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ORIGINAL RESEARCH ARTICLE

Safety and Effectiveness of Prucalopride in Children with Functional Constipation with and without Upper Symptoms

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Abstract

Introduction Pediatric prucalopride studies for treatment of gastrointestinal (GI) disorders have reported mixed results. We aimed to assess the safety and effectiveness of prucalopride in functional constipation (FC) with and without upper GI symptoms.

Methods Retrospective data on patients with FC receiving combined prucalopride and conventional therapy was compared with those receiving conventional therapy alone within 12 months. Thirty patients on combined therapy and those on conventional therapy were each matched on the basis of age, gender, race, and presence of fecal soiling. Response (complete, partial, or no resolution) was compared. Similarly, response to concurrent functional upper GI symptoms (postprandial pain, bloating, weight loss, vomiting, early satiety, or nausea) and dysphagia, as well as adverse effects, were evaluated in the combined group.

Results Mean age of 57 cases was 14.7 ± 4.9 years and 68% were female. Comorbidities included functional upper GI (UGI) symptoms (84%), dysphagia (12%), mood disorders (49%), and hypermobility spectrum disorder (37%). Unmatched cases reported 63% improvement to FC; response did not differ between the matched cohorts (70% versus 76.6%, $p = 0.84$). Cases showed a 56% improvement in functional UGI symptoms and 100% in dysphagia. Adverse effects were reported in 30%, abdominal cramps being most common. Four (7%) patients with a known mood disorder reported worsened mood, of which two endorsed suicidal ideation.

Conclusion Prucalopride efficaciously treated concurrent UGI symptoms and dysphagia in constipated pediatric patients and was overall well tolerated. Preexisting mood disorders seemed to worsen in a small subset of cases.

1 Introduction

Functional constipation (FC) affects 16–25% of the pediatric population [1, 2]. Current treatment modalities include patient and family education about the disease process, behavioral/lifestyle modifications, and a combination of oral and/or rectal laxatives [3]. However, these treatment modalities have limited efficacy [4] and approximately a quarter of children with chronic constipation have persistence of defecation problems in adulthood [5]. Additionally, recent studies have suggested that comorbid conditions such as gastroesophageal reflux not only exist in pediatric patients with FC but also respond to the treatment of constipation [6]. These studies, however, have concentrated on the use of conventional treatments for constipation, and to date, only one other study has investigated how these comorbidities respond to novel promotility medications [7].

As a highly selective serotonin receptor agonist, prucalopride has shown promise in the treatment of a myriad of gastrointestinal (GI) disorders [7–11]. Prucalopride is US Food and Drug Administration (FDA)-approved for the treatment of chronic idiopathic constipation in adults [12] with few side effects [13] and no appreciable cardiogenic effects, unlike its non-selective predecessors —cisapride [14, 15] and tegaserod [15]. While there is data on the efficacy of prucalopride for adult GI disorders [10, 16], the same is not the case in pediatrics. To date, there are few studies on the efficacy of prucalopride in pediatric GI disorders including two contradicting studies in pediatric FC [8, 17], namely a favorable effect on the treatment of upper GI symptoms in children [7] and a case review of its use in pediatric pseudo-obstruction [11]. Hirsch *et al*, published the first and, to date, only study on pediatric patients that evaluated the effect of prucalopride on upper

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Key Points

We show that prucalopride may provide most improvement in patients with difficulty swallowing (dysphagia) and patients with indigestion (dyspeptic) symptoms that are often associated with functional constipation.

Here we also noted that while generally a safe medication to use, prucalopride may worsen mood disorders and suicidal ideation in some patients.

GI symptoms and concluded that those with enteral tubes saw the most improvement in their symptoms [7]. Thus, the objective of this study was to assess the safety and effectiveness of prucalopride in children and adolescents with FC with and without upper GI symptoms such as meal-associated abdominal pain, nausea, vomiting, bloating, early satiety, weight loss, and difficulty swallowing at our institution.

2 Methods

After obtaining institutional research board (IRB) approval, we reviewed charts of all consecutive patients who were prescribed prucalopride between December 2018 and December 2020 and diagnosed with FC at the Cincinnati Children's Hospital Medical Center pediatric gastroenterology clinics. We identified patients with FC from our database using ICD-10 codes (K59.00, K59.01, K.59.04, and/or K59.09). Patients met Rome criteria for FC. We included children and young adults aged 0–24 years diagnosed with FC with or without concomitant functional UGI symptoms and/or dysphagia who were treated with prucalopride at their baseline visit, along with conventional therapy for FC (referred to as combined therapy from now on) and had a documented follow-up within 1 year after commencement of treatment (in the form of clinic visit, emergency room visit, or phone call/email communication with parent documented in the patient's chart). The definition of functional UGI symptoms included meal-associated abdominal pain, nausea, vomiting, bloating, early satiety, and/or weight loss. Dysphagia was defined as symptoms of difficulty swallowing and food getting stuck in the chest. Per institutional standard of care, patients with dysphagic symptoms underwent further evaluation including a contrast study (either as an esophagram or an upper GI series) and an endoscopy. Those with inconclusive or normal findings, underwent manometric evaluation as indicated. Patients with gastrostomy, gastrojejunostomy, and cecostomies without any other GI surgeries, ventriculoperitoneal shunt, organic GI disorders (eosinophilic disorders, celiac disease, and inflammatory bowel disease), mood disorders (anxiety and/or depression), neurogenic disorders or developmental delay (autism spectrum disorder, Down syndrome, etc.), Ehlers Danlos Syndrome, and other hypermobility disorders were included. Patients who were on concurrent laxatives as part of the conventional therapy were included. We excluded patients with Hirschsprung disease, sacral nerve stimulation, gastric electrical stimulation, myelomeningocele, anorectal malformations, and tethered cord syndrome. For the defined study period, after applying exclusion criteria, a total of 57 prucalopride-treated patients could be enrolled and analyzed. Demographics, symptoms, duration of symptoms, medical and medication history, clinical investigations, and dose of prucalopride were collected from the initial visit. Clinical response to constipation, functional UGI symptoms and dysphagia, dose, duration of prucalopride treatment, and adverse effects were documented at the follow-up visit within 12 months. The conventional therapy cohort constituted of 90 patients with a diagnosis of FC at their baseline visit who were started on conventional medical management alone. Conventional management included rectal disimpaction, bowel cleanout, maintenance laxatives (subdivided as osmotic—e.g., polyethylene glycol—or stimulant—e.g., senna), pelvic floor physical therapy, and behavioral modifications. Conducting propensity score matching between those on combined prucalopride and conventional therapy and conventional therapy alone cohorts (stated below) resulted in a final sample size of 30 patients in each group.

3 Outcomes

3.1 Primary Outcome

The primary outcome was defined as the clinical response, as evaluated by their primary GI provider, to combined therapy (prucalopride AND conventional therapy) for FC and was captured as: complete improvement, partial improvement [response in some symptoms (straining, stool character, greater than three spontaneous bowel movements per week, sensation of incomplete evacuation) but not complete resolution], and no improvement. The combined therapy group was then compared with matched conventional therapy alone cohort and examined within 3 months, 6 months, and 12 months from starting prucalopride treatment.

3.2 Secondary Outcomes

- Response of functional UGI symptoms (meal-associated abdominal pain, nausea, vomiting, bloating, early satiety, and/or weight loss) and dysphagia (symptoms of esophageal dysphagia including difficulty swallowing and food getting stuck in chest) to prucalopride.
- Association of prucalopride dose with primary response, adverse effects, and baseline characteristics.
- Distribution of adverse effects.

4 Data Analysis

To examine the primary outcome (response to FC) between combined therapy treated patients and conventional therapy treated cohort, propensity score matching (PSM) was performed to eliminate selection bias between the two study groups. PSM was done using "MatchIt" package in R statistical environment (R Foundation for Statistical Computing, Vienna, Austria) [18]. The ratio was defined as 1:1 match with a caliper width of 0.1 based on nearest neighbor-matching method without replacement. The covariates used for matching were age, gender, race, and fecal incontinence.

Baseline characteristics for continuous variables were summarized as mean (standard deviation) or median (first and third quartile) and group differences examined using Wilcoxon rank sum test. Categorical variables were presented as frequency counts and percentages, and group differences were examined using the chi-squared or Fisher's exact tests.

The response to FC was labeled as "complete improvement," "partial improvement," and "no-improvement." Complete improvement denoted complete resolution of symptoms while partial improvement corresponded with improvement in some symptoms only. The association between clinical response to FC and study groups was then examined at defined timepoints using chi-squared statistics. Response to secondary outcomes (functional UGI symptoms and dysphagia) in the combined therapy cohort were reported as frequency counts and percentages.

Association between prucalopride dose/day (0.5, 1, and 2 mg) in relation to age was examined using the proportional odds model. The odds ratio [95% confidence interval (CI)] was analyzed for being on 2 mg/day dose in comparison with 1 and 0.5 mg/day. All analyses were conducted as two-sided tests with $p \leq 0.05$ considered to be statistically significant, and SAS 9.4 (SAS Institute Inc., Cary, NC) was used.

5 Results

5.1 Patient Characteristics of the Unmatched Cohort at Baseline (*N* = 57)

Of 57 patients on combined therapy (prucalopride and conventional), the mean age was 14.7 ± 4.9 years (2–24 years); 68% were female and 90% Caucasian (Table 1). All patients met at least two of the Rome criteria items for the diagnosis of FC. Ten patients (20%) reported less than three bowel movements (BMs) per week, 20/57 (35%) had hard stools, and 13/57 (23%) had fecal incontinence. All patients in the combined therapy treated group were on at least one concurrent laxative, 80% of patients were on a stimulant laxative, 60% were on an osmotic laxative, and 39% were on both a stimulant and an osmotic laxative.

A total of 48 (84%) patients had concurrent functional UGI symptoms and 7/57 (12%) had concurrent dysphagia. Of those with concurrent dysphagia, none had a baseline organic GI disorder, two had endoscopic findings (chronic gastritis, duodenitis), and one had delayed 4-h gastric emptying study. All seven patients with dysphagia underwent esophageal manometry testing, which was abnormal. Of these, five had ineffective esophageal motility (IEM), one had poor esophageal reserve based on failed augmentation on rapid drink challenge, and one had inadequate bolus clearance.

Four patients (7%) had organic GI disorders at baseline [celiac disease, 2 (3.5%), and eosinophilic esophagitis, 2 (3.5%)]; these patients were noted to be in endoscopic remission at the time of follow-up. Hypermobility spectrum disorder was noted in 21/57 (37%), and 28/57 (49%) had a documented mood disorder. The most common mood disorders included anxiety in 45% and depression in 14% of patients. One patient had developmental delay, one had ventriculoperitoneal (VP) shunt and seven had enteral feeding tubes.

5.2 Response to Prucalopride in FC (*N* = 57)

Of 57 patients on combined therapy (prucalopride and conventional), 36 (63%) reported improvement of FC. Specifically, 20/57 (35%) had complete resolution, 16/57 (28%) responded partially, while 21/57 (37%) were non-responders.

5.3 Response to Prucalopride in the Matched Case-Conventional Therapy Cohort (*N* = 30)

After matching, 30 subjects in each group were examined (Table 1). In the matched combined therapy group, the mean age was 11.7 ± 4.1 years; 63% were females and 97% were Caucasian. In the matched conventional therapy group, the mean age was 11.7 ± 4.3 years; 57% were

Table 1 Baseline characteristics before and after propensity matching at 12-month follow-up

Variable	Before matching			After matching		
	Conventional therapy	Prucalopride with conventional therapy	*p* value	Conventional therapy	Prucalopride with conventional therapy	*p* value
	N = 200	*N* = 57		*N* = 30	*N* = 30	
Age						
Years, median (Q1–Q3)	7 (3–10)	16 (11-19)	< 0.0001	11 (9–15)	12 (9–16)	0.97
Age group						
≤ 5	84 (42%)	2 (3.5%)	< 0.0001	2 (6.7%)	2 (6.7%)	1
> 5	116 (58%)	55 (96.5%)		28 (93.3%)	23 (93.3%)	
Gender						
Male	106 (53%)	18 (31.6%)	0.004	13 (43.3%)	11 (36.7%)	0.60
Race						
White	174 (87%)	51 (89.5%)	0.79	30 (100%)	29 (96.7%)	1
Black	13 (6.5%)	2 (3.5%)		0 (0%)	1 (3.3%)	
Other	13 (6.5%)	4 (7.0%)		0 (0%)	0 (0%)	
Baseline bowel movements per week	*N* = 176	*N* = 51		*N* = 27	*N* = 27	
< 3/week	46 (26.1%)	10 (19.6%)	0.34	7 (25.9%)	6 (22.2%)	0.75
Fecal incontinence	*N* = 200	*N* = 57		*N* = 30	*N* = 30	
Yes	67 (33.5%)	13 (22.8%)	0.12	8 (26.7%)	9 (30%)	0.77
Stool consistency	*N* = 200	*N* = 57		*N* = 30	*N* = 30	
Hard	100 (50%)	20 (35%)	0.0003	16 (53%)	9 (30%)	0.03
Laxative use						
Stimulant laxative	*N* = 196	*N* = 44		*N* = 30	*N* = 22	
	98 (50%)	35 (79.6%)	0.004	19 (63.3%)	18 (81.8%)	0.15
Osmotic laxative	*N* = 196	*N* = 45		*N* = 30	*N* = 23	
	185 (94.4%)	27 (60%)	< 0.0001	28 (93.3%)	12 (52.2%)	0.006
Any laxative	*N* = 196	*N* = 45		*N* = 30	*N* = 23	
	192 (98%)	45 (100%)	1	30 (100%)	23 (100%)	NA
Both laxatives	*N* = 196	*N* = 44		*N* = 30	*N* = 22	
	91 (46.4%)	17 (38.6%)	0.35	17 (56.7%)	7 (31.8%)	0.08

females and all were Caucasian. Since these were propensity-matched cohorts, the demographic data did not differ between matched combined therapy and conventional therapy cohorts ($p > 0.05$). For the conventional therapy group, 93% of patients were on osmotic laxatives and 63% were on stimulant laxatives at baseline. More than half (57%) were noted to be on both stimulant and osmotic laxatives. At baseline, 30% of the combined therapy patients and 63% of the matched conventional therapy patients were found to have hard stool consistency; this was statistically significant ($p = 0.01$). In the matched combined therapy group, 70% of patients showed either a complete (40%) or partial (30%) improvement in FC within the 12-month period. Meanwhile, in the conventional therapy group, 77% of patients showed either complete (43.3%) or partial improvement (33.3%) ($p = 0.84$; Fig. 1). In the combined therapy group, when comparing laxative use at baseline and within the 12-month follow-up, 12/55 (22%) increased their laxatives at follow-up (e.g., increase in dose, addition of another laxative), 19/55 (35%) made no changes to their laxatives, and 24/55 (44%) either reduced ($n = 14$) or stopped ($n = 10$) their concomitant laxatives. Response between the matched combined therapy and the conventional therapy group did not differ when separated by follow-up within 3 months ($p = 0.41$), within 6 months ($p = 0.59$), or within 12 years ($p = 0.84$, Fig. 1).

5.4 Response to Functional UGI Symptoms (*N* = 57)

In the combined therapy group at baseline, 48 (84%) patients reported at least one functional UGI symptom. Among these, 56% noted improvement in their symptoms (25% complete, 31% partial). In subgroup analysis, patients with hypermobility syndrome that were identified to have comorbid

functional UGI symptoms noted a 47% ($n = 48$) improvement in symptoms.

5.5 Response to Dysphagia ($N = 57$)

Dysphagia was reported in seven (12%) of the patients in the combined therapy group at baseline. At follow-up, all of those that reported swallowing issues saw improvement in their symptoms, with most (5/7, 71%) having complete resolution while on prucalopride. All five patients that improved had esophageal manometry pre-prucalopride initiation with these respective findings: three had ineffective esophageal motility disorder, one had poor esophageal reserve (failed peristaltic augmentation during rapid drink challenge), and one had inadequate bolus clearance.

5.6 Prucalopride Dose and Associations ($N = 57$)

The most common dose/day initiated was 2 mg (49.1%) followed by 1 mg (35.1%) and 0.5 mg (15.8%, Table 2). Dose was increased in 12% and decreased in 4% of patients at follow-up. The dose did not differ significantly between baseline and follo- up visit [mean ± standard deviation (SD): 0.031 ± 0.016 versus 0.03 ± 0.015 mg/kg/day, median and interquartile range (IQR): 0.029 (0.02–0.044) versus 0.031 (0.019–0.041) mg/kg/day]. Examining the relationship between prucalopride dose/day and the patient's age, a unit increase in age (years) was found to be significantly associated with 17% higher odds of being on 2 mg/day of prucalopride in comparison with 1 or 0.5 mg/day [odds ratio (OR) (95% CI): 1.17 (1.04–1.31), $p = 0.01$]. However, prucalopride dose was not associated with gender ($p = 1.0$) or response to FC ($p = 0.21$).

The starting and follow-up prucalopride dose did not differ for children younger than 12 years of age [mean ± SD: 0.041 ± 0.016 versus 0.036 ± 0.017 mg/kg/day, median (IQR): 0.044 (0.027–0.05) versus 0.04 (0.026–0.047) mg/kg/day]. The most common dose at follow-up for this age group ($N = 18$) was 2 mg (44.4%) and the least common dose was 0.5 mg per day (16.7%).

There was no statistically significant difference in dose between responders and non-responders for the dysphagia [mean ± SD: 0.027 ± 0.012 versus 0.030 ± 0.016 mg/kg/day, median (IQR): 0.028 (0.019–0.038) versus 0.032 (0.019–0.043) mg/kg/day] and functional upper GI symptom groups [mean ± SD: 0.029 ± 0.014 versus 0.033 ± 0.021

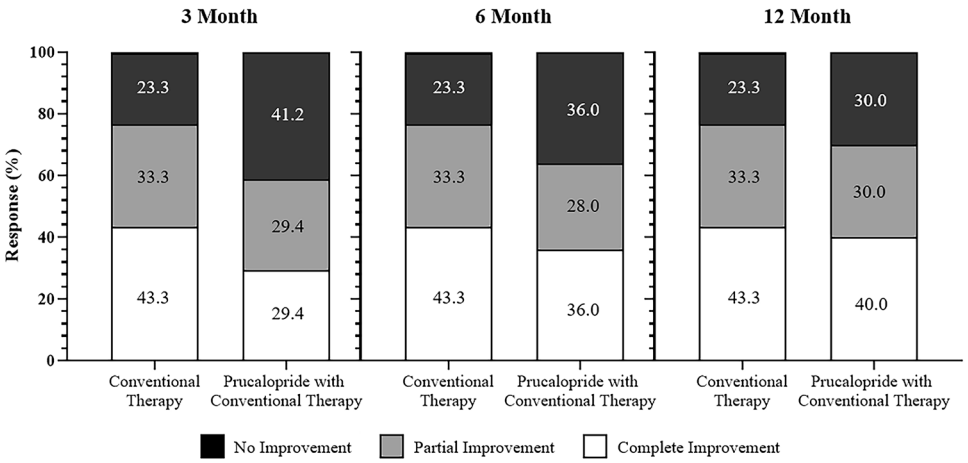

Fig. 1 Response of functional constipation to prucalopride at 3-, 6-, and 12-month follow-up Response was graded as complete improvement, partial improvement, or no improvement over baseline constipation. Conventional therapy cohort are patients with primary diagnosis of FC that only received standard of care conventional therapies. Data represents percent improvement

Table 2 Prucalopride dosing ($n = 57$)

Dose (mg/kg/day)	Baseline	Follow-up	p value[§]
Mean ± SD	0.031 ± 0.016	0.03 ± 0.015	
Median (Q1–Q3)	0.029 (0.02–0.044)	0.031 (0.019–0.041)	0.79
Dose/day	Baseline	Follow-up	p value[Ψ]
	n (%)	n (%)	0.34
0.5 mg	9 (15.8%)	5 (8.8%)	
1 mg	20 (35.1%)	17 (29.8%)	
2 mg	28 (49.1%)	35 (61.4%)	

[§]Wilcoxon rank-sum test, [Ψ]chi-squared test

mg/kg/day, median (IQR): 0.03 (0.019–0.04) versus 0.034 (0.019–0.045) mg/kg/day].

5.7 Adverse Events (*N* = 57)

One or more adverse effects were reported by 17/57 (30%) patients. These are summarized in Table 3. In brief, abdominal cramps were the most common adverse effects in 7/57 (12%) patients, followed by mood disturbances including suicidal ideation, nausea, vomiting, headache, and dizziness. The 1 mg and 2 mg per day doses were associated with the bulk of discontinuation due to adverse events. Prucalopride was discontinued due to side effects in 30% of the patients and due to non-response in 7% (mean dose of 0.024 ± 0.014 mg/kg/day and 0.042 ± 0.016 mg/kg/day, respectively). A total of 26 patients were noted to have an underlying mood disorder at baseline. Four (7%, $N = 57$) reported worsening of their mood disorder, of which two had new onset of suicidal ideation and required drug discontinuation. These four patients were not on any medications for their mood disorder. Most of the patients with worsening mood (3/4) were on 1 mg/day and the remaining patient was on 0.5 mg/day dose of prucalopride. Adverse events associated significantly with response to FC ($p < 0.001$) and 81% of patients with adverse effects demonstrated no improvement. There was a positive association between adverse events and doses of prucalopride ($p = 0.05$) with most events occurring at either 1 mg/day (53%) or 2 mg/day (41%) dose. No association was noted between adverse effects and age ($p = 0.70$) or gender ($p = 0.39$).

Table 3 Adverse effects and lack of response to prucalopride

Adverse effects	*N* = 57	Mean ± SD Dose (mg/kg/day)
Adverse effects		
Abdominal cramping	7 (12%)	0.020 ± 0.017
Worsened constipation	3 (5%)	0.026 ± 0.011
Worsened mood (anxiety and depression)	4 (7%)	0.020 ± 0.010
Suicidal ideation	2 (4%)	0.020 ± 0.007
Diarrhea	2 (4%)	0.038 ± 0.009
Nausea and vomiting	3 (5%)	0.022 ± 0.021
Headache and dizziness	3 (5%)	0.032 ± 0.013
Medication intolerable	3 (5%)	0.041 ± 0.020
Drug discontinuation		
Due to adverse effects	17 (30%)	0.024 ± 0.014
Due to non-response	4 (7%)	0.042 ± 0.016

6 Discussion

Our study is one of few pediatric studies that compares the effectiveness of combined prucalopride and conventional therapy with conventional therapy alone for FC. In our study, prucalopride with conventional combination therapy showed a 70% response for FC that did not differ from conventional therapy alone. This means that in our study population, both combined prucalopride and conventional therapy and conventional therapy alone were noted to be equally efficacious. Two prior pediatric prospective clinical studies have reported the response of FC to prucalopride [8, 17]. The study by Mugie et al. [17] is the only randomized double-blinded study of prucalopride in pediatric FC. They did not report any difference between the prucalopride and placebo group (responder rates of 17% versus 17.8%, $p = 0.90$). On the other hand, Winter et al. used an open label non-controlled design and demonstrated an improvement in mean BM frequency (94.3% with ≥ 3 BMs per week) and reduced fecal incontinence (average number of episodes at week 1 of 5.6 versus 2.4 at week 8) with an adverse event rate of 26/37 (70%) in their pediatric patient population [8]. However, both were clinical studies with short observation periods (4–8 weeks) and tight inclusion criteria. Our study, on the other hand, mirrored the real-world clinical setting as close as possible with follow-up over a longer time frame. The response to conventional therapy alone in our study is higher than previously reported (50–60%) [19], which may be explained by the fact that most were under the care of specialists in neurogastroenterology. In the only other pediatric study to have taken this approach, they found that 66% of their patients with baseline constipation improved with use of prucalopride [7]. It should be noted that both our study, as well as that published by Hirsch et al., included patients that were on laxatives and prucalopride therapy. This means that the independent effect of prucalopride on FC is not easily separated, and it is unclear whether the response in constipation relief is related to prucalopride alone. Thus, it is difficult to ascertain whether the treatment response in our study is an effect of prucalopride on FC or the effect of concomitant use of laxatives. Another possibility for the difference in response between the two groups could be that patients who were started on prucalopride may have had a more severe phenotype of constipation with worse rectosigmoid dilation compared with the conventional therapy group.

Prucalopride has been used for a number of GI disorders and due to its receptor specificity is well tolerated [7–11]. Selective agonism at the 5-HT4 receptors enhances the release of neurotransmitters from their terminals and other terminals in the GI prokinetic reflex pathways [20]. Differential distribution of 5-HT receptor subtypes enables the use

of 5-HT4 agonists to specifically treat intestinal discomfort and motility [20]. 5-HT4 stimulation in enteric cholinergic neurons results in acetylcholine release and smooth muscle contraction, and 5-HT4 stimulation in inhibitory enteric or nitrergic neurons results in nitric oxide release and smooth muscle relaxation [21]. As such, prucalopride may be an adjunctive therapy for patients with FC that may also be suffering from coexisting conditions such as functional UGI symptoms and dysphagia. In the present study, more than half of the prucalopride-treated patients had some resolution in their functional UGI symptoms and all patients had improvement in dysphagia with over 70% experiencing complete resolution of their swallowing issues. This finding parallels that of the Hirsch *et al.* study that reported improvement in 65% of patients with upper GI symptoms (defined as feeding difficulties, nausea, vomiting, reflux, dysphagia, or abdominal pain) on prucalopride with those with enteral tube seeing the most improvement on symptoms while on prucalopride [7]. Additionally, half of our patients with hypermobility syndrome and coexisting functional UGI symptoms, and the majority of those with concurrent dysphagia, showed improvement in symptoms while on prucalopride. This highlights the overlap in pediatric motility disorders and the advantage of prucalopride's prokinetic effect on various segments of the GI tract, making it a feasible choice for treating GI motility disorders affecting other segments of the GI tract other than just the colon.

The safety and tolerability of prucalopride has been previously studied in adults and children [8, 15, 22, 23]. Prucalopride has been noted to have better safety and side-effect profile when compared with cisapride and tegaserod, likely due to its selectivity for the 5-HT4 receptor [22]. In children, the most common reported side effects were headaches, abdominal pain, and nausea with none reporting cardiac side effects [7, 8, 17]. In the randomized controlled trial by Mugie et al., treatment-emergent adverse effects were reported in 65–70% patients on prucalopride versus 60–62% in placebo/Polyethylene Glycol (PEG) groups [19]. In comparison, in our study, 30% of patients had at least one adverse effect attributable to prucalopride with the most common being abdominal cramping, followed by mood disturbances including suicidal ideation, nausea, vomiting, headache, and dizziness. About a quarter of the prucalopride group discontinued the drug due to adverse effects. The adverse effect rate reported in our study was within the previously published pediatric range (19–70%) [7, 8, 17]. The variable rate of adverse events is likely due to variability in the employed methods of reporting. However, adverse effects of prucalopride are nonetheless common and often lead to discontinuation of the drug. Hence, patients and families should be made aware of this possibility at the commencement of treatment.

Among the well-known adverse effects, our study is one of the two to date to report on the potential mood alterations that may occur with prucalopride therapy. This is likely because studies tend to exclude patients with mood disorders and fail to elicit changes in mood as an adverse effect unless identified by the patient directly. About half of our study population prior to matching was noted to have an underlying mood disorder (anxiety, depression) and four (7%) of these endorsed worsened mood after commencing treatment with prucalopride. Alarmingly, two (4%) with pre-existing mood disorder reported new onset suicidal ideation. As part of prescribing information for prucalopride, the FDA includes the section "suicidal ideation and behavior" under their "Adverse Reactions of Special Interest" section detailing that "one patient reported a suicide attempt 7 days after the end of treatment with 2 mg once daily." However, this has only been reported in one other pediatric study by Hirsch et al. [7]. Their study also included an assessment of baseline and posttreatment psychiatric conditions in their pediatric cohort with one patient in the cohort (1/71; 1.4%) noted to have "psychosis" as a possible adverse event while on prucalopride treatment. Our work and the Hirsch et al. study are the only two pediatric studies to include patients with mood disorders and report on the possible mood-altering properties of this drug (relatively higher prevalence in our study). This may be clinically relevant during the selection of patients who would have more benefit than risk with prucalopride therapy. Caution should be taken when prescribing prucalopride in pediatric (especially adolescent) patients and a screening for mental health disorders instituted prior to starting the medication and regularly while on prucalopride therapy.

The advantage of our study was a cohort with a relatively large sample size and inclusion of patients with various comorbidities, including upper GI symptoms, dysphagia, and mood disorders, which are often excluded from randomized controlled trials. Second, we used propensity score matching to assess our outcomes allowing for more robust conclusions similar to a prospective trial. We were able to compare the two groups effectively by using propensity matching and our conclusions are likely stronger than earlier studies where no propensity matching was done. In addition, a provider contemplating the use of prucalopride can assess patients for associated upper GI comorbidities and potential mood disorders as risk factors and make a more informed decision about continuing conventional therapy or the use prucalopride to target the UGI concerns without losing efficacy against constipation. Finally, our study included a thorough investigation of adverse effects which allowed us to identify the potential effect of prucalopride on mood disorders.

Our study had a few limitations. Due to its retrospective design, we were unable to assess response on a symptom–response scale or measure adherence. We were unable to follow patients after a year to assess longer outcomes. We

were also unable to compare our treatment populations to an untreated population. However, we attempted to remove age, gender, race, and presence of fecal incontinence as possible interfering factors by making use of propensity matching. The objective of this study was to assess the effectiveness of prucalopride in FC and comorbid conditions. For the primary efficacy outcome, namely improvement of symptoms, a post hoc power analysis showed that we need about 100 patients per group (as opposed to 30 per matched group) to reach 80% power. Of course, going into the study, we did not have information regarding effect size, therefore this power analysis can serve as a guide for future studies. Additionally, we aimed to study the safety of prucalopride in our pediatric patient population but did not address the adverse event rate of the conventional therapy cohort. Future studies should consider comparing the adverse event rates of both therapies.

The next step in the evaluation of prucalopride should be using a large prospective study design to better assess the effects of prucalopride and prucalopride plus laxative effect on functional constipation and to better delineate the effects on mood disorders by employing standardized measures of anxiety, depression, and suicidal ideation. While we observed worsening mood in a small number of patients in our study, factors determining causality or risk still need to be explored. Further studies are needed to assess the response of prucalopride in functional UGI symptoms and dysphagia independent of FC and also assess the esophageal manometric changes with prucalopride.

7 Conclusion

Our study adds an important insight into the effectiveness, safety, and tolerability of prucalopride in pediatric patients. We were unable to show the independent efficacy of prucalopride in functional constipation as there was no direct comparison of patients on prucalopride alone versus on conventional laxative therapy. We were, however, able to show that prucalopride may be a reasonable option for patients with functional constipation that may have coexisting functional UGI symptoms and dysphagia. Unique to our study is the worrisome finding that prucalopride may lead to worsening of baseline mood disorders and the possible development of suicidal ideation in such patients. Thus, cautious, and judicious use of prucalopride in pediatric patients with underlying mood disorders should be practiced and close monitoring should be done for new onset or worsening mood disturbances in all pediatric patients during prucalopride therapy.

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Declarations

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Conflict of Interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethics Approval This retrospective chart review study involving human participants was done in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of the Cincinnati Children's Hospital approved this study.

Informed Consent Not applicable.

Consent for Publication Not applicable.

Data Availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contribution Statement All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Lesley Knowlton, Erick Madis, and Alejandro Velez Lopez supervised by Dr. Neha R Santucci. Dr. Rashmi Sahay provided statistical expertise, Sarah Stiehl provided pharmaceutical expertise, while Drs. Kaul, El-Chammas and Santucci provided expertise on functional constipation and other motility disorders. The first draft of the manuscript was written by Alejandro Velez Lopez and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Previous Communications: As an abstract/poster for the 2021 North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) that only included the prucalopride cohort results. As an abstract/poster for NASPGHAN 2022 that included the conventional therapy–prucalopride cohort analysis and the propensity matched data. As an abstract/podium presentation for 2022 Pediatric Colorectal and Pelvic Reconstruction Conference (PCPLC).

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