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Efficacy and safety of anticholinergics for children or adolescents with idiopathic overactive bladder: systematic review and meta-analysis

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Abstract

Introduction and hypothesis Anticholinergics have been established for their efficacy and safety in adults with idiopathic overactive bladder syndrome (OAB-s) but not in children and adolescents. This study was aims to investigate the efficacy and safety of anticholinergics in children and adolescents with idiopathic OAB-s.

Method A total of nine studies with 11 trials comprising of 1801 subjects (1116 experimental and 685 controls) were included. Inclusion criteria were idiopathic OAB-s in children or adolescents. Overall SMD of change in diurnal urge incontinence per week, change in mean voiding frequency per 24 h, change in mean voided volume, and incidence of adverse events compared with placebo were investigated.

Results Overall SMD of diurnal urge incontinence per week for the anticholinergic group (experimental group) vs. the placebo group (control group) was −0.15 (95% CI −0.31, 0.01). Overall SMD of mean voiding frequency per 24 h was −0.16 (95% CI −0.33, 0.02). Overall SMD of mean voided volume was 0.49 (95% CI 0.10, 0.88). The overall incidence of any AEs of anticholinergics compared with placebo was OR = 1.06 (95% CI 0.84–1.34) ($p = 0.637$). Among each AEs, the only incidence of urinary tract infection showed a higher incidence rate for anticholinergics (OR = 1.92, 95% CI 1.06–3.49) than for placebo.

Conclusions Apart from oxybutynin, other anticholinergics showed efficacy including an increase in mean voided volume. Moreover, there was no significant difference in the incidence of overall adverse events between anticholinergics and placebo.

Keywords Overactive bladder · Anticholinergics · Children · Adolescents

Introduction

Overactive bladder syndrome (OAB-s) is not only prevalent in adults, but also in children and the rate is estimated to be 12% [1]. OAB-s in children has been defined as the condition with urinary urgency accompanied by frequency or nocturia, with or without urinary incontinence [2]. It is not easy to investigate the real prevalence of OAB-s in children considering underestimation of it and, however, reported that the incidence of daytime incontinence is around 10% as per large pediatric population studies [2, 3] and the weighted overall prevalence of OAB-s in children is 6.4% [4]. The reported data on incidence and prevalence are not small and should be investigated for improvement in general health.

Clinical importance of OAB in children lies on the fact that pediatric OAB-s may be a risk factor for adult OAB-s. Fitzgerald et al. [5] in their large cohort study reported that women with OAB-s (esp. 'urgency') recollected more often

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'daytime frequency' (> 7 times) during their childhood; with an odds ratio of 1.9 (95% CI 1.3–2.6), and also that women with present nocturia in remember significantly more often nocturia during childhood; with an odds ratio of 2.3 (95% CI 1.5–3.5).

The first step to treat OAB-s in children is standard urotherapy, which includes educating them and their family about OAB-s and behavioral modifications [1]. Considering the limited efficacy of the standard urotherapy, oral medication with anticholinergics is warranted to treat OAB-s in children. However, until date, the only oxybutynin has been approved by FDA. Moreover, oxybutynin has a high rate of incidence of adverse events which is related to low compliance rate [6]. Recently, several other anticholinergics including tolterodine, propiverine, and solifenacin have been explored for their efficacy and safety to treat OAB-s in children [7]. However, the optimal dose to guarantee efficacy and safety has not been established and needs to be systematically reviewed. This study aimed to investigate the overall efficacy and safety of anticholinergics in terms of a systematic review and meta-analysis.

Methods

Criteria for considering studies and types of measures

This analysis was focused on randomized controlled clinical trials. Studies were included in this review if their diagnostic tools included a change in diurnal urge incontinence per week, change in mean voiding frequency per 24 h, change in mean voided volume, and incidence of adverse events. Participant's criteria were adolescents or children with idiopathic OAB-s.

Search methods for identification of studies

The search for this review was performed based on patients (adolescents or children with idiopathic OAB), interventions (daily treatment with anticholinergics), comparisons (comparing with placebo group), outcomes (change in diurnal urge incontinence per week, change in mean voiding frequency per 24 h, and change in mean voided volume).

A MEDLINE (1966 to April 2, 2017) database was searched with optimally sensitive Cochrane Collaboration search strategy. Following MeSH headings and drugs with all subheadings were used: "urinary bladder, overactive", "urinary incontinence", "oxybutynin", "tolterodine", "fesoterodine", "propiverine", "solifenacin", and "mirabegron". All these terms were used to screening both supplementary concept and bibliography in the title and abstracts. Studies eligible for quality assessment and data extraction if the following criteria are met: (1) outcome assessment includes at least one outcome among change in diurnal urge incontinence per week, change in mean voiding frequency per 24 h, change in mean voided volume, and incidence of any adverse events; (2) interventions including administration of daily anticholinergics; (3) idiopathic OAB in children or adolescents; and (4) intention-to-treat (ITT) analysis in placebo-controlled RCTs.

Data extraction and synthesis

The initial screening for study inclusion was determined independently by two authors based on the information in the titles and abstracts. Disagreements between the authors were resolved by discussion. Data extraction from the eligible studies was conducted independently by two authors using data extraction form. The following information were extracted: (1) study year; (2) number of subjects; (3) study duration; (4) age; (5) inclusion criteria of individual studies; and (6) types of anticholinergics.

Assessment of risk of bias in the included studies and reporting bias

The risk of bias and methodological qualities was assessed using the Cochrane Collaboration's risk of bias (RoB) tool, with the following six standard criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other risk of bias. Meta-analysis was conducted using the Begg and Mazumdar's rank correlation test to estimate the study effects. Publication bias was assessed using Egger's test and funnel plots.

Meta-analysis assessment

A comparison of the primary outcome was performed by improvement in OAB-s using the weighted mean value of diurnal urge incontinence per week, change in mean voiding frequency per 24 h, change in mean voided volume, and incidence of adverse events. A series of meta-analyses were performed as follows: (1) comparison of weighted mean value of difference in diurnal urge incontinence per week, change in mean voiding frequency per 24 h and change in mean voided volume between anticholinergics and placebo group; (2) sensitivity analysis of weighted mean value of difference in diurnal urge incontinence per week, change in mean voiding frequency per 24 h and change in mean voided volume between anticholinergics and placebo group; and (3) meta-analysis of prevalence of the adverse events between anticholinergics and placebo group. Data were pooled using DerSimonian–Laird

random-effects model in a meta-analysis [8] to estimate overall standardized mean difference (SMD) and 95% confidence interval (CI) for outcomes. The SMD was calculated to summarize the effect of continuous outcomes. It was estimated as difference in mean outcome between treatment and placebo groups divided by the pooled standard deviation. If a probability of $p < 0.05$, it considered as indication of heterogeneity; thus, the random-effect model replaced the fixed-effect model for meta-analysis. Heterogeneity was determined by estimating the I^2 statistics. I^2 values of 25%, and 50% considered to be low, and moderate heterogeneity, respectively. To compare frequency variable by two groups, a comparison of proportions (e.g., AE) was performed using Pearson's Chi-squared test or Fisher's exact test. Sensitivity analysis was performed by omitting each study and re-estimating the SMD to assess the effect of individual studies on the pooled estimates. All statistical analysis were performed using R (version 3.4.1; The R Foundation for Statistical Computing, Vienna, Austria), and significance level was set at 5% (two-tailed).

Results

Inclusion of studies

We initially searched the MEDLINE ($n = 130$), EMBASE ($n = 487$), and Cochrane library ($n = 41$) databases and found a total of 658 articles. After the exclusion of duplicate natures of studies or overlapping data, 591 articles remained. Among them, 298 articles were excluded as irrelevant topics after screening the titles and abstracts. For the remaining 293 studies, 83 studies were identified as fulfill the selection criteria. After reviewing the full manuscripts of them, 74 studies were excluded, as they were: 24 studies in neurogenic OAB-s, 33 studies in idiopathic OAB-s without placebo group, and 13 studies in anticholinergics with other indications. Finally, a total of 1801 subjects (1116 experimental and 685 controls) were enrolled in the 9 included studies (11 trials) to final inclusion and data extraction. In meta-analysis, four studies were included that provided detailed information of treatment differences and subject description (year, country, indications, number of subjects, study duration, age, and number of patients) (Table 1 and Fig. 1).

Methodological quality

The result of quality assessment is summarized in Supplementary Table 1. The author's judgements and detailed explanation about each item by included studies are described.

Meta-analysis between anticholinergic treatment and placebo groups

Details on findings of the meta-analysis of RCTs are summarized in Table 2 and Fig. 2. A total of 4 studies with 5 trials (1047 subjects; 659 experimental and 388 controls) contributed to a meta-analysis of the efficacy. One study with 2 trials reported diurnal urge incontinence per week, 4 studies with 5 trials reported mean voiding frequency per 24 h, and 3 studies with 4 trials reported mean voided volume. Diurnal urge incontinence per week for the anticholinergic group (SMD = −0.15; 95% CI = −0.31 to 0.01; $I^2 = 0\%$) (Fig. 2a) or mean voiding frequency per 24 h (SMD = −0.16; 95% CI = −0.33 to 0.02; $I^2 = 41\%$) (Fig. 2b) vs. the placebo group (control group) did not showed statistically significant differences. On the other hand, mean voided volume showed statistically significant differences compared to placebo group (control group) (SMD = 0.49; 95% CI = 0.10–0.88; $I^2 = 83\%$) (Fig. 2c).

Cumulative analysis and sensitivity analysis

Cumulative meta-analysis was conducted to delineate the trend according to publication year. Results based on year from the cumulative meta-analysis showed that unstable outcome for mean voiding frequency per 24 h and relatively stable outcome for the mean voided volume (Supplementary Fig. 1).

In considering that presence of heterogeneity, a sensitivity analysis was conducted to investigate whether the overall effect was affected by individual characteristic of the studies. There were no significant differences identified both diurnal urge incontinence per week and voiding frequency per 24 h except for Nijiman (b) in voiding frequency per 24 h. In terms of voided volume, no significant impacts were detected in any studies (Supplementary Fig. 2).

Meta-analysis of all the adverse events between anticholinergic treatment and placebo groups or alternative treatment

A meta-analysis was performed to combine the 9 studies with 11 trials comprised of 1801 subjects (1116 experimental and 685 controls) were included in the analysis of the incidence of AE (Table 3). The result revealed that overall incidence following any AEs of anticholinergics was OR = 1.06 (95% CI 0.84–1.34) ($p = 0.637$) in comparison with placebo. According to each AEs, the only showed the significantly higher incidence rate for anticholinergics is the incidence of urinary tract infection (OR = 1.92, 95% CI 1.06–3.49).

Table 1 Characteristics of all studies included in meta-analysis among idiopathic overactive bladder in children or adolescents

Publication and included reason			Country	No. of patients		Age (range)	Subject description	Type of symptom	Experimental description		
Authors	Inclusion for analysis of efficacy or safety	Year		Tx	Placebo				Drug	Dose	F/U duration (week)
Lopez Pereira [24]	Safety	2003	Spain	49	9	8–13	$H_2O > 15$ cm during bladder filling, urinary urgency and day or night-time wetting	Idiopathic OAB	Trospium chloride	10–25 mg	3
Nijman (a) [25]	Efficacy and safety	2005	Netherlands	235	107	5–10	1 diurnal incontinence episode or more per 24 h for 5 or more days out of 7	Idiopathic OAB	Tolterodine	2 mg	12
Nijman (b) [25]	Efficacy and safety	2005	Netherlands	252	117	5–10	6 or more voids per 24 h	Idiopathic OAB	Tolterodine	2 mg	12
Triantafyllidis [26]	Safety	2005	Greece	11	16	7–18	Nocturnal enuresis	Idiopathic OAB and nocturnal enuresis	Oxybutynin	5 mg	12
Nijman [27]	Safety	2007	European countries	234	109	5–10	1 > diurnal incontinence episode per 24 h for 5 > of 7 days and 6 > voids per 24 h at baseline	Idiopathic OAB with urge incontinence	Tolterodine	2 mg	12
Neveus [28]	Safety	2008	Sweden	27	27	6–13	Nocturnal enuresis at least 7 wet nights in 2 weeks	Idiopathic OAB and nocturnal enuresis	Tolterodine	1–2 mg	5
Marschall-Kehrel [9]	Efficacy and safety	2009	European countries	84	80	5–10	17–45 kg body weight, micturition frequency > 8 per day, incontinence episodes > 1 within 7 days	Idiopathic OAB with urge incontinence	Propiverine	10–15 mg	8
Deng (a) [29]	Safety	2011	China	68	68	5–14	N/A	Idiopathic OAB	Tolterodine	0.1 mg/kg	2
Deng (b) [29]	Safety	2011	China	68	68	5–14	N/A	Idiopathic OAB	Oxybutynin	0.25 mg/kg	2

Table 1 (continued)

Publication and included reason			Country	No. of patients		Age (range)	Subject description	Type of symptom	Experimental description		
Authors	Inclusion for analysis of efficacy or safety	Year		Tx	Placebo				Drug	Dose	F/U duration (week)
Quintiliano [30]	Efficacy and safety	2015	Brazil	15	13	4–17	Had urgency, a bell-shaped uroflowmetry curve, post-void residual urine volume less than 10% of bladder capacity expected for age or greater than 20 ml, DVSS greater than normal (6 in boys and 9 in girls), voiding urgency at least 3 times per week and no previous treatment	Idiopathic OAB	Oxybutynin	0.3 mg/kg	12
Newgreen [14]	Efficacy and safety	2017	European countries	73	71	5–12	OAB	Idiopathic OAB	Solifenacin	NA	12

NA not available

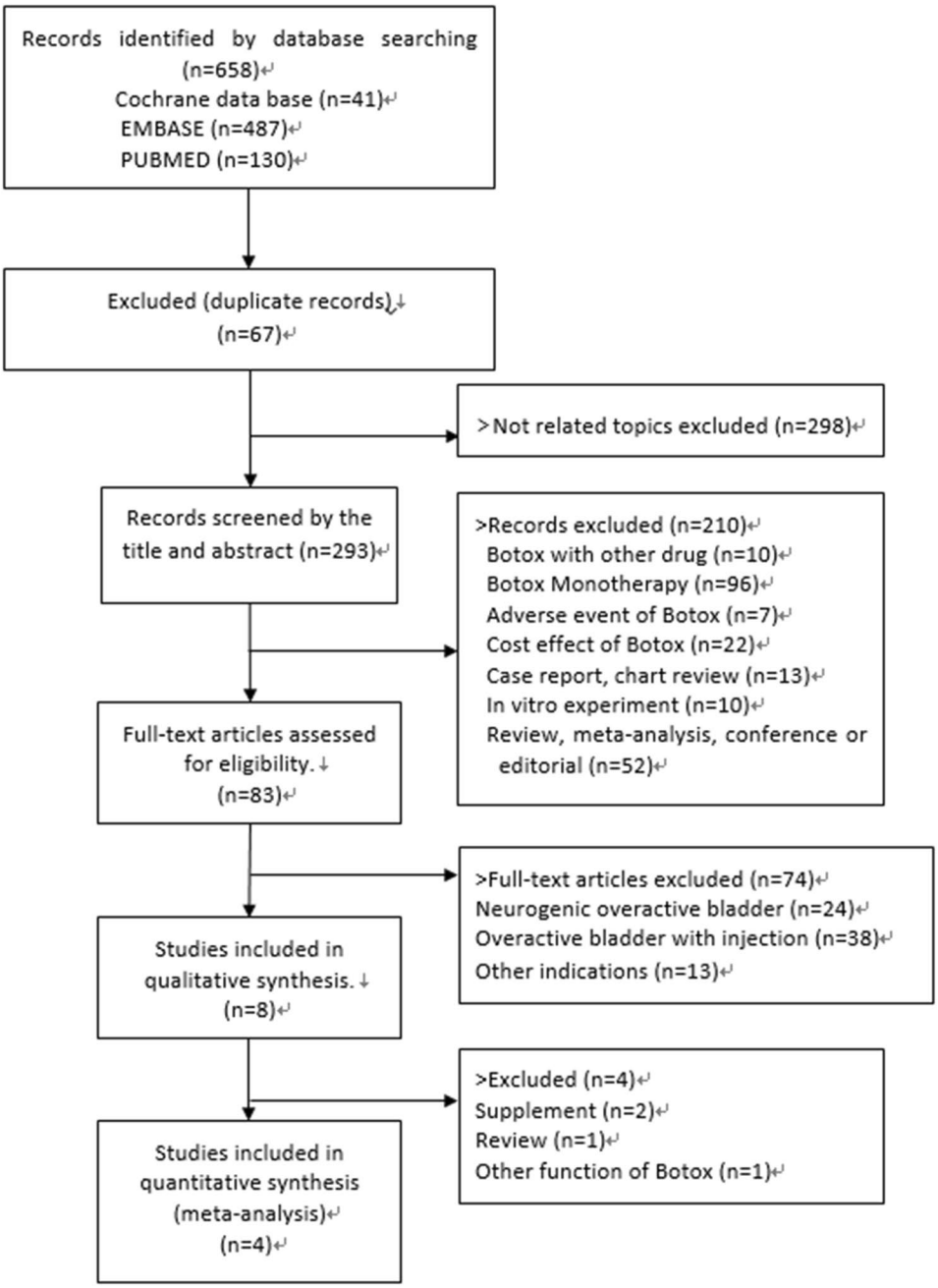

Fig. 1 Flow chart of included studies

Publication bias

Supplementary Fig. 3 portrays a graphical description of funnel plots for voiding frequency per 24 h and voided volume. There is no evidence of significant publication bias considering that distribution was relatively symmetric.

Discussion

Overactive bladder (OAB) has a profound negative impact on the life quality in not only in adults, but also in children. Similar to studies on adults, most of the clinical studies in children have subjective symptom improvement as a primary

Table 2 Overall effect size for each outcome

Variable	No. of studies	No. of anticholinergics	No. of placebo	Effect size			
				SMD	(95% CI)	*p* value	Heterogeneity (I^2)
ΔDiurnal urge incontinence/week							
Tolterodine	2	487	224	−0.15	(−0.31 to 0.01)	0.059	0%
ΔMean VF/24 h							
Tolterodine	2	487	224	−0.03	(−0.19 to 0.13)	0.353	0%
Oxybutynin	1	15	13	−0.72	(−1.49 to 0.05)	0.69	NA
Propiverine	1	84	80	−0.35	(−0.66 to −0.04)	0.025	NA
Solifenacin	1	73	70	−0.18	(−0.51 to 0.15)	0.067	NA
Overall	5	659	387	−0.16	(−0.33 to 0.02)	0.086	41%
ΔMean VV (ml)							
Tolterodine	2	487	224	0.25	(0.09 to 0.41)	<0.001	0%
Oxybutynin	1	15	13	2.41	(1.40 to 3.42)	<0.001	NA
Solifenacin	1	73	70	0.3	(−0.03 to 0.63)	0.089	NA
Overall	4	575	307	0.49	(0.10 to 0.88)	0.014	83%

SMD standardized mean difference

outcome. Considering high prevalence of OAB-s in children and adults, limitation of drug usability in real clinical practice in children demands increased focus.

To date, only one medication, oxybutynin has been approved from both FDA and EMA and tolterodine has been approved from EMA for pediatric use. The main reason for limited drug usability is limited clinical studies on the use of other anticholinergics (tolterodine, solifenacin, darifenacin, and propiverine). Classically, neurogenic OAB-s has been extensively studied than idiopathic OAB-s in children [1]. Moreover, execution of RCTs in idiopathic OAB-s includes potential pitfalls: (1) heterogeneity in inclusion criteria, which demonstrates large confounding factors among OAB-s in children; (2) non-approval from FDA, which hampers clinical design; (3) insufficient placebo group; (4) difficulties in maintaining regular follow-up after clinical improvement of OAB-s symptom; (5) difficulties in acquiring parental consent; (6) lower prevalence of OAB-s in adults than children; and (7) absence of standardized major outcomes [9]. Hence, systematic review and quantification of the efficacy and safety are warranted to expand the role of other anticholinergics other than oxybutynin in the treatment of OAB-s and to provide useful information for the design of more scientific RCTs.

OAB syndrome may be the result of diverse dysfunctions, alone or in combination. For example, excess fluid intake, ineffective micturition, small (for age) bladder capacity, and/or detrusor overactivity are well known and equally prevalent (partial) causes, and anticholinergics or antimuscarinics lack a working mechanism for a proportion of these dysfunctions [10, 11]. Consequently, bladder diaries as well as urodynamics may have a significant role in proof of principle evaluation as well as clinically in treatment resistance after initial (medical) management. Until date, there is no standardized primary outcome measurement in clinical studies on OAB-s in children. Among the measurement outcomes, mostly MVV has been chosen as the primary endpoint and recommended by the European Medicines Agency as a primary endpoint for clinical studies on OAB-s in children [12].

Lee et al. [13] and Newgreen et al. [14] also used MVV as a main primary outcome. Lee et al. [13] reported a significant improvement in MVV (from 90.4 ± 44.4 to 156.2 ± 67.3 ml) in their open-label study on solifenacin after a 12-week treatment. Newgreen et al. [14] reported a significant difference in the change in MVV (12.1 ml with 95% CI 0.2–24.0) after 3 months of treatment in their RCT on solifenacin group and placebo. However, in the long-term open-label study on the oral suspension of solifenacin for 52 weeks (in the absence of MVV), significant improvement in a change in incontinence episode/24 h, change in micturition episode/24 h, change in incontinence free days/7 days, and change in urgency episode/24 h were observed [15]. Our meta-analysis showed that only the overall difference in the change in MVV was statistically significant. Mean change in voiding frequency was also analyzed and no overall difference in improvement was observed.

Although our study used MVV as primary outcome, development of standard definition of clinical improvement in OAB and especially in children OAB is crucial issue. Lack of standard definition of clinical improvement and of related outcome measurement yield small overall treatment effect of anticholinergics, although it is larger than placebo.

Although there exists only one RCT on solifenacin that was included for the present meta-analysis, solifenacin is

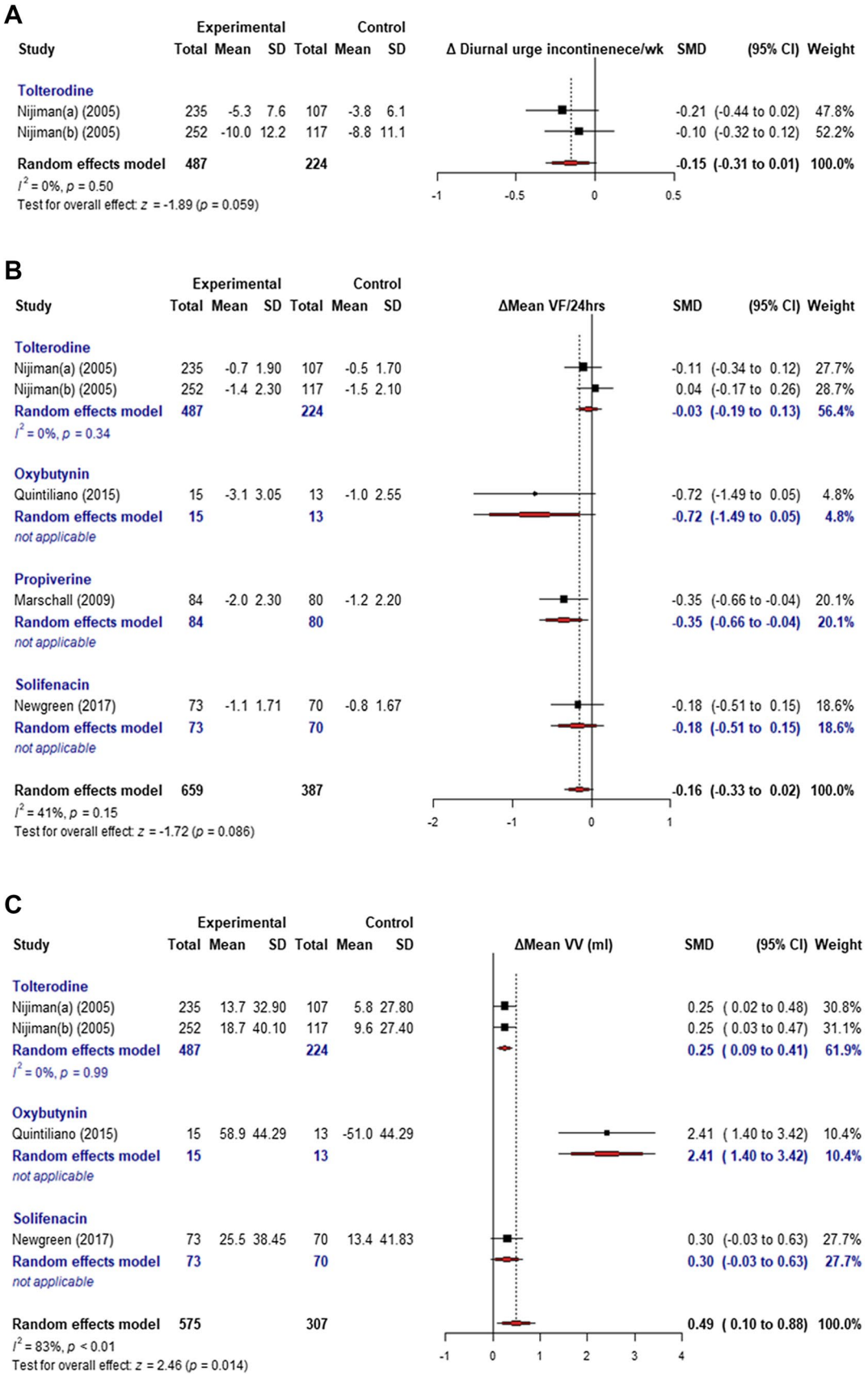

Fig. 2 Effectiveness of anticholinergics for urge incontinence episode (**a**), mean voiding frequency (**b**), and mean voided volume (**c**)

Table 3 Meta-analysis of the adverse events in anticholinergic vs. placebo in pediatric patients with overactive bladder

Complication	Effect size		
	OR (95% CI)	*p* value	I^2
Any AE	1.06 (0.84–1.34)	0.637	31.30%
Nijman (a) [25]	0.95 (0.77–1.16)	0.605	
Nijman (b) [25]	1 (0.77–1.29)	0.993	
Marschall-Kehrel [9]	1.14 (0.64–2.01)	0.663	
Deng (a) [29]	7 (0.37–132.97)	0.195	
Deng (b) [29]	15 (0.87–257.52)	0.062	
Newgreen [14]	1.49 (0.69–3.22)	0.309	
Infection and infestations	0.83 (0.45–1.52)	0.542	0%
Nijman [27]	0.7 (0.24–2.09)	0.526	
Marschall-Kehrel [9]	0.89 (0.43–1.84)	0.756	
Influenza	0.8 (0.27–2.38)	0.682	32.60%
Nijman (a) [25]	1.37 (0.14–12.98)	0.786	
Nijman (b) [25]	0.16 (0.02–1.48)	0.105	
Nijman [27]	0.44 (0.15–1.33)	0.145	
Marschall-Kehrel [9]	3.86 (0.44–33.85)	0.222	
Newgreen [14]	2.88 (0.12–69.47)	0.515	
Urinary tract infection	1.92 (1.06–3.49)	0.031	0%
Nijman (a) [25]	2.28 (0.51–10.21)	0.283	
Nijman (b) [25]	1.79 (0.75–4.27)	0.192	
Nijman [27]	1.98 (0.69–5.68)	0.207	
Marschall-Kehrel [9]	1.93 (0.18–20.9)	0.588	
Gastrointestinal infection	0.19 (0.01–3.96)	0.286	NA
Marschall-Kehrel [9]	0.19 (0.01–3.96)	0.286	
Nasopharyngitis	0.73 (0.3–1.78)	0.483	0%
Nijman [27]	0.73 (0.27–1.96)	0.533	
Marschall-Kehrel [9]	0.19 (0.01–3.96)	0.286	
Newgreen [14]	2.88 (0.12–69.47)	0.515	
Gastrointestinal disorders, dyspepsia	2.57 (0.71–9.38)	0.152	NA
Marschall-Kehrel [9]	2.57 (0.71–9.38)	0.152	
Abdominal pain	1.32 (0.67–2.59)	0.422	27.20%
Nijman (a) [25]	2.28 (0.9–5.78)	0.084	
Nijman (b) [25]	0.67 (0.3–1.53)	0.345	
Nijman [27]	1.1 (0.35–3.41)	0.873	
Marschall-Kehrel [9]	6.76 (0.35–128.91)	0.204	
Deng (a) [29]	NA	NA	
Deng (b) [29]	3 (0.12–72.36)	0.499	
Newgreen [14]	NA	NA	
Dry mouth	2.23 (0.66–7.56)	0.197	41.60%
Lopez Pereira [24]	0.58 (0.03–13.1)	0.729	
Nijman (a) [25]	0.46 (0.09–2.22)	0.33	
Nijman (b) [25]	0.47 (0.03–7.39)	0.588	
Triantafylidis [26]	61.96 (3.16–1215.31)	0.007	
Marschall-Kehrel [9]	6.76 (0.35–128.91)	0.204	
Deng (a) [29]	3 (0.12–72.36)	0.499	
Deng (b) [29]	9 (0.49–163.97)	0.138	
Newgreen [14]	1.92 (0.18–20.68)	0.591	
Constipation	2.33 (0.81–6.65)	0.115	0%
Nijman (a) [25]	1.82 (0.21–16.1)	0.59	
Nijman (b) [25]	2.8 (0.34–22.97)	0.338	

Table 3 (continued)

Complication	Effect size		
	OR (95% CI)	*p* value	I^2
Marschall-Kehrel [9]	4.83 (0.24–99.1)	0.307	
Newgreen [14]	1.92 (0.36–10.14)	0.443	
Eye disorders	8.69 (0.48–158.97)	0.145	NA
Marschall-Kehrel [9]	8.69 (0.48–158.97)	0.145	
Accommodation disorder	4.83 (0.24–99.1)	0.307	NA
Marschall-Kehrel [9]	4.83 (0.24–99.1)	0.307	
Nervous system disorders	1.93 (0.18–20.9)	0.588	NA
Marschall-Kehrel [9]	1.93 (0.18–20.9)	0.588	
Headache	1.39 (0.61–3.16)	0.429	33.10%
Lopez Pereira [24]	0.58 (0.03–13.1)	0.729	
Nijman (a) [25]	0.73 (0.4–1.33)	0.303	
Nijman (b) [25]	2.56 (0.58–11.38)	0.216	
Nijman [27]	2.85 (0.66–12.4)	0.162	
Marschall-Kehrel [9]	4.83 (0.24–99.1)	0.307	
Newgreen [14]	NA	NA	
Respiratory infection	0.68 (0.37–1.26)	0.216	0%
Nijman (a) [25]	0.54 (0.25–1.16)	0.115	
Nijman (b) [25]	1.03 (0.36–2.88)	0.962	
Diarrhea, nausea, vomiting	1.33 (0.76–2.31)	0.316	0%
Nijman (a) [25]	1.67 (0.7–4)	0.25	
Nijman (b) [25]	1.32 (0.53–3.26)	0.547	
Nijman [27]	0.73 (0.18–3)	0.664	
Neveus [28]	5 (0.25–99.43)	0.291	
Newgreen [14]	0.32 (0.01–7.72)	0.483	
Fatigue	0.33 (0.09–1.29)	0.111	0%
Nijman (a) [25]	0.23 (0.04–1.22)	0.085	
Nijman (b) [25]	1.4 (0.06–34.15)	0.836	
Newgreen [14]	0.32 (0.01–7.72)	0.483	
Dizziness	0.48 (0.12–1.96)	0.305	0%
Lopez Pereira [24]	0.58 (0.03–13.1)	0.729	
Nijman (a) [25]	0.46 (0.09–2.22)	0.33	
Nijman (b) [25]	NA	NA	
Newgreen [14]	NA	NA	
Pyrexia	0.67 (0.3–1.48)	0.32	32.10%
Nijman (a) [25]	2.05 (0.45–9.32)	0.353	
Nijman (b) [25]	0.52 (0.21–1.32)	0.172	
Nijman [27]	0.44 (0.15–1.33)	0.145	
Cough, rhinitis, sore throat	0.96 (0.32–2.83)	0.934	69.10%
Nijman (a) [25]	0.37 (0.16–0.87)	0.023	
Nijman (b) [25]	1.32 (0.53–3.26)	0.547	
Nijman [27]	2.41 (0.55–10.69)	0.246	
ECG QT prolonged	1.92 (0.36–10.14)	0.443	NA
Newgreen [14]	1.92 (0.36–10.14)	0.443	
Tachycardia(palpitation)	0.99 (0.11–9.3)	0.992	0%
Neveus [28]	3 (0.13–70.48)	0.495	
Newgreen [14]	0.32 (0.01–7.72)	0.483	
Rectal fissure	2.88 (0.12–69.47)	0.515	NA
Newgreen [14]	2.88 (0.12–69.47)	0.515	
Attention disturbance	2.88 (0.12–69.47)	0.515	NA

Table 3 (continued)

Complication	Effect size		
	OR (95% CI)	*p* value	I^2
Newgreen [14]	2.88 (0.12–69.47)	0.515	
Altered mood	4.06 (0.68–24.14)	0.123	0%
Neveus [28]	7 (0.38–129.23)	0.191	
Deng (a) [29]	3 (0.12–72.36)	0.499	
Deng (b) [29]	NA	NA	
Newgreen [14]	2.88 (0.12–69.47)	0.515	
Tic	2.88 (0.12–69.47)	0.515	NA
Newgreen [14]	2.88 (0.12–69.47)	0.515	
Haematuria	2.88 (0.12–69.47)	0.515	NA
Newgreen [14]	2.88 (0.12–69.47)	0.515	
Erythaema	2.88 (0.12–69.47)	0.515	NA
Newgreen [14]	2.88 (0.12–69.47)	0.515	
Urticaria	2.88 (0.12–69.47)	0.515	NA
Newgreen [14]	2.88 (0.12–69.47)	0.515	
Insomnia	5 (0.25–99.43)	0.291	NA
Neveus [28]	5 (0.25–99.43)	0.291	
Retention	3 (0.32–28.48)	0.339	0%
Deng (a) [29]	3 (0.12–72.36)	0.499	
Deng (b) [29]	3 (0.12–72.36)	0.499	

(Odds ratio shown with 95% confidence intervals)

OR odds ratio, *CI* confidence interval

getting continuous attention for its clinical use in children and adolescent OAB-s. Moreover, solifenacin oral suspension has been developed for convenient flexibility in optimal dosing. Small studies with open-label prospective study or retrospective study have supported the role of solifenacin in children and adolescent OAB-s [16–18].

Regarding safety issue of anticholinergics in children OAB-s, it has been generally accepted that neurological adverse events are of less common occurrence in children OAB-s compared to adult OAB-s due to the presumption that action of anticholinergics in children OAB-s is predominantly mediated by interaction with afferent nerves due to the sensory nature of OAB-s [19, 20]. Most of the adverse events caused by M1 receptors are of rare occurrence in children [1]. The incidence rate of constipation and oral dryness in children OAB-s was much lower than the typical incidence rate in adult OAB-s [1, 7]. Cognitive adverse events can also be present in children; however, they are generally limited to cases of overdose of medication [21–23].

Hoebeke et al. [17] reported the rate of adverse events to be 6.5% in their retrospective study on solifenacin in patients' refractory to oxybutynin in idiopathic OAB-s. Newsgreen et al. [14] reported the overall rate of adverse events as 19.2% (solifenacin) vs. 12.3% (placebo) in their RCT in children, 13.6% (solifenacin) vs. 10.5% (placebo) in adolescents. Long-term overall rate of adverse events due to solifenacin was 34.7% in children and 37.98% in adolescents [15]. Most common adverse events included constipation (11.9%), QT prolongation (8.5%) and dry mouth (4.2%) in children, and QT prolongation (13.8%) and nausea (6.9%) in adolescents. Most of the reported adverse events were well tolerated and clinically not significant.

In the present study, there was no significant overall difference in the adverse events (OR = 1.06, 95% CI 0.84–1.34). Among each category of adverse events, only urinary tract infection showed statistical difference (OR = 1.92, 95% CI 1.06, 3.49). However, due to a very limited number of available studies with sufficient quality in the present work, further investigation is warranted in futuristic studies. To the best of our knowledge, this is the first review to summarize and evaluate the clinical efficacy and safety of anticholinergics among children and adolescent OAB-s and confirm clinical efficacy in MVV and safety.

Conclusions

This systematic review and meta-analysis confirmed efficacy and safety issues in the improvement of MVV in idiopathic children and adolescent OAB-s.

Author contributions JH Kim had full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy

of the data analysis. Study concept and design: JH Kim. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: JW Noh and JH Kim. Statistical analysis: JW Noh, B Lee, and JH Kim.

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Compliance with ethical standards

Conflict of interest All authors have completed and submitted the ICMJE Form for disclosure of potential conflicts of interest and none were reported.

References

1. Franco I (2016) Overactive bladder in children. Nat Rev Urol 13(9):520–532. https://doi.org/10.1038/nrurol.2016.152
2. Kalo BB, Bella H (1996) Enuresis: prevalence and associated factors among primary school children in Saudi Arabia. Acta Paediatr 85(10):1217–1222
3. Butler RJ, Golding J, Northstone K, Team AS (2005) Nocturnal enuresis at 7.5 years old: prevalence and analysis of clinical signs. BJU Int 96(3):404–410. https://doi.org/10.1111/j.1464-410x.2005.05640.x
4. Bakker E, van Sprundel M, van der Auwera JC, van Gool JD, Wyndaele JJ (2002) Voiding habits and wetting in a population of 4,332 Belgian schoolchildren aged between 10 and 14 years. Scand J Urol Nephrol 36(5):354–362. https://doi.org/10.1080/003655902320783863
5. Fitzgerald MP, Thom DH, Wassel-Fyr C, Subak L, Brubaker L, Van Den Eeden SK, Brown JS, Reproductive Risks for Incontinence Study at Kaiser Research G (2006) Childhood urinary symptoms predict adult overactive bladder symptoms. J Urol 175(3 Pt 1):989–993. https://doi.org/10.1016/s0022-5347(05)00416-7
6. Blais AS, Bergeron M, Nadeau G, Ramsay S, Bolduc S (2016) Anticholinergic use in children: persistence and patterns of therapy. Can Urol Assoc J 10(3–4):137–140. https://doi.org/10.5489/cuaj.3527
7. Schroder A, Thuroff JW (2010) New strategies for medical management of overactive bladder in children. Curr Opin Urol 20(4):313–317. https://doi.org/10.1097/MOU.0b013e32833aa185
8. Jackson D, Law M, Barrett JK, Turner R, Higgins JP, Salanti G, White IR (2016) Extending DerSimonian and Laird's methodology to perform network meta-analyses with random inconsistency effects. Stat Med 35(6):819–839. https://doi.org/10.1002/sim.6752
9. Marschall-Kehrel D, Feustel C, Persson de Geeter C, Stehr M, Radmayr C, Sillen U, Strugala G (2009) Treatment with propiverine in children suffering from nonneurogenic overactive bladder and urinary incontinence: results of a randomized placebo-controlled phase 3 clinical trial. Eur Urol 55(3):729–736. https://doi.org/10.1016/j.eururo.2008.04.062
10. Birder L, de Groat W, Mills I, Morrison J, Thor K, Drake M (2010) Neural control of the lower urinary tract: peripheral and spinal mechanisms. Neurourol Urodyn 29(1):128–139. https://doi.org/10.1002/nau.20837
11. Michel MC, Chapple CR (2009) Basic mechanisms of urgency: roles and benefits of pharmacotherapy. World J Urol 27(6):705–709. https://doi.org/10.1007/s00345-009-0446-5
12. European Medicines Agency (2013) Clinical investigation of medicinal products in the treatment of urinary incontinence. European Medicine Agency. https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-treatment-urinary-incontinence. Accessed 30 May 2019
13. Lee SD, Chung JM, Kang DI, Ryu DS, Cho WY, Park S (2017) Efficacy and tolerability of solifenacin 5 mg fixed dose in korean children with newly diagnosed idiopathic overactive bladder: a multicenter prospective study. J Korean Med Sci 32(2):329–334. https://doi.org/10.3346/jkms.2017.32.2.329
14. Newgreen D, Bosman B, Hollestein-Havelaar A, Dahler E, Besuyen R, Sawyer W, Bolduc S, Rittig S (2017) Solifenacin in children and adolescents with overactive bladder: results of a phase 3 randomised clinical trial. Eur Urol 71(3):483–490. https://doi.org/10.1016/j.eururo.2016.08.061
15. Newgreen D, Bosman B, Hollestein-Havelaar A, Dahler E, Besuyen R, Snijder R, Sawyer W, Rittig S, Bolduc S (2017) Long-term safety and efficacy of solifenacin in children and adolescents with overactive bladder. J Urol 198(4):928–936. https://doi.org/10.1016/j.juro.2017.05.038
16. Bolduc S, Moore K, Nadeau G, Lebel S, Lamontagne P, Hamel M (2010) Prospective open label study of solifenacin for overactive bladder in children. J Urol 184(4 Suppl):1668–1673. https://doi.org/10.1016/j.juro.2010.03.124
17. Hoebeke P, De Pooter J, De Caestecker K, Raes A, Dehoorne J, Van Laecke E, Vande Walle J (2009) Solifenacin for therapy resistant overactive bladder. J Urol 182(4 Suppl):2040–2044. https://doi.org/10.1016/j.juro.2009.05.100
18. Nadeau G, Schroder A, Moore K, Genois L, Lamontagne P, Hamel M, Pellerin E, Bolduc S (2014) Long-term use of solifenacin in pediatric patients with overactive bladder: extension of a prospective open-label study. Can Urol Assoc J 8(3–4):118–123. https://doi.org/10.5489/cuaj.1356
19. Andersson KE (2011) Antimuscarinic mechanisms and the overactive detrusor: an update. Eur Urol 59(3):377–386. https://doi.org/10.1016/j.eururo.2010.11.040
20. Finney SM, Andersson KE, Gillespie JI, Stewart LH (2006) Antimuscarinic drugs in detrusor overactivity and the overactive bladder syndrome: motor or sensory actions? BJU Int 98(3):503–507. https://doi.org/10.1111/j.1464-410X.2006.06258.x
21. Ferrara P, D'Aleo CM, Tarquini E, Salvatore S, Salvaggio E (2001) Side-effects of oral or intravesical oxybutynin chloride in children with spina bifida. BJU Int 87(7):674–678
22. Giramonti KM, Kogan BA, Halpern LF (2008) The effects of anticholinergic drugs on attention span and short-term memory skills in children. Neurourol Urodyn 27(4):315–318. https://doi.org/10.1002/nau.20507
23. Sommer BR, O'Hara R, Askari N, Kraemer HC, Kennedy WA 2nd (2005) The effect of oxybutynin treatment on cognition in children with diurnal incontinence. J Urol 173(6):2125–2127. https://doi.org/10.1097/01.ju.0000157685.83573.79
24. Lopez Pereira P, Miguelez C, Caffarati J, Estornell F, Anguera A (2003) Trospium chloride for the treatment of detrusor instability in children. J Urol 170(5):1978–1981. https://doi.org/10.1097/01.ju.0000085667.05190.ad
25. Nijman RJ, Borgstein NG, Ellsworth P, Djurhuus JC (2005) Tolterodine treatment for children with symptoms of urinary urge incontinence suggestive of detrusor overactivity: results from 2 randomized, placebo controlled trials. J Urol 173(4):1334–1339. https://doi.org/10.1097/01.ju.0000152322.17542.63
26. Triantafyllidis A, Charalambous S, Papatsoris AG, Papathanasiou A, Kalaitzis C, Rombis V, Touloupidis S (2005) Management of nocturnal enuresis in Greek children. Pediatr Nephrol 20(9):1343–1345. https://doi.org/10.1007/s00467-005-1921-x
27. Nijman RJ, Borgstein NG, Ellsworth P, Siggaard C (2007) Long-term tolerability of tolterodine extended release in children 5-11 years of age: results from a 12-month, open-label study. Eur Urol 52(5):1511–1516. https://doi.org/10.1016/j.eururo.2007.05.002

28. Neveus T, Tullus K (2008) Tolterodine and imipramine in refractory enuresis; a placebo-controlled crossover study. Pediatr Nephrol 23(2):263–267. https://doi.org/10.1007/s00467-007-0662-4
29. Deng YJ, Ma G, Guo YF, Ge Z, Lu RG, Wang LX, Zhu HB, Chen CJ (2011) Comparisons of efficacy and safety of tolterodine and oxybutynin in children with idiopathic overactive bladder. Zhongguo Dang Dai Er Ke Za Zhi 13(1):26–28
30. Quintiliano F, Veiga ML, Moraes M, Cunha C, de Oliveira LF, Lordelo P, Bastos Netto JM, Barroso Junior U (2015) Transcutaneous parasacral electrical stimulation vs oxybutynin for the treatment of overactive bladder in children: a randomized clinical trial. J Urol 193(5 Suppl):1749–1753. https://doi.org/10.1016/j.juro.2014.12.001