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Efficacy and Safety of Mirabegron Plus Solifenacin Combination Therapy in Comparison with Solifenacin Monotherapy in Overactive Bladder: A Systematic Review and Meta-analysis

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Background and Objective: Overactive bladder (OAB) is one of the most frequent reason for lower urinary tract symptoms (LUTS) in both genders, and is associated with significant impact on quality of life. Antimuscarinic agents represent the cornerstone of pharmacological management of OAB but persistence with treatment is limited by insufficient efficacy and undesirable side effects. Studies have shown that combination of β3-adrenoceptor agonist, mirabegron with solifenacin can be a promising alternative for patients with severe symptoms of OAB, not responding to standard dose of solifenacin monotherapy.

The purpose of this review was to evaluate the efficacy and safety of recently approved combination therapy of mirabegron 50 mg and solifenacin 5 mg in comparison with 5 mg and 10 mg of solifenacin monotherapy in patients with OAB.

Material & Methods: An electronic database search was carried out in EBM (Evidence Based Medicine) Reviews, Cochrane Library and PubMed using keywords Mirabegron, Solifenacin, Combination, Overactive bladder based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guideline to include relevant randomized controlled trials (RCT)s. The meta-analysis was performed by Review Manager 5.4 (RevMan 5.4) software.

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Results: Total 907 studies were identified out of which, 4 RCTs involving a total of 5339 patients were eligible for analysis. In comparison to solifenacin 5 mg monotherapy, combination therapy resulted in significantly more improvement in mean voiding volume (MVV) per micturition (MD =11.90; 95% CI: 8.44 to 15.36, P<0.00001), frequency of micturitions/24h (MD=-0.41; 95% CI: -0.58 to -0.25; P < 0.0001), number of incontinence episodes/24h (MD =-1.36;95% CI: -2.99 to 0.28; P < 0.00001) and frequency of urgency episodes/24h (MD =-0.56;95% CI: -0.83 to - 0.29; P < 0.0001). Even when compared with solifenacin 10 mg monotherapy, combination therapy showed significantly greater improvement in mean voiding volume per micturition(MD =9.01; 95% CI: 3.97 to 14.05, P<0.0005), number of micturitions/24h (MD=-0.43; 95% CI: -0.69 to -0.17; P < 0.001), frequency of incontinence episodes/24h (MD =-0.62;95% CI: -1.42 to 0.17; P=0.12) and frequency of urgency episodes/24h (MD =-0.41; 95% CI: -0.69 to - 0.13; P =0.004). As Compared to solifenacin 5 mg monotherapy, combination therapy was found to have overall acceptable tolerability profile in terms of treatment-emergent adverse events (TEAEs) (OR =1.13; 95% CI: O.99 to 1.28, P=0.07), dry mouth (OR =1.11; 95% CI: O.86 to 1.11, P=0.41), constipation (OR =1.65; 95% CI: 1.12 to 2.44, P=0.01), and prolongation of QTc interval (OR =1.72; 95% CI: O.32 to 9.16, P=0.53). Whereas when compared to solifenacin 10 mg monotherapy, combination therapy was found to be better tolerated for all studied safety outcomes including TEAEs (OR =0.81; 95% CI: O.66 to 0.98, P=0.07), dry mouth (OR =0.53; 95% CI: O.38 to 0.75, P=0.0003), constipation (OR =0.86; 95% CI: 0.54 to 1.38, P=0.53) and prolongation of QTc interval (OR =0.36; 95% CI: O.06 to 1.96, P=0.24).

Conclusion: Combination therapy of mirabegron 50 mg and solifenacin 5 mg leads to significantly greater improvement in OAB symptoms and is better tolerated in comparison with solifenacin 10 monotherapy. In patients refractory to solifenacin 5 mg monotherapy, combination therapy seems to be a better alternative as against escalating the dose of solifenacin.

Keywords: Mirabegron; solifenacin; combination therapy; overactive bladder.

1. INTRODUCTION

Overactive bladder (OAB) syndrome is a chronic medical condition characterized by presence of bothersome lower urinary tract symptoms. International Continence Society (ICS) defines OAB as a symptom complex characterized by "urinary urgency with or without urge incontinence (UI), usually with frequency and nocturia, in the absence of urinary tract infection or other obvious pathology [1]. These debilitating symptoms of OAB have detrimental impact on the quality of life in both men and women affecting performance of daily activities and social functions such as work, traveling, physical exercise, sleep, and sexual function [2].

According to the NOBLE study, the prevalence of OAB is 16.9% in women and 16.0% in men; the prevalence increases with age, with estimates of about 30% in those 65 years of age and older [3]. In India, prevalence of OAB in men is reported to be around 13.6% [4].

First-line therapy in OAB patients include behavioral therapy, lifestyle changes and weight reduction [1]. Yet, concomitant pharmacotherapy is invariably inducted to control and alleviate the troublesome symptoms of urgency, frequency and urinary incontinence, and to improve quality of life (QoL).

Antimuscarinic drugs have been established as the first line of pharmacotherapy for OAB. However, persistence of antimuscarinic therapy is very low, with rate of only 12.0–39.4% after 12 months [5]. Most common reasons due to which patients abandon treatment include unrealistic expectations regarding drug efficacy and bothersome side effects such as dry mouth and constipation [6]. These undesirable effects occur more frequently with higher antimuscarinic doses, although, their severity is not dose-dependent [7].

Another drug Mirabegron, a β3-adrenoceptor agonist, with its different mechanism of action offers an alternative option for management of OAB patients. The efficacy of mirabegron 50 mg is similar to most of the approved antimuscarinic drugs in reducing OAB symptoms [8].

Other options for managing OAB include intra-detrusor botulinum injection which, due to its more invasive nature as well as unique side effect profile has been able to acquire limited popularity and is not considered as a preferred therapy option. Some other options for managing

refractory OAB cases include complex procedures like sacral nerve neuromodulation and percutaneous tibial nerve stimulation which also have limited patient preference [9, 10,11].

A frequently reported clinical situation wherein OAB patients do not respond to lower strength of solifenacin (5mg) poses a challenge to the treating clinicians in choosing upon the optimum next line therapy option. The potential options in such scenario may be either higher dose of solifenacin (10mg) or adding mirabegron to solifenacin (5mg) therapy.

Combination therapy is claimed as a promising option in such cases because of better efficacy due to additive/synergistic effects of both drugs acting by different mechanisms [12]. From the safety point of view, lower dose of antimuscarinic agent in combination treatment can reduce the antimuscarinic side effects such as dry mouth and constipation compared to a higher antimuscarinic dose [13].

In May 2018, the US Food and Drug Administration (FDA) approved mirabegron in combination with solifenacin succinate for the treatment of overactive bladder (OAB) accompanied by symptoms of urge urinary incontinence, urgency, and urinary frequency [14].

The objective of this meta-analysis is to evaluate the safety and efficacy of the combination of solifenacin (5 mg) plus mirabegron (50 mg) in comparison to solifenacin (5 and 10 mg) monotherapy for OAB management.

2. METHOD

A wide EBM Reviews, Cochrane Library and PubMed database search was carried out to identify all published randomized controlled trials evaluating safety and efficacy of mirabegron 50 mg plus solifenacin 5 mg combination in comparison with solifenacin monotherapy (5 and 10 mg) for the treatment of OAB. The following key words were used: Mirabegron, Solifenacin, Combination & Overactive bladder. The present meta-analysis was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist (PRISMA).

2.1 Eligibility Criteria

The following inclusion criteria were used: (i) RCTs reporting original data, published in a peer-reviewed journal; (ii) all double blind RCTs evaluating safety and efficacy of mirabegron and solifenacin combination in comparison with solifenacin monotherapy for the treatment of OAB; and (iii) authors reported data that could be analyzed, clearly specifying the number of participants evaluated, the efficacy and safety outcomes.

Published literature including letter to editor, comment, case report, case series, non-randomized controlled trials, non-comparative observational studies, review articles and meta-analyses were excluded from analysis.

2.2 Information Source, Search and Strategy

The search was restricted to studies from inception up to June 2021 published in English-language and conducted on human participants. A hand search of bibliographies of retrieved papers for additional references was carried out. Details of the literature search process are outlined in the flow chart (Fig. 1). The identification of relevant abstracts, selection of studies based on the criteria described above and subsequent data extraction were carried out independently by two of the authors (SW, ABJ), and conflicts resolved by a third investigator (ND).

2.3 Outcomes and Quality Assessment

We compared the efficacy of mirabegron 50 mg plus solifenacin 5 mg combination therapy with solifenacin monotherapy 5 and 10 mg individually in terms of Mean Voiding Volume, micturition episodes/ 24h, incontinence episodes/ 24h and urgency episodes/ 24h. Safety endpoints included treatment emergent adverse events (TEAEs), dry mouth, constipation, QT prolongation in ECG, tachycardia and urinary retention.

Quality evaluation of included studies was performed with a 5-item instrument proposed by Jadad et al. [15]. A study with 2 points was considered low quality and > 3 points was considered high quality. The quality assessment was completed by 2 authors (SW and ABJ). Any disagreements were resolved by consensus.

It was not appropriate to test the publication bias using the funnel plot since the number of studies included in each comparison was less than ten

[16]. Hence, we did not perform the statistical estimation using Egger's or Begg's test.

2.4 Statistical Analysis

We used the RevMan 5.4 software to perform this meta-analysis. Statistical heterogeneity was calculated by the I^2 test, with significance set at $P < 0.05$. Dichotomous data was presented as odds ratio (OR), and continuous parameters were shown as weighted mean difference with 95% confidence intervals (CIs). We utilized either the fixed-effect method or the random-effect method for this meta-analysis, depending on the presence or absence of significant heterogeneity. The fixed-effect method was used for combining results when statistically significant heterogeneity was absent; when heterogeneity was present, the random-effect method was utilized. In addition, a sensitivity analysis was planned to be executed if low-quality trials were involved.

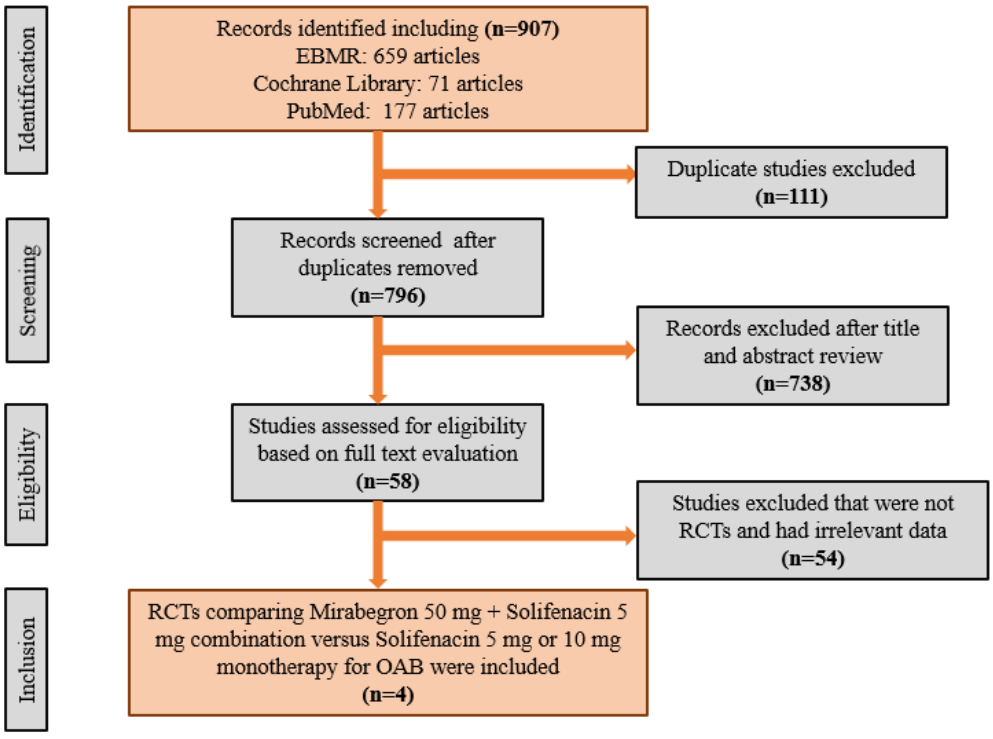
Included RCTs (2 out of 4) didn't mention about Qmax of uroflowmetry or post void residual volume. Instead, they mentioned events of urinary retention. There was only one RCT that compared the events of urinary retention in combination group vs Solifenacin 10 mg group. Hence we did not include this parameter for safety assessment for comparing both Solifenacin regimens against combination therapy.

3. RESULTS

3.1 Characteristics and Quality of the Trials

A total of 907 studies were identified after an extensive search from the databases. After full evaluation of each study, a total of four randomized studies were identified as eligible for the present meta-analysis. The selection process of trials eligible for the meta-analysis is reported in Fig. 1.

All four included studies in the systematic review and meta-analysis were high quality RCTs with Jadad score rating of 5 as enlisted in Table 1.



PRISMA Flow Chart for study selection process.
RCT: Randomized Controlled Trial;
OAB: Overactive Bladder;
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analysis
EBMR: Evidence Based Medicine Reviews

Fig. 1. Screening process for eligible articles

Table 1. Jadad Scoring of individual RCT for quality assessment

Author, Year	Study described as randomized	Method used to generate the sequence of randomization described and appropriate	Study described as double blind	Method of double blinding described and appropriate	Study described withdrawls and dropouts	Total Jadad Score
Abrams, 2015	1	1	1	1	1	5
Drake, 2016	1	1	1	1	1	5
Herschorn, 2017	1	1	1	1	1	5
Gratzke, 2018	1	1	1	1	1	5

Table 2. Study and patient characteristics:

Study	Authors/ year	Design	Treatment group and sample size (n)		Duration of intervention	Inclusion criteria
			Experimental	Control		
1	Abrams, 2015	RCT	Mirabegron 50 mg + Solifenacin 5 mg (n=153)	Solifenacin 5 mg (n=156) and Solifenacin 10 mg (n=78)	12 weeks	Age ≥18 years with OAB symptoms for≥ 3 months with eight or more micturitions per 24h and one or more urgency episode per 24h (with or without incontinence) based on a 3 day electronic patient micturition diary
2	Drake, 2016	RCT	Mirabegron 50 mg + Solifenacin 5 mg (n=725)	Solifenacin 5 mg (n=728) and Solifenacin 10 mg (n=719)	12 weeks	Age ≥18 years with OAB for ≥3 months who recorded ≥2 UI episodes/24h. After 4 weeks of single blind daily Solifenacin 5 mg, patients remaining incontinent at baseline were randomized.
3	Herschorn, 2017	RCT	Mirabegron 50 mg + Solifenacin 5 mg (n=848)	Solifenacin 5 mg (n=423)	12 weeks	Age >18 years with wet OAB for ≥3 months who recorded on average ≥8 micturitions/24h, ≥1 urgency episode/24h and ≥3 UI episodes over 7 day micturition diary
4	Gratzke, 2018	RCT	Mirabegron 50 mg + Solifenacin 5 mg (n=1206)	Solifenacin 5 mg (n=303)	12 months	Age ≥18 years with OAB for ≥3 months who had micturition frequency of ≥8 times/24h, ≥3 incontinence episodes/24h, ≥1 urgency episode/24h during the 7 day micturition diary period

3.2 Patient Characteristics

Overall, 4 trials were included in the meta-analysis evaluating 5339 patients, 2932 (54.91%) assigned to mirabegron 50 mg plus solifenacin 5 mg combination treatment, 1610 (30.15%) to solifenacin 5 mg, and 797 (14.92%) to solifenacin 10 mg monotherapy. Table 2 enlists the relevant characteristics of all included studies.

3.2.1 Clinical efficacy

3.2.1.1 Mean Voiding Volume (MVV)

Four RCTs with a total of 4542 participants (2932 in the combination group and 1610 in the solifenacin 5 mg group) were identified. The fixed-effects estimate of mean difference (MD) was 11.90, and the 95% CI was 8.44 to 15.36 (P<0.00001). This result suggests that the combination treatment experienced greater increases in MVV per micturition in comparison with solifenacin 5 mg. (Fig.2a).

Two RCTs with a total of 1675 participants (878 in the combination group and 797 in the solifenacin 10 mg group) were identified. The fixed-effects estimate of the MD was 9.01, and the 95% CI was 3.97 to 14.05 (P=0.0005). This result suggests that the combination treatment experienced greater increases in the mean voiding volume per micturition in comparison with solifenacin 10 mg. (Fig. 2b).

3.2.1.2 Mean number of micturitions/24h

Four RCTs with a total of 4542 participants (2932 in the combination group and 1610 in the solifenacin 5 mg group. The fixed-effects estimate of the MD was -0.41, and the 95% CI was -0.58 to -0.25 (P<0.00001). This result suggests that mirabegron and solifenacin combination treatment showed superior efficacy in reducing the mean number of micturitions per 24 hours compared with solifenacin 5 mg alone. (Fig. 3a)

Two RCTs with a total of 1675 participants (878 in the combination group and 797 in the solifenacin 10 mg group) were identified. The fixed-effects estimate of the MD was -0.43, and the 95% CI was -0.69 to -0.17 (P=0.001). This result suggests that mirabegron and solifenacin combination treatment showed superior efficacy in reducing the mean number of micturitions per 24 hours compared with solifenacin 10 mg alone. (Fig.3b)

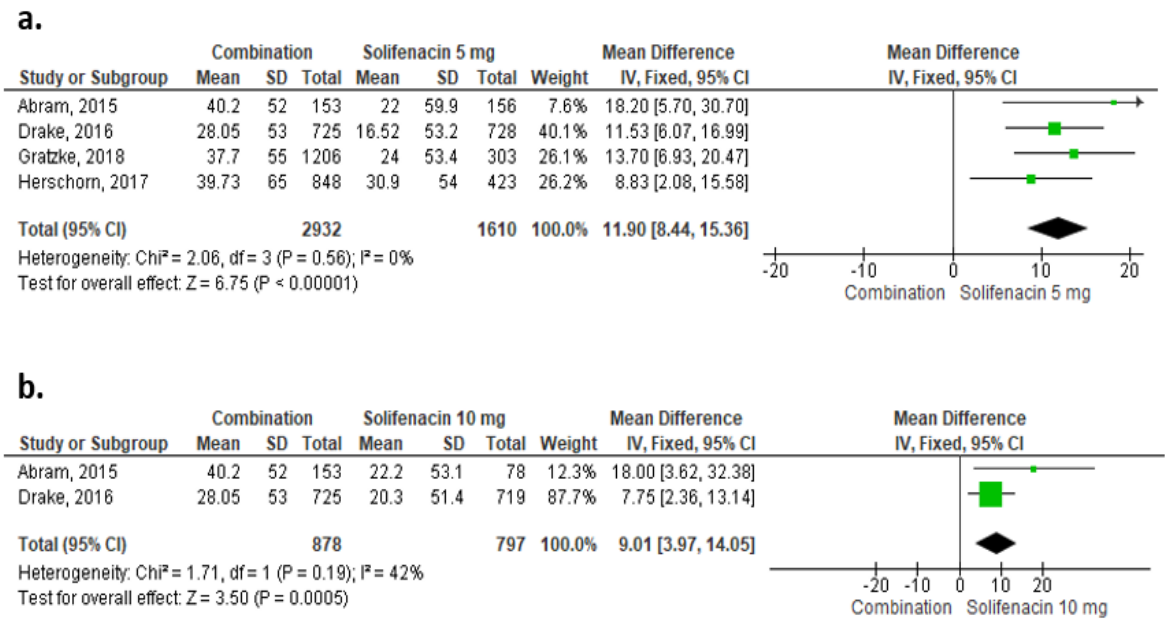


Fig. 2. Forest plots showing changes in the mean voiding volume per micturition; a. Combination Vs Solifenacin 5 mg, b. Combination Vs Solifenacin 10 mg; SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom

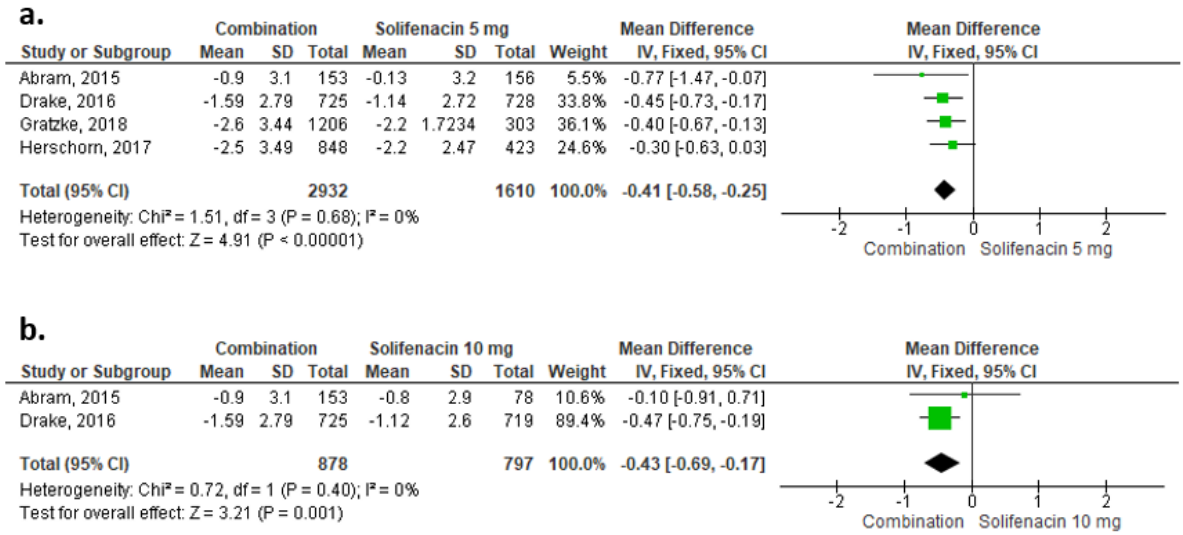


Fig. 3. Forest plots showing change in micturitions/24h; a. Combination Vs Solifenacin 5 mg, b. Combination Vs Solifenacin 10 mg; SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom

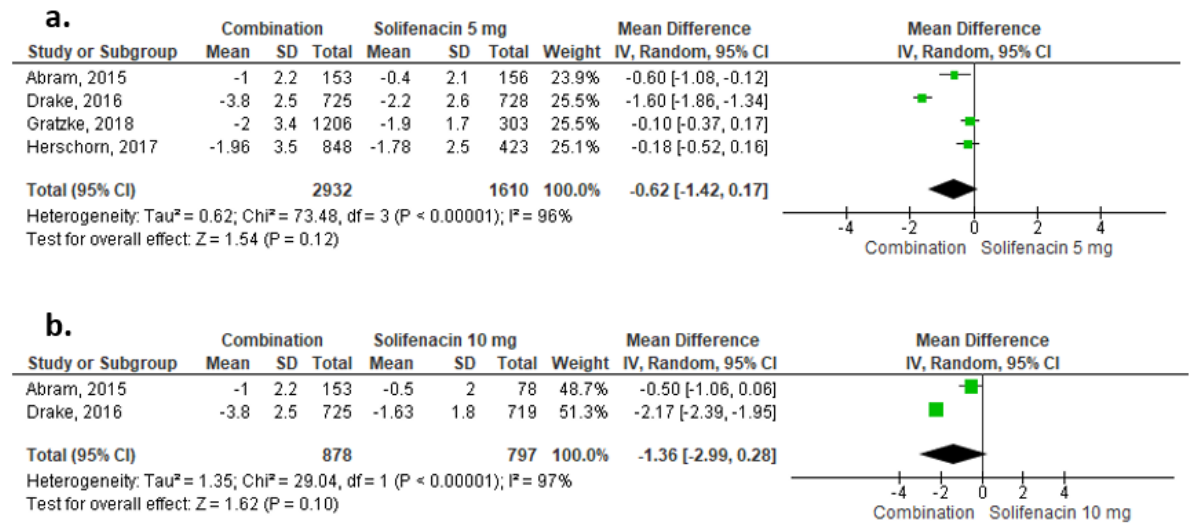


Fig. 4. Forest plots showing change in incontinence episodes/24h; a. Combination Vs Solifenacin 5 mg, b. Combination Vs Solifenacin 10 mg; SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom

3.2.1.3 Mean number of incontinence episodes/24h

Four RCTs with a total of 4542 participants (2932 in the combination group and 1610 in the solifenacin 5 mg group) were identified. The random-effects estimate of the MD was -0.62, and the 95% CI was -1.42 to -0.17 (P=0.12). This result indicates that the combination group experienced greater decreases in episodes of incontinence per 24 hours in comparison with solifenacin 5 mg. (Fig. 4a).

Two RCTs with a total of 1675 participants (878 in the combination group and 797 in the solifenacin 10 mg group) were identified. The fixed-effects estimate of the MD was -1.36, and the 95% CI was -2.99 to 0.28 (P<0.00001). This result indicates that the combination group experienced greater decreases in episodes of

incontinence per 24 hours in comparison with solifenacin 10 mg. (Fig. 4b).

3.2.1.4 Mean number of urgency episodes/24h

Two RCTs with a total of 1762 participants 878in the combination of solifenacin plus mirabegron group and 884 in the solifenacin 5 mg group) were identified. The random-effects estimate of the MD was -0.56, and the 95% CI was -0.83 to -0.29 (P<0.0001). This result suggests that combination treatment successfully reduced the mean number of urgency episodes per 24 hours compared to solifenacin 5 mg. (Fig 5a).

Two RCTs with a total of 1675 participants (878 in the combination group and 797 in the solifenacin 10 mg group) were identified. The random-effects estimate of the MD was -0.41, and the 95% CI was -0.69 to -0.13 (P=0.004). This result indicates that the combination group experienced greater decreases in episodes of incontinence per 24 hours in comparison with solifenacin 10 mg (Fig 5b)

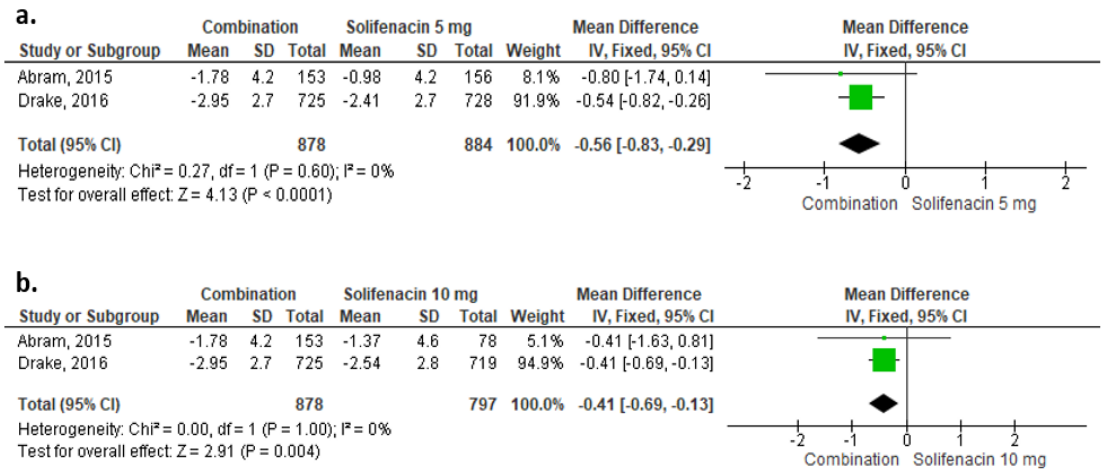


Fig. 5. Forest plots showing change in urgency episodes/24h; a. Combination Vs Solifenacin 5 mg, b. Combination Vs Solifenacin 10 mg; SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

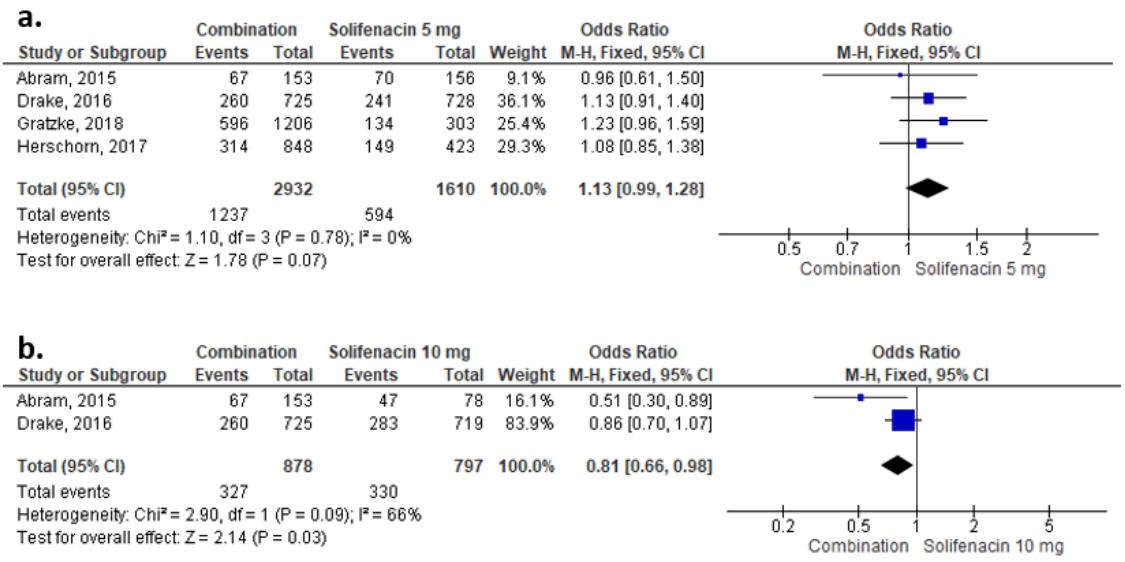


Fig. 6. Forest plots showing changes in treatment-emergent adverse events; a. Combination Vs Solifenacin 5 mg, b. Combination Vs Solifenacin 10 mg; M-H, Mantel-Haenszel; CI, confidence interval; df, degrees of freedom

3.3 Safety

3.3.1 Treatment Emergent Adverse Events (TEAE)

Four RCTs with a total of 4542 participants (2932 in the combination group and 1610 in the solifenacin 5 mg group) included TEAE data. The OR was 1.13, and the 95% CI was 0.99 to 1.28 (P=0.07). This result indicates that the groups were similar in terms of the incidence of TEAEs. (Fig. 6a).

Two RCTs with a total of 1675 participants (878 in the combination group and 797 in the solifenacin 5 mg group) included TEAE data .The OR was 0.81, and the 95% CI was 0.66 to 0.98 (P=0.07). This result indicates combination treatment is better tolerated than solifenacin 10 mg. (Fig. 6b)

3.3.2 Dry mouth

Four RCTs with a total of 4542 participants (2932 in the combination group and 1610 in the solifenacin 5 mg group) include data on dry mouth. The OR was 1.11, and the 95% CI was 0.86 to 1.11 (P=0.41). This result indicates that the groups were similar in terms of the incidence of dry mouth (Fig. 7a).

Two RCTs with a total of 1675 participants (878 in the combination group and 797 in the solifenacin 10 mg group) included data on dry mouth. The OR was 0.53, and the 95% CI was 0.38 to 0.75 (P=0.0003). This result indicates combination treatment is better tolerated than solifenacin 10 mg in terms of incidence of dry mouth (Fig. 7b).

3.3.3 Constipation

Four RCTs with a total of 4542 participants (2932 in the combination group and 1610 in the solifenacin 5 mg group) include data on constipation. The OR was 1.65, and the 95% CI was 1.12 to 2.44 (P=0.01). This result indicates that there was no apparent difference between two groups in terms of the incidence of constipation. (Fig. 8a).

Two RCTs with a total of 1675 participants (878 in the combination group and 797 in the solifenacin 5 mg group) included data on dry mouth. The OR was 0.86, and the 95% CI was 0.54 to 1.38 (P=0.53). This result indicates combination treatment is better tolerated than solifenacin 10 mg in terms of incidence of constipation. (Fig. 8b)

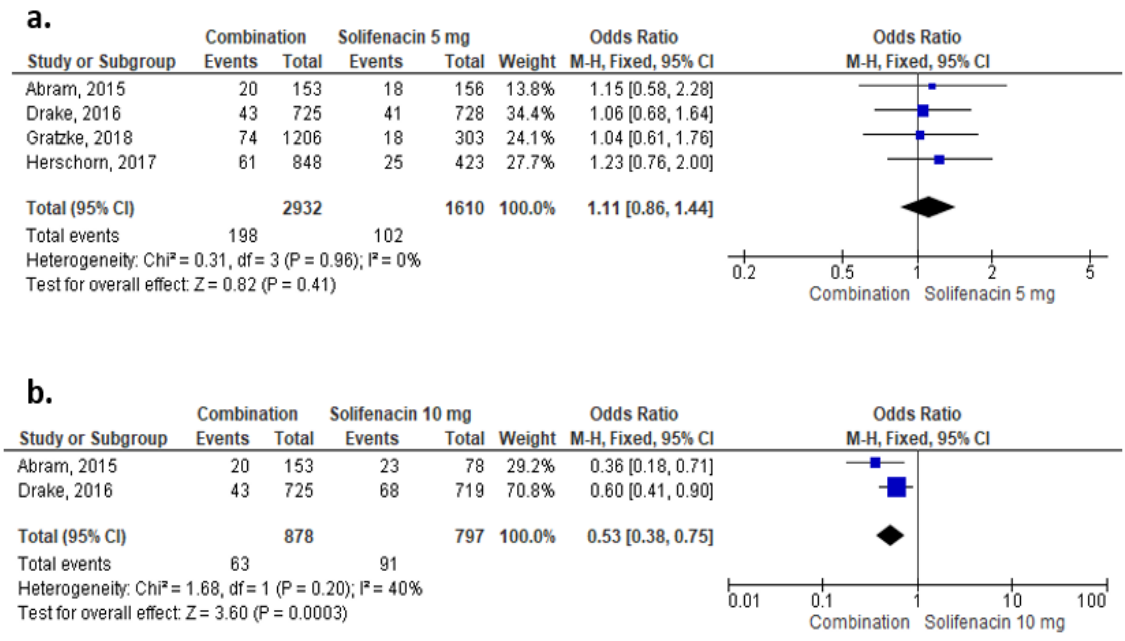


Fig. 7. Forest plots showing incidents of dry mouth; a. Combination Vs Solifenacin 5 mg, b. Combination Vs Solifenacin 10 mg; M-H, Mantel-Haenszel; CI, confidence interval; df, degrees of freedom

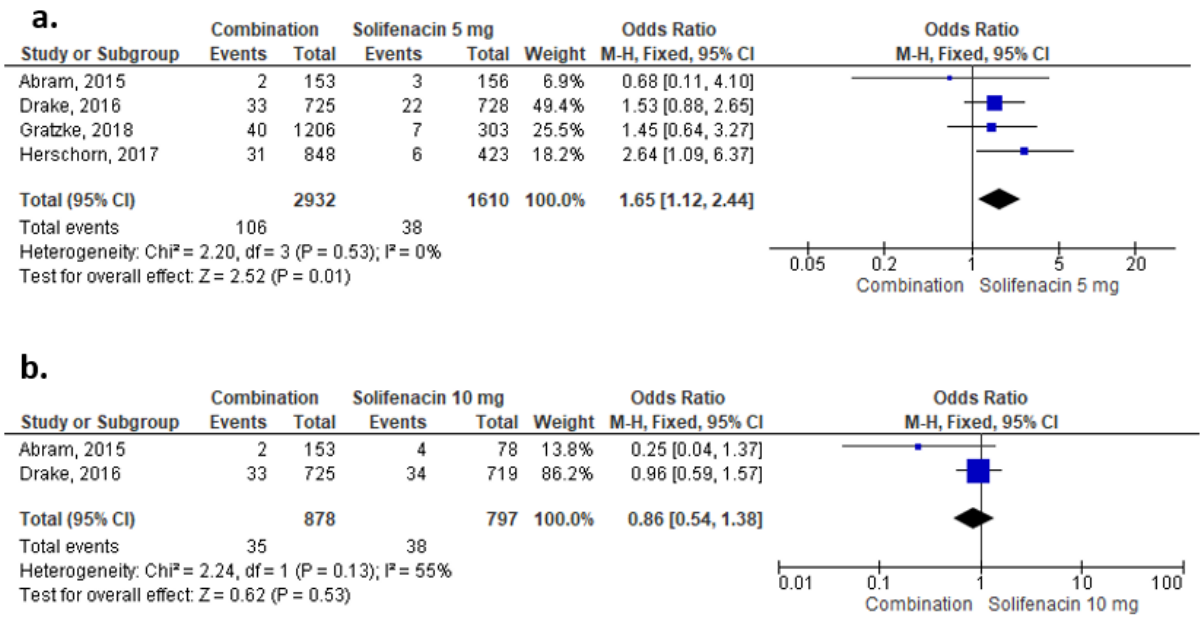


Fig. 8. Forest plots showing incidents of constipation; a. Combination Vs Solifenacin 5 mg, b. Combination Vs Solifenacin 10 mg; M-H, Mantel-Haenszel; CI, confidence interval; df, degrees of freedom

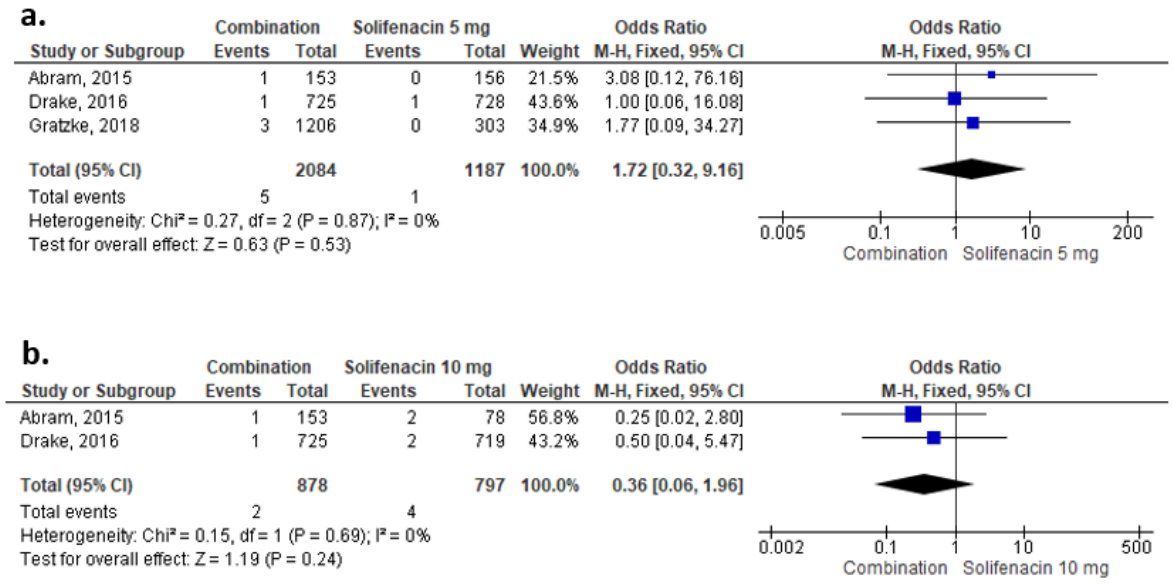


Fig. 9. Forest plots showing incidents of QTc prolongation; a. Combination Vs Solifenacin 5 mg, b. Combination Vs Solifenacin 10 mg; M-H, Mantel-Haenszel; CI, confidence interval; df, degrees of freedom

3.3.4 QTc prolongation

Three RCTs with a total of 3271 participants (2084 in the combination group and 1187 in the solifenacin 5 mg group) include data on QT prolongation. The OR was 1.72, and the 95% CI was 0.32 to 9.16 (P=0.53). This result indicates that there was no apparent difference in between two groups in terms of the incidence of QT prolongation. (Fig. 9a).

Two RCTs with a total of 1675 participants (878 in the combination group and 797 the solifenacin 5 mg group) included data on QT prolongation. The OR was 0.36, and the 95% CI was 0.06 to 1.96 (P=0.24). This result indicates that the combination therapy is comparatively safer than solifenacin 10 mg in terms of the incidence of QT prolongation. (Fig. 9a).

4. DISCUSSION

4.1 Main Findings

To the best of our knowledge this is the first systematic review and qualitative meta-analysis, providing individual comparison of mirabegron (50 mg) plus solifenacin (5 mg) combination therapy with both, 5 & 10mg dose of solifenacin monotherapy. We did an initial search of various databases and retrieved 907 studies, out of that 4 studies with 5339 randomized patients were found to be eligible to include in our analysis. The overall quality of the included studies was high. We included the RCTs evaluating the efficacy and safety of mirabegron 50 mg plus solifenacin 5 mg with solifenacin 5 mg and/or 10 mg monotherpy.

Four parameters of efficacy were evaluated in this review: mean voiding volume per micturition, mean number of micturitions, urgency and incontinence episodes/24h.

Forest plot analysis for efficacy outcomes in this study shows that mirabegron and solifenacin combination has significantly better efficacy in all measured outcomes compared to solifenacin 5 and 10 mg.

Apart from efficacy, four safety outcomes evaluated in this review were TEAEs, dry mouth, constipation and QTc prolongation. Forest plot analysis for safety outcomes in this study shows that combination treatment has an acceptable tolerability vis-à-vis solifenacin 5 mg monotherapy and is better tolerated than solifenacin 10 mg monotherapy.

4.2 Findings in Context to Existing Literature

In MILAI study, Yamaguchi et al. found that add-on therapy with mirabegron to an antimuscarinic agent, such as solifenacin resulted in significant improvements in OAB symptoms with mild to moderate AEs [17].

Imamura et al. also showed that the combination of solifenacin and mirabegron act synergistically to inhibit the cold stress-induced detrusor overactivity in spontaneously hypertensive rats [18].

Recently, in a pressure volume analysis in rats, Peng et al. reported that mirabegron and solifenacin combination induces an acute compliance increase in the filling phase of the capacity-reduced urinary bladder to ameliorate OAB like syndromes [19].

SYMPHONY trial which was a multinational phase II double-blind RCT, reported that combination therapy with solifenacin & mirabegron significantly improved MVV, micturition frequency, and urgency compared with solifenacin 5 mg monotherapy. It also reported that incidence of AEs with combination therapy compared with solifenacin 10 mg was low. It also demonstrated lack of clinically significant additive effects regarding hypertension or pulse rate, suggesting potential benefit of combination therapy over antimuscarinic dose escalation in patients who require additional efficacy [20].

Following this, SYNERGY trial, a large phase 3 trial also reported consistently greater improvements in efficacy parameters like urinary incontinence episodes/24 h and micturition episodes/24 h with combination therapy as compared to solifenacin monotherapy 5mg [21].

In SYNERGY II trial also, clinically meaningful and sustained improvements in clinical outcomes were noted for mirabegron 50 mg plus solifenacin 5 mg combination therapy versus solifenacin 5 mg monotherapy [22].

In both SYNERGY and SYNERGY II trials, combination treatment was well tolerated with no additive side effects [22].

The BESIDE study specifically recruited adults with OAB not responding to 4 weeks of therapy with solifenacin. In patients with an inadequate response to solifenacin 5 mg monotherapy, significantly greater improvements in urinary incontinence episodes/24h were noted with combination treatment versus solifenacin 5 mg. Combination therapy was non inferior to Solifenacin 10 mg for reduction in UI and showed significantly better improvements in terms of micturition frequency and OAB-5 Dimension scores versus both doses of solifenacin

monotherapy. Besides greater improvements in efficacy parameters, combination treatment had an acceptable tolerability profile compared with solifenacin 5 mg and was better tolerated in comparison with solifenacin 10 mg in all major safety outcomes like TEAEs, dry mouth, constipation and QTc prolongation on ECG [23].

One RCT by Kosilov et al, although not part of our meta-analysis, also reported that combination of Mirabegron 50 mg plus solifenacin 10 mg in comparison with both doses of solifenacin monotherapy improves efficacy without compromising tolerability in patients with OAB [24].

Another non-randomized controlled study not included in our meta-analysis showed statistically significant reduction in number of incontinence episodes and micturitions episodes/24h and acceptable tolerability with combination therapy compared to solifenacin 5 mg monotherapy in real world practice [25].

Previous meta-analysis by Xu et al (4RCTs) [26] and Peng et al (3 RCTs) [27] compared the efficacy and safety of combination therapy (mirabegron50 mg plus solifenacin 5 mg or mirabegron 50 mg plus solifenacin 10 mg) to solifenacin monotherapy (5mg or 10 mg). Both these meta-analyses suggest combination treatment provides a satisfactory therapeutic effect for OAB symptoms with a low occurrence of side effect. However, in none of these meta-analyses researchers compared the efficacy and safety of solifenacin 5 mg and 10 mg doses individually with combination treatment (mirabegron 50 mg plus solifenacin 5 mg).
Whereas, we evaluated combination treatment individually with both doses of solifenacin in terms of efficacy and safety outcomes.

4.3 Implications for Clinical Practice

OAB is a common and troublesome condition that significantly impairs quality of life in both genders. Pharmacotherapy is an integral part of OAB management with antimuscarinic drugs being the mainstay of medical treatment with their established efficacy in controlling OAB symptoms [28]. Antimuscarinic drugs block M3 receptors, preventing acetylcholine-induced detrusor contractions [29]. Besides efficacy, the key to a successful OAB treatment is the safety profile of medication considering the need of long-term medical management. Antimuscarinics may cause undesirable side effects due to the muscarinic receptor blockade in other organs like salivary glands, gastrointestinal tract and heart leading to dry mouth, constipation, abnormal heart rate & rhythm respectively [30, 31].

Treatment persistence rates with antimuscarinic drugs has been reported to be as low as approximately 12 to 39.4% at 1 yr [5].

On the other hand, β3-agonists which act by activating bladder adrenoceptors, leading to detrusor relaxation have no safety concern like anticholinergics [32].

Hence, in case of non-response to antimuscarinic therapy, instead of increasing the dose, adding a β3-agonist can be a lucrative option to improve OAB symptoms without aggravating the burden of anticholinergic side effects [33].

Combination therapy with an anti-muscarinic and β3-adrenoceptor agonist has also been recommended by AUA guideline for OAB patients refractory to monotherapy with either anti-muscarinic or β3-adrenoceptor agonist monotherapy [1].

In clinical practice OAB management is normally started with solifenacin 5 mg and titrated in accordance with the clinical need and personal preference to 10 mg dose [34]. In case of nonresponse, the outcomes of this meta-anlysis clearly indicate that, combination of solifenacin 5mg with mirabegron 50 mg can be a preferred option over increasing the dose of solifenacin to 10 mg.

5. LIMITATIONS AND FUTURE SCOPE

The results of our meta-analysis acquire great importance in the day to day clinical practice for management of OAB in patients refractory to antimuscarinic monotherapy. However, this meta-analysis also has some limitations. The number of included articles was not much. Out of four included RCTs, only two compared the combination therapy (mirabegron 50 mg plus solifenacin 5 mg) with solifenacin 10 mg monotherapy. Number of patients who discontinued the treatment was not part of our safety outcomes. The long term efficacy, safety, and persistence of combination treatment and solifenacin monotherapy could not be extrapolated from this meta-analysis as none of the RCTs had treatment duration of more than a year. More high-quality trials are warranted to

learn more about the long term efficacy and safety of combination therapy vs solifenacin monotherapy for OAB.

6. CONCLUSION

Combination therapy has broadened the therapeutic armamentarium for OAB management. In patients with OAB symptoms despite solifenacin monotherapy, combination therapy (mirabegron 50 mg plus solifenacin 5 mg) leads to better clinical improvement as compared to high dose of solifenacin without raising any additional safety concerns.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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