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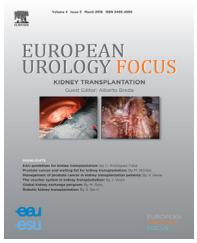

Review – Neuro-urology

# Choosing the Most Efficacious and Safe Oral Treatment for Idiopathic Overactive Bladder: A Systematic Review and Network Meta-analysis

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## Abstract

*Context:* The choice of the most efficacious drug for patients with idiopathic overactive bladder (IOAB) remains challenging.
*Objective:* The aim of this network meta-analysis was to determine the most efficacious oral antimuscarinic or β-adrenoceptor agonist accounting for adverse events for the management of IOAB.
*Evidence acquisition:* A comprehensive electronic search was done in MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, and Ovid for studies in any language in February 2021 considering the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. We included all randomized controlled trials assessing oral antimuscarinics or β-adrenoceptor agonists for the treatment of IOAB. We determined the effect of specific bothersome symptoms separately.
*Evidence synthesis:* Fifty-four articles were included in our analysis. The most efficacious agents considering the evaluated outcomes were oxybutynin 15 mg/d in reducing incontinence episodes, imidafenacin 0.5 mg/d together with solifenacin 10 and 5 mg/d in reducing micturition episodes, fesoterodine 4 and 8 mg/d as well as solifenacin 10 mg/d in reducing urgency episodes, imidafenacin 0.5 mg/d and solifenacin 10 mg/d in reducing urgency urinary incontinence episodes, and solifenacin 10 mg/d, vibegron 50 mg/d, and fesoterodine 8 mg/d in improving the voided volume. Gastrointestinal problems, especially due to antimuscarinic agents, were the most prevalent adverse events.

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*Conclusions:* Taken together, there is only minimal difference between the efficacy of oral antimuscarinics and that of β-adrenoceptor agonists. Although finding the best medication for all is impossible, finding the best treatment for every individual patient can be done by considering the efficacy of a medicine for the most bothersome symptom (s) in balance with drug-specific adverse events.
*Patient summary:* This study aimed to find the most efficient oral medication to treat overactive bladder, taking into consideration the adverse events. Based on our study, there is a minimal difference in the efficacy between the two major drug classes used to treat overactive bladder. Gastrointestinal problems were the most common adverse events in medical treatment of overactive bladder. Selection of the best treatment is possible through shared decision-making between the doctor and the patient based on the patient's most bothersome symptom. We provide a framework for physicians to facilitate shared decision-making with each individual patient.


## 1. Introduction

Overactive bladder (OAB), defined as "urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection (UTI) or other obvious pathology" [1], is a highly prevalent and often debilitating condition [2,3] with significant detrimental impact on quality of life (QOL) [4,5].

Its primary management is most commonly behavioral (ie, dietary and lifestyle modification) with pelvic muscle and bladder training [6]. In case of nonsatisfactory results, oral pharmacological therapy is initiated for idiopathic OAB (IOAB) [7,8]. The most widely used therapy includes antimuscarinics such as oxybutynin, solifenacin, propiverine, tolterodine, trospium chloride, fesoterodine, imidafenacin, darifenacin, and tarafenacin [9–12] with variations in dosages, formulations, and routes of administration. While the efficacy of these antimuscarinic agents is clinically proven, the compliance and persistence on therapy of the patients are limited due to their adverse events [13]. The introduction of newer bladder selective drugs has led to an improvement in the rate of patients staying on therapy. Beta-adrenergic receptor agonists (β-adrenoceptor agonists), which are 97% specific to the bladder, have indeed enriched the armamentarium in the management of OAB [14]. Given the multitude of available oral antimuscarinic and β-adrenoceptor agonist agents with different dosages and formulations, caregivers face a choice dilemma. Therefore, to facilitate decision-making, we decided to perform a network meta-analysis (NMA) aimed to determine the most efficacious antimuscarinic and/or β-adrenoceptor agonist with the fewest adverse events for the management of IOAB. We analyzed results according to specific bothersome symptoms/signs.

## 2. Evidence acquisition

### 2.1. Search strategy

We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, and Ovid for studies in any language (timestamp: February 2021) using the following MeSH terms: lower urinary tract dysfunction, lower urinary tract symptom, incontinence, urinary retention, overactive bladder, antimuscarinics, tolterodine ER, solifenacin succinate, trospium chloride, oxybutynin, β-adrenoceptor agonist, vibegron, solabegron, mirabegron, imidafenacin, darifenacin, propiverine hydrochloride, duloxetine, desmopressin, and fesoterodine. Additionally, we reviewed the reference lists and conference abstracts of all publications from other potential data sources. Three investigators independently assessed reports for eligibility. First, they independently read the titles and abstracts; if all potential eligibility criteria were achieved, the relevant articles were assessed independently by reading the full text for inclusion.

### 2.2. Inclusion criteria

We used the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement for this systematic review and meta-analysis [15]. We included randomized controlled trials (RCTs) related to IOAB in which patients were treated with oral antimuscarinics and β-adrenoceptor agonists for bothersome symptoms/signs.

Comparisons were made with the reported efficacy or adverse event rate in the placebo arm. The diagnosis of symptoms must have been based, at least, on one validated questionnaire or urodynamic studies.

### 2.3. Exclusion criteria

Trials with nonoral antimuscarinic or intravesical administrations, drugs with less direct antimuscarinic effects (ie, smooth muscle relaxants, flavoxate hydrochloride, calcium channel blockers, potassium channel openers, and tricyclic antidepressants) and drugs no longer used in the clinical setting (ie, antihistamines, tricyclic antidepressants, and parasympatholytic medications) were excluded. Retrospective studies, withdrawn trials, pooled studies, open-label trials, and studies without any access to full text were also excluded. In addition, we excluded all RCTs conducted on patients with neurogenic OAB.

### 2.4. Primary outcomes

The primary endpoints included the mean change of incontinence episodes per 24 h, micturition episodes per 24 h,

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urgency incontinence episodes per 24 h, urgency episodes per 24 h, and voided volume per micturition.

### 2.5. Secondary outcomes

Secondary endpoints included related adverse events including dry mouth, constipation, diarrhea, blurred vision, nausea and vomiting, urinary retention, dizziness, fatigue, and UTI.

### 2.6. Study selection

After removing duplications, two independent reviewers screened the titles and abstracts. Eligible titles/abstracts were identified for full-text screening. Subsequently, these reviewers independently reviewed full texts of eligible articles for final inclusion and data extraction. Disagreements were resolved by discussion with coauthors.

### 2.7. Data extraction

Three reviewers independently extracted the information related to participants including patient characteristics, study methods, risks of different biases, interventions, outcomes, as well as other data including country, setting, publication year, and sources of funding. Non–English-language journal articles were translated before assessment.

### 2.8. The efficacy NMA

A frequentist approach was used for the NMA [16]. The efficacy NMA of the included medications was limited to five previously mentioned outcome measures. Antimuscarinics and β-adrenoceptor agonists were classified based on the use of daily dosage into the following groups: 4 and 8 mg (daily) fesoterodine; 0.1, 0.2, and 0.5 mg (BID) imidafenacin; 3 and 5 mg (TID) oxybutynin; 25, 50, and 100 mg (daily) mirabegron; 20 and 30 mg (daily) propiverine hydrochloride; 2.5, 5, and 10 mg (daily) solifenacin; 4 mg (daily) and 2 mg (BID) tolterodine; 40 and 60 mg (daily) trospium chloride; 0.2 and 0.4 mg (daily) tarafenacin; and 50 and 100 mg (daily) vibegron. The mean difference and 95% confidence interval (95% CI) were calculated for the analyses. For each endpoint, a network forest plot was generated. The NMA was performed using a one-line program (Lumley, programming language R, version 1.14, and framework 2.21).

### 2.9. The safety NMA

The NMA was used for simultaneous comparison of adverse effects related to multiple IOAB treatments through direct and indirect comparisons. For each endpoint, a network forest plot was generated. Peripheral or central adverse effects were presented as odds ratios (ORs) and 95% CI (all based on the number of patients who experienced these outcomes at the end of treatment). For estimating the models used, placebo was chosen as the reference comparator.

### 2.10. Assessment of methodological quality

The methodological quality of the selected trials was evaluated by three independent reviewers using the Cochrane risk of bias checklist with six criteria: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other biases.

### 2.11. Assessment of heterogeneity

We expected substantial heterogeneity between studies, so we used the random-effect model that is presented in forest plots. Statistical heterogeneity was assessed using the $I^2$ value and the result of the $\chi^2$ test.

### 2.12. Data collection

For each outcome, the efficacy was standardized with the mean of all reported outcomes. Stata SE v.11.1. (Stata Corp LP, College Station, TX, USA) was used for analysis.

## 3. Evidence synthesis

### 3.1. Study selection and study characteristics

We identified a total of 2094 studies during the search and an additional 320 citations in the updated search. After removing the duplicates and the full-text review, 54 articles met our inclusion criteria. The summary of this process is presented in the PRISMA flow diagram (Fig. 1).

### 3.2. Risk of bias of included studies

Three independent reviewers evaluated all the included articles for the detection of potential biases (Fig. 2). Owing to the methodological purposes and overall acceptable quality of the included articles, none of the studies was excluded because of a high risk of bias.

### 3.3. Publication bias

To assess the publication bias of the extracted data, a funnel plot was established. Owing to methodological reasons and a low risk of bias based on the funnel plot, no study was excluded because of a publication bias (Fig. 3).

### 3.4. Study characteristics

The final 54 articles underwent the process of data extraction for efficacy and safety. The complete summary of the extracted data is presented in Table 1.

### 3.5. Principal findings

We assessed the effect of 25 different drug formulations and dosages on reducing daily micturition episodes, 18 combinations for incontinence episodes per 24 h, 22 combinations for the urgency episodes per 24 h, 20 combinations for the change in urgency incontinence episodes per 24 h, and

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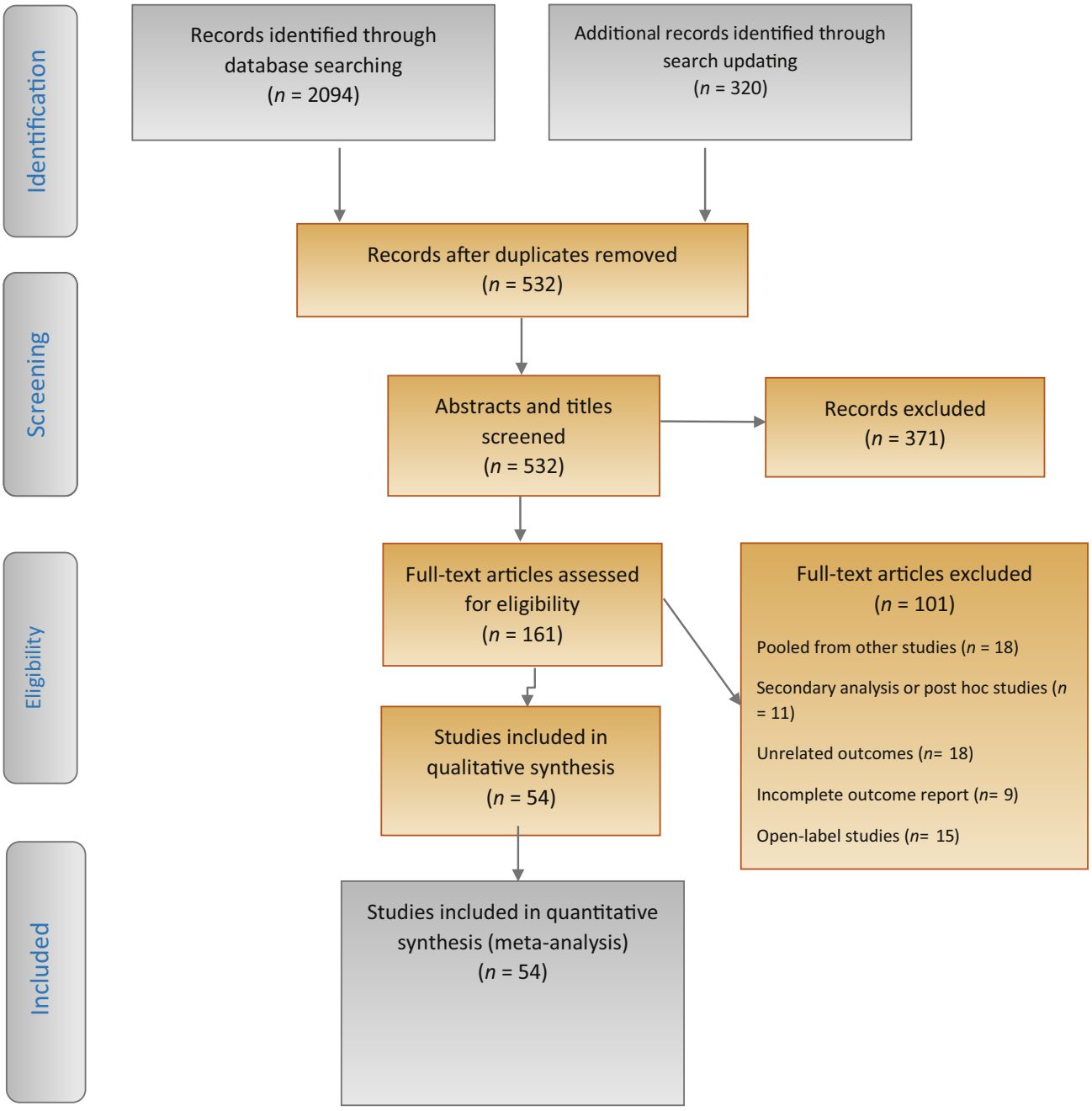


**Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram. At last, 54 studies met the inclusion criteria for this study.**

25 combinations for the change in voided volume per micturition endpoint.

Figure 4 illustrates the forest plots of each treatment and dosage assessed for every outcome compared with placebo. Among different types, dosages, and formulations of the included medications, tolterodine 4 mg/d, mirabegron 50 mg/d, and solifenacin 5 mg/d were the most frequently examined medications in the management of IOAB in the medical literature, and thus had higher weights and narrower CIs due to their large sample sizes.

*3.5.1. Mean change in incontinence episodes per 24 h*

According to our analysis results, oxybutynin with a dose of 5 mg administered TID was the most effective agent in reducing incontinence episodes compared with placebo. Solifenacin 10 mg/d and extended-release propiverine hydrochloride 30 mg/d were the second and third most effective agents in reducing incontinence episodes, respectively. The efficacy of fesoterodine 8 mg/d and vibegron 50 mg was statistically insignificant for this endpoint. Although the mean change of reduction in urinary

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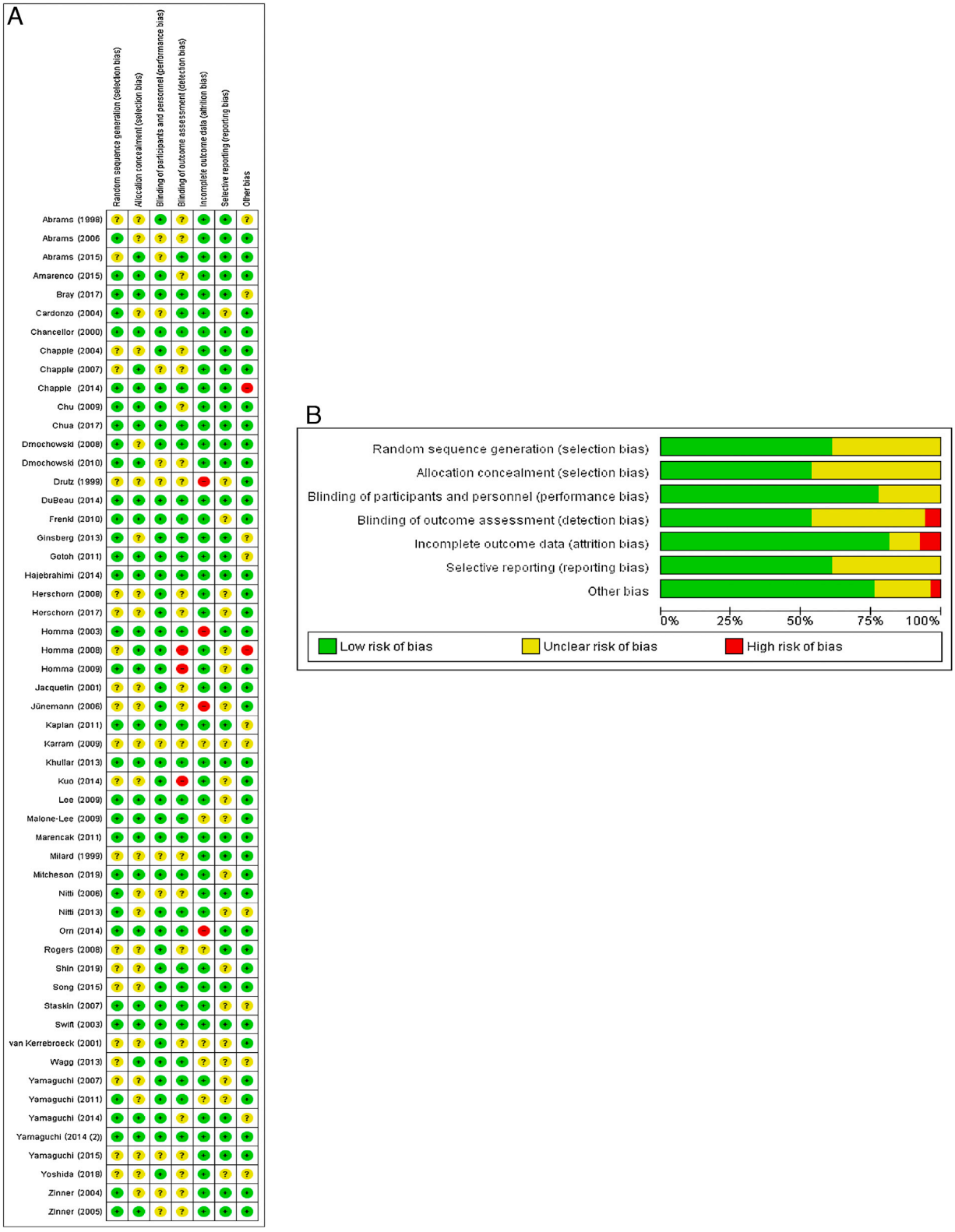


**Fig. 2 – (A) Risk of bias graph of the included studies for network meta-analysis. (B) Risk of bias summary of the included studies for network meta-analysis.**

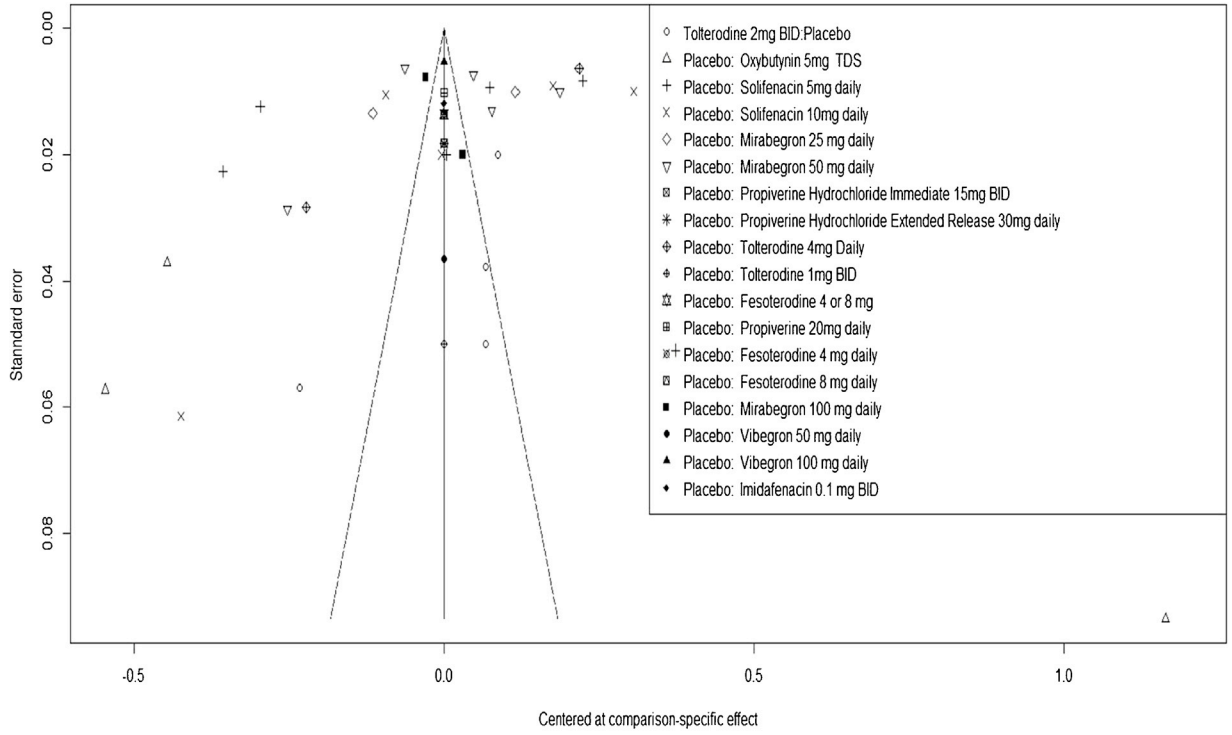


**Fig. 3 – Funnel plot for assessing the publication bias (incontinence episodes). BID = twice daily.**

incontinence episodes in the studies assessing tolterodine 2 mg/d was not optimal (–0.44), within the included studies this agent had the greatest weight with a low CI (Fig. 4).

### 3.5.2. *Mean change in micturition episodes per 24 h*

Imidafenacin 0.5 mg/d and solifenacin 10 and 5 mg/d were the most efficacious drugs in reducing micturition episodes compared with placebo. Despite being the most effective agent, imidafenacin studies showed low weights and wide CIs. Conversely, solifenacin 5 and 10 mg/d had a higher weight and a narrow CI. Tolterodine 4 and 2 mg/d alongside solifenacin 5 mg/d and mirabegron 50 mg/d, due to their major weight and narrow CI, could be considered more reliable choices considering their acceptable efficacy and statistical power (Fig. 4).

### 3.5.3. *Mean change in urgency episode per 24 h*

Compared with placebo, fesoterodine 4 or 8 mg/d and solifenacin 10 mg/d were the most efficacious drugs in reducing urgency episodes. However, tolterodine 4 mg/d, solifenacin 5 mg/d, and mirabegron 50 mg/d had higher weights and narrow CIs when compared with fesoterodine. Most of the studies assessed tolterodine and mirabegron 50 mg/d for this outcome (Fig. 4).

### 3.5.4. *Mean change in urgency urinary incontinence episode per 24 h*

All the antimuscarinics and β-adrenoceptor agonists reduced urgency urinary incontinence episodes effectively except for oxybutynin 3 mg TID. Imidafenacin 0.5 mg/d and solifenacin 10 mg/d had the highest efficacy. According to the NMA results, the drug assessed in the largest number of conducted studies (similar to the previously reported efficacy data) was tolterodine 4 mg/d (Fig. 4).

### 3.5.5. *Mean change in voided volume per micturition*

When compared with placebo, the majority of antimuscarinics and β-adrenoceptor agonists improved the amount of voided volume. Solifenacin 10 mg/d, vibegron 50 mg/d, and fesoterodine 8 mg/d were the most efficient agents. Conversely, tarafenacin 0.2 mg/d, oxybutynin 3 mg TID, and imidafenacin 0.2 mg/d did not improve the voided volume per micturition. Mirabegron 50 mg/d, solifenacin 5 mg/d, and tolterodine 4 and 2 mg/d were the agents with the greatest weight and most number of trials for this endpoint (Fig. 5).

### 3.5.6. *Adverse events*

We assessed the safety of 25 different drug formulations and dosages based on 49 RCTs. Gastrointestinal complications were the most common adverse events. All the antimuscarinics and β-3 agonists were accompanied by high rates of dry mouth except for vibegron 100 and 3 mg. The risk of dry mouth with vibegron 15 mg (OR: 1.05 [95% CI: 0.33–3.38]) and mirabegron 50 mg (OR: 1.09 [95% CI: 0.72, 1.65]) was similar to that in the placebo group. Among different medications, oxybutynin 5 mg had the highest rate of dry mouth. The majority of IOAB medical therapies

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**Table 1 – Summary of the extracted data of the included studies**

| Author | Drug and dosage | | Sample size | Disease (OAB or DO)? | Gender % | | Mean age | Duration of intervention (wk) | Granted by a drug company |
|---|---|---|---|---|---|---|---|---|---|
| | Drug | Dosage | | | Male | Female | | | |
| Abrams (1998) [33] | Tolterodine IR 2 mg | BID | 118 | OAB | 22.88 | 77.12 | 55 | 12 | Yes |
| | Oxybutynin 5 mg | TID | 118 | | 25.42 | 74.5 | 58 | | |
| | Placebo | | 57 | | 24.56 | 75.44 | 58 | | |
| Abrams (2006) [34] | Propiverine 20 | Daily | 42 | OAB | 23.4 | 76.6 | 51.5 | 2 | No |
| | Propiverine 15 | Daily | 38 | | | | | | |
| | Oxybutynin 5 | TID | 41 | | | | | | |
| | Placebo | | 24 | | | | | | |
| Abrams (2015) [35] | Solifenacin 2.5 mg | Daily | 79 | OAB | 35.4 | 64.6 | 56.1 | 12 | Yes |
| | Solifenacin 5 mg | Daily | 156 | | 34 | 66.0 | 54.2 | | |
| | Solifenacin 10 mg | Daily | 78 | | 32.1 | 67.9 | 55.0 | | |
| | Mirabegron 25 mg | Daily | 77 | | 32.5 | 67.5 | 55.2 | | |
| | Mirabegron 50 mg | Daily | 78 | | 33.3 | 66.7 | 53.4 | | |
| | Placebo | | 81 | | 33.3 | 66.7 | 54.6 | | |
| Amarenco (2017) [36] | Solifenacin 5 mg | Daily | 48 | DO | 56.3 | 43.8 | 44.6 | 4 | Yes |
| | Solifenacin 10 mg | Daily | 51 | | 51 | 49 | 45.7 | | |
| | Oxybutynin 5 mg | TID | 47 | | 40.4 | 59.6 | 43.9 | | |
| | Placebo | | 44 | | 53.5 | 46.5 | 40 | | |
| Bray (2018) [37] | Tolterodine ER 4 mg | Daily | 37 | OAB | 21 | 79 | 47 | 12 | Yes |
| | Placebo | | 42 | | | | | | |
| Cardozo (2004) [38] | Solifenacin 5 mg | Daily | 299 | OAB | 18.1 | 81.9 | 74.1 | 12 | No |
| | Solifenacin 10 mg | Daily | 307 | | | | 74.6 | | |
| | Placebo | | 301 | | | | 74.1 | | |
| Chancellor (2000) [39] | Tolterodine IR 2 mg | BID | 514 | OAB | 20 | 80 | 60 | 60 | Yes |
| | Placebo | | 508 | | | | 61 | | |
| Chapple (2004) [40] | Solifenacin 5 mg | Daily | 266 | OAB | 27.1 | 72.9 | 58.1 | 12 | Yes |
| | Solifenacin 10 mg | Daily | 264 | | 28.8 | 71.2 | 57.2 | | |
| | Tolterodine IR 2 mg | BID | 250 | | 20.0 | 80.0 | 56.9 | | |
| | Placebo | | 253 | | 23.7 | 76.3 | 57.8 | | |
| Chapple (2007) [41] | Fesoterodine 4 mg | Daily | 272 | OAB | 19 | 81 | 57.1 | 12 | Yes |
| | Fesoterodine 8 mg | Daily | 288 | | 19 | 82 | 55.6 | | |
| | Tolterodine ER 4 mg | Daily | 290 | | 22 | 78 | 57.7 | | |
| | Placebo | | 285 | | 19 | 81 | 56.0 | | |
| Chapple (2014) [42] | Tolterodine ER 4 mg | Daily | 83 | OAB | 21 | 79 | 58 | 12 | Yes |
| | Placebo | | 80 | | 23 | 77 | 57 | | |
| Chua (2018) [43] | Solifenacin 5 mg | Daily (dose increased based on symptoms) | 31 | OAB | 23 | 77 | 57.2 | 12 | Yes |
| | Placebo | | 32 | | 28 | 72 | 53.9 | | |
| Chu (2009) [44] | Solifenacin 10 mg | Daily | 340 | OAB | 16.6 | 83.4 | 59 | 12 | Yes |
| | Placebo | | 332 | | 20 | 80 | 58 | | |
| Dmochowski (2008) [45] | Trospium chloride 60 mg | Daily | 280 | OAB | 17.9 | 82.1 | 61.2 | 12 | No |
| | Placebo | | 284 | | 12.3 | 87.7 | 58.4 | | |
| Dmochowski (2010) [46] | Fesoterodine 4 mg at week 2, patients could increase the fesoterodine dose to 8 mg | Daily | 438 | OAB | 17 | 83 | 59.7 | 12 | Yes |
| | Placebo (sham escalation for placebo) | | 445 | | | | 60.1 | | |

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**Table 1 (*Continued*)**

| Author | Drug and dosage | | Sample size | Disease (OAB or DO)? | Gender % | | Mean age | Duration of intervention (wk) | Granted by a drug company |
|---|---|---|---|---|---|---|---|---|---|
| | Drug | Dosage | | | Male | Female | | | |
| Drutz (1999) [47] | Tolterodine IR 2 mg | BID | 109 | OAB | 19 | 81 | 63 | 12 | Yes |
| | Oxybutynin 5 mg | TID | 112 | | 28 | 72 | 66.3 | | |
| | Placebo | | 56 | | 20 | 80 | 62.1 | | |
| DuBeau (2014) [48] | Fesoterodine 4 mg for 4 wk/increase to 8 mg | Daily | 281 | (Urgency incontinence) | 20 | 80 | 74.8 | 12 | Yes |
| | Placebo | | 281 | | 16 | 84 | 75.3 | | |
| Frenkl (2010) [49] | Tolterodine 4 mg | Daily | 114 | OAB | 11.3 | 88.7 | 61.8 | 8 | Yes |
| | Placebo | | 109 | | 6.4 | 93.6 | 61.2 | | |
| Ginsberg (2013) [50] | Fesoterodine 4 mg for 1 wk, then 8 mg for 11 wk | Daily | 265 | OAB | 16 | 84 | 57.9 | 12 | Yes |
| | Tolterodine ER 4 mg | Daily | 275 | | 17 | 83 | 58.3 | | |
| | Placebo | | 133 | | 16 | 84 | 59.1 | | |
| Gotoh (2011) [51] | Propiverine hydrochloride 20 mg | Daily | 284 | OAB | 23.9 | 76.1 | 56.6 | 12 | Yes |
| | Placebo | | 270 | | 23.3 | 76.7 | 58.7 | | |
| Hajebrahimi (2014) [52] | Tolterodine IR 2 mg | BID | 30 | OAB | | 100 | 40.8 ± 8 | 4 | No |
| | Placebo | | 30 | | | | 38.5 ± 7 | | |
| Herschorn (2017) [53] | Mirabegron 25 mg | Daily | 423 | OAB | 22.7 | 77.3 | 56.9 | 12 | Yes |
| | Mirabegron 50 mg | Daily | 422 | | 23.5 | 76.5 | 56.7 | | |
| | Solifenacin 5 mg | Daily | 423 | | 21.7 | 78.3 | 58.2 | | |
| | Placebo | | 429 | | 23.8 | 76.2 | 57.9 | | |
| Herschorn (2008) [54] | Tolterodine ER 4 mg | Daily | 402 | OAB | 28 | 72 | 58 | 12 | Yes |
| | Placebo | | 201 | | 29 | 71 | 57 | | |
| Herschorn (2010) [55] | Tolterodine ER 4 mg | Daily | 684 | OAB | 18 | 82 | 58.5 | 12 | Yes |
| | Fesoterodine 8 mg | Daily | 679 | | 18 | 82 | 58.4 | | |
| | Placebo | | 334 | | 18 | 82 | 57.8 | | |
| Homma (2003) [56] | Tolterodine ER 4 mg | Daily | 239 | OAB | 32 | 68 | 61.2 | 12 | Yes |
| | Oxybutynin 3 mg | TID | 244 | | 27 | 73 | 57.9 | | |
| | Placebo | | 122 | | 31 | 69 | 58.4 | | |
| Homma (2008) [57] | Imidafenacin 0.1 mg | BID | 91 | OAB | 25.3 | 74.7 | 62.5 | 12 | Yes |
| | Imidafenacin 0.2 mg | BID | 93 | | 32.3 | 67.7 | 64.5 | | |
| | Imidafenacin 0.5 mg | BID | 76 | | 34.2 | 65.8 | 63.6 | | |
| | Placebo | | 95 | | 27.4 | 72.6 | 61.9 | | |
| Homma (2009) [58] | Imidafenacin 0.1 mg | BID | 318 | OAB | 12.6 | 87.4 | 57.7 | 12 | Yes |
| | Propiverine hydrochloride 20 mg | Daily | 305 | | 15.7 | 84.3 | 59.8 | | |
| | Placebo | | 143 | | 12.6 | 87.4 | 58 | | |
| Jacquetin (2001) [59] | Tolterodine IR 1 mg | BID | 97 | OAB and DO | 31 | 69 | 53 | 4 | Yes |
| | Tolterodine IR 2 mg | BID | 103 | | 22.6 | 77.4 | 58 | | |
| | Placebo | | 51 | | 24.4 | 75.6 | 56 | | |
| Junemann(2006) [60] | Propiverine hydrochloride IR 15 mg | BID | 391 | OAB | 10.6 | 89.4 | Male (61), female (55.8) | (32 d) | Yes |
| | Propiverine hydrochloride ER 30 mg | Daily | 384 | | 11 | 89 | Male (53.6), female (55.5) | | |
| | Placebo | | 199 | | 9.4 | 90.6 | Male (55.8), female (57.3) | | |
| Kaplan (2011) [61] | Fesoterodine 4 mg (increasing dose) | Daily | 960 | OAB | 15 | 85 | 57.9 | 12 | Yes |
| | Tolterodine ER 4 mg | Daily | 973 | | 16 | 84 | 58.1 | | |
| | Placebo | | 478 | | 14 | 86 | 59.5 | | |
| Karram (2009) [62] | Solifenacin 5 or 10 mg | Daily | 357 | OAB | 15.8 | 84.2 | 57 | 12 | Yes |
| | Placebo | | 350 | | | | | | |
| Khullar (2013) [63] | Mirabegron 50 mg | Daily | 493 | OAB | 27.6 | 72.4 | 59.1 | 12 | Yes |

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**Table 1 (*Continued*)**

| Author | Drug and dosage | | Sample size | Disease (OAB or DO)? | Gender % | | Mean age | Duration of intervention (wk) | Granted by a drug company |
|---|---|---|---|---|---|---|---|---|---|
| | Drug | Dosage | | | Male | Female | | | |
| | Mirabegron 100 mg | Daily | 496 | | 28.4 | 71.6 | 59 | | |
| | Tolterodine ER 4 mg | Daily | 495 | | 27.1 | 72.9 | 59.1 | | |
| | Placebo | | 494 | | 27.9 | 72.1 | 59.2 | | |
| Kuo (2015) [64] | Mirabegron 50 mg | Daily | 313 | OAB | 32.5 | 67.5 | 54.3 | 12 | Yes |
| | Tolterodine ER 4 mg | Daily | 311 | | 36 | 64 | 53.9 | | |
| | Placebo | | 302 | | 30.3 | 69.7 | 55.3 | | |
| Lee (2009) [65] | Propiverine hydrochloride 20 mg | Daily | 142 | OAB | 26.6 | 73.4 | 53.3 | 12 | Yes |
| | Placebo | | 79 | | 25.4 | 74.6 | 51.4 | | |
| Malone-Lee (2009) [66] | Tolterodine ER 4 mg | Daily | 155 | OAB | 20 | 80 | 56.4 | 12 | Yes |
| | Placebo | | 130 | | | | | | |
| Marencak (2011) [67] | Tolterodine ER 4 mg | Daily | 104 | OAB | | 100 | 52.9 ± 13.3 | 4 | Yes |
| | Placebo | | 103 | | | 100 | 52.9 ± 13.3 | | |
| Millard (1999) [68] | Tolterodine IR 1 mg | BID | 129 | DO | 22 | 78 | 60.1 | 12 | Yes |
| | Tolterodine IR 2 mg | BID | 123 | | 23 | 77 | 60.2 | | |
| | Placebo | | 64 | | 34 | 66 | 60.5 | | |
| Mitcheson (2019) [69] | Vibegron 3 mg | Daily | 144 | OAB | 9 | 91 | 59.4 | 8 | No |
| | Vibegron 15 mg | Daily | 134 | | 6.7 | 93.3 | 58.6 | | |
| | Vibegron 50 mg | Daily | 150 | | 14 | 86 | 60.3 | | |
| | Vibegron 100 mg | Daily | 261 | | 9.6 | 90.4 | 59 | | |
| | Tolterodine ER 4 mg | Daily | 257 | | 10.1 | 89.9 | 58.5 | | |
| | Placebo | | 205 | | 9.8 | 90.2 | 57.8 | | |
| Nitti (2006) [70] | Tolterodine ER 4 mg | Daily | 270 | OAB | 57.8 | 42.2 | 57 | 12 | Yes |
| | Placebo | | 243 | | | | 58 | | |
| Nitti (2013) [71] | Mirabegron 50 mg | Daily | 442 | OAB | 27.10 | 72.9 | 59.2 | 8 | Yes |
| | Mirabegron 100 mg | Daily | 433 | | 26.10 | 73.9 | 61 | | |
| | Placebo | | 453 | | 23.80 | 76.2 | 60.1 | | |
| Orri (2014) [72] | Tolterodine ER 4 mg | Daily | 6 | OAB | 0 | 100 | 48.4 | 12 | Yes |
| | Placebo | | 12 | | | | 46.2 | | |
| Rogers (2008) [73] | Tolterodine ER 4 mg | Daily | 202 | OAB | 0 | 100 | 47 | 12 | Yes |
| | Placebo | | 211 | | | | 49 | | |
| Shin (2019) [74] | Mirabegron 50 mg | Daily | 310 | OAB | 100 | 0 | 66.4 | 26 | Yes |
| | Placebo | | 154 | | | | | | |
| Song (2015) [75] | Tarafenacin 0.2 mg | Daily | 77 | OAB | 33.8 | 66.2 | 59 | 12 | Yes |
| | Tarafenacin 0.4 mg | Daily | 76 | | | | 60.18 | | |
| | Placebo | | 72 | | | | 58.35 | | |
| Staskin (2007) [76] | Trospium chloride 60 mg | Daily | 292 | OAB | 15.10 | 84.9 | 59.6 | 12 | Yes |
| | Placebo | | 300 | | | | 59.3 | | |
| Swift (2003) [77] | Tolterodine IR 2 mg | BID | 417 | OAB | 0.00 | 100 | 59 | 12 | Yes |
| | Tolterodine ER 4 mg | Daily | 408 | | | | 59 | | |
| | Placebo | | 410 | | | | 60 | | |
| Van Kerrebroeck (2001) [78] | Tolterodine ER 4 mg | Daily | 507 | OAB | 17.75 | 82.25 | 60 | 12 | Yes |
| | Tolterodine IR 2 mg | BID | 514 | | 20.62 | 79.38 | 60 | | |
| | Placebo | | 508 | | 19.29 | 80.71 | 61 | | |
| Wagg (2013) [79] | Fesoterodine 4 or 8 mg | Daily | 392 | OAB | 46 | 54 | 72.6 | 12 | Yes |
| | Placebo | | 393 | | 48 | 52 | 72.8 | | |
| Yamaguchi (2007) [80] | Solifenacin 5 mg | Daily | 383 | OAB | 17 | 83 | 60.4 | 12 | Yes |
| | Solifenacin 10 mg | Daily | 371 | | 14.3 | 85.7 | 59.9 | | |
| | Propiverine hydrochloride 20 mg | Daily | 384 | | 16.4 | 83.6 | 59.6 | | |

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**Table 1 (*Continued*)**

| Author | Drug and dosage | | Sample size | Disease (OAB or DO)? | Gender % | | Mean age | Duration of intervention (wk) | Granted by a drug company |
|---|---|---|---|---|---|---|---|---|---|
| | Drug | Dosage | | | Male | Female | | | |
| | Placebo | | 395 | | 15.7 | 84.3 | 60.8 | | |
| Yamaguchi (2011) [81] | Fesoterodine 4 mg | Daily | 320 | OAB | 21.6 | 78.4 | 57.2 | 12 | Yes |
| | Fesoterodine 8 mg | Daily | 313 | | 18.5 | 81.5 | 58.5 | | |
| | Placebo | | 318 | | 21.1 | 78.9 | 56.7 | | |
| Yamaguchi (2014) [82] | Mirabegron 50 mg | Daily | 369 | OAB | 15.7 | 84.3 | 58.3 | 16 | Yes |
| | Tolterodine ER 4 mg | Daily | 368 | | 17.4 | 82.6 | 58.3 | | |
| | Placebo | | 368 | | 15.8 | 84.2 | 58.2 | | |
| Yamaguchi (2014) [82] | Oxybutynin patch 35 cm2 | | | OAB | | | | 12 | Yes |
| | Propiverine hydrochloride 20 mg | Daily | 381 | | 10.6 | 89.4 | 56.2 | | |
| | Placebo | | 579 | | 10.6 | 89.4 | 55.6 | | |
| Yamaguchi (2015) [83] | Mirabegron 25 mg | Daily | 211 | OAB | 19.6 | 80.4 | 54.9 | 12 | Yes |
| | Mirabegron 50 mg | Daily | 208 | | 14.9 | 85.1 | 56.2 | | |
| | Mirabegron 100 mg | Daily | 209 | | 16.9 | 83.1 | 56.9 | | |
| | Placebo | | 214 | | 19.9 | 80.1 | 55.7 | | |
| Yoshida (2018) [84] | Vibegron 50 mg | Daily | 370 | OAB | 9.7 | 90.3 | 58 | 12 | Yes |
| | Vibegron 100 mg | Daily | 368 | | 10.3 | 89.7 | 58.7 | | |
| | Imidafenacin 0.1 mg | BID | 117 | | 10.3 | 89.7 | 59.7 | | |
| | Placebo | | 369 | | 9.8 | 90.3 | 58.9 | | |
| Zinner (2004) [85] | Trospium chloride 20 mg | Daily | 262 | OAB | 26 | 74 | 63 | 12 | No |
| | Placebo | | 261 | | | | 61.5 | | |
| Zinner (2005) [86] | Oxybutynin 5 mg | TID | 61 | OAB | 10.6 | 89.4 | 59.5 | 2 | Yes |
| | Darifenacin 15 mg | Daily | | | | | | | |
| | Darifenacin 30 mg | Daily | | | | | | | |
| | Placebo | | | | | | | | |

BID = twice daily; DO = detrusor overactivity; ER = extended release; IR = immediate release; OAB = overactive bladder; TID = three times daily.
Only study arms with oral antimuscarinics or β-adrenoceptor agonists have been indicated.

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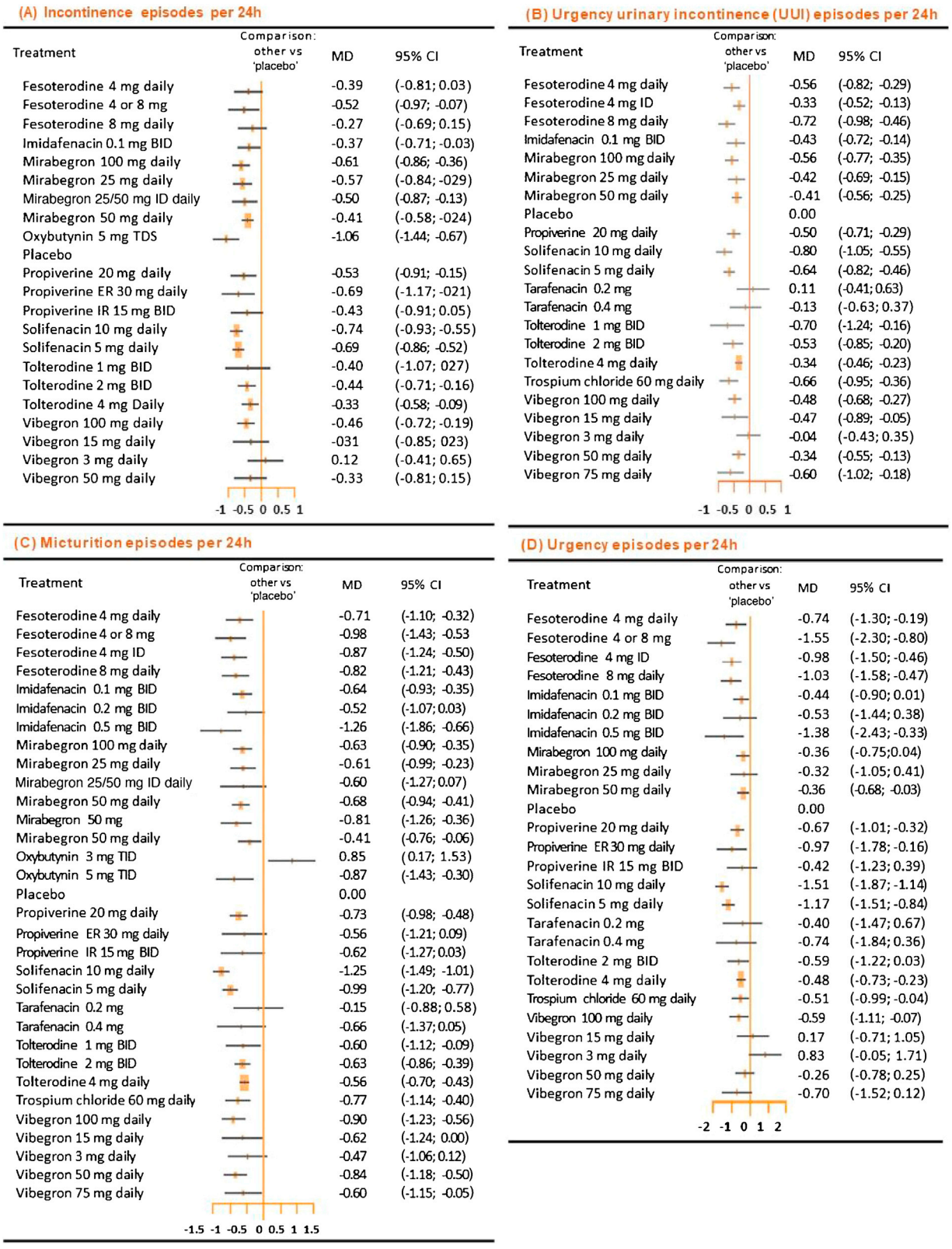


**Fig. 4 – Forest plots demonstrate the efficacy of oral medications for the treatment of OAB compared with placebo. (A) Incontinence episodes per 24 h; 19 RCTs comprising 16 084 patients studied this outcome. (B) Urgency urinary incontinence episodes per 24 h; 23 RCTs comprising 18 555 patients studied this outcome. (C) Micturition episodes per 24 h; 43 RCTs comprising 33 815 patients studied this outcome. (D) Urgency episodes per 24 h; 30 RCTs comprising 25 875 patients studied this outcome. BID = twice daily; CI = confidence interval; ER = extended release; ID = increasing dose; IR = immediate release; MD = mean difference; OAB = overactive bladder; RCT = randomized controlled trial; TID = three times daily.**

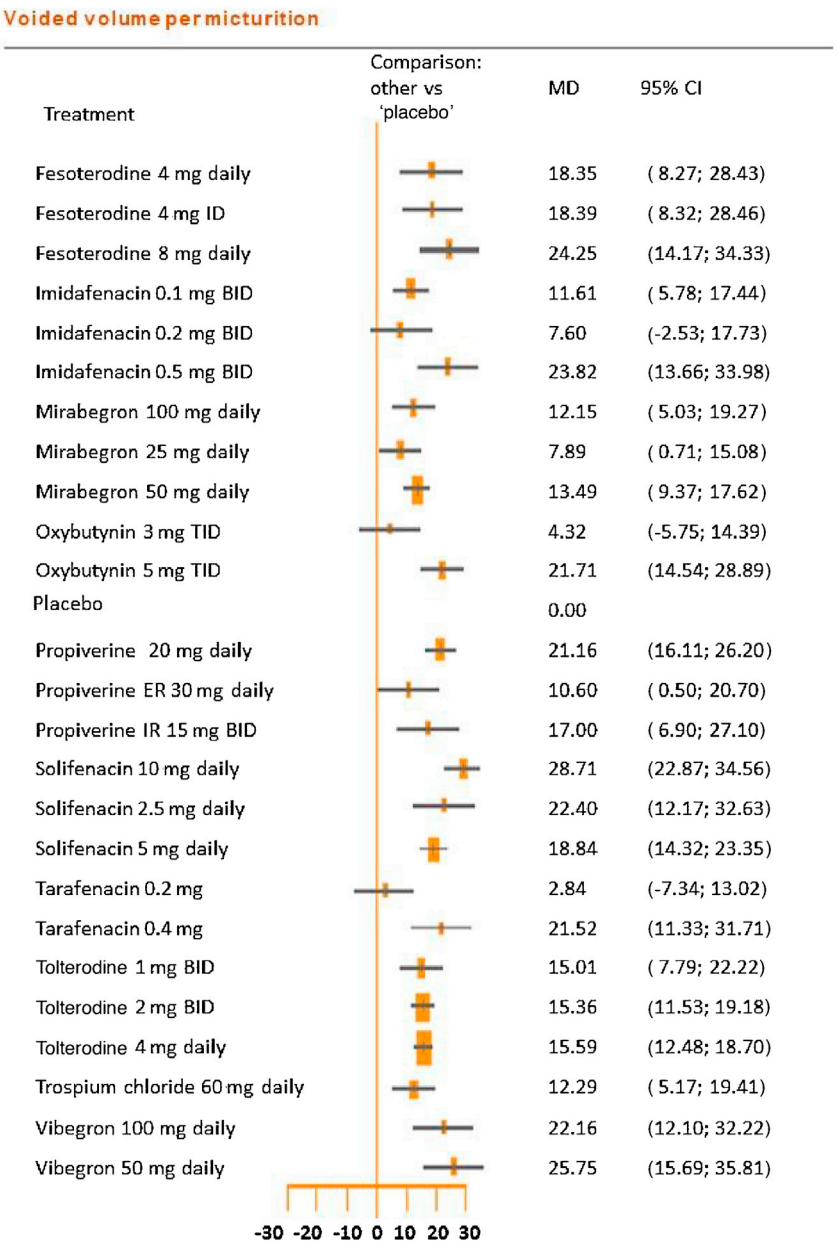


**Fig. 5 – Forest plot demonstrates the efficacy of oral medications for the improvement of voided volume per micturition compared with placebo; 30 RCTs comprising 23 974 patients studied this outcome. BID = twice daily; CI = confidence interval; ER = extended release; ID = increasing dose; IR = immediate release; MD = mean difference; RCT = randomized controlled trial; TID = three times daily.**

led to constipation. However, this risk was significantly lower for vibegron 100 mg and imidafenacin 0.1 mg, and highest for propantheline 15 mg and darifenacin 30 mg.

Mirabegron 25 mg had the highest risk of diarrhea. Vibegron 15 mg and solifenacin 10 mg had the lowest rates of diarrhea when compared with placebo. All IOAB therapies led to blurred vision. However, when compared with placebo, tolterodine 4 mg had the highest rate.

Most drugs were not accompanied by nausea and vomiting, and had a similar rate to that of placebo. The effects of darifenacin 15 mg, fesoterodine 4 mg, and vibegron 100 mg were similar to that of placebo. Compared with placebo, mirabegron 50 mg had the lowest rate (OR: 0.17 [95% CI: 0.02, 1.40]).

Most agents increased the rate of urinary retention compared with placebo; trospium 60 mg/d had the worst effect. Surprisingly, placebo led to more dizziness and vertigo than most antimuscarinics and β-adrenoceptor agonists.

Mirabegron 25 and 50 mg had the lowest fatigue events, when compared with those with placebo. Considering UTI, trospium 60 mg (OR: 2.25 [95% CI: 0.79, 6.38]) was accompanied by a high UTI rate, and conversely, mirabegron 50 and 25 mg alongside an adjustable dose of fesoterodine

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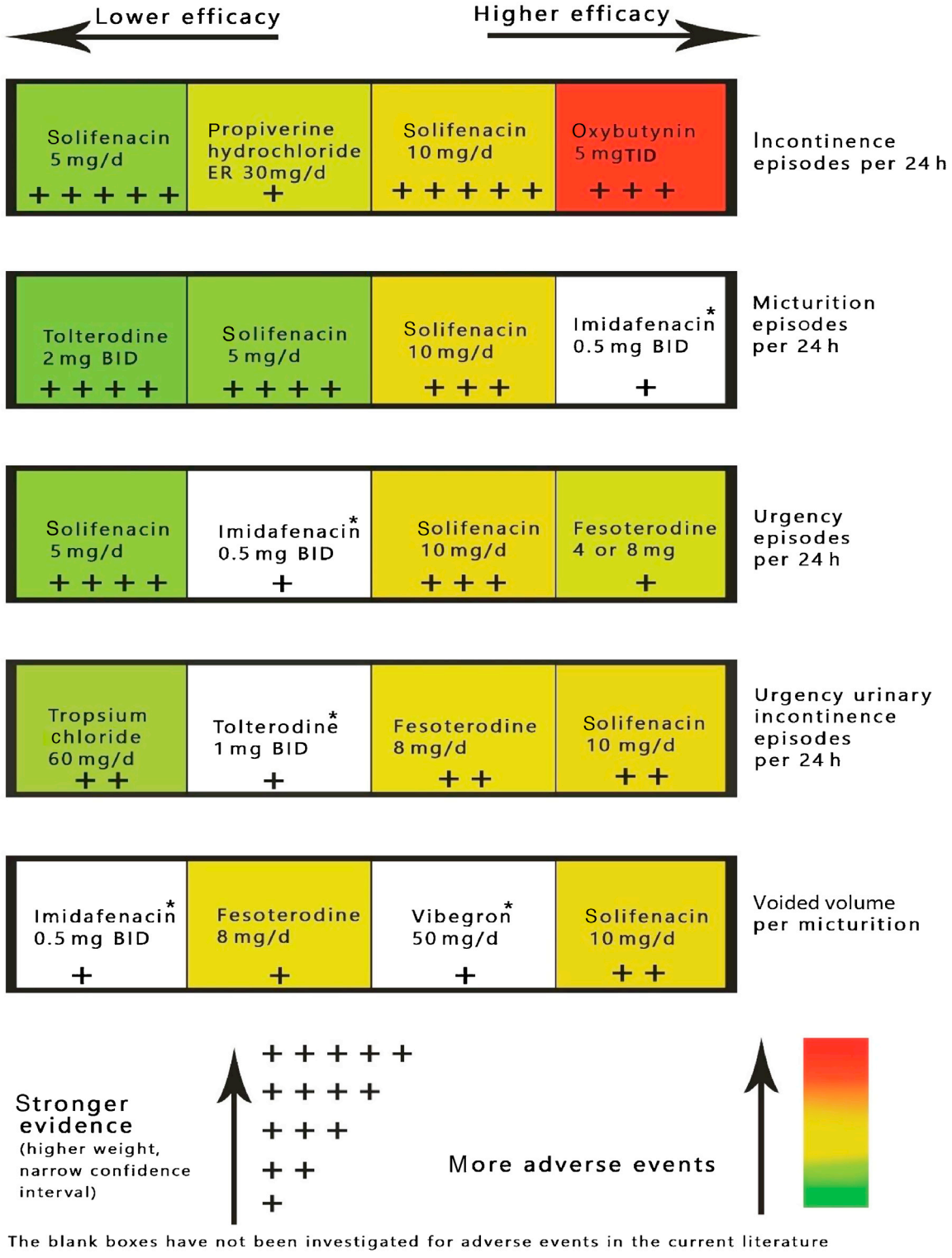


**Fig. 6 – Heat chart illustrating the most efficient drugs in the treatment of different OAB symptoms considering drug-related adverse events and statistical power. BID = twice daily; ER = extended release; OAB = overactive bladder; TID = three times daily.**

(4 and 8 mg/d) had the lowest rates of UTI among the IOAB therapies when compared with that in placebo. The results of the other adverse events are illustrated in the Supplementary material.

### *3.6. Discussion*

In the current study, we compared, directly and indirectly, various oral antimuscarinics and β-adrenoceptors, with

different formulations and dosages, with regard to their efficacy and adverse events across different symptoms and signs in 29 551 patients affected by IOAB. Our aim was to provide a comprehensive overview of the efficacy and safety of currently available medications to serve as a framework for clinicians and their patients.

Although statistically significant differences were observed when comparing the efficacy of drugs with placebo, the differences in efficacies between the included drug types and dosages were minimal. Among different types, dosages, and formulations of the included medications, oxybutynin 15 mg/d was the most efficacious antimuscarinic in reducing incontinence episodes compared with placebo. However, it was also a drug with remarkable adverse events [17]. Solifenacin 10 mg/d and extended-release propiverine hydrochloride 30 mg/d were the second and third most efficacious agents, both having only mild to moderate adverse events. In the study by Buser et al [18], the uncommon dose of 7.5 mg/d oxybutynin IR was defined as the most efficient dosage in reducing incontinence episodes despite being evaluated in a limited number of trials.

Imidafenacin alongside solifenacin 10 and 5 mg/d was the most efficacious drug in reducing micturition episodes when compared with placebo. Considering the statistical weights of these agents, imidafenacin 0.5 mg BID showed low weight and a wide CI. Among the top effective drugs, solifenacin 5 mg/d was the most frequently studied agent in reducing micturition episodes per 24 h.

Solifenacin 10 mg/d was one of the most efficacious medications in reducing urgency and urgency urinary incontinence episodes per 24 h, while increasing the amount of voided volume per micturition when compared with placebo. Moreover, solifenacin is an agent with moderate adverse events; it can, thus, deliver a good balance considering both efficacy and safety, and should, based on our findings, be considered for patients with mainly urgency symptoms and urge incontinence. In terms of reducing urgency episodes, Buser et al [18] recommended fesoterodine 12 mg/d, which was also an uncommon and less studied drug.

Tolterodine 4 and 2 mg/d had a medium effect on improving all the measured outcomes despite being the most frequently studied agent in IOAB trials with the highest weight and narrowest CI.

We have schematically presented the efficacy of oral medications for IOAB and the weight of the variables (drugs) considering our results on drug safety and efficacy (Fig. 6). We divided their reported adverse events into five groups, from severe (red) to mild (green) and not reported (white). The statistical power (evidence strength) of the drugs is presented as a scale from "+" for those with lower weight and wider CIs to "+++++" for those with higher weight and narrower CIs. This graph can be used as a guide for clinicians to choose the relevant medication based on efficacy, adverse events, and strength of the evidence; patient preference in shared decision-making can, thereby, be facilitated. According to our results, gastrointestinal problems, especially following antimuscarinics, were the most prevalent adverse events, with dry mouth being the first followed by constipation. These results were in accordance with the study by Kessler et al [19] and the previous systematic reviews [20–22]. In a previous NMA on the efficacy and safety of antimuscarinics on IOAB, Buser et al [18] evaluated the global adverse events in comparison with placebo by measuring the cumulative sum of seven major adverse events. In other words, they focused on domains rather than individual adverse events (ie, "gastrointestinal" instead of "constipation" and "diarrhea", etc.). By adding the observed adverse events in different domains, they reported adverse event profiles for individual drugs. Gastrointestinal adverse events were the most commonly observed adverse events in their study. However, they did not include β-adrenoceptor agonists. In our study, constipation was more common in patients taking antimuscarinics than in those taking other agents. The range varied, however, significantly. This is because the affinity of antimuscarinics to special subtypes of receptors varies. For example, darifenacin has the highest selectivity for the M3 receptor, higher than that for the M1 or M2 subtypes, whereas solifenacin and oxybutynin have moderate selectivity [23–25]. Interestingly, placebo led to more constipation than β-adrenoceptor agonists.

In the current NMA, dizziness was the only significant cognitive and functional-related adverse event that we were able to assess. Vibegron 3 mg/d had the smallest rate of central nervous system (CNS) adverse effect, whereas oxybutynin 5 mg led to the highest rates of dizziness and vertigo. The rate of dizziness was low for the majority of other antimuscarinics. This is in agreement with the study of Vouri et al [20], who assessed older patients.

The previous studies showed that oral oxybutynin, either immediate- or extended-release forms, is associated with the worst adverse event profile resulting in high withdrawal rates [19,22], especially due to cognitive function decline [26–28], psychotic behavior, and hallucinations [29]. On the contrary, previous clinical trials have reported fewer CNS adverse events for darifenacin and trospium chloride; data on the CNS adverse events for solifenacin are limited [30]. Other CNS-specific adverse events were scarce, minimizing our ability to evaluate them in our NMA.

In the current study, treatment with oxybutynin 5 mg TID resulted in a ten-fold higher rate of headache compared with placebo. The other agent with a higher rate of headache was darifenacin 5 mg. In agreement with this finding, Vouri et al [20] reported that darifenacin was the drug with the highest rate of headache as an adverse event.

### 3.7. *Implication for research*

One of the strengths of our analysis was putting steps beyond conventional reviews; we performed an NMA to enable an indirect comparison, thereby allowing physicians to make informed decision with their patients based on the best available evidence. Personalized medicine in the oral pharmacological management of IOAB means to tailor the drug to the symptom/sign complex of each individual patient while considering adverse event probability. Therefore, we tried to identify the best agent for each symptom/

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sign. In contrast to previous studies, we also assessed β-adrenoceptor agonists alongside antimuscarinics. As most patients with IOAB already suffer from other age-related ailments, our adverse-event–specific NMA may aid in selecting the agent less likely to impact the health negatively due to undesired side effects. Interestingly, the rate and amplitude of the placebo and nocebo effects are quite significant in IOAB [31,32]. Evidence shows that a high degree of improvement in the IOAB symptoms is due to the placebo effect and factors such as the nature of the disease and regression to the mean [31]. We found only minimal differences between the efficacies of most of the agents when it comes to improving bothersome QOL endpoints, even when analyzed separately. Indeed, IOAB is a debilitating condition with a major impact on patient's QOL; hence, physicians have to consider patient values and preferences when choosing an appropriate treatment. Our readily available, easy-to-use decision framework serves to facilitate an individualized treatment approach in order to improve the outcomes based on patient preferences while minimizing adverse events.

### 3.8. Limitations

It is very likely that the results were influenced by a bias. The major limitation of this study lies in the reporting of quality of outcomes in some of the included studies. In the absence of precision estimates (standard deviations and CIs), we contacted the corresponding authors of specific articles for more information; however, we did not receive any response in most of the cases. Another problem we faced was reporting the "median difference" in some of the studies; thus, we used statistical formulas to estimate the mean change in these settings. For graphically presented data, we measured values using the Universal Desktop Ruler, version 2.9.

In this NMA, adverse events occurred at a higher rate in the medical therapy arms (especially antimuscarinics) than in the placebo arm. However, it should be considered that the duration of most of the studies is only up to 12 wk. Moreover, as most patients who are willing to participate in a clinical trial are not representative of general patients, the effects and adverse effects may not be generalizable.

Another limitation was the lack of a unified approach for recording the adverse events and a complete lack of reporting in some cases. For some of the agents, especially for the recent ones, only a limited number of trials were available. This led to smaller power for some of the endpoints, potentially hampering statistical significance.

## 4. Conclusions

Taken together, there are only minimal differences between the efficacy of oral antimuscarinics and that of β-adrenoceptor agonists across different bothersome OAB symptomology. Although finding the best medication for all is impossible, finding the best treatment for every patient can be done by considering their most bothersome symptoms/signs, their general health and predisposition to specific adverse events, and their values and preferences. Yet, we need more high-quality head-to-head studies with unified, systematic data collection methods to make a valid and reliable judgment on the real level of efficacy and adverse events. Finally, our report may facilitate clinicians in the design of a personalized decision-making strategy based on efficacy and adverse events together with their patients receiving the pharmacological oral treatment of IOAB.

***Author contributions*:** Shahrokh F. Shariat 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*: Mostafaei, Hajebrahimi, Shariat.
*Acquisition of data*: Jilch, Carlin, Mori.
*Analysis and interpretation of data*: Mostafaei, Schuettfort, Rajwa.
*Drafting of the manuscript*: Salehi-Pourmehr, Katayama, Pradere, Aydh, Quhal, Grossmann, Aydh, König, Roehrborn.
*Critical revision of the manuscript for important intellectual content*: Salehi-Pourmehr, Hajebrahimi, Grossmann.
*Statistical analysis*: Mostafaei, Laukhtina, Motlagh.
*Obtaining funding*: None.
*Administrative, technical, or material support*: Hajebrahimi, Shariat, Quhal.
*Supervision*: Shariat, Hajebrahimi.
*Other*: None.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.euf.2021.08.011.

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