The Effectiveness of Anticholinergic Therapy for Overactive Bladders: Systematic Review and Meta-Analysis

Eficácia da terapia anticolinérgica na bexiga hiperativa: revisão sistemática e metanálise

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Abstract

The overactive bladder (OAB) has a significant negative impact on the quality of life of patients. Antimuscarinics have become the pharmacological treatment of choice for this condition. The objective of this systematic review and meta-analysis is to examine the evidence from randomized clinical trials about the outcomes of the antimuscarinic drugs available in Brazil on OABs. We searched MEDLINE and the Cochrane Central Register of Controlled Trials from the inception of these databases through to September 2015. The primary outcome measures were the mean decrease in urge urinary incontinence episodes and the mean decrease in the frequency of micturition. The results suggest that there is a moderate to high amount of evidence supporting the benefit of using anticholinergic drugs in alleviating OAB symptoms when compared with placebo. It is still not clear whether any of the specific drugs that are available in Brazil offer advantages over the others. These drugs are associated with adverse effects (dry mouth and constipation), although they are not related to an increase in the number of withdrawals.

Keywords

- overactive bladder
- urge incontinence
- urinary frequency and antimuscarinics

Resumo

A bexiga hiperativa determina um impacto negativo na qualidade de vida dos nossos pacientes. Os antimuscarínicos tornaram-se o tratamento farmacológico de escolha para essa condição. O objetivo desta revisão sistemática e metanálise é examinar as melhores evidências científicas sobre estas medicações disponíveis no Brasil no tratamento de mulheres com bexiga hiperativa. As bases de dados utilizadas foram MEDLINE e a biblioteca da Cochrane, das quais selecionamos os ensaios clínicos

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Palavras chaves
- bexiga hiperativa
- incontinência de urgência
- frequência urinária e antimuscarínicos

randomizados até setembro de 2015. Os principais desfechos analisados foram a diminuição dos episódios de incontinência urinária de urgência e a diminuição da frequência de micção. Os resultados sugerem que as drogas existentes no Brasil sustentam o benefício dos anticolinérgicos no alívio dos sintomas da bexiga hiperativa quando comparadas com o placebo. Em termos de eficácia, as medicações apresentam resultados semelhantes no controle dos sintomas. Essas drogas estão associadas a efeitos adversos importantes, tais como boca seca e constipação, e esses efeitos adversos não influenciaram no uso da medicação.

Introduction

Overactive bladder (OAB) is defined by the International Continence Society as the presence of urinary urgency, usually accompanied by frequency and nocturia, with or without urge urinary incontinence (UUI), in the absence of a urinary tract infection or another obvious pathology.[1] Overactive bladder is a highly prevalent disease in both men and women, affecting 12–17% of the adult population. This condition has a significant negative impact on the quality of life of patients, affecting emotional, physical, social, occupational, and domestic functions.[2–4]

Overactive bladder symptoms are thought to develop as a result of inappropriate contractions of the bladder detrusor during the filling phase of the micturition cycle. Normal and abnormal bladder contractions occur via cholinergic activation of the muscarinic receptors. As is the case in other chronic conditions, OAB typically requires long-term persistence and adherence to therapy.[5] Behavior modification, which includes education about the disorder, lifestyle changes (, such as avoiding caffeinated beverages, for example), as well as pelvic floor muscle training and bladder retraining, represent the first-line therapy options for this condition. However, when these approaches are insufficient, second-line therapy involves pharmacological treatment, and antimuscarinic agents are the treatment of choice.[6–8]

Although anticholinergic medications have been shown to improve patients' symptoms, they create a widespread blockade of cholinergic activity that often results in side effects such as dry mouth, cognitive changes, constipation, urinary retention, blurred vision, and dyspepsia.[9] These problems can be difficult to manage, and may contribute to poor patient adherence to treatment.[10]

The objective of this systematic review and meta-analysis was to examine the currently available evidence from randomized clinical trials (RCTs) about the outcomes of the pharmacological management of OAB, and to summarize the comparative effectiveness of the drugs available in Brazil. Only antimuscarinic agents commercialized in Brazil were included in the analysis, since this meta-analysis is the basis for the development of Brazilian urogynecology guidelines.[11]

Methods

This study was exempt from institutional review board approval, given that it was a systematic review and meta-analysis; it did not involve the use of any interventions on humans. To report the results of this meta-analysis, we utilized the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement.[12]

Search Strategy

An exhaustive electronic search was performed using the MEDLINE database, as well as the Cochrane Central Register of Controlled Trials, with the dates of the included articles spanning from the inception of these databases through to September 2015. We also searched the references of the identified articles and restricted the search to articles published in English. The search combined relevant terms and descriptors related to OAB, anticholinergic drugs, oxybutynin, darifenacin, tolterodine, solifenacin, and RCTs.

Eligibility Criteria and Data Extraction

The review only included RCTs featuring adult male and female patients diagnosed with OAB or with a diagnosis of detrusor over activity, and who were also submitted to any of the anticholinergic treatments available in Brazil. The selection criteria are described in ►**Table 1**. In a first screening, two independent authors (AMRMF and MVCM) assessed all of the abstracts retrieved from the search; they then obtained the full manuscripts of the citations that met the inclusion criteria. These authors evaluated the studies' eligibility and quality, and extracted the data subsequently. Any discrepancies were solved by agreement, and, if needed, the authors reached a consensus with a third author (MR). The meta-analysis included studies that provided accurate data related to those primary outcomes that could be analyzed. Thus, only studies that provided the mean, sample size, and standard deviation (SD) values of the primary outcomes were included in the analysis. Otherwise, when the available data were expressed as the median, it was necessary that the study provided the range values (lowest and highest values) to extrapolate the mean. If only the ranges of continuous variables were reported, we would estimate the SD by dividing the range by four. Dose escalation and crossover studies were excluded, as it was not possible to abstract the data related to our primary outcomes.

Outcome Measures

The primary outcomes of interest for this systematic review and meta-analysis were the mean decrease in the number of UUI episodes per day and the mean decrease in the number

Table 1 Selection criteria of included studies (PICOs)

	Included	Excluded
Population	Symptomatic diagnosis of overactive bladder (OAB) or a urodynamic diagnosis of detrusor over activity	OAB as consequence of surgery
Intervention	Anticholinergic drugs available in Brazil (oxybutynin 5 mg and 10 mg; darifenacin 7.5 mg and 15 mg; tolterodine 1 mg, 2 mg, and 4 mg; solifenacin 5 mg and 10 mg)	Anticholinergic drugs not available in Brazil or with different doses or routes of administration that are not available in Brazil
Comparison	Placebo, comparison between different drugs, or comparison between different doses of the same drug	
Outcomes	Primary outcomes • Mean decrease in urge urinary incontinence (UUI) episodes per day • Mean decrease in the number of micturitions per day Secondary outcomes • Mean decrease in total incontinence episodes (related or not to urgency) • Dry mouth • Constipation • Withdrawals resulting from drug-related adverse effects	
Study type	Randomized controlled trials (RCTs)	Non RCTs

Abbreviation: PICOs, population, intervention, comparison and outcomes.

of micturitions per day. The secondary outcomes included the mean decrease in total incontinence episodes (either related or not to urgency), dry mouth, constipation, and withdrawals resulting from drug-related adverse effects. We tried to perform meta-analytic comparisons between each drug (and their different dosages) versus placebo, comparisons between different drugs, and comparisons between different dosages of the same drug.

Risk of Bias Assessment

We followed the guidance suggested by the Cochrane Collaboration[13] to assess the risk of bias from the included studies. We evaluated sequence generation, allocation concealment, blinding, and incomplete outcome data for each trial included in the review. A low risk of bias was considered when a judgment of "yes" for all domains was obtained, whereas a high risk of bias was considered when a judgment of "no" for one or more domains was obtained. An unclear risk of bias was defined when an "unclear" judgment in any domain was considered. The quality assessment of the included trials is shown in ►**Table 2**.

Analysis

We pooled the data of the continuous outcomes from the original studies to obtain the mean difference (MD) for the occurrence of an outcome event, and presented their corresponding 95% confidence intervals (CIs). Data for dichotomous outcomes from the original studies were pooled to obtain the relative ratio (RR), and the corresponding 95% CIs were calculated. Statistical significance was set at a p-value of < 0.05. In order to quantify the statistical heterogeneity, we used the I2 statistic to describe the variations across trials that were due to heterogeneity and not to sampling error. We pooled the outcome data from each study using a Mantel–Haenszel model, and applied the fixed-effects model. When the heterogeneity was greater than 50% ($I2 > 50\%$), we applied the random-effects model.[14] We used the software Review Manager (RevMan, Version 5.3; Copenhagen) to conduct the meta-analysis.

Results

Our electronic search retrieved 468 articles. After screening the titles and abstracts, we ended up with 37 articles that were considered eligible for inclusion in this review by one or both reviewers, and the full texts were subsequently assessed. The complete article selection process is presented in ►**Fig. 1**.

Description of Included Studies

Fifteen RCTs assessing the pharmacological management (drugs and dosages available in Brazil) of OAB met the inclusion criteria and provided data to perform the meta-analysis. With the available data of the included studies,[15–29] it was only possible to perform comparisons between tolterodine (and its different dosages) versus placebo, solifenacin versus placebo, and oxybutynin versus tolterodine.

Excluded Studies

Twenty-two articles were excluded because they either did not meet the inclusion criteria[30–35] or they did not provide adequate data to be included in the meta-analysis.[36–51]

Table 2 Quality assessment of included trials

Study	Sequence generation	Allocation concealed	Blinding	Incomplete outcome data
Appell et al.[15]	Unclear	Yes	Yes	Yes
Drutz et al.[16]	Unclear	Yes	Yes	Yes
Lee et al.[17]	Yes	Yes	Yes	Yes
Malone-Lee et al.[18]	Unclear	Unclear	Yes	Yes
Chapple et al.[19]	Unclear	Yes	Unclear	Yes
Jacquetin et al.[20]	Unclear	Yes	Unclear	Yes
Khullar et al.[21]	Yes	Yes	Yes	Yes
Millard et al.[22]	Unclear	Unclear	Unclear	Yes
Swift et al.[23]	Yes	Yes	Yes	Yes
Van Kerrebroeck et al.[24]	Unclear	Unclear	Unclear	Yes
Van Kerrebroeck et al.[25]	Yes	Yes	Yes	Yes
Zinner et al.[26]	Yes	Yes	Yes	Yes
Cardozo et al.[27]	Unclear	Unclear	Unclear	Yes
Karram et al.[28]	Unclear	Unclear	Unclear	Yes
But et al.[29]	Yes	Unclear	Unclear	Yes

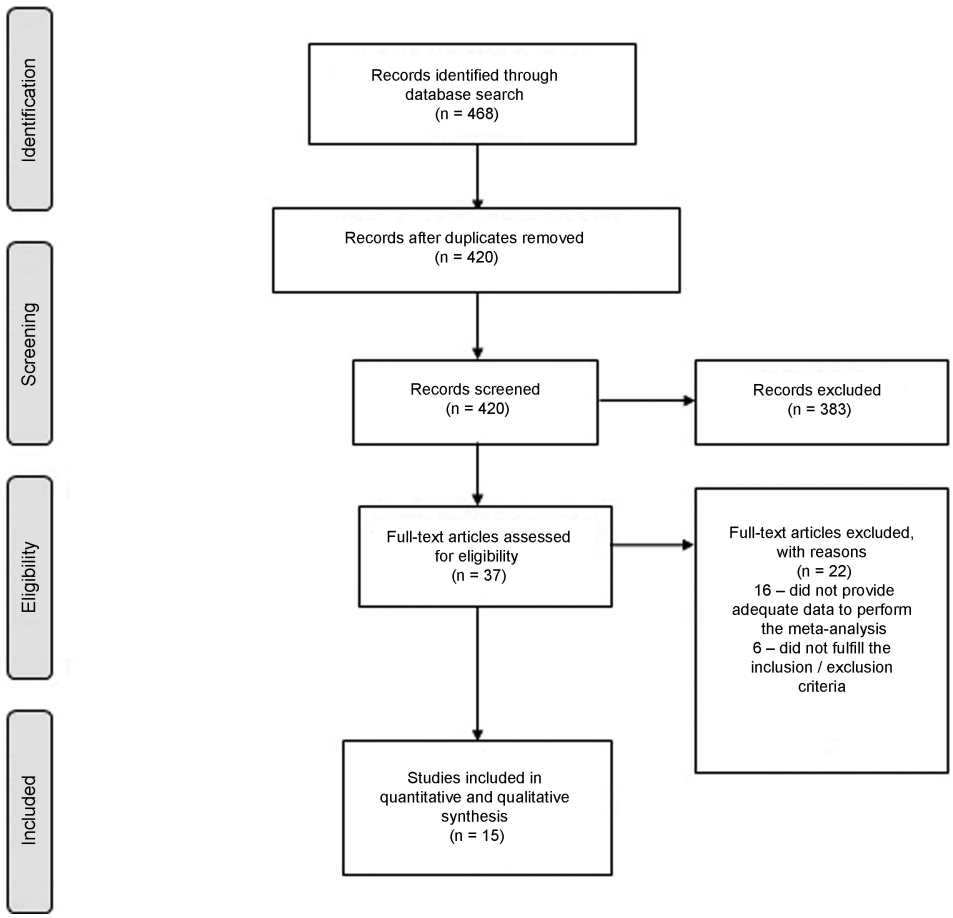

Fig. 1 Flowchart for the trial identification and selection process.

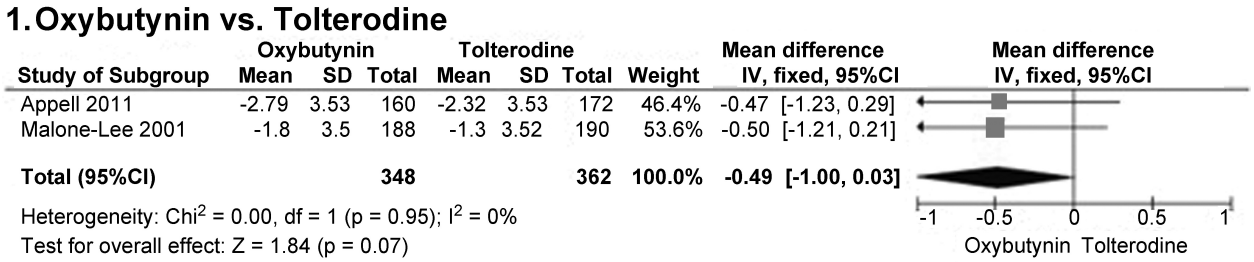

Fig. 2 Forest plot – mean difference in decrease in urge urinary incontinence (UUI) episodes per day.

Primary Outcomes

- Mean decrease in UUI episodes per day

For this outcome, it was only possible to perform a comparison between oxybutynin and tolterodine. The MD in the mean decrease in UUI episodes per day was higher for patients that used oxybutynin than for those that used tolterodine (MD = –0.49; 95% CI: –1.00, 0.03; I2 = 0; $p = 0.07$); however, this difference was not significant (►**Fig. 2**).

- Mean decrease in the number of micturitions per day

We were able to perform the following comparisons: oxybutynin versus tolterodine; tolterodine (and its different doses) versus placebo; different doses of tolterodine; and solifenacin versus placebo. We found significant differences that favored tolterodine 1 mg when compared with placebo (MD = –0.55; 95% CI: –1.08, –0.02; I2 = 0; $p = 0.04$); tolterodine 2 mg versus placebo (MD = –0.57; 95% CI: –0.82, –0.32; I2 = 0; $p < 0.001$); and tolterodine 4 mg versus placebo (MD = –0.66; 95% CI: –0.85, –0.47; I2 = 0; $p < 0.001$). Moreover, significant differences favored the use of solifenacin when compared with placebo (MD = –0.77; 95% CI: –1.09, –0.45; I2 = 0; $p < 0.001$) (►**Fig. 3**). All of these outcome data were pooled from each study using a Mantel–Haenszel model, and a fixed-effects model was applied, as there was no heterogeneity (I2 = 0) among the studies. For all other available comparisons for this outcome (oxybutynin versus tolterodine; tolterodine 2 mg versus tolterodine 1 mg; and tolterodine 4 mg versus tolterodine 2 mg), the MD was not significant, as presented in ►**Fig. 3**.

Secondary Outcomes

- Mean decrease in incontinence episodes per day

Significant differences were found that favored tolterodine 2 mg when compared with placebo (MD = –0.45; 95% CI: –0.76, –0.14; I2 = 0; $p = 0.005$); tolterodine 4 mg versus placebo (MD = –0.46; 95% CI: –0.83, –0.08; I2 = 0; $p = 0.02$); and solifenacin versus placebo (MD = –0.77; 95% CI: –1.09, –0.45; I2 = 0; $p < 0.001$) (►**Fig. 4**). All of these outcome data were pooled from each study using a Mantel–Haenszel model, and a fixed-effects model was applied, as there was no heterogeneity (I2 = 0) among the studies. We did not find significant differences across any of the other available comparisons (oxybutynin versus tolterodine; tolterodine 1 mg versus placebo; tolterodine 2 mg versus tolterodine 1 mg; and tolterodine 4 mg versus tolterodine 2 mg).

- Dry mouth

There were significant differences and higher RRs in patients treated with oxybutynin when compared with tolterodine (RR = 1.49; 95% CI: 1.06, 2.10; I2 = 84%; $p = 0.02$); tolterodine 1 mg versus placebo (RR = 2.33; 95% CI: 1.26, 4.29; I2 = 84%; $p = 0.02$); tolterodine 2 mg versus placebo (RR = 3.72; 95% CI: 3.05, 4.54; I2 = 0%; $p < 0.001$); tolterodine 4 mg versus placebo (RR = 2.88; 95% CI: 2.40, 3.45; I2 = 0%; $p < 0.001$); tolterodine 2 mg versus tolterodine 1 mg (RR =1.69; 95% CI: 1.26, 2.28; I2 = 0%; $p < 0.001$), and solifenacin versus placebo (RR =3.73; 95% CI: 1.80, 7.77; I2 =0%; $p < 0.001$). The group of patients that used tolterodine 4 mg exhibited a lower risk (RR = 0.79; 95% CI: 0.68, 0.92; I2 = 0%; $p = 0.02$) when compared with tolterodine 2 mg. All of these results are presented in ►**Fig. 5**.

- Constipation

The findings indicated that there was a significant difference and a higher RR in patients treated with tolterodine 2 mg versus those treated with placebo (RR = 1.61; 95% CI: 1.11, 2.32; I2 = 0%; $p = 0.01$), and those treated with tolterodine 4 mg versus placebo (RR = 1.52; 95% CI: 1.11, 2.09; I2 =0%; $p = 0.009$). We did not find significant differences across any of the other available comparisons (oxybutynin versus tolterodine; solifenacin versus placebo). All of these results are presented in ►**Fig. 6**.

- Withdrawals resulting from drug-related adverse effects

We did not find statistical differences in any of the available comparisons (oxybutynin versus tolterodine, $p = 0.18$; tolterodine 1 mg versus placebo, $p = 0.47$; tolterodine 2 mg versus placebo, $p = 0.32$; tolterodine 4 mg versus placebo, $p = 0.13$; tolterodine 2 mg versus tolterodine 1 mg, $p = 0.59$; tolterodine 4 mg versus tolterodine 2 mg, $p = 0.92$; and solifenacin versus placebo, $p = 0.67$) when evaluating the risk of withdrawals due to drug-related adverse effects.

Discussion

To our knowledge, this is the first comprehensive review featuring a pooled analysis that has addressed the question of efficacy and the main adverse effects of all antimuscarinic drugs available in Brazil for the treatment of OAB.

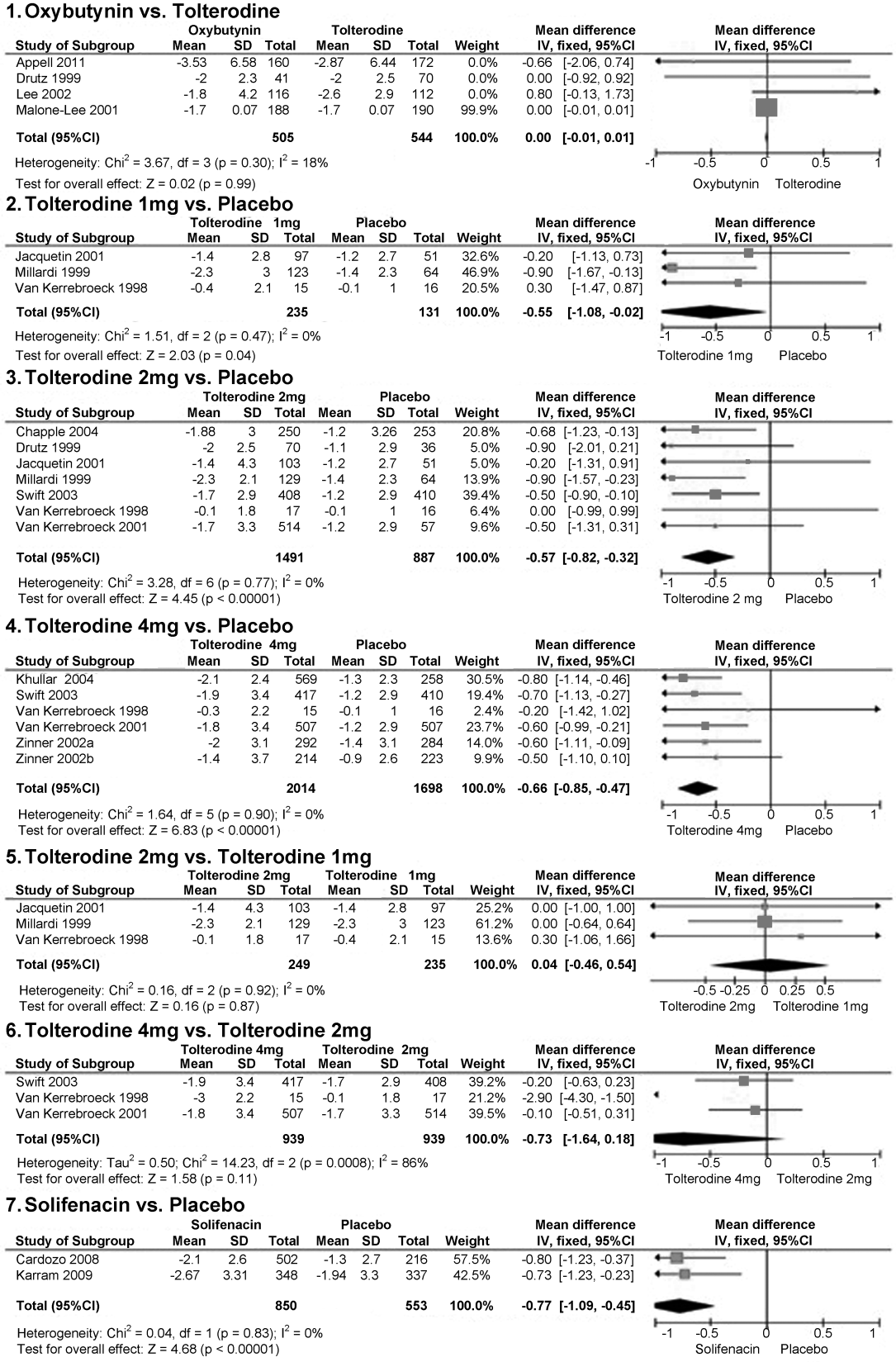

Fig. 3 Forest plot – mean difference in decrease in the number of micturitions per day.

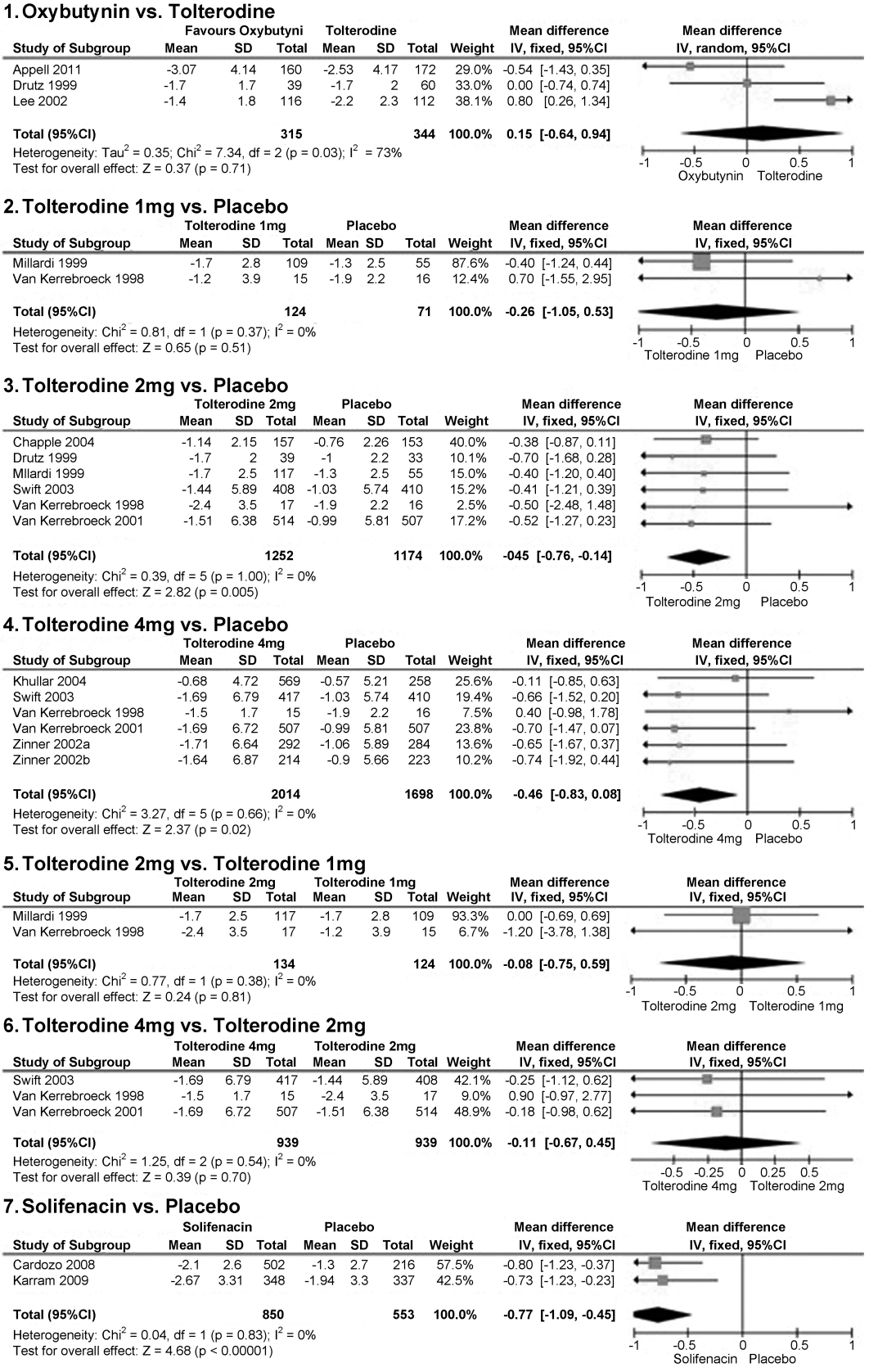

Fig. 4 Forest plot – mean difference in decrease of total incontinence episodes per day.

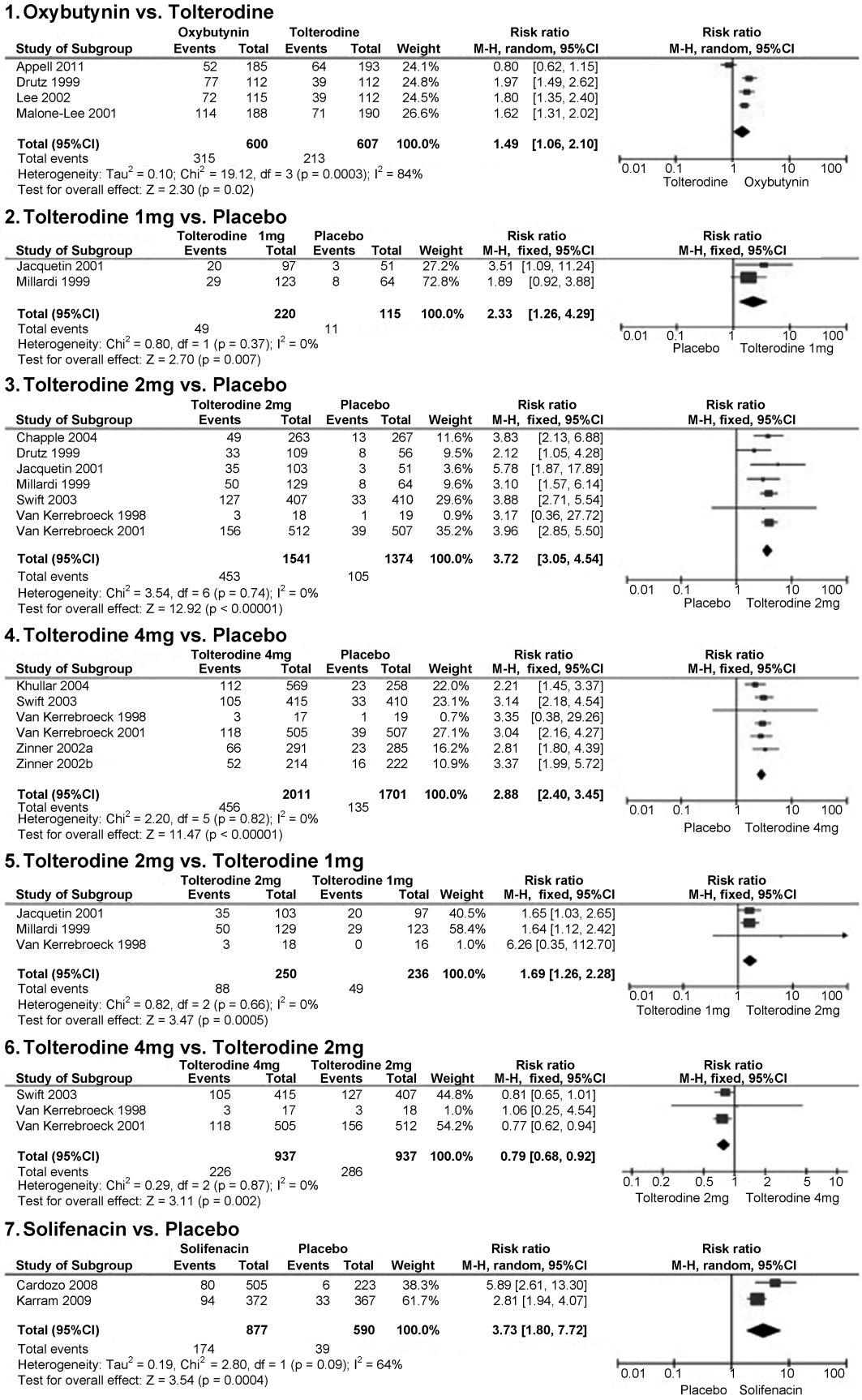

Fig. 5 Forest plot – Risk Ratio (RR) of dry mouth.

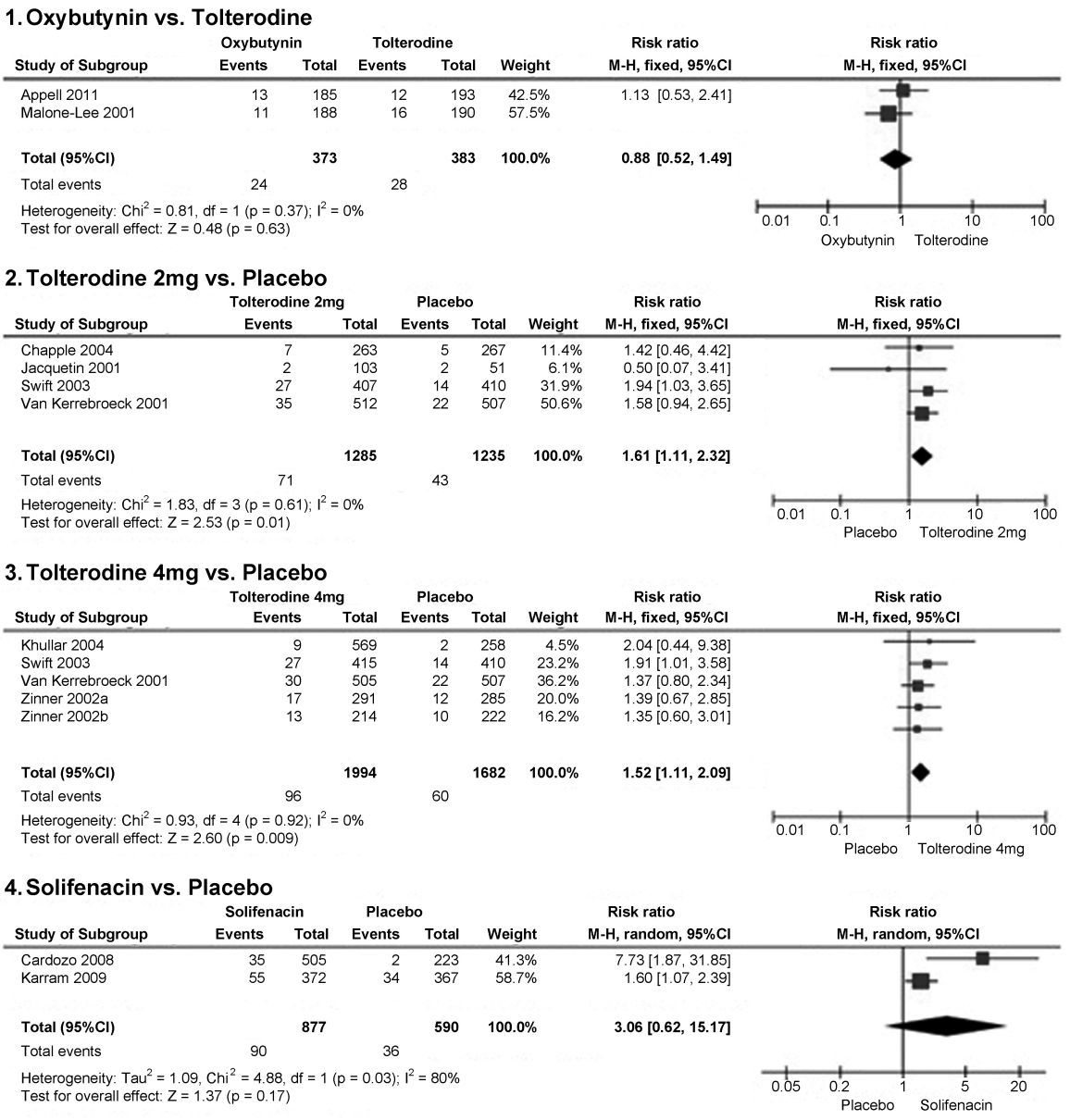

Fig. 6 Forest plot – Risk Ratio (RR) of constipation.

This systematic review showed that there is no significant difference in the mean decrease in UUI episodes per day between oxybutynin and tolterodine. Although there was a trend of a higher reduction in UUI episodes with the use of oxybutynin, the difference was not statistically significant. It was not possible to perform comparisons between oxybutynin versus solifenacin, oxybutynin versus darifenacin, tolterodine versus solifenacin, tolterodine versus darifenacin, and solifenacin versus darifenacin due to limitations in data reporting (that is, studies without a measure of variation) and the lack of similarity in measures.

Regarding the decrease in the number of micturitions per day, which was another important primary outcome, the results favored tolterodine in its various dosages and solifenacin when compared with placebo. The comparison between oxybutynin and tolterodine showed no significant difference in treatment efficacy across any of the outcomes; the same was found for the comparisons of tolterodine in its various dosages. As result of the relative paucity of data that qualified for inclusion in the meta-analysis – and that directly compared pharmacological agents –, it is impossible to report definitively whether any specific agent is superior to another in terms of efficacy.

Antimuscarinic agents may be associated with adverse effects. The human bladder tissue contains M2 and M3 muscarinic receptors. The M3 subtype has been identified as the primary mediator of detrusor contraction in response to cholinergic activation.[52,53] Different subtypes of muscarinic receptors are widely distributed in the body. M1 receptors in the brain and salivary glands are involved in cognition and in the

production of mucous saliva;[54,55] M2 receptors in the cardiovascular system play a role in mediating heart rate and cardiac output;[56] and M5 receptors in the eye are involved in ciliary muscle contraction.[57–59] As a result, antimuscarinic agents, which bind to some or all of these receptors, are effective in treating OAB symptoms, but they may also be associated with adverse effects such as dry mouth, constipation, cognitive impairment, tachycardia, and blurred vision.[57] This systematic review showed that oxybutynin was associated with significantly higher rates of dry mouth when compared with tolterodine. When compared with placebo, tolterodine, in its various dosages, and solifenacin were associated with significantly higher rates of dry mouth. The group of patients that used tolterodine 4 mg presented lower risk when compared with the group treated with tolterodine 2 mg. This can be explained by the fact that tolterodine 4 mg is an extended-release (ER) presentation. Compared with the immediate-release drug, tolterodine ER releases the drug in a steady and constant manner, thus lowering peaks. This translates into more constant serum concentrations and theoretically improves patient tolerability.[60] Concerning constipation, differences were not found between oxybutynin and tolterodine. Significantly high rates of constipation were found in patients treated with tolterodine 2 mg and 4 mg when compared with placebo.

The current data demonstrate that a substantial proportion of patients discontinue anticholinergic drugs, with 75–90% of patients discontinuing therapy within 12 months. Among those studies that provided information about the reasons for the discontinuation of the therapy, the most frequently cited reasons were that the medication did not work as expected, and that the medication's side effects were not desirable.[7] We did not find a statistical difference associated with withdrawals resulting from drug-related adverse effects.

New drugs for the treatment of OAB are emerging, such as imidafenacin and tarafenacin, but they are not available in Brazil yet. Mirabegron, a β3-adrenoreceptor agonist, has just recently been released into the Brazilian market with some promising results, especially when associated with regular antimuscarinic drugs.[61,62]

The quality of the available evidence that supports these results is moderate. The main limitation of the available evidence concerning OAB treatment is that although there is a large amount of RCTs, it is not possible to combine all of the data in a meta-analysis due to their heterogeneity. If the goal of a meta-analysis is to estimate the MD between two treatments, then the means, sample sizes, and a measure of variation (standard deviation, standard error, or a confidence interval) are required. Thus, many of the available RCTs on OAB treatment did not contribute to the meta-analysis, and were excluded from our study. Unfortunately, we discovered a lack of high-quality evidence pertaining to the available drugs and dosages for the treatment of OAB in Brazil that can inform clinical decision making for patients and care providers.

In summary, the results of this meta-analysis suggest that there is a moderate to high quality of evidence supporting the benefits of using anticholinergic drugs in alleviating OAB symptoms when compared with placebo. Despite its lower improvement in primary and secondary outcomes when compared with anticholinergics, the use of placebo contributed to many of the improvements in OAB symptoms. It is still not clear if any one specific drug available in Brazil has any advantage over the others. The use of these drugs is associated with adverse effects (mainly dry mouth and constipation), although the use of these agents is not related to an increase in the number of withdrawals.

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