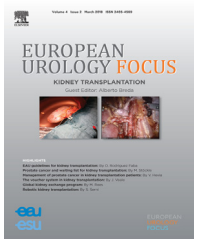
available at www.sciencedirect.com
journal homepage: www.europeanurology.com/eufocus



Review

Placebo Response in Patients with Oral Therapy for Overactive Bladder: A Systematic Review and Meta-analysis

Hadi Mostafaei [a,b], *Florian Janisch* [a,c], *Keiichiro Mori* [a,d], *Fahad Quhal* [a,e], *Benjamin Pradere* [a,f], *Sakineh Hajebrahimi* [b], *Claus G. Roehrborn* [g], *Shahrokh F. Shariat* [a,g,h,i,j,k,l,m,*]

[a] *Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria;* [b] *Research Center for Evidence Based Medicine, Tabriz University of Medical Sciences, Tabriz, Iran;* [c] *Department of Urology, Medical University of Hamburg, Hamburg, Germany;* [d] *Department of Urology, The Jikei University School of Medicine, Tokyo, Japan;* [e] *King Fahad Specialist Hospital-Dammam, Dammam, Saudi Arabia;* [f] *Department of Urology, CHRU Tours, Francois Rabelais University, Tours, France;* [g] *Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX, USA;* [h] *Institute for Urology and Reproductive Health, I.M. Sechenov First Moscow State Medical University, Moscow, Russia;* [i] *Department of Urology, Second Faculty of Medicine, Charles University, Prague, Czech Republic;* [j] *Department of Urology, Weill Cornell Medical College, New York, NY, USA;* [k] *Karl Landsteiner Institute of Urology and Andrology, Vienna, Austria;* [l] *Department of Urology, University of Jordan, Amman, Jordan;* [m] *European Association of Urology Research Foundation, Arnhem, The Netherlands*

Article info

Associate Editor: Dr. Richard Lee

Keywords:
Overactive bladder
Placebo response
Systematic review

Abstract

Context: The role of a placebo response in the management of overactive bladder (OAB) remains unclear.
Objective: The aim of this review is to methodically study the placebo response extracted from the control arms of randomized clinical trials assessing therapy in patients with OAB.
Evidence acquisition: Medline (PubMed), The Cochrane Library, EMBASE, and Scopus were searched to identify randomized controlled trials (RCTs) published until September 2019. Randomized placebo-controlled trials investigating oral drug therapy for OAB were included. The articles were critically appraised by two reviewers. The primary outcomes were the placebo response in the main patient-reported urinary outcomes together with assessing the impact of patient demographic factors on the placebo response.
Evidence synthesis: The initial search resulted in 1982 records after reviewing the titles and abstracts, and reference lists of other systematic reviews; 57 studies with an overall estimated 12 901 patients were included in the meta-analysis. The included studies were of overall high/acceptable quality. The standardized mean difference was −0.45 (95% confidence interval [CI] −0.51 to −0.40; $p < 0.001$) for daily micturition episodes, −0.33 (95% CI −0.42 to −0.24; $p < 0.001$) for daily nocturia episodes, −0.46 (95% CI −0.55 to −0.37; $p < 0.001$) for urgency urinary incontinence episodes, −0.50 (95% CI −0.61 to −0.39; $p < 0.001$) for daily urgency episodes, −0.51 (95% CI −0.60 to −0.43; $p < 0.001$) for daily incontinence episodes, and 0.25 (95% CI 0.211–0.290; $p < 0.001$) for volume voided per micturition. The meta-regression of age-related impact of the placebo response on nocturia showed a slope of −0.02 ($p < 0.001$).
Conclusions: Placebo has a statistically significant effect on improving symptoms and signs associated with OAB; this effect is age dependent. However, there is no consensus on what change of OAB symptoms and signs is clinically meaningful for the affected patient. Taken together, the placebo response seems to be non-negligible in OAB, supporting the need for placebo control in RCTs.

* Corresponding author at: Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Vienna General Hospital, Währinger Gürtel 18-20, A-1090 Vienna, Austria. Tel. +43 664 800 165 1010.
E-mail addresses: sfshariat@gmail.com, shahrokh.shariat@meduniwien.ac.at (S.F. Shariat).

https://doi.org/10.1016/j.euf.2021.02.005

Please cite this article in press as: Mostafaei H, et al. Placebo Response in Patients with Oral Therapy for Overactive Bladder: A Systematic Review and Meta-analysis. Eur Urol Focus (2021), https://doi.org/10.1016/j.euf.2021.02.005

Patient summary: Placebo is an inert treatment method often used in clinical research for comparison with active treatment. However, studies show that placebo has an effect of its own. A placebo response means the total improvement resulting from receiving a placebo. In our study, placebo had a significant role in improving the symptoms of overactive bladder.

1. Introduction

Placebo has been shown to be an effective treatment option in several studies in the past decades [1]. However, the amplitude, clinical efficacy, and sustainability of its effect remain heterogeneous and unclear [2]. A main reason is the regression to the mean (due to random error) and the natural history of some illnesses, which can reduce improvement with time without receiving treatments [2,3]. On the contrary, the complex neurobiological mechanisms and biopsychosocial aspects of the placebo response are real and effective in concrete clinical scenarios [4,5]. Expectations that patients have from a treatment also contribute to health outcomes and the placebo response in specific [6].

Overactive bladder (OAB) syndrome is defined as "urinary urgency, usually accompanied by increased daytime frequency and/or nocturia, with urinary incontinence or without, in the absence of urinary tract infection or other detectable diseases" [7]. It is a highly prevalent and debilitating disease with significant social, emotional, and public health/economic aspects [8–10]. Behavioral therapy is the first-line treatment option for OAB, followed by pharmacological interventions. As OAB is a quality of life disease, the subjective perception of its symptoms and signs is determining treatment seeking as well as the choice of therapy. Various pharmacological agents have been tested and approved based on randomized controlled trials (RCTs) comparing the test agent with placebo. Interestingly, the placebo response, in this disease specifically, has shown significant improvement of OAB symptoms and signs [11,12]. In most of the trials for OAB management, the placebo response seems to be significant, but in comparison with the active intervention, this significance is not important [13]. The placebo response is a well-described phenomenon that can be harvested and enhanced to help relieve pain and suffering in a proportion of patients. There is a major interest in using the placebo response to improve and enhance clinical outcomes [6]. To date, there has not been any assessment of the magnitude of the placebo response from pharmacological therapy in OAB patients. OAB is a chronic condition; the patient could experience active or remission phases during the disease course.

In this systematic review and meta-analysis, we set out to assess the short- to mid-term effect of placebo on established subjective and objective endpoints in OAB trials. We hypothesized that placebo may result in a statistically significant improvement of the symptoms and signs associated with OAB.

2. Evidence acquisition

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and Cochrane guidelines for the study methodology [14,15]. This study is registered with the International Prospective Register of Systematic Reviews (number CRD42019129769).

2.1. Data sources and searches

We searched Medline (PubMed), Cochrane Library, EMBASE, and Scopus to identify RCTs published from January 1995 until September 2019. We used the following keywords for our research strategies: "random controlled trial" and "placebo" in combination with anticholinergics, antimuscarinics, β3 receptor agonists, and overactive bladder and urgency incontinence. The detailed search strategy is provided in Supplementary Figure 1. We excluded trials in which there was no placebo arm and no active treatment. We also performed a manual search for relevant studies in the references of all assessed studies.

2.2. Eligibility criteria

We included randomized placebo-controlled studies of adult (age ≥18 yr) patients with OAB and/or detrusor overactivity. We conducted electronic searches for RCTs assessing oral pharmacological interventions for OAB. We only included studies that compared the change of the outcomes from the baseline in both the drug and the placebo group.

2.3. Study selection

Using a standardized form, two independent reviewers screened the titles, abstracts, and full texts. Disagreements were resolved by a third reviewer. The final list was then approved for data extraction.

2.4. Data extraction

We extracted all outcomes that the patients recorded in their voiding diary, including episodes of incontinence, urgency, micturition, and urgency incontinence and volume voided per micturition, together with treatment satisfaction visual analog scale, symptom bother scale as assessed by the Overactive Bladder questionnaire, patient perception of bladder condition, King's Health Questionnaire, incontinence impact questionnaire, and Overactive Bladder Symptom Composite Score.

Please cite this article in press as: Mostafaei H, et al. Placebo Response in Patients with Oral Therapy for Overactive Bladder: A Systematic Review and Meta-analysis. Eur Urol Focus (2021), https://doi.org/10.1016/j.euf.2021.02.005

In addition, we extracted all available data regarding gender ratio, mean age of the study sample, as well as the year of publication, financial support, follow-up period, and conflict of interest. To assess changes, we calculated effect size, based on the mean and standard deviation (SD), before and after treatment in placebo arms of all included trials. For some of the studies, we monitored the values from graphs using Universal Desktop Ruler (version 2.9, AVPSoft Inc). In order to assess the pure placebo effect, the changes in the placebo group should also be compared with those in a no-treatment group since the outcomes might improve due to the natural process of the disease and due to regression to the mean [16]. However, this was not possible since only a negligible number of RCTs had a no-treatment arm. Thus, the term "placebo response" in this study refers to the mean difference or standardized mean difference from the baseline to the last study data in the placebo arm of the RCTs.

2.5. Risk of bias assessment

Two reviewers independently selected the evidence, critically appraising it using the Cochrane Collaboration tool for assessing the risk of bias [14]. In case of disagreement, a third researcher re-evaluated the documents. If non-English evidence had an abstract in English that was accessible, it was included. Crossover trials were excluded to reduce possible biases in estimating the true placebo response. If needed and in case of missing data, we e-mailed the authors for raw data, and if there was no response, the study was excluded. For duplicated studies, we used the version with more complete data. We used funnel plots to illustrate the publication bias.

2.6. Data synthesis and analysis

The effect size of each study was calculated considering the "standardized mean difference" (Cohen's [17] *D*) script. The standardized mean difference is a summary statistic that is used in meta-analyses when the included studies report the same outcomes but with different measurements. Based on the value calculated for standardized mean difference, Cohen [17] divides the effect size into minor (0–0.2), moderate (0.2–0.8), and major (>0.8) changes. For this purpose, we converted the results reported as median and range and/or interquartile range to mean and SD [18]. The confidence intervals (CIs) and standard errors (SEs) were also converted to SDs [19], and if none of them was reported, we used the mean difference and *p* value for the meta-analysis.

In this study, we calculated the minimally important differences for individual studies in every outcome measure. The minimally important difference is the smallest quantity of improvement or a change in score that is recognized as an important change by the patient [20]. There are several methods to calculate the minimally important difference for different outcomes, one of them being the distribution-based methods [21]. This method allows expressing observed changes in a standardized metric model. This standardization makes it easier to compare the measures that have different degrees of deviation within the sample, which is typically important in a systematic review.

One of the various ways to calculate the minimally important difference in this method is to use the SD, in which, a change of $>{}^{1}/_{2}$ SD can be recognized as a minimally important difference [22]. We calculated it to find the studies with change equal to or greater than the minimally important difference.

Considering the clinical heterogeneity, we expected to see different approaches for evaluating and reporting treatment effects; thus, we used random-effect models for the meta-analysis.

The heterogeneity of the included studies was tested by reporting the I^2 statistic. We generated summary forest plots for each outcome of the meta-analysis using CMA (Comprehensive Meta-analysis version 2; Biostat Inc., Englewood, NJ, USA).

2.7. Meta-regression

We performed meta-regression of mean age on standardized mean difference to evaluate the possible correlation of advancing age and the change of the placebo response in various outcomes of OAB treatment.

3. Evidence synthesis

3.1. Study characteristics

The initial search found 1982 records. After eliminating duplicates, 583 study titles and abstracts were screened. After reviewing the titles and abstracts, 137 studies were eligible for full-text review. Finally, 57 studies were included for the meta-analysis and were grouped based on the reported outcomes (Fig. 1).

3.1.1. Publication bias

We illustrated funnel plots to show the direction of the publication bias in every outcome. No study was excluded due to the high risk of publication bias. The funnel plots can be found in Supplementary Figure 1.

3.1.2. Risk of bias in the studies

Using the Cochrane Collaboration tool for quality assessment of RCTs, studies were classified to have low, intermediate, or high risk of biases. The most common bias was "attrition bias" (due to incomplete outcome data) in 33% of the publications. The overall quality of the studies was acceptable; thus, no further study was excluded. Fig. 2 shows the risk of bias table and the final summary.

The meta-analysis included 57 studies comprising 12 901 patients. The sample size of the included studies ranged from 12 to 508 patients. Of the assessed outcomes, six were consistently reported: urgency urinary incontinence (UUI) episodes per 24 h (UUI/24 h), urgency episodes per 24 h,

Please cite this article in press as: Mostafaei H, et al. Placebo Response in Patients with Oral Therapy for Overactive Bladder: A Systematic Review and Meta-analysis. Eur Urol Focus (2021), https://doi.org/10.1016/j.euf.2021.02.005

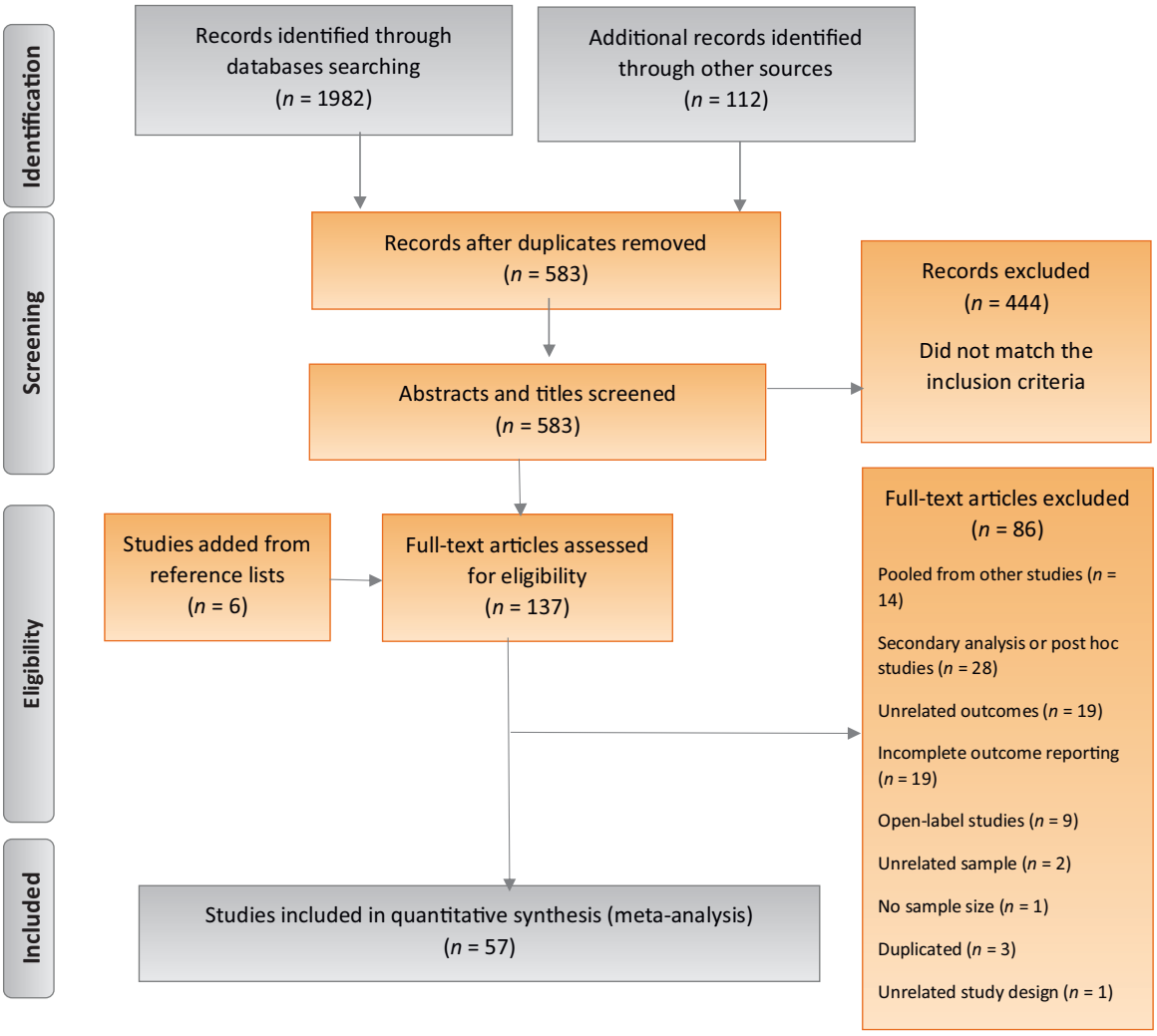


Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.

volume voided per micturition, episodes of nocturia, frequency of micturition per 24 h, and incontinence episodes per 24 h. We chose these outcomes for our comparative analysis since they were the most commonly used endpoints reported in most clinical trials. Realizing the differential effect of placebo with regard to the amplitude of these outcomes, we decided to run meta-analyses for each individual outcome.

3.2. *Principal findings*

3.2.1. *Placebo response in UUI*

A total of 27 RCTs with 6309 patients assessed the change in UUI/24 h after receiving placebo. There was a consistent reduction of UUI/24 h across trials. The standardized mean difference in the number of UUI/24 h was −0.46 (95% CI −0.554 to −0.375; $p < 0.001$). The highest change reported in UUI/24 h was −1.93) in the study by Staskin et al [87] The minimally important difference was observed in 11 of the total 27 studies and SD was not reported in two studies (Table 1 and Fig. 3).

3.2.2. *Placebo response in urgency episodes per 24 h*

A total of 31 studies comprising 8105 patients were included for this outcome. The largest decrease reported in the mean difference was "−3" in the study by Dmochowski et al [59]; most of the studies reported a reduction in urgency episodes per 24 h consistently (Table 1). The standardized mean difference in urgency episodes per 24 h was −0.50 (95% CI −0.62 to −0.40; $p < 0.001$). Most of the studies with a sample size of ≥300 showed at least a reduction in one urgency episode per 24 h. The mean difference was equal to or greater than the minimally important difference in 14 of the total 31 studies, and SD was not reported in two studies (Fig. 3).

3.2.3. *Placebo response in micturition episodes per 24 h*

This outcome included 52 studies comprising 11 998 patients. The micturition episodes per 24 h reduced significantly in most of the studies, with the smallest being −0.4 episodes per 24 h and the largest being −3.3 episodes per 24 h. Contrarily, a minor increase in micturition episodes was reported in one of the studies (Table 1). The

Please cite this article in press as: Mostafaei H, et al. Placebo Response in Patients with Oral Therapy for Overactive Bladder: A Systematic Review and Meta-analysis. Eur Urol Focus (2021), https://doi.org/10.1016/j.euf.2021.02.005

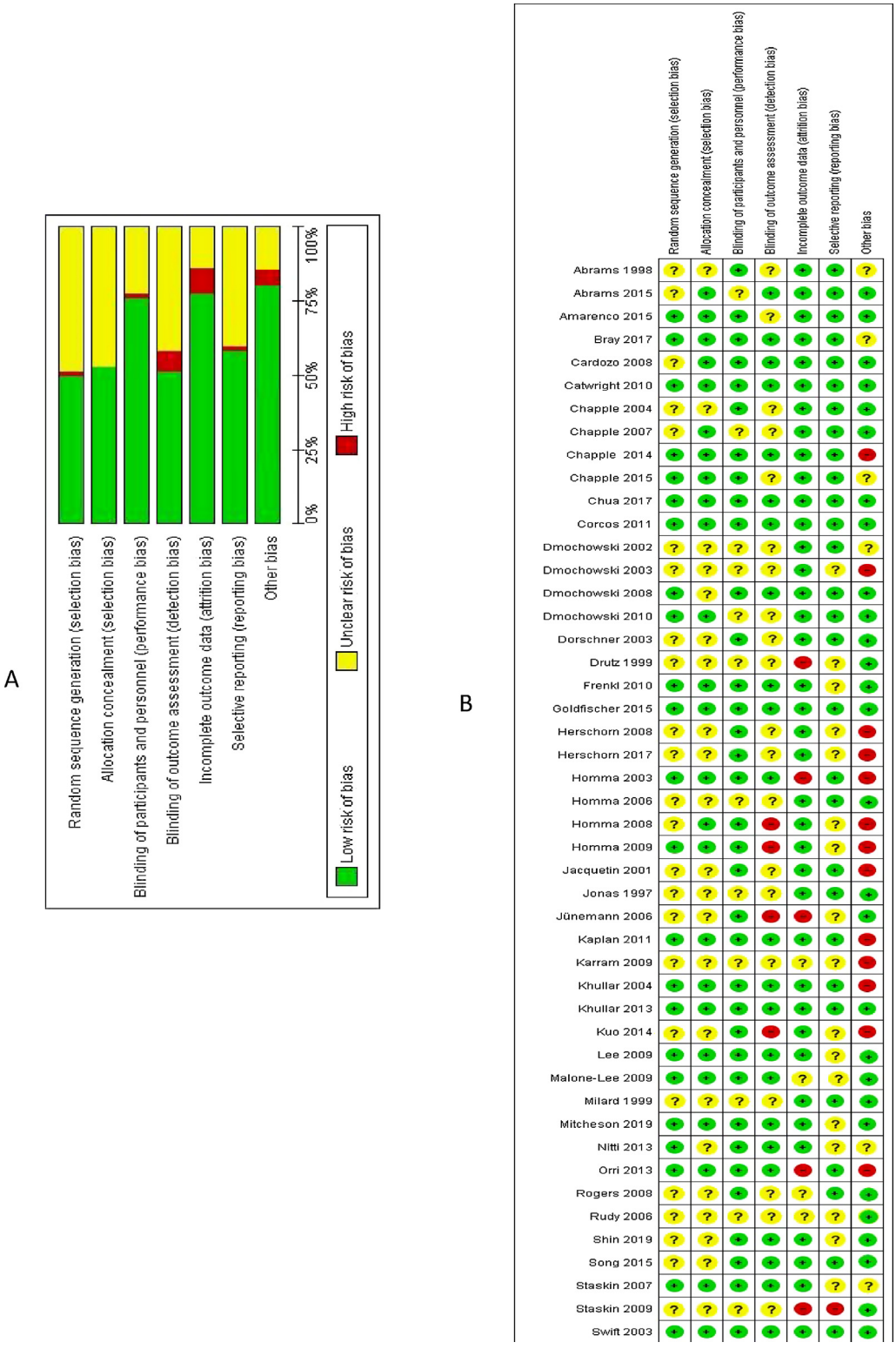


Fig. 2 – Risk of biases table and the final summary.

standardized mean difference was −0.45 (95% CI −0.51 to −0.40; $p < 0.001$). The mean difference was equal to or greater than the minimally important difference in 23 of the total 52 studies, and SD was not reported in four studies (Fig. 3).

3.2.4. *Placebo response in incontinence episodes per 24 h*

A total of 28 studies comprising 6362 patients assessed the effect of placebo on the rate of incontinence episodes per 24 h, and a wide range of Cohen's [17] D (i.e., from −0.16 to −0.83) was seen. The standardized mean

Table 1 – Characteristics of trials assessing efficacy of placebo in micturition episodes per 24 h, UUI episodes per 24 h, urgency episodes per 24 h, incontinence episodes per 24 h, volume voided per micturition, and nocturia episodes[a]

Study (1st author, year, Ref)	Duration (wk)	Sponsored	Micturition episodes per 24 h					UUI episodes per 24 h					Urgency episodes per 24 h					Incontinence episodes per 24 h					Volume voided per micturition					Nocturia episodes				
			n	CD	MD	SD	*p* value	*n*	CD	MD	SD	*p* value	*n*	CD	MD	SD	*p* value	*n*	CD	MD	SD	*p* value	*n*	CD	MD	SD	*p* value	*n*	CD	MD	SD	*p* value
Abrams (1998) [45]	12	Yes	56	−0.44	−1.6	3.6	NR											40	−0.60	−0.9	1.5	NR	56	**0.14**	6	42	NR					
Amarenco (2015) [46]	4	Yes	26	−0.26	−0.7	2.6	NR											29	−0.25	−0.3	1.2	NR	80	**0.26**	14	53.7	NR					
Bray (2018) [47]	12	Yes	42	−0.28	−0.7	2.5	NR	42	−0.29	−0.5	1.7	NR	42	−0.70	−1.4	2	NR						42	**0.21**	40.6	189	NR					
Cardozo (2008) [48]	12	Yes	216	−0.48	−1.3	2.7	NR	158	−0.38	−1.3	2	NR						158	−0.70	−1.4	2	NR										
Catwright (2011) [49]	4	Yes	41	0.03	0.1	1.5	NR	41	−0.65	−0.2	0.6	0.04	41	−0.13	−0.2	1.6	0.01															
Chapple (2004) [50]	12	No	267	−0.37	−1.2	3.3	NR	267	−0.32	−0.6	1.9	NR	267	−0.38	−1.4	3.7	NR	267	−0.34	−0.8	2.3	NR	267	**0.20**	7.4	36.3	NR					
Chapple (2007) [51]	12	Yes	252	−0.37	−0.9	2.5	NR	252	−0.45	−1.1	2.5	NR	252	−0.35	−1.1	3	NR											254	−0.33	−0.32	0.96	NR
Chapple (2014) [52]	12	No	80	−0.52	−1.4	2.7	NR	80	−0.72	−1.8	2.6	NR	80	−0.59	−2.2	3.7	NR						80	**0.15**	7	45.6	NR					
Chapple (2014) [53] (EIGHT)	12	Yes	352	−0.12	−1.6	NR	0.01	352	−0.12	−2.2	NR	0.01	352	−0.12	−3	NR	0.01															
Chua (2018) [54]	12	No	32	−0.30	−0.3	1.1	NR	32	−0.20	−0.1	0.8	NR	32	−0.87	−0.7	0.8	NR											32	−0.33	−0.17	0.51	NR
Corcos (2011) [55]	1	Yes	313	−0.11	−0.4	3.5	NR	313	−0.30	−0.6	1.9	NR	313	−0.08	−0.4	5.3	NR						313	**0.07**	9.3	131.8	NR	309	−0.11	−0.2	1.76	NR
Dmochowski (2002) [56]	12	Yes	132	−0.57	−1.7	3	NR											132	−0.91	−2.7	3	NR										
Dmochowski (2003) [57]	12	Yes	117	−0.52	−1.4	2.7	NR											117	−0.70	−2.1	3	NR	117	**0.14**	9	63	NR					
Dmochowski (2008) [58]	12	No	276	−0.54	−1.8	3.3	NR	276	−0.48	−1.6	3.3	NR											276	**0.32**	17.8	54.8	NR					
Dmochowski (2010) [59]	12	Yes	445	−0.21	−2.1	10.2	NR	445	−0.57	−1.2	2.1	NR	445	−1.42	−3	2.1	NR															
Dorschner (2003) [60]	4	Yes																					49	**0.19**	19.1	101	NR					
Drutz (1999) [61]	12	No	56	−0.27	−1.1	NR	0.03											56	−0.45	−1	2.2	NR	56	**0.29**	12	41	NR					
Frenkl (2010) [62]	4	No	102	−0.28	−0.5	1.8	NR																									
Goldfischer (2015) [63]	12	Yes	151	−0.57	−1.9	3.3	NR											151	−0.63	−2.6	4.1	NR	151	**0.15**	9.8	65	NR					
Herschorn (2008) [64]	12	Yes	201	−0.60	−1.7	2.8	NR	201	−0.67	−1.9	2.8	NR	201	−1.06	−1.5	1.4	NR															
Herschorn (2017) [65] (SYNERGY)	12	Yes	429	−0.36	−1.6	4.5	NR											429	−0.36	−1.3	3.7	NR	429	**0.08**	8.4	99.4	NR					
Homma (2003) [66]	12	Yes	122	−0.95	−3.3	3.5	NR																122	**0.33**	22	66	NR					
Homma (2006) [67]	8	No																167	−0.83	−1.4	1.7	NR									
Homma (2008) [68]	12	Yes	95	−0.55	−1.1	1.9	NR						95	−0.56	−2	3.6	NR						95	**0.05**	2.3	42.7	NR					
Homma (2009) [69]	12	Yes	143	−0.67	−1.1	1.6	NR						143	−0.55	−1.9	3.5	NR						143	**0.28**	9.3	32.6	NR					
Jacquetin (2001) [70]	4	Yes	51	−0.44	−1.2	2.7	NR	51	−0.21	−0.4	1.9	NR						51	−0.21	−0.4	1.9	NR	51	**0.18**	7	40	NR					
Jonas (1997) [71]	4	Yes	44	−0.20	−0.6	3	NR											44	−0.75	−1.5	2	NR	44	**0.31**	11	35	NR					
Junemann (2006) [72]	4	Yes	199	−0.72	−3.1	4.3	NR						199	−0.38	−1.6	4.2	NR	199	−0.53	−1.8	3.4	NR	199	**0.36**	29.5	81.8	NR					
Karram (2009) [73] (VENUS)	12	Yes	350	−0.38	−1.2	3.3	NR						350	−0.97	−2.7	2.8	NR	350	−0.84	−1.9	2.3	NR										
Khullar (2004) [74]	8	Yes	285	−0.57	−1.3	2.3	NR						285	−0.33	−0.9	2.7	NR	285	−0.52	−1.1	2.1	NR	285	**0.36**	18.9	51.9	NR					
Khullar (2013) [75] (SCORPIO)	12	Yes	494	−0.55	−1.3	2.4	NR						494	−0.48	−1.6	3.3	NR						494	**0.28**	12.3	44.2	NR					
Kuo (2015) [76]	12	Yes	302	−0.32	−1.8	5.7	NR	302	−0.14	−1	6.9	NR	302	−0.33	−2.4	7.3	NR	302	−0.19	−1.2	6.3	NR	302	**0.10**	10.4	99.7	NR	302	−0.17	−0.45	2.61	NR
Lee (2010) [77]	12	Yes	79	−0.62	−2.6	4.2	NR						79	−0.42	−0.3	0.6	NR						79	**0.40**	20	49.5	NR	79	−0.41	−0.42	1.03	NR
Milard (1999) [78]	12	Yes	64	−0.61	−1.4	2.3	NR											64	−0.52	−1.3	2.5	NR	64	**0.21**	10	47	NR					

Table 1 (*Continued*)

Study (1st author, year, Ref)	Duration (wk)	Sponsored	Micturition episodes per 24 h					UUI episodes per 24 h					Urgency episodes per 24 h					Incontinence episodes per 24 h					Volume voided per micturition					Nocturia episodes				
			n	CD	MD	SD	*p* value	*n*	CD	MD	SD	*p* value	*n*	CD	MD	SD	*p* value	*n*	CD	MD	SD	*p* value	*n*	CD	MD	SD	*p* value	*n*	CD	MD	SD	*p* value
Malone-Lee (2009) [79]	4	Yes	130	−0.67	−1.6	2.4	NR																130	**0.51**	15.5	30.6	NR					
Mitchelson (2019) [80]	8	No						205	−0.78	−1.3	1.7	NR																				
Nitti (2013) [81]	8	Yes	453	−0.38	−1.1	2.8	NR	453	−0.42	−0.9	2.1	NR	453	−0.13	−0.1	0.6	NR	453	−0.45	−1.05	2.3	NR	453	**0.14**	7	51.3	NR	453	−0.30	−0.38	1.28	NR
Orri (2013) [82] (REMOTE)	12	Yes	12	−0.33	−0.8	2.4	NR																									
Rogers (2008) [83]	12	Yes	167	−0.89	−2.3	2.6	NR	167	−1.08	−1.4	1.3	NR																				
Rudy (2006) [84]	12	Yes	325	−0.17	−1.8	NR	<0.001	325	−0.17	−1.3	NR	<0.001											320	**0.17**	9.4	NR	<0.001	319	−0.16	−0.29	NR	<0.001
Shin (2018) [85]	12	Yes	154	−0.34	−1.4	4.3	NR																									
Song (2015) [86]	12	Yes	72	−0.60	−1.8	2.9	NR	72	−0.24	−0.5	2.2	NR	72	−0.67	−2.7	4	NR						72	**0.30**	12.8	43.1	NR	72	−0.28	−0.3	1.06	NR
Staskin (2007) [87]	12	No	300	−0.72	−2	2.8	NR	300	−0.70	−1.9	2.8	NR	300	−0.64	−2.12	3.3	NR						300	**0.39**	18.9	48.3	NR					
Staskin (2009) [88]	12	Yes	355	−0.71	−2	2.8	NR											355	−0.81	−2.5	3.1	NR	355	**0.07**	3.8	53.8	NR	355	−0.50	−0.65	1.30	NR
Swift (2003) [89]	12	Yes	410	−0.41	−1.2	2.9	NR						410	−0.12	−1.2	9.7	NR						410	**0.32**	13.3	41.1	NR					
Van Kerrebroeck (2001) [90]	12	Yes	508	−0.42	−1.2	2.9	NR																508	**0.34**	14	41	NR					
Vardy (2009) [91] (VIBRANT)	12	Yes	333	−0.17	−1.4	NR	<0.001						333	−0.17	−1.8	NR	<0.001	333	−0.16	−1.2	NR	<0.01										
Wagg (2013) [92] (SOFIA)	12	Yes	393	−0.40	−0.9	2.3	NR						393	−0.48	−1.9	4	NR	393	−0.47	−0.9	2	NR						393	−0.68	−0.27	0.40	NR
Yamaguchi (2007) [93]	12	Yes	395	−0.41	−0.9	2.3	NR	395	−0.29	−0.7	2.4	NR	395	−0.44	−1.3	2.9	NR	395	−0.30	−0.7	2.4	NR	395	**0.35**	11.7	33.8	NR	395	−0.33	−0.3	0.91	NR
Yamaguchi (2011) [94]	12	Yes	309	−0.14	−0.6	4.4	NR	309	−0.38	−1	2.7	NR	309	−0.19	−1	5.3	NR	309	−0.29	−0.9	3	NR						243	−0.10	−0.18	1.79	NR
Yamaguchi (2014) [95]	12	Yes	373	−0.65	−1.4	2.2	NR	255	−0.62	−0.9	1.5	NR	373	−0.65	−1.5	2.3	NR	259	−0.61	−0.9	1.6	NR	358	**0.35**	11.8	34.2	NR	329	−0.51	−0.42	0.83	NR
Yamaguchi (2014) [96]	12	Yes	368	−0.36	−0.9	2.4	NR	368	−0.35	−0.6	1.7	NR	368	−0.51	−1.4	2.7	NR	368	−0.36	−0.7	1.8	NR	368	**0.33**	9.7	29.1	NR	368	−0.34	−0.36	1.06	NR
Yamaguchi (2015) [97]	12	Yes	211	−0.55	−1.2	2.1	NR	132	−0.50	−0.7	1.4	NR	211	−0.62	−1.8	2.9	NR	140	−0.47	−0.6	1.4	NR	211	**0.30**	11.2	37	NR	168	−0.25	−0.24	0.98	NR
Yamaguchi (2016) [98]	8	Yes	147	−0.66	−1.2	1.8	NR	147	−0.48	−0.4	0.9	NR	147	−0.47	−1	2.1	NR	147	−0.49	−0.5	1	NR	147	**0.38**	11.7	30.7	NR	147	−0.19	−0.12	0.63	NR
Yoshida (2018) [99]	12	Yes	369	−0.70	−1.2	1.7	NR	369	−0.94	−1.1	1.1	NR	369	−0.92	−1.8	1.9	NR	369	−0.81	−1.1	1.4	NR	369	**0.20**	7.8	39.6	NR	369	−0.70	−0.47	0.67	NR

CD, Cohen's *D* (standardized mean difference); MD, mean difference; *n*, sample size; NR, not reported; SD, standard deviation; UUI, urgency urinary incontinence.
[a] Reported outcomes in every trial are colored in gray.

Please cite this article in press as: Mostafaei H, et al. Placebo Response in Patients with Oral Therapy for Overactive Bladder: A Systematic Review and Meta-analysis. Eur Urol Focus (2021), https://doi.org/10.1016/j.euf.2021.02.005

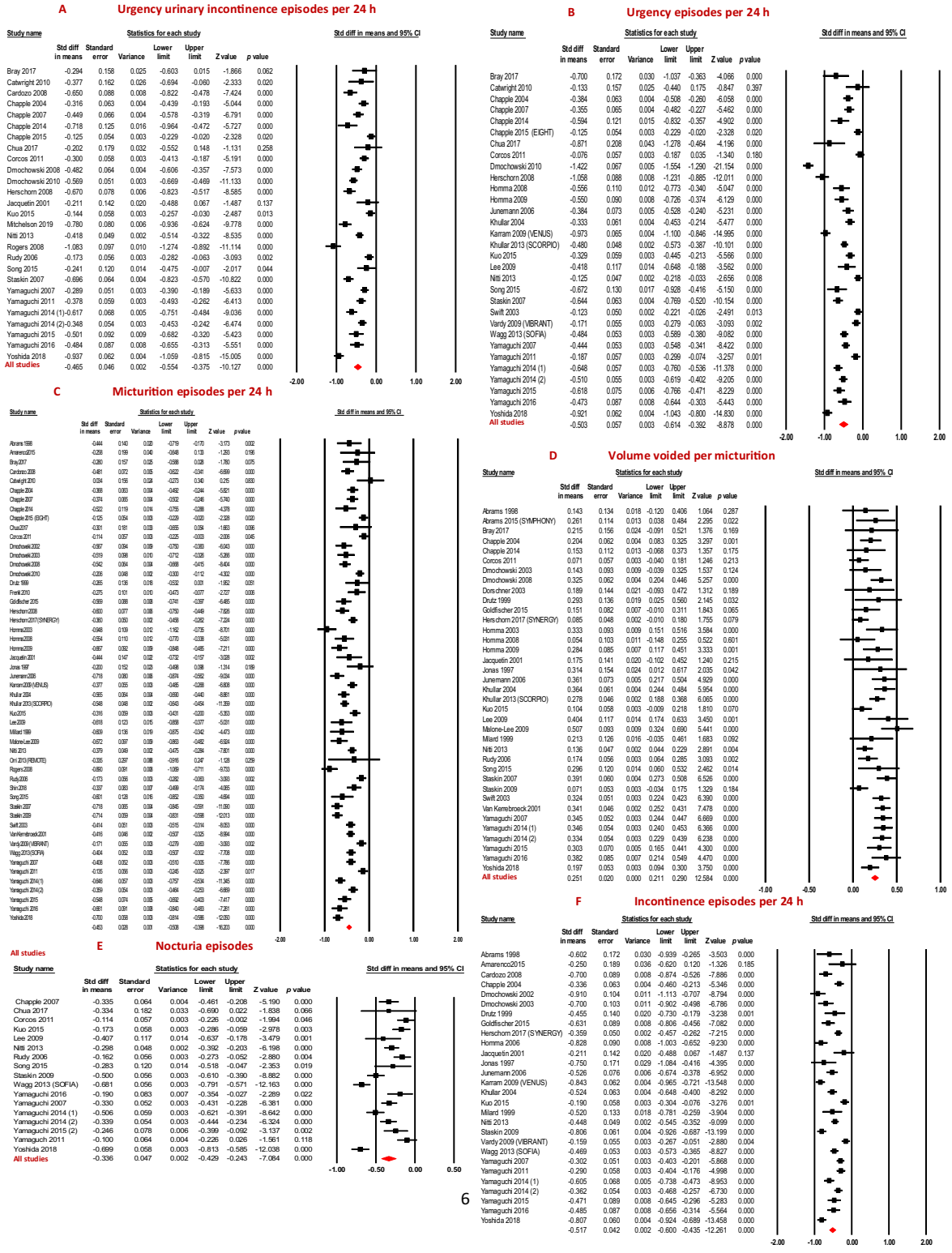


Fig. 3 – Placebo response results of various outcomes.
CI, confidence interval; Std diff, standardized difference.

difference in the number of incontinence episodes per 24 h was −0.517 (95% CI −0.60 to −0.43; $p < 0.001$). The lowest reduction reported in the mean difference for incontinence episodes per 24 h was −0.3 and the highest was −2.74. The mean difference was equal to or greater than the minimally important difference in 13 of the total 28 studies, and SD was not reported in one study (Table 1 and Fig. 3).

Please cite this article in press as: Mostafaei H, et al. Placebo Response in Patients with Oral Therapy for Overactive Bladder: A Systematic Review and Meta-analysis. Eur Urol Focus (2021), https://doi.org/10.1016/j.euf.2021.02.005

3.2.5. Placebo response in volume voided per micturition

A total of 37 studies comprising 8190 patients evaluated the volume voided per micturition. Although the increase in voided volume was not as notable as that in the other outcomes, the increase per micturition was consistent across the studies. The standardized mean difference in the volume voided per micturition was 0.251 (95% CI 0.21–0.29; $p < 0.001$). The minimally important difference was not observed in any of the studies, and SD was not reported in one study (Table 1 and Fig. 3).

3.2.6. Placebo response in nocturia

A total of 17 studies comprising 4587 patients evaluated this outcome. Nocturia episodes were reduced in the placebo arms of most studies assessed. The standardized mean difference of the placebo response was −0.33 with $p < 0.001$. The highest rate of standardized mean difference was reported as "−0.69" in the study by Yoshida et al [99] The studies by Chua et al [54] and Yamaguchi et al [94] showed no statistically significant changes in the nocturia episodes in the placebo arms. The mean difference was equal to or greater than the minimally important difference in four of the total 17 studies, and SD was not reported in one study (Table 1 and Fig. 3).

3.2.7. Other results

Of the included studies, few (16%) were not sponsored by a drug company, while the rest were. The duration of the studies varied, but the majority selected a 12-wk duration for their trials.

3.2.8. Meta-regression model of the placebo response by the increase of age

Considering the increased prevalence of lower urinary tract symptoms with older age, we ran a meta-regression of age-related changes on the placebo response. The meta-regression results of various outcomes are represented in several graphs (Fig. 4). In the meta-regression for incontinence episodes, the regression had a slope of −0.005 (tau square: 0.043) but no statistical significance ($p = 0.11$). The placebo response in decreasing micturition episodes per day was reduced by the increase of age, with a slope of 0.008 ($p = 0.001$). The most dramatic change in the placebo response was seen in the reduction of nocturia episodes.

This meta-regression showed that with the increase of age, patients benefit more from the placebo response in reducing nocturia episodes, with a slope of −0.02 ($p < 0.001$). The regression for urgency episodes along with volume voided per micturition was nearly a plateau and statistically insignificant ($p = 0.34$ and 0.33, respectively). On the contrary, patients were less likely to benefit from the placebo response in reducing urgency urinary incontinence episodes with advancing age (slope: 0.02, $p < 0.001$).

4. Discussion

The aim of the current systematic review and meta-analysis was to determine the range of the placebo response in the oral treatment of OAB. Being an often debilitating "quality of life" disease, many therapeutic strategies including behavioral training, oral medications, and up to finally neuromodulation and bladder surgery are used to alleviate the suffering of affected patients. In a systematic review of placebo responses in various diseases, the highest placebo response was reported in the trials assessing voiding dysfunction drugs [23]. We hypothesized that the placebo response may be statistically and clinically significant in patients with OAB. To test this, we performed a systematic review and meta-analysis of the placebo response in OAB patients by extracting longitudinal data from the placebo arms of OAB RCTs. Our results confirmed the findings of previous studies that felt that the placebo response in OAB is substantial [12,24,25]. Indeed, Lee et al. [25] stated that this effect may be under-reported since the trials tend to highlight the drug efficacy by including more severely affected patients and large study sizes, resulting in a decreased placebo response.

We found that the placebo response was statistically significant in improving all endpoints, including incontinence episodes per 24 h, micturition episodes per 24 h, nocturia episodes, urgency episodes per 24 h, urgency urinary incontinence episodes per 24 h, and volume voided per micturition (Fig. 3). This was in agreement with the study by Lee et al. [25], but they evaluated only three outcomes (incontinence episodes per 24 h, micturition episodes per 24 h, and volume voided per micturition). By contrast, Mangera et al. [24] reported no statistically meaningful change resulting from the placebo response in the urge incontinence episodes per 24 h but statistically significant changes in the other outcomes that may have been due to the lack of sufficient RCTs in their analysis.

The reasons underlying the placebo response remain heterogeneous and not fully elucidated. Potential factors, among others, underlying the placebo response in OAB patients include behavioral aspects, use of voiding diaries, neuropsychological aspects, contextual factors, education of and information given to the patients, as well as the nature of the condition [1,26–29]. For instance, the use of voiding diaries in the management of OAB can be a form of behavior therapy for patients, leading to unconscious changes in their voiding habits resulting in improvement of outcomes [30]. By contrast, OAB has strong psychological components that can be due to psychosomatization, neuroendocrine pathways, and functions of regulatory neurotransmitters [31]. Placebo effect is dependent on the psychological response created in the brain when being in a therapeutic context [32]. This partly explains the reduction of the placebo effect in cases with Alzheimer's disease [33]. Hence, placebo effect might improve the OAB symptoms through neuropsychological pathways [34].

Indeed, this minimal and yet not negligible effect size could be a statistically or practically significant change that is acceptable for health professionals, or a "clinically meaningful" change to the patients [35]. In this study, we calculated the "minimally important difference" for every trial, which is a statistical estimate of a change that can also be meaningful for the patients [20]. In four major outcomes,

Please cite this article in press as: Mostafaei H, et al. Placebo Response in Patients with Oral Therapy for Overactive Bladder: A Systematic Review and Meta-analysis. Eur Urol Focus (2021), https://doi.org/10.1016/j.euf.2021.02.005

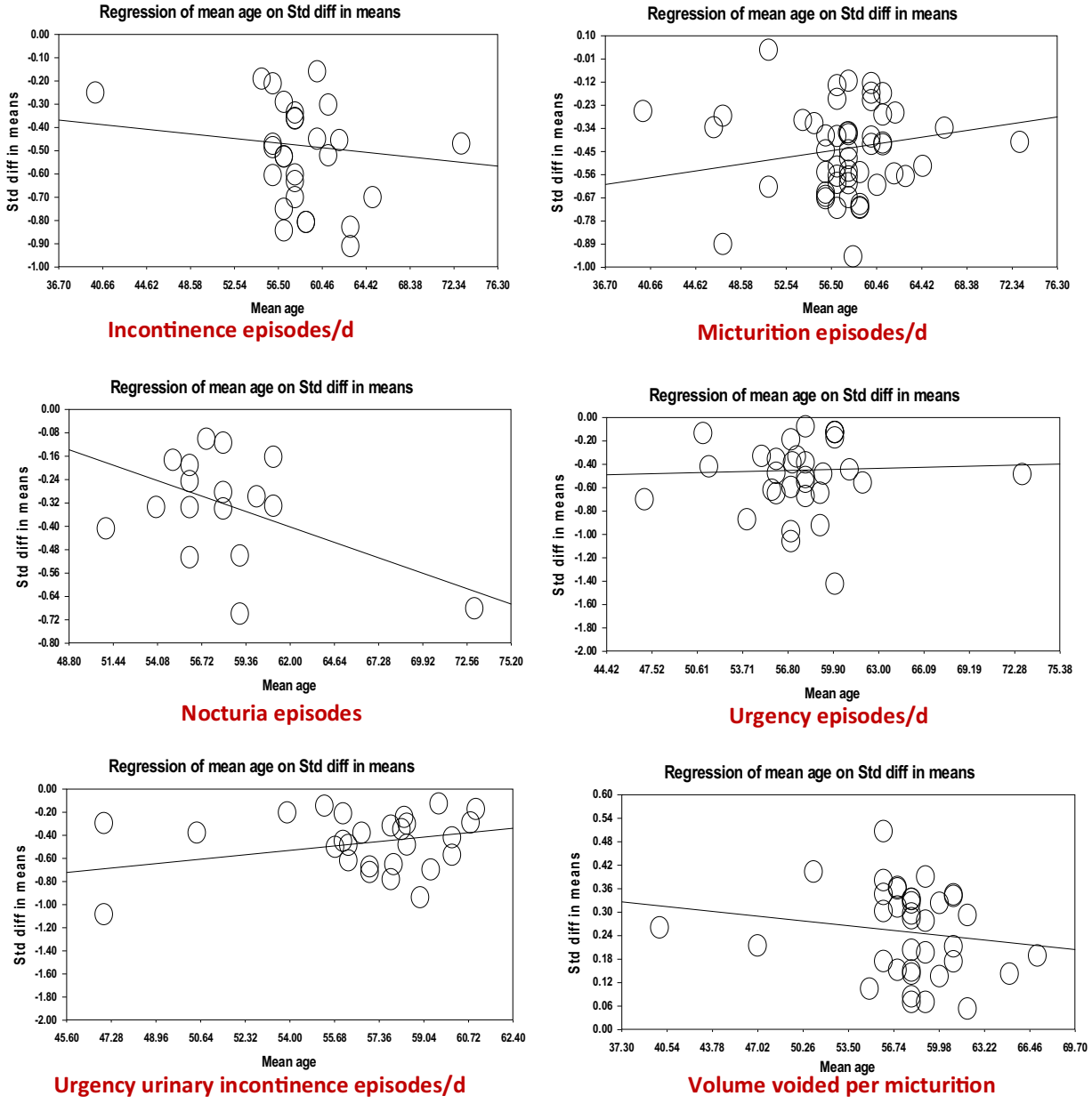


Fig. 4 – Meta-regression results of various outcomes.
Std diff, standardized difference.

the mean difference was equal to or greater than the minimally important difference in almost half of the trials; however, this amount was lower for nocturia. By contrast, a minimally important difference was not observed in any of the trials reporting volume voided per micturition. This indicates the importance of the placebo as a response with possible clinically important change for the patient.

We found that the placebo response is influenced by age. This is in contrast to the findings of Weimer et al. [36] who reported that the placebo response, in general, is not influenced by age. We noticed a dramatic increase in the placebo response in reducing nocturia with advancing age. An explanation could be the higher prevalence of nocturia in the elderly [37]. The meta-regressions (Fig. 4) show a statistically significant change in the opposite direction for UUI and micturition episodes, whereas the other outcomes were nearly neutral. A general assumption regarding the different day- and nighttime differences in alleviating or reducing the placebo response is that patients are less affected by some influencing factors in placebo response at nighttime and hence are less influenced by the nocebo effect. Another explanation is different pathogenesis of nocturia in young and older patients, such that in older patients increased nocturnal urine output plays the most important role in nocturia [37] and behavior changes (e.g., less water consumption) may have a more positive impact in the elderly.

Please cite this article in press as: Mostafaei H, et al. Placebo Response in Patients with Oral Therapy for Overactive Bladder: A Systematic Review and Meta-analysis. Eur Urol Focus (2021), https://doi.org/10.1016/j.euf.2021.02.005

Khullar et al. [34] recommend certain strategies that can be used by care providers to harness the placebo effect to improve clinical outcomes, such as having a good doctor–patient relationship and maintaining constant environmental clues (same time and same room). Caregivers can also enhance the placebo effect by reducing patients' anxiety and encouraging them to talk with the patients who had a successful treatment experience [38]. Another matter of concern is the highly reported adverse events of OAB drugs. Considering "first do no harm", there is no strong evidence on placebo causing harm or adverse events in patients [39]. By contrast, any prescription of unnecessary medication may increase the demand for more advanced diagnostic or therapeutic interventions (i.e., antibiotic therapy for asymptomatic bacteriuria or medical therapy for mild lower urinary tract symptoms), leading to more adverse events and a higher economic burden. In fact, positive results of trials may lead to treatment of patients with low risk who may receive no benefit [40]. In every treatment, there is a group that purely benefits from the medication, and there is the other group that benefits from the placebo response or does not respond to the treatment at all; the latter group is the subject of overtreatment [41].

4.1. Implication for research

The beneficial effects of the placebo in reducing the symptoms in patients with chronic disorders are reported being approximately 75% [4,42,43], and in a systematic review of open-label placebos, improvement of the symptoms has been reported [44]. However, the ethical aspect of placebo prescription, having a degree of deception, is still controversial. Considering all the benefits derived from the placebo, Mangera et al. [24] advise not to prescribe it, and rather have a deeper understanding of the placebo mechanism and utilize it in the management of OAB.

The clinical meaningfulness of the measurable placebo response remains unclear, as no absolute threshold has been set. As clinicians, we should consider how prepared the patients are for receiving treatment and its accompanying side effects for a benefit that might not be optimal. Considering this important point for any medication, we should not only think about the clinical meaningfulness of the study, but also prevent any overtreatment. We can recommend conducting further qualitative studies with OAB patients to elucidate their wants and needs, and important expectations from therapeutic interventions. Only then health professionals can provide a level of meaningfulness for this special condition. In addition, for detecting the superiority of the placebo, some RCTs should be designed to compare the placebo with the no-treatment arm.

4.2. Limitations

One of the limitations of our study was the incomplete report of the outcomes that included not reporting the SD/SE and not reporting the change from baseline (reporting change only in comparison with the placebo). We tried to retrieve these missing data but did not receive any replies from the authors. Not many RCTs had a no-treatment arm, so comparing the placebo arm with a no-treatment arm was not possible. All the placebo responses were the mean differences from baseline in the related outcome. In addition, in the current study, only RCTs with reports of changes in the placebo compared with baseline were included. Therefore, RCTs that compared the placebo with the target medication and lacked a baseline value were excluded from the analysis. Another limitation of this study was the short clinical observation period (mostly 12 wk) in the included studies.

Although first we aimed to evaluate the functional bladder capacity improvement as a main outcome, due to limited data in this issue, we could not analyze this outcome in our review.

5. Conclusions

Placebo has a clear effect on the improvement of OAB signs and symptoms, and the overall placebo responses in various outcomes studied are statistically significant and, in some of the outcomes, possibly clinically significant. This can be influenced by the bothersome nature of OAB and possible mechanisms in the placebo response that may be in the same direction as the improvement of OAB. The placebo response, in particular in nocturia, is also highly influenced by age. However, there is no concrete consensus among health professionals regarding clinical meaningfulness of treatment versus placebo, and having such a definition is mandatory for future trials or systematic reviews.

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

Financial disclosures: Shahrokh F. Shariat 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 (e.g., 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*:** None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.euf.2021.02.005.

References

[1] Beecher HK. The powerful placebo. J Am Med Assoc 1955;159:1602–6.
[2] Kienle GS, Kiene H. The powerful placebo effect: fact or fiction? J Clin Epidemiol 1997;50:1311–8.
[3] Kaptchuk TJ. Powerful placebo: the dark side of the randomised controlled trial. Lancet 1998;351:1722–5.
[4] Kaptchuk TJ, Miller FG. Placebo effects in medicine. N Engl J Med 2015;373:8–9.
[5] Finniss DG, Kaptchuk TJ, Miller F, Benedetti F. Biological, clinical, and ethical advances of placebo effects. Lancet 2010;375:686–95.
[6] Petrie KJ, Rief W. Psychobiological mechanisms of placebo and nocebo effects: pathways to improve treatments and reduce side effects. Annu Rev Psychol 2019;70:599–625.
[7] Hashim H, Blanker MH, Drake MJ, Djurhuus JC, Meijlink J, Morris V, et al. International Continence Society (ICS) report on the terminology for nocturia and nocturnal lower urinary tract function. Neurourol Urodyn 2019;38:499–508.
[8] Abrams P, Kelleher C, Kerr LA, Rogers RG. Overactive bladder significantly affects quality of life. Am J Manag Care 2000;6(11 Suppl):S580–90.
[9] Stewart W, Van Rooyen J, Cundiff G, Abrams P, Herzog A, Corey R, et al. Prevalence and burden of overactive bladder in the United States. World J Urol 2003;20:327–36.
[10] Milsom I, Abrams P, Cardozo L, Roberts R, Thüroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. BJU Int 2001;87:760–6.
[11] Lozo S, Sand PK. The placebo effect in overactive bladder syndrome. In: Cox L, Ronver ES, editors. Contemporary pharmacotherapy of overactive bladder. Cham, Switzerland: Springer; 2019. p. 27–45.
[12] Nabi G, Cody JD, Ellis G, Hay-Smith J, Herbison GP. Anticholinergic drugs versus placebo for overactive bladder syndrome in adults. Cochrane Database Syst Rev 2006.
[13] Chapple CR, Khullar V, Gabriel Z, Muston D, Bitoun CE, Weinstein D. The effects of antimuscarinic treatments in overactive bladder: an update of a systematic review and meta-analysis. Eur Urol 2008;54:543–62.
[14] Higgins J, Altman D, Gøtzsche P, Jüni P, Moher D, Oxman A, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
[15] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;8:336–41.
[16] Howick J, Friedemann C, Tsakok M, Watson R, Tsakok T, Thomas J, et al. Are treatments more effective than placebos? A systematic review and meta-analysis. PLoS One 2013;8:e62599.
[17] Cohen J. Statistical power analysis for the behavioral sciences. 2 New York, NY: Lawrence Erlbaum Associates; 2013.
[18] Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014;14:135.
[19] Chandler J, Cumpston M, Li T, Page MJ, Welch VA. Cochrane handbook for systematic reviews of interventions. Hoboken, NJ: John Wiley & Sons; 2019.
[20] Schünemann HJ, Guyatt GH. Commentary—goodbye M (C) ID! Hello MID, where do you come from? Health Services Res 2005;40:593–7.
[21] Guyatt GH, Osoba D, Wu AW, Wyrwich KW, Norman GR, Group CSCM. Methods to explain the clinical significance of health status measures. Mayo Clin Proc 2002;77:37183.
[22] Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care 2003;41:582–92.
[23] Walach H, Sadaghiani C, Dehm C, Bierman D. The therapeutic effect of clinical trials: understanding placebo response rates in clinical trials—a secondary analysis. BMC Med Res Methodol 2005;5:26.
[24] Mangera A, Chapple CR, Kopp ZS, Plested M. The placebo effect in overactive bladder syndrome. Nat Rev Urol 2011;8:495.
[25] Lee S, Malhotra B, Creanga D, Carlsson M, Glue P. A meta-analysis of the placebo response in antimuscarinic drug trials for overactive bladder. BMC Med Res Methodol 2009;9:55.
[26] Herschorn S, Chapple CR, Snijder R, Siddiqui E, Cardozo L. Could reduced fluid intake cause the placebo effect seen in overactive bladder clinical trials? Analysis of a large solifenacin integrated database. Urology 2017;106:55–9.
[27] van Leeuwen JHS, Castro R, Busse M, Bemelmans BL. The placebo effect in the pharmacologic treatment of patients with lower urinary tract symptoms. Eur Urol 2006;50:440–53.
[28] Balsam PD, Gallistel CR. Temporal maps and informativeness in associative learning. Trends Neurosci 2009;32:73–8.
[29] Wennberg A-L, Molander U, Fall M, Edlund C, Peeker R, Milsom I. A longitudinal population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in women. Eur Urol 2009;55:783–91.
[30] Baines G, Araklitis G, Flint R, Robinson D, Cardozo L. What affects the placebo effect? Eur J Obstet Gynecol Reprod Biol 2020;246:134–7.
[31] Cortes E, Sahai A, Pontari M, Kelleher C. The psychology of LUTS: ICI-RS 2011. Neurourol Urodyn 2012;31:340–3.
[32] Ashar YK, Chang LJ, Wager TD. Brain mechanisms of the placebo effect: an affective appraisal account. Annu Rev Clin Psychol 2017;13:73–98.
[33] Benedetti F, Arduino C, Costa S, Vighetti S, Tarenzi L, Rainero I, et al. Loss of expectation-related mechanisms in Alzheimer's disease makes analgesic therapies less effective. Pain 2006;121:133–44.
[34] Khullar V, Rahnama'i MS, Veit-Rubin N, Cardozo L, Wein AJ. Can we harness the placebo effect to improve care in lower urinary tract dysfunction? ICI-RS 2019. Neurourol Urodyn 2020;39(Suppl 3):S80–7.
[35] Tufanaru C, Munn Z, Stephenson M, Aromataris E. Fixed or random effects meta-analysis? Common methodological issues in systematic reviews of effectiveness. Int J Evidence Based Healthcare 2015;13:196–207.
[36] Weimer K, Colloca L, Enck P. Age and sex as moderators of the placebo response—an evaluation of systematic reviews and meta-analyses across medicine. Gerontology 2015;61:97–108.
[37] Weiss JP, Blaivas JG, Jones M, Wang JT, Guan Z, Group S. Age related pathogenesis of nocturia in patients with overactive bladder. J Urol 2007;178:548–51.
[38] Enck P, Bingel U, Schedlowski M, Rief W. The placebo response in medicine: minimize, maximize or personalize? Nat Rev Drug Discov 2013;12:191.
[39] Nolan T. The placebo effect in general practice. InnovAiT 2019;12,1755738019842596.
[40] Moynihan R, Henry D, Moons KG. Using evidence to combat overdiagnosis and overtreatment: evaluating treatments, tests, and disease definitions in the time of too much. PLoS Med 2014;11:e1001655.
[41] Pezeshki MZ, Pezeshki S. 152: A measure for estimating the magnitude of unnecessary overtreatment, over testing and over preventing. BMJ Open 2017;7(Suppl 1), bmjopen-2016-015415.015152.
[42] Derry S, Conaghan P, Da Silva JAP, Wiffen PJ, Moore RA. Topical NSAIDs for chronic musculoskeletal pain in adults. Cochrane Database Syst Rev 2016;4:CD007400.

Please cite this article in press as: Mostafaei H, et al. Placebo Response in Patients with Oral Therapy for Overactive Bladder: A Systematic Review and Meta-analysis. Eur Urol Focus (2021), https://doi.org/10.1016/j.euf.2021.02.005

[43] Wechsler ME, Kelley JM, Boyd IO, Dutile S, Marigowda G, Kirsch I, et al. Active albuterol or placebo, sham acupuncture, or no intervention in asthma. N Engl J Med 2011;365:119–26.
[44] Charlesworth JE, Petkovic G, Kelley JM, Hunter M, Onakpoya I, Roberts N, et al. Effects of placebos without deception compared with no treatment: a systematic review and meta-analysis. J Evidence Based Med 2017;10:97–107.
[45] Abrams P, Freeman R, Anderström C, Mattiasson A. Tolterodine, a new antimuscarinic agent: as effective but better tolerated than oxybutynin in patients with an overactive bladder. Br J Urol 1998;81:801–10.
[46] Amarenco G, Sutory M, Zachoval R, Agarwal M, Del Popolo G, Tretter R, et al. Solifenacin is effective and well tolerated in patients with neurogenic detrusor overactivity: results from the double-blind, randomized, active-and placebo-controlled SONIC urodynamic study. Neurourol Urodyn 2017;36:414–21.
[47] Bray R, Cartwright R, Cardozo L, Hill S, Guan Z, Khullar V, Tolterodine ER. reduced increased bladder wall thickness in women with overactive bladder. A randomized, placebo-controlled, double-blind, parallel group study. Neurourol Urodyn 2018;37:237–43.
[48] Cardozo L, Heßdörfer E, Milani R, Arañó P, Dewilde L, Slack M, et al. Solifenacin in the treatment of urgency and other symptoms of overactive bladder: results from a randomized, double-blind, placebo-controlled, rising-dose trial. BJU Int 2008;102:1120–7.
[49] Cartwright R, Srikrishna S, Cardozo L, Robinson D. Patient-selected goals in overactive bladder: a placebo controlled randomized double-blind trial of transdermal oxybutynin for the treatment of urgency and urge incontinence. BJU Int 2011;107:70–6.
[50] Chapple CR, Rechberger T, Al-Shukri S, Meffan P, Everaert K, Huang M, et al. Randomized, double-blind placebo- and tolterodine-controlled trial of the once-daily antimuscarinic agent solifenacin in patients with symptomatic overactive bladder. BJU Int 2004;93:303–10.
[51] Chapple C, Van Kerrebroeck P, Tubaro A, Haag-Molkenteller C, Forst H-T, Massow U, et al. Clinical efficacy, safety, and tolerability of once-daily fesoterodine in subjects with overactive bladder. Eur Urol 2007;52:1204–12.
[52] Chapple C, Abrams P, Andersson K-E, Radziszewski P, Masuda T, Small M, et al. Phase II study on the efficacy and safety of the EP1 receptor antagonist ONO-8539 for nonneurogenic overactive bladder syndrome. J Urol 2014;191:253–60.
[53] Chapple C, Schneider T, Haab F, Sun F, Whelan L, Scholfield D, et al. Superiority of fesoterodine 8 mg vs 4 mg in reducing urgency urinary incontinence episodes in patients with overactive bladder: results of the randomised, double-blind, placebo-controlled EIGHT trial. BJU Int 2014;114:418–26.
[54] Chua ME, See IV MC, Esmeña EB, Balingit JC, Morales Jr ML. Efficacy and safety of gabapentin in comparison to solifenacin succinate in adult overactive bladder treatment. Low Urin Tract Symptoms 2018;10:135–42.
[55] Corcos J, Angulo JC, Garely AD, Carlsson M, Gong J, Guan Z, et al. Effect of fesoterodine 4 mg on bladder diary and patient-reported outcomes during the first week of treatment in subjects with overactive bladder. Curr Med Res Opin 2011;27:1059–65.
[56] Dmochowski RR, Davila GW, Zinner NR, Gittelman MC, Saltzstein DR, Lyttle S, et al. Efficacy and safety of transdermal oxybutynin in patients with urge and mixed urinary incontinence. J Urol 2002;168:580–6.
[57] Dmochowski RR, Sand PK, Zinner NR, Gittelman MC, Davila GW, Sanders SW, et al. Comparative efficacy and safety of transdermal oxybutynin and oral tolterodine versus placebo in previously treated patients with urge and mixed urinary incontinence. Urology 2003;62:237–42.
[58] Dmochowski RR, Sand PK, Zinner NR, Staskin DR. Trospium 60 mg once daily (QD) for overactive bladder syndrome: results from a placebo-controlled interventional study. Urology 2008;71:449–54.
[59] Dmochowski RR, Peters KM, Morrow JD, Guan Z, Gong J, Sun F, et al. Randomized, double-blind, placebo-controlled trial of flexible-dose fesoterodine in subjects with overactive bladder. Urology 2010;75:62–8.
[60] Dorschner W, Stolzenburg J, Griebenow R, Halaska M, Brünjes R, Frank M, et al. The elderly patient with urge incontinence or urge-stress incontinence-efficacy and cardiac safety of propiverine. Aktuelle Urol 2003;34:102–8.
[61] Drutz H, Appell R, Gleason D, Klimberg I, Radomski S. Clinical efficacy and safety of tolterodine compared to oxybutynin and placebo in patients with overactive bladder. Int Urogynecol J 1999;10:283–9.
[62] Frenkl TL, Zhu H, Reiss T, Seltzer O, Rosenberg E, Green S. A multicenter, double-blind, randomized, placebo controlled trial of a neurokinin-1 receptor antagonist for overactive bladder. J Urol 2010;184:616–22.
[63] Goldfischer ER, Sand PK, Thomas H, Peters-Gee J. Efficacy and safety of oxybutynin topical gel 3% in patients with urgency and/or mixed urinary incontinence: a randomized, double-blind, placebo-controlled study. Neurourol Urodyn 2015;34:37–43.
[64] Herschorn S, Heesakkers J, Castro-Diaz D, Wang JT, Brodsky M, Guan Z, et al. Effects of tolterodine extended release on patient perception of bladder condition and overactive bladder symptoms. Curr Med Res Opin 2008;24:3513–21.
[65] Herschorn S, Chapple CR, Abrams P, Arlandis S, Mitcheson D, Lee KS, et al. Efficacy and safety of combinations of mirabegron and solifenacin compared with monotherapy and placebo in patients with overactive bladder (SYNERGY study). BJU Int 2017;120:562–75.
[66] Homma Y, Paick J, Lee JG, Kawabe K, Japanese, Group KTS. Clinical efficacy and tolerability of extended-release tolterodine and immediate-release oxybutynin in Japanese and Korean patients with an overactive bladder: a randomized, placebo-controlled trial. BJU Int 2003;92:741–7.
[67] Homma Y, Koyama N. Minimal clinically important change in urinary incontinence detected by a quality of life assessment tool in overactive bladder syndrome with urge incontinence. Neurourol Urodyn 2006;25:228–35.
[68] Homma Y, Yamaguchi T, Yamaguchi O. A randomized, double-blind, placebo-controlled phase II dose-finding study of the novel antimuscarinic agent imidafenacin in Japanese patients with overactive bladder. Int J Urol 2008;15:809–15.
[69] Homma Y, Yamaguchi O, Group IS. A randomized, double-blind, placebo-and propiverine-controlled trial of the novel antimuscarinic agent imidafenacin in Japanese patients with overactive bladder. Int J Urol 2009;16:499–506.
[70] Jacquetin B, Wyndaele J-J. Tolterodine reduces the number of urge incontinence episodes in patients with an overactive bladder. Eur J Obstet Gynecol Reprod Biol 2001;98:97–102.
[71] Jonas U, Höfner K, Madersbacher H, Holmdahl T, Participants of the International Study Group. Efficacy and safety of two doses of tolterodine versus placebo in patients with detrusor overactivity and symptoms of frequency, urge incontinence, and urgency: urodynamic evaluation. World J Urol 1997;15:144–51.
[72] Junemann KP, Hessdorfer E, Unamba-Oparah I, Berse M, Brunjes R, Madersbacher H, et al. Propiverine hydrochloride immediate and extended release: comparison of efficacy and tolerability in patients with overactive bladder. Urol Int 2006;77:334–9.
[73] Karram MM, Toglia MR, Serels SR, Andoh M, Fakhoury A, Forero-Schwanhaeuser S. Treatment with solifenacin increases warning time and improves symptoms of overactive bladder: results from

Please cite this article in press as: Mostafaei H, et al. Placebo Response in Patients with Oral Therapy for Overactive Bladder: A Systematic Review and Meta-analysis. Eur Urol Focus (2021), https://doi.org/10.1016/j.euf.2021.02.005

VENUS, a randomized, double-blind, placebo-controlled trial. Urology 2009;73:14–8.
[74] Khullar V, Hill S, Laval KU, Schiotz HA, Jonas U, Versi E. Treatment of urge-predominant mixed urinary incontinence with tolterodine extended release: a randomized, placebo-controlled trial. Urology 2004;64:269–74, discussion 274-275.
[75] Khullar V, Amarenco G, Angulo JC, Cambronero J, Hoye K, Milsom I, et al. Efficacy and tolerability of mirabegron, a beta(3)-adrenoceptor agonist, in patients with overactive bladder: results from a randomised European-Australian phase 3 trial. Eur Urol 2013;63: 283–95.
[76] Kuo HC, Lee KS, Na Y, Sood R, Nakaji S, Kubota Y, et al. Results of a randomized, double-blind, parallel-group, placebo- and active-controlled, multicenter study of mirabegron, a beta3-adrenoceptor agonist, in patients with overactive bladder in Asia. Neurourol Urodyn 2015;34:685–92.
[77] Lee KS, Lee HW, Choo MS, Paick JS, Lee JG, Seo JT, et al. Urinary urgency outcomes after propiverine treatment for an overactive bladder: the 'Propiverine study on overactive bladder including urgency data'. BJU Int 2010;105:1565–70.
[78] Millard R, Tuttle J, Moore K, Susset J, Clarke B, Dwyer P, et al. Clinical efficacy and safety of tolterodine compared to placebo in detrusor overactivity. J Urol 1999;161:1551–5.
[79] Malone-Lee JG, Al-Buheissi S. Does urodynamic verification of overactive bladder determine treatment success? Results from a randomized placebo-controlled study. BJU Int 2009;103:931–7.
[80] Mitcheson HD, Samanta S, Muldowney K, Pinto CA, Rocha BA, Green S, et al. Vibegron (RVT-901/MK-4618/KRP-114V) administered once daily as monotherapy or concomitantly with tolterodine in patients with an overactive bladder: a multicenter, phase IIb, randomized, double-blind, controlled trial. Eur Urol Feb 2019;75:274–82.
[81] Nitti VW, Auerbach S, Martin N, Calhoun A, Lee M, Herschorn S. Results of a randomized phase III trial of mirabegron in patients with overactive bladder. J Urol 2013;189:1388–95.
[82] Orri M, Lipset CH, Jacobs BP, Costello AJ, Cummings SR. Web-based trial to evaluate the efficacy and safety of tolterodine ER 4 mg in participants with overactive bladder: REMOTE trial. Contemp Clin Trials 2014;38:190–7.
[83] Rogers R, Bachmann G, Jumadilova Z, Sun F, Morrow JD, Guan Z, et al. Efficacy of tolterodine on overactive bladder symptoms and sexual and emotional quality of life in sexually active women. Int Urogynecol J Pelvic Floor Dysfunct 2008;19:1551–7.
[84] Rudy D, Cline K, Harris R, Goldberg K, Dmochowski R. Multicenter phase III trial studying trospium chloride in patients with overactive bladder. Urology 2006;67:275–80.
[85] Shin DG, Kim HW, Yoon SJ, Song SH, Kim YH, Lee YG, et al. Mirabegron as a treatment for overactive bladder symptoms in men (MIRACLE study): efficacy and safety results from a multicenter, randomized, double-blind, placebo-controlled, parallel comparison phase IV study. Neurourol Urodyn 2019;38:295–304.
[86] Song M, Kim JH, Lee KS, Lee JZ, Oh SJ, Seo JT, et al. The efficacy and tolerability of tarafenacin, a new muscarinic acetylcholine receptor M3 antagonist in patients with overactive bladder; randomised, double-blind, placebo-controlled phase 2 study. Int J Clin Pract 2015;69:242–50.
[87] Staskin D, Sand P, Zinner N, Dmochowski R. Trospium Study Group. Once daily trospium chloride is effective and well tolerated for the treatment of overactive bladder: results from a multicenter phase III trial. J Urol 2007;178(3 Pt 1):978–83, discussion 983-4.
[88] Staskin DR, Dmochowski RR, Sand PK, Macdiarmid SA, Caramelli KE, Thomas H, et al. Efficacy and safety of oxybutynin chloride topical gel for overactive bladder: a randomized, double-blind, placebo controlled, multicenter study. J Urol 2009;181:1764–72.
[89] Swift S, Garely A, Dimpfl T, Payne C, Tolterodine Study G. A new once-daily formulation of tolterodine provides superior efficacy and is well tolerated in women with overactive bladder. Int Urogynecol J Pelvic Floor Dysfunct 2003;14:50–4, discussion 54-5.
[90] Van Kerrebroeck P, Kreder K, Jonas U, Zinner N, Wein A, Group TS. Tolterodine once-daily: superior efficacy and tolerability in the treatment of the overactive bladder. Urology 2001;57:414–21.
[91] Vardy MD, Mitcheson HD, Samuels TA, Wegenke JD, Forero-Schwanhaeuser S, Marshall TS, et al. Effects of solifenacin on overactive bladder symptoms, symptom bother and other patient-reported outcomes: results from VIBRANT—a double-blind, placebo-controlled trial. Int J Clin Pract 2009;63:1702–14.
[92] Wagg A, Khullar V, Marschall-Kehrel D, Michel MC, Oelke M, Darekar A, et al. Flexible-dose fesoterodine in elderly adults with overactive bladder: results of the randomized, double-blind, placebo-controlled study of fesoterodine in an aging population trial. J Am Geriatr Soc 2013;61:185–93.
[93] Yamaguchi O, Marui E, Kakizaki H, Itoh N, Yokota T, Okada H, et al. Randomized, double-blind, placebo- and propiverine-controlled trial of the once-daily antimuscarinic agent solifenacin in Japanese patients with overactive bladder. BJU Int 2007;100:579–87.
[94] Yamaguchi O, Nishizawa O, Takeda M, Yoshida M, Choo MS, Gu Lee J, et al. Efficacy, safety and tolerability of fesoterodine in Asian patients with overactive bladder. Low Urin Tract Symptoms 2011;3:43–50.
[95] Yamaguchi O, Uchida E, Higo N, Minami H, Kobayashi S, Sato H, et al. Efficacy and safety of once-daily oxybutynin patch versus placebo and propiverine in Japanese patients with overactive bladder: a randomized double-blind trial. Int J Urol 2014;21:586–93.
[96] Yamaguchi O, Marui E, Kakizaki H, Homma Y, Igawa Y, Takeda M, et al. Phase III randomised, double-blind, placebo-controlled study of the beta3-adrenoceptor agonist mirabegron, 50 mg once daily, in Japanese patients with overactive bladder. BJU Int 2014;113: 951–60.
[97] Yamaguchi O, Marui E, Igawa Y, Takeda M, Nishizawa O, Iked Y, et al. Efficacy and safety of the selective beta3-adrenoceptor agonist mirabegron in Japanese patients with overactive bladder: a randomized, double-blind, placebo-controlled, dose-finding study. Low Urin Tract Symptoms 2015;7:84–92.
[98] Yamaguchi O, Uchida E, Higo N, Minami H, Kobayashi S, Sato H, et al. Optimum dose of once-daily oxybutynin patch in Japanese patients with overactive bladder: a randomized double-blind trial versus placebo. Low Urin Tract Symptoms 2016;8:150–8.
[99] Yoshida M, Takeda M, Gotoh M, Nagai S, Kurose T. Vibegron, a novel potent and selective beta3-adrenoreceptor agonist, for the treatment of patients with overactive bladder: a randomized, double-blind, placebo-controlled phase 3 study. Eur Urol 2018;73:783–90.

Please cite this article in press as: Mostafaei H, et al. Placebo Response in Patients with Oral Therapy for Overactive Bladder: A Systematic Review and Meta-analysis. Eur Urol Focus (2021), https://doi.org/10.1016/j.euf.2021.02.005