EUROPEAN UROLOGY FOCUS XXX (2019) XXX–XXX

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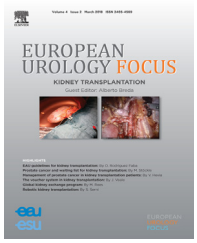

Review

Nocebo Response in the Pharmacological Management of Overactive Bladder: A Systematic Review and Meta-analysis

Hadi Mostafaei [a,*], *Keiichiro Mori* [a,b], *Fahad Quhal* [a,c], *Noriyoshi Miura* [a,d], *Reza Sari Motlagh* [a], *Benjamin Pradere* [a,e], *Ekaterina Laukhtina* [a,f], *Ivan Lysenko* [a], *Sajjad Ghaffari* [g], *Sakineh Hajebrahimi* [g], *Shahrokh F. Shariat* [a,f,h]

[a] *Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria;* [b] *Department of Urology, The Jikei University School of Medicine, Tokyo, Japan;* [c] *Department of Urology, King Fahad Specialist Hospital, Dammam, Saudi Arabia;* [d] *Department of Urology, Ehime University Graduate School of Medicine, Ehime, Japan;* [e] *Department of Urology, CHRU Tours, Francois Rabelais University, Tours, France;* [f] *Institute for Urology and Reproductive Health, I.M. Sechenov First Moscow State Medical University, Moscow, Russia;* [g] *Research Center for Evidence Based Medicine, Tabriz University of Medical Sciences, Tabriz, Iran;* [h] *Department of Urology, Weill Cornell Medicine, New York, NY, USA*

Article info

Associate Editor: Malte Rieken

Keywords:
Nocebo
Pharmacological
Overactive bladder

Abstract

Context: The role of a nocebo response in managing urology patients is unclear.
Objective: To assess the nocebo response in randomized placebo-controlled overactive bladder (OAB) trials of pharmacological treatment by investigating the adverse events in the placebo arms.
Evidence acquisition: PubMed, Scopus, Embase, and Cochrane Central Register of Controlled Trials were searched to identify potential randomized controlled trials published from 1998 to November 2019. After evaluating the risk of bias in the selected studies, all selected full-text articles were included due to their overall acceptable quality. We extracted the event rate of the most commonly reported adverse events in the placebo arms of OAB trials, and finally, we performed a meta-analysis to calculate the cumulative rate of certain adverse events. The primary outcomes were the event rate of adverse events in the placebo arms of OAB trials of pharmacological treatment, and differences in adverse events in the placebo groups based on drug type and routes of administration.
Evidence synthesis: After a systematic search and risk of bias assessment, 57 trials comprising 15 446 patients were included in this systematic review. We selected 13 commonly reported adverse events for the meta-analysis. Owing to the possible differences in study samples and design, we used a random model for the analysis. The average age of the patients was 59.5 yr and 79.8% were female. Dry mouth was the most commonly evaluated adverse event reported in 57 studies comprising 15 324 patients; the mean event rate was 4.9% (95% confidence interval [CI] 0.042–0.057, $p < 0.001$). Constipation was the second most commonly reported adverse event in 49 studies comprising 14 556 patients; the mean event rate of constipation was 2.6% (95% CI 0.022–0.031, $p < 0.001$). The event rate of headache was evaluated in 33 studies comprising 10 202 patients, with a mean event rate of 3.1% (95% CI 0.026–0.037, $p < 0.001$).
Conclusions: Dry mouth, constipation, headache, and nasopharyngitis were the most prevalent events in the included studies. The nocebo response plays a statistically significant role in causing and/or facilitating adverse events. Health care providers should have a better understanding of the positive and negative expectations associated with therapies to achieve the best possible outcomes for each individual patient. Finally,

* Corresponding author. Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Lazarettgasse, 14, Wien, Östrreich 1090, Austria. Tel. +43 6602379363.
E-mail addresses: hadimosta@gmail.com, hadi.mostafaei@meduniwien.ac.at (H. Mostafaei).

https://doi.org/10.1016/j.euf.2020.10.010

Please cite this article in press as: Mostafaei H, et al. Nocebo Response in the Pharmacological Management of Overactive Bladder: A Systematic Review and Meta-analysis. Eur Urol Focus (2020), https://doi.org/10.1016/j.euf.2020.10.010

identification of the real effect of nocebo requires studies that also include a no-treatment arm. Research could help us better understand and potentially modify the nocebo response.

Patient summary: In this meta-analysis of 57 studies comprising 15 446 patients, we reviewed the adverse events extracted from the placebo arms of randomized controlled trials studying therapies for overactive bladder. Dry mouth, constipation, headache, and urinary tract infection were the most common adverse events. Adverse events varied based on the drug type and the route of administration. Negative expectations from the therapy and giving verbal information to the patient can cause/alleviate adverse events.

1. Introduction

While the placebo effect is widely recognized, little is known about its opposite, the "nocebo" effect [1]. The term "nocebo" (ie, I shall harm), which is the reverse of the term "placebo" (ie, I shall please), was first used by Walter Kennedy [2] in 1961, and it was described to distinguish between the positive and noxious effects of placebo [3]. Having said that, placebo or a "placebo response" includes all the processes that have an impact on the change of symptoms (ie, regression to the mean, natural history). The nocebo or placebo "effect", however, refers to the health changes purely related to the placebo or nocebo [4]. A nocebo response involves giving an inert drug and verbally communicating that this drug could result in, usually specific, adverse events. A nocebo-related response is also reported in noninert drugs, where the negative expectations of their efficacy result in less improvement and even, possibly, more adverse events [3,5,6]. Unwanted adverse events may occur as a consequence of the informed consent procedure and/or prior side-effect expectation. The nocebo response can, thus, impair the treatment procedure in various ways [7].

Several studies have evaluated the role of the placebo response in urology [8–10]. On the contrary, the effect of the nocebo response is not clearly analyzed, partly due to the ethical barriers of conducting such studies [11].

Overactive bladder (OAB) is a highly prevalent and debilitating condition with variable severity and perception of its associated signs and symptoms. Drug therapy is the most commonly used treatment modality with variable adherence due to variable perceived efficacy and adverse events [12,13]. We hypothesize a statistically significant role of nocebo in adverse events in the pharmacological treatment of OAB. The aim of this study was to assess the type, rate, and severity of a nocebo response by assessing the adverse events in the placebo arms of randomized placebo-controlled clinical trials of OAB drug therapy.

2. Evidence acquisition

2.1. Protocol

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and Cochrane guidelines for the study methodology [14,15]. The study protocol was published on the International Prospective Register of Systematic Reviews (registration number 163419).

2.2. Data sources and searches

A comprehensive electronic search was conducted in all languages for randomized controlled trials (RCTs) assessing pharmacological interventions for OAB. We searched Medline (PubMed), Embase, Scopus, and Cochrane Central Register of Controlled Trials to identify potential RCTs published from 1998 to November 2019. In addition, we searched the reference lists of similar systematic reviews in case of missing articles and clinicaltrials.gov for unpublished data. A recursive search was also performed in the bibliographies of included studies, together with a hand search of the reference lists of relevant studies. If the non-English evidence had an accessible English abstract, it was included. We used "random controlled trial" and "placebo" in combination with anticholinergics, antimuscarinics, β-3 receptor agonists, adverse events, overactive bladder, and detrusor overactivity as the keywords for our search strategy. The detailed search strategy is provided in the Supplementary material.

2.3. Eligibility criteria

We included RCTs of adults (age $\geq$18 yr) with OAB and/or detrusor overactivity. We considered an RCT eligible only when it compared a pharmacological agent with a placebo arm and assessed the adverse events in both groups. Crossover trials were excluded due to difficulty in assessing the true placebo effect. RCTs assessing the combination therapy were included only if they reported the adverse events in the placebo group.

2.4. Study selection

By using a standardized form, two reviewers screened the titles and abstracts. Disagreements were resolved by the Delphi method. The selected abstracts were then included for full-text screening.

2.5. Data extraction

We extracted the demographic characteristics of the articles, including the name of the author, publishing year,

sample size of each group, mean age, gender (%), duration of the trial, and conflict of interest. For the safety assessment, we extracted the event rate as the number of cases experiencing a certain adverse event (if reported as percentage, the true number was calculated) in the placebo arm of all trials. We extracted common adverse events, including dry mouth, constipation, diarrhea, thirst, nausea, vomiting, dyspepsia, abdominal pain, flatulence, nasal dryness, dry eye, blurred vision, keratoconjunctivitis sicca, urinary retention, voiding difficulty, dysuria, polyuria, urinary tract infection (UTI), pyuria, fatigue, somnolence, sedation, insomnia, lack of concentration, memory problem, depression, lethargy, dizziness, vertigo, headache, palpitation, tachycardia, long QT, hypertension, orthostatic disturbance, flushing, bronchitis, cough, nasopharyngitis, sinusitis, influenza, dry skin, rash, dermatitis, erythema, pruritus, irritation, cold sensation, back pain, arthralgia, peripheral edema, increase of eosinophil, increase of monocyte, increase of lymphocyte, decrease of aspartate aminotransferase and alanine aminotransferase, increase of creatine phosphokinase, increase of gamma-glutamine transferase, and increase of alkaline phosphatase.

2.6. Risk of bias assessment

Two reviewers selected the evidence independently. The Cochrane Collaboration tool for assessing the risk of bias was used to critically appraise the articles [14]. In case of disagreement, a third reviewer re-evaluated the documents to solve the discrepancies. In cases of incomplete outcome reporting, we contacted the authors to receive complementary data; if they did not respond, the articles were excluded.

2.7. Data synthesis and analysis

We performed a systematic review and meta-analysis of different outcomes. However, a meta-analysis was not possible in some cases since there were only limited reports of some adverse events. Owing to differences in study design, a random effect model was used for the meta-analysis. We performed a subgroup analysis to study the possible difference in the nocebo response due to different drug groups and roots of administration (ie, a placebo that is identical to a drug or gel in a drug group), with the subgroups being β-3 agonists, both drug groups (antimuscarinics and β-3 agonists), gel antimuscarinics, oral antimuscarinics, and patch antimuscarinics. This analysis was carried out to evaluate whether providing the patient with verbal information, during acquiring informed consent, regarding the type of drug received affects the adverse events or not. We also performed meta-regressions in order to evaluate the relation between the adverse events and the continuous patient/study characteristics, including age, gender ratio, and publication year. For the categorical covariates (ie, study duration and conflict of interest), we performed a subgroup analysis. For the analysis, we considered the intention-to-treat model in the sample size of each arm of trials. Heterogeneity test of the included studies was conducted in Comprehensive Meta-analysis (CMA) V2 by reporting I^2 and p values.

3. Evidence synthesis

3.1. Description of included studies

After screening and eligibility assessment, 56 studies comprising 15 446 patients in their placebo arm were included in the meta-analysis of adverse events in the placebo group (Fig. 1). We included OAB trials that investigated all variants of pharmacological interventions, including oral drugs, subcutaneous patches, and gels (except for intravesical injection with botulinum toxin derivatives).

In the evaluation of risk of bias using Cochran checklist, the studies were of good qualities so that no study was excluded due to its risk of bias. No study was excluded because of publication bias. The risk of bias summary and graph are shown in Fig. 2. The average age of the patients was 59.5 yr (minimum: 38.5 and maximum: 75), and 79.8% (minimum: 42.2% and maximum: 100%) were female. The majority of the trials (47) had a duration of 12 wk, followed by some having a duration of 4 wk (three trials), 8 wk (two trials), 2 wk (two trials), and 16 wk (one trial; Table 1). An intention-to-treat model was used for extraction of the sample size data. We recorded numerous adverse events, of which 13 commonly reported adverse events (dry mouth, constipation, diarrhea, nausea and vomiting, dyspepsia, headache, nasopharyngitis, abdominal pain, blurred vision, urinary retention, dizziness and vertigo, fatigue, and UTI) were included in the final analysis.

3.2. Principal findings

3.2.1. Safety of interventions

Dry mouth was the most commonly evaluated adverse event, with 56 studies, comprising 15 324 patients, reporting on it. The mean event rate of dry mouth within the studies was 4.9% (95% confidence interval [CI] 4.2–5.7%; $p < 0.001$; Fig. 3). Constipation was the second most commonly reported adverse event, with 49 studies, comprising 14 556 patients, reporting on it. The mean event rate of constipation was 2.6% (95% CI 2–3%; $p < 0.001$; Fig. 3). In 33 studies comprising 10 202 patients, the mean event rate of headache was 3.1% (95% CI 2.6–3.7%; $p < 0.001$; Fig. 3). Nasopharyngitis was also a prevalent event, with a mean rate of 3.4% (95% CI 4.4–5.7%; $p < 0.001$) in 15 studies comprising 5713 patients (Fig. 3). UTI was also among the commonly reported adverse events, with an event rate of 3% (95% CI 2.6–3.6%; $p < 0.001$) in 18 studies comprising 6615 patients (Fig. 3). In 14 studies, comprising 4339 patients, the mean rate of diarrhea was 2%. A relatively lower event rate was recorded for the remaining outcomes: 1.4%, 1.5%, 1.7%, 1.7%, 1.5%, 1.5%, 1.6%, and 1.6% for abdominal pain, blurred vision, dizziness, vertigo, dyspepsia, fatigue, nausea, and vomiting, respectively. The lowest mean event rate was estimated for urinary retention at 0.4%. We found no relationship between age, gender ratio, and publication year with the nocebo response in the meta-regressions.

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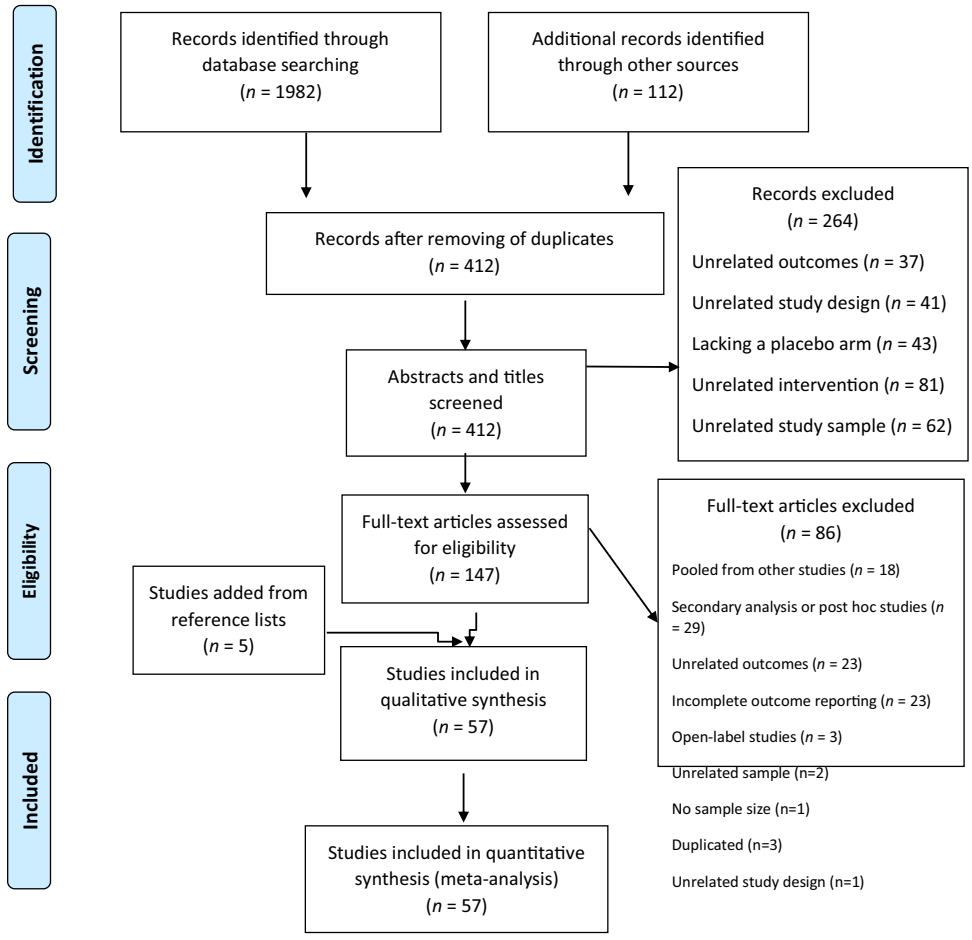

Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram. A total of 56 studies met the inclusion criteria for this study.

3.2.2. *Nocebo response in different drug groups and routes of administration*

Dry mouth and headache were the two outcomes of which a sufficient number of studies performed a comprehensive subgroup analysis. Considering dry mouth, the mean event rates in all placebo arms were 1.2% (95% CI 0.5–3.1%; $p <$ 0.001; Fig. 4) for β-3 agonists, 2.8% (95% CI 1.8–4.4%; $p <$ 0.001; Fig. 4) for both drug groups, 3.4% (95% CI 2.3–4.9%; $p <$ 0.001; Fig. 4) for gel antimuscarinics, 5.9% (95% CI 5–6.9%; $p <$ 0.001; Fig. 4) for oral antimuscarinics, and 2.6% (95% CI 1–6.6%; $p <$ 0.001; Fig. 4) for patch antimuscarinics. For headache, the mean event rates in all placebo arms were 2% (95% CI 1–3.8%; $p <$ 0.001; Fig. 4) for β-3 agonists, 3% (95% CI 0.8–10.9%; $p <$ 0.001; Fig. 4) for both drug groups, 3.1% (95% CI 2.1–4.4%; $p <$ 0.001; Fig. 4) for gel antimuscarinics, and 3.1% (95% CI 2.5–3.8%; $p <$ 0.001; Fig. 4) for oral antimuscarinics.

3.2.3. *History of previous medication, washout period before enrolment, and adverse event assessment*

Approximately one-fifth of the studies did not report on having a washout period prior to sampling. In the remaining studies, the most reported run-in time was 2 wk prior to randomization. Only 30% of studies considered OAB medication usage within a range of 2–12 wk prior to enrolment as an exclusion criterion, and in 27% of studies it was not mentioned. The remaining studies (37%) reported the history of previous OAB medication. In the included studies, adverse events were assessed and categorized considering intensity (mild, moderate, and severe), laboratory tests, vital signs, electrocardiograms, and residual urine volume. In 20% of studies, the investigators evaluated the adverse events or their intensity. A limited number of studies clearly reported on using structured checklists to assess the adverse events, and one of them used an appropriate page of the Case Report Form for data recording [16]. Table 2 represents the characteristics of the included studies in terms of the history of previous medications, washout period, and assessment of adverse events.

3.3. *Discussion*

Negative expectation from the treatment is a factor that can result in or facilitate adverse events [7]. We hypothesized that there is a statistically significant rate of adverse events in the placebo group due to the nocebo response. To test this hypothesis, we performed a systematic review and meta-analysis of the types and rates of adverse events in the

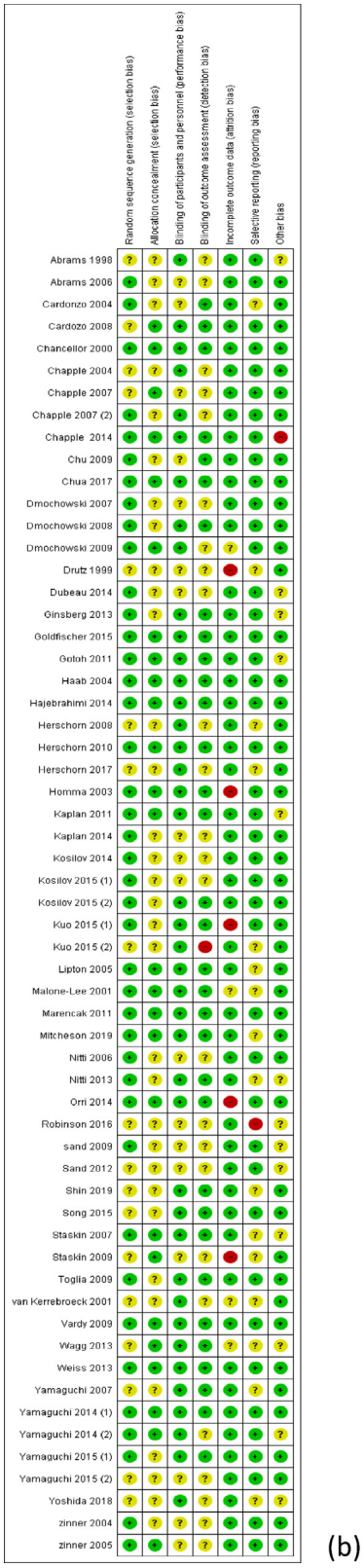

Fig. 2 – Quality of the studies based on the Cochrane Risk of Bias assessment tool: (A) risk of bias summary and (b) risk of bias table.

Table 1 – Characteristics of 57 trials reporting on the rate of adverse events in the placebo arms.

No.	Author (publication year)	Sample size of the placebo arm	Mean age (SD)/(range)	Female no. (%) in the placebo arm	Duration (mo)	Sponsorship
1	Abrams (1998) [30]	57	58 (26–78)	43 (75.5)	12	Yes
2	Abrams (2006) [31]	24	51.5 (47–56)	76.6 (NR)	2	No
3	Cardozo (2004) [32]	301	56.1 (13.3)	227 (80.8)	12	No
4	Cardozo (2008) [33]	223	57.9 (NR)	191 (85.7)	16	Yes
5	Chancellor (2000) [16]	508	61 (21–93)	410 (80)	12	Yes
6	Chapple (2004) [34]	253	57.8 (13.7)	193 (76.3)	12	Yes
7	Chapple (2007) [35]	283	56 (13.7)	229 (81)	12	Yes
8	Chapple (2007) [36]	133	73 (5)	100 (75.2)	12	Yes
9	Chapple (2014) [37]	386	59.6 (19–85)	316 (82)	12	Yes
10	Chu (2009) [38]	332	58 (13)	277 (83.4)	12	Yes
11	Chua (2018) [39]	32	53.9 (12.1)	23 (72)	12	Yes
12	Dmochowski (2007) [40]	850	61 (NR)	476 (60.5)	12	Yes
13	Dmochowski (2008) [41]	284	58.4 (11.8)	249 (87.7)	12	No
14	Dmochowski (2010) [42]	445	60.1 (12.9)	368 (83)	12	Yes
15	Drutz (1999) [43]	56	62.1 (26–87)	45 (80)	12	No
16	DuBeau (2014) [44]	281	75.3 (65–90)	236 (84)	12	Yes
17	Ginsberg (2013) [45]	812	59.1 (13.4)	679 (84)	12	Yes
18	Goldfischer (2015) [46]	202	57.8 (13.3)	178 (88.1)	12	Yes
19	Gotoh (2011) [47]	274	58.7 (14.1)	207 (76.7)	12	Yes
20	Haab (2004) [48]	164	56.5 (19–81)	138 (84.8)	12	Yes
21	Hajebrahimi (2014) [49]	30	38.5 (6.1)	30 (100)	4	No
22	Herschorn (2008) [50]	204	57 (14)	143 (71)	12	Yes
23	Herschorn (2010) [51]	334	58.4 (13.7)	269 (81)	12	Yes
24	Herschorn (2017) [52]	429	57.9 (13)	327 (76.2)	12	Yes
25	Homma (2003) [53]	122	58.4 (14)	84 (69)	12	Yes
26	Kaplan (2011) [54]	478	59.5 (13.2)	410 (86)	12	Yes
27	Kaplan (2014) [55]	301	58.2 (13.2)	244 (81)	12	Yes
28	Kosilov (2014) [56]	59	69.4 (NR)	NR	8	No
29	Kosilov (2015) [57]	102	65.1 (NR)	NR	12	No
30	Kosilov (2015) [58]	59	71.2 (NR)	NR	6	No
31	Kuo (2015) [59]	68	58.4 (13)	42 (61.8)	12	No
32	Kuo (2015) [60]	366	55.3 (13.6)	225 (69.7)	12	Yes
33	Lipton (2005) [61]	69	71.2 (65–84)	75 (58.1)	2	Yes
34	Malone-Lee (2001) [62]	43	75 (66–88)	32 (74)	4	No
35	Marencak (2011) [63]	103	52.9 (13.3)	103 (100)	4	Yes
36	Mitcheson (2019) [64]	141	57.8 (9.5)	185 (90.2)	12	Yes
37	Nitti (2006) [65]	243	58 (14)	96 (39.5)	12	Yes
38	Nitti (2013) [66]	453	60.1 (13.8)	345 (76.2)	12	Yes
39	Orri (2014) [67]	6	46.2 (31–64)	6 (100)	12	Yes
40	Robinson (2016) [68]	186	53.7 (13)	186 (100)	12	Yes
41	Sand (2009) [69]	505	58.2 (11.2)	505 (100)	12	No
42	Sand (2012) [70]	352	59 (12.2)	352 (100)	12	No
43	Song (2015) [71]	76	58.35 (12.4)	51 (63.4)	12	Yes
44	Staskin (2007) [72]	303	59.3 (12.2)	256 (84.5)	12	No
45	Staskin (2009) [73]	400	59.3 (12.2)	352 (89)	12	No
46	Toglia (2009) [74]	367	57 (15)	305 (83)	12	Yes
47	Van Kerrebroeck (2001) [75]	507	61 (22–93)	410 (81)	12	No
48	Vardy (2009) [76]	374	60 (12)	314 (84)	12	Yes
49	Wagg (2020) [77]	442	71.9 (6)	324 (73)	12	Yes
50	Weiss (2013) [78]	474	NR	NR	12	Yes
51	Yamaguchi (2007) [79]	395	60.8 (12.5)	333 (84.3)	12	Yes
52	Yamaguchi (2014) [80]	373	56.2 (13.2)	344 (92.2)	12	Yes
53	Yamaguchi (2014) [81]	368	58.2 (14.2)	310 (84.2)	12	Yes
54	Yamaguchi (2016) [82]	147	56.2 (13.7)	130 (88.4)	8	Yes
55	Yamaguchi (2015) [83]	211	55.7 (12.9)	169 (80.1)	12	Yes
56	Yoshida (2018) [84]	369	58.9 (11.8)	333 (90.2)	12	Yes
57	Zinner (2004) [85]	261	61.5 (12.9)	186 (71.3)	12	No

NR = not reported; SD = standard deviation.

placebo arms of clinical trials evaluating pharmacological treatments for OAB (except for intravesical botulinum toxin). After a comprehensive review of the literature, we recorded considerable rates of adverse events for some of the outcomes.

Of these factors, methodological difference, in other words, how the data of adverse events were acquired, assessed, and analyzed, can have a major impact on the final reported outcome. Rief et al [17] claim that structured assessment approaches (eg, questionnaires, checklists, or

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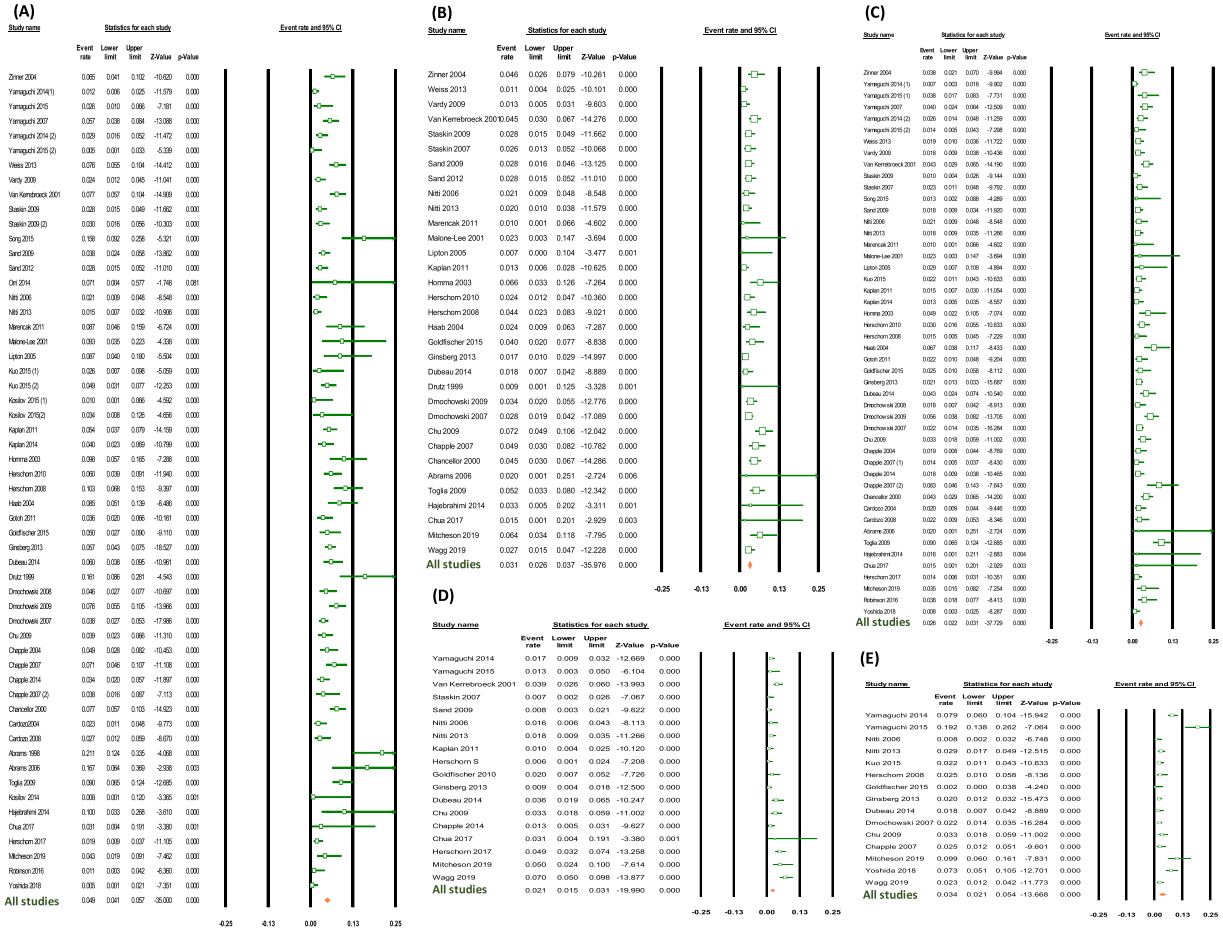

Fig. 3 – Forest plots showing the cumulative event rate of (A) dry mouth, (B) headache, (C) constipation, (D) UTI and (E) nasopharyngitis in the placebo arms of clinical trials. CI = confidence interval; UTI = urinary tract infection.

rating scales) are more sensitive in revealing symptoms than nonstructured approaches. Indeed, the results of the placebo group are highly influenced by the study methodology, and this shows the importance of the assessment procedures in having a reliable outcome [18,19].

The investigators can also be a source of misdirection. Expectancy of the investigators may influence the experimental investigation; this is known as the Rosenthal [20] effect. It has also been reported that physicians tend to ignore patient-reported adverse events. Thus, having a rigorous assessment approach, if not overestimated, and a good research methodology can play a great role in having reliable outcomes [17,21].

In our study, dry mouth (cumulative rate of 4.9%), headache (3.1%), and nasopharyngitis (3.4%) were the most prevalent adverse events. Indeed, patient expectations can influence the occurrence of adverse events [17]. Our study shows that verbal communication with the patient about the possible adverse event plays a major role in causing/facilitating adverse events; patients who were told about the possible oral antimuscarinic adverse events experienced more adverse events than those who were not told. However, we believe that the true values are underestimated. Evidence shows that in most of the trials, the patients and the investigator guess which medication (active drug or placebo) the patients are receiving, and when they know that they are receiving the active treatment, they respond even more. The opposite occurs in the placebo group [17,22,23]. We believe that, in our study, the same phenomena may increase the expectation of having more adverse events in the active treatment group, thus increasing the nocebo response when they know that they are receiving the active treatment. On the contrary, the group receiving placebo may have reduced expectations of having drug-related adverse events and therefore have a lower nocebo response.

The effect of expectations on the nocebo response can be explained by neurobiological mechanisms. Benedetti et al [24] argue that pain-related brain activities are highly affected by the positive and negative expectations from the treatment. Furthermore, cholecystokinin can be affected by negative expectations and facilitate pain transmission [25]. This can explain the 3.1% incidence of headache and 1.4% incidence of abdominal pain. However, some argue that these reports can be due to pre-existing symptoms, since such symptoms are very prevalent in the general population and can be misdirected as adverse events of the treatment. Most of the patients in our study have already

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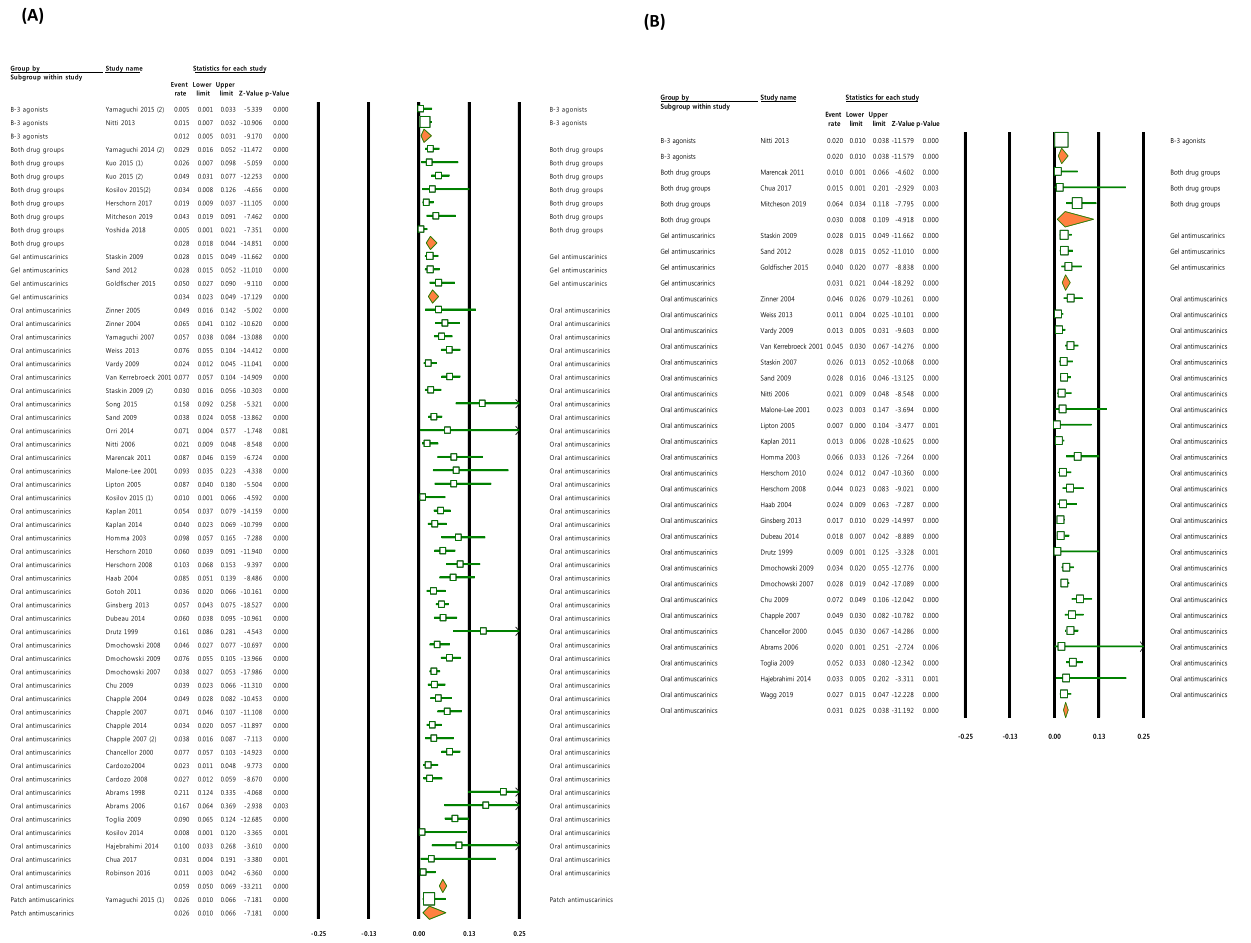

Fig. 4 – Subgroup analyses of adverse events based on drug type and rout of administration: (A) dry mouth and (B) headache.

received several OAB medications prior to participating in such trials. Therefore, the prior experience can trigger the sensitization process and the classical conditioning that can increase the nocebo response [17,26]. In other words, patients with experience of adverse events in prior treatment may experience the same adverse events when receiving placebo [17].

It is crucial for health care providers to minimize the adverse events and improve overall health of their patients. In case of the nocebo effect, health care providers should frame the information they provide by focusing on the positive side of the treatment (eg, the possibility of not developing adverse events) [27]. A caring and empathic relationship with the patients can also help reduce the nocebo-related adverse events [28]. Finally, it is crucial to identify patients who are more prone to experiencing nocebo effect such as the patients who have previously experienced adverse events.

3.4. *Limitations*

To begin with, the limitation in inclusion of studies is a major problem that can lead to selection bias. Another source of error can be the publication bias. However, we did not see a major publication bias within the included studies. A major source of unreliability was the difference in individual trials in recording the adverse events. Despite having a long list of adverse events, we were able to run a meta-analysis only for a limited number of adverse events. The rest of the adverse events were either not reported or not enough to run a pooled study. We tried to limit the selection bias in our study by not being too rigorous in the selection of studies for analysis and including studies with medium-good qualities. The differences in study design, informed consent, methods of recording adverse events, and patient-physician interactions were also major contributors of bias.

In 2018, a "consensus statement" was published by a group of top placebo researchers, which defines the placebo and nocebo responses as all the health changes after administration of inert treatment; thus, a placebo or nocebo response includes all the processes that have an impact on the change of symptoms (ie, regression to the mean, natural history). The nocebo or placebo effect, however, refers to the health changes purely related to the placebo or nocebo [4]. In our study, a considerable nocebo response was reported in some of the placebo arms, but we were unable to assess the nocebo effect. To assess the pure

Table 2 – Characteristics of included studies in terms of the history of previous medication, washout period before enrollment, and adverse event assessment.

No.	Author (publication year)	Previous OAB medication, *N* (%)	Washout period prior to intervention (wk)	Assessment of AEs (investigator, checklist, and self-report)
1	Abrams (1998) [30]	43 (75)	2	All AEs were recorded and categorized in terms of intensity (mild, moderate, and severe).
2	Abrams (2006) [31]	Exclusion criteria: use of investigational drugs in the 30 d preceding the study	2	AEs were recorded at each visit.
3	Cardozo (2004) [32]	95 (33.8)	2	AEs were categorized by severity and likelihood of causal relationship to study medication.
4	Cardozo (2008) [33]	About 45% of patients had received previous drug therapy for OAB within a year of the start of the study	2	The nature, frequency, and intensity of AEs were documented.
5	Chancellor (2000) [16]	263 (52)	1–2	AEs were categorized in terms of intensity (mild, moderate, and severe).
6	Chapple (2004) [34]	83 (32.8)	2	AEs were categorized by severity and likelihood of causal relationship to study medication.
7	Chapple (2007) [35]	184 (63.4)	2	AEs reported in response to general and nonspecific questioning by the investigator, or volunteered by the patient, were recorded in the appropriate page of the case report form.
8	Chapple (2007) [36]	Exclusion criteria: treatment with drugs known to affect urinary bladder function (eg, anticholinergics, antispasmodics)	1	AEs were recorded.
9	Chapple (2014) [37]	Exclusion criteria: treatment with other anticholinergic medications within 2–3 wk of screening	2	AEs were monitored throughout the study, with severity and causal relationship to study drug assessed by the study investigator.
10	Chu (2009) [38]	Not mentioned	2	AEs were assessed by investigators and by monitoring AEs; the Medical Dictionary for Regulatory Activities was used to code AEs.
11	Chua (2018) [39]	19 (59)	3	AEs were monitored throughout the study.
12	Dmochowski (2007) [40]	Not mentioned	2	Not mentioned.
13	Dmochowski (2008) [41]	156 (54.9)	Not mentioned	Standard safety assessments, including monitoring of vital signs, physical examination, standard laboratory tests, and spontaneously reported AEs, were conducted.
14	Dmochowski (2010) [42]	Exclusion criteria: treatment with an antimuscarinic OAB medication	Not mentioned	AEs, either reported by the patient or observed by the investigator, were recorded, as was the investigator's opinion of whether the event was treatment related.
15	Drutz (1999) [43]	Exclusion criteria: treatment with any investigational drug in the 2 mo prior to entry	2	The severity of each AE was assessed by the investigator after discussion with the patient and a review of pertinent laboratory and physical findings.
16	DuBeau (2014) [44]	Exclusion criteria: antimuscarinic medication use within 3 wk	Not mentioned.	The incidence, severity, and potential relationship to treatment of all treatment-emergent AEs and withdrawals from the trial due to AEs were monitored throughout the trial.
17	Ginsberg (2013) [45]	Not mentioned	Not mentioned	Treatment-emergent AEs were monitored during the studies and assessed descriptively.
18	Goldfischer (2015) [46]	Not mentioned	2	AEs were summarized by the treatment group and the Medical Dictionary for Regulatory Activities preferred term.
19	Gotoh (2011) [47]	Not mentioned	2	The severity of AEs was classified into mild, moderate, and severe. AEs judged as causally related to the test drug by the investigators were regarded as adverse effects.
20	Haab (2004) [48]	21.3%	2	All observed or volunteered AEs were evaluated by the investigator and the patient in terms of severity; seriousness and potential relationship to treatment were also evaluated by the investigator.
21	Hajebrahimi (2014) [49]	Not mentioned	Not mentioned	Not mentioned.
22	Herschorn (2008) [50]	Patients were screened and excluded from the study if they had received any drug used to treat UUI or OAB within 14 d before the study treatment period	Not mentioned	AEs were recorded at each visit.
23	Herschorn (2010) [51]	Exclusion criteria: treatment with antimuscarinic OAB medication within 2 wk before screening	2	Not mentioned.

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Table 2 (*Continued*)

No.	Author (publication year)	Previous OAB medication, *N* (%)	Washout period prior to intervention (wk)	Assessment of AEs (investigator, checklist, and self-report)
24	Herschorn (2017) [52]	205 (47.8)	4	AEs were coded using MedDRA version 16.0 and summarized by the System Organ Class and Preferred Term
25	Homma (2003) [53]	31 (25)	1 or 2 wk	Directly observed and spontaneously reported AEs were recorded at visits 3–6 and classified by intensity as mild, moderate, or severe
26	Kaplan (2011) [54]	Exclusion criteria: antimuscarinic treatment within 2 wk before screening	2	There was one fatal serious AE in the placebo group during the course of the study; this death was reported as unrelated to study treatment.
27	Kaplan (2014) [55]	Exclusion criteria: treatment with ≥3 antimuscarinic OAB medications within 12 mo before screening	2	Safety data, from both the tolterodine ER run-in phase and the double-blind phase, were summarized by the treatment group.
28	Kosilov (2014) [56]	Not mentioned	Not mentioned	Not mentioned.
29	Kosilov (2015) [57]	Not mentioned	Not mentioned	Not mentioned.
30	Kosilov (2015) [58]	Not mentioned	Not mentioned	Not mentioned.
31	Kuo (2015) [59]	Over two-thirds had a history of previous drug medication for OAB	2	An independent cardiovascular adjudication committee determined all deaths and serious potential cardiovascular AEs using the categorization of APTC/MACE or non-APTC/MACE.
32	Kuo (2015) [60]	169 (52.3)	2	All observed or spontaneously reported AEs were recorded, including a description of the event, dates of onset and end of the event, intensity, seriousness, action with respect to study drug, treatment required, relationship to study drug, and outcome of the event.
33	Lipton (2005) [61]	Exclusion criteria: those who had been treated with another investigational drug within the previous 3 mo	1	All observed or volunteered AEs were recorded and evaluated in terms of seriousness, intensity (mild, moderate, or severe), and causal relationship to treatment.
34	Malone-Lee (2001) [62]	Exclusion criteria: concomitant antimuscarinic medication, previous treatment with tolterodine, and exposure to any other investigational drug in the preceding 2 mo	1	Patients returned to the clinic during which spontaneously reported AEs and a 12-lead ECG were recorded.
35	Marencak (2011) [63]	Not mentioned	4	Safety was assessed via the frequency and severity of all observed or volunteered treatment-emergent AEs.
36	Mitcheson (2019) [64]	64 (31.2)	1	Safety endpoints were assessed using vital signs, ECG, laboratory tests, and a tiered AE reporting approach.
37	Nitti (2006) [65]	Exclusion criteria: any anticholinergic or other drug for OAB within 2 mo of the baseline visit	2	Not mentioned.
38	Nitti (2013) [66]	Exclusion criteria: use of OAB medications that could not be stopped safely at screening	2	Cardiovascular-related events for patients who died or experienced a serious cardiovascular event were evaluated by an independent adjudication committee according to the type of cardiovascular event (APTC/MACE or non-APTC/MACE) or as a noncardiovascular event.
39	Orri (2014) [67]	Not mentioned	2	Treatment-emergent AEs were reported either directly by the participant or by a treating healthcare professional via a call center linked to the investigator site or via a secure e-mail or study web link; all AEs were followed up by the study investigator's team at the clinical site.
40	Robinson (2016) [68]	19 (10.2)	2	AEs were reported throughout the study.
41	Sand (2009) [69]	272 (53.9)	1	Safety parameters collected during the study comprised clinical laboratory tests, including resting 12-lead electrocardiograms, spontaneously reported AEs, and vital signs.
42	Sand (2012) [70]	Not mentioned	Not mentioned	Through the recording of patient-reported AEs, assessment of skin tolerability and vital signs, physical examination, clinical laboratory and pregnancy tests (for women of childbearing potential only), electrocardiograms, and postvoid residual urine volume measurement were performed.

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Table 2 (*Continued*)

No.	Author (publication year)	Previous OAB medication, *N* (%)	Washout period prior to intervention (wk)	Assessment of AEs (investigator, checklist, and self-report)
43	Song (2015) [71]	Not mentioned	2	At each visit, any AEs reported in response to questioning by the investigator or self-reported by the patient were recorded with the severity and casualty to study medication. Other safety data (eg, ECG, vital signs, and PVR) were considered as appropriate.
44	Staskin (2007) [72]	151 (49.8)	1	Safety was assessed by clinical examination, AE monitoring, clinical laboratory values, and resting electrocardiograms.
45	Staskin (2009) [73]	Not mentioned	Not mentioned	Safety was monitored through AE reporting.
46	Toglia (2009) [74]	Not mentioned	Not mentioned	Not mentioned.
47	Van Kerrebroeck (2001) [75]	Exclusion criteria: treatment with an investigational drug in the 2 mo before study entry; 50% of patients in each treatment group had received previous treatment for overactive bladder	1 or 2 wk	Follow-up visit was performed to record any AEs.
48	Vardy (2009) [76]	Any OAB medications were eligible after discontinuation and completion of a ≥14-d washout period	2	Study investigators classified AEs by severity (mild, moderate, and severe), reported any serious AEs, and determined the relationship of all AEs to study drug.
49	Wagg (2020) [77]	OAB medications received before the start of the study was collected only for 30 d prior to enrollment	2	Determined by the study investigator according to the protocol.
50	Weiss (2013) [78]	Exclusion criteria: treatment with antimuscarinic OAB medication within 2 wk of screening	2	AEs were monitored throughout the study and assessed descriptively using the safety analysis set.
51	Yamaguchi (2007) [79]	Patients were excluded if they were taking concomitant anticholinergic medications	2	AEs were recorded and categorized by severity and likelihood of causal relationship to the study medication.
52	Yamaguchi (2014) [80]	Exclusion criteria: other medications for urinary frequency and incontinence, other drugs with anticholinergic activity, and cholinergic agents from week 2 to week 12	2	Safety was assessed from AEs, laboratory tests, vital signs, 12-lead electrocardiography, and residual urine volume.
53	Yamaguchi (2014) [81]	240 (65.2)	2	Laboratory tests and vital signs were assessed.
54	Yamaguchi (2016) [82]	Not mentioned	2	Safety was determined by assessment of AEs, laboratory tests, vital signs, 12-lead electrocardiogram, and residual urine volume.
55	Yamaguchi (2015) [83]	122 (57.8)	2	Safety was evaluated based on AEs, laboratory findings, vital signs, 12-lead electrocardiogram, and postvoid residual volume.
56	Yoshida (2018) [84]	62 (16.8)	2	Safety was assessed according to AEs, clinical tests, postvoided residuals, vital signs, and 12-lead electrocardiogram.
57	Zinner (2004) [85]	142 (54.4)	2	The safety parameters collected during this study included AEs, clinical laboratory tests, vital signs, and 12-lead electrocardiograms.

AE = adverse event; APTC = Antiplatelet Trialists' Collaboration; ECG = electrocardiogram; ER = extended release; MACE = major adverse cardiovascular events; OAB = overactive bladder; PVR = postvoid residual; UUI = urge urinary incontinence.

nocebo effect, adverse events in the placebo group should also be compared with those in a "no-treatment" arm in the trials [29]. Another limitation of the current study was excluding non–English-language papers.

4. Conclusions

Dry mouth, constipation, headache, and nasopharyngitis were the most prevalent adverse events reported in the included studies. This work has revealed that nocebo plays a major role in causing and/or facilitating adverse events. The results also show the potential effect of verbal communication on the nocebo response. The incidence of adverse events is not high in comparison with the adverse events caused by active medications. Yet, we believe that the nocebo group is underestimated since patients often guess which medication they receive in a trial, hence reducing the nocebo response. Health care providers should have a better understanding of the positive and negative expectations associated with therapies to achieve the best possible outcomes for each individual patient. They should focus on framing information by highlighting the positive aspects of the treatment. Finally, we recommend conducting well-structured trials by using more systematic approaches in recording the adverse events, maintaining blinding, and including a no-treatment arm.

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***Author contributions*:** Hadi Mostafaei 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, Mori, Quhal.
Acquisition of data: Mostafaei, Janisch, Pradere, Quhal.
Analysis and interpretation of data: Mori, Shariat, Hajebrahimi.
Drafting of the manuscript: Mostafaei, Pradere, Shariat.
Critical revision of the manuscript for important intellectual content: Roehrborn, Shariat, Hajebrahimi.
Statistical analysis: Mostafaei, Janisch, Shariat.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Shariat, Hajebrahimi.
Other: None.

Financial disclosures: Hadi Mostafaei certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

***Funding/Support and role of the sponsor*:** None.

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.2020.10.010.

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