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Efficacy and Tolerability of Mirabegron Compared with Antimuscarinic Monotherapy or Combination Therapies for Overactive Bladder: A Systematic Review and Network Meta-analysis

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Abstract

Background: Mirabegron is an established treatment alternative to antimuscarinic therapy for patients with overactive bladder (OAB), as shown by efficacy and tolerability data from phase III trials.
Objective: To assess efficacy and tolerability of mirabegron 50 mg versus antimuscarinic monotherapies and combination therapies.
Design, setting, and participants: Systematic literature review and network meta-analysis of randomised controlled trials (2000–2017) assessing eligible treatments for OAB.
Outcome measurements and statistical analysis: Efficacy assessments included micturition frequency, urgency urinary incontinence, dry rate, and 50% reduction in incontinence. Tolerability assessments included dry mouth, constipation, blurred vision, and hypertension.
Results and limitations: A total of 64 studies (n = 46 666) were included in the network meta-analysis. Mirabegron 50 mg was significantly more efficacious than placebo for all efficacy endpoints. Comparable overall efficacy was observed for mirabegron 50 mg versus most active treatments, but solifenacin 10 mg monotherapy and solifenacin 5 mg plus mirabegron 25 or 50 mg in combination were more efficacious for some/all outcomes. Mirabegron 50 mg was significantly better tolerated regarding dry mouth, constipation, and urinary retention than 21/22, 9/20, and 7/10 active comparators, respectively; similar overall tolerability was observed between mirabegron 50 mg and all treatments (including placebo) for the remaining endpoints. Limitations of the study included between-trial variations in the definition of certain endpoints and heterogeneity of the available data (eg, number of studies and patients assessed) for comparator treatments across different endpoints.
Conclusions: The relief of key OAB symptoms produced by mirabegron 50 mg is significantly better than placebo, and similar to a range of common antimuscarinics, with the benefit of significantly fewer bothersome anticholinergic side effects such as dry mouth. Combination treatment of solifenacin 5 mg plus mirabegron 25 or 50 mg appears to provide an efficacy benefit compared with mirabegron 50 mg, with the expected side effects of individual antimuscarinics.
Patient summary: This study assessed the efficacy and tolerability of different drug treatments for OAB. Mirabegron 50 mg was as effective as antimuscarinic therapy, with fewer common, bothersome side effects such as dry mouth, constipation, and urinary retention. Combination treatment of solifenacin 5 mg plus mirabegron 25 or 50 mg was more effective than mirabegron 50 mg alone, but with more anticholinergic side effects.

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1. Introduction

Overactive bladder (OAB) is a symptom complex defined by urinary urgency, with or without urgency urinary incontinence (UUI), usually accompanied by frequency and nocturia, in the absence of urinary tract infection (UTI) or any other obvious pathology [1]. OAB is prevalent, with an incidence of up to 17% in adults in Europe and the USA, and 30–40% in those ≥75 yr of age [2,3].

Current treatments for OAB include behavioural therapy, pharmacological treatment, minimally invasive procedures, and other surgical options [4–6]. Although oral antimuscarinics have established efficacy and provide a mainstay of pharmacotherapy for OAB treatment [5], they are associated with a high incidence of bothersome anticholinergic adverse events (AEs), such as dry mouth and constipation [5,7], which can be a concern for older patients with OAB [8]. Overall, persistence rates for continuing antimuscarinic therapy are low in patients with OAB [9], with tolerability cited as a key reason for treatment discontinuation [10].

Mirabegron is an oral β_3-adrenoceptor agonist that offers an alternative option to antimuscarinics for patients with OAB, as shown by significant improvements in key efficacy measures (eg, incontinence and micturition frequency) for mirabegron versus placebo in phase III trials [11–13]. Overall, rates of AEs reported for mirabegron in phase III trials appeared similar to those for placebo, whilst the incidence of dry mouth appeared to be lower than for tolterodine [14]. Significantly improved 12-mo persistence rates have been observed for mirabegron compared with antimuscarinics in a retrospective, observational study, which utilised anonymised prescription data from 21 996 patients, collected from a large database in the United Kingdom (UK) [15].

A recent systematic literature review (SLR) and network meta-analysis (NMA) compared the relative efficacy and tolerability between mirabegron 50 mg and antimuscarinics in patients with OAB, using peer-reviewed articles (published 2000–2013) [16]. Results from 44 randomised controlled trials (RCTs) involving 27 309 patients showed that mirabegron 50 mg was as efficacious as antimuscarinics (except for solifenacin 10 mg) for micturition frequency, incontinence, and UUI episodes. This study corroborated the results of the phase III studies by showing that mirabegron 50 mg provides a more favourable tolerability profile, including significantly lower rates of dry mouth, compared with antimuscarinics.

New evidence has emerged following the publication of the prior SLR/NMA, including improved efficacy for solifenacin 5 mg plus mirabegron versus solifenacin 5 mg monotherapy in patients with OAB [17–19]. In the current study, a new SLR/NMA was performed to assess the efficacy and tolerability of mirabegron 50 mg compared with antimuscarinic monotherapies and oral combination therapies. Our study utilised a wider range of endpoints and a broader collection of comparator interventions, and incorporated more recent clinical trial evidence (up to November 2017), compared with the previous SLR/NMA.

2. Patients and methods

2.1. Systematic literature review

Electronic literature searches were performed according to a review protocol and guidelines of the Centre for Reviews and Dissemination [20] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [21]. MEDLINE®, MEDLINE® In-Process, Excerpta Medica database (via Ovid), and Cochrane Library databases were searched for RCTs published from 1 January 2000 to 24 November 2017, measuring efficacy and tolerability endpoints in adults with OAB (including "detrusor overactivity" or "urinary urgency", but excluding "neurogenic detrusor activity" and men with lower urinary tract symptoms associated with benign prostatic hyperplasia); only full papers written in English or French were included. Other relevant studies were identified from www.clinicaltrials.gov (search performed on 5 December 2017 with no date restriction) and clinical study reports were provided from the study sponsor, if data of interest had not been published prior to this study. An overview of the literature search methodology and full search terms are shown in Supplementary Table 1.

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; duplicates were removed during this stage. Records of the selection process were retained and a PRISMA flowchart was generated. The quality of evidence for retrieved references was determined using the Cochrane risk of bias tool [22]. All disputes arising during the SLR process were resolved by a third reviewer. Data from the list of agreed studies were extracted from the full-text articles; when not available, the required data were obtained from www.clinicaltrials.gov, clinical study reports, or raw study data tables.

2.2. Network meta-analysis

The NMA allowed a simultaneous comparison of multiple OAB treatments (accounting for correlations between arms in trials with three or more arms) and pooling of direct and indirect evidence, as described previously [16]; a Bayesian framework was used.

2.2.1. Eligibility criteria

Inclusion and exclusion criteria used in the NMA are summarised in Table 1. RCTs with 4–16 wk of follow-up assessing mirabegron or antimuscarinics were included (only data from the first treatment period were included for crossover trials); efficacy results specifically reported at 12 wk were included over other time points, as this time point has been used to assess treatment effect in many OAB clinical trials. Eligible interventions were most approved drugs used in Europe; combinations comprised two agents with distinct modes of action, which demonstrated an acceptable efficacy/tolerability balance in phase II studies and entered phase III development. Therefore, combinations of two antimuscarinics or those including solifenacin 10 mg were excluded, as were flexible-dose or non-comparative and comparative studies versus placebo patch. Intervention treatments were an antimuscarinic, mirabegron 50 mg, or combinations; control treatments included an antimuscarinic (different drug, formulation, or dose) or placebo.

2.2.2. Data analysis

Analyses were performed using WinBUGS 1.4.3 software (MRC Biostatistics Unit, Cambridge, UK; codes are provided in the Supplementary material, Appendix 1). All efficacy and safety endpoints were assessed using random- or fixed-effect models (for each endpoint, the model with best fit was selected, based on the lowest Bayesian deviance

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