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Review Article

Systematic review and meta-analysis on the efficacy and tolerability of mirabegron for the treatment of storage lower urinary tract symptoms/overactive bladder: Comparison with placebo and tolterodine

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Abbreviations & Acronyms
AE = adverse event
β-AR = β-adrenoceptor
ER = extended release
LUTS = lower urinary tract symptoms
Mir = mirabegron
Mir50 = mirabegron 50 mg
Mir100 = mirabegron 100 mg
OAB = overactive bladder
RCT = randomized controlled trial
TEAE = treatment-emergent adverse event
Tol = tolterodine
WMD = weighted mean difference

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Abstract: A systematic review and meta-analysis was carried out to evaluate the efficacy and safety of mirabegron 50 mg and 100 mg in the treatment of storage lower urinary tract symptoms/overactive bladder in comparison with a placebo and tolterodine 4 mg. A total of 491 articles were collected and eight randomized studies were identified as eligible for this meta-analysis. Overall, eight trials were included in the meta-analysis evaluating 10 248 patients. Mirabegron at both doses of 50 mg and 100 mg, and and tolterodine 4 mg were significantly associated with the reduction of incontinence episodes per 24 h, reduction of mean number of micturitions per 24 h, increase of voided volume and reduction of urgency episodes per 24 h, compared to a placebo. Both mirabegron 50 mg and mirabegron 100 mg were associated with a significant reduction of nocturia episodes when compared with a placebo. Conversely, tolterodine 4 mg did not prove to be more effective than a placebo in the reduction of nocturia episodes. Furthermore, mirabegron 50 mg showed a slightly, but significantly, better efficacy than tolterodine 4 mg in the improvement of nocturia episodes. Mirabegron 50 mg and mirabegron 100 mg shared the same risk of overall treatment-emergent adverse events rate with the placebo. Otherwise, tolterodine 4 mg was associated with a significantly greater risk than the placebo. However, mirabegron 100 mg showed a slight trend toward an increased risk of hypertension (odds ratio 1.41; $P = 0.08$) and cardiac arrhythmia (odds ratio 2.18; $P = 0.06$). Mirabegron is an effective treatment for patients with storage lower urinary tract symptoms/overactive bladder, providing a reduction of incontinence, urgency and frequency; an improvement of voided volume with a slight, but statistically, significant improvement of nocturia; with a good safety profile. These findings should be considered for the treatment planning of patients with storage lower urinary tract symptoms/overactive bladder.

Key words: mirabegron, nocturia, overactive bladder, storage lower urinary tract symptoms, tolterodine.

Introduction

OAB is a multifactorial and common health disorder, defined by the International Continence Society as a syndrome characterized by urgency, with or without urinary incontinence, usually accompanied by frequency and nocturia, in the absence of urinary tract infection or other obvious pathology.[1] OAB is a high-prevalence condition that increases with age in both female and male patients, affecting 30–40% of the population aged >75 years, leading to detrimental effects on patients' health-related quality of life and a significant economic burden.[2,3] In order to obtain symptom relief without affecting the voiding phase of micturition, the role of proper therapies appears crucial.

Conservative therapeutic strategies, including behavioral therapies, weight loss, bladder training, bladder control strategies, pelvic floor muscle training and fluid intake management,

currently represent the first-line treatment for patients with OAB symptoms. Nevertheless, the gold standard of pharmacological therapy are antimuscarinic drugs, such as oxybutynin, Tol, fesoterodine, solifenacin, darifenacin or trospium.[4] Furthermore, extensive patients' counseling is always required in order to evaluate all the possible treatments and their expected results, as the limited effectiveness and the possible occurrence of bothering AEs can reduce a patient's compliance. Indeed, because of inadequate symptom control and/or intolerable AEs (e.g. dry mouth, constipation), >60% of patients discontinue antimuscarinic therapy over a 12-month period.[5]

In order to obtain novel pharmacological compounds with a better efficacy/side-effect profile and improve the compliance of patients, the role of β-AR (β1, β2, β3) in relaxation of the detrusor has been recently evaluated. In particular, β3-AR, which represents the main actor in mediating human detrusor relaxation.[6]

Mir, a selective β3-AR agonist approved for the treatment of OAB symptoms by the US Food and Drug Administration in 2012, is the first of this new class of compounds with a different mechanism of action from antimuscarinic agents. Indeed, Mir improves the storage capacity of the bladder, without impairing bladder contraction during voiding phase.[7]

Both sympathetic and parasympathetic nervous systems innervate the urinary bladder. Activation of sympathetic nerves contributes to urine storage by relaxing the detrusor muscle through activation of β-AR.[8] In several preclinical studies on various species, both β-agonists and β-antagonists have been tested to identify the functional involvement of β-AR subtypes in bladder relaxation. A dose-dependent detrusor relaxation with β3-AR agonists has been shown during the storage phase of the micturition cycle, as well as inhibition of neurogenic overactivity and experimentally-induced OAB, and OAB associated with bladder outlet obstruction, by the reduction of afferent signals and reduction of micromotion in the detrusor.[9,10] Likewise, in human detrusor muscle, neither dobutamine (a β1-AR agonist) nor procaterol (a β2-AR agonist) produced significant relaxation.[11] Conversely, all the selective β3-AR agonists, BLR37344, CL316243 and CGP12177A, produced a concentration-dependent relaxation. Hence, it has been found that >95% of all β-AR mRNA in the human bladder can be attributed to β3-AR.[6,12]

Data from *in vitro* studies on human bladder strips showed that the activation of β3-AR induces bladder relaxation through the adenylyl cyclase pathway and subsequent cyclic adenosine monophosphate formation, suggesting the basis for the therapeutic effect of β3-agonists in OAB. However, recent studies focused their attention on bladder calcium-dependent potassium channels, in particular big potassium calcium channels, which might be involved in β-AR-mediated relaxation independently of cyclic adenosine monophosphate.[13] However, all the underlying cellular mechanisms are not yet fully clarified.[14,15]

Mir (YM178) shows an high intrinsic activity for β3-AR, and a very low intrinsic activity for β1- and β2-AR. In a preclinical study on Chinese hamster ovary cells, Mir was more than 446-fold as selective for human β3-ARs as for β2-ARs and β1-ARs. Taken together, the aforementioned results suggest Mir as a suitable drug for the treatment of OAB, including storage symptoms secondary to bladder outflow obstruction. Two reviews with meta-analysis on Mir for the treatment of OAB have been previously published. In 2014, Cui *et al.* evaluated the efficacy and safety of Mir versus placebo, but not versus Tol, meta-analyzing four phase III RCTs.[13] In the same year, Wu *et al.* added to the four RCTs phase III trials another two phase II RCTs, evaluating the efficacy and safety of Mir versus Tol too.[16] However, they did not analyze all the efficacy compounds of Mir, such as the reduction of nocturia episodes. Furthermore, two large RCTs on Mir versus placebo and Tol were published in 2014.[22,25]

The aim of the present systematic review and meta-analysis was to evaluate the safety and efficacy of different dosages of Mir in the treatment of OAB, in comparison with a placebo and Tol.

Methods

A wide MEDLINE, EMBASE, Cochrane Library and Science Citation Index Expanded Medline search was carried out to identify all published randomized trials evaluating Mir for the treatment of OAB/storage LUTS. The following MeSH terms were used: beta-agonists, adrenergic beta-3 receptor agonists, urinary bladder, overactive, lower urinary tract symptoms, human and Mir with every possible combination considered. We tried to contact all corresponding authors when data were missing.

The present meta-analysis was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist (http://www.prisma-statement.org/).

Eligibility criteria

The following inclusion criteria were used: (i) RCTs reporting original data, published in a peer-reviewed journal (i.e. not meeting abstract, or review article); (ii) all RCTs specifically evaluating the efficacy and/or safety of Mir in comparison with a placebo and/or Tol; and (iii) authors reported data that could be analyzed, clearly specifying the number of participants evaluated, and the efficacy and safety outcomes.

Information source and search strategy

The search up to 31 May 2016 was restricted to English-language articles and studies of human participants. A handsearch of bibliographies of retrieved papers for additional references was carried out. Details of the literature search process are outlined in the flow chart (Fig. 1). The identification of relevant abstracts, the selection of studies based on the criteria described above and the subsequent data extraction were carried out independently by two of the authors (AS, GIR), and conflicts resolved by a third investigator (MG).

Outcomes and quality assessment

We evaluated the mean difference to assess the efficacy profile of Mir in terms of incontinence episodes per 24 h,

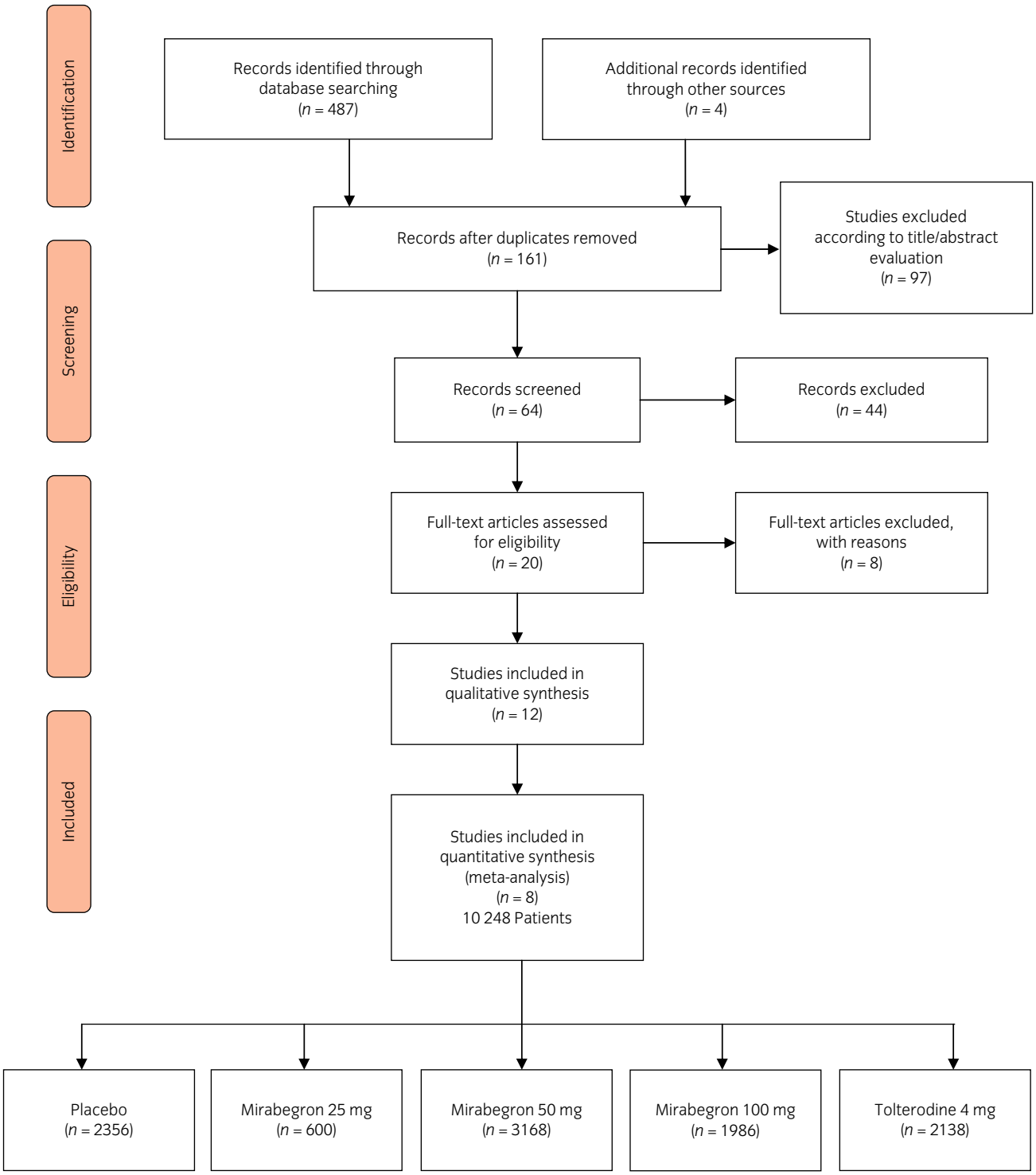

Fig. 1 Flow diagram of literature searches according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

number of micturitions per 24 h, voided volume per micturition and urgency episodes. In addition, the reduction of nocturia episodes was analyzed.

The safety profile of Mir was assessed analyzing the TEAEs rate, reporting the most common TEAEs and the discontinuation rate as a result of AEs. In addition, a comparison between different Mir dosages was carried out. The quality of the studies was assessed using the Cochrane criteria. Begg's and Egger's methods were used to assess publication bias. Statistical heterogeneity was assessed using the Cochran's Q rest and I^2 statistics. A P-value ≤ 0.05 was considered statistically significant.

Results

Characteristics and quality of the trials

A total of 491 studies were identified with an extensive research from the databases. After a full evaluation of each study, a total of eight randomized studies were identified as eligible for the present meta-analysis. The selection process of trials eligible for the meta-analysis is reported in Figure 1. We did not find any publication bias among analyzed studies.

Patient characteristics

Overall, eight trials were included in the meta-analysis evaluating 10 248 patients, 600 (5.8%) assigned to Mir25, 3168 (30.9%) to Mir50, 1986 (19.4%) to Mir100, 2138 (20.8%) to Tol and 2356 (23.1%) to a placebo. The median age of the patients was 59 years. Table 1 lists the main characteristics of all included studies.

Clinical Efficacy

Mir50 (WMD −0.38, $P < 0.0001$), Mir100 (WMD −0.49, $P < 0.0001$) and Tol (WMD −0.21, $P = 0.02$) were significantly associated with the reduction of incontinence episodes per 24 h when compared with the placebo. Mir100 did not provide greater efficacy than Mir50 (WMD 0.15, $P = 0.08$) or Tol (WMD −0.07, $P = 0.48$) in reducing the number of incontinence episodes per 24 h. In addition, Mir50 was statistically equivalent to Tol (WMD −0.09, $P = 0.49$) in terms of the number of incontinence episodes per 24 h, as shown in Figure 2.

In regard to the reduction in mean number of micturitions per 24 h, Mir50 (WMD −0.60, $P < 0.0001$), Mir100 (WMD −0.72, $P < 0.0001$) and Tol (WMD −0.34, $P = 0.0005$) showed greater efficacy than the placebo. We did not find any differences when comparing Mir50 with Tol (WMD −0.11, $P = 0.12$), Mir50 with Mir100 (WMD 0.03, $P = 0.70$) and Mir100 with Tol (WMD −0.08, $P = 0.39$), as shown in Figure 3.

Mir50 (WMD 12.67, $P < 0.0001$), Mir100 (WMD 10.85, $P < 0.0001$) and Tol (WMD 13.75, $P < 0.0001$) were significantly associated with an increase of voided volume (mL) when compared with the placebo. Mir100 did not provide greater efficacy than Mir50 (WMD 0.03, $P = 0.70$) or Tol (WMD −0.08, $P = 0.39$) in the increase of voided volume (mL). Furthermore, Mir50 was statistically equivalent to Tol, in respect to voided volume (WMD −0.11, $P = 0.12$), as shown in Figure 4.

In regard to the reduction of urgency episodes per 24 h, Mir50 (WMD −0.53, $P < 0.0001$), Mir100 (WMD −0.66, $P < 0.00001$) and Tol (WMD −0.23, $P = 0.02$) were all associated with a significantly greater efficacy than the placebo. No significant differences were observed among drug treatments, as shown in Figure 5.

Mir50 was associated with a significant reduction of nocturia episodes (WMD −0.13, $P = 0.003$), whereas only a marginally significant reduction was found for Mir100 (WMD −0.16, $P = 0.05$), when compared with the placebo. Conversely, Tol did not prove to be more effective than the placebo in the reduction of nocturia episodes (WMD −0.05, $P = 0.36$). Furthermore, Mir50 showed a slightly, but significantly, better efficacy than Tol (WMD −0.07, $P = 0.03$), but not than Mir100 (WMD −0.07, $P = 0.15$). Conversely, Mir100 was not statistically superior to Tol (WMD 0.08, $P = 0.33$), as the heterogeneity was high due to $I^2 = 81\%$, as shown in Figure 6.

Side-effects

Mir50 and Mir100 were not associated with an increased risk of TEAEs when compared with the placebo (OR 0.94; $P = 0.32$ and OR 0.97; $P = 0.31$, respectively). Conversely, Tol was associated with a significantly greater risk of overall TEAEs rate than the placebo (OR 1.38; $P < 0.0001$), as shown in Figure 7.

In particular, Mir50 was not associated with an increased risk of hypertension (OR 1.02; $P = 0.90$) or cardiac arrhythmia (OR 1.0; $P = 1.00$) when compared with the placebo.

Table 1 Characteristics of the included studies

	JADAD score	Patients (*n*)	Age (mean)	Men (%)	Follow up (weeks)	Mir 25 mg (*n*)	Mir 50 mg (*n*)	Mir 100 mg (*n*)	Placebo (*n*)	Tol 4 mg (*n*)
Khullar *et al.* SCORPIO[25]	5	1978	59.1	28.0	12		493	496	494	495
Herschorn *et al.* CAPRICORN[17]	5	1305	59	31.0	12	433	440		433	
Chapple *et al.* DRAGON[24]	3	919	57.1	11.0	12	167	167	168	166	85
Chapple *et al.* TAURUS[20]	5	2452	59.6	25.9	48		815	824		813
Nitti *et al.*[19]	3	200	62.9	100	12		70	65	65	
Nitti *et al.* ARIES[18]	5	1328	60.1	25.7	12		442	433	453	
Yamaguchi *et al.*[27]	5	1105	58.2	16.3	12		369		368	368
Kuo *et al.*[26]	5	1126	54.6	29.1	12		372		377	377

Otherwise, Mir100 showed a slight trend toward a significantly increased risk of hypertension (OR 1.41; $P = 0.08$) and cardiac arrhythmia (OR 2.18; $P = 0.06$).

Tol was associated with an increased risk of dry mouth (OR 2.97; $P < 0.001$) versus the placebo, but also versus Mir50 and Mir100 (OR 2.49; $P < 0.00001$, and OR 2.43; $P < 0.001$, respectively).

The risk of urinary tract infections was not statistically associated with Mir50 or Mir100 treatments. The risk of acute urinary retention was not analyzed because of the lack of data reported by included studies. However, acute urinary retention was not observed in any patients treated with Mir50 in three of the studies,[17–19] and in one of 812 patients in the study by Chapple *et al.*[20] Accordingly, Mir100 was associated with a negligible incidence of acute urinary retention (1/820; 0/433; 1/58).[18–20]

The discontinuation rate as a result of adverse events was not statistically significant for Mir50 (OR 0.97; $P = 0.80$), Mir100 (OR 0.89; $P = 0.63$) or Tol (OR 1.42; $P = 0.12$) versus the placebo. When analyzing the comparison, we did not find any statistical association of the discontinuation rate for Mir50 versus Mir100 ($P = 0.42$) and versus Tol ($P = 0.63$), and for Mir100 versus Tol ($P = 0.65$).

Discussion

Current pharmacotherapy for storage LUTS/OAB consists primarily of antimuscarinic drugs that also affect organs outside the LUT, such as salivary glands, intestines, eyes and the central nervous system, producing detrimental side-effects, such as dry mouth, constipation, blurred vision and possibly cognitive impairment in the elderly population. Together with an insufficient response to treatment, these side-effects lead to low patients' compliance seen with antimuscarinic therapy.[21] Furthermore, the possible negative effect on post-void residual urine has limited the use of antimuscarinic drugs for the management of OAB in male patients, despite none of the available studies showing an increased risk of urinary retention, even in men with bladder outlet obstruction.[22]

The introduction of Mir, the first β3-AR agonist to enter clinical practice, tends to overcome these limitations. In fact, Mir improves bladder storage capacity without impairing the voiding phase of the micturition cycle, through the mediation of the detrusor relaxation during the storage phase. Currently, the labeling of Mir for the treatment of OAB symptoms differs between countries. In the USA, the recommended starting dose is 25 mg, with the further possibility to increase to 50 mg; in Europe, the licensed starting dose is 50 mg, with a 25-mg preparation available for patients with severe renal impairment or moderate liver impairment.[23] Indeed, as confirmed by our analysis, Mir50 showed the same efficacy profile of Mir100.

In all of the studies evaluated, Mir has shown a remarkable efficacy for the treatment of OAB symptoms, with a safety and tolerability profile comparable with a placebo.[17–20,24–27] In our meta-analysis, similarly to Tol, Mir50 was significantly associated with the reduction of the mean number of incontinence episodes per 24 h (mean −1.25, range −1.62 to −0.89) and micturitions per 24 h (mean −1.7, range −2.08

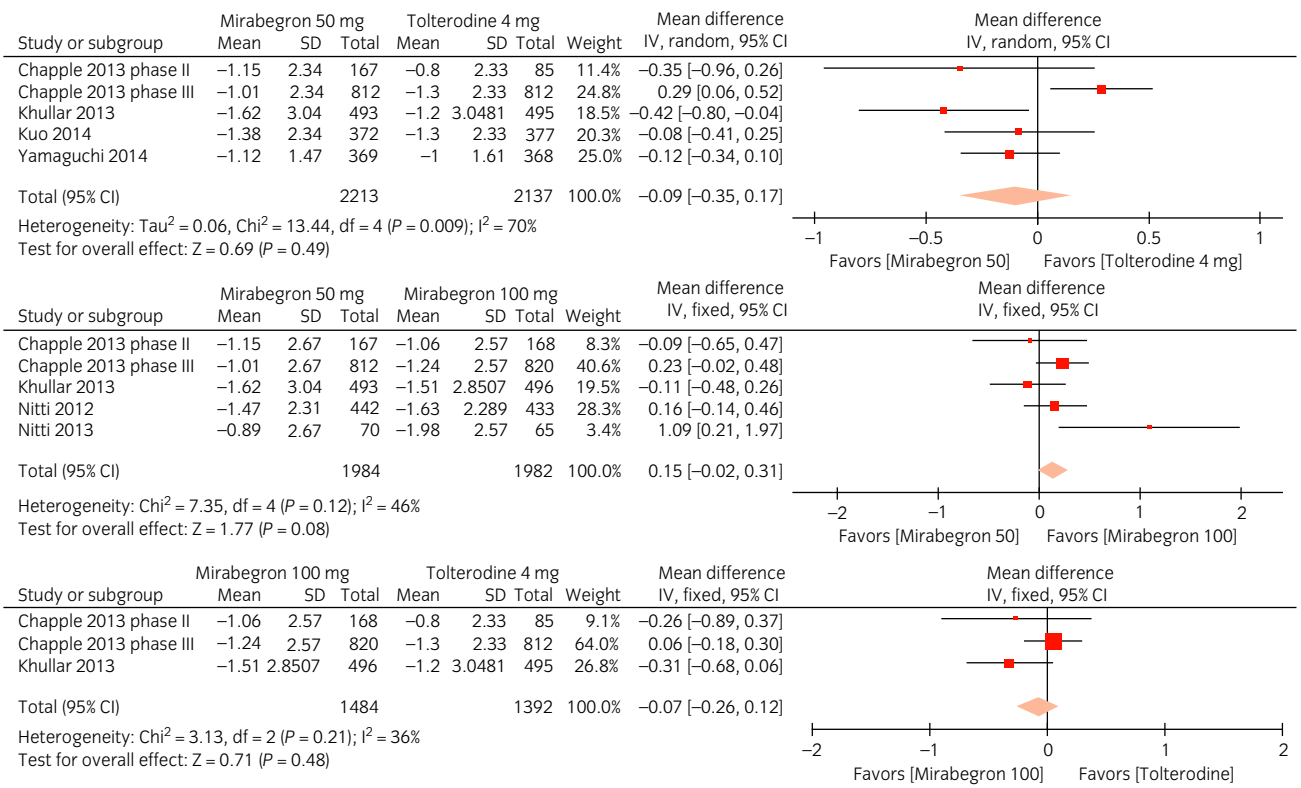

Fig. 2 WMD for number of episodes of incontinence per 24 h. Mir50 versus Tol; Mir50 versus Mir100; Mir100 versus Tol.

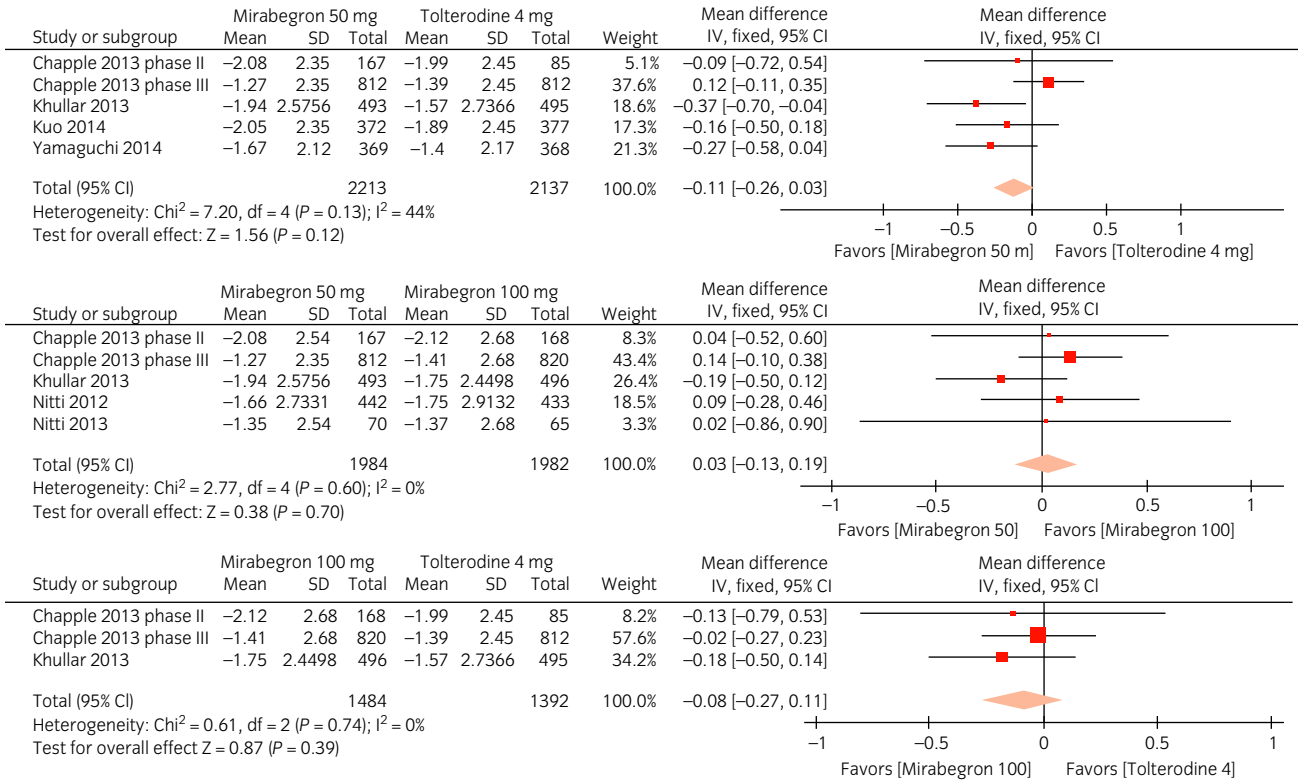

Fig. 3 WMD in the mean number of micturitions per 24 h. Mir50 versus Tol; Mir50 versus Mir100; Mir100 versus Tol.

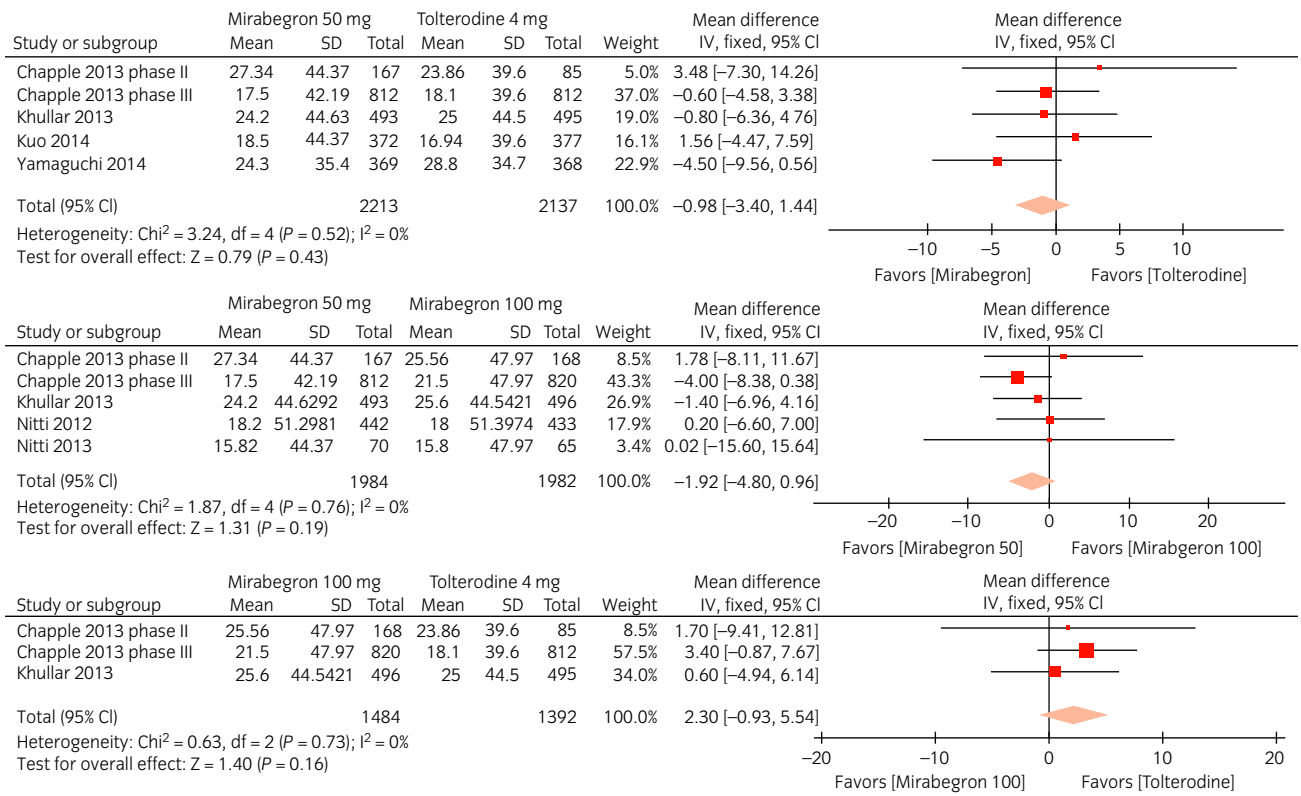

Fig. 4 WMB in the mean volume voided per micturition. Mir50 versus Tol; Mir50 versus Mir100; Mir100 versus Tol.

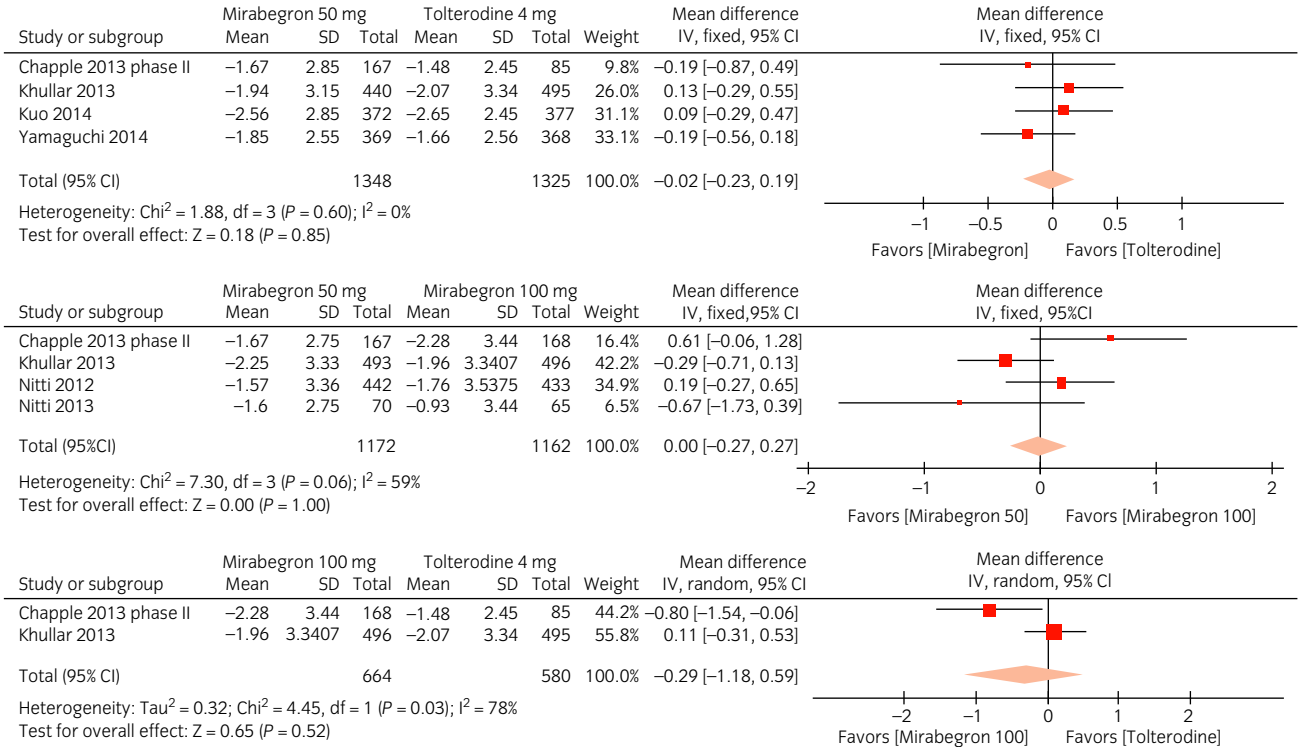

Fig. 5 WMD for urgency. Mir50 versus Tol; Mir50 versus Mir100; Mir100 versus Tol.

to −1.27), with an increase of voided volume (mean 20.8 mL, range 15.8–20.8) and a decrease of urgency episodes per 24 h (mean −1.9, range −2.56 to −1.57), when compared with a placebo. Interestingly, Mir50 showed a better efficacy than Tol in reducing the number of nocturia episodes (mean −0.52, range −0.6 to −0.46 *vs* −0.47, range −0.59 to −0.42).

Our meta-analysis of eight RCTs confirms the data published in 2013 by Nitti *et al.* in a pooled analysis of three randomized, double-blind, placebo-controlled studies, which evaluated the efficacy of Mir50 and Mir100, including an active control arm with Tol 4 mg ER.[28] In fact, compared with the placebo, Mir showed a statistically significant improvement from baseline to the 12 weeks final visit in reducing the mean number of urgency episodes (grade 3 or 4) per 24 h, the mean number of urge incontinence episodes per 24 h and the mean number of micturitions per 24 h ($P < 0.05$), at both doses of 50 mg and 100 mg.

Another systematic review and meta-analysis of six RCTs (BLOSSOM,[23] DRAGON,[24] SCORPIO,[25] ARIES,[18] CAPRICORN[17] and TAURUS[20]) showed that Mir was more effective in terms of the mean number of incontinence episodes per 24 h, although there were no differences between Mir and Tol in the mean number of micturitions per 24 h.[16]

Four studies were meta-analyzed to compare the efficacy of Mir50 versus Tol in the reduction of nocturia episodes.[20,24,26,27] Even if in these studies a statistically significant difference between the two active treatment arms has not been found, Chapple *et al.* reported a significant reduction of nocturia episodes with Mir50 when compared with a placebo (adjusted mean change from baseline −0.6 *vs* −0.38; $P < 0.05$), but not for Tol versus A placebo (adjusted mean change from baseline −0.59 *vs* −0.38).[24] Accordingly, a statistically significant difference was also observed by Nitti *et al.* in the mean number of nocturia episodes per 24 h in the Mir50 group, −0.55 (range −0.62 to −0.49), versus the placebo, −0.42 (range −0.48 to −0.35; $P < 0.05$). Furthermore, accordingly with the present results, Mir100 also showed a significantly better efficacy than the placebo in reducing the mean number of nocturia episodes per 24 h, −0.54 (range −0.62 to −0.46; $P < 0.05$).[28] In our meta-analysis, only Mir50, and not Mir100, appeared to be slightly, but statistically significantly, superior to Tol in reducing nocturia episodes, probably because of the high heterogeneity ($I^2 = 81\%$) in the comparison between Mir100 and Tol.

Therefore, data from the present systematic review, corroborated with the current literature, suggest a slight, but statistically significant, improvement in nocturia: further trials, targeted on this specific issue, are required to measure the amount of clinical efficacy of Mir for the management of nocturia.

The overall incidence of TEAEs was similar between Mir at both doses of 50 mg and 100 mg (31.3% and 31.8%, respectively) and the placebo (31.1%) arms, and there was no evidence of a dose–response relationship across the Mir treatment groups for overall rates of TEAEs. Otherwise, only a certain trend toward a significantly increased risk of hypertension and cardiac arrhythmia was found for Mir100.

As β3-ARs might also be present in cardiac and vascular tissue, a thorough cardiovascular safety evaluation of Mir was previously carried out, without finding a clinically significant increase in cardiovascular TEAEs, such as tachycardia and palpitations.[23]

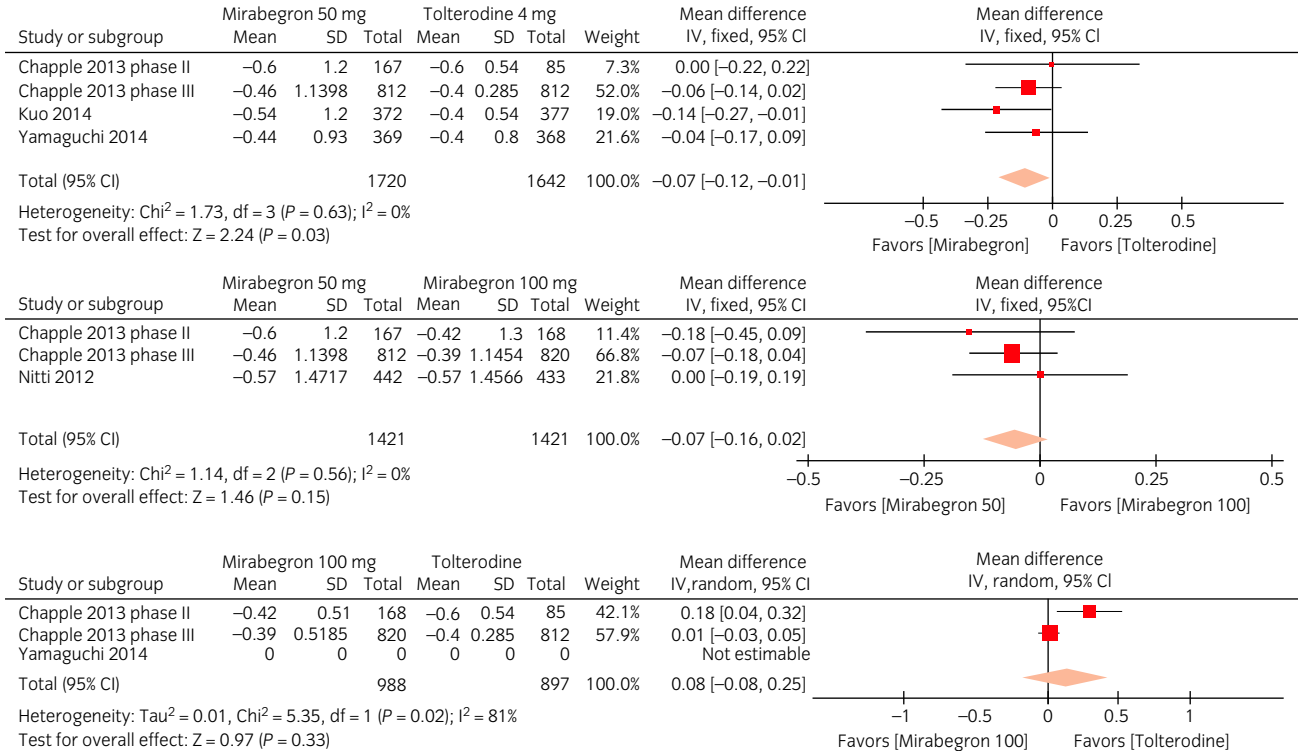

Fig. 6 WMD for nocturia. Mir50 versus Tol; Mir50 versus Mir100; Mir100 versus Tol.

Several studies pointed out the cardiovascular safety of Mir. In 2012, a randomized, placebo, and active-controlled (moxifloxacin 400 mg) trial on 352 healthy individuals showed that Mir at doses of 50 or 100 mg did not cause QTc prolongation.[29] Otherwise, Mir was found to increase heart rate on electrocardiogram in a dose-dependent manner, but this last finding has not been long-established in clinical studies on OAB populations. Although Mir is a highly selective β3-AR agonist with low intrinsic activity for the β1- and β2-ARs, there is a small theoretical risk of unwanted cardiovascular effects despite reassuring data from the phase II clinical trials.

Furthermore, cardiovascular safety has been assessed in a four-arm, parallel, two-way cross-over double-blind QT/QTc study that included supratherapeutic doses of Mir in addition to the licensed doses: overall, there was no QTc interval prolongation in men or women at 50-mg or 100-mg doses.[30]

Only a small increase in heart rate has been found in the 12-month TAURUS[20] study, similar for both Mir100 and Tol ER 4 mg, and with a lower impact of Mir50: approximately 1 b.p.m. change from baseline to final visit.[20] The same study confirmed the long-term safety of Mir on systolic and diastolic blood pressure. Adjusted mean systolic blood pressure changes from baseline to final visit were 0.2, 0.4 and −0.5 mmHg for AM measurements, and −0.3, 0.1 and −0.0 mmHg for PM measurements in patients receiving Mir50, Mir100 and Tol, respectively. Similar findings have been shown for adjusted mean diastolic blood pressure changes (−0.3, 0.4 and 0.1 mmHg for AM measurements, and −0.0, 0.1 and 0.6 mmHg for PM measurements, respectively). In a study analyzing TEAEs of Mir, the authors found a maximum rise of 1.9 mmHg in blood pressure of patients treated with Mir at any dose level, and this was not statistically significant when compared with the placebo. There were no significant changes in the morning pulse heart rate with the placebo, 25 mg and 50 mg of Mir versus baseline (0.51 b.p.m., 0.34 and 1.64, respectively). However, there were statistically significant increases in heart rate of 2.15–2.71 for Mir100 ($P \leq 0.05$), and 4.63–4.66 b.p.m. for Mir200 mg ($P \leq 0.001$). Furthermore, this increase in heart rate, however, was not associated with an increase in cardiovascular adverse effects, such as atrial fibrillation or palpitations.[24] Indeed, β3-ARs show a rather restricted expression in human tissues, which may explain the overall good tolerability of agonists acting on this receptor.[31]

Conversely, Tol was associated with a statistically significant greater risk of overall TEAEs rate than the placebo (34.2% *vs* 31.1%; OR 1.38, $P < 0.0001$). Furthermore, it was associated with a threefold increased risk of dry mouth when compared with the placebo, and a 2.5-fold when compared with Mir. As dry mouth is the most bothersome TEAE related to antimuscarinic therapies, Mir might represent a valid option for the treatment of these patients. The present results confirm a previous meta-analysis on six RCTs in which Mir showed a similar incidence of AEs when compared with a placebo, and a lower adverse reaction rate than Tol (OR 0.9; $P = 0.04$).[16] Furthermore, antimuscarinics can also contribute to a patient's anticholinergic cognitive burden, so the Beers Criteria recommends cautious use of antimuscarinics in elderly patients who take multiple anticholinergic medications or have cognitive

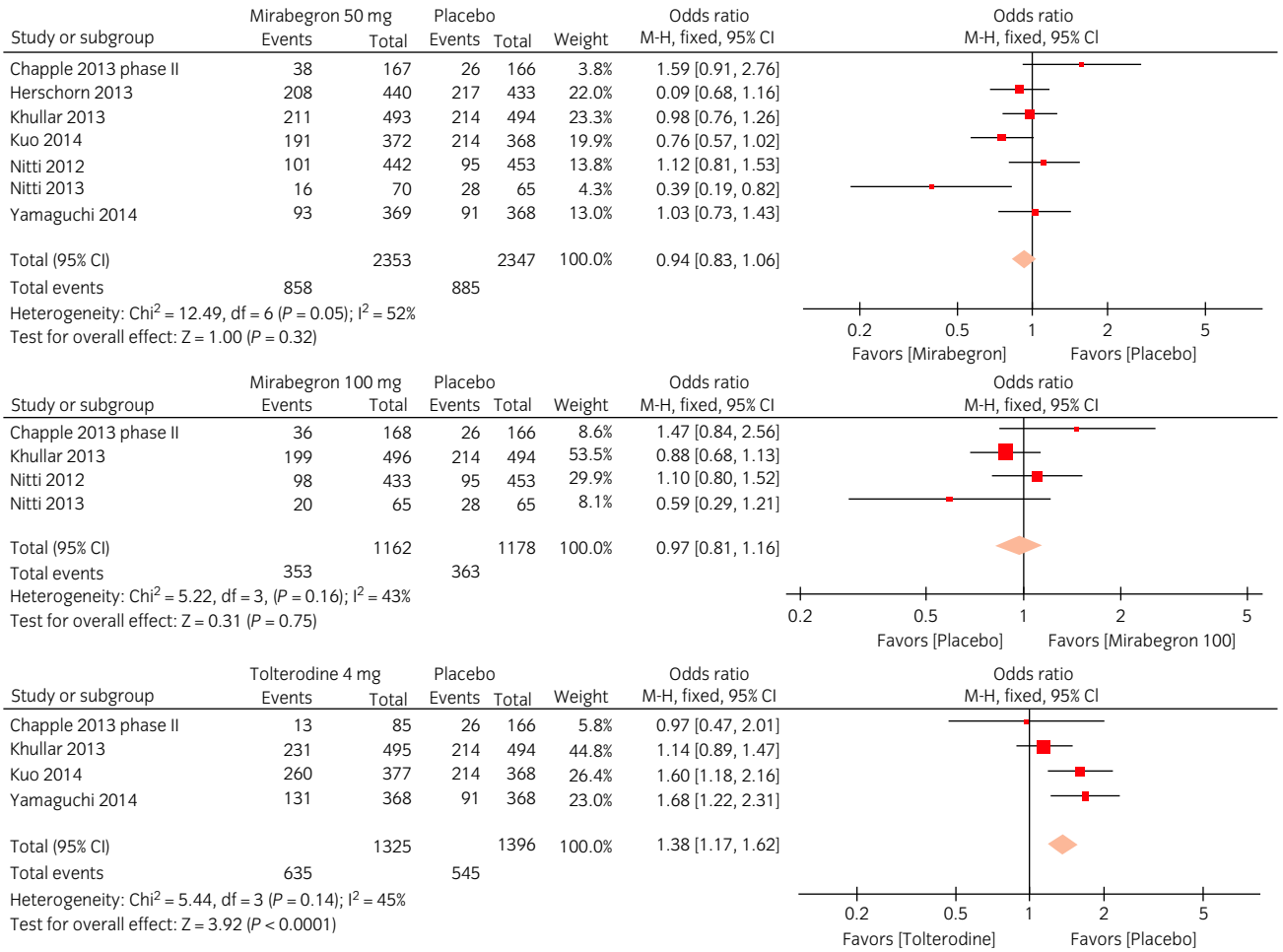

Fig. 7 Risk of TEAEs. Mir50 versus placebo; Mir100 versus placebo; Tol versus placebo.

impairment. As Mir does not affect the cholinergic pathways, it is unlikely to contribute to a patient's anticholinergic cognitive burden.[32]

Despite these data, the discontinuation rate as a result of TEAEs was not greater for Mir50, Mir100 or Tol when compared with the placebo (3.6%, 3.5%, 3.7% and 3%, respectively). Probably due to the follow-up period of the studies. Indeed, the major discontinuation for antimuscarinics is reported after 12 months of treatment. A recent prospective, randomized trial on long-term persistence with Mir versus another antimuscarinic drug, solifenacin, showed that discontinuation as a result of TEAEs was significantly less frequent in the Mir group than the solifenacin group (7.9% *vs* 27.3, $P < 0.05$) over 12 months.[33] Furthermore, a recent retrospective, longitudinal, observational study of anonymized data from the UK Clinical Practice Research Datalink GOLD database on 21 996 patients aimed to compare persistence and adherence with Mir versus Tol ER and other antimuscarinics in routine clinical practice over a 12-month period, showed that 12-month persistence rates were significantly increased with Mir compared with all antimuscarinics.[34]

The main limitation of the present review was the 12 months design of most of the studies. Despite the high quality of the included studies, most available data were from industry-led trials. Furthermore, the lack of data did not allow the comparison of efficacy and safety for Mir 25 mg. Finally, we were not able to include in the analysis some other relevant urological parameters, such as maximum urinary flow rate or post-void residual volume. Mir is an effective and safe treatment option for patients with storage LUTS/OAB, allowing to achieve similar results compared with Tol in terms of the reduction of incontinence episodes per 24 h, number of micturition per 24 h, improvement of voided volume and decrease of urgency. Moreover, it presents a greater efficacy profile in reducing the number night-time frequency episodes compared with both a placebo and Tol. Furthermore, Mir50 shows a safety profile similar to a placebo, with a low occurrence of TEAEs, without any increased risk of hypertension or arrhythmia and an acceptable low discontinuation rate due to AEs. The results of the present meta-analysis provide the basis for further prospective trials with Mir.

Conflict of interest

Dr Gacci received support for travel to meetings for the study, manuscript preparation or other purposes, and payment for lectures from GSK, Eli Lilly, Menarini, Pfizer, Bayer and Astellas. Dr McVary received consulting fees from Allergan

(Consultant or Advisor; Honorarium), Lilly/ICOS (Consultant or Advisor; Honorarium), NxThera (Consultant or Advisor; Honorarium), Watson Pharmaceuticals (Consultant or Advisor; Honorarium) and GSK (Honorarium), and payment for lectures from GSK (Meeting participant or Lecturer). Drs Sebastianelli, Russo, Kaplan, Moncada, Gravas, Morgia and Serni declare no conflict of interest.

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