0.29 , 5.64]
Khullar 2004	12	569	2	285	4.5%	3.01 [0.68 , 13.34]
Malone-Lee 2001	9	134	5	43	12.8%	0.58 [0.20 , 1.63]
Van Kerrebroeck 1998	0	34	0	19		Not estimable
Van Kerrebroeck 2001	32	1017	8	507	18.0%	1.99 [0.93 , 4.30]
Subtotal (95% CI)		**2193**		**966**	**51.4%**	**1.43 [0.89 , 2.27]**
Total events:	77		21			



Analysis 1.6. (Continued)

Subtotal (95% CI)		**2193**		**966**	**51.4%**	**1.43 [0.89 , 2.27]**
Total events:	77		21			
Heterogeneity: Chi² = 5.35, df = 4 (P = 0.25); I² = 25%						
Test for overall effect: Z = 1.49 (P = 0.14)						
1.6.8 Trospium						
Staskin 2007	3	298	2	303	3.3%	1.53 [0.26 , 9.06]
Zinner 2004	8	256	3	256	5.1%	2.67 [0.72 , 9.94]
Subtotal (95% CI)		**554**		**559**	**8.4%**	**2.21 [0.77 , 6.32]**
Total events:	11		5			
Heterogeneity: Chi² = 0.24, df = 1 (P = 0.62); I² = 0%						
Test for overall effect: Z = 1.48 (P = 0.14)						
Total (95% CI)		**5587**		**2608**	**100.0%**	**1.67 [1.20 , 2.33]**
Total events:	182		42			
Heterogeneity: Chi² = 11.83, df = 13 (P = 0.54); I² = 0%						
Test for overall effect: Z = 3.01 (P = 0.003)						
Test for subgroup differences: Chi² = 4.23, df = 6 (P = 0.65), I² = 0%						

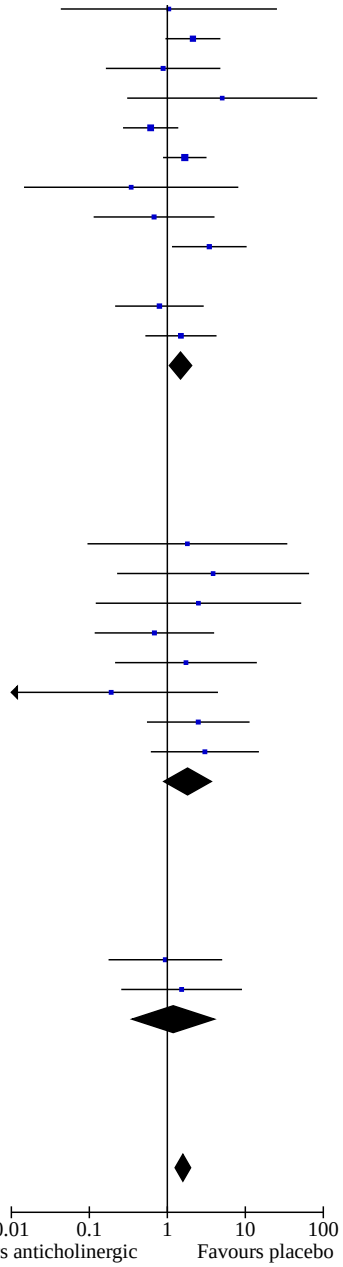


Analysis 1.7. Comparison 1: Anticholinergics versus placebo, Outcome 7: Adverse events: Blurred vision

Study or Subgroup	Anticholinergic Events	Anticholinergic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.7.1 Darifenacin						
Hill 2005	2	215	0	109	0.5%	2.55 [0.12 , 52.58]
Subtotal (95% CI)		**215**		**109**	**0.5%**	**2.55 [0.12 , 52.58]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.61 (P = 0.55)						
1.7.2 Fesoterodine						
DuBeau 2014	0	281	5	281	4.4%	0.09 [0.01 , 1.64]
Nitti 2005	2	90	2	43	2.2%	0.48 [0.07 , 3.28]
Subtotal (95% CI)		**371**		**324**	**6.6%**	**0.22 [0.05 , 1.04]**
Total events:	2		7			
Heterogeneity: Chi² = 0.99, df = 1 (P = 0.32); I² = 0%						
Test for overall effect: Z = 1.91 (P = 0.06)						
1.7.3 Imidafenacin						
Homma 2008	2	100	1	101	0.8%	2.02 [0.19 , 21.92]
Homma 2009	17	627	3	145	3.9%	1.31 [0.39 , 4.41]
Subtotal (95% CI)		**727**		**246**	**4.7%**	**1.43 [0.49 , 4.20]**
Total events:	19		4			
Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%						
Test for overall effect: Z = 0.65 (P = 0.51)						
1.7.4 Oxybutynin						
Burgio 1998	10	65	6	62	4.9%	1.59 [0.61 , 4.11]
Homma 2003	8	244	0	61	0.6%	4.30 [0.25 , 73.52]
Thuroff 1991	2	63	0	26	0.6%	2.11 [0.10 , 42.49]
Subtotal (95% CI)		**372**		**149**	**6.2%**	**1.92 [0.80 , 4.60]**
Total events:	20		6			
Heterogeneity: Chi² = 0.47, df = 2 (P = 0.79); I² = 0%						
Test for overall effect: Z = 1.46 (P = 0.14)						
1.7.5 Propantheline						
Thuroff 1991	2	54	0	26	0.5%	2.45 [0.12 , 49.36]
Subtotal (95% CI)		**54**		**26**	**0.5%**	**2.45 [0.12 , 49.36]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.56)						
1.7.6 Propiverine						
Gotoh 2011	1	291	0	274	0.4%	2.83 [0.12 , 69.06]
Junemann 2006	33	786	1	202	1.3%	8.48 [1.17 , 61.64]
Madersbacher 1999	66	299	10	72	13.0%	1.59 [0.86 , 2.93]
Yamaguchi 2007	15	400	4	203	4.3%	1.90 [0.64 , 5.66]
Subtotal (95% CI)		**1776**		**751**	**18.9%**	**2.15 [1.29 , 3.59]**
Total events:	115		15			
Heterogeneity: Chi² = 2.85, df = 3 (P = 0.41); I² = 0%						
Test for overall effect: Z = 2.94 (P = 0.003)						
1.7.7 Solifenacin						
Abrams 2013	1	234	0	81	0.6%	1.05 [0.04 , 25.44]
Cardozo 2004a	30	606	7	301	7.5%	2.13 [0.95 , 4.79]

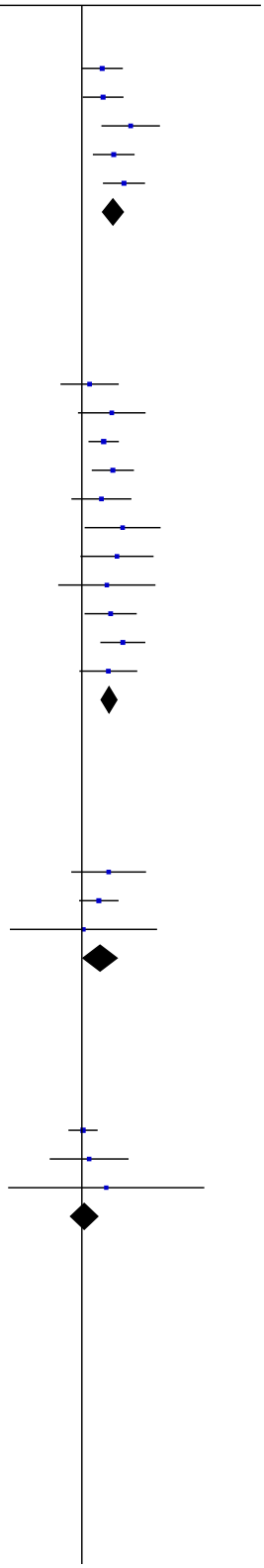
Analysis 1.7. (Continued)

Abrams 2015	1	254	0	61	0.6%	1.03 [0.04 , 25.44]
Cardozo 2004a	30	606	7	301	7.5%	2.13 [0.95 , 4.79]
Cardozo 2008a	4	505	2	223	2.2%	0.88 [0.16 , 4.79]
Chapple 2004b	12	187	0	37	0.7%	5.05 [0.31 , 83.52]
Chapple 2004c	29	1810	7	267	9.8%	0.61 [0.27 , 1.38]
Chu 2009	24	340	14	332	11.4%	1.67 [0.88 , 3.18]
Chua 2018	0	31	1	32	1.2%	0.34 [0.01 , 8.13]
Herschorn 2017a	2	423	3	429	2.4%	0.68 [0.11 , 4.03]
Karram 2009	14	372	4	367	3.2%	3.45 [1.15 , 10.39]
Kosilov 2015a	0	52	0	59		Not estimable
Vardy 2009	4	386	5	382	4.0%	0.79 [0.21 , 2.93]
Yamaguchi 2007	23	777	4	202	5.1%	1.49 [0.52 , 4.27]
Subtotal (95% CI)		**5723**		**2712**	**48.3%**	**1.48 [1.06 , 2.05]**
Total events:	143		47			
Heterogeneity: Chi² = 11.27, df = 10 (P = 0.34); I² = 11%						
Test for overall effect: Z = 2.33 (P = 0.02)						
1.7.8 Tolterodine						
Homma 2003	3	239	0	61	0.6%	1.81 [0.09 , 34.55]
Jonas 1997	8	197	0	44	0.7%	3.86 [0.23 , 65.72]
Khullar 2004	2	569	0	285	0.5%	2.51 [0.12 , 52.08]
Malone-Lee 2001	3	134	2	61	2.2%	0.68 [0.12 , 3.98]
Rentzhog 1998	4	30	1	13	1.1%	1.73 [0.21 , 14.05]
Van Kerrebroeck 1998	0	34	1	19	1.5%	0.19 [0.01 , 4.46]
Van Kerrebroeck 2001	10	1017	2	507	2.1%	2.49 [0.55 , 11.33]
Zinner 2002	6	503	2	508	1.6%	3.03 [0.61 , 14.94]
Subtotal (95% CI)		**2723**		**1498**	**10.5%**	**1.82 [0.90 , 3.66]**
Total events:	36		8			
Heterogeneity: Chi² = 4.03, df = 7 (P = 0.78); I² = 0%						
Test for overall effect: Z = 1.67 (P = 0.09)						
1.7.9 Trospium						
Alloussi 1998	4	178	2	84	2.2%	0.94 [0.18 , 5.05]
Staskin 2007	3	298	2	303	1.6%	1.53 [0.26 , 9.06]
Subtotal (95% CI)		**476**		**387**	**3.8%**	**1.19 [0.35 , 4.00]**
Total events:	7		4			
Heterogeneity: Chi² = 0.15, df = 1 (P = 0.70); I² = 0%						
Test for overall effect: Z = 0.28 (P = 0.78)						
Total (95% CI)		**12437**		**6202**	**100.0%**	**1.58 [1.26 , 1.99]**
Total events:	346		91			
Heterogeneity: Chi² = 25.22, df = 33 (P = 0.83); I² = 0%						
Test for overall effect: Z = 3.94 (P < 0.0001)						
Test for subgroup differences: Chi² = 8.50, df = 8 (P = 0.39), I² = 5.8%						

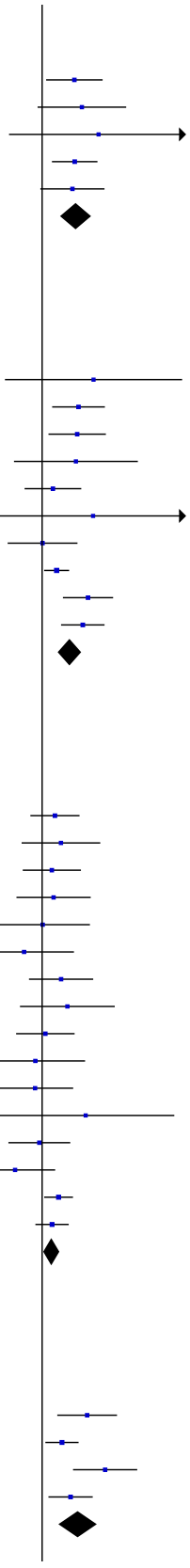


Analysis 1.8. Comparison 1: Anticholinergics versus placebo, Outcome 8: Adverse events: Constipation

Study or Subgroup	Anticholinergic Events	Anticholinergic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Darifenacin						
Chapple 2007b	41	266	11	133	2.9%	1.86 [0.99 , 3.51]
Haab 2004	51	397	11	164	3.0%	1.92 [1.02 , 3.58]
Hill 2005	44	215	5	109	1.7%	4.46 [1.82 , 10.93]
Steers 2004	56	268	10	127	2.9%	2.65 [1.40 , 5.03]
Zinner 2006	38	214	11	225	2.9%	3.63 [1.91 , 6.92]
Subtotal (95% CI)		**1360**		**758**	**13.4%**	**2.59 [1.89 , 3.55]**
Total events:	230		48			
Heterogeneity: Tau² = 0.01; Chi² = 4.44, df = 4 (P = 0.35); I² = 10%						
Test for overall effect: Z = 5.90 (P < 0.00001)						
1.8.2 Fesoterodine						
Chapple 2004a	21	505	6	183	1.7%	1.27 [0.52 , 3.09]
Chapple 2007a	30	849	4	283	1.3%	2.50 [0.89 , 7.03]
Dmochowski 2010	48	438	25	445	4.4%	1.95 [1.23 , 3.11]
DuBeau 2014	31	281	12	281	2.9%	2.58 [1.35 , 4.93]
Herschorn 2009a	37	679	5	167	1.6%	1.82 [0.73 , 4.56]
Kaplan 2011	42	960	3	239	1.1%	3.49 [1.09 , 11.15]
Kaplan 2014	12	308	4	301	1.2%	2.93 [0.96 , 8.99]
Nitti 2005	9	90	2	43	0.7%	2.15 [0.49 , 9.53]
Nitti 2007	35	561	7	271	2.1%	2.42 [1.09 , 5.37]
Wagg 2013a	35	392	10	393	2.6%	3.51 [1.76 , 6.99]
Weiss 2013	15	381	7	400	1.7%	2.25 [0.93 , 5.46]
Subtotal (95% CI)		**5444**		**3006**	**21.3%**	**2.30 [1.81 , 2.92]**
Total events:	315		85			
Heterogeneity: Tau² = 0.00; Chi² = 4.75, df = 10 (P = 0.91); I² = 0%						
Test for overall effect: Z = 6.79 (P < 0.00001)						
1.8.3 Imidafenacin						
Homma 2008	9	100	4	101	1.1%	2.27 [0.72 , 7.14]
Homma 2009	80	627	11	145	3.1%	1.68 [0.92 , 3.08]
Yoshida 2018	1	117	3	369	0.3%	1.05 [0.11 , 10.01]
Subtotal (95% CI)		**844**		**615**	**4.6%**	**1.75 [1.04 , 2.93]**
Total events:	90		18			
Heterogeneity: Tau² = 0.00; Chi² = 0.41, df = 2 (P = 0.81); I² = 0%						
Test for overall effect: Z = 2.10 (P = 0.04)						
1.8.4 Oxybutynin						
Burgio 1998	25	65	23	62	4.6%	1.04 [0.66 , 1.62]
Homma 2003	15	244	3	61	1.0%	1.25 [0.37 , 4.18]
Thuroff 1991	2	63	0	26	0.2%	2.11 [0.10 , 42.49]
Subtotal (95% CI)		**372**		**149**	**5.8%**	**1.07 [0.71 , 1.63]**
Total events:	42		26			
Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 2 (P = 0.87); I² = 0%						
Test for overall effect: Z = 0.34 (P = 0.73)						
1.8.5 Propantheline						
Thuroff 1991	0	54	0	26		Not estimable
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.8.6 Propiverine						



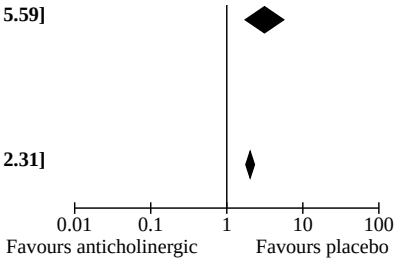
Analysis 1.8. (Continued)



1.8.6 Propiverine						
Gotoh 2011	18	291	6	274	1.7%	2.82 [1.14 , 7.01]
Junemann 2006	28	786	2	202	0.8%	3.60 [0.86 , 14.98]
Lee 2006	5	142	0	79	0.2%	6.15 [0.34 , 109.86]
Yamaguchi 2007	45	400	8	203	2.4%	2.85 [1.37 , 5.94]
Yamaguchi 2014	32	1149	4	381	1.3%	2.65 [0.94 , 7.45]
Subtotal (95% CI)		**2768**		**1139**	**6.3%**	**2.93 [1.84 , 4.67]**
Total events:	128		20			
Heterogeneity: Tau² = 0.00; Chi² = 0.38, df = 4 (P = 0.98); I² = 0%						
Test for overall effect: Z = 4.53 (P < 0.00001)						
1.8.7 Solifenacin						
Abrams 2013	7	234	0	81	0.2%	5.23 [0.30 , 90.63]
Cardozo 2004a	39	606	6	301	1.9%	3.23 [1.38 , 7.54]
Cardozo 2008a	35	505	5	223	1.6%	3.09 [1.23 , 7.79]
Chapple 2004b	15	187	1	37	0.4%	2.97 [0.40 , 21.78]
Chapple 2004c	48	1810	5	267	1.7%	1.42 [0.57 , 3.53]
Chua 2018	2	31	0	32	0.2%	5.16 [0.26 , 103.27]
Herschorn 2017a	6	423	6	429	1.2%	1.01 [0.33 , 3.12]
Karram 2009	55	372	34	367	5.1%	1.60 [1.07 , 2.39]
Vardy 2009	31	386	7	382	2.0%	4.38 [1.95 , 9.83]
Yamaguchi 2007	114	777	8	202	2.5%	3.70 [1.84 , 7.46]
Subtotal (95% CI)		**5331**		**2321**	**16.8%**	**2.41 [1.70 , 3.41]**
Total events:	352		72			
Heterogeneity: Tau² = 0.08; Chi² = 12.53, df = 9 (P = 0.19); I² = 28%						
Test for overall effect: Z = 4.93 (P < 0.00001)						
1.8.8 Tolterodine						
Chapple 2014	43	1569	7	386	2.1%	1.51 [0.69 , 3.33]
Herschorn 2008	11	408	3	204	0.9%	1.83 [0.52 , 6.50]
Herschorn 2009a	28	684	5	167	1.6%	1.37 [0.54 , 3.49]
Homma 2003	17	239	3	61	1.0%	1.45 [0.44 , 4.78]
Jacquetin 2001	8	200	2	51	0.7%	1.02 [0.22 , 4.66]
Jonas 1997	5	197	2	44	0.6%	0.56 [0.11 , 2.78]
Kaplan 2011	30	973	4	239	1.3%	1.84 [0.66 , 5.18]
Khullar 2004	9	569	2	285	0.7%	2.25 [0.49 , 10.36]
Kuo 2015	9	371	8	366	1.6%	1.11 [0.43 , 2.85]
Malone-Lee 2001	5	134	2	43	0.6%	0.80 [0.16 , 3.99]
Mitcheson 2019	5	257	5	205	1.0%	0.80 [0.23 , 2.72]
Rentzhog 1998	4	30	0	13	0.2%	4.06 [0.23 , 70.46]
Rogers 2008	7	201	8	210	1.4%	0.91 [0.34 , 2.47]
Rovner 2005	3	77	8	86	0.9%	0.42 [0.12 , 1.52]
Van Kerrebroeck 2001	75	1017	22	507	4.4%	1.70 [1.07 , 2.70]
Zinner 2002	30	503	22	508	3.7%	1.38 [0.81 , 2.35]
Subtotal (95% CI)		**7429**		**3375**	**22.8%**	**1.34 [1.06 , 1.70]**
Total events:	289		103			
Heterogeneity: Tau² = 0.00; Chi² = 8.96, df = 15 (P = 0.88); I² = 0%						
Test for overall effect: Z = 2.47 (P = 0.01)						
1.8.9 Trospium						
Dmochowski 2008	21	280	5	284	1.5%	4.26 [1.63 , 11.14]
Rudy 2006	36	329	19	329	3.7%	1.89 [1.11 , 3.23]
Staskin 2007	29	289	4	303	1.3%	7.60 [2.71 , 21.35]
Zinner 2004	25	256	10	256	2.5%	2.50 [1.23 , 5.10]
Subtotal (95% CI)		**1154**		**1172**	**9.0%**	**3.13 [1.75 , 5.59]**
Total events:	111		38			

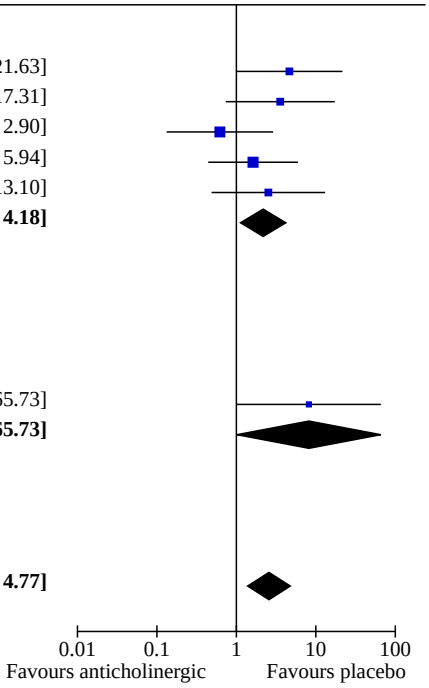
Analysis 1.8. (Continued)

Subtotal (95% CI)		**1154**		**1172**	**9.0%**	**3.13 [1.75 , 5.59]**
Total events:	111		38			
Heterogeneity: Tau² = 0.19; Chi² = 6.64, df = 3 (P = 0.08); I² = 55%						
Test for overall effect: Z = 3.86 (P = 0.0001)						
Total (95% CI)		**24756**		**12561**	**100.0%**	**2.03 [1.78 , 2.31]**
Total events:	1557		410			
Heterogeneity: Tau² = 0.04; Chi² = 69.17, df = 56 (P = 0.11); I² = 19%						
Test for overall effect: Z = 10.77 (P < 0.00001)						
Test for subgroup differences: Chi² = 29.73, df = 7 (P = 0.0001), I² = 76.5%						

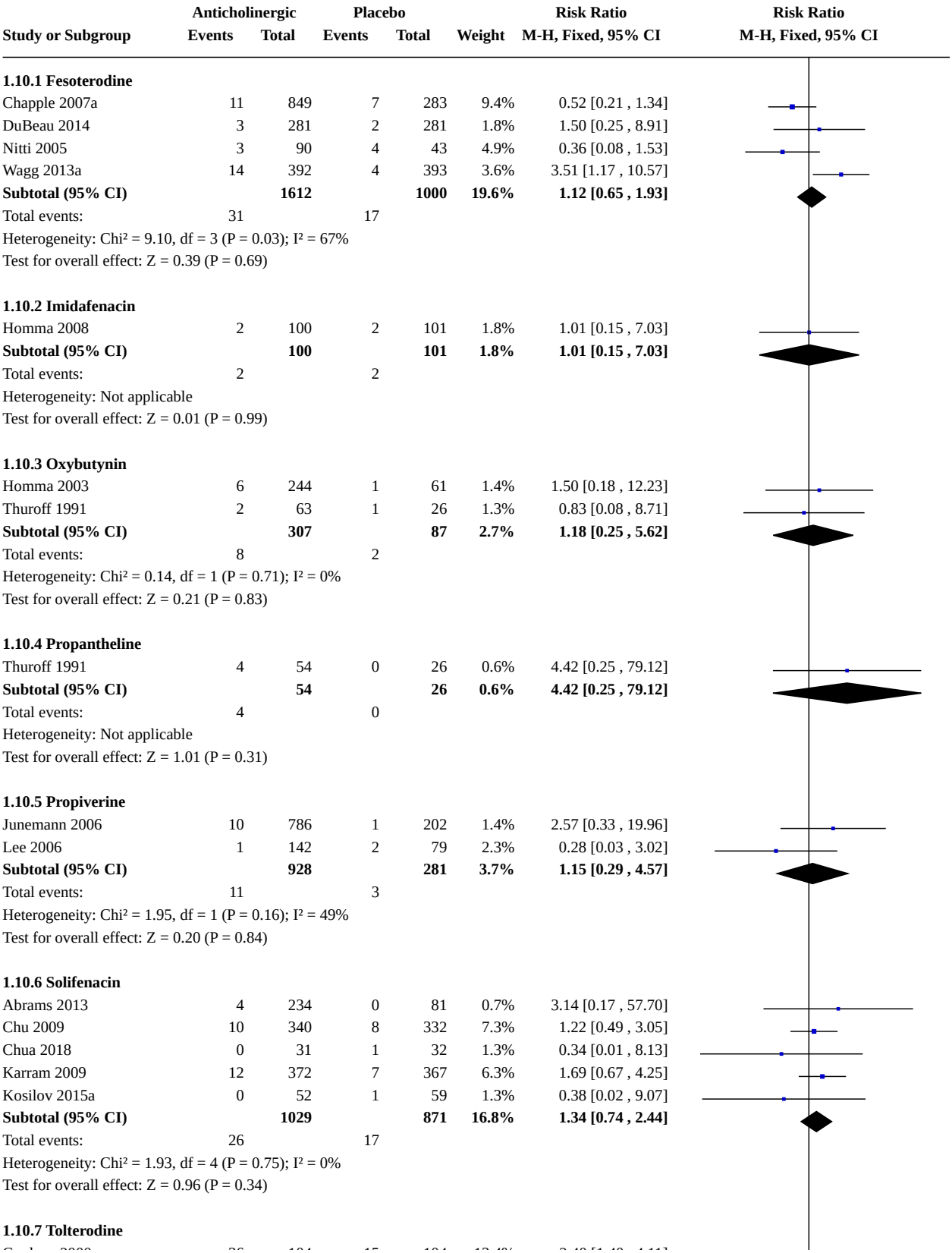


Analysis 1.9. Comparison 1: Anticholinergics versus placebo, Outcome 9: Adverse events: Cough

	Anticholinergic		Placebo			Odds Ratio	Odds Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
1.9.1 Fesoterodine							
Dmochowski 2010	9	438	2	445	13.2%	4.65 [1.00 , 21.63]	
DuBeau 2014	7	281	2	281	13.3%	3.56 [0.73 , 17.31]	
Nitti 2005	4	90	3	43	26.4%	0.62 [0.13 , 2.90]	
Nitti 2007	10	561	3	271	27.0%	1.62 [0.44 , 5.94]	
Wagg 2013a	5	392	2	393	13.4%	2.53 [0.49 , 13.10]	
Subtotal (95% CI)		**1762**		**1433**	**93.4%**	**2.17 [1.13 , 4.18]**	
Total events:	35		12				
Heterogeneity: Chi² = 4.08, df = 4 (P = 0.40); I² = 2%							
Test for overall effect: Z = 2.32 (P = 0.02)							
1.9.2 Trospium							
Rudy 2006	8	329	1	329	6.6%	8.17 [1.02 , 65.73]	
Subtotal (95% CI)		**329**		**329**	**6.6%**	**8.17 [1.02 , 65.73]**	
Total events:	8		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.98 (P = 0.05)							
Total (95% CI)		**2091**		**1762**	**100.0%**	**2.57 [1.39 , 4.77]**	
Total events:	43		13				
Heterogeneity: Chi² = 5.66, df = 5 (P = 0.34); I² = 12%							
Test for overall effect: Z = 3.00 (P = 0.003)							
Test for subgroup differences: Chi² = 1.41, df = 1 (P = 0.23), I² = 29.2%							

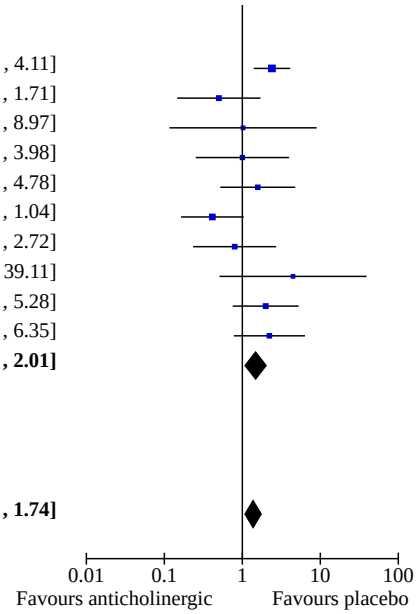


Analysis 1.10. Comparison 1: Anticholinergics versus placebo, Outcome 10: Adverse events: Dizziness



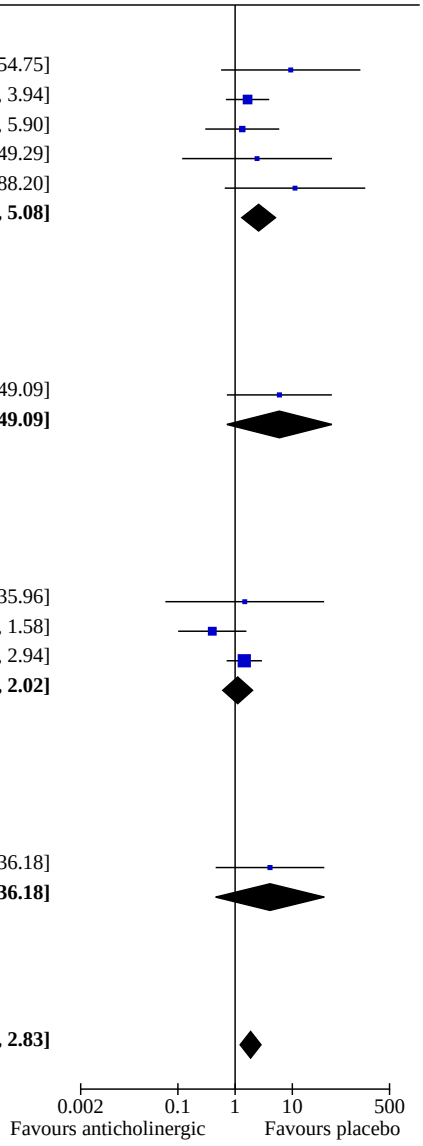
Analysis 1.10. (Continued)

1.10.7 Tolterodine						
Cardozo 2000	36	104	15	104	13.4%	2.40 [1.40 , 4.11]
Herschorn 2008	5	408	5	204	6.0%	0.50 [0.15 , 1.71]
Homma 2003	4	239	1	61	1.4%	1.02 [0.12 , 8.97]
Khullar 2004	6	569	3	285	3.6%	1.00 [0.25 , 3.98]
Kuo 2015	8	371	5	366	4.5%	1.58 [0.52 , 4.78]
Malone-Lee 2001	9	134	7	43	9.5%	0.41 [0.16 , 1.04]
Mitcheson 2019	5	257	5	205	5.0%	0.80 [0.23 , 2.72]
Rovner 2005	4	77	1	86	0.8%	4.47 [0.51 , 39.11]
Van Kerrebroeck 2001	20	1017	5	507	6.0%	1.99 [0.75 , 5.28]
Zinner 2002	11	503	5	508	4.5%	2.22 [0.78 , 6.35]
Subtotal (95% CI)		**3679**		**2369**	**54.7%**	**1.48 [1.09 , 2.01]**
Total events:	108		52			
Heterogeneity: Chi² = 16.75, df = 9 (P = 0.05); I² = 46%						
Test for overall effect: Z = 2.49 (P = 0.01)						
Total (95% CI)		**7709**		**4735**	**100.0%**	**1.37 [1.09 , 1.74]**
Total events:	190		93			
Heterogeneity: Chi² = 31.89, df = 24 (P = 0.13); I² = 25%						
Test for overall effect: Z = 2.65 (P = 0.008)						
Test for subgroup differences: Chi² = 1.60, df = 6 (P = 0.95), I² = 0%						



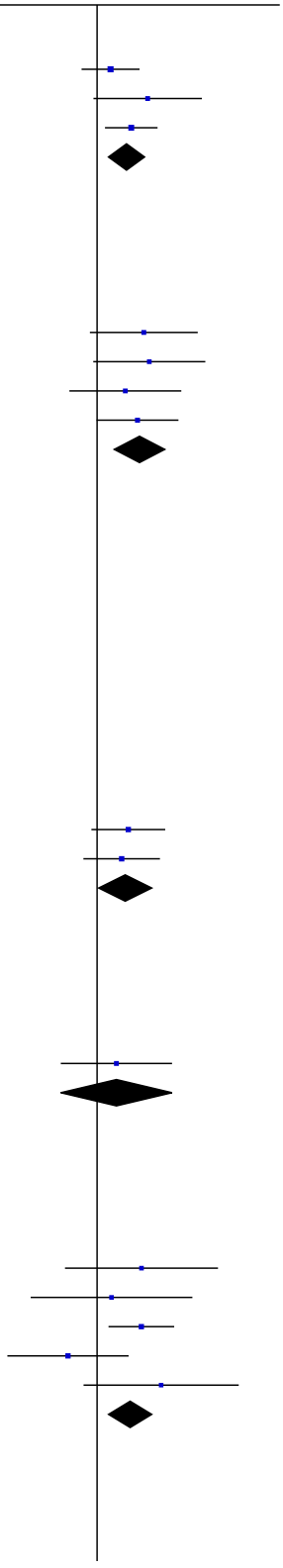
Analysis 1.11. Comparison 1: Anticholinergics versus placebo, Outcome 11: Adverse events: Dry eyes

Study or Subgroup	Anticholinergic Events	Anticholinergic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.11.1 Fesoterodine						
Chapple 2007a	18	559	0	141	2.2%	9.38 [0.57 , 154.75]
Dmochowski 2010	13	438	8	445	22.2%	1.65 [0.69 , 3.94]
DuBeau 2014	4	281	3	281	8.4%	1.33 [0.30 , 5.90]
Nitti 2005	2	90	0	43	1.9%	2.42 [0.12 , 49.29]
Nitti 2007	11	561	0	271	1.9%	11.13 [0.66 , 188.20]
Subtotal (95% CI)		**1929**		**1181**	**36.6%**	**2.58 [1.31 , 5.08]**
Total events:	48		11			
Heterogeneity: Chi² = 3.61, df = 4 (P = 0.46); I² = 0%						
Test for overall effect: Z = 2.74 (P = 0.006)						
1.11.2 Solifenacin						
Vardy 2009	6	386	1	382	2.8%	5.94 [0.72 , 49.09]
Subtotal (95% CI)		**386**		**382**	**2.8%**	**5.94 [0.72 , 49.09]**
Total events:	6		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.65 (P = 0.10)						
1.11.3 Tolterodine						
Chapple 2007a	1	290	0	142	1.9%	1.47 [0.06 , 35.96]
Mitcheson 2019	3	257	6	205	18.7%	0.40 [0.10 , 1.58]
Van Kerrebroeck 2001	29	1017	10	507	37.3%	1.45 [0.71 , 2.94]
Subtotal (95% CI)		**1564**		**854**	**57.8%**	**1.11 [0.61 , 2.02]**
Total events:	33		16			
Heterogeneity: Chi² = 2.69, df = 2 (P = 0.26); I² = 26%						
Test for overall effect: Z = 0.34 (P = 0.74)						
1.11.4 Trospium						
Staskin 2007	4	298	1	303	2.8%	4.07 [0.46 , 36.18]
Subtotal (95% CI)		**298**		**303**	**2.8%**	**4.07 [0.46 , 36.18]**
Total events:	4		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.26 (P = 0.21)						
Total (95% CI)		**4177**		**2720**	**100.0%**	**1.86 [1.23 , 2.83]**
Total events:	91		29			
Heterogeneity: Chi² = 10.11, df = 9 (P = 0.34); I² = 11%						
Test for overall effect: Z = 2.91 (P = 0.004)						
Test for subgroup differences: Chi² = 5.34, df = 3 (P = 0.15), I² = 43.8%						



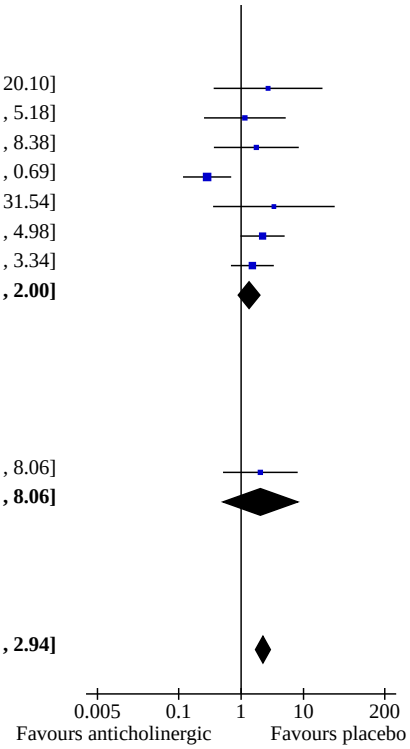
Analysis 1.12. Comparison 1: Anticholinergics versus placebo, Outcome 12: Adverse events: Dyspepsia/indigestion

Study or Subgroup	Anticholinergic Events	Anticholinergic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.12.1 Darifenacin						
Haab 2004	16	397	4	164	7.3%	1.65 [0.56 , 4.87]
Hill 2005	13	215	1	109	1.7%	6.59 [0.87 , 49.73]
Zinner 2006	17	214	5	225	6.2%	3.57 [1.34 , 9.52]
Subtotal (95% CI)		**826**		**498**	**15.2%**	**2.99 [1.53 , 5.87]**
Total events:	46		10			
Heterogeneity: Chi² = 1.87, df = 2 (P = 0.39); I² = 0%						
Test for overall effect: Z = 3.20 (P = 0.001)						
1.12.2 Fesoterodine						
Chapple 2004a	17	545	1	183	1.9%	5.71 [0.76 , 42.59]
DuBeau 2014	7	281	1	281	1.3%	7.00 [0.87 , 56.52]
Nitti 2005	6	90	1	43	1.7%	2.87 [0.36 , 23.07]
Wagg 2013a	9	392	2	393	2.6%	4.51 [0.98 , 20.75]
Subtotal (95% CI)		**1308**		**900**	**7.5%**	**4.86 [1.90 , 12.45]**
Total events:	39		5			
Heterogeneity: Chi² = 0.40, df = 3 (P = 0.94); I² = 0%						
Test for overall effect: Z = 3.30 (P = 0.0010)						
1.12.3 Imidafenacin						
Homma 2008	0	100	0	101		Not estimable
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.12.4 Oxybutynin						
Abrams 1998	27	118	2	28	4.1%	3.20 [0.81 , 12.68]
Homma 2003	20	244	2	61	4.1%	2.50 [0.60 , 10.41]
Subtotal (95% CI)		**362**		**89**	**8.2%**	**2.85 [1.06 , 7.67]**
Total events:	47		4			
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² = 0%						
Test for overall effect: Z = 2.08 (P = 0.04)						
1.12.5 Propiverine						
Junemann 2006	8	786	1	202	2.0%	2.06 [0.26 , 16.34]
Subtotal (95% CI)		**786**		**202**	**2.0%**	**2.06 [0.26 , 16.34]**
Total events:	8		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
1.12.6 Solifenacin						
Abrams 2013	7	234	0	81	0.9%	5.23 [0.30 , 90.63]
Chapple 2004b	2	107	0	36	1.0%	1.71 [0.08 , 34.87]
Chu 2009	16	340	3	332	3.9%	5.21 [1.53 , 17.71]
Herschorn 2017a	1	423	3	429	3.8%	0.34 [0.04 , 3.24]
Vardy 2009	5	386	0	382	0.6%	10.89 [0.60 , 196.20]
Subtotal (95% CI)		**1490**		**1260**	**10.3%**	**3.43 [1.53 , 7.67]**
Total events:	31		6			
Heterogeneity: Chi² = 5.39, df = 4 (P = 0.25); I² = 26%						
Test for overall effect: Z = 3.00 (P = 0.003)						
1.12.7 Tolterodine						



Analysis 1.12. (Continued)

1.12.7 Tolterodine						
Abrams 1998	11	118	1	29	2.1%	2.70 [0.36 , 20.10]
Homma 2003	9	239	2	61	4.1%	1.15 [0.25 , 5.18]
Khullar 2004	7	569	2	285	3.4%	1.75 [0.37 , 8.38]
Malone-Lee 2001	8	134	9	43	17.5%	0.29 [0.12 , 0.69]
Rovner 2005	3	77	1	86	1.2%	3.35 [0.36 , 31.54]
Van Kerrebroeck 2001	31	1017	7	507	12.0%	2.21 [0.98 , 4.98]
Zinner 2002	15	503	10	508	12.8%	1.51 [0.69 , 3.34]
Subtotal (95% CI)		**2657**		**1519**	**53.0%**	**1.34 [0.90 , 2.00]**
Total events:	84		32			
Heterogeneity: Chi² = 14.46, df = 6 (P = 0.02); I² = 59%						
Test for overall effect: Z = 1.45 (P = 0.15)						
1.12.8 Trospium						
Staskin 2007	6	298	3	303	3.8%	2.03 [0.51 , 8.06]
Subtotal (95% CI)		**298**		**303**	**3.8%**	**2.03 [0.51 , 8.06]**
Total events:	6		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.01 (P = 0.31)						
Total (95% CI)		**7827**		**4872**	**100.0%**	**2.24 [1.70 , 2.94]**
Total events:	261		61			
Heterogeneity: Chi² = 34.07, df = 22 (P = 0.05); I² = 35%						
Test for overall effect: Z = 5.78 (P < 0.00001)						
Test for subgroup differences: Chi² = 10.80, df = 6 (P = 0.09), I² = 44.5%						



Analysis 1.13. Comparison 1: Anticholinergics versus placebo, Outcome 13: Adverse events: Flu-like symptoms/ fatigue

Study or Subgroup	Anticholinergic Events	Anticholinergic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.13.1 Darifenacin						
Hill 2005	5	215	5	109	8.1%	0.51 [0.15 , 1.71]
Subtotal (95% CI)		**215**		**109**	**8.1%**	**0.51 [0.15 , 1.71]**
Total events:	5		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.09 (P = 0.27)						
1.13.2 Fesoterodine						
Chapple 2004a	32	545	15	183	27.5%	0.72 [0.40 , 1.29]
Chapple 2007a	13	559	3	142	5.9%	1.10 [0.32 , 3.81]
Dmochowski 2010	11	438	2	445	2.4%	5.59 [1.25 , 25.06]
DuBeau 2014	3	281	4	281	4.9%	0.75 [0.17 , 3.32]
Nitti 2005	4	90	5	43	8.3%	0.38 [0.11 , 1.35]
Wagg 2013a	9	392	10	393	12.2%	0.90 [0.37 , 2.20]
Subtotal (95% CI)		**2305**		**1487**	**61.3%**	**0.94 [0.64 , 1.38]**
Total events:	72		39			
Heterogeneity: Chi² = 8.35, df = 5 (P = 0.14); I² = 40%						
Test for overall effect: Z = 0.31 (P = 0.75)						
1.13.3 Oxybutynin						
Thuroff 1991	1	63	0	26	0.9%	1.27 [0.05 , 30.10]
Subtotal (95% CI)		**63**		**26**	**0.9%**	**1.27 [0.05 , 30.10]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.15 (P = 0.88)						
1.13.4 Propantheline						
Thuroff 1991	4	54	0	26	0.8%	4.42 [0.25 , 79.12]
Subtotal (95% CI)		**54**		**26**	**0.8%**	**4.42 [0.25 , 79.12]**
Total events:	4		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.01 (P = 0.31)						
1.13.5 Solifenacin						
Abrams 2013	3	234	1	81	1.8%	1.04 [0.11 , 9.84]
Karram 2009	10	372	4	367	4.9%	2.47 [0.78 , 7.79]
Vardy 2009	5	386	2	382	2.5%	2.47 [0.48 , 12.67]
Subtotal (95% CI)		**992**		**830**	**9.2%**	**2.19 [0.93 , 5.16]**
Total events:	18		7			
Heterogeneity: Chi² = 0.49, df = 2 (P = 0.78); I² = 0%						
Test for overall effect: Z = 1.79 (P = 0.07)						
1.13.6 Tolterodine						
Chapple 2007a	12	290	4	141	6.6%	1.46 [0.48 , 4.44]
Herschorn 2008	11	408	4	204	6.5%	1.38 [0.44 , 4.26]
Van Kerrebroeck 2001	17	1017	4	507	6.5%	2.12 [0.72 , 6.26]
Subtotal (95% CI)		**1715**		**852**	**19.7%**	**1.65 [0.87 , 3.13]**
Total events:	40		12			
Heterogeneity: Chi² = 0.35, df = 2 (P = 0.84); I² = 0%						
Test for overall effect: Z = 1.54 (P = 0.12)						
Total (95% CI)		**5344**		**3330**	**100.0%**	**1.19 [0.89 , 1.59]**

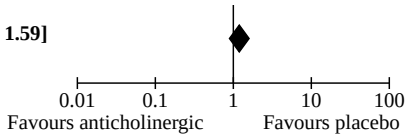
Analysis 1.13. (Continued)

Total (95% CI)	**5344**	**3330**	**100.0%**	**1.19 [0.89 , 1.59]**	
Total events:	140	63			

Heterogeneity: Chi² = 17.08, df = 14 (P = 0.25); I² = 18%

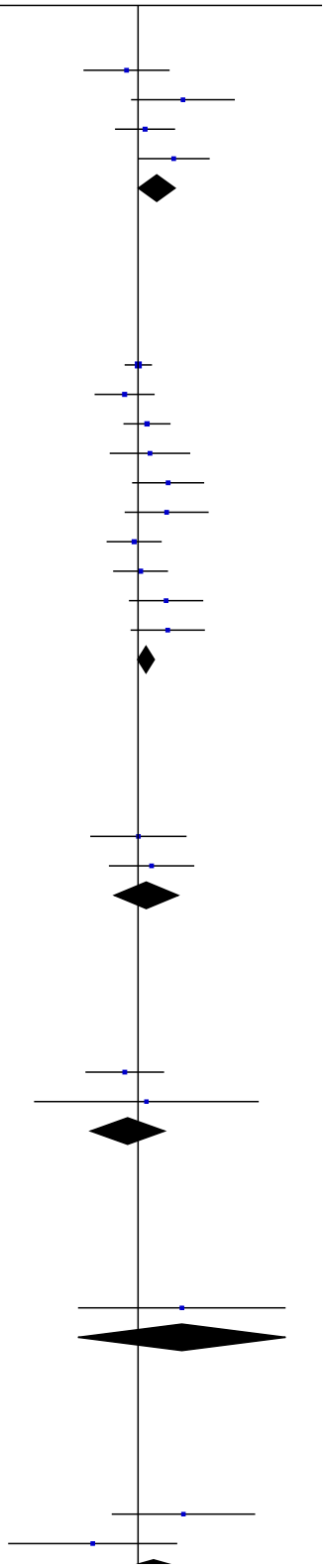
Test for overall effect: Z = 1.19 (P = 0.23)

Test for subgroup differences: Chi² = 7.02, df = 5 (P = 0.22), I² = 28.8%



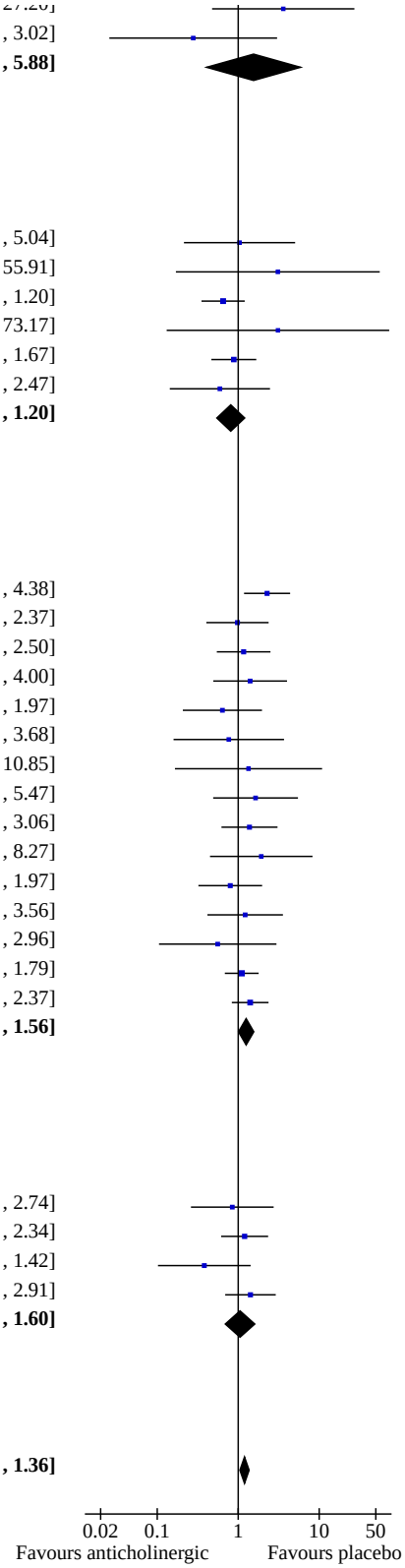
Analysis 1.14. Comparison 1: Anticholinergics versus placebo, Outcome 14: Adverse events: Headache

Study or Subgroup	Anticholinergic Events	Anticholinergic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.14.1 Darifenacin						
Haab 2004	7	397	4	164	1.4%	0.72 [0.21 , 2.44]
Hill 2005	14	215	2	109	0.7%	3.55 [0.82 , 15.34]
Steers 2004	18	268	7	127	2.4%	1.22 [0.52 , 2.84]
Zinner 2006	13	214	5	225	1.2%	2.73 [0.99 , 7.54]
Subtotal (95% CI)		**1094**		**625**	**5.7%**	**1.69 [1.01 , 2.84]**
Total events:	52		18			
Heterogeneity: Chi² = 4.30, df = 3 (P = 0.23); I² = 30%						
Test for overall effect: Z = 1.99 (P = 0.05)						
1.14.2 Fesoterodine						
Chapple 2004a	87	545	29	183	10.9%	1.01 [0.69 , 1.48]
Chapple 2007a	19	559	7	141	2.8%	0.68 [0.29 , 1.60]
Dmochowski 2010	19	438	15	445	3.7%	1.29 [0.66 , 2.50]
DuBeau 2014	7	281	5	281	1.3%	1.40 [0.45 , 4.36]
Herschorn 2009a	38	679	4	167	1.6%	2.34 [0.85 , 6.46]
Kaplan 2011	27	960	3	239	1.2%	2.24 [0.69 , 7.32]
Nitti 2005	15	90	8	43	2.7%	0.90 [0.41 , 1.95]
Nitti 2007	20	561	9	271	3.1%	1.07 [0.50 , 2.33]
Wagg 2013a	11	392	5	393	1.3%	2.21 [0.77 , 6.29]
Weiss 2013	11	381	5	400	1.2%	2.31 [0.81 , 6.59]
Subtotal (95% CI)		**4886**		**2563**	**29.8%**	**1.25 [0.99 , 1.58]**
Total events:	254		90			
Heterogeneity: Chi² = 8.89, df = 9 (P = 0.45); I² = 0%						
Test for overall effect: Z = 1.87 (P = 0.06)						
1.14.3 Imidafenacin						
Homma 2008	4	100	4	101	1.0%	1.01 [0.26 , 3.93]
Homma 2009	19	627	3	145	1.2%	1.46 [0.44 , 4.88]
Subtotal (95% CI)		**727**		**246**	**2.2%**	**1.26 [0.51 , 3.10]**
Total events:	23		7			
Heterogeneity: Chi² = 0.16, df = 1 (P = 0.69); I² = 0%						
Test for overall effect: Z = 0.50 (P = 0.61)						
1.14.4 Oxybutynin						
Homma 2003	11	244	4	61	1.6%	0.69 [0.23 , 2.08]
Thuroff 1991	1	63	0	26	0.2%	1.27 [0.05 , 30.10]
Subtotal (95% CI)		**307**		**87**	**1.8%**	**0.74 [0.26 , 2.12]**
Total events:	12		4			
Heterogeneity: Chi² = 0.13, df = 1 (P = 0.72); I² = 0%						
Test for overall effect: Z = 0.55 (P = 0.58)						
1.14.5 Propantheline						
Thuroff 1991	3	54	0	26	0.2%	3.44 [0.18 , 64.17]
Subtotal (95% CI)		**54**		**26**	**0.2%**	**3.44 [0.18 , 64.17]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.83 (P = 0.41)						
1.14.6 Propiverine						
Junemann 2006	14	786	1	202	0.4%	3.60 [0.48 , 27.20]
Lee 2006	1	142	2	79	0.6%	0.28 [0.03 , 3.02]



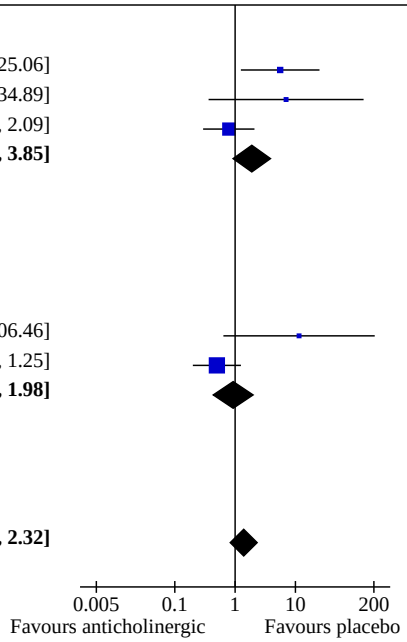
Analysis 1.14. (Continued)

Lee 2006	1	142	2	79	0.6%	0.28 [0.03 , 3.02]
Subtotal (95% CI)		**928**		**281**	**1.0%**	**1.55 [0.41 , 5.88]**
Total events:	15		3			
Heterogeneity: Chi² = 2.66, df = 1 (P = 0.10); I² = 62%						
Test for overall effect: Z = 0.64 (P = 0.52)						
1.14.7 Solifenacin						
Abrams 2013	6	234	2	81	0.7%	1.04 [0.21 , 5.04]
Chapple 2004b	4	107	0	36	0.2%	3.08 [0.17 , 55.91]
Chu 2009	16	340	24	332	6.1%	0.65 [0.35 , 1.20]
Chua 2018	1	31	0	32	0.1%	3.09 [0.13 , 73.17]
Karram 2009	17	372	19	367	4.8%	0.88 [0.47 , 1.67]
Vardy 2009	3	386	5	382	1.3%	0.59 [0.14 , 2.47]
Subtotal (95% CI)		**1470**		**1230**	**13.3%**	**0.81 [0.54 , 1.20]**
Total events:	47		50			
Heterogeneity: Chi² = 2.34, df = 5 (P = 0.80); I² = 0%						
Test for overall effect: Z = 1.05 (P = 0.29)						
1.14.8 Tolterodine						
Cardozo 2000	25	104	11	104	2.8%	2.27 [1.18 , 4.38]
Chapple 2007a	14	290	7	142	2.4%	0.98 [0.40 , 2.37]
Herschorn 2008	21	408	9	204	3.0%	1.17 [0.54 , 2.50]
Herschorn 2009a	23	684	4	167	1.6%	1.40 [0.49 , 4.00]
Homma 2003	10	239	4	61	1.6%	0.64 [0.21 , 1.97]
Jacquetin 2001	6	200	2	51	0.8%	0.77 [0.16 , 3.68]
Jonas 1997	6	197	1	44	0.4%	1.34 [0.17 , 10.85]
Kaplan 2011	20	973	3	239	1.2%	1.64 [0.49 , 5.47]
Khullar 2004	22	569	8	285	2.7%	1.38 [0.62 , 3.06]
Malone-Lee 2001	12	134	2	43	0.8%	1.93 [0.45 , 8.27]
Mitcheson 2019	9	257	9	205	2.5%	0.80 [0.32 , 1.97]
Rogers 2008	7	201	6	210	1.5%	1.22 [0.42 , 3.56]
Rovner 2005	2	77	4	86	1.0%	0.56 [0.11 , 2.96]
Van Kerrebroeck 2001	51	1017	23	507	7.7%	1.11 [0.68 , 1.79]
Zinner 2002	32	503	23	508	5.8%	1.41 [0.83 , 2.37]
Subtotal (95% CI)		**5853**		**2856**	**35.7%**	**1.25 [1.01 , 1.56]**
Total events:	260		116			
Heterogeneity: Chi² = 8.20, df = 14 (P = 0.88); I² = 0%						
Test for overall effect: Z = 2.04 (P = 0.04)						
1.14.9 Trospium						
Dmochowski 2008	5	280	6	284	1.5%	0.85 [0.26 , 2.74]
Rudy 2006	18	329	15	329	3.8%	1.20 [0.62 , 2.34]
Staskin 2007	3	298	8	303	2.0%	0.38 [0.10 , 1.42]
Zinner 2004	17	256	12	256	3.0%	1.42 [0.69 , 2.91]
Subtotal (95% CI)		**1163**		**1172**	**10.3%**	**1.05 [0.69 , 1.60]**
Total events:	43		41			
Heterogeneity: Chi² = 3.22, df = 3 (P = 0.36); I² = 7%						
Test for overall effect: Z = 0.24 (P = 0.81)						
Total (95% CI)		**16482**		**9086**	**100.0%**	**1.20 [1.05 , 1.36]**
Total events:	709		329			
Heterogeneity: Chi² = 36.39, df = 45 (P = 0.82); I² = 0%						
Test for overall effect: Z = 2.69 (P = 0.007)						
Test for subgroup differences: Chi² = 7.60, df = 8 (P = 0.47), I² = 0%						

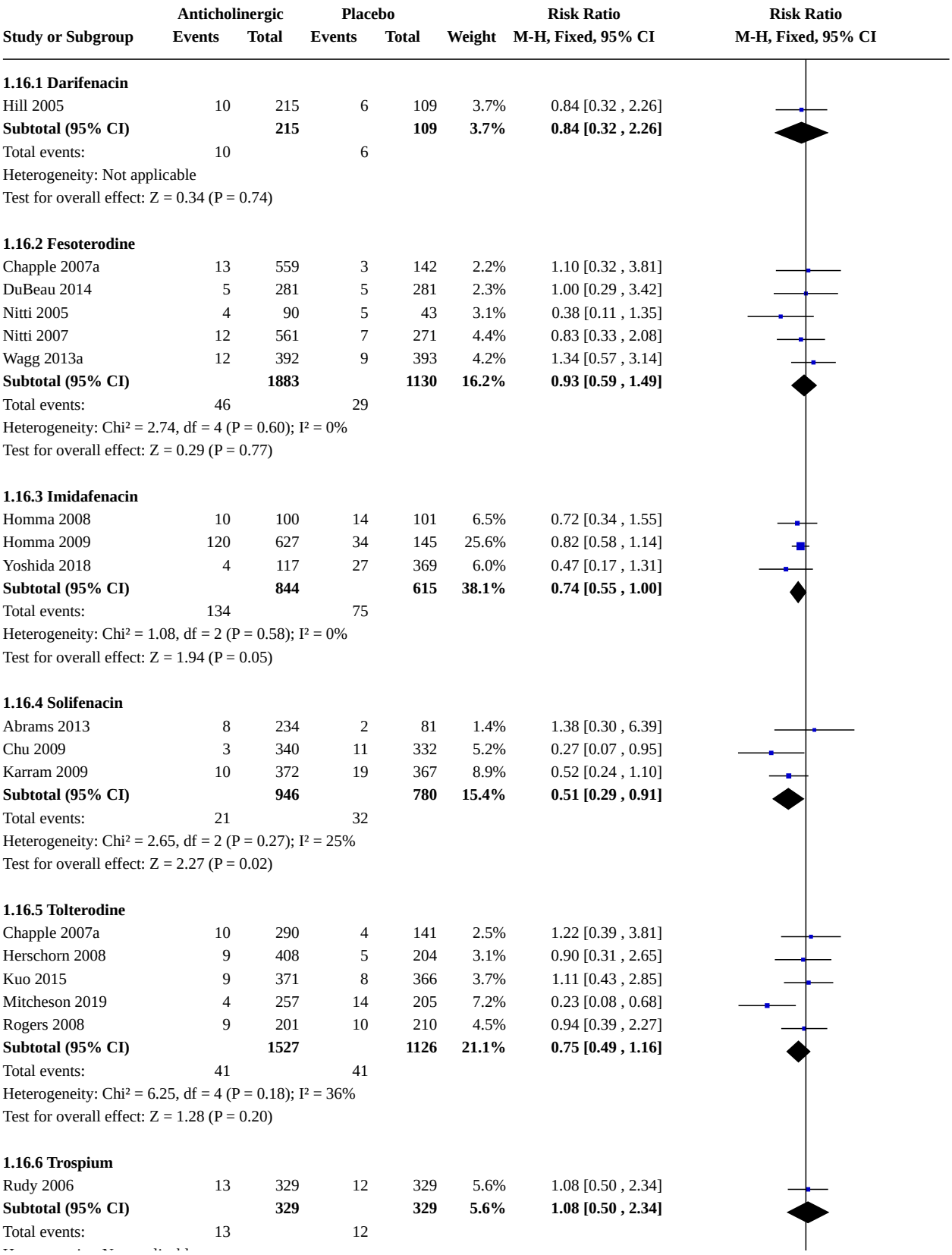


Analysis 1.15. Comparison 1: Anticholinergics versus placebo, Outcome 15: Adverse events: Insomnia (unable to sleep)

Study or Subgroup	Anticholinergic Events	Anticholinergic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.15.1 Fesoterodine						
Dmochowski 2010	11	438	2	445	8.3%	5.59 [1.25 , 25.06]
DuBeau 2014	3	281	0	281	2.1%	7.00 [0.36 , 134.89]
Zinner 2002	7	503	9	508	37.4%	0.79 [0.29 , 2.09]
Subtotal (95% CI)		**1222**		**1234**	**47.8%**	**1.89 [0.93 , 3.85]**
Total events:	21		11			
Heterogeneity: Chi² = 5.84, df = 2 (P = 0.05); I² = 66%						
Test for overall effect: Z = 1.75 (P = 0.08)						
1.15.2 Tolterodine						
Rogers 2008	5	201	0	210	2.0%	11.49 [0.64 , 206.46]
Van Kerrebroeck 2001	9	1017	9	507	50.2%	0.50 [0.20 , 1.25]
Subtotal (95% CI)		**1218**		**717**	**52.2%**	**0.93 [0.43 , 1.98]**
Total events:	14		9			
Heterogeneity: Chi² = 4.68, df = 1 (P = 0.03); I² = 79%						
Test for overall effect: Z = 0.19 (P = 0.85)						
Total (95% CI)		**2440**		**1951**	**100.0%**	**1.39 [0.83 , 2.32]**
Total events:	35		20			
Heterogeneity: Chi² = 12.59, df = 4 (P = 0.01); I² = 68%						
Test for overall effect: Z = 1.25 (P = 0.21)						
Test for subgroup differences: Chi² = 1.79, df = 1 (P = 0.18), I² = 44.2%						



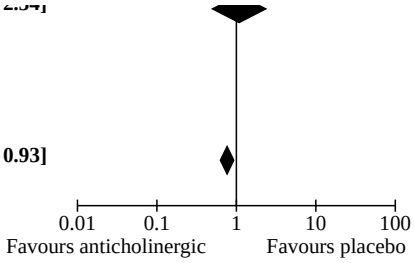
Analysis 1.16. Comparison 1: Anticholinergics versus placebo, Outcome 16: Adverse events: Nasopharyngitis/sore throat



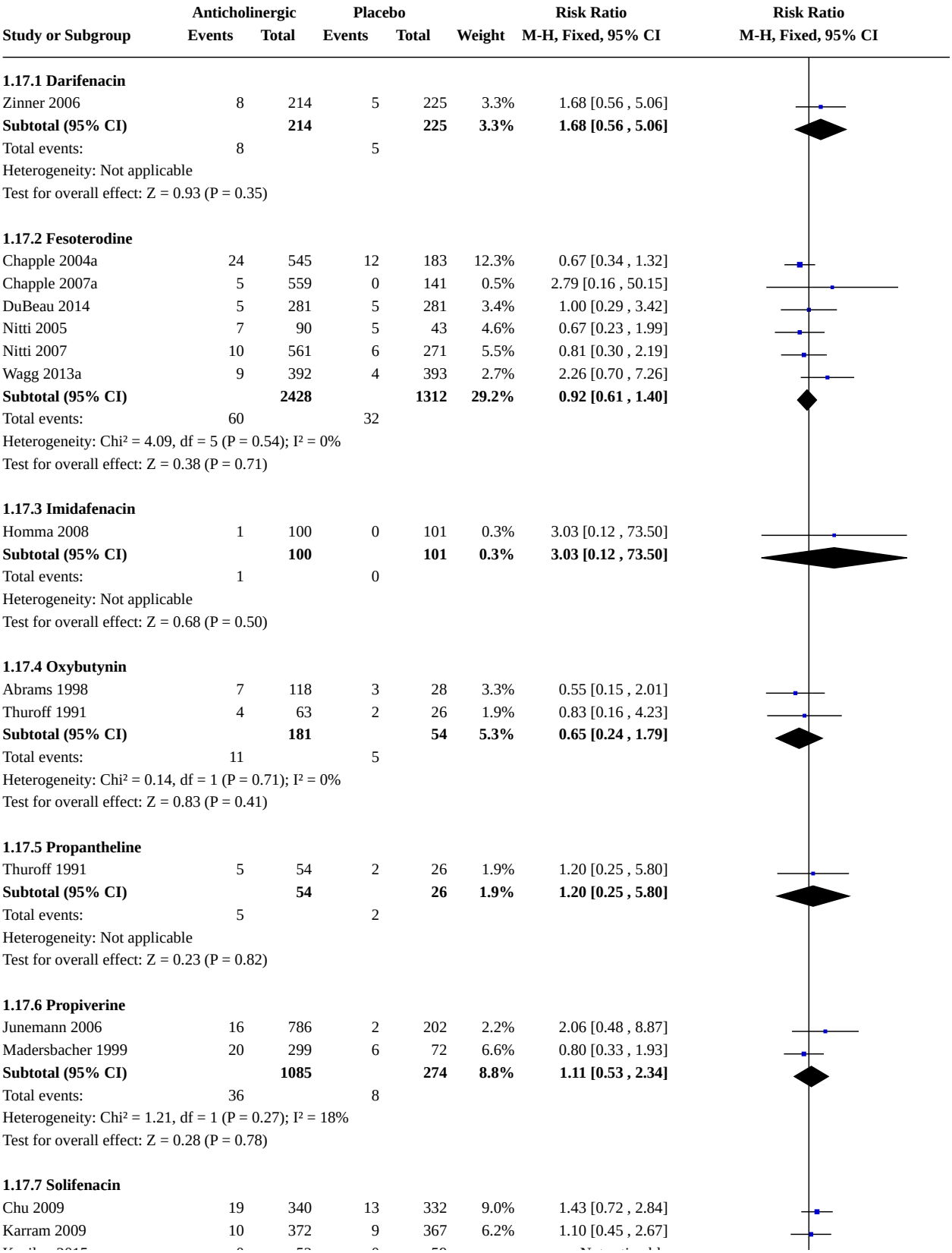
Study or Subgroup	Anticholinergic Events	Anticholinergic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.16.1 Darifenacin						
Hill 2005	10	215	6	109	3.7%	0.84 [0.32 , 2.26]
Subtotal (95% CI)		**215**		**109**	**3.7%**	**0.84 [0.32 , 2.26]**
Total events:	10		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.34 (P = 0.74)						
1.16.2 Fesoterodine						
Chapple 2007a	13	559	3	142	2.2%	1.10 [0.32 , 3.81]
DuBeau 2014	5	281	5	281	2.3%	1.00 [0.29 , 3.42]
Nitti 2005	4	90	5	43	3.1%	0.38 [0.11 , 1.35]
Nitti 2007	12	561	7	271	4.4%	0.83 [0.33 , 2.08]
Wagg 2013a	12	392	9	393	4.2%	1.34 [0.57 , 3.14]
Subtotal (95% CI)		**1883**		**1130**	**16.2%**	**0.93 [0.59 , 1.49]**
Total events:	46		29			
Heterogeneity: Chi^2 = 2.74, df = 4 (P = 0.60); I^2 = 0%						
Test for overall effect: Z = 0.29 (P = 0.77)						
1.16.3 Imidafenacin						
Homma 2008	10	100	14	101	6.5%	0.72 [0.34 , 1.55]
Homma 2009	120	627	34	145	25.6%	0.82 [0.58 , 1.14]
Yoshida 2018	4	117	27	369	6.0%	0.47 [0.17 , 1.31]
Subtotal (95% CI)		**844**		**615**	**38.1%**	**0.74 [0.55 , 1.00]**
Total events:	134		75			
Heterogeneity: Chi^2 = 1.08, df = 2 (P = 0.58); I^2 = 0%						
Test for overall effect: Z = 1.94 (P = 0.05)						
1.16.4 Solifenacin						
Abrams 2013	8	234	2	81	1.4%	1.38 [0.30 , 6.39]
Chu 2009	3	340	11	332	5.2%	0.27 [0.07 , 0.95]
Karram 2009	10	372	19	367	8.9%	0.52 [0.24 , 1.10]
Subtotal (95% CI)		**946**		**780**	**15.4%**	**0.51 [0.29 , 0.91]**
Total events:	21		32			
Heterogeneity: Chi^2 = 2.65, df = 2 (P = 0.27); I^2 = 25%						
Test for overall effect: Z = 2.27 (P = 0.02)						
1.16.5 Tolterodine						
Chapple 2007a	10	290	4	141	2.5%	1.22 [0.39 , 3.81]
Herschorn 2008	9	408	5	204	3.1%	0.90 [0.31 , 2.65]
Kuo 2015	9	371	8	366	3.7%	1.11 [0.43 , 2.85]
Mitcheson 2019	4	257	14	205	7.2%	0.23 [0.08 , 0.68]
Rogers 2008	9	201	10	210	4.5%	0.94 [0.39 , 2.27]
Subtotal (95% CI)		**1527**		**1126**	**21.1%**	**0.75 [0.49 , 1.16]**
Total events:	41		41			
Heterogeneity: Chi^2 = 6.25, df = 4 (P = 0.18); I^2 = 36%						
Test for overall effect: Z = 1.28 (P = 0.20)						
1.16.6 Trospium						
Rudy 2006	13	329	12	329	5.6%	1.08 [0.50 , 2.34]
Subtotal (95% CI)		**329**		**329**	**5.6%**	**1.08 [0.50 , 2.34]**
Total events:	13		12			

Analysis 1.16. (Continued)

Subtotal (95% CI)		**529**	**529**	**5.0%**	**1.06 [0.56 , 2.04]**
Total events:	13	12			
Heterogeneity: Not applicable					
Test for overall effect: Z = 0.20 (P = 0.84)					
Total (95% CI)	**5744**		**4089**	**100.0%**	**0.76 [0.63 , 0.93]**
Total events:	265	195			
Heterogeneity: Chi² = 15.70, df = 17 (P = 0.54); I² = 0%					
Test for overall effect: Z = 2.74 (P = 0.006)					
Test for subgroup differences: Chi² = 3.43, df = 5 (P = 0.63), I² = 0%					

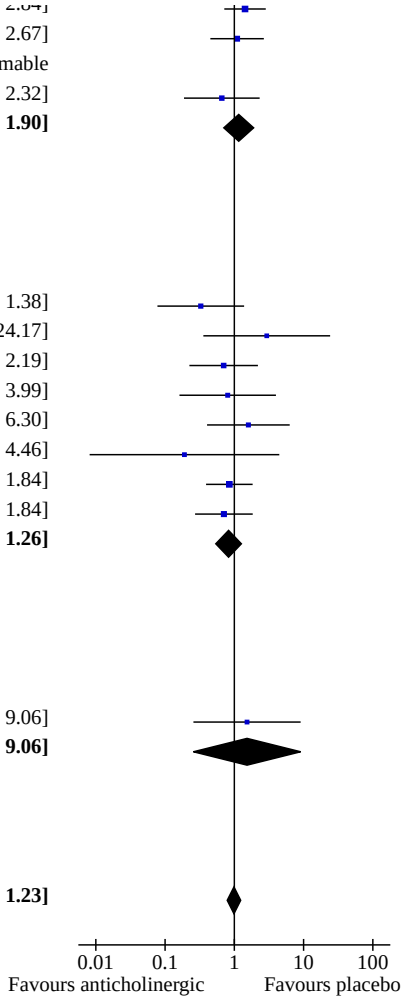


Analysis 1.17. Comparison 1: Anticholinergics versus placebo, Outcome 17: Adverse events: Nausea



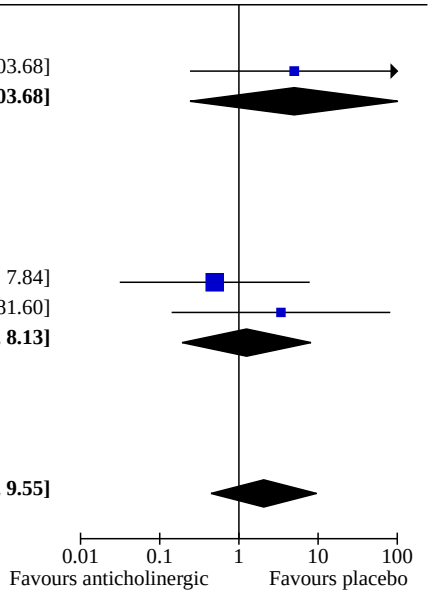
Analysis 1.17. (Continued)

Karram 2009	10	372	9	367	6.2%	1.10 [0.45 , 2.67]
Kosilov 2015a	0	52	0	59		Not estimable
Vardy 2009	4	386	6	382	4.1%	0.66 [0.19 , 2.32]
Subtotal (95% CI)		**1150**		**1140**	**19.4%**	**1.16 [0.71 , 1.90]**
Total events:	33		28			
Heterogeneity: Chi² = 1.14, df = 2 (P = 0.57); I² = 0%						
Test for overall effect: Z = 0.58 (P = 0.56)						
1.17.8 Tolterodine						
Abrams 1998	4	118	3	29	3.3%	0.33 [0.08 , 1.38]
Chapple 2007a	6	290	1	142	0.9%	2.94 [0.36 , 24.17]
Khullar 2004	7	569	5	285	4.6%	0.70 [0.22 , 2.19]
Malone-Lee 2001	5	134	2	43	2.1%	0.80 [0.16 , 3.99]
Mitcheson 2019	6	257	3	205	2.3%	1.60 [0.40 , 6.30]
Van Kerrebroeck 1998	0	34	1	19	1.3%	0.19 [0.01 , 4.46]
Van Kerrebroeck 2001	17	1017	10	507	9.2%	0.85 [0.39 , 1.84]
Zinner 2002	7	503	10	508	6.8%	0.71 [0.27 , 1.84]
Subtotal (95% CI)		**2922**		**1738**	**30.4%**	**0.83 [0.54 , 1.26]**
Total events:	52		35			
Heterogeneity: Chi² = 4.87, df = 7 (P = 0.68); I² = 0%						
Test for overall effect: Z = 0.88 (P = 0.38)						
1.17.9 Trospium						
Staskin 2007	3	298	2	303	1.4%	1.53 [0.26 , 9.06]
Subtotal (95% CI)		**298**		**303**	**1.4%**	**1.53 [0.26 , 9.06]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.64)						
Total (95% CI)		**8432**		**5173**	**100.0%**	**0.99 [0.79 , 1.23]**
Total events:	209		117			
Heterogeneity: Chi² = 15.36, df = 24 (P = 0.91); I² = 0%						
Test for overall effect: Z = 0.11 (P = 0.91)						
Test for subgroup differences: Chi² = 3.57, df = 8 (P = 0.89), I² = 0%						



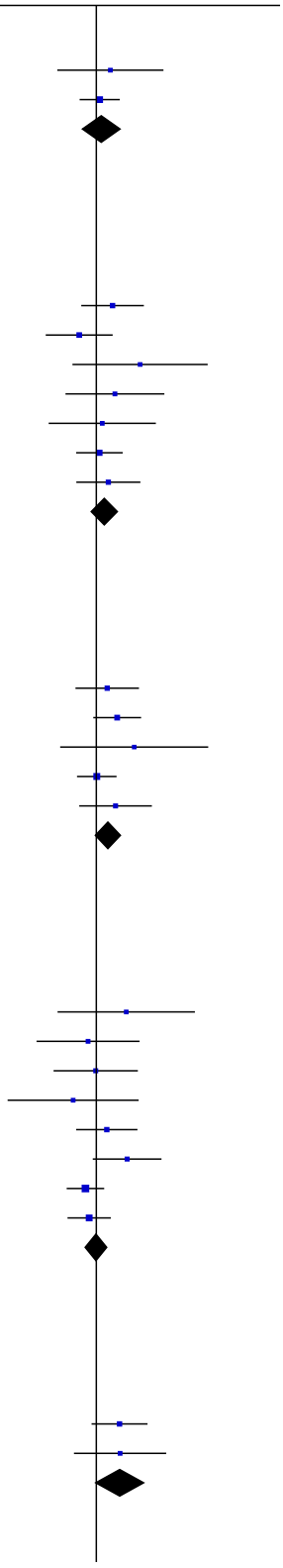
Analysis 1.18. Comparison 1: Anticholinergics versus placebo, Outcome 18: Adverse events: Pruritus/erythema

Study or Subgroup	Anticholinergic Events	Anticholinergic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.18.1 Fesoterodine						
DuBeau 2014	2	281	0	281	21.7%	5.00 [0.24 , 103.68]
Subtotal (95% CI)		**281**		**281**	**21.7%**	**5.00 [0.24 , 103.68]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0.30)						
1.18.2 Solifenacin						
Kosilov 2015b	1	206	1	102	58.0%	0.50 [0.03 , 7.84]
Kosilov 2015a	1	52	0	59	20.3%	3.40 [0.14 , 81.60]
Subtotal (95% CI)		**258**		**161**	**78.3%**	**1.25 [0.19 , 8.13]**
Total events:	2		1			
Heterogeneity: Chi² = 0.81, df = 1 (P = 0.37); I² = 0%						
Test for overall effect: Z = 0.23 (P = 0.82)						
Total (95% CI)		**539**		**442**	**100.0%**	**2.06 [0.44 , 9.55]**
Total events:	4		1			
Heterogeneity: Chi² = 1.45, df = 2 (P = 0.48); I² = 0%						
Test for overall effect: Z = 0.92 (P = 0.36)						
Test for subgroup differences: Chi² = 0.58, df = 1 (P = 0.45), I² = 0%						



Analysis 1.19. Comparison 1: Anticholinergics versus placebo, Outcome 19: Adverse events: Urinary tract infection (UTI)

Study or Subgroup	Anticholinergic Events	Anticholinergic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.19.1 Darifenacin						
Hill 2005	6	215	2	109	1.4%	1.52 [0.31 , 7.41]
Zinner 2006	20	214	19	225	9.4%	1.11 [0.61 , 2.02]
Subtotal (95% CI)		**429**		**334**	**10.8%**	**1.16 [0.66 , 2.03]**
Total events:	26		21			
Heterogeneity: Chi² = 0.14, df = 1 (P = 0.71); I² = 0%						
Test for overall effect: Z = 0.51 (P = 0.61)						
1.19.2 Fesoterodine						
Chapple 2014	33	1569	5	386	4.1%	1.62 [0.64 , 4.13]
DuBeau 2014	6	281	10	281	5.1%	0.60 [0.22 , 1.63]
Herschorn 2009a	15	679	1	167	0.8%	3.69 [0.49 , 27.73]
Kaplan 2011	14	960	2	239	1.6%	1.74 [0.40 , 7.62]
Nitti 2005	5	90	2	43	1.4%	1.19 [0.24 , 5.91]
Nitti 2007	25	561	11	271	7.5%	1.10 [0.55 , 2.20]
Wagg 2013a	10	392	7	393	3.6%	1.43 [0.55 , 3.72]
Subtotal (95% CI)		**4532**		**1780**	**24.1%**	**1.27 [0.86 , 1.87]**
Total events:	108		38			
Heterogeneity: Chi² = 3.92, df = 6 (P = 0.69); I² = 0%						
Test for overall effect: Z = 1.20 (P = 0.23)						
1.19.3 Solifenacin						
Abrams 2013	20	234	5	81	3.8%	1.38 [0.54 , 3.57]
Chu 2009	21	340	11	332	5.7%	1.86 [0.91 , 3.81]
Chua 2018	3	31	1	32	0.5%	3.10 [0.34 , 28.19]
Herschorn 2017a	21	423	21	429	10.6%	1.01 [0.56 , 1.83]
Karram 2009	9	372	5	367	2.6%	1.78 [0.60 , 5.25]
Subtotal (95% CI)		**1400**		**1241**	**23.1%**	**1.41 [0.97 , 2.05]**
Total events:	74		43			
Heterogeneity: Chi² = 2.45, df = 4 (P = 0.65); I² = 0%						
Test for overall effect: Z = 1.81 (P = 0.07)						
1.19.4 Tolterodine						
Herschorn 2009a	10	684	1	167	0.8%	2.44 [0.31 , 18.94]
Jonas 1997	7	197	2	44	1.7%	0.78 [0.17 , 3.64]
Kaplan 2011	12	973	3	239	2.5%	0.98 [0.28 , 3.45]
Khullar 2004	2	569	2	285	1.4%	0.50 [0.07 , 3.54]
Mitcheson 2019	12	257	7	205	4.0%	1.37 [0.55 , 3.41]
Rogers 2008	12	201	5	210	2.5%	2.51 [0.90 , 6.99]
Van Kerrebroeck 2001	29	1017	20	507	13.6%	0.72 [0.41 , 1.27]
Zinner 2002	16	503	20	508	10.1%	0.81 [0.42 , 1.54]
Subtotal (95% CI)		**4401**		**2165**	**36.4%**	**0.99 [0.72 , 1.36]**
Total events:	100		60			
Heterogeneity: Chi² = 6.53, df = 7 (P = 0.48); I² = 0%						
Test for overall effect: Z = 0.07 (P = 0.95)						
1.19.5 Trospium						
Rudy 2006	16	329	8	329	4.1%	2.00 [0.87 , 4.61]
Staskin 2007	6	298	3	303	1.5%	2.03 [0.51 , 8.06]
Subtotal (95% CI)		**627**		**632**	**5.6%**	**2.01 [0.98 , 4.10]**
Total events:	22		11			
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.98); I² = 0%						



Analysis 1.19. (Continued)

Total events: 22 11

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.98); I² = 0%

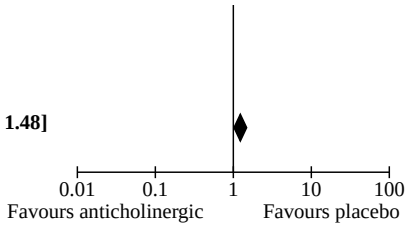
Test for overall effect: Z = 1.92 (P = 0.06)

Total (95% CI)	**11389**	**6152**	**100.0%**	**1.23 [1.02 , 1.48]**	
Total events:	330	173			

Heterogeneity: Chi² = 17.47, df = 23 (P = 0.79); I² = 0%

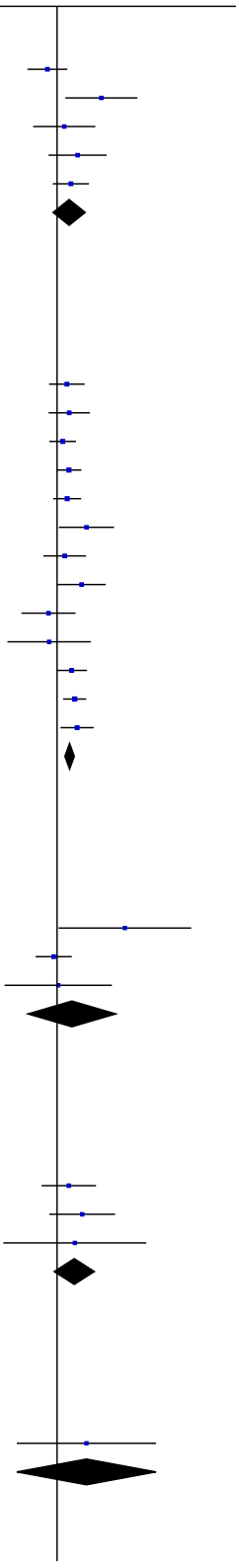
Test for overall effect: Z = 2.17 (P = 0.03)

Test for subgroup differences: Chi² = 4.18, df = 4 (P = 0.38), I² = 4.3%



Analysis 1.20. Comparison 1: Anticholinergics versus placebo, Outcome 20: Withdrawal due to adverse events

Study or Subgroup	Anticholinergic Events	Anticholinergic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.20.1 Darifenacin						
Chapple 2007b	12	266	9	133	1.9%	0.67 [0.29 , 1.54]
Haab 2004	9	115	2	164	0.7%	6.42 [1.41 , 29.15]
Hill 2005	8	215	3	109	0.9%	1.35 [0.37 , 4.99]
Steers 2004	15	268	3	127	1.0%	2.37 [0.70 , 8.04]
Zinner 2006	17	214	10	225	2.3%	1.79 [0.84 , 3.82]
Subtotal (95% CI)		**1078**		**758**	**6.8%**	**1.66 [0.84 , 3.27]**
Total events:	61		27			
Heterogeneity: Tau² = 0.29; Chi² = 8.00, df = 4 (P = 0.09); I² = 50%						
Test for overall effect: Z = 1.47 (P = 0.14)						
1.20.2 Fesoterodine						
Chapple 2004a	36	545	8	183	2.3%	1.51 [0.72 , 3.19]
Chapple 2007a	30	849	6	283	1.8%	1.67 [0.70 , 3.96]
Chapple 2014	72	1569	14	386	3.5%	1.27 [0.72 , 2.22]
Dmochowski 2010	34	438	21	445	3.8%	1.64 [0.97 , 2.79]
DuBeau 2014	26	281	17	281	3.3%	1.53 [0.85 , 2.76]
Herschorn 2009a	42	679	3	167	1.1%	3.44 [1.08 , 10.97]
Huang 2012	11	322	8	323	1.7%	1.38 [0.56 , 3.38]
Kaplan 2011	45	960	4	239	1.4%	2.80 [1.02 , 7.71]
Kaplan 2014	5	308	7	301	1.1%	0.70 [0.22 , 2.18]
Nitti 2005	3	90	2	43	0.5%	0.72 [0.12 , 4.13]
Nitti 2007	42	561	11	271	2.9%	1.84 [0.96 , 3.53]
Wagg 2013a	46	392	22	393	4.2%	2.10 [1.29 , 3.42]
Weiss 2013	25	463	11	474	2.6%	2.33 [1.16 , 4.67]
Subtotal (95% CI)		**7457**		**3789**	**30.4%**	**1.69 [1.39 , 2.06]**
Total events:	417		134			
Heterogeneity: Tau² = 0.00; Chi² = 8.74, df = 12 (P = 0.73); I² = 0%						
Test for overall effect: Z = 5.21 (P < 0.00001)						
1.20.3 Imidafenacin						
Homma 2008	25	300	0	101	0.2%	17.28 [1.06 , 281.33]
Homma 2009	30	634	8	147	2.3%	0.87 [0.41 , 1.86]
Yoshida 2018	1	117	3	369	0.3%	1.05 [0.11 , 10.01]
Subtotal (95% CI)		**1051**		**617**	**2.8%**	**1.86 [0.29 , 11.81]**
Total events:	56		11			
Heterogeneity: Tau² = 1.73; Chi² = 5.80, df = 2 (P = 0.05); I² = 66%						
Test for overall effect: Z = 0.66 (P = 0.51)						
1.20.4 Oxybutynin						
Abrams 1998	20	118	3	29	1.1%	1.64 [0.52 , 5.14]
Drutz 1999	23	112	2	28	0.8%	2.88 [0.72 , 11.48]
Thuroff 1991	2	63	0	26	0.2%	2.11 [0.10 , 42.49]
Subtotal (95% CI)		**293**		**83**	**2.1%**	**2.06 [0.89 , 4.80]**
Total events:	45		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.38, df = 2 (P = 0.83); I² = 0%						
Test for overall effect: Z = 1.68 (P = 0.09)						
1.20.5 Propantheline						
Thuroff 1991	3	54	0	26	0.2%	3.44 [0.18 , 64.17]
Subtotal (95% CI)		**54**		**26**	**0.2%**	**3.44 [0.18 , 64.17]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.83 (P = 0.41)						



Analysis 1.20. (Continued)

Heterogeneity: Not applicable
Test for overall effect: Z = 0.83 (P = 0.41)

1.20.6 Propiverine

Gotoh 2011	2	291	1	274	0.3%	1.88 [0.17 , 20.65]
Junemann 2006	26	786	1	202	0.4%	6.68 [0.91 , 48.95]
Lee 2006	6	176	1	88	0.4%	3.00 [0.37 , 24.53]
Madersbacher 1999	20	294	6	77	1.8%	0.87 [0.36 , 2.10]
Stohrer 1999	5	60	1	53	0.4%	4.42 [0.53 , 36.61]
Yamaguchi 2007	26	400	6	202	1.8%	2.19 [0.92 , 5.23]
Yamaguchi 2014	1	574	1	381	0.2%	0.66 [0.04 , 10.58]
Subtotal (95% CI)		**2581**		**1277**	**5.2%**	**1.74 [1.01 , 3.01]**
Total events:	86		17			

Heterogeneity: Tau² = 0.02; Chi² = 6.21, df = 6 (P = 0.40); I² = 3%
Test for overall effect: Z = 2.00 (P = 0.05)

1.20.7 Solifenacin

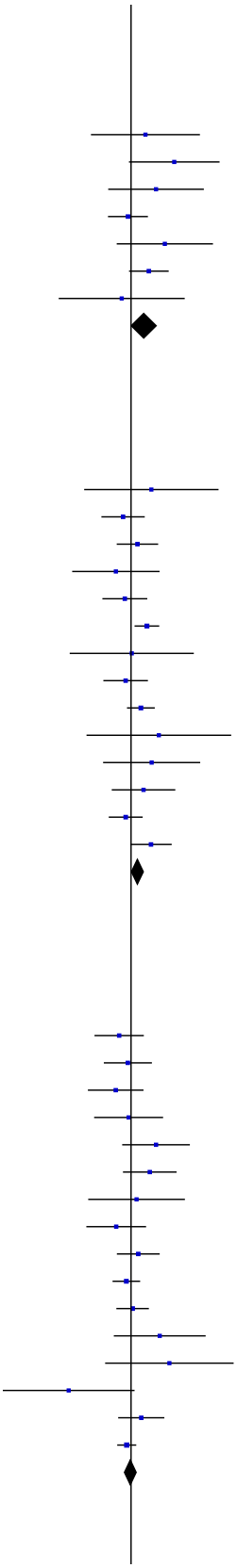
Abrams 2013	3	234	0	81	0.2%	2.44 [0.13 , 46.78]
Cardozo 2004a	7	299	10	301	1.6%	0.70 [0.27 , 1.83]
Cardozo 2008a	18	505	6	223	1.7%	1.32 [0.53 , 3.29]
Chapple 2004b	2	74	2	38	0.4%	0.51 [0.08 , 3.50]
Chapple 2004c	16	559	5	133	1.5%	0.76 [0.28 , 2.04]
Chu 2009	37	340	18	332	3.7%	2.01 [1.17 , 3.45]
Chua 2018	1	31	1	32	0.2%	1.03 [0.07 , 15.79]
Herschorn 2017a	7	423	9	429	1.5%	0.79 [0.30 , 2.10]
Karram 2009	25	372	16	367	3.1%	1.54 [0.84 , 2.84]
Kosilov 2015a	1	52	0	59	0.2%	3.40 [0.14 , 81.60]
Kosilov 2015b	5	206	1	102	0.4%	2.48 [0.29 , 20.91]
Oreskovic 2012	5	77	3	80	0.8%	1.73 [0.43 , 7.00]
Vardy 2009	12	385	15	381	2.3%	0.79 [0.38 , 1.67]
Yamaguchi 2007	46	777	5	203	1.7%	2.40 [0.97 , 5.97]
Subtotal (95% CI)		**4334**		**2761**	**19.1%**	**1.32 [1.02 , 1.71]**
Total events:	185		91			

Heterogeneity: Tau² = 0.00; Chi² = 11.92, df = 13 (P = 0.53); I² = 0%
Test for overall effect: Z = 2.10 (P = 0.04)

1.20.8 Tolterodine

Abrams 1998	10	118	4	28	1.2%	0.59 [0.20 , 1.75]
Abrams 2001	9	149	5	72	1.3%	0.87 [0.30 , 2.50]
Chapple 2004c	5	263	5	134	1.0%	0.51 [0.15 , 1.73]
Drutz 1999	7	109	2	28	0.7%	0.90 [0.20 , 4.09]
Herschorn 2008	12	402	2	201	0.7%	3.00 [0.68 , 13.28]
Herschorn 2009a	28	684	3	167	1.1%	2.28 [0.70 , 7.41]
Jacquetin 2001	5	200	1	51	0.4%	1.27 [0.15 , 10.67]
Jonas 1997	7	197	3	44	0.9%	0.52 [0.14 , 1.94]
Kaplan 2011	28	973	5	239	1.6%	1.38 [0.54 , 3.52]
Khullar 2004	26	569	16	285	3.2%	0.81 [0.44 , 1.49]
Kuo 2015	15	377	14	377	2.5%	1.07 [0.52 , 2.19]
Malone-Lee 2001	11	134	1	43	0.4%	3.53 [0.47 , 26.56]
Millard 1999	10	252	0	64	0.2%	5.40 [0.32 , 90.87]
Rentzhog 1998	0	30	3	13	0.2%	0.06 [0.00 , 1.17]
Rogers 2008	9	201	6	210	1.4%	1.57 [0.57 , 4.32]
Van Kerrebroeck 2001	55	1021	33	507	5.0%	0.83 [0.54 , 1.26]
Subtotal (95% CI)		**5679**		**2463**	**21.7%**	**0.97 [0.75 , 1.25]**
Total events:	237		103			

Heterogeneity: Tau² = 0.02; Chi² = 15.94, df = 15 (P = 0.39); I² = 6%
Test for overall effect: Z = 0.25 (P = 0.80)



Analysis 1.20. (Continued)

Heterogeneity: Tau² = 0.02; Chi² = 15.94, df = 15 (P = 0.39); I² = 6%
Test for overall effect: Z = 0.25 (P = 0.80)

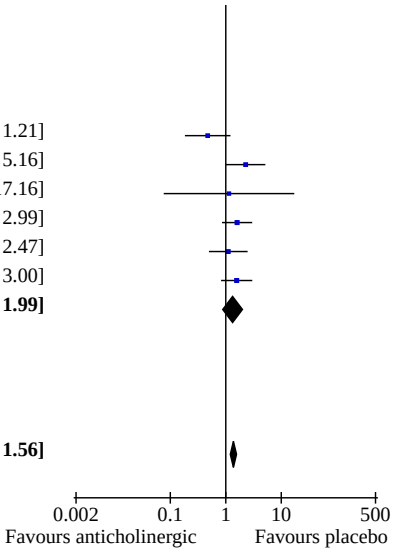
1.20.9 Trospium

Alloussi 1998	8	178	8	84	1.6%	0.47 [0.18 , 1.21]
Dmochowski 2008	18	280	8	284	2.0%	2.28 [1.01 , 5.16]
Geller 2013	1	21	1	24	0.2%	1.14 [0.08 , 17.16]
Rudy 2006	24	329	15	329	3.0%	1.60 [0.85 , 2.99]
Staskin 2007	12	298	11	303	2.1%	1.11 [0.50 , 2.47]
Zinner 2004	22	256	14	256	2.9%	1.57 [0.82 , 3.00]
Subtotal (95% CI)		**1362**		**1280**	**11.8%**	**1.33 [0.88 , 1.99]**
Total events:	85		57			

Heterogeneity: Tau² = 0.07; Chi² = 7.08, df = 5 (P = 0.21); I² = 29%
Test for overall effect: Z = 1.35 (P = 0.18)

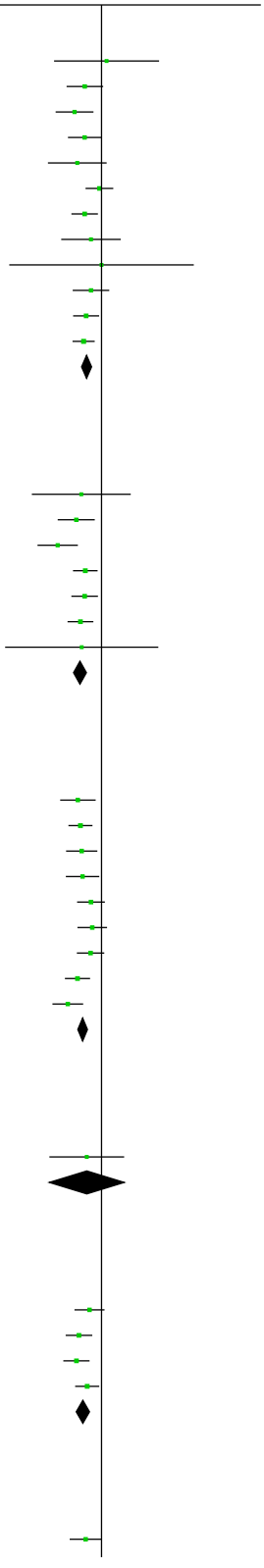
Total (95% CI)		**23889**		**13054**	**100.0%**	**1.37 [1.21 , 1.56]**
Total events:	1175		445			

Heterogeneity: Tau² = 0.04; Chi² = 78.73, df = 67 (P = 0.15); I² = 15%
Test for overall effect: Z = 4.84 (P < 0.00001)
Test for subgroup differences: Chi² = 13.96, df = 8 (P = 0.08), I² = 42.7%



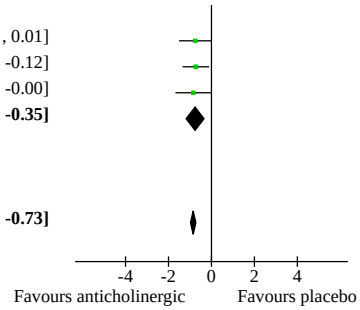
Analysis 1.21. Comparison 1: Anticholinergics versus placebo, Outcome 21: Mean number of micturitions per 24 hours

Study or Subgroup	Anticholinergic Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.21.1 Tolterodine								
Chapple 2004b	10.31	3.79	37	10.07	4.7	18	0.3%	0.24 [-2.25 , 2.73]
Chapple 2004c	10.2	3.71	250	10.99	4.21	126	2.1%	-0.79 [-1.66 , 0.08]
Chapple 2007a	9.77	3.79	283	11.05	4.7	139	1.9%	-1.28 [-2.18 , -0.38]
Herschorn 2009a	9.6	3.79	634	10.4	4.7	157	2.5%	-0.80 [-1.59 , -0.01]
Jacquetin 2001	9.35	3.79	200	10.5	4.7	51	0.8%	-1.15 [-2.54 , 0.24]
Kaplan 2011	9.6	3.79	935	9.7	4.7	227	3.6%	-0.10 [-0.76 , 0.56]
Khullar 2004	8.5	3.79	569	9.3	4.7	285	4.0%	-0.80 [-1.43 , -0.17]
Kuo 2015	11.4	3.79	74	11.9	4.7	68	0.8%	-0.50 [-1.91 , 0.91]
Orri 2014	9.1	3.79	11	9.1	4.7	6	0.1%	0.00 [-4.38 , 4.38]
Rogers 2008	9.7	3.79	182	10.2	4.7	189	2.1%	-0.50 [-1.37 , 0.37]
Yamaguchi 2012	9.7	3.79	368	10.43	4.7	368	4.1%	-0.73 [-1.35 , -0.11]
Zinner 2002	9.2	3.79	506	10.05	4.7	507	5.6%	-0.85 [-1.38 , -0.32]
Subtotal (95% CI)			**4049**			**2141**	**27.8%**	**-0.71 [-0.95 , -0.47]**
Heterogeneity: Chi² = 6.64, df = 11 (P = 0.83); I² = 0%								
Test for overall effect: Z = 5.87 (P < 0.00001)								
1.21.2 Solifenacin								
Chapple 2004b	9.11	3.79	70	10.07	4.7	18	0.3%	-0.96 [-3.31 , 1.39]
Chapple 2004c	9.79	3.79	530	10.99	4.7	127	2.0%	-1.20 [-2.08 , -0.32]
Chua 2018	9.61	1.558974	31	11.69	2.262742	32	1.7%	-2.08 [-3.04 , -1.12]
Herschorn 2017a	8.56	3.79	413	9.33	4.7	412	4.6%	-0.77 [-1.35 , -0.19]
Karram 2009	9	3.79	357	9.8	4.7	350	3.9%	-0.80 [-1.43 , -0.17]
Vardy 2009	9.55	3.79	374	10.55	4.7	374	4.2%	-1.00 [-1.61 , -0.39]
Zesiewicz 2015	8	3.79	9	8.94	4.7	12	0.1%	-0.94 [-4.57 , 2.69]
Subtotal (95% CI)			**1784**			**1325**	**16.8%**	**-1.02 [-1.33 , -0.72]**
Heterogeneity: Chi² = 6.06, df = 6 (P = 0.42); I² = 1%								
Test for overall effect: Z = 6.58 (P < 0.00001)								
1.21.3 Fesoterodine								
Chapple 2007a	9.93	3.79	541	11.05	4.7	140	2.2%	-1.12 [-1.96 , -0.28]
Dmochowski 2010	9.9	3.79	428	10.9	4.7	434	4.8%	-1.00 [-1.57 , -0.43]
DuBeau 2014	9.76	3.79	258	10.7	4.7	253	2.8%	-0.94 [-1.68 , -0.20]
Herschorn 2009a	9.5	3.79	628	10.4	4.7	157	2.5%	-0.90 [-1.69 , -0.11]
Kaplan 2011	9.2	3.79	916	9.7	4.7	227	3.6%	-0.50 [-1.16 , 0.16]
Kaplan 2014	10.4	3.79	292	10.84	4.7	279	3.2%	-0.44 [-1.14 , 0.26]
Nitti 2007	10.6	3.79	534	11.12	4.7	266	3.7%	-0.52 [-1.17 , 0.13]
Wagg 2013a	9.81	3.79	392	10.95	4.7	393	4.4%	-1.14 [-1.74 , -0.54]
Yonguc 2019	7	1.2	32	8.6	1.7	31	2.9%	-1.60 [-2.33 , -0.87]
Subtotal (95% CI)			**4021**			**2180**	**30.1%**	**-0.90 [-1.12 , -0.67]**
Heterogeneity: Chi² = 8.93, df = 8 (P = 0.35); I² = 10%								
Test for overall effect: Z = 7.72 (P < 0.00001)								
1.21.4 Oxybutynin								
Drutz 1999	9.6	3.2	41	10.3	3.2	18	0.5%	-0.70 [-2.47 , 1.07]
Subtotal (95% CI)			**41**			**18**	**0.5%**	**-0.70 [-2.47 , 1.07]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.77 (P = 0.44)								
1.21.5 Propiverine								
Gotoh 2011	9.17	3.79	284	9.74	4.7	270	3.1%	-0.57 [-1.28 , 0.14]
Homma 2009	9.36	2.46	305	10.43	2.44	71	3.9%	-1.07 [-1.70 , -0.44]
Junemann 2006	9.1	3.66	723	10.29	3.92	187	4.0%	-1.19 [-1.81 , -0.57]
Yamaguchi 2014	9.19	3.79	559	9.87	4.7	373	4.8%	-0.68 [-1.25 , -0.11]
Subtotal (95% CI)			**1871**			**901**	**15.8%**	**-0.89 [-1.20 , -0.57]**
Heterogeneity: Chi² = 2.50, df = 3 (P = 0.48); I² = 0%								
Test for overall effect: Z = 5.52 (P < 0.00001)								
1.21.6 Imidafenacin								
Homma 2008	9.59	2.49	93	10.34	2.82	95	2.7%	-0.75 [-1.51 , 0.01]



Analysis 1.21. (Continued)

1.21.6 Imidafenacin								
Homma 2008	9.59	2.49	93	10.34	2.82	95	2.7%	-0.75 [-1.51 , 0.01]
Homma 2009	9.7	2.23	318	10.43	2.44	72	4.1%	-0.73 [-1.34 , -0.12]
Yoshida 2018	9.15	3.79	117	9.99	4.7	369	2.2%	-0.84 [-1.68 , -0.00]
Subtotal (95% CI)			**528**			**536**	**9.0%**	**-0.76 [-1.18 , -0.35]**
Heterogeneity: Chi² = 0.04, df = 2 (P = 0.98); I² = 0%								
Test for overall effect: Z = 3.60 (P = 0.0003)								
Total (95% CI)			**12294**			**7101**	**100.0%**	**-0.85 [-0.98 , -0.73]**
Heterogeneity: Chi² = 27.17, df = 35 (P = 0.83); I² = 0%								
Test for overall effect: Z = 13.36 (P < 0.00001)								
Test for subgroup differences: Chi² = 2.99, df = 5 (P = 0.70), I² = 0%								



ADDITIONAL TABLES

Table 1. Quality of life outcome of studies that were not included in meta-analysis

Study ID	QoL measure	Direction and measurement of the scale, MCID	Result (mean change from baseline*)	Interpretation
Chapple 2004b	Contilife score	Scores range from 0 to 100, lower score indicates higher QoL MCID: unknown	Tolterodine (n = 37): 9.9 Solifenacin (n = 70): 16.4 Placebo (n = 36): 4.1	Anticholinergics improve QoL compared to placebo
Chapple 2013	ICIQ-OABqol	25 to 160 overall score with greater values indicating increased impact on QoL MCID: unknown/unclear	Tolterodine (n = 84): -17.42 Placebo (n = 162): - 16.11	Anticholinergics improve QoL compared to placebo
Chapple 2014	OAB-q (total HRQL)	0- to 100-point scale, higher HRQL scores indicate better HRQL MCID: 10 points	Fesoterodine (n = 1378): 26 Placebo (n = 347): 19	Anticholinergics improve QoL compared to placebo
Dmochowski 2010	KHQ incontinence impact score	0- to 100-point scale, lower scores indicates higher QoL MCID: 5 points	Trospium (n = 530): -23 Placebo (n = 556): -17	The result shows improvement of QoL in terms of incontinence impact score, but the improvement was also demonstrated in all of the other KHQ domains
Gotoh 2011	KHQ incontinence impact score	0- to 100-point scale, lower scores indicates higher QoL MCID: 5 points	Propiverine (n = 284): -21 Placebo (n = 270): -14	The result shows improvement of QoL in terms of incontinence impact score, but the improvement was also demonstrated in all of the other KHQ domains
Herschorn 2009a	OAB-q (total HRQL)	0– to 100-point scale, higher HRQL scores indicate better HRQL MCID: 10 points	Tolterodine (n = 641): 16.3 Fesoterodine (n = 636): 19.3 Placebo (n = 313): 12.0	Anticholinergics improve QoL compared to placebo

Table 1. Quality of life outcome of studies that were not included in meta-analysis *(Continued)*

Homma 2003	KHQ	Not applicable as data are not shown	Results are not presented in a table. In the text, oxybutynin and tolterodine are described as better than placebo according to P values.	Anticholinergics improve QoL compared to placebo
Homma 2009	KHQ	Not applicable as data are not shown	Results are not presented in a table. In the text, imidafenacin and propiverine are described as better than placebo according to P values.	Anticholinergics improve QoL compared to placebo
Kaplan 2011	OAB-q (total HRQL)	0– to 100-point scale, higher HRQL scores indicate better HRQL MCID: 10 points	Tolterodine (n = 942): 19.5 Fesoterodine (n = 930): 22.9 Placebo (n = 462): 17.2	Anticholinergics improve QoL compared to placebo
Karram 2009	OAB-q (total HRQL)	0– to 100-point scale, higher HRQL scores indicate better HRQL MCID: 10 points	Solifenacin (n = 357): 22.6 Placebo (n = 350): 17.2	Anticholinergics improve QoL compared to placebo
Khullar 2004	KHQ incontinence impact score	0- to 100-point scale, lower scores indicates higher QoL MCID: 5 points	Tolterodine (n = 569): -20.4 Placebo (n = 285): -15.5	The result shows improvement of QoL in terms of incontinence impact score, but the improvement was also demonstrated in all of the other KHQ domains
Oreskovic 2012	UDI and IIQ	UDI: range 0 to 300, lower scores indicate better QoL IIQ: 0 to 400, lower scores indicate better QoL MCID: unclear	UDI score was significantly improved after solifenacin (22.26 ± 5.91 vs 29.61 ± 8.45) compared to placebo. IIQ score was decreased in patients with solifenacin (36.25 ± 10.34 vs 46.86 ± 6.81, P < 0.001) compared to placebo	Anticholinergics improve QoL compared to placebo
Vardy 2009	OAB-q (total HRQL)	0– to 100-point scale, higher HRQL scores indicate better HRQL MCID: 10 points	Solifenacin (n = 374): 25.5 Placebo (n = 374): 16.65	Anticholinergics improve QoL compared to placebo
Weiss 2013	OAB-q (total HRQL)	0– to 100-point scale, higher HRQL scores indicate better HRQL MCID: 10 points	Fesoterodine (n = 381): 17 Placebo (n = 400): 14.9	Anticholinergics improve QoL compared to placebo
Yamaguchi 2007	KHQ incontinence impact score	0- to 100-point scale, lower scores indicates higher QoL MCID: 5 points	Solifenacin (n = 754): -21.5 Propiverine (n = 384): -17 Placebo (n = 395): -7	The result shows improvement of QoL in terms of incontinence impact score, but the improvement was also demonstrated in all of the other KHQ domains

Table 1. Quality of life outcome of studies that were not included in meta-analysis *(Continued)*

Yamaguchi 2014	KHQ incontinence impact score	0- to 100-point scale, lower scores indicates higher QoL MCID: 5 points	Propiverine (n = 559): -16 Placebo (n = 3737): -14	The result shows improvement of QoL in terms of incontinence impact score, but the improvement was also demonstrated in all of the other KHQ domains
Zinner 2004	IIQ	0 to 400, lower scores indicate better QoL MCID: unclear	Trospium change from baseline score indicated improvement in all IIQ domains (travel, social relationships, emotional health, physical activity) compared to placebo	Anticholinergics improve QoL compared to placebo
Zinner 2006	OAB-q, KHQ and ICIQ	Not applicable as data are not shown	Darifenacin showed improvement compared to placebo in all domains of all three measures	Anticholinergics improve QoL compared to placebo

*unless specified otherwise
HRQL: health-related quality of life
ICIQ: International Consultation of Incontinence Questionnaire
IIQ: Incontinence Impact Questionnaire
KHQ: King's Health Questionnaire
MCID: minimal clinically important difference
OAB-q: overactive bladder questionnaire
QoL: quality of life
UDI: Urogenital Distress Inventory

Table 2. Patient perception of cure or improvement outcome in studies that were not included in meta-analysis (using PPBC measure)

Study ID	Score/measure	Interpretation
De Ridder 2012	PPBC (change from baseline) Placebo: -0.1 Solifenacin: -0.5 Oxybutynin: -0.5	Solifenacin and oxybutynin may improve patient perception of bladder condition compared to placebo.
Herschorn 2017a	PPBC (change from baseline) Placebo: -0.9 Solifenacin: -1.3	Solifenacin may improve patient perception of bladder condition compared to placebo.

PPBC: patient perception of cure or improvement.
A decrease in PPBC score indicates improvement.
Minimal clinically important difference is unclear.

Table 3. Patient perception of cure or improvement - direction of effect plot

Study	Study design	Patient perception of cure or improvement
Geller 2013	RCT	▲
Zesiewicz 2015	RCT	▲
Burgio 1998	RCT	▲
Khullar 2004	RCT	▲
Vardy 2009	RCT	▲
Millard 1999	RCT	▲
Rovner 2005	RCT	▲
Takayasu 1990	Not reported	▲

▲ - represents improvement

APPENDICES

Appendix 1. Glossary of terms

Anticholinergics: Drugs that block the action of neurotransmitter 'acetylcholine' in the nervous system.

Autonomic nervous system: Regulates bodily functions such as heart rate.

Detrusor hyperreflexia: Involuntary contraction of the detrusor muscle causing increased frequency, urge and urgency incontinence.

Detrusor overactivity: Involuntary contraction of the detrusor muscle during the filling phase of the bladder.

Idiopathic detrusor overactivity: Involuntary contraction of the detrusor muscle during the filling phase of the bladder due to an unknown cause.

Neurogenic detrusor overactivity: Involuntary contraction of the detrusor muscle during the filling phase of the bladder due to an acquired or congenital (from birth) neurological condition.

Overactive bladder: A collection of symptoms including a sudden urge to urinate (pass urine), involuntary loss of urine and frequent urination.

Parasympathetic nervous system: Part of the autonomic nervous system, which monitors and regulates various bodily processes.

Urge urinary incontinence: A strong and sudden urge to urinate and leakage of urine.

Urinary incontinence: Involuntary leakage of urine.

Urodynamics: Tests to evaluate the function of the urinary bladder, sphincter and urethra.

Appendix 2. Cochrane Incontinence Specialised Register search strategy

The Cochrane Incontinence Specialised Register was searched using the Group's own keyword system. The search terms used were:

{design.rct*} OR {design.cct*}
AND
{TOPIC.URINE.INCON*} OR {TOPIC.URINE.overactivebladder*}
AND
({INTVENT.CHEM.DRUG.ANTICHOLINERGIC*} AND {INTVENT.CHEM.PLACEBO}) OR {relevant.review.anticholinergicVSplacebo}

All searches were of the keywords field of EndNote 2018.

The date of the last search that was fully incorporated into the review was 14 January 2020.

An updated search was performed on 3 May 2022 but was not fully incorporated into the review. At the time of this updated search the Cochrane Incontinence Specialised Register had been updated to 20 April 2022.

The Cochrane Incontinence Specialised Register search does not include a search of Embase as the Cochrane Centralised Search Service includes Embase in its search for records to be included in CENTRAL. During informal testing for a number of our Cochrane Reviews we have found that additional searches of Embase do not locate additional relevant records for our Cochrane Reviews.

FEEDBACK

Chapple 2004b: Study characteristics, July 2007

Summary

We believe that the study characteristics quoted on pages 27 and 28 do not appear to correlate to those in the published paper. Whereas the study cited in the review investigated only solifenacin, with tolterodine as a comparator, the characteristics quoted include details about another anticholinergic compound, darifenacin, implying that this compound was included for comparison in the study. It seems possible that a second paper by Chapple et al, reporting on the efficacy of darifenacin, has been included in the description of the study characteristics by mistake (this second paper, entitled 'A pooled analysis of three phase III studies to investigate the efficacy, tolerability and safety of darifenacin, a muscarinic M3 selective receptor antagonist, in the treatment of overactive bladder' (BJU 2005;95(7):993-1001), discusses two doses of darifenacin (7.5 mg, n = 337 and 15 mg, n = 334) versus placebo (n=388)).
We would therefore like to request a review of the text on pages 27 and 28, and a potential amendment to the study characteristics as necessary. In addition, as quality of life (QoL) data is not discussed in either of the above papers by Chapple et al, statements such as 'QoL data reported favours solifenacin' in the table of study characteristics are potentially misleading to the reader.

We look forward to your review of the text and modification of the study characteristics table.

Reply

The information in the 'Characteristics of included studies' has now been changed.

Contributors

Response prepared by: Nabi Ghulam (review author), Peter Herbison (Feedback Editor), June Cody (Managing Editor)

WHAT'S NEW

Date	Event	Description
9 May 2023	New search has been performed	For this update, we made the following changes: 1. The search was updated to January 2020 and we included 71 new studies (Abrams 2013; Baert 1995; Bray 2018; Cardozo 2008a; Chapple 2004c; Chapple 2007a; Chapple 2007b; Chapple 2013; Chapple 2014; Chu 2009; Chua 2018; De Ridder 2012; Dmochowski 2008; Dmochowski 2010; DuBeau 2014; Elbaset 2019; EUCTR2004-001116-31-ES; EUCTR2004-002143-27-AT; EUCTR2007-004126-24-CZ; Geller 2013; Gotoh 2011; Griebenow 1994; Hajebrahimi 2014; Herschorn 2008; Herschorn 2009a; Herschorn 2017a; Herschorn 2017b; Hill 2005; Homma 2008; Homma 2009; Huang 2012; Junemann 2006; Kaplan 2011; Kaplan 2014; Karram 2009; Khullar 2013; Kosilov 2014a; Kosilov 2015a; Kosilov 2015b; Kreder 2002; Kuo 2015;Lackner 2011; Lee 2006; Luis 2018; Mitcheson 2019; Nitti 2005; Nitti 2007; Olshansky 2006; Oreskovic 2012; Orri 2014; Resnick 2006; Robinson 2013; Rogers 2008; Romanzi 2005; Rudy 2006; Staskin 2004; Staskin 2007; Staskin 2019; Steers 2004; Takayasu 1990; Van Kerrebroeck 2001; Vardy 2009; Wagg 2013a; Weiss 2013; Yamaguchi 2007; Yamaguchi 2012; Yamaguchi 2014; Yonguc 2019; Yoshida 2018; Zesiewicz 2015; Zinner 2006).

Date	Event	Description
		2. In accordance with Cochrane standards, we performed a full risk of bias assessment on all studies and evaluated the certainty of the evidence by adopting the GRADE approach.
9 May 2023	New citation required but conclusions have not changed	The byline has changed.

HISTORY

Protocol first published: Issue 4, 1999
Review first published: Issue 3, 2002

Date	Event	Description
16 September 2008	Amended	Converted to new review format.
22 August 2006	New citation required and conclusions have changed	Substantive amendment: 14 trials added.

CONTRIBUTIONS OF AUTHORS

AS: performed title and abstract screening, full-text screening and data extraction, contributed to data entry and analyses, risk of bias and GRADE assessment of papers and drafted sections of the manuscript.

PM: completed all aspects of data screening, extraction, analysis and drafting of an unpublished version of this manuscript written in 2016, which was used as a basis for this update. Shared data and provided feedback on this update.

MS: contributed to full-text screening, performed data extraction, analyses, risk of bias and GRADE assessment of papers, and contributed to drafting of the manuscript.

EBM: updated the protocol for this review, performed title and abstract screening, full-text screening and data extraction, contributed to data entry and analyses, and contributed to the draft of the manuscript.

GN: provided critical analysis and comment on the current update as published, as well as contributing to the 2016 version and the last update of this review in 2006.

MIO: assessed the quality of evidence, offered methodological advice and contributed to the draft of the unpublished 2016 version of this review. Provided clinical advice and comments on this update.

DECLARATIONS OF INTEREST

The declarations below are current up to three years prior to publication date of this protocol, in accordance with Cochrane's Commercial Sponsorship Policy.

AS: none known.
PM: none known.
MS: none known.
EBM: none known.
GN: none known.
MIO: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- National Institute for Health Research, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In this version of the review, we made the following changes:

Criteria for considering studies for this review

- We excluded studies that had combined types of interventions (e.g. pharmacological and behavioural).
- We excluded studies of relevant anticholinergic drugs, which were not orally administered.
- We excluded cluster-randomised trials and cross-over trials.
- We excluded dicyclomine anticholinergic, because it is an anticholinergic used to treat irritable bowel syndrome and is not used in clinical practice for overactive bladder syndrome.
- We used up-to-date therapeutic dosages of the anticholinergics, following British National Formulary guidance.

Data collection and analysis

We have substantively revised, updated and reformatted the review in accordance with current Cochrane standards, including reconsidering the outcomes and comparisons, performing a full risk of bias assessment for all included studies, adding a summary of findings table and using the GRADE approach to assess the certainty of the body of evidence.

Funnel plots were published and interpreted for outcomes with at least 10 included studies, and were limited to those outcomes in the summary of findings table.

INDEX TERMS

Medical Subject Headings (MeSH)

Cholinergic Antagonists [*therapeutic use]; Randomized Controlled Trials as Topic; Syndrome; Urinary Bladder, Overactive [*drug therapy]

MeSH check words

Adult; Humans