Systematic Review and Meta-Analysis

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Monotherapy with mirabegron had a better tolerance than the anticholinergic agents on overactive bladder

A systematic review and meta-analysis

Wei Yi, MD, Yue Yang, MD*, Jin Yang, MD

Abstract

Background: We conducted this meta-analysis to explore the tolerance of monotherapy with mirabegron (50 mg) on an overactive bladder, compared with a common dosage of anticholinergic agents.

Materials and methods: A comprehensive search for all randomized controlled trials that evaluated the safety of mirabegron and anticholinergic agents on overactive bladder was performed, and we searched the Cochrane Central Register of Controlled trials databases, Pubmed, Embase, and relevant trials from 2013.02 to 2019.10.

Results: Eight studies included 5500 patients with treatment of monotherapy on overactive bladder were identified. The total number of treatment-emergent adverse events had no significantly difference between two monotherapies (RR = 0.88 95%CI: 0.76–1.01; $P = .08$); however, patients would have a better tolerance with mirabegron (50 mg) in adverse events of dry mouth (RR = 0.42; 95%CI: 0.33–0.53; $P < .01$) and tachycardia (RR = 0.52; 95%CI: 0.29–0.94; $P = .03$); and there were no significant differences between two groups in hypertension (RR = 1.02; 95%CI: 0.80–1.30; $P = .90$), constipation (RR = 0.91; 95%CI: 0.65–1.26; $P = 0.57$), blurred vision (RR = 1.03; 95%CI: 0.60–1.77; $P = 0.92$), and urinary tract infection (RR = 0.90; 95%CI: 0.70–1.16; $P = .41$).

Conclusions: Treatment-emergent adverse events in patients with overactive bladder who underwent monotherapy of mirabegron (50 mg) or the anticholinergic agents had no significant differences, but mirabegron has a better tolerance in the aspect of dry mouth and tachycardia.

Abbreviations: 95% CI = 95% confidence interval, ICS = International Continence Society, OAB = Overactive bladder, OR = odds ratio, RCTs = randomized controlled trials, RR = risk ratio, TEAEs = treatment-emergent adverse events, UTI =Urinary Tract Infection.

Keywords: anticholinergic agents, meta-analysis, mirabegron, monotherapy, overactive bladder, TEAEs

1. Introduction

According to the International Continence Society (ICS), overactive bladder (OAB) is defined as a symptom syndrome that is characterized by urgency, frequency, and nocturia without any obvious pathology.[1] Several studies have demonstrated that the prevalence of OAB would be increased in women from middle age and men after their 50s.[2,3] It is reported that 3.4% of men and 8.7% of women aged from 40 to 44 years old would have symptoms of OAB, and more than 80% of individuals aged 80 to 90 years may have at least one void per night.[4–6] As the globe is expected to step into old-age society, the OAB is likely to place an increasing strain on healthcare resources. Anticholinergic agents,[7] such as solifenacin and tolterodine, are used as the cornerstone of pharmacotherapy for OAB symptoms. However, they were accompanied by some bothering adverse effects, such as dry mouth, blurred vision, constipation, even cognitive effects, which were leading to poor adherence to the prescribed medications.[8,9] In 2011, mirabegron, a β3-adrenoceptor agonist, was developed as a potential alternative treatment for OAB symptoms and had a distinct mechanism of action from anticholinergic agents. It is mainly responsible for promoting human detrusor relaxation and urine storage in the bladder.[10] Compared with anticholinergic agents, plenty of randomized controlled trials have reported that mirabegron could have better efficacy in monotherapy of the OAB symptoms.[11–13] However,

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Urological Department, The Affiliated Hospital of Chengdu University, Chengdu, Sichuan, China.

** Correspondence: Yue Yang, Urological Department, The Affiliated Hospital of Chengdu University, Chengdu, Sichuan, China (e-mail: sduyangyue@163.com).*

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they are also associated with specific side effects, including hypertension, constipation, dry mouth, tachycardia, and UTI.[14] Both mirabegron and anticholinergic agents could improve OAB symptoms, but the safety of them was not so clear. Considering the divergence about mirabegron or anticholinergic agents for patients with OAB, we conducted this meta-analysis and review to elucidate the safety of such two kinds of monotherapies in this study.

2. Methods

2.1. Selection criteria

All the studies should be published in English and conform to the following criteria:

1. All patients should have OAB symptoms.
2. All patients were only treated with therapeutic drugs: mirabegron and anticholinergic agents: solifenacin, or imidafenacin, or tolterodine.
3. The studies should illuminate the therapeutic regimen including the dose and name of drugs, observation period, the general data of patients, and the adverse effect.
4. The studies should contain monotherapies of mirabegron (50 mg) and anticholinergic agents: solifenacin (5 mg), or imidafenacin (0.2 mg), or tolterodine (4 mg).
5. The therapeutic drug in the study should be recorded in detail.
6. All the studies should be designed as randomized controlled trials (RCTs).
7. The same trial that was reported by different articles should also be excluded.

2.2. Search strategy

According to the above selection criteria, we searched Pubmed, Embase, and the Cochrane Library (from 2013.02 to 2019.10). Besides, potentially relevant trials from the references of relative studies were also searched by hand. The following medical subject headings (MeSH) or non-MeSH terms were used in the method: "overactive bladder," or "overactive urinary bladder," or "overactive detrusor," or "overactive detrusor function," and "adrenergic beta-3 receptor agonists" or "mirabegron" or "anticholinergic agonists."

2.3. Data extraction

Two reviewers independently assessed all eligible publications, and any disagreements were discussed with a third reviewer and solved by all reviewers. With selection criteria and excluding criteria, each reviewer used a standardized extraction form to extract the data from all full-text studies included details of author names, the year of publication, country, study period, the general data of patients, duration of follow-up, and results of side effect.

2.4. Outcome measures

The primary outcome measure in this meta-analysis was the total number of treatment-emergent adverse events (TEAEs), defined as adverse events starting or worsening after initiating the first dose of the drug.[15] The secondary outcome measures included all the TEAEs: dry-mouth, tachycardia, influenza, constipation, hypertension, blurred vision, UTI, headache, and so on. These outcomes should not exist from the beginning but develop as a side effect during the treatment.

2.5. Statistical analysis

Differences were expressed as RR (95% CIs) for the primary outcome and secondary outcome. A RR of <1 meant an advantage of monotherapy on mirabegron (50 mg) when compared with a single and common dose of anticholinergic agents. Heterogeneity across trials was quantified by using the I^2 statistic. When an I^2 statistic was below 50% by chi-square test, which indicted to have a low level of heterogeneity, a fix-effects model was used for estimates; and if I^2 was over 50%, a random-effects model was chosen. A P-value $< .05$ was affirmed as statistically significant. All statistical analyses were performed by Revman 5.3.

2.6. Quality assessment

The Cochrane collaboration's tool which was recommended for assessing the risk of bias was used for evaluating the methodological quality of each RCT, which included seven aspects: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias, to provide a qualification of risk of bias.[16] Each reviewer would assess included studies in the risk of bias. Disagreements were resolved through discussion.

2.7. Level of evidence

We classified the quality of each included study by the Jadad scale.[17] All of the RCTs were assigned according to the quality classification standards as follows:

A. Satisfying almost all of the quality criteria, the study would be considered to have a low probability of bias;
B. Satisfying the partial quality criteria or unclear, the study was thought of having a second probability of bias;
C. Satisfying bare quality criteria, the study was considered to have a high probability of bias.

3. Results

After careful review, 8 eligible studies that were published from 2013.02 to 2019.10 were finally included. The selection strategy was shown in Figure 1. A total of 5500 patients were involved in this meta-analysis and the characteristics of 8 studies were summarized in Table 1.[11,18–25]

3.1. Effect of interventions on the outcome measure

The total number of TEAEs was the primary outcome measure in this meta-analysis and they were extracted from studies directly (Fig. 2A). Considering there was heterogeneity ($I^2 = 74\%$) in the analysis, a random-effects model was used. The pooled RR was 0.88 (95%CI: 0.76–1.01; $P = .08$), which represented no significant difference between the two monotherapies in the rate of TEAEs. Furthermore, subgroup analysis was conducted by excluding the studies of midafenacin and tolterodine. The heterogeneity decreased, but no significant difference was

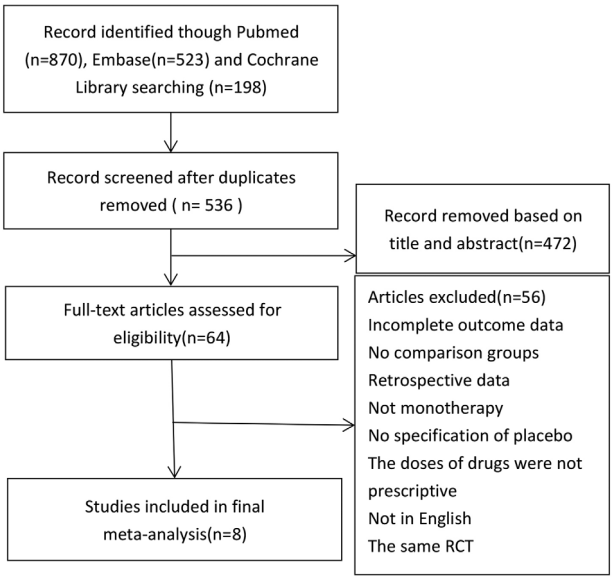


Figure 1. Selecting flowchart for included studies in the meta-analysis.

observed between the two therapies (Fig. 2B, RR = 0.89; 95%CI: 0.75–1.07; $P = .21$; heterogeneity: $I^2 = 70\%$).

The secondary outcome measures included the particular TEAEs. There was significant difference between two groups in dry mouth (Fig. 3A RR = 0.42; 95%CI: 0.33–0.53; $P < .001$, heterogeneity: $I^2 = 26\%$) and tachycardia (Fig. 3B, RR = 0.52; 95%CI: 0.29–0.94; $P = .03$, heterogeneity: $I^2 = 48\%$), which indicated a better tolerance of patients with mirabegron (50 mg) in these aspects, and no significant heterogeneity was observed as well. However, as for blurred vision (Fig. 4A, RR = 1.03; 95%CI: 0.60–1.77; $P = .92$, heterogeneity: $I^2 = 0\%$), constipation (Fig. 4B, RR = 0.91; 95%CI: 0.65–1.26; $P = .57$, heterogeneity: $I^2 = 13\%$), hypertension (Fig. 4C, RR = 1.02; 95%CI: 0.80–1.30; $P = .90$, heterogeneity: $I^2 = 0\%$), UTI (Fig. 4D, RR = 0.90; 95% CI: 0.70–1.16; $P = .41$, heterogeneity: $I^2 = 0\%$), there was not significant difference between two groups.

In addition, the rates of TEAEs in both groups were counted. In the group of mirabegron, hypertension (4.17%), UTI (3.99%), dry-mouth (3.10%), constipation (2.36%), and nasopharyngitis (2.33%) were the most common TEAEs, and headache (1.66%), influenza (1.14%), back pain (1.14%), s-AE (1.07%), somnolence (1.07%), sinusitis (1.00%), and so on also occurred but not so usual in patients (Fig. 5A). Compared with anticholinergic agents, the rate of TEAEs was lower in the mirabegron group (Fig. 5B).

3.2. Qualitative risk of bias and quality assessment

According to the Cochrane Collaboration handbook, the quality of RCTs was provided in detail (Fig. 6A) and most included studies showed a low risk of bias (Fig. 6B and C).

4. Discussion

For the last decade, mirabegron is the first β3-adrenoceptor agonist that is used in clinical practice for the treatment of OAB. Several RCTs have shown that mirabegron exhibits significant therapeutic efficacy, but it is also accompanied by various unpredictable side effects, which could contribute to poor tolerance and a suboptimal response.[26,27]

Anticholinergic agents,[28] such as solifenacin, imidafenacin, and tolterodine, are first-line treatments for OAB. The most common adverse effects reported were hypertension, constipation, and dry mouth. As previous studies[7] have shown a relationship between the increasing dose of anticholinergic agents and AE, controlling the doses of drugs in the therapies with OAB must be taken into consideration when we compared the safety of different anticholinergic agents with mirabegron.

In our studies, we conducted this whole meta-analysis with the most common and basic mono-therapeutic dose of OAB: mirabegron (50 mg) and solifenacin (5 mg), or imidafenacin (0.2 mg), or tolterodine (4 mg), which were widely recommended in clinics.[7,10,28,29] The pathogenesis and etiology of OAB were not explicit, and the main theories still were held in two aspects: neurogenic and myogenic.[30] Anticholinergic agents act through the inhibition of the muscarinic receptors (M2 and M3), which would decrease both Aδ and C fibers acting in the bladder afferent pathway, thus it results in increase of the bladder storage and improvement of the OAB symptoms.[28] However, muscarinic receptors are widely existed in muscles, not only in the urothelium and suburothelial myofibroblasts. Improvements in OAB symptoms were affected by dose escalation at the price of increasing systemic adverse effects such as hypertension, dry mouth, UTI, and constipation.[21,31]

In our studies, it indicated no significant difference between the two monotherapies in the rate of total TEAEs, but the mirabegron group had a better tolerance than the anticholinergic group in the aspect of dry-mouth and tachycardia. Mirabegron, a β3-adrenergic receptors (β3-AR) agonist, alleviates the symptoms

Table 1

Characteristics of included studies.

Study (year)	Follow-up (month)	Sex (male/female)		Age (year ± SD)		Drug in control group (drug + dose)
		Mira	Control	Mira	Control	
Ozkidik Mete 2019	3m–12m	All female		47.3 ± 4.82	49.1 ± 2.73	Solifenacin 5 mg
Otuska Atsushi 2016	1.5m	All female		73.5 ± 8.5	74.0 ± 8.2	Imidafenacin 0.2 mg
Kinjo Manami 2018	12m	All female		63.4 ± 11.0	61.5 ± 10.7	Solifenacin 5 mg
Herschorn Sender 2017	4.5m	99/323	92/331	56.7 ± 13.3	58.2 ± 12.8	Solifenacin 5 mg
Gratzke Christian 2018	12m	63/239	58/241	61	60	Solifenacin 5 mg
Chapple Christopher 2013	12m	210/602	212/600	59.2 ± 12.56	59.6 ± 12.47	Tolterodine 4 mg
Abrams Paul 2015	3m	26/52	53/103	53.4 ± 14.0	54.2 ± 15.5	Solifenacin 5 mg
Jose E. Batista 2015	3m	224/712	225/709	56.7 ± 14.3	57.4 ± 13.6	Solifenacin 5 mg

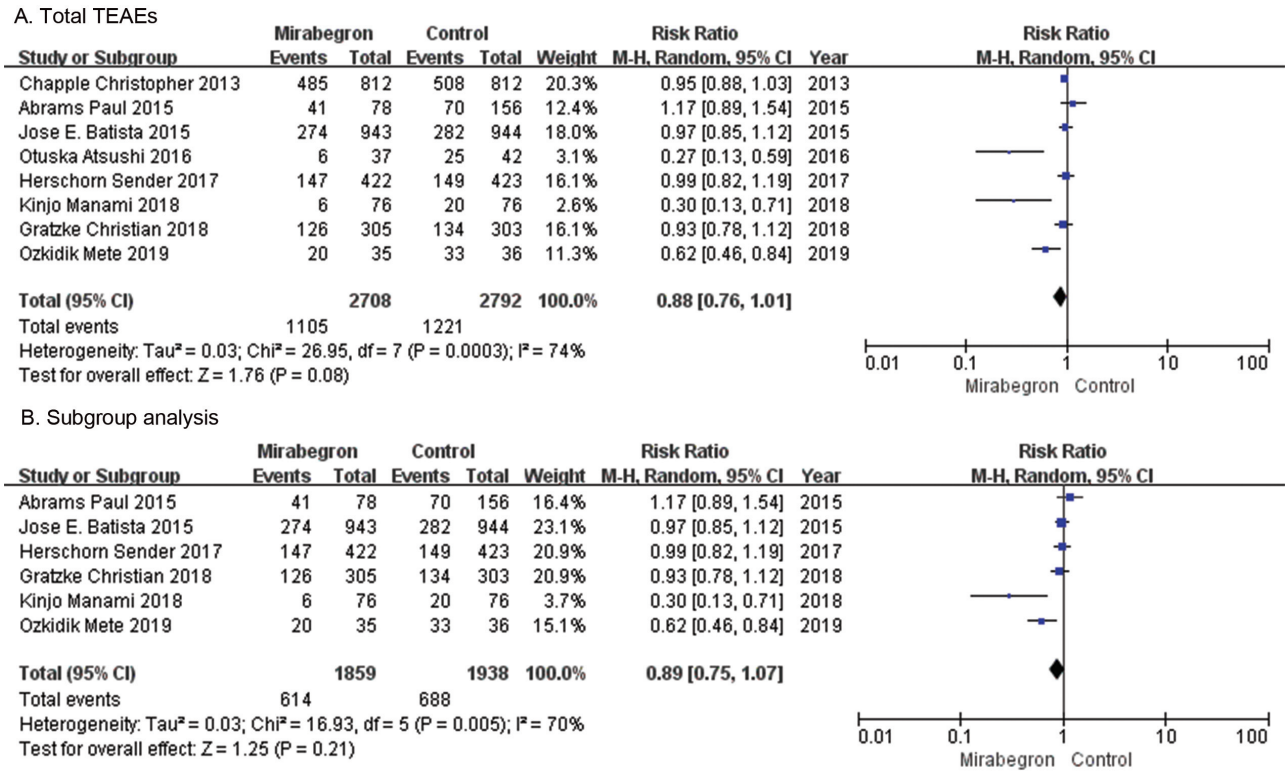


Figure 2. (A) Forest plots showing changes in total TEAEs; (B) subgroup analysis of total TEAEs: exclude the studies of imidafenacin and tolterodine.

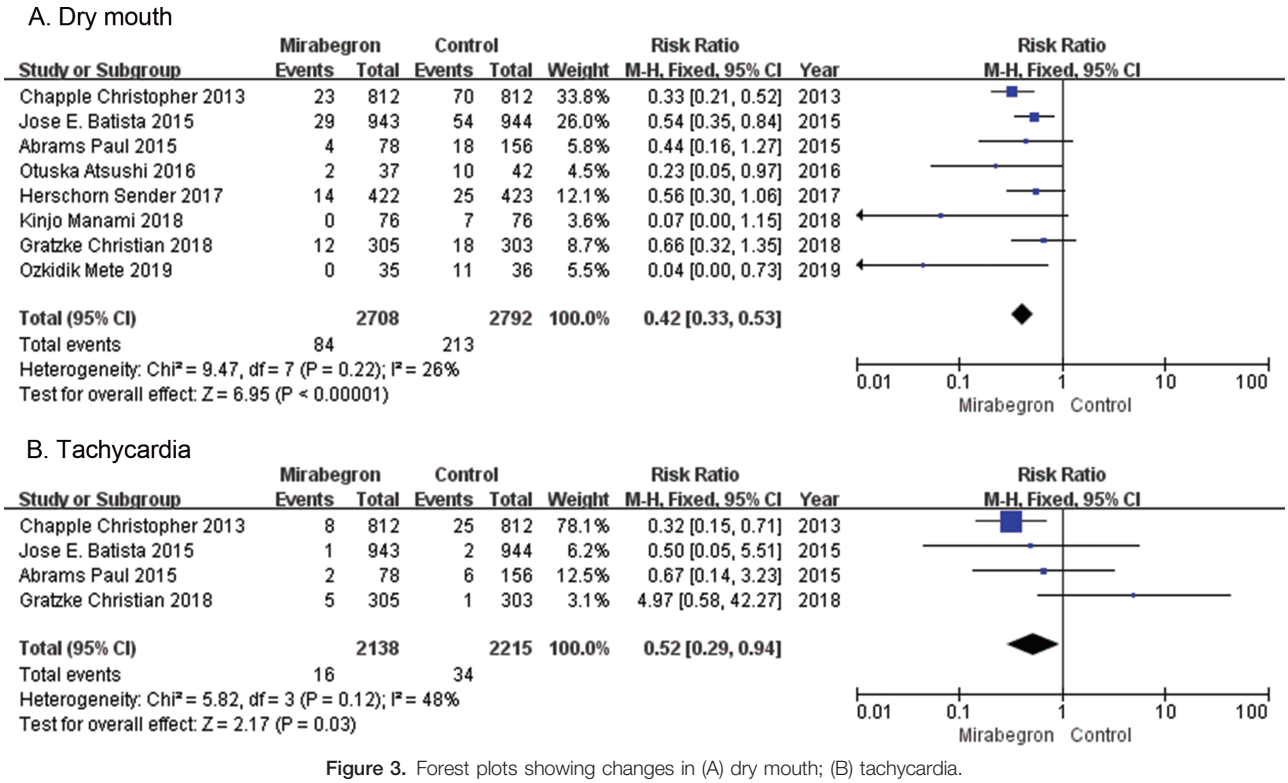


Figure 3. Forest plots showing changes in (A) dry mouth; (B) tachycardia.

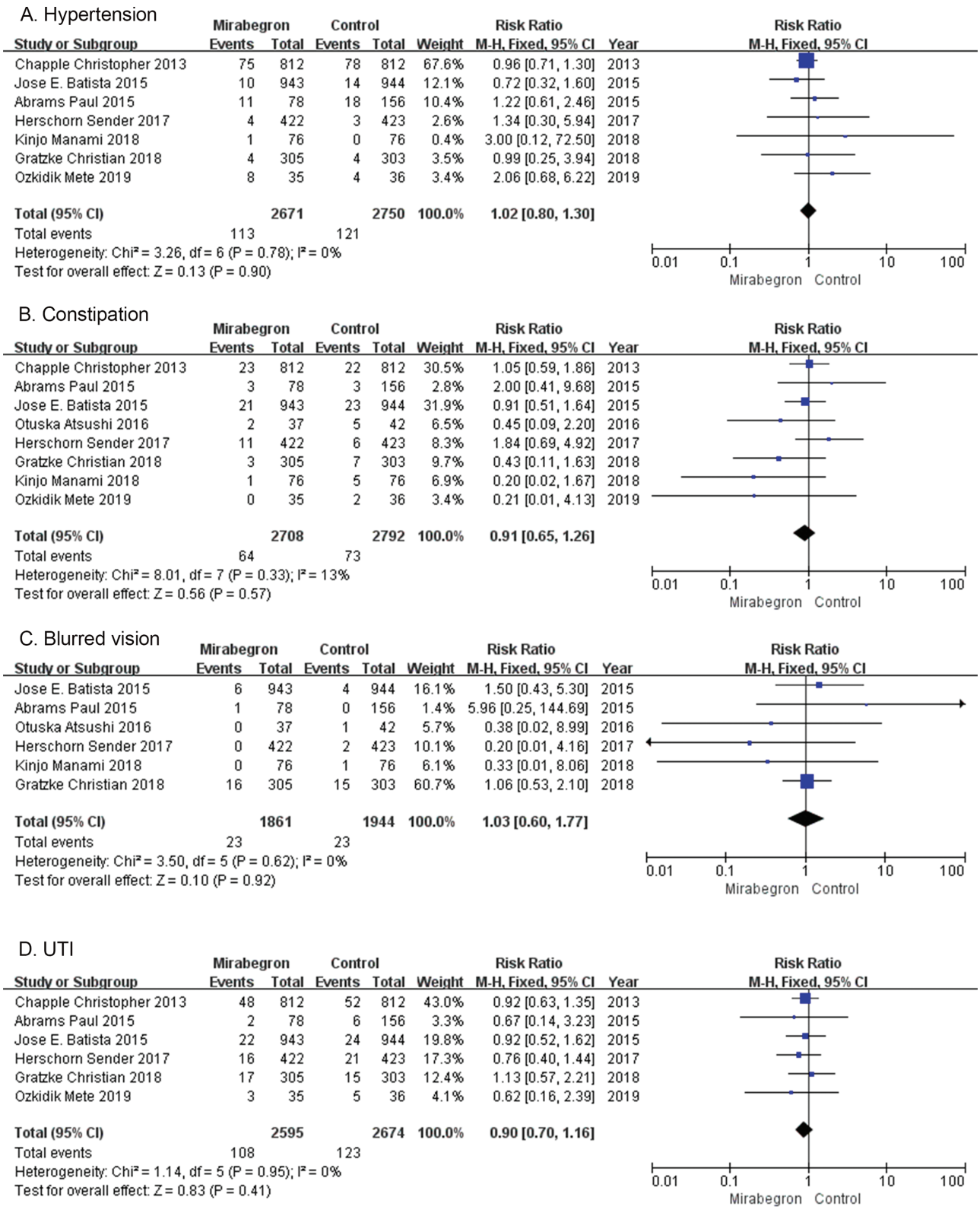


Figure 4. Forest plots showing changes in (A) blurred vision, (B) constipation, (C) hypertension, and (D) UTI.

of OAB through activation of prejunctional β3-adrenoceptors, resulting in downregulation of A.ch release in the cholinergic terminal during the storage phase and inhibiting the control of parasympathetic activity to decrease urgency sensation.[10] Thus, patients with mirabegron would experience a lower rate of antimuscarinics' deterring side effects. In the recent RCT: SYNERGY II, Christian Gratzke. et al[22] compared mirabegron (50 mg, n = 305) with solifenacin (5 mg, n = 303). They pointed

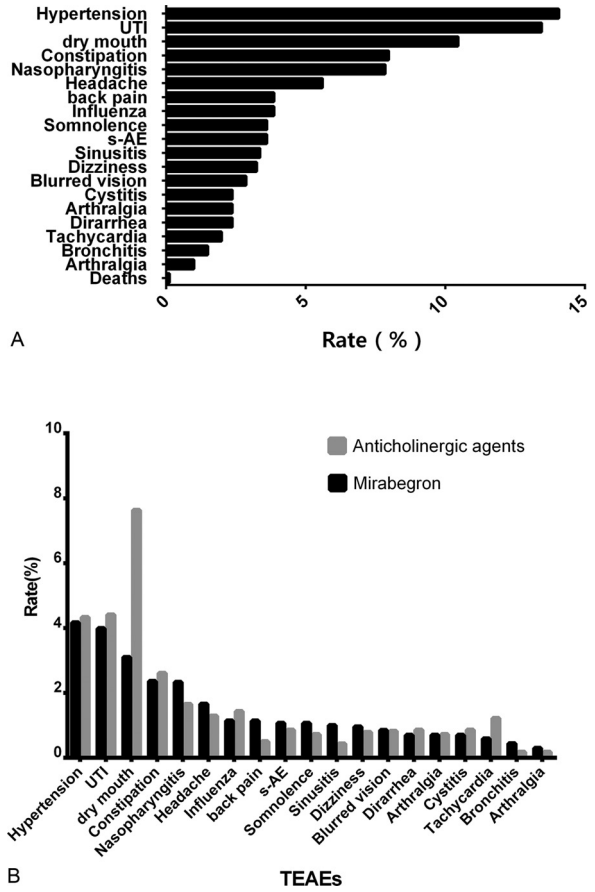


Figure 5. (A) Common TEAEs in mirabegron group (ranking list); (B) rate of TEAEs in therapies of mirabegron and anticholinergic agents.

out that the frequency of serious TEAEs was lower in the group of mirabegron (11% vs 14%), and the dry mouth (3.9% vs 5.9%), constipation (1.0% vs 2.3%), nasopharyngitis (5.2% vs 5.0%), and UTI (3.6% vs 4.0%) were the relatively common TEAEs.

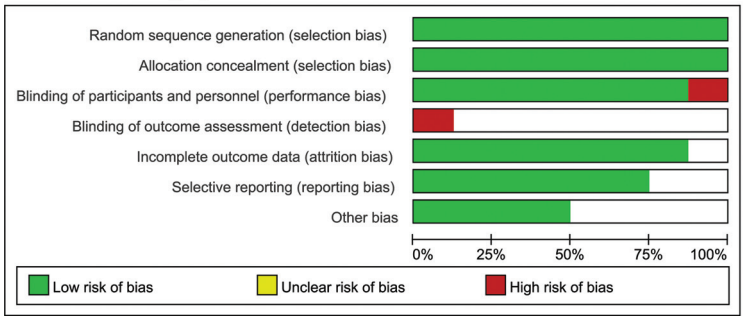
Meanwhile, our meta-analysis also indicates that various TEAEs would be accompanied in therapies of mirabegron or anticholinergic agents. In the group of mirabegron, patients would be more susceptible to hypertension, UTI, dry-mouth, constipation, and nasopharyngitis. Compared with the anticholinergic agents, our study indicated that the rate of TEAEs was lower in the group of mirabegron. Notable, better tolerability of dry mouth (3.10% vs 7.63%) and tachycardia (0.59% vs 1.22%) were observed in patients with mirabegron (50 mg), thus we may recommend mirabegron (50 mg) for OAB as the first monotherapy when the patients were sensitive to these aspects. Furthermore, in our studies, the incidences of sinusitis (1.00% vs 0.43%) and bronchitis (0.44% vs 0.18%) were several-fold higher in the group of mirabegron over anticholinergic agents, but we could not draw any conclusions due to the small size of patients included and affected. We expected more trials to confirm these results.

The present meta-analysis also carries several limitations that must be taken into account. Our studies contained 8 RCTs and the quality of each RCT included is high. But different patients with different therapeutic schedules and follow-up times in different RCTs were hard for us to get every data in detail, which was the gold standard for meta-analysis. Meanwhile, all possible various biases in studies included could contribute to a higher heterogeneity among studies. Only English studies were searched for and included in this meta-analysis, which could exist potential publication bias. Because of these limitations, larger and randomized control trials were needed to confirm these results.

A:Quality assessment of individual study

Study	Allocation sequence generation	Allocation concealment	Blinding	Loss to follow-up	Calculation of sample size	Statistical analysis	Level of quality	ITT analysis
Ozkidik Mete 2019	A	A	A	3	Yes	ANCOVA	A	No
Otuska Atsushi 2016	B	A	B	2	Yes	ANCOVA	B	No
Kinjo Manami 2018	B	A	B	29	Yes	ANCOVA	B	No
Herschorn Sender 2017	A	A	A	6	Yes	ANCOVA	A	No
Gratzke Christian 2018	A	A	A	3	Yes	ANCOVA	A	No
Chapple Christopher 2013	A	A	A	21	Yes	ANCOVA	A	No
Abrams Paul 2015	A	A	A	7	Yes	ANCOVA	A	No
Jose E. Batista 2015	A	A	A	4	Yes	ANCOVA	A	No

A, all quality criteria met (adequate): low risk of bias; B, most quality criteria met (adequate): moderate risk of bias; ITT, intention-to-treat; ANCOVA, analysis of covariance.



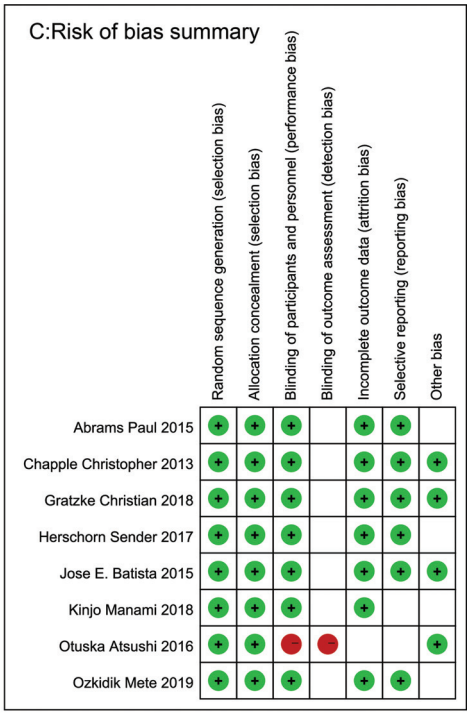


Figure 6. Quality assessment and risk of bias of included studies.

5. Conclusions

In conclusion, TEAEs in patients with OAB who underwent mono-therapy of mirabegron (50 mg) or the anticholinergic agents have no significant differences, but mirabegron (50 mg) has a better tolerance in the aspect of dry mouth and tachycardia.

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Author contributions

Study design, data extraction, and data analysis: YW, YY; manuscript writing and edition: YW, YY, and JY.
Conceptualization: Wei Yi.
Data curation: Wei Yi, Jin Yang.
Formal analysis: Yue Yang.
Investigation: Jin Yang.
Methodology: Wei Yi.
Project administration: Jin Yang.
Resources: Yue Yang.
Software: Yue Yang, Jin Yang.
Supervision: Yue Yang.
Validation: Yue Yang.
Writing – original draft: Wei Yi.
Writing – review & editing: Wei Yi, Yue Yang.

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