Safety and effectiveness of mirabegron for children and adolescents with refractory idiopathic overactive bladder for improving urinary symptoms: a systematic review

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Introduction The aim of this study was to determine the safety and effectiveness of mirabegron in children with refractory overactive bladder (OAB) for improving urinary symptoms.

Material and methods We conducted a search strategy in MEDLINE (OVID), EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), and LILACS from inception to September 2023. We performed a systematic review of studies evaluating the effectiveness of improving urinary symptoms and the safety of mirabegron at any dose in children and adolescents with idiopathic refractory OAB. We searched the interception to September 2023. The risk of bias was assessed using the Cochrane risk of bias tool for clinical trials and the MINORS tool for non-randomized studies.

Results We included three studies in the analysis. All of them included children and adolescents receiving mirabegron as monotherapy at different doses. Also, none of them reported a control group. Improvement and safety rates were high in every study in objective and subjective measurements. Compliance was also high in all studies. Most of the evaluated items had a low risk of bias within and across studies.

Conclusions Mirabegron as monotherapy appears to be a safe and effective alternative for children with refractory idiopathic OAB or those who are intolerant to antimuscarinic therapy.

Key Words: idiopathic overactive bladder ‹› mirabegron ‹› urinary symptoms ‹› beta-3 agonist

INTRODUCTION

Overactive bladder (OAB) has been reported as the most common voiding dysfunction in the pediatric population, with a prevalence ranging from 5%–12% (5–10 years old) and 0.5% (16–18 years old) [1], to as high as 15–20%. [2, 3]. This condition is especially troublesome and highly impacts the quality of life [4]. It also negatively influences social, emotional, and behavioral well-being [5], affecting overall children's development and even the adulthood of some of them [1].

A stepwise approach has been accepted as the standard of care to treat this condition, starting with urotherapy (lifestyle modifications, behavioral therapy, biofeedback-assisted therapy), followed by pharmacological therapy, before moving on to more invasive options (electrical stimulation and surgical intervention) [1].

Anticholinergics or so-called antimuscarinics are still the mainstays of medical treatment [6]. However, the muscarinic receptors block leads to frequent bothersome side effects such as dry mouth, constipation, and headaches [7]. Also, some children have a suboptimal response [8]. Although there are several anticholinergics, most of them have proven effective in children, only oxybutynin and, recently, solifenacin have been officially approved for pediatric use by the US Food and Drug Administration [9, 10].

Furthermore, mirabegron is a selective beta 3-adrenoceptor agonist that has shown acceptable effectiveness and safety for adults with an idiopathic OAB. FDA and the European Medicines Agency approved it for use in adults in 2012; consequently, it was included in NICE guidelines in 2013 [11]. However, it is still not licensed for use in the pediatric population. Nonetheless, mirabegron may be a valid option for children with refractory idiopathic OAB, according to emerging studies [12, 13]. This study aimed to determine the safety and effectiveness of mirabegron for improving urinary symptoms in children with refractory idiopathic OAB.

MATERIAL AND METHODS

We performed this review according to the recommendations of the Cochrane Collaboration and following the PRISMA Statement. The PROSPERO registration number was CRD42021262356.

Eligibility criteria

Study design: We searched clinical trials, quasi-experiments, and descriptive and analytical observational studies.
Participants: Children and adolescents with refractory idiopathic OAB
Intervention: Mirabegron at any dose
Comparisons: No treatment/placebo, no comparison, any antimuscarinic medication or combination (mirabegron and any antimuscarinic medication).
Primary outcome: Improvement of symptoms (frequency, voided volume, incontinence episodes) before and after the treatment. Also, at the end of the treatment among groups.
Secondary outcome: adverse effects
Timing: none defined

Search strategy

We conducted a search strategy in MEDLINE (OVID), EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), and LILACS from inception to September of 2023 (Appendix 1). We also saturated information by searching in Google Scholar, thesis databases, conference abstracts, clinical trials register databases and reference lists. There were no language restrictions.

Data collection

We examined the references obtained from databases on a title/abstract level and then, if potentially relevant, retrieved them as complete articles for pre-specified inclusion and exclusion criteria. We collected data using a standardized format containing the study design, aims, participants, intervention, comparisons, and results. The authors confirmed the data entry and verified the information for greater accuracy. Disagreements were resolved by consensus.

Risk of bias assessment

We performed the risk of bias assessment with the Cochrane risk of bias tool for clinical trials and the MINORS tool for non-randomized studies.

Data analysis and synthesis of results

We performed a descriptive data synthesis. We could not perform a meta-analysis due to the limited number of studies and the lack of information.

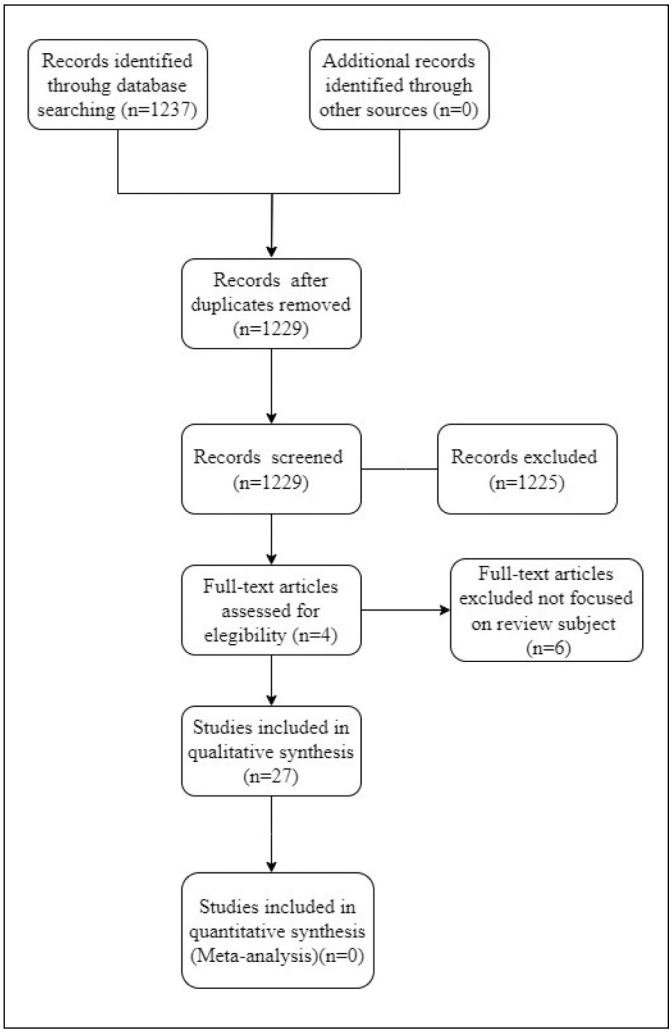

Figure 1. *Flowchart.*

Subgroup analysis

Subgroup analysis was not possible, given the reduced number of studies included in the analysis.

RESULTS

We identified 1237 studies through the database search. After applying the inclusion criteria and excluding duplicates, we included four studies in the qualitative analysis [14–17] (Figure 1).

Characteristics of the included studies

We included four studies analyzing the effects of mirabegron as monotherapy at different dosing in the pediatric population (children and adolescents) [16–19]. Two were performed in Europe, one in the United States, and the last in Egypt. Two of them were prospective studies, the other had a retrospective design, and the last was a Prospective Randomized Single-Blind Controlled Trial. One of them included two multicenter, open-label phase 1 studies aiming to determine the pharmacokinetics of this medication in the pediatric population. However, none of them included a control group (Table 1).

Characteristics of the excluded studies

The articles excluded treated different topics or populations or had a study design that did not accomplish the inclusion criteria, such as reviews.

Risk of bias assessment

Most of the evaluated items had a low risk of bias within and across studies. Nonetheless, none of the studies included a control group, representing a high risk of bias for the four of them. Also, there was uncertainty regarding assessing the

Table 1. *Characteristics of included studies*

Author	Year	Study design	Participants	Intervention	Outcome
Blais et al.	2016	Prospective off-label study	58 children (14 females, 44 males). Median age 10.1 years (IQR 8.8–13.5)	Adjusted-dose regimen of mirabegron (25–50mg)	• Primary outcomes: better reported efficacy than with the use of prior medication in terms of number of incontinence episodes per day, grade 2 or 3 urgency episodes, median voided volume per micturition, and median number of micturitions per day. • Secondary end points: tolerability, satisfaction, and safety.
Fryer et al.	2019	Retrospective review of medical records	70 children (50 females, 20 males). Median age 15 years [range 8–16]. 37 still receiving at 6 months:	Mirabegron 25 mg (n = 29) or 50 mg (n = 41). • Monotherapy: 30 patients • Combination treatment: 7 patients: solifenacin n = 4, desmopressin n = 2, both n = 1	• Primary outcomes: Frequency, urgency, nocturnal, and daytime incontinence (DI) by patient reported symptom improvement. • Secondary outcomes: cardiovascular monitoring, tolerability, reason for discontinuation, and suspected side effects. Measured at baseline and at 6 months.
Rittig et al.	2020	Two multicenter, open-label, single-dose Phase 1 studies	43 children and adolescents (28 females, 15 males). Mean age for children 8.1 years [range study 1: 7–10, study 2: 4–10], and 14.5 years for adolescents [range 12–17].	Study 1: single tablet- fed or fasted conditions • Cohort 1 Adolescents, Low-dose, Fed, Tablets • Cohort 2 Children, Low-dose, Fed, Tablets • Cohort 3 Adolescents, High-dose Fed, Tablets • Cohort 4 Children, High-dose, Fed, Tablets • Cohort 5 Children, High-dose, Fasted, Tablets Study 2: single oral suspension dose-fed conditions. • Cohort 6 Children, High-dose, Fed, Oral suspension.	To assess the predictive value of the preliminary pharmacokinetics model and to update it to analyze mirabegron pharmacokinetics in pediatric patients. To evaluate the safety/tolerability and palatability/ acceptability of the formulations.
Soliman et al.	2021	Prospective Randomized Single-Blind Controlled Trial	210 children and adolescents (125 females, 85 males) Mean age for children 9 years [range study: 5–14 years] Idiopatic OAB: 85,6% at leats 3 months	Mirabegron (50 mg once daily) in group I, solifenacin (5 mg) in group II, and placebo in group III	Primary outcome: Reduction of alterations in 87.5% in I and 90.2% in II vs. placebo, being more significant in group II.

study endpoints, the calculation of the study size, and the groups' contemporaneity and equivalence. Besides, Fryer's study had a high risk of bias regarding collecting data and the equivalence of groups. (Figure 2a and 2b))

Outcomes

In 2016, Blais et al. [16] performed a prospective off-label study to evaluate the effectiveness and safety of mirabegron in treating urinary incontinence in 58 children with refractory incontinence due to OAB. They included patients without symptom improvement or with a partial response with intensive behavioral – 3–6 months- and medical therapies – ≥2 different antimuscarinic medications- and/or with significant side effects. The median duration of treatment was 11.5 months (IQR: 6.0–15.0), and the dosage was significantly increased during treatment–subjective improvements correlated with changes in voiding diaries. Also, there were no differences in response rates between patients included because of failure vs. those included because of adverse effects with anticholinergics. Overall, there was a compliance rate of >90%. Mirabegron appeared as a safe and effective alternative for these children.
In 2019, Fryer et al. (17) reviewed mirabegron's effectiveness, tolerability, and side effects alone or in combination therapy for children with resistant OAB. Seventy children received mirabegron as a second or third-line treatment after bladder retraining and anticholinergics. Thirty-seven patients (53%) still received treatment at six months; the median treatment duration was seven months (IQR 3–12). Overall, 70% of children experienced an improvement in at least one symptom after six months of treatment, and three patients achieved complete resolution of all symptoms.
In 2020, Rittig et al. (18) conducted two multicenter, open-label, single-dose phase 1 studies in children and adolescents with neurogenic detrusor overactivity – most commonly due to spina bifida- or idiopathic OAB. Almost every patient (94.1%) received baseline antimuscarinic and/or mirabegron. Furthermore, based on an adult pharmacokinetic model, they received mirabegron in tablets or suspension in a dose according to body weight. Median AUC24 values were within the range of the adult steady-state values obtained during dosing with once-daily tablets of mirabegron 25 and 50 mg. No clinically relevant changes in post-void volume were observed, and no post-dose post-void volumes were significantly elevated. There were no reports of bad taste or swallowing difficulties for the tablets. Table 2 depicts the main results of the included studies.
In 2021, Soliman conducted a study evaluating the effectiveness of mirabegron and Solifenacin in children 5–14 with reported OAB; 92% (194 patients) completed the treatment scheme in three months. It was a single dose of 50 mg of mirabegron per day, finding an improvement in OAB symptoms of 99% in both groups and a significant value and minimal side effects [17].

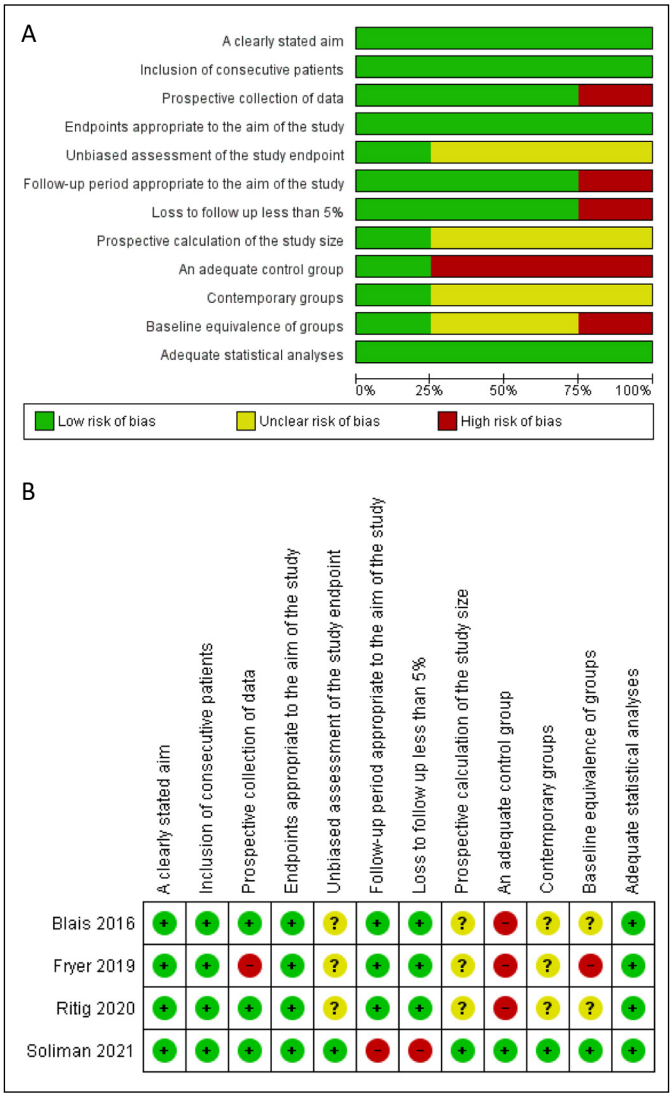

Figure 2. *Risk of bias assessment* **(A)**. *Within studies* **(B)** *Across studies*

DISCUSSION

Summary of the main results

Mirabegron as monotherapy improved the objective and subjective outcomes in the pediatric population with refractory idopathic OAB or intolerance to antimuscarinic treatment. Most patients had

no adverse effects; when present, they were described as mild and rarely associated with treatment discontinuation.

Contrast with literature

Given the high incidence of adverse effects and the rate of non-responders to conventional treatment, off-label medications are being used widely, either alone or in combination with antimuscarinic medications, in children with OAB. Combining two drugs with a different mechanism of action may improve treatment effectiveness. Nonetheless, the combination may also increase adverse effects. That is, the use of alternative drugs as monotherapy is being evaluated.

Mirabegron, a B3 adrenoreceptor agonist, acts on the bladder urothelium during storage, relaxing the detrusor muscle and increasing bladder capacity. It does not disturb micturition pressure, residual volume, or voiding contraction [13]. The overall incidence of adverse effects appears similar to that of anticholinergics. Cardiovascular safety is particularly concerned, given that it might prolong the QT interval on ECG or increase blood pressure. Nonetheless, mirabegron has proven to be a safe and effective medication for adults with OAB. Moreover, evidence supporting pediatric use is limited and still not approved by international pharmacological organizations.

One of the studies reviewed the pharmacokinetics of mirabegron in the pediatric population; the median AUC24 values were consistent with steady-state obtained with once-daily 25 and 50 mg tablets in adults. With their data, they updated the previously known pharmacokinetics model so it can be

Table 2. *The main results of the included studies*

Author	Improvement	Side effects	Reason for treatment discontinuation	Electrocardiography and vital signs
Blais et al.	Any: 52/58 (90%) 100%: 13/58 (22%) >90%: 14/58 (24%) 50–89%: 25/58 (43%) <50% (failure): 6/58 (10%) Voided volume +73.3 cc: from 150 cc to 200 cc Incontinence episodes: -1.5 episodes: from 2 to 0.4 Patient Perception of Bladder Condition questionnaire score: -2.3 points	None: 86% Mild: 9% (abdominal colic, constipation, blurred vision)	Adverse effects: 5% (nasopharyngitis, nausea, change in behavior).	
Fryer et al.	Any: 70% 100%: 3/70 (4.3%) Monotherapy: Enuresis: 6/17 (35%) Day incontinence: 11/19 (58%) Frequency: 12/20 (60%) Urgency: 8/21 (38%) Combination: Enuresis: 2/6 (33%) Day incontinence: 2/4 (50%) Frequency: 2/4 (50%) Urgency: 4/6 (67%)		Ineffectiveness: 40% Worse symptoms: 5.7% Adverse effects: 10% (dry mouth, headaches, dizziness, nausea/vomiting, increased seizures, rash)	When measured electrocardiography and blood pressure were normal.
Rittig et al.		Mild: 11.6%	Adverse effects: 0%	QT interval prolongation in 1 child and 1 adolescent. No clinically relevant changes in vital signs.
Soliman et al.	Placebo: 100%: 6/61 (9,8%) Monotherapy: Enuresis: 1/61 (0,9%) Day incontinence: 2/61 (1,8%)	Dry mouth, nasopharyngitis, nausea, change in behavior, other: 2,8%	Adverse effects: 2,8% (abdominal coli)	No vital changes

used for creating weight-based dosing algorithms in future studies.

In 2016, Morin et al. published the first study on the efficacy of mirabegron as an add-on therapy in children treated with antimuscarinics. A prospective off-label study included 35 pediatric patients with refractory overactive bladder or intolerant to conventional treatment [20]. The dose ranged from 25 to 50 mg based on efficacy and tolerability. The inclusion criteria and dosing were similar to what was found in the studies included in our review. Morin et al. found a significant improvement in median bladder capacity: from 50% to 74%. One study reported improved voided volumes: from 150 to 200 cc. They also found that continence improved in all patients, with 34% completely dry.

Through our systematic review of studies of mirabegron as monotherapy, we found that one study reported an improvement in the number of incontinence episodes, and another reported 58% improved daytime incontinence. That same study reported that 50% of those receiving combination therapy improved their continence. At last, Morin et al. reported that 20% of patients presented mild or moderate adverse effects, with 5.7% discontinuing treatment. We found a 9-11% rate of mild adverse effects and a 0-5% discontinuation rate because of adverse reactions. Only 2 cases of QT interval prolongation were reported, and there were no clinically relevant vital signs changes in either study. These findings suggest similar safety and efficacy benefits with monotherapy and combined therapy.

Interestingly, in 2019, a National Survey of Practice in the United Kingdom was published [21]. Fifty-five pediatric urologists responded to 20 questions regarding OAB treatment in children. Oxybutynin was considered the first-line treatment for 85%. Mirabegron alone was never used as a first-line, but it was reported as the third- or fourth-line medication by 21% of urologists. It was most commonly used in combination with solifenacin than alone.

Strengths and limitations

We present a very well-designed systematic review, accomplishing all international standards. As far as we know, it is the first study of this kind. The reduced number of included studies represents the principal limitation. Nonetheless, given that mirabegron is still an off-label medication for the pediatric population, this limitation was expected. Also, we focused on idiopathic OAB. The neurogenic OAB has a different pathophysiology, and that is why therapeutic approaches might differ between both entities.

CONCLUSIONS

Mirabegron as monotherapy appears to be a safe and effective alternative for children with refractory idiopathic OAB or those who are intolerant to antimuscarinic therapy.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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