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Adult Urology

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ABSTRACT

Purpose: To evaluate the efficacy and safety of combining antimuscarinics with alpha-blockers to treat storage symptoms in men with benign prostatic hyperplasia.

Materials and Methods: Searches were carried out on PubMed, MEDLINE, EMBASE, and Cochrane databases to identify randomized, placebo-controlled trials published before February 15, 2022, assessing the efficacy or safety of antimuscarinics in men with benign prostatic hyperplasia treated with alpha-blockers. Further meta-analyses were performed using standardized mean difference (SMD) and risk ratio (RR).

Results: A total of 12 randomized trials were included in the systematic review. The meta-analysis showed no impact of antimuscarinics on the number of urgencies per day (SMD= -0.23 [95%CI: -0.64–0.17]; p=0.21). However, the use of antimuscarinics was associated with a small reduction of micturition episodes per day (SMD= -0.19 [95%CI: -0.37; -0.01]; p=0.045). With regards to side-effects, post-void residual increased slightly in patients treated with antimuscarinics (SMD=0.26 [95%CI: 0.15; 0.37]; p<0.01). In addition, there was a higher risk of acute urinary retention (RR=3.26 [95%CI: 1.35; 7.86]; p=0.02), dry mouth (RR=3.43 [95%CI: 1.86; 6.32]; p<0.001), and constipation (RR=2.92 [95%CI: 1.48; 5.73]; p<0.001) with the use of antimuscarinics. Finally, the risk of treatment interruption due to adverse events was higher for the patients treated with antimuscarinics (RR=1.74 [95%CI: 1.27; 2.38]; p<0.01).

Conclusion: The addition of antimuscarinics to alpha-blockers was not associated with a substantial reduction in urgencies and micturition episodes in BPH patients with storage symptoms. In addition, the toxicity profile was not in favor of antimuscarinic use in these patients.

INTRODUCTION

Benign prostatic hyperplasia (BPH) results from active proliferation of the transitional zone of the prostate gland. While the prevalence of this condition among men over 65-years of age is high,[1] the severity of related lower urinary tract symptoms and their impact on quality of life (QoL) vary from one patient to another.[2] Bladder outlet obstruction (BOO) is frequently associated with voiding symptoms, but storage symptoms including urgency and frequency are also observed in patients with BPH.[3]

Although BOO has long been considered the predominant etiology for storage symptoms in BPH patients, many recent data suggest that other bladder-related mechanisms may also be involved.[4, 5] For example, a large population-based survey showed that the prevalence of storage symptoms increased with age without any difference between men and women.[2] In addition, several urodynamic studies reported that detrusor over-activity was more frequent in aging men, regardless of the presence of BOO.[6, 7] As a consequence, storage symptoms may be primarily age-related rather than prostate-centered.

Based on these data, the historically contra-intuitive use of antimuscarinics has been proposed to treat storage symptoms in BPH patients. Given the risk of acute urinary retention related to the inhibition of bladder contractions, it has been suggested that antimuscarinics should only be used in patients with a post-void residual (PVR) of less than 200 ml.[8] However, there is contradictory evidence to support the efficacy and safety of antimuscarinics in BPH patients. The last meta-analyses specifically assessing the efficacy of antimuscarinics on storage symptoms in men with BPH were published in 2013[9] and 2014,[8] and several large, randomized, controlled trials (RCTs) have been published since then.[9-12] The meta-analysis published in 2017 by Dahm et al. was not specifically dedicated to the evaluation of antimuscarinics in the setting of BPH and the main endpoint was the evaluation of the global International Prostate Symptoms Score (IPSS), which does not specifically assess storage symptoms.[13]

Against this backdrop, our aim was to provide an updated systematic review and meta-analysis of available data from RCTs evaluating the role of antimuscarinics combined with alpha-blockers to treat BPH patients with storage symptoms using more specific instruments.

MATERIALS AND METHODS

Search strategy

A computerized, bibliographic search of PubMed, MEDLINE, EMBASE, and the Cochrane database was conducted in February 2022 using a free text protocol applying only "Humans" and "English" filters. Different combinations of the following keywords were used: (Muscarinic Antagonists[MeSH] OR Tolterodine[All Fields] OR Fesoterodine[All Fields] OR Propiverine[All Fields] OR Trospium[All Fields] OR Darifenacin[All Fields] OR Solifenacin[All Fields] OR Oxybutynin[All Fields]) AND (Prostatic Hyperplasia[All Fields] OR 'Lower Urinary Tract symptoms'[All Fields]). Studies including the following keywords were excluded from the search: (Review[Publication Type] OR Surgery[MeSH] OR Compliance[MeSH] OR Cost Analysis[MeSH] OR Validation Study[Publication Type]). This systematic review was registered on PROSPERO (registration number CRD42022310941).

Inclusion and exclusion criteria

Based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[14] the Patient-Intervention-Comparison-Outcome-Study design (PICOS) approach was used to further select only double-blinded, placebo-controlled RCTs comparing the efficacy and/or safety of antimuscarinics plus alpha-blockers versus alpha-blockers and placebo to treat BPH patients with storage symptoms. Thus, open-label and retrospective studies as well as case reports were excluded from this systematic review. RCTs evaluating antimuscarinics in patients with storage symptoms related to idiopathic or neurogenic overactive bladder syndrome were also excluded. Diagnosis of storage symptoms had to be based on either patient-reported symptoms, such as frequency, or urgency, or confirmed by urodynamic studies. Intervention drugs had to be explicitly labeled as tolterodine, fesoterodine, propiverine, trospium, darifenacin, solifenacin, or oxybutynin, and studies involving non-oral

administrations of antimuscarinics were excluded. Finally, reports had to evaluate the efficacy and/or safety of antimuscarinics, and those focusing on patient adherence or cost-effectiveness were excluded.

Systematic review process

After the removal of duplicates, 496 reports were independently reviewed by two authors (L.L. and U.P.) based on title and/or abstract screening to further select 52 studies for full-text assessment. Any disagreement regarding study inclusion was resolved by discussion between the two reviewers (L.L. and U.P.) and a third reviewer (T.S.) was asked to decide if no consensus could be reached. Based on the aforementioned inclusion and exclusion criteria, a final cross-checked selection was made of 12 RCTs published between 2005 and 2016.[9-12, 15-23] Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) was used to select the studies during the systematic review process, as presented in the PRISMA flowchart (**Figure 1)**.

Data extraction

Data were independently extracted from all included studies by two authors (L.L. and U.P.) with subsequent cross-checks to ensure their accuracy. Covidence systematic review software was used to create a standardized data extraction form that was created *a priori*. First, study-level data included the reference, study design, study period, country, overall number of patients included, as well as inclusion and exclusion criteria. Second, patient-level data included mean IPSS and age at inclusion. Third, treatment-level data included the drug and dosage administered and the sample size of each intervention group. It should be noted that when several antimuscarinic dosages were evaluated in the included RCTs, only data from the highest dosage group were extracted. Fourth, efficacy outcomes included the number of urgency and

micturitions per day as well as IPSS QoL scores. Finally, safety outcomes included the PVR, and the occurrence of adverse events, such as acute urinary retention (AUR), dry mouth, constipation, and dizziness.

Risk of bias assessment

Two reviewers (L.L. and U.P.) independently assessed the risk of bias (RoB) in each included study using the Cochrane Collaboration RoB tool, which includes seven domains for RCTs: random sequence generation, allocation concealment, participant and staff blinding, outcome assessment blinding, incomplete outcome data, selective reporting, and other sources of bias.[24] Any disagreement with regards RoB assessment was resolved by discussion between the two reviewers (L.L. and U.P.) and a third reviewer (T.S.) was asked to decide if no consensus could be reached.

Data and statistical analyses

A narrative synthesis of included RCTs was first performed. Descriptive statistics were used to summarize extracted baseline study-, patient- and treatment-level data. Continuous outcomes were described using raw mean differences and standard deviation, or alternatively, median and interquartile ranges, whereas frequencies and proportions were used for categorical outcomes. A similar methodology was used to report subjective outcomes for efficacy including QoL data.

In addition, meta-analyses were also performed of objective efficacy and safety data. Our primary endpoint was the efficacy of antimuscarinics using mean changes in urgency and frequency. Raw effect size data in the form of means and standard deviations of the two groups were pooled to calculate standardized mean differences (SMDs). The secondary endpoint was the safety of antimuscarinics including mean changes in PVR calculated using similar a SMD methodology, but also the risk of AUR, dry mouth, constipation, and dizziness calculated using

risk ratios (RRs) with the Mantel-Haenszel method to evaluate the weights of studies for binary outcome data. A random effect model was used to calculate these pooled estimates of treatment effects and their 95% confidence intervals [CIs]. Between-study heterogeneity was assessed using the Higgins and Thompson's I^2 statistic, which quantifies inconsistency across trials to assess the impact of heterogeneity on the meta-analyses. If substantial heterogeneity was observed (I^2 >50%), we attempted to determine possible reasons by examining individual trials and subgroup characteristics to check for outlier studies. Sensitivity analyses were further conducted by excluding outlier studies to evaluate the robustness of the pooled effect estimate. Meta-regression analyses were performed for clinically relevant covariates to further explore potential reasons for heterogeneity and to assess if differences in true effect sizes could be explained outcomes at the study level. Finally, Funnel plots were used to explore bias in the results of meta-analyses.[25] Egger's test was used to assess funnel plot asymmetry for continuous outcomes with intervention effects measured as mean differences.[26] All meta-analyses were performed using open-source R statistical software v.4.0.4 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Overall characteristics of the included studies

Overall, 12 RCTs were included[9-12, 15-23] among which two types of patient populations were identified. In six studies, patients without prior BPH treatment were randomized to alpha-blockers alone or in combination with antimuscarinics.[9, 11, 12, 18-20] Of the remaining studies, five included patients with persistent storage symptoms despite prior treatment with alpha-blockers[10, 16, 17, 21, 23] and one study did not report whether or not alpha-blockers were used before randomization.[22] Several RCTs reported the results for each of the antimuscarinics tolterodine, solifenacin, and propiverine, while two single trials reported the results for oxybutynin and fesoterodine. The sample size in the overall population was 4634 patients of whom 2273 received tamsulosin alone and 2361 received alpha-blockers in combination with antimuscarinics. The overall characteristics of the included studies are shown in **Table 1.**

Baseline patient characteristics

At inclusion, the lower age limit ranged between 40- and 50-years, daily urgency and frequency had to be >1–3 and 8, respectively, and the upper limit of PVR varied from 50–200 ml. Mean IPSS at inclusion ranged from 13.3–29.2 and the primary endpoint was assessed at 12 weeks in most studies. The baseline study characteristics are presented in **Table 1.**

Risk of bias assessment

Despite the high level of evidence of these placebo-controlled RCTs, more than half of the studies had a high or uncertain RoB regarding either random sequence generation, allocation concealment, blinding of participant and personnel, or blinding of outcomes. In these reports, the method of randomization was often not described precisely leading to uncertainty regarding the RoB. **Figure 2** shows the RoB assessment for the included studies.

Efficacy outcomes

Subjective measures

IPSS QoL scores were reported in five trials including 1656 patients. The raw mean reduction of IPSS QoL ranged between -1.08 and -0.25. However, the meta-analysis showed no significant reduction in the IPSS QoL score with the use of antimuscarinics (SMD= -0.48 [95%CI: -1.05; 0.09]; I^2=86% p=0.08; **Figure 3A**). The substantial between-study heterogeneity was caused by the RCTs of Lee et al. and Cai et al. reporting extreme effects.[9, 20] Meta-regression analysis showed that previous treatment with alpha-blockers did not influence the study effect size (p=0.7) and that 94% of the data variability could be attributed to the remaining between-study heterogeneity.

Objective efficacy outcomes

Urgency

Overall, eight RCTs including 3602 patients evaluated the impact of antimuscarinics on urgency.[10-12, 16-18, 20, 23] The raw mean reduction in urgency episodes ranged from 0 to -1.4 per 24 h. However, the meta-analysis showed no significant reduction in the number of urgency episodes per 24 h with the use of antimuscarinics (SMD= -0.25 [95%CI: -0.68; 0.19]; I^2=88% p=0.2; **Figure 3B**). The substantial between-study heterogeneity was caused by the RCT of Lee et al. reporting an extreme effect.[21] After excluding this study, the sensitivity meta-analysis showed a SMD= -0.07 [95%CI: -0.12; -0.02]; p=0.01, I^2=0%.

Meta-regression analysis showed that previous treatment with alpha-blockers did not influence the study effect size (p=0.35) and that 95% of the data variability could be attributed to the remaining between-study heterogeneity.

Frequency

Overall, eight RCTs including 3398 patients evaluated the impact of antimuscarinics on frequency.[10-12, 16, 17, 19, 20, 23] The raw mean reduction in frequency episodes ranged between -0.2 and -1.1 per 24 h. The meta-analysis confirmed the significant reduction in number of frequency episodes per 24 h with the use of antimuscarinics (SMD= -0.19 [95%CI: -0.37; -0.01]; p=0.045, I^2=63%; **Figure 3C**).

The substantial between-study heterogeneity was caused by the RCT of Lee et al. reporting an extreme effect.[21] After excluding this study, the sensitivity meta-analysis showed a SMD= -0.10 [95%CI: -0.19; -0.02]; p=0.01, I^2=0%.

Meta-regression analysis showed that previous treatment with alpha-blockers did not influence the study effect size (p=0.20) and that 67% of the data variability in could be attributed to the remaining between-study heterogeneity.

Risk of publication bias for urgency and frequency

Funnel plots for urgency and frequency including all studies from each meta-analyses showed asymmetry (p=0.07 and p<0.01 for the Egger's test for funnel plot asymmetry, respectively; **Figure 4**).

Objective safety outcomes

Post-void residual and acute urinary retention

Overall, seven RCTs including 2003 patients evaluated the impact of antimuscarinics on PVR.[9, 10, 16, 19, 21-23] The meta-analysis showed a statistically significant increase in PVR with the use of antimuscarinics (SMD=0.26 [95%CI: 0.13; 0.39]; p<0.01, I^2=26%; **Figure 5A**). However, the raw mean increase in PVR ranged from 1–25.5 mL which was not considered clinically

significant. Nevertheless, the impact of antimuscarinics on the risk of AUR was evaluated in nine RCTs,[9, 11, 12, 16-19, 21, 23] which showed an increased relative risk ranging from 0–14.5. The meta-analysis confirmed the significantly increased risk of AUR with the use of antimuscarinics (RR=3.26 [95%CI: 1.35; 7.86]; p=0.02, I^2=0%; **Figure 5B**).

Other adverse events

Overall, the risk of dry mouth, constipation, and dizziness was evaluated in 11,[9-12, 15-19, 21-23] 10, [9-12, 16-19, 22, 23] and four[9, 11, 18, 19]RCTs, respectively. Contradictory findings were observed for all these side-effects with the risk of dry mouth, constipation, and dizziness ranging from 0.94–34.2, 0.97–16.1, and 0.48–8.3, respectively. The meta-analyses showed a significantly increased risk of dry mouth (RR=3.10 [95%CI: 1.71; 5.62]; p<0.001, I^2=76%; **Figure 5C**), constipation (RR=3.52 [95%CI: 2.23; 5.54]; p<0.001, I^2=0%; **Figure 5D**), and dizziness (RR=1.02 [95%CI: 0.22; 4.69]; p=0.9, I^2=34%; **Figure 5E)** with the use of antimuscarinics. The substantial between-study heterogeneity regarding the side-effect dry mouth was caused by the VICTOR trial reporting extreme effects. After excluding this study, the sensitivity meta-analysis showed RR=3.03 [95%CI: 2.30; 4.00]; p<0.001, I^2=0%. Meta-regression analysis for dry mouth showed that previous treatment with alpha-blockers did not influence the study effect size (p=0.22) and that 73% of the variability in our data could be attributed to the remaining between-study heterogeneity. Finally, the risk of treatment interruption due to adverse events assessed in nine RCTs including 3810 patients was higher for those treated with antimuscarinics (RR=1.74 [95%CI: 1.27; 2.38]; p<0.01, I^2=0%, **Figure 5F**).

DISCUSSION

This systematic review and meta-analysis evaluated the efficacy and safety of antimuscarinics to treat storage symptoms in men with BPH. Our principal finding was that treatment with antimuscarinics was not associated with any substantial benefit on urgency and frequency over established treatment with alpha-blockers. Furthermore, there were more side-effects with antimuscarinics compared to alpha-blockers when the data were sufficient to have a pooled comparison.

The main strength of this systematic review is that it addresses a clinically relevant issue that most urologists frequently encounter in their daily practice. It is the first review to specifically evaluate the efficacy of antimuscarinics on storage symptoms in patients with BPH. Indeed, most reviews have evaluated the efficacy of antimuscarinics on total IPSS or Qmax,[13, 27] but these parameters do not specifically assess storage symptoms. It was deemed necessary to fill this gap by evaluating the effect of antimuscarinics on frequency and urgency in a systematic review with a stringent methodology following a pre-established protocol and PRISMA criteria, including randomized, placebo-controlled studies with a high level of evidence. Most previous systematic reviews included open-label studies and did not include a rigorous assessment of the quality of evidence beyond the study design, which despite randomization was often subject to measurement bias.

Tolterodine and solifenacin were the most frequently studied agents in this review and were evaluated in five and four RCTs, respectively. Their efficacy at reducing urgency and micturition was limited. The maximum raw mean reduction of urgency and frequency were -1.4 and -1.1 episodes per day, respectively. As shown previously in the setting of idiopathic overactive bladder,[30] the differences in efficacy between the types of drugs were minimal and the overall efficacy was limited, despite statistically significant but small differences when comparing the efficacy of the drugs with placebo.

A meta-analysis of urgency and frequency showed substantial between-study heterogeneity. The examination of individual trials and subgroup characteristics identified Lee et al. 2011[22] as an outlier for both outcomes, mainly because of its wide confidence interval. Further sensitivity analyses excluding outliers reported statistically significant results showing a non-clinically relevant reduction of urgency (SMD=0.07). Six studies included patients without prior BPH treatment[9, 11, 12, 18-20] while five studies included patients with persistent storage symptoms despite prior treatment with alpha-blockers.[10, 16, 17, 21, 23] However, meta-regression analyses showed that previous treatment with alpha-blockers did not influence the study effect size with regard to urgency and frequency.

The risk of publication bias estimation through funnel plots and Eger's test showed significant asymmetry. The asymmetry was particularly observed for frequency ($p<0.01$) with studies seeming to be missing in areas of non-significance, which could be due to reporting bias. Several factors might explain the limited observed efficacy of antimuscarinics: first, the heterogeneity between studies regarding the selection criteria, and particularly the difference in severity of storage symptoms at baseline, complicates the comparison. Whereas the ADAM, VICTOR, Lee at al. 2011, and Lee et al. 2005 studies[11, 16, 20] required that eligible subjects had ≥1 urgency episodes per 24 h at baseline, the TIMES, Sener et al. 2013, and 2012 Kaplan et al. studies[17, 18, 22] required ≥3 urgency episodes per 24 h at baseline. Second, differences between alpha-blocker treatments may also be accountable for the differences in efficacy between studies. Tamsulosin was the alpha-blocker prescribed in the majority of studies, but other studies included patients with other alpha-blockers prescribed before study initiation. Third, variability in the prescribed dose of antimuscarinic and, in particular, the difference in protocol with flexible-dose escalation (VICTOR and Kaplan et al. 2012 studies[11, 17]) or fixed-dose studies may also account for the variation in treatment efficacy. The variability in efficacy associated with the higher rate of side-effects could lead to a rethink of the prescribing model

by moving towards on-demand treatment, which could be useful to maximize patient compliance and have a reasonable ratio between benefit and adverse effects.

The pathophysiological mechanism leading the patient to have urgency may vary from patient to patient and may also explain the differences in efficacy of symptomatic treatment with antimuscarinics. When urgency is related to an irritative spike in the bladder mucosa triggering uninhibited detrusor contractions, the expected benefit of antimuscarinics may be high. In other patients, sphincter insufficiency due to fatigue and age-related amyotrophy can lead to urine passage through the urethra and trigger an urge to urinate through a uretrovesical reflex mechanism without real bladder hyperactivity. For these patients, the expected efficacy of antimuscarinics would be quite limited. Identifying patients with muscarinic receptor dysregulation resulting in increased sensitivity to acetylcholine due to chronic obstruction warrants further research. Understanding which patients are likely to respond, or not, could significantly shift the outcomes of future similar studies.

One of the main concerns about prescribing antimuscarinics in patients with BPH is the risk of AUR and increased PVR. In this meta-analysis, we found a significant, yet not clinically relevant, PVR mean difference for patients treated with antimuscarinics (SMD=13.3 [95%CI: 5.2; 21.3]; $p<0.01$). However, most of these studies excluded patients with high PVR before treatment. Therefore, these results are not transferable to BPH patients with significant PVR. Notwithstanding the exclusion of patients with high PVR and the small difference in mean PVR after treatment, the risk of AUR was increased more than threefold in patients treated with antimuscarinics (RR=3.26 [95%CI: 1.35; 7.86]; $p=0.02$, $I^2=0\%$), but the overall incidence was less than 3% in all trials.

Our results are consistent with those of a previous meta-analysis. Füllhase et al. reported that add-on combination therapy, compared with alpha-blockers alone, showed a 9.2% reduction in 24-h voiding frequency and a reduction of 1.1 urgency episodes per day.[27] In a

more recent meta-analysis, Dahm et al. evaluated the effect of add-on therapy with an antimuscarinic on the mean change in IPSS score and IPSS QoL, but did not report any findings regarding urgency or frequency. In this study, darifenacin, fesoterodine, solifenacin, oxybutynin, tolterodine, and trospium were not associated with a significant improvement in the IPSS score compared to the control group. Finally, a systematic review by Kaplan et al.[28] reported the results of the randomized, double-blind TIMES, ADAM, VICTOR, MacDiarmid et al. studies and several other prospective studies,[29-31] and concluded that antimuscarinic plus alpha-blocker therapy provided a significant benefit to men with BPH and storage symptoms. However, this was a systematic review without any meta-analysis and the authors did not provide detailed results on mean change in micturition or urgency. The meta-analysis conducted in our study found a significant but small reduction in urgency and frequency. Although our results are in line with current EAU and AUA guidelines,[32, 33] which advocate cautious use of antimuscarinics in patients with high PVR, we also relativize the observed clinical effectiveness of antimuscarinics on storage symptoms. The level of evidence on which the recommendations were based was intermediate (i.e., Level 2) because it was partly derived from open-label studies and post-hoc analysis. Our meta-analysis of high-level evidence studies should be useful in tempering these recommendations and in guiding patients towards on-demand treatment while warning of the risk of side-effects and variable efficacy.

Despite the aforementioned strengths and the add-on value to the existing literature, this study is not devoid of limitations. First, the placebo group cannot be considered a no-treatment group in these studies, especially because patients were required to complete a voiding diary. The latter provides insight into behavioral adjustments that can improve symptoms by educating patients about their voiding habits. Second, the primary endpoint was measured at 12 weeks for most studies. Thus, there is no clear evidence that the efficacy of treatment, however limited, persists beyond this period. Similarly, there is no evidence that the safety profile and side-

effects remain the same after 3 months of treatment in patients with BPH. However, since bladder alterations due to chronic obstruction may take months to completely resolve, studies with longer follow-up may yield different results. Third, the current study did not identify any predictive factors of efficacy of antimuscarinic therapy in patients with BPH. Previous post-hoc analyses showed that a combination therapy with tolterodine and tamsulosin was effective in subjects regardless of whether their baseline prostate size or serum prostate-specific antigen level was above or below the respective study median.[34, 35] Fourth, some studies were not designed specifically to measure the improvement in frequency and urgency as main endpoints and this might lead to possible bias. Finally, the variability between inclusion and exclusion criteria in all the studies included leads to heterogeneity in the severity of baseline symptoms, which complicates the comparison of raw mean reduction in the main outcomes of interest.

CONCLUSION

Treatment with antimuscarinics was not associated with a short-term substantial reduction of urgency and frequency over established treatment with alpha-blockers. Furthermore, there were also more adverse events with antimuscarinics than with alpha-blockers when the data were sufficient for a pooled comparison. Clinicians should be aware of these findings in order to explain to their patients the expected limited short-term benefit of antimuscarinic therapy on storage symptoms and the potential side-effects of this treatment.

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Data availability Statement

The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Figure Legends

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.

Figure 2. Risk of bias assessment.

Figure 3. Comparison of alpha-blockers vs. alpha-blockers plus antimuscarinics on (A) IPSS QoL, (B) urgency/24 h, and (C) and micturition/24 h.

QoL: quality of life; A negative SMD means that the experimental group has a lower mean score than the control group (i.e., a reduction in the assessed outcome for the antimuscarinic group)

Figure 4. Funnel plot for estimation of publication bias risk for urgency and frequency

Figure 5. Comparison of alpha-blockers vs. alpha-blockers plus antimuscarinics on (A) mean increase in post-void residual (PVR), (B) risk of acute urinary retention (AUR), (C) risk of dry mouth, (D) risk of constipation, (E) risk of dizziness, and (F) treatment interruption due to adverse events.

A negative SMD means that the experimental group has a lower mean score than the control group (i.e., a reduction in the assessed outcome for the antimuscarinic group)