

Review – Neuro-urology

Comparative Efficacy and Safety of Medical Treatments for the Management of Overactive Bladder: A Systematic Literature Review and Mixed Treatment Comparison

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Abstract

Context: Overactive bladder (OAB) treatment guidelines recommend antimuscarinics as first-line pharmacologic therapy. Mirabegron is a first-in-class β_3 -adrenoceptor agonist licensed for the treatment of OAB and has shown to be well tolerated and effective in the treatment of OAB symptoms.

Objective: To assess the relative efficacy and tolerability of OAB medications, specifically mirabegron 50 mg versus antimuscarinics in patients with OAB.

Evidence acquisition: A systematic literature search was performed on published peer-reviewed articles from 2000 to 2013. This review included randomised controlled trials (RCTs) studying changes in symptoms (micturition frequency, incontinence, and urgency urinary incontinence [UUI] episodes) and incidence of the most frequently reported adverse events (dry mouth, constipation) associated with current OAB medications. The following drugs were considered in addition to mirabegron: darifenacin, tolterodine immediate release (IR) and extended release (ER), oxybutynin IR/ER, trospium, solifenacin, and fesoterodine. Bayesian mixed treatment comparisons (MTCs) were performed for efficacy (micturition, incontinence, UUI) and tolerability (dry mouth, constipation, blurred vision).

Evidence synthesis: Overall, 44 RCTs involving 27 309 patients were included. The MTCs showed that mirabegron 50 mg was as efficacious as antimuscarinics in reducing the frequency of micturition incontinence and UUI episodes, with the exception of solifenacin 10 mg that was more efficacious than mirabegron 50 mg in improving micturition frequency and frequency of UUI. Mirabegron 50 mg had an incidence of dry mouth similar to placebo and significantly lower than all included antimuscarinics.

Conclusions: Mirabegron 50 mg had similar efficacy to most antimuscarinics and lower incidence of dry mouth, the most common adverse event reported with antimuscarinics and one of the main causes of discontinuation of treatment. Despite being a powerful tool for evidence-based health care evaluation, the Bayesian MTC method has limitations. Further head-to-head comparisons between mirabegron and antimuscarinics should be conducted to confirm our results.

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1. Introduction

Overactive bladder (OAB) is specifically defined by the International Continence Society as urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence [UUI], in the absence of urinary tract infection (UTI) or other obvious pathology [1]. The prevalence of OAB in the general population was estimated at 11.8% in a population-based survey conducted across five European countries [2].

Several treatment options are available for OAB including bladder and behavioural training, pharmacologic treatment, and surgical therapies [3]. Oral antimuscarinics represent the mainstay of pharmacologic treatment for the management of OAB. They are recognised to be effective in the improvement of OAB symptoms and have a good safety profile. However, the incidence of antimuscarinic-induced adverse events is relatively high [4]. Dry mouth and constipation are the most commonly reported adverse events. Persistence rates with antimuscarinic therapy are low, with lack of efficacy and adverse events among the most frequent reasons for discontinuation [5]. A study based on prescription data from the United Kingdom estimated that discontinuation rates at 12 mo for OAB patients on antimuscarinics ranged between 65% and 86% [6].

Several systematic reviews and meta-analyses of OAB drugs conducted within the last few years showed that antimuscarinics provide better efficacy compared with placebo, but no clear differences in efficacy between antimuscarinics were found [7–10]. Novara et al. reported that extended-release (ER) formulations offered advantages in terms of efficacy and safety compared with immediate-release (IR) formulations [10]. The latest review to date by Buser et al., including RCTs of different formulations and dosage strengths of antimuscarinics, concluded that there was no clinically relevant difference in efficacy between treatments, and that in terms of adverse events, high dosages of oxybutynin and propiverine were associated with a greater risk of adverse events [7].

The β 3-adrenoreceptor agonist mirabegron was investigated in patients with OAB against placebo and was shown to be effective and to have a good safety and tolerability profile. It led to improvements in the key OAB symptoms of urinary incontinence and frequency of micturition [11]. To assess whether this drug with a new mode of action offers a valuable therapeutic alternative or complement to the current treatment of OAB, a comparison with existing pharmacologic treatments is required. In this regard, and because limited head-to-head evidence is available, we performed a systematic review and Bayesian mixed treatment comparison (MTCs) for OAB treatments.

The aim of this quantitative synthesis of the literature was to compare the clinical efficacy and safety of the most widely used OAB pharmacologic treatments and more specifically to estimate the efficacy and safety of mirabegron compared with antimuscarinics.

2. Evidence acquisition

2.1. Search strategy

The literature search was undertaken according to the guidelines of the Centre for Reviews and Dissemination and Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [12]. To identify randomised controlled trials (RCTs) analysing the efficacy and safety of mirabegron and other OAB pharmacologic treatments, a systematic literature search was conducted using Ovid Medline In-Process and Other Non-Indexed Citations, Ovid Medline, and Embase (Ovid) databases. We also searched the Cochrane Central Register of Controlled Trials using search terms similar to those used for the Embase/Medline searches on June 20, 2013. Supplemental Appendix 1 provides the full list of search terms. The manufacturer of mirabegron and solifenacin (Astellas) provided clinical reports of RCTs of those treatments. In addition, we searched the bibliographies of previous systematic reviews [8,9].

2.2. Eligibility criteria

This review considered all RCTs studying the efficacy or the safety of pharmacologic treatments in the management of OAB. Case report studies, case series, and database studies were excluded from the review. No language restriction and no geographic restriction were applied. All publications from 2000 onwards were included in the search. Only full published articles were included. Letters, abstracts, and literature reviews were excluded.

Reviewed studies enrolled adults (≥ 18 yr of age, men and/or women) who had a diagnosis of OAB. Studies referring to a diagnosis of “detrusor overactivity” or “urinary urgency” were also included. Studies among patients with neurogenic detrusor overactivity and men with lower urinary tract symptoms associated with benign prostatic hyperplasia were excluded from the review. Supplemental Appendix 2 lists the inclusion/exclusion criteria for the MTC analysis.

This review included studies on most approved drugs used in Europe for the management of OAB (ie, darifenacin 7.5, 15 mg; fesoterodine 4, 8 mg; oxybutynin ER 5, 10, 15 mg; oxybutynin IR 10, 15 mg; solifenacin 5, 10 mg; tolterodine IR 4 mg; tolterodine ER 4 mg; or trospium 40, 60 mg) as well as studies of mirabegron 50 mg. The intervention group should have received an antimuscarinic or mirabegron 50 mg; the control group could use an antimuscarinic (different drug, formulation, or dosage) or placebo.

To be eligible, a study had to report a measure of efficacy or safety of OAB treatment. The following measures of OAB symptoms improvement were considered: changes over 8–16 wk in the number of micturition, incontinence, or UUI episodes per 24 h. Where reported, changes over 12 wk were retained. Studies reporting safety outcomes were considered if numbers of patients with dry mouth, constipation, and/or blurred vision over 4–16 wk could be derived from publications.

2.3. Study selection

Publications identified through the electronic searches were assessed independently for relevance by two reviewers. Any disagreement between reviewers was resolved by discussion and consensus.

In a second step, the reviewers read the full text of the retrieved references and selected the articles that met the inclusion criteria. The articles finally selected for the review were checked to identify different articles related to the same study. Records of the selection process were kept, and a PRISMA flowchart was generated.

2.4. Assessment of risks of bias

2.4.1. Assessment of the quality of evidence

Two reviewers independently assessed the included studies for risk of bias using criteria associated with randomisation, allocation concealment, baseline comparability, blinding, follow-up, and selective reporting, as recommended by the UK National Institute for Health and Care Excellence. Disagreements between reviewers were resolved by discussion and consensus.

2.5. Data analysis: mixed treatment comparison

A Bayesian MTC was conducted to estimate the relative efficacy and safety of mirabegron compared with all OAB treatments of interest. MTC is an extension of meta-analysis [13]. It allows comparing treatments even if all the treatments have not been directly compared head to head in randomised clinical trials. A strength of the MTC approach is that the estimation of the relative effect between two treatments uses all the information available from the network of evidence including direct comparisons and indirect comparisons.

Analyses were conducted for the general OAB population and incontinent subgroup. For each population, a fixed-effect and a random-effect model were estimated. The model with the best quality of fit, as assessed by the Bayesian deviance information criterion, was selected. Analyses were performed using WinBUGS v.1.4 statistical software (MRC Biostatistics Unit, Cambridge, UK). Supplemental Appendix 3 provides the WinBUGS codes.

Mean changes from baseline in frequency of micturition, incontinence, or UUI episodes reported in clinical trials were assumed to follow a normal distribution centred on the “true” effect of treatment. This true effect was expressed as the sum of a change from baseline for the comparator arm, and the difference between each treatment and the comparator. Tolterodine ER 4 mg was chosen as the reference comparator for estimating the MTC models because it was the most widely used active treatment in reviewed studies and one of the most commonly prescribed antimuscarinics in practice. However, differences in efficacy versus mirabegron 50 mg are reported to facilitate results interpretation.

For adverse events, the number of events reported in each treatment of a given trial was assumed to follow a binomial distribution with parameters n , the number of patients in a treatment arm, and p , the “true” probability of adverse events for each treatment.

Mean values and 95% credibility intervals (95% CrIs) are reported for differences in changes in symptoms from baseline to 12 wk between treatments and odds ratios (ORs) for adverse events. A result was considered statistically significant when it had a probability of at least 97.5%. For example, a treatment was considered significantly more efficacious than mirabegron against micturition if the probability of the difference in change in micturition frequency being negative was at least 97.5% (ie, if the upper limit of the 95% CrI around the difference was less than zero).

3. Evidence synthesis

3.1. Flow diagram and quality assessment of the included studies

The PRISMA flow diagram in [Figure 1](#) presents the study selection process with the reasons for exclusion in the different screening phases. After removing duplicates, a total of 2731 references were obtained by searching electronic databases, and 8 clinical study reports provided by the manufacturer were added to the list. We excluded 2475 articles after the first phase of screening consisting of reviewing the titles and/or abstracts. Thus 256 potentially relevant articles were identified, and full articles were retrieved to assess their eligibility. Of these, 212 were excluded. Overall, 44 studies met the inclusion criteria for the MTC. These 44 trials enrolled 27 309 patients. Most of the studies were conducted in North America or Europe (61.4%) from 2000 to 2013. Most studies (77.3%) were placebo controlled. Tolterodine ER 4 mg was administered in 16 trials, tolterodine IR 4 mg (2 mg twice daily) in 7 trials, solifenacin 5 mg in 6 trials, solifenacin 10 mg in 5 trials, mirabegron 50 mg in 6 included Astellas trials (DRAGON, SCORPIO, ARIES, CAPRICORN, CL-045, and CL-048), and fesoterodine 4 mg, fesoterodine 8 mg, and oxybutynin 10 mg ER in 4 trials. Other treatments (darifenacin, oxybutynin IR, trospium) were also included in reviewed trials. Supplemental Appendix 4 displays the complete list of the 129 treatment arms from the studies included in this MTC.

None of the 44 trials were identified at a high risk of bias; all studies were therefore included in the MTC analyses (see Supplemental Appendix 5). Supplemental Appendix 6 lists the references of the included studies.

3.2. Bayesian mixed treatment comparison results

All results on each outcome can be viewed in Supplemental Appendix 7 and 8. For each outcome analysed, a network diagram displayed all direct comparisons included in the analysis. Supplemental Appendix 7 presents all network

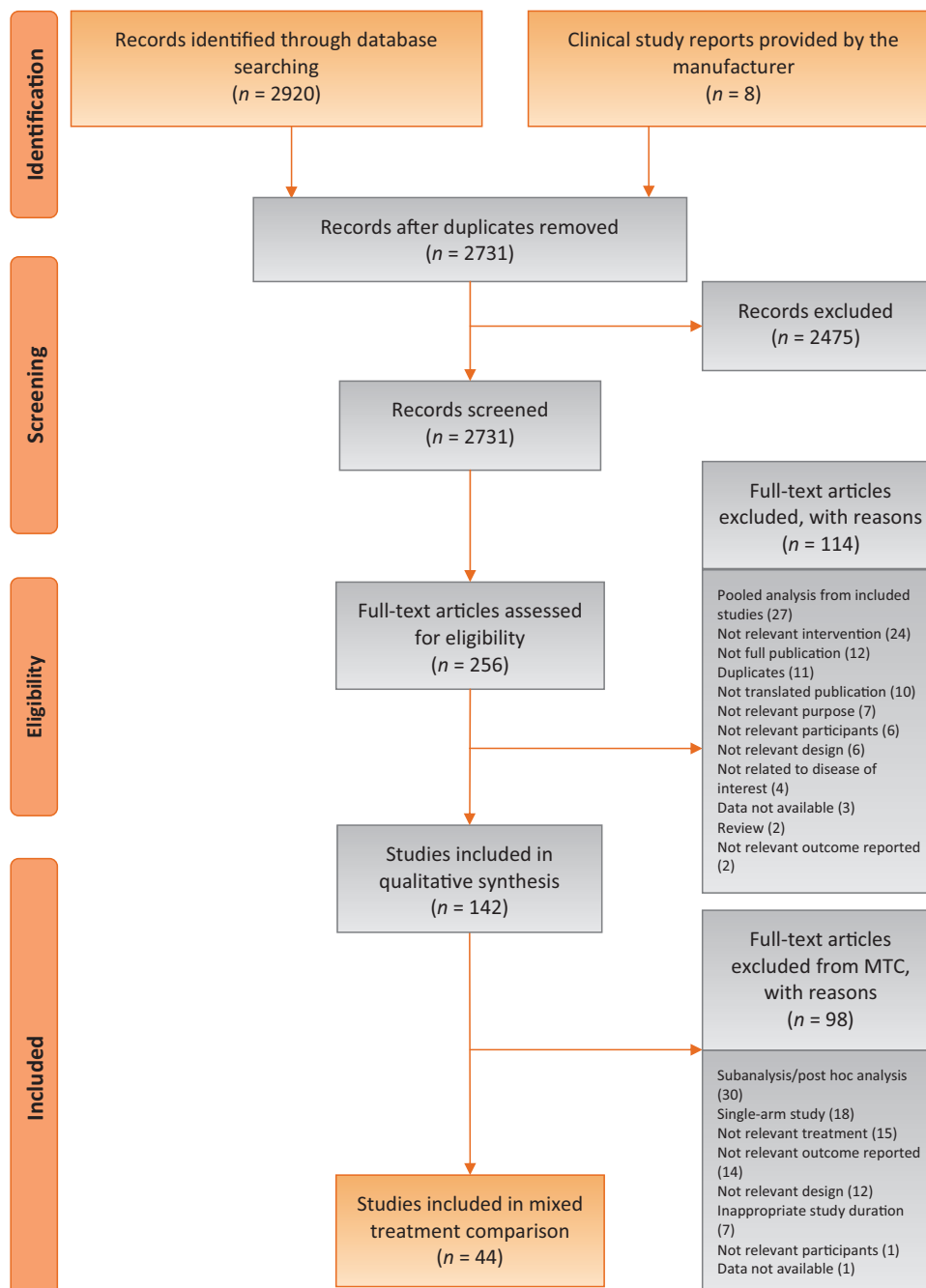


Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-analysis flow diagram. MTC = mixed treatment comparison.

diagrams. Fixed-effect models were used for all outcomes with the exception of dry mouth, for which a random-effect model was required due to the heterogeneity between studies. The probability of each treatment being more effective compared with mirabegron was calculated for different superiority margins (0, 0.5, and 1 episode per day) and is presented in Supplemental Appendix 10.

3.2.1. Efficacy outcomes

3.2.1.1. Micturition frequency. The MTC analysis on micturitions was based on 26 studies (22 040 patients) [14–39].

It showed that the effect of mirabegron 50 mg did not differ significantly from other treatments, except solifenacin 10 mg, which is more effective (mean difference vs mirabegron 50 mg of -0.584 [95% CrI, -0.837 to -0.332]). The estimated mean difference of tolterodine versus mirabegron was not significant (0.157 micturition episodes per day [95% CrI, -0.001 to 0.315]) (Fig. 2). Solifenacin 10 mg had a probability of 100% of being more effective in reducing the frequency of micturition compared with mirabegron.

The numbers of studies reporting efficacy estimates in incontinent subgroup were smaller: 19 studies for

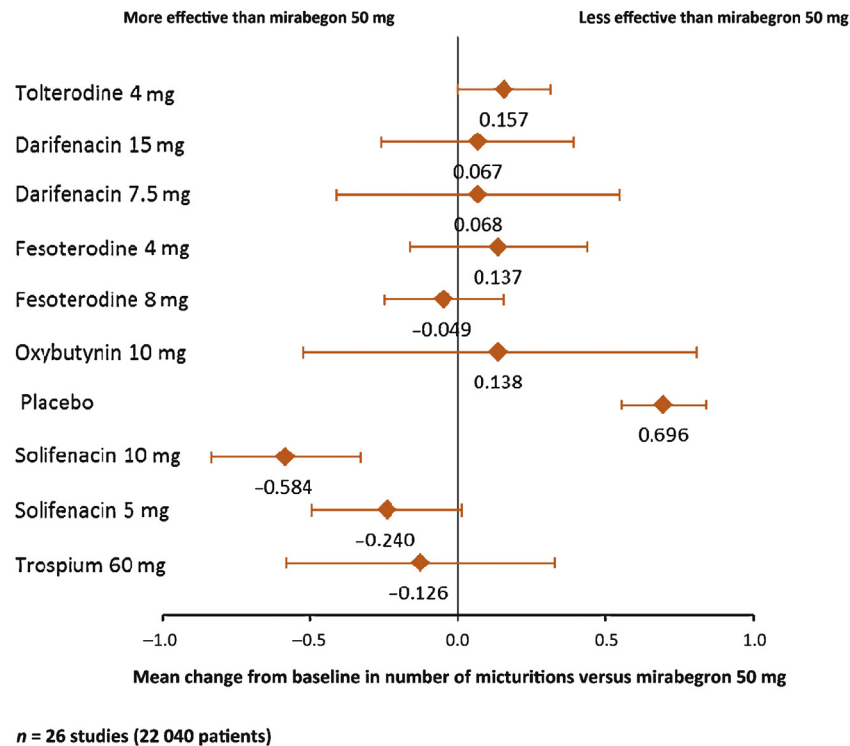


Fig. 2 – Forest plot for change from baseline in the number of micturitions per 24 h. CrI = credibility interval.

micturition frequency (including 3 studies on mirabegron). Results were consistent with those for the general OAB population. There was no significant difference observed between mirabegron and tolterodine 4 mg. Full details of results are provided in Supplemental Appendix 9.

3.2.1.2. Incontinence. Seventeen trials (13 101 patients) reported data on the change from baseline to end of study in incontinence episodes per 24 h [14–21,23,25–27,30,33, 36–38]. The improvement in daily number of incontinence episodes with mirabegron 50 mg was not significantly different from improvements with tolterodine 4 mg, oxybutynin 10 mg, darifenacin 7.5 mg and 15 mg, and fesoterodine 4 and 8 mg. Mirabegron 50 mg was statistically superior to placebo with a mean difference estimated at 0.493 incontinence episodes per day (95% CrI, 0.368–0.619) (Fig. 3). Solifenacin 5 mg had a probability of 97% of being more effective in reducing the number of incontinence episodes compared with mirabegron. An equal probability was estimated for solifenacin 10 mg.

3.2.1.3. Urgency urinary incontinence. For the UUI analysis, 18 studies (16 044 patients) were included [14–20,22–24, 29,31,32,34,35,37–39]. The analysis showed that mirabegron 50 mg was significantly less efficacious than solifenacin 10 mg (mean difference vs mirabegron 50 mg of -0.422 urgency incontinence episodes per day [95% CrI, -0.786 to -0.060]) and did not differ significantly from other antimuscarinics (Fig. 4).

3.2.2. Safety outcomes

3.2.2.1. Dry mouth. A total of 44 studies (27 309 patients) reported the number of patients with dry mouth [14–57]. Mirabegron 50 mg had an incidence of dry mouth similar to placebo (OR: 1.344; 95% CrI, 0.863–2.004). All antimuscarinics were associated with a significantly higher risk of dry mouth compared with mirabegron 50 mg. The OR for the occurrence of dry mouth with antimuscarinics compared with mirabegron 50 mg ranged from 4.213 (95% CrI, 2.431–6.897) with solifenacin 5 mg to 40.702 (95% CrI, 15.210–91.590) with oxybutynin IR 15 mg (Fig. 5).

3.2.2.2. Constipation. Overall, 41 eligible studies (25 257 patients) reported data on constipation [14–27,29–32,34–4,43–57]. The incidence of constipation associated with mirabegron 50 mg was comparable with placebo (OR: 0.732; 95% CrI, 0.484–1.066). Other antimuscarinics except darifenacin 15 mg, fesoterodine 8 mg, solifenacin 5 mg, solifenacin 10 mg, and trospium 60 mg had similar incidences of constipation. These five treatments were associated with significantly greater risks of constipation compared with mirabegron 50 mg with ORs ranging from 1.914 (95% CrI, 1.135–3.032) to 7.603 (95% CrI, 2.076–22.660) (Fig. 6).

3.2.2.3. Blurred vision. Data on blurred vision occurrences were available in 25 studies (14 348 patients) that were included in this analysis [14–21,23–25,27,32,35,36,38, 41–45,47,49,51,53]. This event is relatively rare, and no significant difference in risk of developing blurred vision was found between treatments.

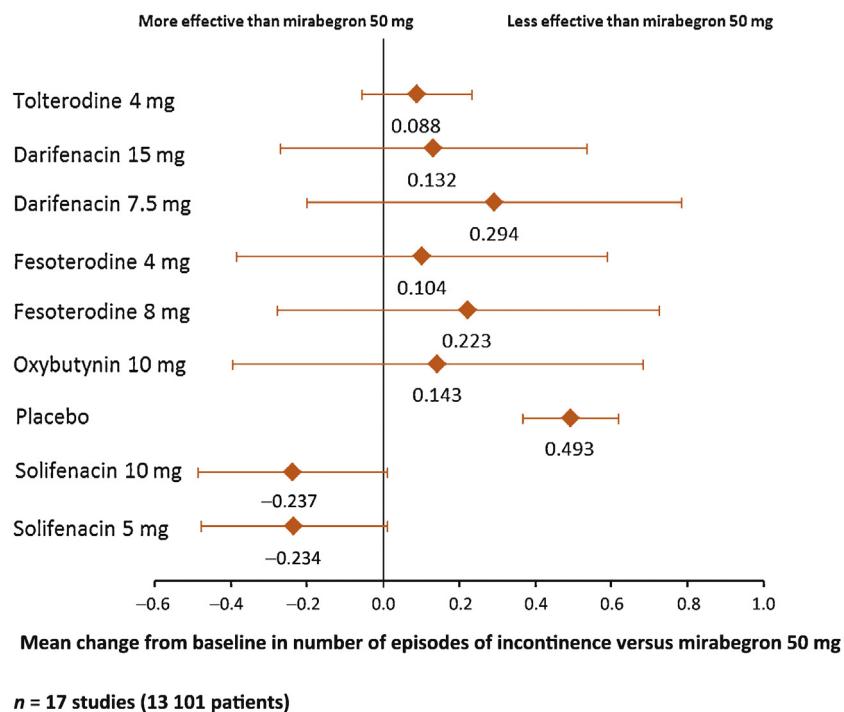


Fig. 3 – Forest plot for change from baseline in the number of incontinence episodes per 24 h. CrI = credibility interval.

3.3. Discussion

Based on data from 44 trials, this MTC analysis suggests that mirabegron 50 mg has similar efficacy against micturition, incontinence, and UUI compared with most of the approved OAB drugs used in Europe. Only solifenacin 10 mg showed a significantly superior efficacy in the improvement of

micturition and UUI episode frequency compared with mirabegron 50 mg.

However, solifenacin 10 mg, along with fesoterodine 8 mg, were among the treatments with the highest incidence of adverse events, especially dry mouth. The drug with the most favourable tolerability profile was mirabegron 50 mg. It was shown to be associated with a risk of dry mouth similar

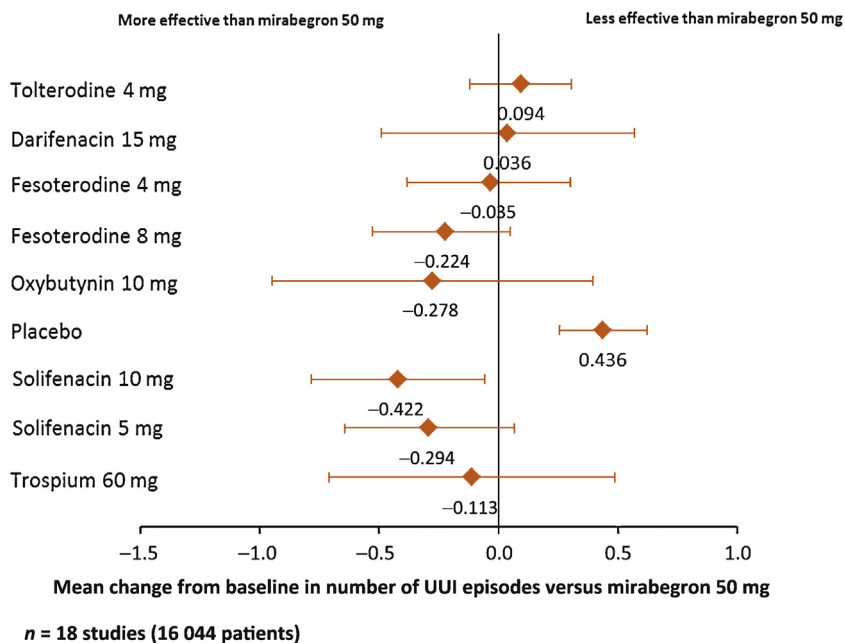


Fig. 4 – Forest plot for change from baseline in the number of urgency urinary incontinence episodes per 24 h. CrI = credibility interval; UUI = urgency urinary incontinence.

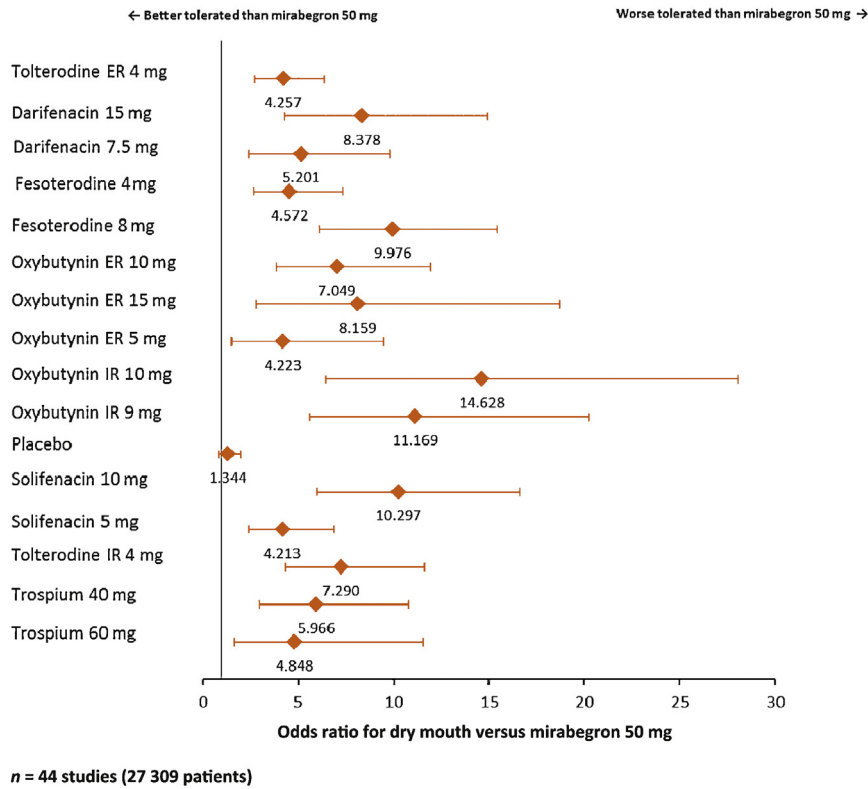


Fig. 5 – Odds ratios for occurrences of dry mouth versus mirabegron 50 mg. CrI = credibility interval; ER = extended release; IR = immediate release. OR for oxybutynin IR 15 mg (40.702 (95% CrI, 15.210–91.590)) was not reported because of a large credibility interval.

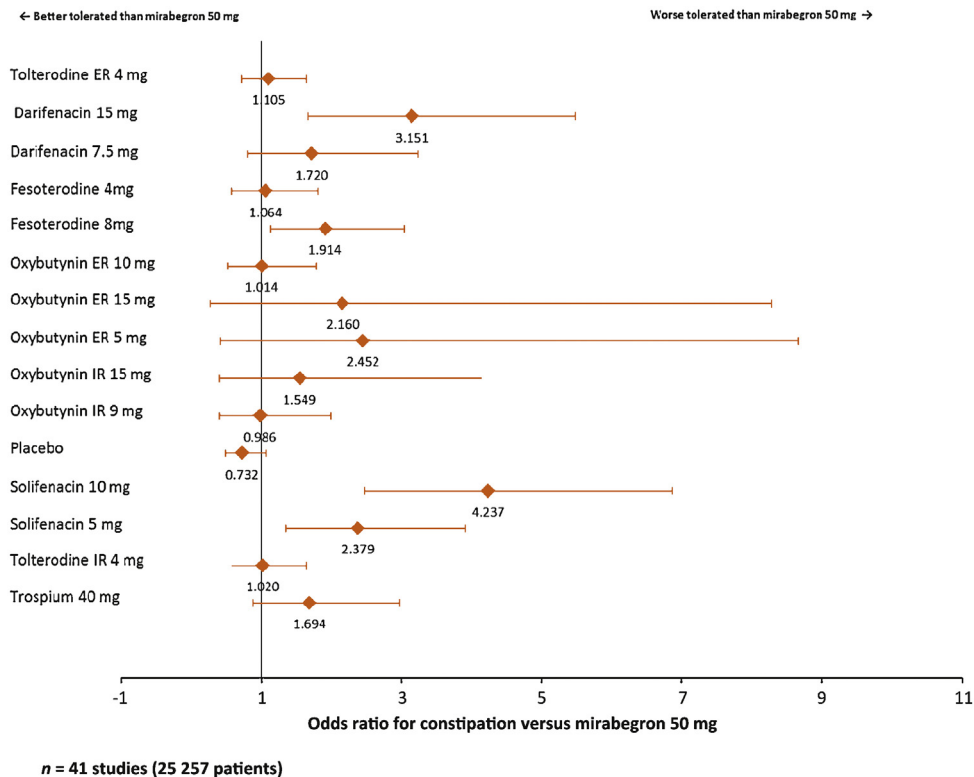


Fig. 6 – Odds ratios for occurrences of constipation versus mirabegron 50 mg. CrI = credibility interval; ER = extended release; IR = immediate release.

to placebo, and significantly lower compared to tolterodine 4 mg and other antimuscarinics. This is an important finding because dry mouth has been reported to be a frequent cause of treatment discontinuation [58]. The MTC also suggested that the risk of constipation was lower with mirabegron 50 mg than most antimuscarinics. No significant difference was found between treatments regarding blurred vision because this event is relatively rare.

The previous systematic literature review and meta-analysis conducted by Chapple et al. showed that antimuscarinics were more efficacious than placebo as concluded by our analysis [9]. This new review adds to the previous one in two ways. First, it focuses on one new drug, mirabegron 50 mg, versus antimuscarinics; second, a greater amount of evidence was available (except for older drugs such as oxybutynin IR and tolterodine IR). Twenty trials published after 2007 were included in this analysis and not in Chapple et al. In addition, owing to the use of MTC approach, we were able to use information based on head-to-head comparisons as well as comparisons versus placebo. However, we did not consider all the placebo-controlled evidence available for all included antimuscarinics with the exception of mirabegron 50 mg. Comparisons against placebo based on our analysis could therefore be biased.

Although the MTC design and presentation of results between our analysis and the latest review to date by Buser et al. [7] are different, both meta-analyses suggest that there are few important differences in efficacy between antimuscarinics. Solifenacin 10 mg ranked first in both analyses, in terms of efficacy (micturition, incontinence), among antimuscarinics included in our analysis. Comparisons of safety results were more difficult to perform; however, both MTC rankings for dry mouth were quite similar: solifenacin 5 mg and the ER formulations (oxybutynin ER 5 mg and tolterodine ER 4 mg) had relatively low ORs, whereas oxybutynin IR 10 and 15 mg had the highest ORs.

Results from a pooled analysis of three large mirabegron phase 3 studies (only one study had a tolterodine arm) were in accordance with our MTC results. It revealed that mirabegron and tolterodine had similar effects on micturition and incontinence and that mirabegron was well tolerated with an incidence of dry mouth comparable with placebo and lower than tolterodine [59]. However, further prospective head-to-head comparisons between mirabegron and antimuscarinics should be conducted to confirm our results.

One possible criticism of our study is that our MTC on safety outcomes focused on dry mouth and constipation, adverse events known to be associated with antimuscarinics, and ignored adverse events associated with mirabegron. The pooled analysis of three phase 3 mirabegron RCTs showed that the treatment-emergent adverse events most commonly reported in patients treated with mirabegron 50 mg were hypertension (7.5%), nasopharyngitis (3.9%), headache (3.4%), and UTIs (2.9%) [59]. The proportions of patients experiencing these adverse events were not significantly different between mirabegron and placebo

arms, based on pooled data analysis, except for nasopharyngitis. However, no MTC analysis could be performed on the probability of nasopharyngitis because this event is not usually reported in publications on antimuscarinics.

The efficacy outcomes considered in this MTC were limited to micturition, incontinence, and UUI episode frequency and did not include outcomes analysed in other reviews such as urgency, volume voided per micturition, or dry rate. Urgency is an important symptom in OAB, but the measurement of this symptom is difficult due to the subjective nature of urgency. Several instruments can be used to measure it, making comparisons between studies challenging. The volume voided per micturition was not included because it was considered a surrogate outcome measure of less clinical relevance. Other efficacy outcomes such as number of patients with resolution of incontinence, mean change from baseline in daytime micturitions, nighttime micturitions, and urgency-driven micturitions are also relevant but less frequently reported, and therefore they were not considered in our MTC.

Heterogeneity found between studies included in our MTC might stem from the selection of patients with different characteristics at baseline (eg, with differences in OAB severity at baseline). Thus patients included in fesoterodine studies had relatively severe symptoms at baseline and therefore greater potential for improvement. Two studies with fesoterodine arms included patients with more than six urgency episodes per day at baseline [22,34]. The proportion of previously treated patients also varied between studies. For example, the FACT-2 placebo-controlled trial comparing fesoterodine 8 mg and tolterodine ER 4 mg included approximately 30% of previously treated patients [31], whereas a placebo-controlled trial of tolterodine reported efficacy results in a population with 70% of previously treated patients [60].

Another potential source of heterogeneity lies in the variability in follow-up periods between trials: from 8 and 16 wk for the efficacy outcomes and from 4 and 16 wk for the safety outcomes. However, 72.7% of the included studies had a follow-up of 12 wk, and we verified that relative effects at 8 and 12 wk or 12 and 16 wk were similar when results at both time points were reported. Therefore the variability in follow-up duration is probably not a major cause of heterogeneity.

One way to account for heterogeneity between studies in MTC is to use random-effect models. The random-effect model assumes that every RCT measures the same effect with a degree of variation [61]. Thus the CrI around the treatment effect estimated from the MTC accounts for variability between studies; the presence of heterogeneity between studies will lead to a relatively wide CrI. The fact that CrIs do not overlap between two treatments despite the presence of heterogeneity indicates that the estimated difference in treatment effect exceeds the difference potentially due to heterogeneity. The fixed-effect model was selected for all outcomes except for dry mouth. This suggests that heterogeneity between studies affected the estimation of differences between treatments in the probability of dry mouth, but reported CrIs around ORs

for dry mouth account for this heterogeneity. Thus we can conclude that the probability of dry mouth is significantly lower with mirabegron than with antimuscarinics despite the presence of heterogeneity between studies.

Another approach to account for heterogeneity between studies would be to conduct a meta-regression adjusting for bias associated with effect-modifying covariates [62]. However, this would necessitate that variables driving heterogeneity between studies (eg, OAB severity at baseline) are systematically reported in the same way in publications. This would have led to the exclusion of many studies.

Studies published before 2000 were not included to ensure greater homogeneity between study populations. Before 2000, more patients were treatment naive, and the definition of OAB was introduced in 2001. The drawback of this approach is that we have little data on older treatments such as oxybutynin IR. Consequently, we obtained very wide CIs around results for oxybutynin IR. However, a head-to-head trial found that oxybutynin 10 mg IR was inferior to tolterodine 4 mg IR [33].

4. Conclusions

Reductions in OAB symptoms were demonstrated for all OAB treatments. Our MTC analysis showed that the efficacy of mirabegron 50 mg in OAB patients is similar to the efficacy of most approved antimuscarinics drugs in the general OAB population, as well as in the incontinent population and that solifenacin 10 mg is significantly superior to mirabegron in reducing micturition and UUI episodes per 24 h. However, mirabegron 50 mg had the most favourable tolerability profile, with an incidence of dry mouth and constipation similar to placebo and a significantly lower incidence of dry mouth compared with all antimuscarinics. Therefore, with efficacy similar to most antimuscarinics and a more favourable tolerability profile, mirabegron has the potential to optimise the efficacy tolerability balance for an OAB patient. The Bayesian MTC method is a powerful tool for evidence-based health care evaluation; however, further head-to-head comparisons between mirabegron and antimuscarinics should be conducted to confirm our results.

Author contributions: Khaled Maman had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Maman, Aballea, Hakimi, Nazir, Siddiqui, Odeyemi.

Acquisition of data: Nazir, Hakim.

Analysis and interpretation of data: Maman, Aballea, Neine, Hakimi, Nazir, Siddiqui, Odeyemi.

Drafting of the manuscript: Maman, Aballea.

Critical revision of the manuscript for important intellectual content: Maman, Aballea, Nazir, Desroziars, Neine, Siddiqui, Odeyemi, Hakim.

Statistical analysis: Maman, Aballea, Desroziars, Neine.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.eururo.2013.11.010>.

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