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Efficacy and safety of combination therapy compared to monotherapy for overactive bladder: A Meta-Analysis

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Introduction. Overactive Bladder (OAB) Syndrome is urinary urgency often accompanied by increased daytime frequency and nocturia, with or without urgency incontinence. Individuals with OAB report significant impairment to quality of life. Antimuscarinic becomes first line therapy of OAB patients with dose escalation or change of antimuscarinic if symptom improvement is inadequate. Increasing the antimuscarinic dose often exacerbates anticholinergic Adverse Events (AEs) that can lead to treatment discontinuation. The aim of this meta-analysis is to find out the efficacy and safety of combination therapy compared to solifenacin alone.

Methods. We searched for data of Randomized clinical trials in PUBMED, EMBASE, and the Cochrane Library. There was no year restriction and only English was allowed. The outcomes were Micturition Episode/24h , Incontinence Episode/24h , AEs and Discontinue medication due to AEs. The data were carried out using PRISMA guidelines and statistically analysed by using RevMan 5.3.0.

Results. Three RCTs studies, including 7007 patients, were assessed for efficacy and safety of combination therapy compared to solifenacin alone. It is revealed Micturition [HR -0.46; 95%CI: -0.63, -0.29; I^2 13%; p<0.00], Incontinence [HR -0.27; 95%CI: -0.42, -0.13; I^2 13%; p<0.00], Adverse Events [HR 1.09; 95%CI: 0.94, 1.27; I^2 0%; p=0.27] and Discontinue Medication due to AEs [HR 1.26; 95%CI: 0.70, 2.24; I^2 0%; p=0.44].

Conclusion. The efficacy of combination therapy of mirabegron plus solifenacin significantly improved storage symptoms regarding micturition and incontinence episode, compared to solifenacin monotherapy. Combination therapy provides better therapeutic benefits for patients with overactive bladder syndrome.

Keywords: combination therapy, monotherapy, overactive bladder

Introduction

Overactive Bladder (OAB) syndrome is a form of bladder dysfunction, excluding other defined pathology (i.e. infection), marked by increased daytime voiding frequency, nocturnal polyuria, and could be accompanied by urgency incontinence [1]. In Europe, United States, and Asia the prevalence of OAB is approximately 15% among adults and as high as 40% in ≥ 75 y.o. population [2]. OAB diagnosed patients usually report a major impairment to their quality of life, as it could reduce one's productivity, and rather increase the healthcare resources requirement. Urgency Urinary Incontinence (UUI) occurs in approximately one third of the OAB population. Moreover, the presence of UUI is considered to be the most impactful to QoL [3]. Notable prevalence of the condition combined with the unsatisfactory treatment outcome have prompted the perseverance to establish up-to-date strategies [4].

Treatment modalities for OAB consist of lifestyle or behavioral modification, pharmacological medication, minimally invasive procedures, and surgical intervention [5-6]. In current clinical practice, prescription of oral muscarinic receptor antagonists become the mainstay choice of treatment for treating OAB/storage symptoms. Several formulated drugs include fesoterodine, tolterodine, oxybutynin, darifenacin, and solifenacin [4]. A number of studies have evaluated the efficacy of antimuscarinics as a single agent in improving

episodes of urgency/incontinence, daytime/24h frequency, nocturia, OAB questionnaire scores, and overall patient's perception of bladder condition [5-8]. Escalating the dose and switching antimuscarinics for inadequate symptom improvement are still a propensity and as often stated, a higher dose of antimuscarinic will substantially exacerbate the adverse events (AEs) through anticholinergic pathway. This can lead to a patient's withdrawal, the treatment eventually becoming less potent as the efficacy takes time to progress [9]. The most reported AEs are dry mouth, dizziness, constipation, nasopharyngitis, and micturition problems. Patients with OAB were reported to have a low persistence rate of adhering to antimuscarinic medication, suggesting that tolerability could be an issue that hinders satisfactory treatment [10, 11].

Mirabegron, a selective β3 adrenoreceptor agonist which modulates relaxation to the detrusor smooth muscle, has a comparable efficacy with antimuscarinics. Mirabegron is proven to be an effective and more tolerable preference for antimuscarinics, as indicated by better treatment continuity [12]. Leading studies such as SYMPHONY [13], BESIDE [14], and SYNERGY [15], have investigated dose-combination efficacy and tolerability of solifenacin plus mirabegron compared to separate monotherapies and placebo, the result of which firmly suggested that dual therapy is a feasible option for OAB. Prior evidence have showed a marked symptoms improvement with mirabegron plus 5 mg solifenacin compared to 5 mg solifenacin alone, while supplementary studies mentioned that mirabegron 50 mg provided less AEs, enhancing patient's adherence, and equivalent in efficacy [16-18]. In the current systematic review/meta-analysis, we aim to confirm the efficacy and safety profile of the selected dose combination of mirabegron (50 mg) plus solifenacin (5 mg), in comparison to solifenacin (5 mg) monotherapy.

Materials and Methods

Search Strategy

Our study is undertaken as a systematic review and a substantial meta-analytical approach of pooled data. Literature and references were searched through the database of PubMed, EMBASE, MEDLINE, and Cochrane Library. Primary searching attribute was specifically randomized clinical trials, comprising multiple treatment and/or control arms. Keywords for database inquiry were "Overactive Bladder", "OAB", "Detrusor Overactivity", "Solifenacin", "Mirabegron", and "Randomized Controlled Trials". Various relevant terms and phrases regarding the patient's population and the therapeutic intervention were also comprehensively run. Published evidence was as updated as March 31st, 2021.

Inclusion and Exclusion

The search of desired studies allowed English-written full-text articles only, no time-of-publication restriction (most notable studies were published in the last 10 years), and removal of duplicates. Selection processes were performed by two evaluators, starting from the title and the abstract. Full review was based on the framework of patient/population, intervention, comparison, and study design. Clinical findings and data set regarding the use of mirabegron (50 mg) plus solifenacin (5 mg) vs solifenacin (5 mg) monotherapy were extracted from respective studies. Treatment interval across all trials was set at 24 weeks minimum, after run-in period and randomization. Mean changes from baseline to endpoint applied as primary outcomes were micturition episode/24h and incontinence episode/24h. Adverse events (AEs), and AEs-related treatment discontinuation recorded during the follow-ups and at study endpoints served as the secondary outcomes.

Quality Assessment of Studies

An overview of the literature search conducted according to the specification of Preferred Reporting Items for Systematic Reviews and Meta-Analyses [20] is illustrated in Figure 1. In depth quality view of each study was assessed over a 25-item checklist from Consolidated Standard for Reporting Trials (CONSORT) Statement [19], shown in Table 1. Subsequently, the Cochrane risk of bias tool was implemented to assess the quality of obtained studies. Modified jaded scale for assessed bias RCT.

Data Extraction and Analysis

Main characteristics of selected studies were highlighted in Table 2. Pooled data analysis was operated using RevMan software (version 5.3.0). The efficacy and safety measures were calculated using a random or fixed effect model based on total and inter-variability of the data, reflected from the P value and I2 index [17]. The change from

Table 1. Modified jaded scale table

Corresponding Author	Was the research described as randomized?	Was the approach of randomization appropriate?	Was the research described as blinding?	Was the approach of blinding appropriate?	Was there a presentation of withdrawals and dropouts?	Was there a presentation of the inclusion/exclusion criteria?	Was the approach used to assess adverse effects described?	Was the approach of statistical analysis described?	Total
Drake 2016	1	1	1	1	1	1	1	1	8
Abrams 2014	1	1	1	1	1	1	1	1	8
Herschorn 2017	1	1	1	1	1	1	1	1	8
Kosilov 2015	1	1	0	0	0	1	1	1	5

Table 2. Characteristics of included studies

Author (year)	Trial's Name	Tria's Number	Phase of RCT	Patient Number	Country	Intervention	Duration	Follow Up
Drake 2016	BESIDE	NCT01908829	Phase 3B	2174	Global	Solifenacin 5 mg + Mirabegron 50 mg VS Solifenacin 5 mg Solifenacin 5 mg + Mirabegron 50 mg VS Solifenacin 10 mg	12 weeks	week 12
Abrams 2014	SYMPHONY	NCT01340027	Phase 2	1306	EU and USA	Solifenacin 5 mg + Mirabegron 50 mg vs Solifenacin 5 mg Solifenacin 5 mg + Mirabegron 25 mg vs Solifenacin 5 mg Solifenacin 10 mg + Mirabegron 50 mg vs Solifenacin 5 mg Solifenacin 10 mg + Mirabegron 25 mg vs Solifenacin 5 mg	12 weeks	week 14
Herschorn 2017	SYNERGY	NCT01972841	Phase 3	3527	Global	Solifenacin 5 mg + Mirabegron 50 mg VS Solifenacin 5 mg Solifenacin 5 mg + Mirabegron 25 mg VS Solifenacin 5 mg Solifenacin 5 mg + Mirabegron 25 mg VS Mirabegron 25 mg Solifenacin 5 mg + Mirabegron 50 mg VS Mirabegron 50 mg	12 weeks	week 18
Kosilov 2015				239	Russia	Solifenacin 10 mg + Mirabegron 50 mg vs Solifenacin 10 mg	6 weeks	week 8

Table 3. Study Data

	Treatment Arm				
	S5	**S10**	**S5+M25**	**S5+M50**	**Another Dose**
	1287	828	997	1708	227
Sex					
Male	266	158	246	368	79
Female	1021	670	751	1340	148
Mean Age, yr (SD)	56.43 (13.4)	61.16 (13.1)	56.05 (13.5)	56.5 (13.2)	63.35 (12.9)
BMI, kg/m2 (SD)	27.92 (3.8)	28.1 (4.2)	27.45 (4.1)	28.03 (3.8)	27.1 (3.9)
OAB Symptoms Duration, months (SD)	65.55 (56)	53.5 (66.9)	64.63 (57.8)	66.13 (65.9)	58 (63.7)
Previous OAB Medication (%)	253.67 (47)	254 (48)	222.4 (46.5)	306.6 (46.4)	129 (53)
Mean Volume Voided (SD)	148,7 (60.78)	135 (58.8)	156,41 (55.4)	153,535 (51.3)	136.85 (50.1)
Micturation/24h (SD)	10.42 (2)	11.3 (2.6)	10.23 (2.5)	10.28 (3.2)	11,1 (3.1)
Incontinence/24h (SD)	2.68 (1.2)	2.35 (1.1)	2.21 (0.9)	2.53 (1.3)	2.3 (1.2)

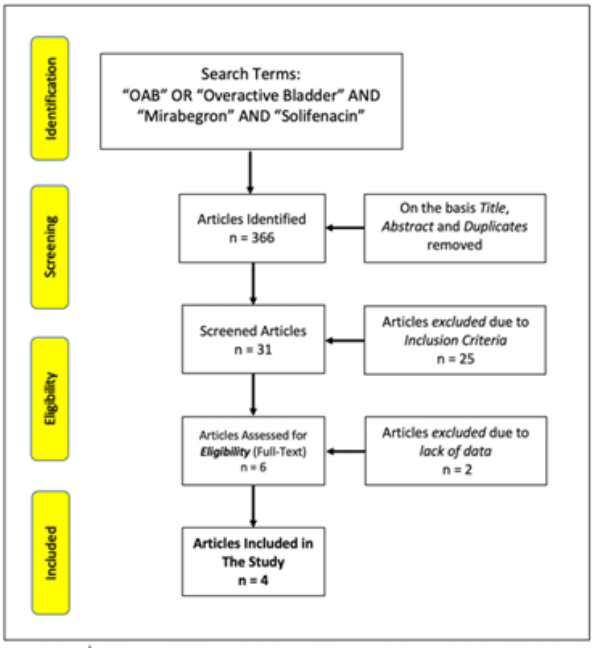

Figure 1. Prisma flow chart

baseline of micturition episode/24h and incontinence episode/24h were estimated using mean differences (MDs) in 95% confidence intervals (CIs), and Odds Ratios (ORs) in 95% CIs for adverse events and treatment discontinuation. The addition of Begg's Test or Egger's Test was applied to assess publication bias of the studies.

Result

Characteristics of eligible studies

We found 366 articles from PubMed, EMBASE and the Cochrane Controlled trials Register. Titles and abstracts of 366 studies were evaluated. The remaining 31 articles were screened and 335 were excluded by title and abstract. Full texts were read carefully and more than 25 studies excluded due to inclusion criteria. Two studies also exclude due to lack of data. In the end, 4 studies were ultimately selected for the meta-analysis, with a total of 7246 patients.

Solifenacin 5 mg + Mirabegron 25 mg vs Solifenacin 5 mg

From two studies, combination solifenacin 5 mg and Mirabegron 25 mg showed insignificant result in MVV compared to monotherapy solifenacin 5 mg only with MD of 10.61(95% CI: -0.065 - 21.88, P=0.06)(Fig 2). The Cochrane Q test (Chi2: 3.32, P=0.07) showed the inconsistency of clinical methodological aspects between studies, I2 (I2: 70 %) revealed a significant heterogeneity and a random effect model was applied.

Solifenacin 5 mg + Mirabegron 50 mg vs Solifenacin 5 mg

From three studies, combination solifenacin 5 mg and Mirabegron 50 mg showed significant result in MVV compared to monotherapy solifenacin 5 mg only with MD of 11.17(95% CI: 7.27 – 15.07, P<0.000)(Fig. 2). The Cochrane Q test (Chi2: 1.91, P=0.02) showed the consistency of clinical methodological aspects between studies, I2 (I2: 0 %) revealed a low heterogeneity and a fixed effect model was applied.

Another Dose

From three studies, combination therapy showed significant results in MVV compared to monotherapy with MD of 17.31(95% CI: 4.35 – 30.27, P=0.009)(Fig. 2). The Cochrane Q test (Chi2: 8.03, P=0.02) showed the inconsistency of clinical methodological aspects between studies, I2 (I2: 75 %) revealed a significant heterogeneity and a random effect model was applied.

From total analysis, combination therapy showed significant results in MVV compared to monotherapy with MD of 11.89(95% CI: 7.82 – 15.95, P<0.000)(Fig. 2). The Cochrane Q test (Chi2: 16.07, P=0.02) showed the inconsistency of clinical methodological aspects between studies, I2 (I2: 56 %) revealed a significant heterogeneity and a random effect model was applied.

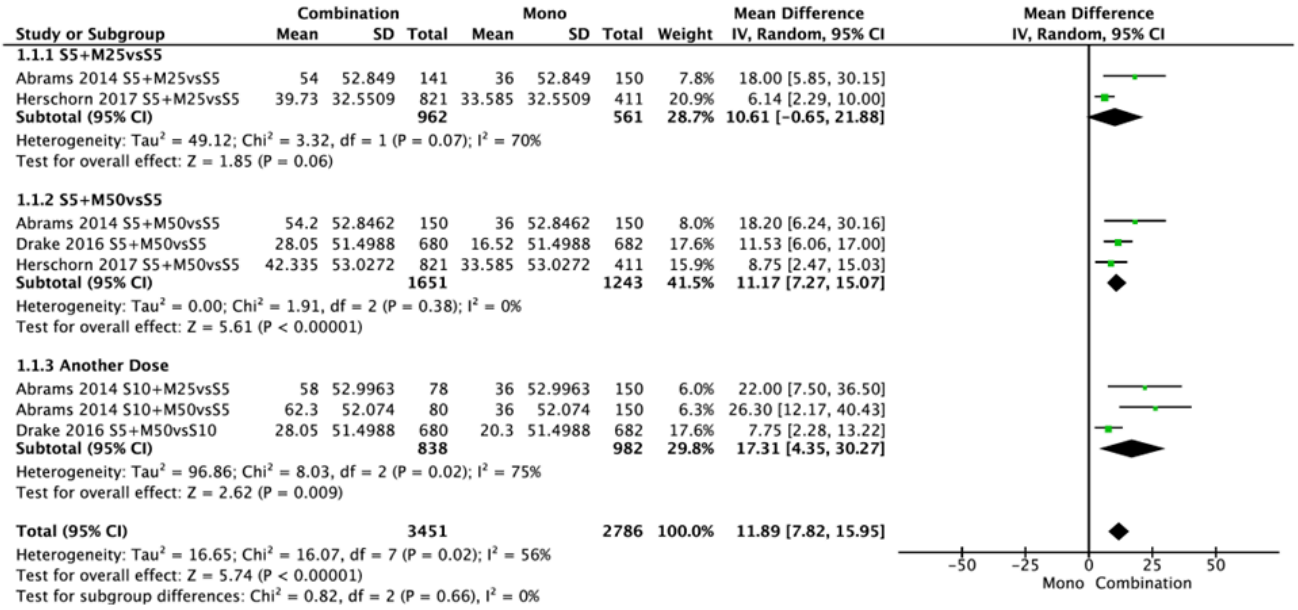

Figure 2. Combination vs Monotherapy Forrest Plot

Solifenacin 5 mg + Mirabegron 25 mg vs Solifenacin 5 mg

From two studies, combination solifenacin 5 mg and Mirabegron 25 mg showed significant result in Micturition/24h compared to monotherapy solifenacin 5 mg only with MD of -0.28 (95% CI: -0.54 - -0.02, P=0.04)(Fig. 3). The Cochrane Q test (Chi2: 3.32, P=0.06) showed the consistency of clinical methodological aspects between studies, I2 (I2: 0 %) revealed low heterogeneity and a fixed effect model was applied.

Solifenacin 5 mg + Mirabegron 50 mg vs Solifenacin 5 mg

From three studies, combination solifenacin 5 mg and Mirabegron 50 mg showed significant result in Micturition/24h compared to monotherapy solifenacin 5 mg only with MD of -0.46 (95% CI: -0.63 - -0.29, P<0.000)(Fig. 3). The Cochrane Q test (Chi2: 2.23, P=0.33) showed the consistency of clinical methodological aspects between studies, I2 (I2: 0 %) revealed low heterogeneity and a fixed effect model was applied.

Another Dose

From three studies, combination therapy showed significant results in Micturition/24h compared to monotherapy with MD of -0.55 (95% CI: -0.76 – -0.34, P<0.000) (Fig. 3). The Cochrane Q test (Chi2: 2.88, P=0.41) showed the consistency of clinical methodological aspects between studies, I2 (I2: 0 %) revealed low heterogeneity and a fixed effect model was applied.

From total analysis, combination therapy showed significant results in Micturition/24h compared to monotherapy with MD of -0.45(95% CI: -0.57 – -0.33, P<0.000)(Fig. 3). The Cochrane Q test (Chi2: 7.73, P=0.46) showed the consistency of clinical methodological aspects between studies, I2 (I2: 0 %) revealed low heterogeneity and a fixed effect model was applied.

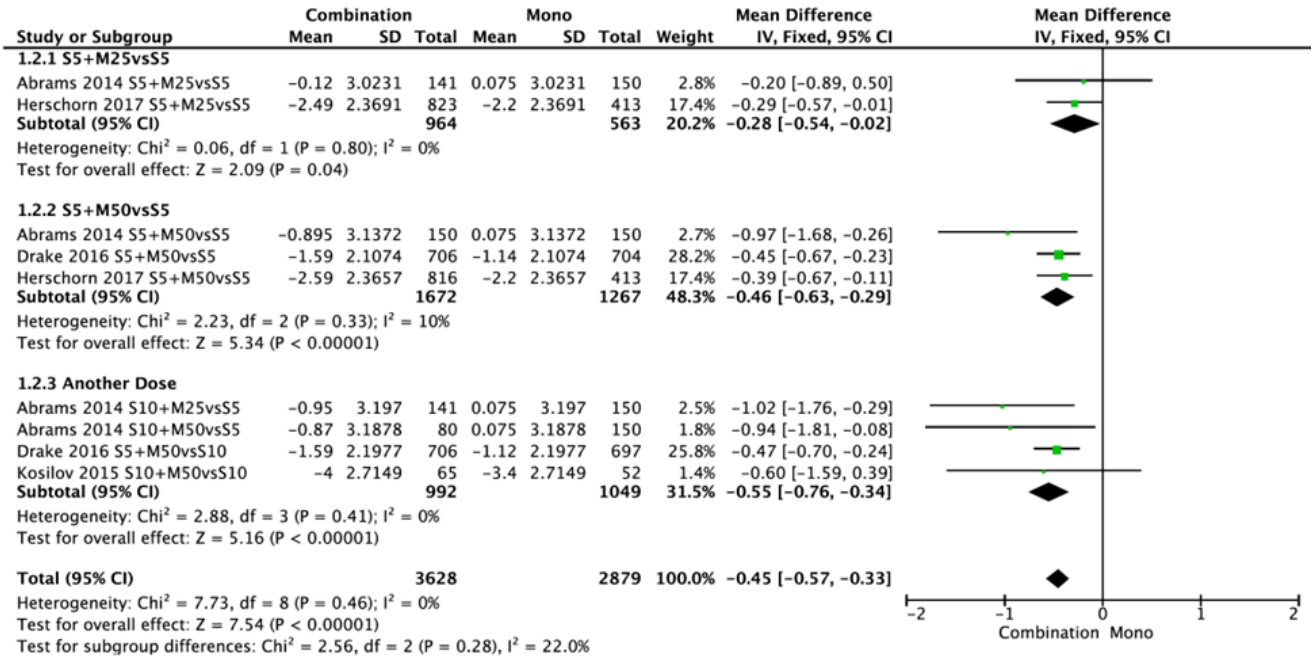

Figure 3. Combination vs Monotherapy Micturition Forrest Plot

Solifenacin 5 mg + Mirabegron 25 mg vs Solifenacin 5 mg

From two studies, combination solifenacin 5 mg and Mirabegron 25 mg showed insignificant result in Incontinence/24h compared to monotherapy solifenacin 5 mg only with MD of -0.45(95% CI: -0.91 – 0.02, P=0.06) (Fig. 4). The Cochrane Q test (Chi2: 3.18, P=0.07) showed the inconsistency of clinical methodological aspects between studies, I2 (I2: 69 %) revealed a significant heterogeneity and a random effect model was applied.

Solifenacin 5 mg + Mirabegron 50 mg vs Solifenacin 5 mg

From three studies, combination solifenacin 5 mg and Mirabegron 50 mg showed significant result in Incontinence/24h compared to monotherapy solifenacin 5 mg only with MD of -0.41(95% CI: -0.75 – -0.07, P=0.02) (Fig. 4). The Cochrane Q test (Chi2: 8.58, P=0.01) showed the consistency of clinical methodological aspects between studies, I2 (I2: 77 %) revealed a significant heterogeneity and a random effect model was applied.

Another Dose

From three studies, combination therapy showed significant results in Incontinence/24h compared to monotherapy with MD of -0.63(95% CI: -1.16 – -0.10, P=0.02) (Fig. 4). The Cochrane Q test (Chi2: 12.16, P=0.007) showed the inconsistency of clinical methodological aspects between studies, I2 (I2: 75 %) revealed a significant heterogeneity and a random effect model was applied.

From total analysis, combination therapy showed significant results in Incontinence/24h compared to monotherapy with MD of -0.45 (95% CI: -0.65 – -0.24, P<0.000) (Fig. 4). The Cochrane Q test (Chi2: 24.10, P=0.002) showed the inconsistency of clinical methodological aspects between studies, I2 (I2: 67 %) revealed a significant heterogeneity and a random effect model was applied.

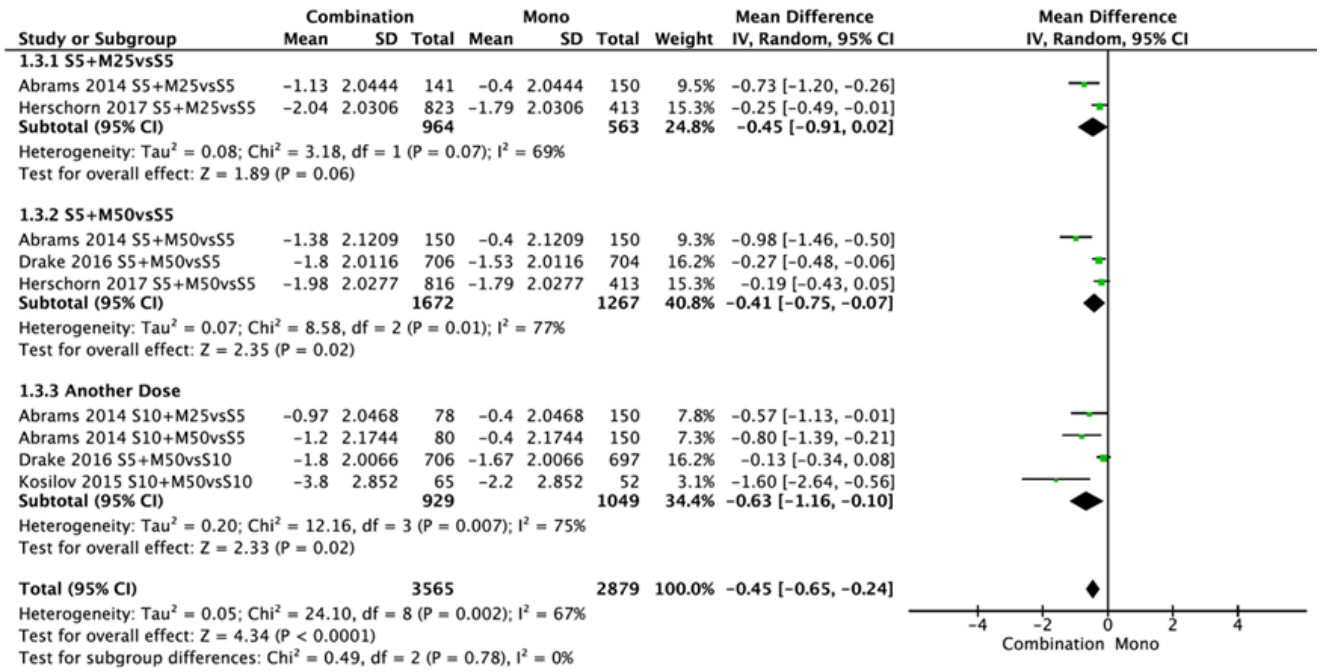

Figure 4. Combination vs Monotherapy Incontinence Forrest Plot

Safety

Adverse Events

Nine RCTs total 6644 participants (3675 in combination group and 2969 in monotherapy group). Based on data (table) showed the OR was 1.10 and the 95% CI was 1.00 to 1.22 (P =0.06) (Fig. 5). This result indicates that the combination and monotherapy group were similar in terms of the incidence of Adverse events.

Discontinuation due to medication

Total of 6644 participants from 9 RCTs (3675 in combination group and 2969 in monotherapy group) report discontinuation due to medication (table). The pooled estimate of the odds ratio was 1.40 and 95 % confidential interval 0.95 to 2.07 (P=0.09) (Fig. 6). There was no apparent significance in terms of side effects between the combination therapy group and monotherapy group in terms of discontinuing medication due to medication.

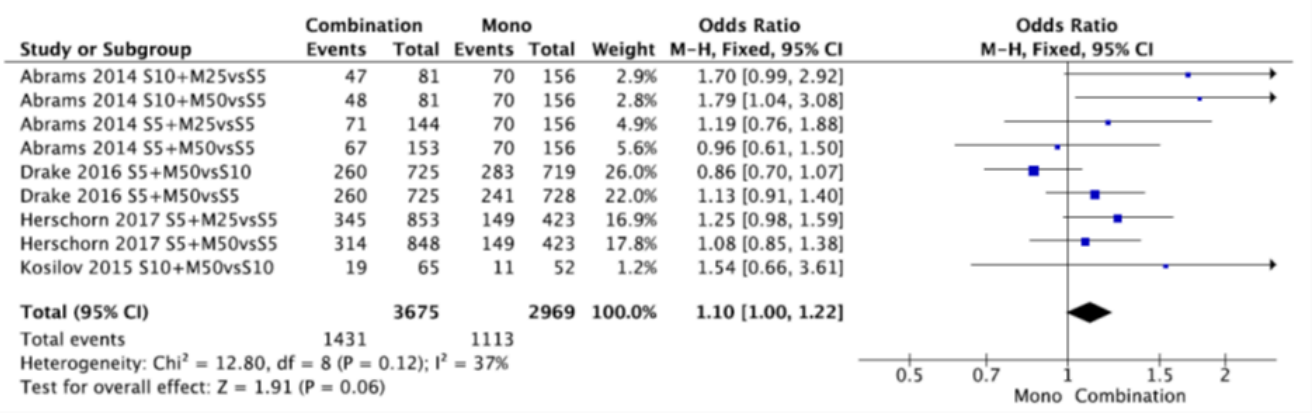

Figure 5. Combination vs Monotherapy Adverse Event Forrest Plot

Constipation

Total of 6532 participants from 8 RCts (3615 in combination group and 2917 in monotherapy group). Based on data (table) The pooled estimate of the OR was 1.59 and the 95 % CI was 1.00 to 2.51 (P=0.05) (Fig. 7). These results suggest that there were no bold differences in terms of constipation between the combination group and the monotherapy group in terms of constipation.

Dry Mouth

Total of 6644 participants from 9 RCTs (3675 in combination group and 2969 in monotherapy group) report discontinuation due to medication (table). The pooled estimate of the OR was 1.09 and the 95% CI was 0.91 to 1.31 (P= 0.37) (Fig. 8). These results indicate that there are no apparent differences in terms of dry mouth between the combination group and the monotherapy group in terms of dry mouth.

UTI

Total of 6532 participants from 8 RCts (3615 in combination group and 2917 in monotherapy group) report UTI (table) . The pooled estimate of the OR was 0.96 and the 95% CI was 0.73 to 1.27 (P=0.79) (Fig. 9). These results suggest that there are no bold differences between, in terms of UTI, the combination group and the monotherapy group in terms of UTI.

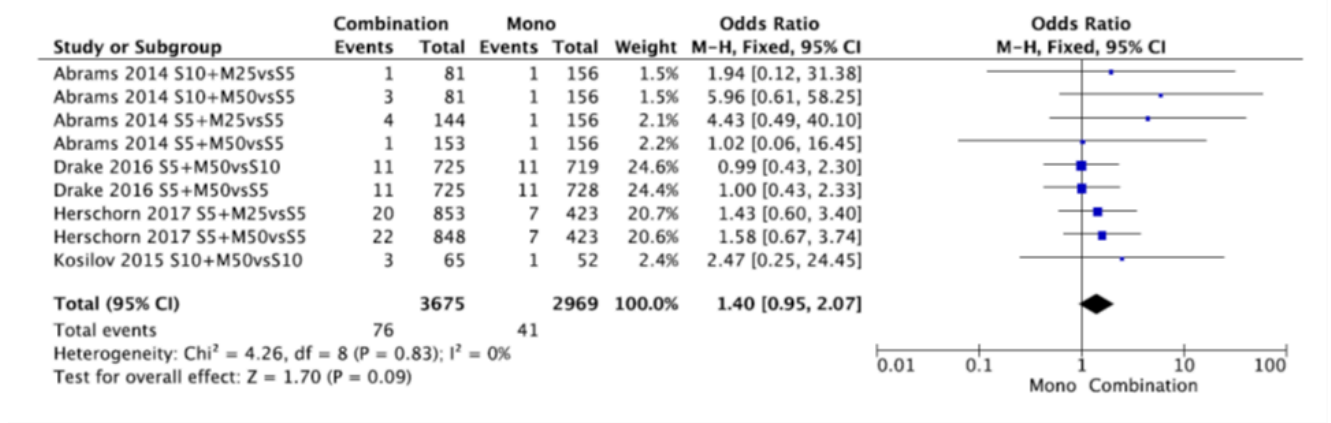

Figure 6. Combination vs Monotherapy Micturition Discontinue due to Medication Forrest Plot

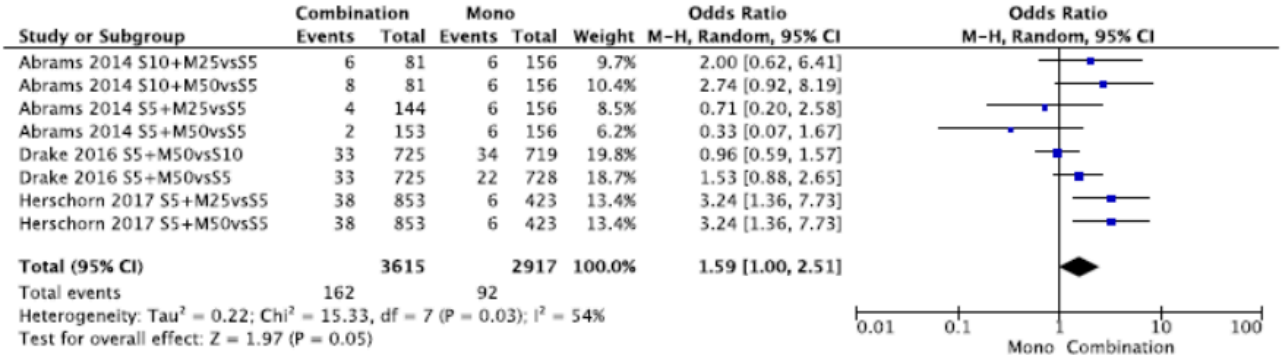

Figure 7. Combination vs Monotherapy Micturition Discontinue due to Constipation Forrest Plot

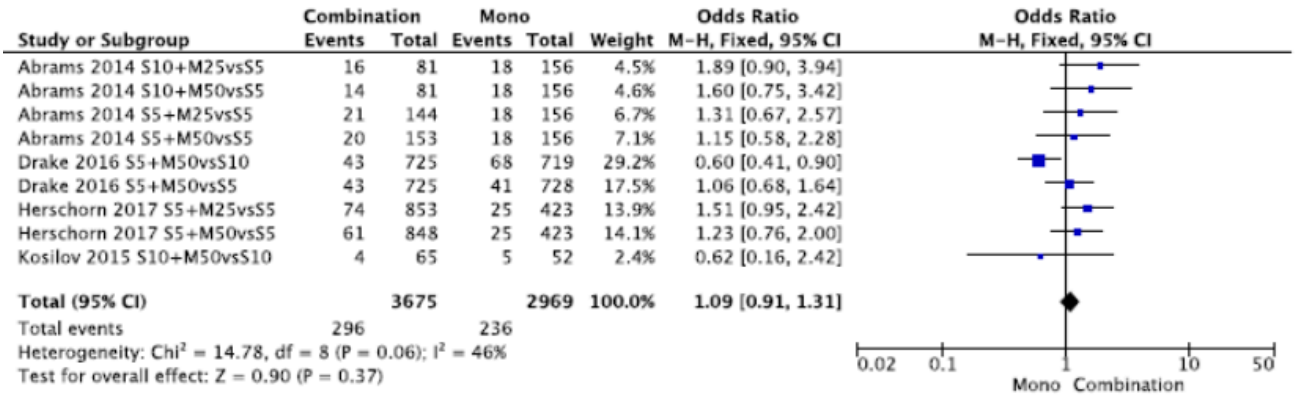

Figure 8. Combination vs Monotherapy Micturition Discontinue due to Dry Mouth Forrest Plot

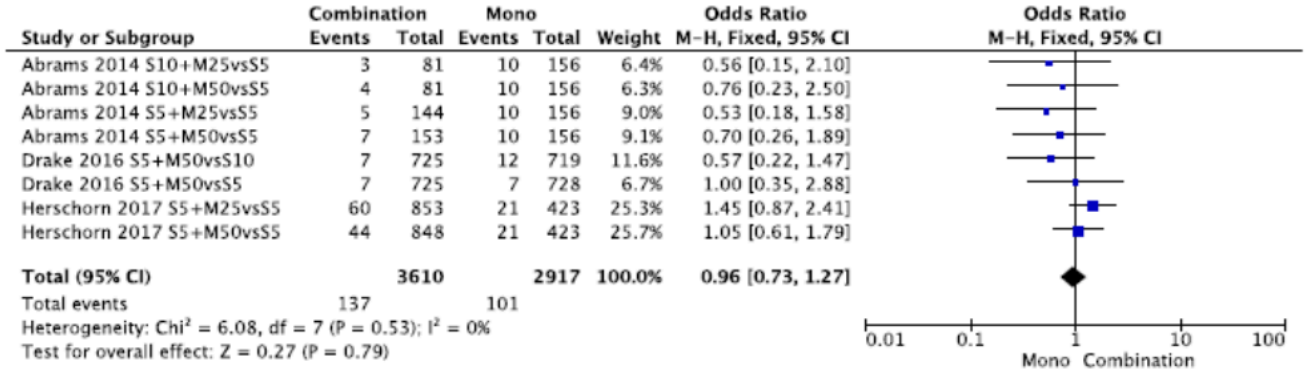

Figure 9. Combination vs Monotherapy Micturition Discontinue due to UTI Forrest Plot

Discussion

The symptoms of overactive bladder have a detrimental effect on a patient's daily activities and quality of life (QoL) [1, 2]. Antimuscarinic agents, such as solifenacin, are first-line pharmacotherapy for the treatment of OAB symptoms. Solifenacin inhibits contractions of human detrusor smooth muscles mainly by the antimuscarinic action but persistence with treatment is limited by insufficient efficacy and Antimuscarinic associated adverse events (AEs) [3]. Mirabegron has a different mechanism of action as the b3-adrenoceptor is the predominant b-receptor subtype in the human urinary bladder [4]. B3-adrenoceptor agonists relax detrusor smooth muscle during the bladder storage phase and increase bladder capacity without negatively affecting voiding parameters, including maximum urinary flow rate (Qmax), detrusor pressure at Qmax (PdetQmax), and residual volume [5]. Combining these two oral pharmacotherapies with distinct modes of action and proven efficacy may improve OAB symptoms without exacerbating anticholinergic burden.

This systematic review and meta-analysis conducted to determine which dose combination therapies of solifenacin and mirabegron resulted in better outcome compared to solifenacin alone. Two pooled RCT's results determine combination therapy (Solifenacin 5 mg + mirabegron 25 mg) do not improve MVV and incontinence episode/24h but significantly improve micturition/24h. Three pooled RCT's result determines combination therapy (Solifenacin 5 mg + mirabegron 50 mg) significantly improves MVV, incontinence episode/24h, and micturition/24h. Three pooled RCT's results determine combination therapy consisting of several doses showed significantly improved OAB symptoms. From the results of this study, it was found that the optimal combination therapy dose to improve symptoms of OAB patients was solifenacin 5 or 10 mg plus 50 mg of mirabegron. The add-on dose of 25 mg mirabegron did not have significant results on symptoms of OAB patients. With the addition of mirabegron 50

mg, it can reduce symptoms and can be an add-on therapy option for this group of patients.

Consistent with previous clinical SYMPHONY studies [1], Solifenacin 5 mg + mirabegron 25 mg group statistically do not improve MVV and incontinence episode/24h otherwise for all treatment combinations, a trend towards improving OAB symptom was observed with increasing solifenacin and mirabegron doses. This evidence was also supported in prior study of SYNERGY, the lower dose of combination did not significantly improve incontinence episode/24h and MVV. A selective b3-AR agonist (mirabegron) significantly decreased baseline pressure and increased bladder capacity in rats with oxo-M-induced bladder overactivity [6]. M3-receptor inhibition can suppress not only spontaneous contraction of detrusor muscle, but also the release of ATP and PGE2 from the urothelium. It has been reported that the increases in ATP and PGE2 in the bladder were induced by the distention of isolated rat bladders [7]. Furata et al. [6] reported the results of a study that suggested that the combination therapy of b3-adrenoceptor agonists plus muscarinic acetylcholine receptor3 antagonists is more effective compared with monotherapy for the treatment of bladder overactivity.

OAB is one of the most cases of lower urinary tract symptoms (LUTS) in both women and men and is associated with significant bothersome symptoms and a poorer quality of life. The most case of OAB considered idiopathic on many patient. Pharmacological therapy for OAB treatment is widely used until now. The main 2 classes of drugs used are antimuscarinic and the newer beta 3 -AR agonist. The most common drug is mirabegron and solifenacin, both of them can be a combination to treat OAB.

The present studies report safety of mirabegron and solifenacin as monotherapy and combination therapy. Incidence of drug related adverse events in the present study was similar between combination and monotherapy. Yamaguchi et al reported in a previous study that the results of the MILAI study , which explained the effects of mirabegron as an add on therapy in patients whom OAB was treated with solifenacin. The writers found that the combination of mirabegron to solifenacin resulted in only mild to moderate adverse events. Therefore the combination of solifenacin and mirabegron showed lack of serious side effects in patients with cold stress exacerbated LUTS.

The safety data which included in this study suggest that the combination therapy between mirabegron and solifenacin is well tolerated. Considered of adverses reactions, such as adverse events, discontinuation of medication, constipation, dry mouth , and UTI were similar in term of safety between combination and monotherapy. Drymouth, which was the most frequently reported adverse event with antimuscarinic. And a common reason for treatment discontinuation.

Our meta-analysis involved four RCTs and the quality of each RCT was high. Some limitations have been found from this meta-examination. First, We could not acquire the long-term efficacy and tolerance of combination therapy. Second, Second, because of the limited data, the population ratio was used to subdivide studies for analysis. Third, in some subgroups, the number of studies and patients is relatively small. Third Heterogeneity has been observed and influenced our final results. . So it still needs a lot of RCTs including sufficient sample size and statistics to confirm our findings. More high-quality RCTs with suitable study cohorts are needed to ascertain the efficacy and tolerance of combination therapy. Despite all the limitations, our research supports that add-on mirabegron is more effective compared with monotherapy for the treatment of OAB patients.

Conclusion

This study showed the efficacy of combination therapy of mirabegron plus solifenacin which significantly improved storage symptoms regarding micturition and incontinence episode, compared to solifenacin monotherapy. As for safety profile, there is no significant result of adverse effects and discontinuation of medication due to AEs. Combination therapy provides better therapeutic benefits, while generally is well tolerated for patients with overactive bladder syndrome.

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