LITERATURE REVIEW

Adverse events associated with mirabegron 50 mg versus placebo: A systematic review and meta-analysis

Effets secondaires du mirabegron 50 mg versus placebo : revue systématique et méta-analyse

J. Hou, F. Xu, H. Du, N. Li*

Department of Urology, Fourth Affiliated Hospital, China Medical University, 4 Chong Shan East Road, Shenyang, Liaoning, China

Received 2 April 2021; accepted 11 May 2021
Available online 24 July 2021

KEYWORDS
Meta-analysis; Safety; Adverse events; Mirabegron; Nasopharyngitis

Summary
Purpose. — The safety of mirabegron 50 mg monotherapy was comprehensively assessed versus placebo for overactive bladder.
Methods. — A systematic literature search was conducted up to June, 2020 using PUBMED, EMBASE and Cochrane Library. Randomized controlled trials evaluating safety of mirabegron in overactive bladder were collected, and safety was assessed according to 15 adverse events. Adverse events were widely selected to be assessed if they could be calculated. Heterogeneity among studies was assessed by using the $\chi^2$ test based on the Q and $I^2$ tests. Pooled effect sizes were calculated using fixed model if $I^2 < 50\%$, otherwise a random-effects model was chosen. The outcomes were nasopharyngitis, dry mouth, hypertension, constipation, headache, dyspepsia, urinary tract infection, dizziness, blurred vision, nausea, cardiovascular events, influenza, electrocardiogram QT prolonged, upper respiratory tract infection and high blood pressure.
Results. — In all, 10 peer-reviewed trials comprising 6135 patients were identified. Compared with placebo, mirabegron 50 mg had an unfavorable safety profile resulting in nasopharyngitis (OR, 1.54[95% credible interval, 1.05–2.25]; $P=0.03$. No statistical difference was found between mirabegron 50 mg and placebo groups in other 14 outcomes.

* Corresponding author.
E-mail address: air-nick@hotmail.com (N. Li).

https://doi.org/10.1016/j.purol.2021.05.005
1166-7087/© 2021 Elsevier Masson SAS. All rights reserved.
Conclusion. — Mirabegron 50 mg is further confirmed to be nearly as safe as placebo, expect for nasopharyngitis. Nasopharyngitis is associated with mirabegron 50 mg monotherapy for patients with overactive bladder.

© 2021 Elsevier Masson SAS. All rights reserved.

**MOTS CLÉS**
Méta-analyse ; Mirabegron ; Essai randomisé ; Syndrome d’hyperactivité vésicale

**Résumé**
**Objectif.** — Étudier les effets secondaires du mirabegron 50 mg en monothérapie dans le traitement de l’hyperactivité vésicale dans les essais randomisés le comparant à un placebo.

**Méthodes.** — Une revue systématique a été effectuée jusqu’en juin 2020, sur les bases de données Medline/PubMed, Embase et Cochrane. Nous avons retenu les essais randomisés menés pour le traitement de l’hyperactivité vésicale. Les effets secondaires et l’innocuité ont été évalués sur la base de 15 événements indésirables. L’hétérogénéité entre les études a été évaluée par des tests de Chi² et des tests Q et I². Critères de jugement: symptômes de rhinopharyngite, bouche sèche, hypertension artérielle, constipation, céphalées, dyspepsie, infection urinaire, troubles visuels, nausées, complication cardiovasculaire, allongement du QT à l’ECG.

**Résultats.** — Dix essais ont été évalués, incluant au total 6135 patients. Le traitement par mirabegron 50 mg était associé à une prévalence accru de symptômes de rhinopharyngite par rapport au placebo (RC, 1,54 [IC à 95 %, 1,05–2,25] ; p = 0,03). Aucune différence statistiquement significative n’a été observée entre les deux groupes pour les autres effets secondaires.

**Conclusion.** — Dans les essais randomisés contre placebo, seuls les symptômes de rhinopharyngite étaient plus fréquents dans le groupe mirabegron 50 mg.

© 2021 Elsevier Masson SAS. Tous droits réservés.

**Introduction**
Overactive bladder (OAB) is a syndrome with complex symptoms, characterized by urgency of urination, with or without urgency urinary incontinence, with urinary frequency and nocturia, without lower urinary tract infection [1]. It is estimated that more than 50 million people worldwide suffer from the disease [2]. Antimuscarinic agents are applied as the first-line treatments for patients with OAB; however, patients often give up using the therapies due to serious adverse events (AEs) such as dry mouth, constipation and blurred vision [3]. Mirabegron, a β3 adrenergic agonist, is the first of a new class of drugs developed for the treatment of OAB [4]. At present, mirabegron 50 mg, the most representative of them, is the most widely used therapy. In the recent meta-analysis, no significant difference was found in the safety outcomes between mirabegron and other therapies or placebo [5—8]. The adverse events induced by mirabegron and placebo were similar, or mirabegron did not increase the risk of adverse events [8]. However, for safety outcomes, nearly all previous meta-analysis were focused on anticholinergic side effects or cardiovascular events (CV), and there were nothing worthy of concern [5—9]. Whether other safety outcomes deserve our attention remains a question? Thus, it is necessary to comprehensively analysis the research progress of safety and AEs of mirabegron monotherapy for patients with OAB.

In the current study, a systemic review and meta-analysis was designed, versus placebo over a 12-week cycle, aiming to comprehensively evaluate the safety of mirabegron 50 mg therapy for OAB patients.

**Materials and methods**

**Search strategy**
Cochrane Library, PubMed, and EMBASE were searched for randomized controlled trials (RCTs) (search performed on 3 JUNE 2020 with no date restriction). The search terms that we used were “mirabegron”, “overactive bladder”, “randomized controlled trials” (Supplementary table 1).

We also reviewed the references of relevant articles, and no additional papers were obtained.

Each article identified through the electronic searches was screened by two reviewers for relevance, initially using the title and the abstract, and subsequently by reading the full text to select articles that met inclusion criteria. Records of the selection process were retained and a PRISMA flowchart was generated (Fig. 1). Finally, 10 articles containing 10 RCTs [10—19] were included; the baseline characteristics of these 10 studies are summarized in Table 1. All disputes arising during the systematic literature review process were resolved by a third reviewer.

**Inclusion and exclusion criteria**
Inclusion: (1) patients with OAB, age ≥ 18years; (2) RCTs; (3) mirabegron 50 mg monotherapy; (4) placebo controlled; (5) safety outcomes. Exclusion: (1) neurogenic bladder or lower urinary tract symptoms associated with benign prostatic hyperplasia, et al.; (2) conference papers; (3) flexible-dose therapy.
**Fig. 1.** PRISMA flow diagram showing study selection process and rationale for exclusions. EMBASE: Excerpta Medica database; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

**Table 1** Assessment of basic characteristic.

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial design</th>
<th>Race, n (%) or location</th>
<th>Female, n (%)</th>
<th>Number</th>
<th>Duration, week</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapple 2013 [10]</td>
<td>Phase II, RCT, double blind</td>
<td>White, 328(90.7)</td>
<td>300 (88.8)</td>
<td>338</td>
<td>12</td>
<td>OAB, 18years</td>
</tr>
<tr>
<td>Herschorn 2013 [11]</td>
<td>RCT, double blind</td>
<td>White, 789(90.3)</td>
<td>604 (69.2)</td>
<td>873</td>
<td>12</td>
<td>OAB, 18years</td>
</tr>
<tr>
<td>Khullar 2013 [12]</td>
<td>RCT, double blind</td>
<td>White, 978(99.1)</td>
<td>713 (72.2)</td>
<td>987</td>
<td>12</td>
<td>OAB, 18years</td>
</tr>
<tr>
<td>Nitti 2013 [13]</td>
<td>Phase III, RCT, double blind</td>
<td>White, 786(87.8)</td>
<td>667 (74.5)</td>
<td>895</td>
<td>12</td>
<td>OAB, 18years</td>
</tr>
<tr>
<td>Yamaguchi 2014 [14]</td>
<td>Phase III, RCT, double blind</td>
<td>Japan</td>
<td>621 (81.9)</td>
<td>758</td>
<td>12</td>
<td>OAB, 18years</td>
</tr>
<tr>
<td>Abrams 2015 [15]</td>
<td>Phase II, RCT, double blind</td>
<td>White, 159(100)</td>
<td>106 (66.7)</td>
<td>159</td>
<td>12</td>
<td>OAB, 20years</td>
</tr>
<tr>
<td>Kosilov 2015 [16]</td>
<td>RCT, single blind</td>
<td>Russia, Unclear</td>
<td>122</td>
<td>12</td>
<td>18years</td>
<td>OAB, 65years</td>
</tr>
<tr>
<td>Kuo 2015 [17]</td>
<td>RCT, double blind</td>
<td>China, Korea, India</td>
<td>453 (61.9)</td>
<td>732</td>
<td>12</td>
<td>OAB, 18years</td>
</tr>
<tr>
<td>Yamaguchi 2015 [18]</td>
<td>RCT, double blind</td>
<td>Japan</td>
<td>346 (82.4)</td>
<td>420</td>
<td>12</td>
<td>OAB, 18years</td>
</tr>
<tr>
<td>Herschorn 2017 [19]</td>
<td>RCT, double blind</td>
<td>White, 677(79.6)</td>
<td>650 (76.4)</td>
<td>851</td>
<td>12</td>
<td>OAB, 18years</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>6135</td>
<td>12</td>
<td>18years</td>
<td></td>
</tr>
</tbody>
</table>

**Assessment of quality and baseline characteristics**

All 10 RCTs are randomized, double blind, placebo controlled study except Kosilov et al. [16] is single blind. None mentioned allocation concealment, selective report, intention-to-treat (ITT), et al (Table 2). The quality of evidence for retrieved references was determined using the Cochrane risk of bias tool [20]. (1) Was randomization carried out appropriately? (2) Was the baseline between groups comparable? (3) Was the concealment of treatment allocation adequate? (4) Were the care providers, participants...
Table 2  Assessment of quality.

<table>
<thead>
<tr>
<th>Study</th>
<th>RandomizationAllocated</th>
<th>Blinding</th>
<th>Baseline</th>
<th>Loss of follow-up</th>
<th>Selective report results</th>
<th>ITT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapple 2013 [10]</td>
<td>Unclear</td>
<td>Yes</td>
<td>Double blind</td>
<td>Comparable</td>
<td>Yes (n=2)</td>
<td>Unclear</td>
</tr>
<tr>
<td>Khullar 2013 [12]</td>
<td>Computer generated</td>
<td>Yes</td>
<td>Double blind</td>
<td>Comparable</td>
<td>Yes (n=7)</td>
<td>Unclear</td>
</tr>
<tr>
<td>Yamaguchi 2014 [14]</td>
<td>Unclear</td>
<td>Yes</td>
<td>Double blind</td>
<td>Comparable</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Kosilov 2015 [16]</td>
<td>Simple probability sampling</td>
<td>Yes</td>
<td>Double blind</td>
<td>Comparable</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Kuo 2015 [17]</td>
<td>Computer generated</td>
<td>Yes</td>
<td>Double blind</td>
<td>Comparable</td>
<td>Yes (n=9)</td>
<td>Unclear</td>
</tr>
<tr>
<td>Yamaguchi 2015 [18]</td>
<td>Unclear</td>
<td>Yes</td>
<td>Double blind</td>
<td>Comparable</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Herschorn 2017 [19]</td>
<td>Unclear</td>
<td>Yes</td>
<td>Double blind</td>
<td>Comparable</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

and outcome assessors blind to treatment allocation? (5) Were the lost visit reported and the specific number of missing data? (6) Was there any evidence to suggest that the authors measured more outcomes than they reported? (7) Did the analysis include an ITT analysis?

Data analysis

Data were analyzed by using RevMan v5.3.0 (Cochrane Collaboration, Oxford, UK). Odds ratio (OR) was employed to assess dichotomous data. We analyzed comparable data using 95% credible intervals (CIs). Heterogeneity among studies was assessed by using the $\chi^2$ test based on the Q and I$^2$ tests ($I^2 > 50\%$ will be considered of substantial heterogeneity; a P value of Q test < 0.10 will be considered statistically significant), an individual study could be characterized as a fixed model if $P > 0.1$, $I^2 < 50\%$, otherwise a random-effects model was chosen.

Results

Nasopharyngitis

In all, 5 RCTs [11–13,15,17] involving 3646 participants (1819 in the mirabegron group and 2407 in the placebo group) contained data on nasopharyngitis. No obvious between-study heterogeneity ($P=0.81$, $I^2 = 0\%$) was found. Using a fixed-effects model, for nasopharyngitis (OR: 1.54 [95%CI: 1.05, 2.25]; $P=0.03 < 0.05$; Fig. 2 or Table 3), showing the significant differences between mirabegron 50 mg and placebo.

Other 14 safety outcomes

Dry mouth, hypertension, constipation, headache, dyspepsia, urinary tract infection (UTI), Dizziness, Blurred vision, Nausea, CV, Influenza, electrocardiogram(EGC) QT prolonged, upper respiratory tract infection and high blood pressure, the results of which showed no differences ($P > 0.05$) between mirabegron 50 mg and placebo, respectively (Fig. 2 or Table 3).

Discussion

Anticholinergics are the current mainstay of pharmacotherapy for OAB; however, patients, with the therapies, often give up the medication because of their bothering side effects [21]. Mirabegron, a $\beta_3$-adrenoceptor agonist, has a potential to increase blood pressure and heart rate [22]. For all these reasons, safety of drug therapy got widely attention, previous studies as we described, had proved that mirabegron 50 mg was safe for patients with OAB. However, the studies usually focused on assessing anticholinergic side effects or CV events as safety outcomes. Other safety outcomes were not analyzed comprehensively, for safety endpoints might be more complex than efficacy in terms of quantities and various definitions. To deep assess the safety of mirabegron 50 mg versus placebo for patients with OAB, we selected the data more accurately, and analyzed these data more comprehensively. The key finding of current study is that mirabegron 50 mg is nearly as safe as placebo. However, for nasopharyngitis (OR: 1.54 [95%CI: 1.05, 2.25]; $P=0.03 < 0.05$; Fig. 2 or Table 3), showing mirabegron 50 mg monotherapy is a remarkable risk of nasopharyngitis for patients with overactive bladder.

Acute nasopharyngitis has been known to cause human work failure, economic loss and even death, but no effective treatment has already been established for the disease [23,24]. Nasopharyngitis, as a safety outcome, ignored by previous meta-analyses [5–8], was assessed as a mirabegron related adverse event in our meta-analysis. The mechanisms between mirabegron and nasopharyngitis are not known. The future progression of nasopharyngitis is also needed to be researched.
Our studies showed a higher similarity between mirabegron 50 mg and placebo, in terms of wider adverse events assessed as safety outcomes. Those other 14 safety results were consistent with the findings of previous meta-analyses or agreed with the outcomes showed in 10 original documents, which meant the safety of mirabegron 50 mg therapy was similar to placebo.

There are some particular merits of our study. First, results of the present study were providing reference for clinical practice; nasopharyngitis, as the drug-related adverse event, the risk of which was remarkably increased by mirabegron 50 mg. Second, a greater number of safety outcomes were analyzed in our study compared with previous meta-analyses, enhancing the power of the present study, mirabegron is nearly as safe as placebo. Third, no significant heterogeneity was observed among the studies, and nearly all heterogeneity analysis indicated that no obvious between-study heterogeneity (P > 0.1, I² < 50%) was found, this means the results are highly credible. However, some caveats of our report should be taken into consideration. First, the follow-up period of the total studies were 12 weeks, making the long-term safety of mirabegron uncertain. Second, limited information about basic characteristics was provided 5 of 10 included trials (Table 1), leading to potential selection bias and detection bias. More RCTs, longer follow-up periods and larger sample sizes, were recommended to strengthen the credibility of the conclusions of the analysis.

Conclusions

In conclusion, evidences from the current study indicate that nasopharyngitis is associated with mirabegron therapy...
for patients with overactive bladder. With the exception of nasopharyngitis, mirabegron 50 mg therapy is nearly as safe as placebo for patients with OAB.

**Author contributions**

J.H., H.X., F.D., N.L. conceived and designed the studies; J.H., H.X., F.D. performed the studies; J.H., H.X., F.D. reviewed the literatures and analyzed the data; N.L. contributed technical and material support; J.H., N.L. wrote the paper.

**Acknowledgments**

The research was supported by the educational department of Liaoning Province No.: QN2019018 Grant to Ning Li.

**Disclosure of interest**

The authors declare that they have no competing interest.

**Appendix A. Supplementary data**

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.purol.2021.05.005.

**References**


[22] Rosa GM, Ferrero S, Nitti VW, Wagg A, Saleem T, Chapple CR. Cardiovascular safety of beta3-adrenoceptor agonists for the
