A randomized, crossover trial comparing the efficacy and safety of fesoterodine and extended-release oxybutynin in children with overactive bladder with 12-month extension on fesoterodine: The FOXY study

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Abstract

Introduction: We sought to assess and compare safety and efficacy of fesoterodine and oxybutynin extended-release in the treatment of pediatric overactive bladder (OAB).

Methods: We conducted a non-inferiority, randomized, double-blind, crossover trial comparing fesoterodine 4–8 mg and oxybutynin 10–20 mg once daily (QD) in children with OAB aged 5–14 years (2015–2018). Every child received the first medication for eight weeks, followed by crossover to the second antimuscarinic after a three-days washout. Dose up-titration was possible at mid-course. Patients could enter a fesoterodine 12-month extension. Endpoints were assessed through changes on voiding diaries, Patient's Perception of Bladder Condition score (PPBC), adverse events, vital signs, electrocardiogram, post-void residual, urinalysis, and blood tests. The Wilcoxon rank sum and Wilcoxon signed rank tests were used for statistical analysis.

Results: A total of 62 patients were randomized (two early drop-outs). Expected class effects (dry mouth/constipation) were present but no significant difference was observed. There was a 10.1 beats/minute increase in heart rate with fesoterodine ($p<0.01$) (oxybutynin -1.9 beats/min; p=non-significant [ns]). No life-threatening or serious adverse events occurred. Efficacy was similar for both drugs. Bladder capacity improved over the 16 months of the study; baseline capacity of 125 mL (44.5% expected bladder capacity for age [%EBC]) to 171 mL (53.9 %EBC) at the end of the extension phase. No clinical or statistical difference was shown between efficacy measures for fesoterodine or oxybutynin.

Conclusions: The use of fesoterodine or oxybutynin appear safe and effective for the treatment of OAB in children. Based on our study, long-term treatment to achieve the ultimate goal of urinary continence is needed in this population.

Introduction

Overactive bladder (OAB) is defined as: "urinary urgency, usually with frequency and nocturia, with or without urge incontinence, in the absence of urinary tract infection [UTI] or other pathology."[1] Lower urinary tract symptoms (LUTS) are a burdensome healthcare issue, accounting for up to 40% of pediatric urology visits,[2] and OAB has an estimated prevalence of 15–20% in children.[3-4] LUTS are recognized as having harmful impact on children's quality of life, including poor self-esteem, social isolation, and behavioral changes.[5]

Conservative measures are the backbone of OAB treatment and should not be neglected. When these conservative measures are insufficient to treat symptoms, other options should be considered. Antimuscarinics are the first-line pharmacological OAB therapy,[6] but their use has not been as extensively studied in children. Oxybutynin (Oxy) immediate-release (IR) has long been the sole U.S. Food and Drug Administration (FDA)-approved antimuscarinic for pediatric OAB treatment. Its treatment-emergent adverse reactions (TEAR) (xerostomia, dry eyes/skin, constipation, flushing, blurred vision, dizziness, sleep difficulties) have also been reported in children and are often the reason for dose reduction or discontinuation.[7-9] The extended-release (ER) Oxy (OxyER) formulation has been shown to be superior to IR in various studies,[10-12] but its safety and efficacy in children has not been established.[13]

In January 2017, propiverine, used in Europe for many years, was approved by Health Canada for OAB treatment in adults and children. Other antimuscarinic agents are currently exclusively approved for OAB treatment in adults.

Fesoterodine (Feso) (5-hydroxy-methyltolterodine prodrug, ER antimuscarinic) was approved in Canada in

2012. It has demonstrated significant improvement against placebo in OAB symptoms and quality of life in adults in phase 3 trials.[14-16] Feso is administered daily (4–8 mg tablets).

Given the trivial number of officially approved pharmacological options for children and considering that their use is limited by suboptimal clinical response or TEAR, there is a need for additional drugs to gain approval by recognized authorities, especially ER formulations, to improve compliance and decrease TEAR. Our hypothesis is that Feso and OxyER are safe and effective for the treatment of OAB in children. Our main objective was to assess the safety of Feso (Toviaz®) and OxyER (Ditropan XL®) in children with OAB. Our secondary objectives were to compare the short-term efficacy of both medications and to evaluate the long-term efficacy of Feso.

Methods

Study population

All patients underwent urotherapy before initiating any medication: resolution of constipation, good hydration habits**,** voiding schedule, and optimal voiding position. Anomaly on flow rate electromyography (EMG) (dyssynergia, staccato, etc.) would lead to physiotherapy/biofeedback with bladder retraining for 3–6 months before antimuscarinics are initiated. Prior to inclusion, questionnaire, physical exam, urinalysis/cultures, and uroflows/EMG were obtained and normal flow rate index was confirmed.

Patients attending pediatric urology clinic for LUTS were offered to enter the trial if they fulfilled inclusion and exclusion criteria (Supplementary Table 1; available at *cuaj.ca*). If symptoms did not improve with conservative measures with or without trial of IR Oxy, and less than 65% of the expected bladder capacity (%EBC) for age was confirmed (30 + [age in years x 30] mL)[1] on a three-day voiding diary, a single long-acting antimuscarinic (Feso or OxyER) was initiated. Subjects were randomly assigned (1:1) by pharmacy. Patients completing the crossover study were eligible to enrol in a 12-month Feso open-label extension study if they demonstrated good tolerance to Feso.

Study design

We conducted a single-center, prospective, non-inferiority, double-blind, crossover, randomized trial (2015–18). Our main objective was to assess safety of Feso (Toviaz®) and OxyER (Ditropan XL®) in children with OAB. Our secondary objectives were to compare the short-term efficacy of both medications and evaluate long-term efficacy of Feso in an open-label 12-month extension. Both trials were granted non-objection letters from Health Canada and approved by our institutional review board. Parents provided written consent.

Study power was based on efficacy endpoint. To estimate sample size, we assumed that patients to be included were refractory to conservative treatment (success <50% improvement). Sample size was estimated for 2x2 crossover design for testing non-inferiority, using PASS 13 (Power Analysis and Sample Size Software, 2014). The total sample size was set at ≥56 patients with complete data to achieve 80% power, one-sided alpha 2.5%, 15% margin of non-inferiority, and 0.31 for coefficient of variance. Allowing 10% dropout (six patients), we planned to recruit 62 patients.

Prior to and at first visit (V1), children and their parents were again educated on conservative treatment of OAB (timed voiding, adequate voiding technique, fluid management, and bowel management if necessary) and were instructed to reinforce those measures and to continue them throughout the course of the trial. Study design is detailed in Fig. 1 and Supplementary Table 2 (the latter available at *cuaj.ca*).

Safety assessment

The primary endpoint was to assess safety of Feso and OxyER. Safety was evaluated on the basis of TEAR at the end of each crossover phase, and every four months during the extension phase, using medical history, physical exam, post-void residual (PVR) (bladder scan), vital signs, triplicate 12-lead electrocardiogram (ECG), and laboratory parameters.

Efficacy assessment

The secondary endpoints were to compare the short-term efficacy of Feso and OxyER and to assess the long-term efficacy of Feso. Efficacy was objectively quantified using three-day voiding diary at each visit. The primary efficacy variable was change in mean voided volume. Secondary efficacy variables were: urinary frequency, urgency (grade 2–3), and urge incontinence episodes/24 hours. We calculated the relative %EBC by dividing mean voided volume on voiding diary by EBC for age. Efficacy was also subjectively evaluated using the patient perception of bladder condition (PPBC) scale (Supplementary Table 3; available at *cuaj.ca*).[17] Finally, pharmacists calculated medication adherence based on returned pill containers.

Statistical analysis

Quantitative variables are described as mean ± standard deviation (SD), and qualitative variables as frequencies and percentages. Parametric (F-test or t-test) or non-parametric (Kruskal-Wallis, Wilcoxon rank-sum) tests were used to compare continuous data by independent groups after normality verification; chi-squared or exact tests were used for categorical data comparisons. The McNemar's test was used to compare paired binary data and the Wilcoxon signed-

rank test for paired continuous data. To test the primary and secondary crossover outcomes, mixed linear regression models were fitted for continuous outcomes and generalized estimating equation (GEE) logistic models for binary outcomes. Statistical analyses were performed using SAS Statistical Software v.9.4 (SAS Institute, Cary, NC, U.S.), with a two-sided significance level set at $p<0.05$.

Results

The study screened 70 patients and enrolled 62 patients (38 boys, 24 girls). Mean age was 8.5 years (range 5–12). Demographic details are provided in Table 1. We had two early dropouts (two boys) not included in the analysis. There were no missed visits and no loss to followup.

In the extension phase, we had 26 children. Two children were excluded because they took the medication for only one month and then switched back to OxyER for efficacy reasons and one child dropped out after V6 due to anxiety toward blood sampling.

Safety

There were no life-threatening or serious adverse events during the study. Expected class TEARs were observed, such as dry mouth and constipation (Table 2). No statistical difference between the two drugs was demonstrated.

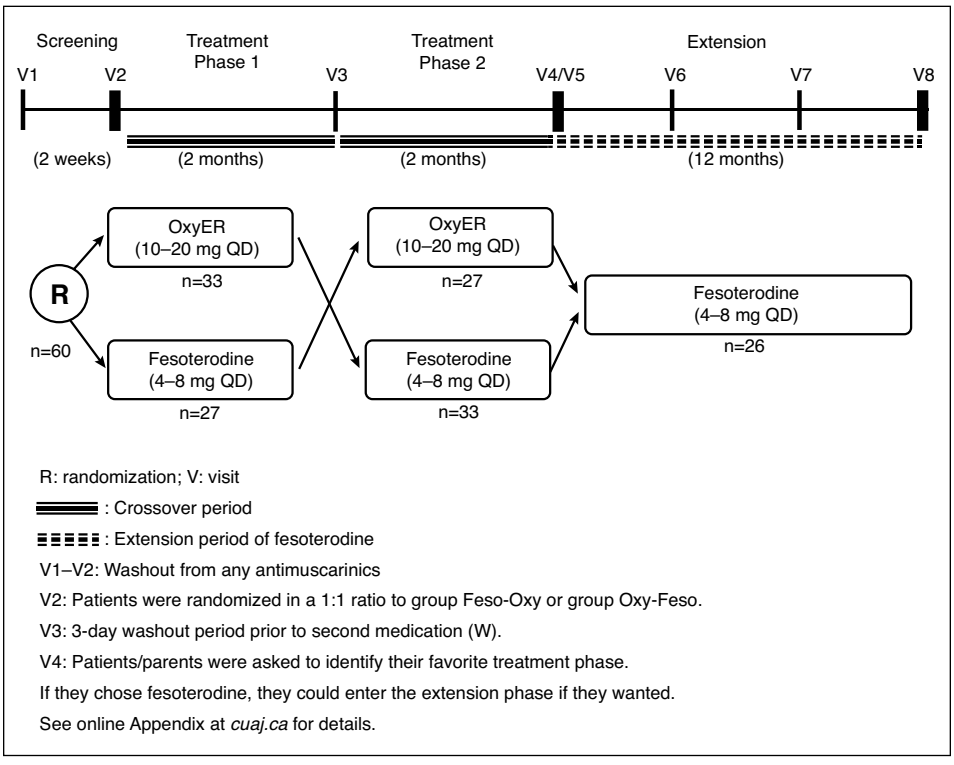

Fig. 1. Study design.

Cardiovascular TEARs were observed but none were severe. There was no change in blood pressure, but one patient experienced an increased QTcB interval during the crossover phase. This patient was receiving OxyER and QTcB normalized rapidly on repeated ECG four and 12 days later, without treatment. Ten asymptomatic >20% elevations of heart rate (HR) were observed in the crossover phase; nine of 10 were taking Feso. At baseline, mean HR was 85.4 heartbeats/minute. Mean HRs after two months of treatment with OxyER and Feso were 83.5 and 95.6 beats/minutes, respectively. From baseline, there was an increase in HR of 10.1 beats/minute ($p<0.01$) with Feso vs. OxyER (-1.9 beats/minute; p=non-significant). Five of these events occurred with Feso 8 mg and three with concomitant attention deficit hyperactivity disorder ADHD medication, and recovered once the dosage was decreased or medication changed. One child had an elevated HR on both antimuscarinics. This patient also had an increase in his ADHD medication during the trial, and this type of side effect is also possible with this class of medication and could explain his HR increase with both medications.

In the extension phase, one patient had QTcB increase and seven had HR increases, all without symptom. Of these seven children, four returned to normal HR without intervention, supporting the inherent variability for this parameter in children. Two decreased the dosage and one stopped the medication, with HR normalizing afterward.

A total of 15 UTIs occurred in 10 different patients during the crossover segment. All of these infections were in female participants (seven had prior UTI). There was no difference between the two drugs. One of those patients was excluded from the study because of recurrent UTI with an increased PVR. She developed de novo detrusor sphincter dyssynergia not present on initial flow rate. In the 12-month extension phase, there were five UTI episodes reported in three female participants; two participants also had a UTI in the crossover segment. None had elevated PVR.

Efficacy

The EBC was adjusted to the age of the child at the visit, therefore, did compensate for the growth of the child. In general, the normal growth of a child over the 12 months of the study (V1–V7) would mean an increase EBC of 30 mL between the

Table 1. Study participants' description randomized in the crossover phase and included in the 12-months open-label extension on fesoterodine

	Crossover study Mean ± SD n=60*				Extension phase Mean ± SD n=26
	Groupe 1 (oxy-feso) n= 33	Groupe 2 (feso-oxy) n= 27	p	Total	
Male (%)	19 (57.6%)	17 (63%)	0.79	36 (60%)	17(65%)
Age, (year)	8.5±1.8	8.4±1.9	0.95	8.5±1.8	8.8±2.2
ADHD medication	6 (18.2%)	2 (7.4%)	0.28	8	5
Weight, (kg)	29.3±8.9	28.1±7.3	0.8	28.8±8.2	29.0±9.8
Height, (m)	1.31±0.14	1.29±0.1	0.74	1.30±0.12	1.32±0.14
BMI, kg/m^2	16.6±2	16.6±2.4	1.00	16.6±2.2	16.6±2.0

*62 randomized patients. 70 patients were screened, two children were excluded from analysis: 1 did not initiate the treatment and the second did not complete the first phase. 58 children completed the crossover phase of the trial (self-exclusion [1], recurrent urinary tract infection [1] between V3 and V4). ADHD: attention deficit and hyperactivity disorder; BMI: body mass index; SD: standard deviation.

start (125 ml) to the end (155 ml) of trial, without change in %EBC. %EBC mildly improved during the course of the crossover study (Table 3). Using specific patients on the extension segment, we noted an improved %EBC of almost 10% over the course of the 12 months.

Changes in 24-hour frequency, urgency, and 24-hour urinary incontinence were equivalent between the two drugs. The PPBC score was not significantly different between Feso and OxyER (3.5 vs. 3.3, respectively; p=0.12). At the end of the crossover phase, we observed a significant improvement from baseline for each parameter (p<0.0001) (Table 4).

In the extension phase, parameters were also improved at V7 compared to baseline. The PPBC score was at 3.3 at V7 but seemed to continue to improve at V8, one or two months after participants had stopped the study medication (2.6).

The adherence to medication remained above 90%.

Table 2. Specific treatment-emergent adverse reactions

		Crossover phase		Extension phase	
Body system	**Total (%)**	**Fesoterodine events, n**	**OxyER events, n**	**Events, n**	**Total (%)**
Cardiovascular					
Variation blood pressure	0	0	0	1	3.8
Variation in heart rate (≥20%)	14.5	9[3]	1	7[4]	26.9
Increased QTcB	1.6	0	1	1	3.8
Flushing (skin, cheeks)	3.2	2	0	0	0
Genitourinary					
Urinary tract infection	16.1	7	8	5	11.5
Increased PVR	1.6	0	1	0	0
Gastrointestinal					
Nasal bleeding/epistaxis	6.4	2	2	3	1.1
Dry mouth/eyes/hands	43.5	17	17	11	42.3
Constipation	13.3	5	3	5	19.2
Diarrhea	8.0	1	4	0	0
Abdominal pain	20.9	8	7	6	23.0
Appetite modification	8.0	2	4	0	0
Nausea/vomiting	4.8	2	1	2	7.6
Variation AST/ALT value[1]	1.6	1	0	1	3.8
Nervous system[2]					
Headache	3.2	2	0	3	1.1
Irritability	6.4	2	3	4	15.3
Insomnia	1.6	0	1	0	0

[1]Mild elevation at V4. One month later, the control was normal without intervention. [2]Of the 6 children that experienced either irritability or insomnia, two had ADHD. [3]Five of the HR increase occurred with Feso 8 mg and three with concomitant ADHD medication, and recovered once Feso dosage was decreased or changed to OxyER at crossover. [4]Six of the 7 children with HR increase in extension phase were on Feso 8 mg. One on 4 mg also had increase in the dosing of his ADHD medication. AST/ALT: aspartate transaminase/alanine transaminase; PVR: post-void residual.

Table 3. Functional bladder capacity

Period	Baseline		End of crossover V4 (n=60)		Extension phase V7[2] (n=26)	
Bladder capacity	Mean volume (mL)	%EBC[1]	Mean volume (mL)	%EBC	Mean volume (mL)	%EBC
	125	44.5	146	50.0	171	53.9[3]

[1]EBC was adjusted to the age of the child at each visit to compensate for the growth of the child ([age (years) + 1] x 30 mL). The normal growth of a child over the 12-months of the study (V1–V7) would mean an increase EBC of 30 mL between baseline (125 ml) to the end of trial, without change in %EBC. [2]%EBC was calculated at V7 because in the last four months of the extension phase, participants had the opportunity to decrease and stop the medication and consequently some patients could present worsening of their bladder capacity at V8, underestimating the gain in capacity. [3]Comparing baseline %EBC vs. end of extension phase (n-26), p<0.05. %EBC: relative expected bladder capacity for age

Post-study data

To document long-term evolution, we retrieved information on the 34 patients not enrolled for the extension phase. Twenty-three of these 34 children (68%) are now continent (mean followup 18 months). Of the 26 children that enrolled in the extension phase, 23 children completed the 12-month extension phase and 18 are now continent (78%). Due to lack of improvement in symptoms or %EBC, some patients underwent treatment escalation to dual treatment (antimuscarinic + mirabegron)[18] or switched to mirabegron.[19] Active treatment at last followup visit is shown in Table 5.

Discussion

We present the first prospective, randomized study comparing OxyER to Feso for the treatment of OAB in children. This condition is very bothersome and effective, well-tolerated treatments are needed. Treatment objectives are to improve quality of life by diminishing episodes of urinary incontinence and urgency, and by improving bladder capacity. Our double-blind, crossover study showed that both Feso and OxyER were well-tolerated and safe. Both groups had similar demographics and efficacy results at the end. Feso and OxyER had similar TEAR profiles and both dosages appeared safe to use in children.

Increase in HR is a well-known class effect of antimuscarinics. The dose-effect correlation on HR elevation was demonstrated in a randomized trial (Feso 4 mg/day and supratherapeutic 28 mg/day vs. placebo). There was a mean HR elevation of 3 beats/minutes for the 4 mg/day dosage and 11 beats/minutes with 28 mg/day dosage. There was no change in QTc measures with either dosage.[20] In a phase 3, placebo-controlled study, the mean HR increase with Feso 4 mg/day and 8 mg/day was 3–4 beats/minutes and 3–5 beats/minutes, respectively.[14] Nitti and al compared the mean HR change with placebo and Feso 4 mg/day and 8 mg/day. There was a change of 1, 3, and 4 beats/minutes, respectively.[15] Variation in HR was studied with oxybutynin IR vs. placebo and no difference was noted.[21] Similar to those studies, we observed more HR increase with Feso than with OxyER. It also occurred more often with 8 mg than the 4 mg dose. We noted that some children with elevated HR at 4 mg/day also had concomitant changes in their ADHD medications. Elevation in blood pressure and HR is also well-described for ADHD medications, mostly with amphetamines and atomoxetine.[22] It is possible that these elevations were secondary to ADHD medication or could have been worsened by the simultaneous use of both medications. In conclusion, no significant clinical event occurred because of these HR elevations. In fact, a systematic review on the subject by Fleming et al confirmed that at a mean age of eight years (patients in our study), the mean HR is 90 beats/minute and the 99th percentile is at 120 beats/min.[23] Therefore, our patients' HR did fall within normal limits but exceeded the limit we set in the protocol (≤20% increase from baseline) for safety reasons. Similar to the literature, we had no concern about QTcB changes with the two drugs. Nonetheless, we would suggest a closer cardiac monitoring of children who are taking both ADHD medications and Feso.

Some patients presented with UTI during the study, although this occurred only in girls. There was no difference in UTI rates between the two drugs. As in the cur-

Table 4. Efficacy variables

	Baseline	Crossover study			Extension	
		Fesoterodine	OxyER	End of crossover (V4) n=60	V7 n=26	V8 n=26
Mean voided volume per micturition, (mL) (SD)	125 (53)	147 (56)*	156 (56)*	146 (53)*	171 (74)*	160 (90)#
Urinary frequency per 24h, mean (SD)‡	6.8 (2.4)	6.0 (2.2)*	5.9 (2.2)*	5.9 (2.6)*	5.8 (1.5)*	6.2 (2.2)#
Urinary incontinence per 24h, mean (SD)‡	1.8 (1.7)	1.0 (1.1)*	0.9 (1.1)*	0.9 (1.2)*[1]	1.2 (1.7)*	1.2 (2.1)*
Grade 2-3 urgency episodes per 24 h, mean (SD)‡	1.7 (2.3)	1.0 (1.4)*	1.1 (1.4)*	1.0 (1.5)*	1.4 (2.3)#	1.3 (2.1)#
PPBC score (SD)	3.6 (1.1)	3.5 (1.2)#	3.3 (1.2)*	3.4 (1.2)*	3.2 (1.4)*	2.6 (1.3)*

The primary efficacy variable was the change in mean voided volume, calculated using the 3-day VD, excluding the morning void. ‡Secondary efficacy variables, calculated with the 3-day VD. Efficacy was also subjectively measured using the patient perception of bladder condition (PPBC) scale (Supplementary Table 2 at *cuaj.ca*) at baseline, at the end of each crossover phase, and every 4 months during the extension phase. *Comparison from baseline to end of crossover (n=60) or end of extension phase (n=26), p<0.0001. #Comparison from baseline to end of crossover (n=60) or end of extension phase (n=26), p<0.01. [1]At the end of the crossover phase, 28 patients achieved daytime continence (15 Feso, 13 OxyER). SD: standard deviation.

Table 5. Long-term evolution after crossover study or beyond the 12-month extension phase

	Participants in the crossover study only[1] n=34	Participants in the extension phase[2] n=26
Gender (M/F)	19/15	17/9
Active treatment at last visit		
None	12	9
OxyER	11	2
Fesoterodine	0	5
Mirabegron	4	3
Dual treatment*	6	7
Lost to followup	1	0
Continent	23 (68%)	18 (69%)

[1]Patients not participating to the extension phase, therefore ending at visit 4, active treatment after the study if symptoms persisted (34 of the 60 patients; mean followup 18 months). [2]Patients who were on the 12-month extension phase with fesoterodine, active treatment after visit 8 if symptoms persisted (26 remaining patients of the initial 60 patients; mean followup 9 months). *Dual: antimuscarinic plus mirabegron.[25]

rent literature, the incidence of UTI does not seem to be increased from the general pediatric population by either Feso or OxyER.[15,24]

As OAB is sometimes associated with ADHD,[25,26] Feso seemed to be an interesting choice of medication since it has very low likelihood of crossing the blood-brain barrier.[27] We had a low incidence of central nervous system adverse events in our study. OxyER had a tendency toward more events of irritability and insomnia over Feso (p=non-significant) (Table 2). To support this observation, in a phase 1, four-treatment, crossover, double-blind, placebo- and positive-controlled study in elderly healthy volunteers, there was no difference in cognitive impairment between placebo and Feso.[28] In another study evaluating cognitive impact of antimuscarinics, Oxy was associated with more cognitive impairment than other antimuscarinics.[29] Our trial was not designed to study this outcome specifically but further research on the subject would be interesting.

%EBC improved over time. The major factor in improving bladder capacity with antimuscarinics has been associated with treatment duration. Using %EBC automatically corrects EBC according to the age of the patients at a given time. Normal growth would keep the EBC stable over time**.** In a study of 27 children with daytime incontinence that switched from OxyIR to OxyER, there was an improvement of 15% in %EBC ($p<0.01$).[10] In our study, in addition to the improvement in urge and urge incontinence, we had 10% improvement of %EBC after one year of treatment on Feso (V2–V7), reflecting the potential efficacy of the medication. There was no significant statistical or clinical difference in efficacy between the two drugs. There was an improvement from baseline with all variables with both medications. In the extension phase, the improvement was progressive. It was interesting to see that even though the mean voided volume deteriorated between V7 and V8 (11 of the 24 children either stopped or decreased the dosage of their medication before V8), the PPBC score improved. We think that children who stopped their medication probably had a better perception of their condition being off medication and having fewer side effects, making their quality of life better.

Beyond the study period, most children became completely continent (69%) and a few were able to taper off medication (33%) (Table 5). The most important thing we get from these data is that OAB is a chronic condition that necessitates an extended medical followup, sometimes attempting several approaches/drugs before finding the one that fulfills the patient's needs. Conservative measures need to be reinforced at every visit, and compliance to those measures and medication need to be verified.[30] Any modification in concomitant medication must be considered regarding pharmacological interactions and potential new side effects, especially for patients with ADHD.

Limitations

Although we performed a prospective, randomized, double-blind study, the trial remains of moderate size for pediatric OAB, as it was designed as a non-inferiority study. Also, the trial was a single-center study; a multicenter trial would have helped making the findings more generalizable. We did not include a placebo-controlled group nor made a comparison with OxyIR. In addition, we could have included an extension phase for OxyER, but we do report on their outcomes (Table 5). The extension phase was only offered to children responding to Feso, which could have introduced a selection bias contributing to the improvement of PPBC scores.

Take-home message

Long-acting formulations of oxybutynin and fesoterodine are effective in the treatment of OAB in children, as they improve median voided volume, quality of life, and number of incontinence episodes with few side effects.

Conclusions

Feso or OxyER appear to be safe and effective treatment options for OAB in children. The efficacy of both drugs was similar. Based on the 12-month extension phase and beyond, OAB in children needs long-term treatment to achieve the ultimate goal of urinary continence.

Competing interests: Dr. Moore has been an advisory board member for Pfizer; has received speaker honoraria from Duchesnay and Hollister; and has participated in clinical trials supported by Astellas and Pfizer. Dr. Bolduc has been the principal investigator in clinical trials supported by Astellas and Pfizer. The remaining authors report no competing personal or financial interests related to this work.

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This paper has been peer-reviewed.

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