Review Article

Efficacy and safety of solifenacin for overactive bladder: An updated systematic review and meta-analysis

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Abstract

Overactive bladder (OAB) is a chronic disease with the symptoms of urgency with or without incontinence. Solifenacin is an antimuscarinic drug that Excels in OAB treatment due to its specific bladder receptor targeting. While previous research had positive outcomes, reports of adverse events (AEs) highlight the need for regular updates on the safety and efficacy of solifenacin for OAB management. This study followed PRISMA 2020 guidelines and was registered to PROSPERO CRD42023445318. A comprehensive search of PubMed, ScienceDirect, and Scopus databases was conducted until July 2023. Data were analyzed using Review Manager version 5.4 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). Solifenacin had a significantly better effect in decreasing urgency episode (mean difference (MD) = −1.09, 95% confidence interval [CI]: −1.29–−0.89, $P < 0.00001$), incontinence episode (MD = −0.56, 95% CI: −0.80–−0.32, $P < 0.00001$), micturition frequency (MD = −1.01, 95% CI: −1.16–−0.85, $P < 0.00001$), nocturia episode (MD = −0.13, 95% CI: −0.25–−0.01, $P = 0.04$), and had a higher urine volume (MD = 26.88, 95% CI: 24.17–29.59, $P < 0.00001$) per 24 h compared to placebo. Solifenacin had a significant number of AEs compared to placebo (MD = 1.75, 95% CI: 1.25–2.45, $P = 0.001$). Solifenacin significantly decreased urgency episode, incontinence episodes, micturition frequency, and nocturia episode, and had a higher urine volume per 24 h. There was a significant number of AEs in patients receiving solifenacin.

Keywords: Incontinence, overactive bladder, placebo, solifenacin, urgency

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INTRODUCTION

Overactive bladder (OAB) is a condition involving urinary urgency along with increased daytime urination and nocturia, with or without urge incontinence, and without any signs of infection or underlying medical issues.[1] Around 10%–15% of the worldwide population struggle with OAB. Like other chronic conditions, patients with OAB experience significantly decreased quality of life, and most of them complained of urgency as the main symptom.[2] The goal of the therapy is to decrease the symptoms and increase the health-related quality of life.[3]

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There are several treatment approaches to OAB, but pharmacological therapy is still the mainstay treatment. The primary pharmacotherapy for OAB is the antimuscarinic agents.[4] This type of drug affects bladder function through the neuronal (parasympathetic nerve) and nonneuronal acetylcholine pathways.[5] Solifenacin succinate is one of the newest antimuscarinic drugs with functional selectivity for the bladder in animals.[6] *In vivo* study revealed that solifenacin has a higher affinity and specificity for the muscarinic-3 (M3) subtype.[7] Solifenacin comes in 5 mg and 10 mg formulations, taken once a day.[8] In terms of safety, antimuscarinic agents are linked with various adverse events (AEs), including dry mouth, constipation, urinary retention, and blurred vision due to the distribution of muscarinic receptors outside the bladder.[5]

Solifenacin is still one of the drug choices to treat OAB patients. The last meta-analysis assessing the efficacy of solifenacin for OAB patients was conducted by Luo *et al*. in 2012.[9] They stated that solifenacin had a significant effect in reducing urgency episode, incontinence episode, micturition frequency, and nocturia episode, and improved urine volume voided compared to placebo. They reported that solifenacin exhibited notable AEs such as dry mouth, constipation, and blurred vision compared to placebo.[9] This study was conducted more than 10 years ago. Hence, it is crucial to reassess the effectiveness and safety of solifenacin in accordance with the most recent publication. This study aims to provide updates on the latest systematic review and meta-analysis of solifenacin for OAB patients.

METHODOLOGY

Study design

This updated systematic review and meta-analysis, registered with PROSPERO (CRD42023445318) and following the PRISMA 2020 guidelines, aims to comprehensively assess the efficacy and safety of solifenacin for the treatment of OABby synthesizing data from relevant randomized controlled trials (RCTs) and observational studies.

Search strategy

A meticulous search strategy was implemented by a proficient team comprising four authors (IGYPA, RNHS, PAS, and AP) across reputable scientific databases such as PubMed, ScienceDirect, and Scopus, culminating in July 2023. The search was strategically crafted using pertinent keywords, including "solifenacin," "placebo," and "overactive bladder." Initial screening was conducted to identify articles aligning with predetermined criteria and subsequently subjected to rigorous full-text screening. Any discrepancies were judiciously resolved through thorough discussions moderated by DPA, ensuring methodological consistency and reliability.

Eligibility criteria

The inclusion criteria for this systematic review encompass studies involving only adult patients, with RCTs as the preferred study design, and articles written in English, focusing on the primary outcomes of interest related to OAB symptoms, including urgency, incontinence, and micturition frequency, while the exclusion criteria involve the exclusion of studies with a pediatric population and articles not written in English, aiming to ensure a focused and rigorous selection of studies that align with the research objectives by specifying the type of study design, patient population, language, and primary and secondary outcomes of interest, thereby streamlining the identification and inclusion of studies relevant to the topic of OAB.

Data extraction

Two independent reviewers extracted data using a standardized form. Discrepancies were resolved through discussion or consultation with a third reviewer. A systematic and structured approach was employed to extract pertinent information, including but not limited to details such as first author, publication year, study design, country of origin, sample size, age, sex, changes in symptoms per 24 h, follow-up duration, and AEs. This meticulous process ensured comprehensive data acquisition, essential for subsequent analysis and interpretation.

Data analysis

Review Manager version 5.4 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) was used in analysis. Continuous data were meticulously evaluated using mean difference (MD) and dichotomous data with odds ratio accompanied by robust statistical analyses incorporating 95% confidence intervals (CIs) and *P* values. In instances, where multiple studies presented identical data, meta-analysis was seamlessly executed. The robustness of the findings was further substantiated through a rigorous assessment of heterogeneity using Cochran's Q and I2 statistics. Statistical homogeneity ($P > 0.1$, $I^2 < 50\%$) warranted the application of a fixed-effects model; conversely, a random-effects model was judiciously employed in instances of statistical heterogeneity. A significance level of $P < 0.05$ was meticulously adhered to ensuring the robustness and reliability of the findings. Notably, ethical approval was deemed unnecessary for this systematic review and meta-analysis, given its noninvasive nature.

Quality appraisal

To ascertain the methodological integrity of the selected studies, the Cochrane risk of bias 2 (RoB2) tool was meticulously employed. This tool encompasses five

distinct domains, including bias stemming from the randomization process, bias due to deviations from the intended intervention, bias related to missing outcome data, bias in outcome measurement, and bias in the selection of reported outcomes. Each of the included studies underwent independent assessment by two authors (IGYPA and RHS) using RoB2. Any discrepancies in bias assessment or justifications were resolved through discussion with the other authors, reaching a consensus until a final agreement was reached. The authors obtained an overall summary of bias risk (low, some concern, and high) for each specific outcome, determining the study's overall risk based on the highest level of bias in any assessed domain.

RESULTS

Study selection

The search resulted in 3094 records, of which 1544 records were removed due to duplicates and irrelevances. There left 1550 potentially relevant articles after the initial review. After a thorough examination of full texts, eight studies met the inclusion criteria for this systematic review. The process is depicted below in the PRISMA flowchart [Figure 1].

Risk of bias

In this study, eight RCTs were classified as having a low risk of bias. Further details on the assessment's quality are summarized in Figure 2.

Study characteristics

Eight studies with a total of 4387 participants with OAB were identified. There were 2390 patients allocated to the solifenacin group, while 1997 were allocated to the placebo group. Most of the studies included in this review were conducted across multiple countries. Table 1 provides a summary of the subject's characteristics.

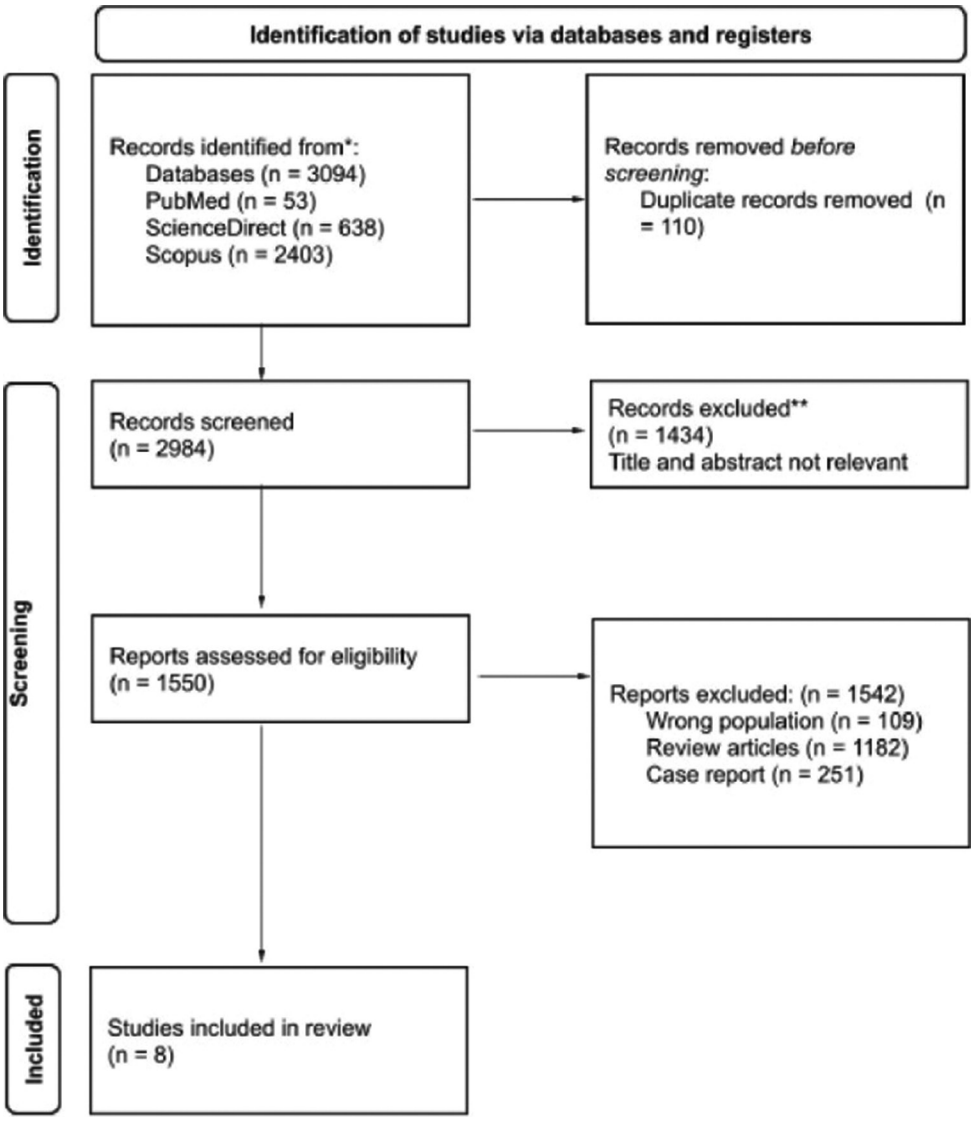

Figure 1: PRISMA flow diagram of search strategies

Patients characteristics

There are eight studies included with a total of 4387 patients with OAB. Among them, 2390 participants were using solifenacin, and 1997 participants were in the placebo group.

Change in urgency episode

Seven studies were examined in the analysis of urgency episodes [Figure 3] involving 2239 patients receiving solifenacin and 1937 patients receiving placebo. The forest plot, utilizing a fixed-effects model, revealed that compared to the placebo group, patients receiving solifenacin experienced significantly fewer urgency episodes per 24 h (MD = −1.09, 95% CI: −1.29–−0.89, $P < 0.00001$).

Change in incontinence episode

Seven studies were examined in the analysis of incontinence episodes [Figure 4], involving 2239 patients receiving solifenacin and 1937 patients receiving placebo. The forest plot, utilizing a random-effects model, demonstrated that compared to the placebo group, the group receiving solifenacin experienced significantly fewer incontinence episodes per 24 h (MD = −0.56, 95% CI: −0.80–−0.32, $P < 0.00001$).

Table 1: Study characteristics

Study	Patient number		Mean age (years)	
	Male	Female	Male	Female
Cardozo, 2004	290	281	55.9±14.2	55.4±13.8
Cardozo, 2008	505	223	57.7	57.9
Chapple, 2004 A	266	253	58.1±13.4	57.8±13.7
Chapple, 2004 B	37	36	N/A	N/A
Crosby, 2011	377	374	N/A	N/A
Herschorn, 2017	151	60	62.9±11.8	61.2±12.2
Karram, 2009	372	367	N/A	N/A
Vardy, 2009	386	382	59±13	60±12
Yamaguchi, 2007	383	395	60.4±13.3	60.8±12.5

N/A: Not available

Change in micturition frequency

In the evaluation of micturition frequency reduction [Figure 5], a total of eight studies were examined, involving 2390 patients receiving solifenacin and 1997 patients receiving placebo. The forest plot, utilizing a fixed-effects model, showcased that compared to the placebo group, patients receiving solifenacin experienced a significant decrease in micturition frequency per 24 h (MD = −1.01, 95% CI: −1.16–−0.85, $P < 0.00001$).

Change in nocturia episode

Two studies were examined in the analysis of nocturia episodes [Figure 6], involving 534 patients receiving solifenacin and 455 patients receiving placebo. The forest plot, employing a fixed-effects model, illustrated that compared to the placebo group, patients receiving solifenacin had significantly fewer nocturia episodes per 24 h (MD = −0.13, 95% CI: −0.25–−0.01, $P = 0.04$).

Change in urine volume

Three studies were examined to analyze the change in urine volume [Figure 7] involving 686 patients receiving solifenacin and 684 patients receiving placebo. The

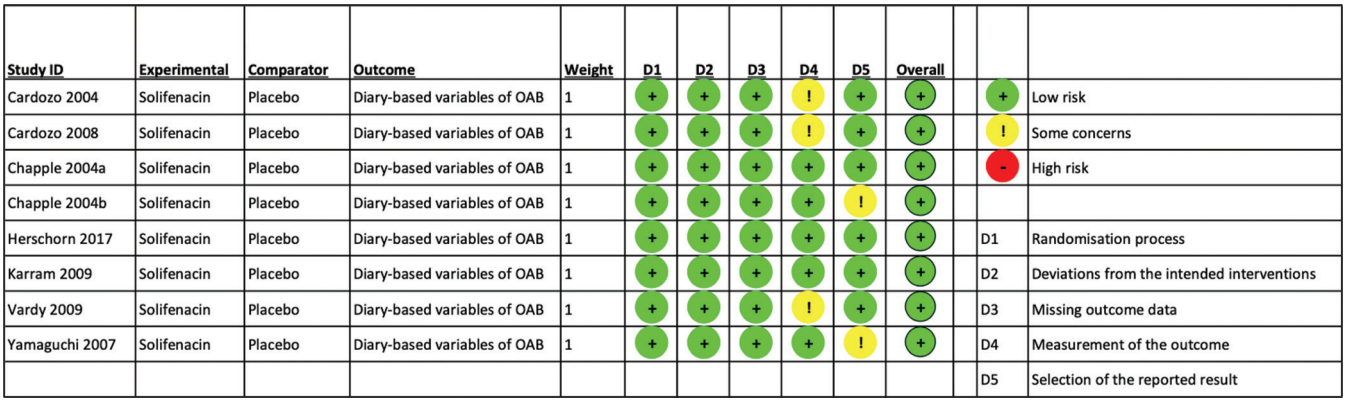

Figure 2: Risk of bias

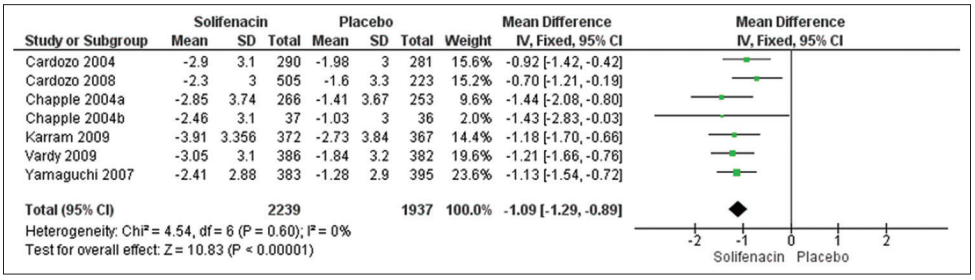

Figure 3: Forest plot of change in urgency episode per 24 h. CI: Confidence interval, SD: Standard deviation, IV: Intravenous

forest plot, utilizing a fixed-effects model, demonstrated that compared to the placebo group, patients receiving solifenacin had a significantly higher volume voided per 24 h (MD = 26.88, 95% CI: 24.17–29.59, $P < 0.00001$).

Adverse events

In evaluating the AEs [Figure 8], eight studies were examined, involving 2390 patients receiving solifenacin and 1997 patients receiving placebo. The forest plot with a random-effects model revealed that compared to the placebo group, patients receiving solifenacin had a significantly higher increase in the number of AEs (MD = 1.75, 95% CI: 1.25–2.45, $P = 0.001$).

DISCUSSION

OAB is a condition involving urinary urgency along with increased daytime urination and nocturia, with or without urge incontinence and without any signs of infection or underlying medical issues.[1] The occurrence of OAB and its symptoms rises with advancing age in both males and females.[10] In 2013, the prevalence of OAB was 7.2% globally divided into 7.7% males and 6.7% females. In terms of age, the prevalence was the highest in people more than 74 years old.[11]

Solifenacin is one of the newest antimuscarinic drugs that show selectivity for the bladder over other organs.[6] It is also an anticholinergic agent that is highly selective to M3 receptors.[12] Solifenacin exerts its therapeutic effects on frequency and urgency by inhibiting the binding of acetylcholine to M3 receptors in the bladder, consequently reducing detrusor muscle contractility and inhibiting its contractions.[13]

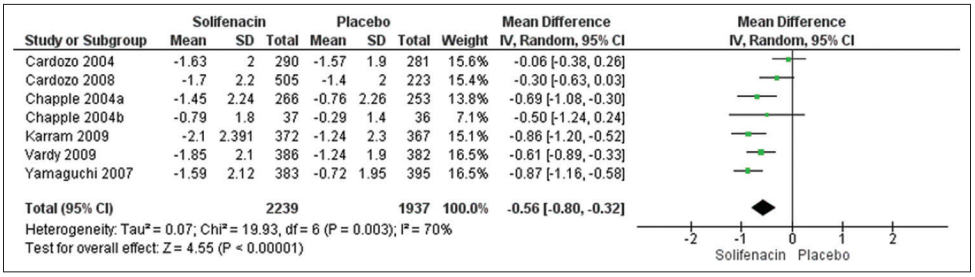

Figure 4: Forest plot of change in incontinence episode per 24 h. CI: Confidence interval, SD: Standard deviation, IV: Intravenous

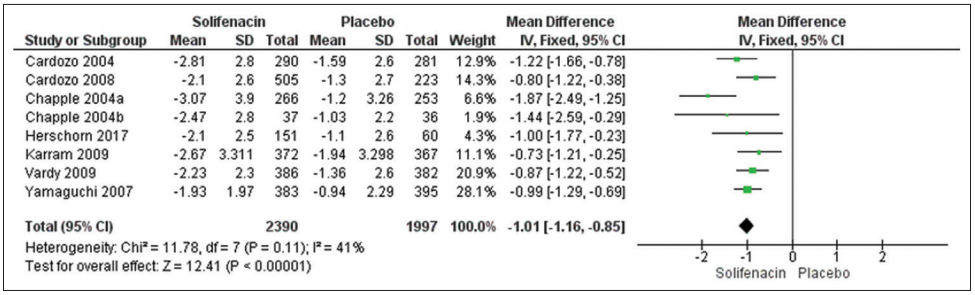

Figure 5: Forest plot of change in micturition frequency per 24 h. CI: Confidence Interval, SD: Standard deviation, IV: Intravenous

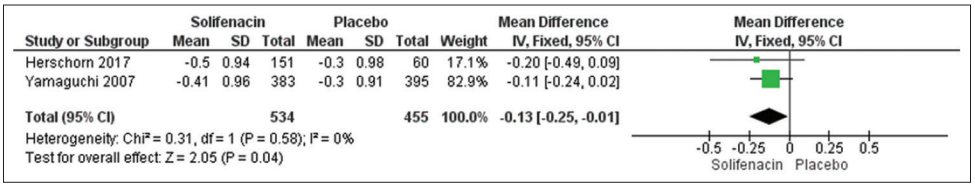

Figure 6: Forest plot of change in nocturia episode per 24 h. CI: Confidence Interval, SD: Standard deviation, IV: Intravenous

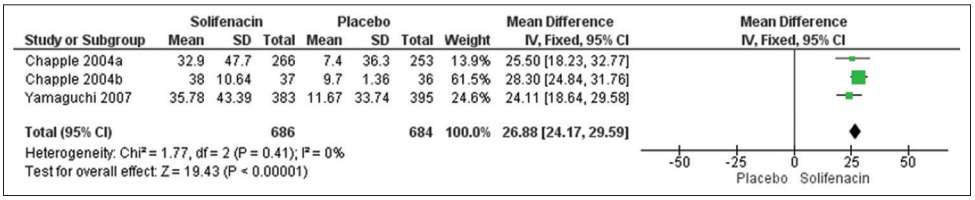

Figure 7: Forest plot of change in urine volume voided per 24 h. CI: Confidence Interval, SD: Standard deviation, IV: Intravenous

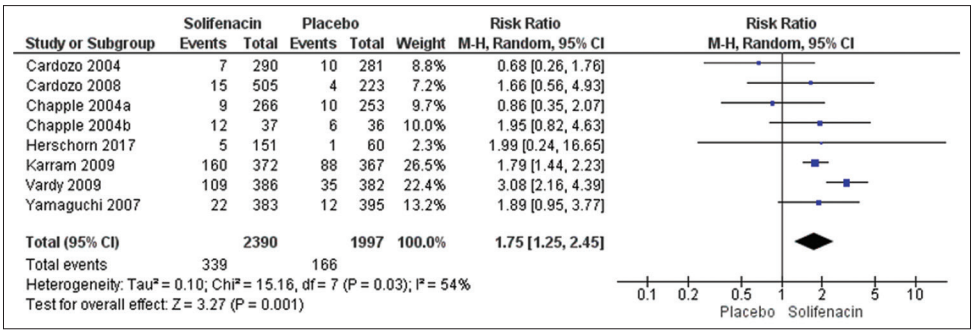

Figure 8: Forest plot of adverse events of using solifenacin versus placebo. CI: Confidence Interval, SD: Standard deviation, IV: Intravenous

In our study, it was found that the group of patients receiving solifenacin experienced significantly fewer urgency episodes per 24 h ($P < 0.00001$), fewer incontinence episodes per 24 h ($P < 0.00001$), fewer nocturia episodes per 24 h ($P = 0.04$), and significantly higher volume voided per 24 h ($P < 0.00001$). Yamaguchi *et al.* found that OAB patients receiving solifenacin once daily at doses of 5 and 10 mg significantly improved more than in the placebo group. Significant reductions were observed in episodes of urgency and incontinence ($P < 0.001$). In addition, solifenacin showed a significant decrease in nocturia episodes ($P = 0.021$) and an improvement in urine voided volume ($P = 0.009$) compared to the placebo.[14] A study by Vardy *et al.* stated that solifenacin significantly improved quality of life (QOL) by reducing the daily episodes of urgency, incontinence, and frequency but not nocturia ($P < 0.0001$; $P = 0.002$; $P < 0.0001$; and $P = 0.341$).[15] We found that patients receiving solifenacin experienced a significant decrease in micturition frequency per 24 h ($P < 0.00001$). In 2009, Karram *et al.* conducted a study that aligns with these findings, reporting that patients in the solifenacin therapy group experienced a significant decrease in urgency, incontinence, and micturition frequency, surpassing the reductions observed in the control group (2.24 ± 3.04 vs. 3.30 ± 3.84, $P < 0.0001$; 0.72 ± 1.45 vs. 1.32 ± 2.64, $P < 0.0001$; and 8.98 ± 3.25 vs. 9.76 ± 3.50, $P = 0.001$).[16]

According to Herschorn *et al.*, solifenacin had significantly better effects in urgency, incontinence, and frequency (4.7 ± 3.2 vs 3.8 ± 2.0, $P < 0.001$; 5.2 ± 3.3 vs 4.4 ± 2.5; 10.4 ± 2.7 vs 10.2 ± 2.5), but had no significant effect in main volume voided (159 ± 63.1 vs 160.8 ± 52.8).[17,18] Meanwhile, Cardozo *et al.* conducted a study which reported that patients undergoing solifenacin therapy had significantly higher main volume voided in 24 h than the placebo group (30.75 vs. 10.67, $P = 0.0001$).[19] Cardozo *et al.* in 2008 also stated that solifenacin at 5 or 10 mg doses demonstrated significantly greater efficacy in reducing urgency and incontinence episodes within 24 h compared to placebo (1.58 vs. 1.96; 1.63 vs. 2.01).[20]

Like other antimuscarinic agents, solifenacin can cause various side effects, including constipation, dry mouth, and blurred vision. Our results suggest that patients receiving solifenacin, compared to the placebo group, had a significantly higher increase in the number of AEs ($P = 0.001$). In a study by Cardozo *et al.*, AEs such as constipation, dry mouth, and blurred vision occurred in 23.1%, 9.1%, and 5.9% of patients receiving 10 mg of solifenacin. In contrast, they occurred in 2.3%, 2.0%, and 2.3% of the placebo group. No instances of severe dry mouth were reported.[19]

This review has several limitations. Only a few new studies have been conducted on using solifenacin for OAB patients. All of the studies in this review focused on investigating the safety and efficacy of solifenacin for adults, not for children and the elderly. Further investigation is needed to ascertain the safety and effectiveness of solifenacin in both the pediatric and elderly populations, given that OAB can also manifest in these demographic groups.[21] The duration of follow-up also differs between each study. A standardized follow-up duration is needed to understand solifenacin use for OAB patients better. In future, more research about the safety and efficacy of solifenacin needs to be conducted regularly. They must contain all desired outcomes, including episodes of urgency, incontinence, frequency, voided volume, and nocturia, to thoroughly understand solifenacin's safety and efficacy for patients with OAB.

CONCLUSIONS

Solifenacin is one of the treatment choices to treat OAB patients. Solifenacin significantly decreased urgency episodes, incontinence episodes, micturition frequency, and nocturia episodes and had a higher urine volume per 24 h. It is worth noting that there is a significant number of AEs in patients receiving solifenacin.

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Conflicts of interest

There are no conflicts of interest.

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