Original article

THAI BULLETIN OF PHARMACEUTICAL SCIENCES
ISSN 2586-8659 (online)

EFFICACY AND SAFETY OF LUBIPROSTONE FOR FUNCTIONAL CONSTIPATION IN CHILDREN :A SYSTEMATIC REVIEW

Pattarapan Sukwuttichai[1,2,3], Suthinee Taesotikul[1,2,3], Mantiwee Nimworapan[1,2,3], Unchalee Permsuwan[1,3], Jirawit Yadee[1,3], Witoo Dilokthornsakul[1,3,*], Piyameth Dilokthornsakul[1,3]

[1] Center for Medical and Health Technology Assessments (CM-HTA), Department of Pharmaceutical Care, Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand

[2] Pharmaceutical Care Training Center, Department of pharmaceutical care, Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand

[3] Department of pharmaceutical care, Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand

* Corresponding author: witoo.dilok@cmu.ac.th

ABSTRACT

Pediatric functional constipation (PFC) is an important gastrointestinal disease in children. Oral and rectal laxatives have been recommended for treating PFC; however, almost half of the patients did not fully recover after 6 – 12 months of treatment. Lubiprostone is an alternative to treat PFC. However, the efficacy and safety of lubiprostone have not been summarized. This study aimed to summarize the efficacy and safety of lubiprostone for PFC. A systemic review was conducted in PubMed, Embase®, and Cochrane CENTRAL from their inception to August 2022. Studies examining the efficacy or safety of lubiprostone compared to placebo or different dosages of lubiprostone were eligible. The primary efficacy outcome was the number of responders according to spontaneous bowel movement (SBM), while the serious adverse event was the primary safety outcome. A qualitative summary was performed to summarize the evidence. A total of three articles with 1,264 patients met the inclusion criteria. Of those, one article was a randomized controlled trial (RCT) with an open-label, long-term extension and two studies were quasi-experimental. All included studies reported serious adverse events but only two studies reported SBM. The RCT indicated that 12 micrograms of lubiprostone twice daily (BID) or 24 µg BID had no statistical difference in terms of treatment response than the placebo (relative risk [RR]= 1.32; 95% confidence interval (CI) 0.89 to 10.97, p=0.22). However, when sub-grouped, lubiprostone 12 µg BID had a higher chance of being responsive than the placebo (RR= 1.89 [1.19 to 3.00], p=0.007), while lubiprostone 24 µg BID did not have a higher chance of being response than the placebo (RR= 1.12 [0.73 to 1.72], p=0.60). A non-RCT study demonstrated significant improvement of average SBM from the baseline for lubiprostone 12 µg once daily (OD), 12 µg BID, and 24 µg BID at week 4, however no significant difference among the doses was observed. No difference in serious adverse events between lubiprostone and the placebo was found. In conclusion, lubiprostone showed potential efficacy for treating children with functional constipation without any serious adverse events.

Keywords: pediatric functional constipation, lubiprostone, spontaneous bowel movement, serious adverse events

Received: 16 March 2023; Revised: 17 April 2023; Accepted: 19 April 2023

Introduction

Pediatric functional constipation (PFC) is an important type of constipation in children. It accounts for approximately 95% of constipation in children.[1] Prevalence of PFC was 9.5% with a 95% confidence interval (CI) of 7.5% to 12.1%.[2] Several factors were associated with PFC, such as geographic location, diet, stressfulness, and age.[2,3] Prevalence of PFC was higher in toddlers than infants. The median age of its onset was 2.3 years old. The occurrence of PFC might be associated with toilet training or school entry.[4]

PFC causes painful defecation resulting in stool withholding behavior. The stool withholding leads to the worsening of constipation because it increases water absorption from retained stool, leading to a larger stool mass and more difficulty to defecate. The painful stool passaging leads to a vicious cycle of stool withholding resulting in loss of rectal sensation and fecal soiling.[5-8]

Non-pharmacological interventions have been recommended as the first-line treatment for PFC. The interventions include patient education, dietary, physical, and behavioral modification. Pharmacological interventions are also recommended when non-pharmacological interventions do not work. Pharmacological interventions are divided into two following steps. First is the use of stool disimpaction and the second is maintenance therapy.[9,10] To increase the success rate of treatment, the stool disimpaction should be initiated and accomplished before maintenance therapy.[11]

Oral or rectal laxatives are usually used in disimpaction therapy, but an oral laxative is recommended over rectal laxatives because rectal laxatives are an invasive treatment for children. Maintenance therapy should be given after the disimpaction to prevent stool re-impaction by maintaining stool softening and bowel movement. Oral polyethylene glycol (PEG) with or without electrolytes is recommended as the first-line maintenance treatment because of its superior efficacy, non-invasive nature, and well-tolerated for long-term use in children.[1,5,6] The common side effects of PEG include abdominal distension, flatulence, diarrhea, and nausea.[12] Duration of treatment of PFC is usually 6 – 12 months before weaning. However, only 60% of patients with PFC could achieve the success of treatment. Early discontinuation of treatment causes the recurrence of PFC.[5,13,14]

Lubiprostone, a selectively type-2 chloride channel agonist, could exhibit a stool softener effect by stimulating chloride efflux into the gastrointestinal lumen .Consequently, sodium ions and water could be transported into the bowel to maintain isoelectric neutrality and isotonic equilibrium .It results in the enhancement of intestinal fluid.[15,16] Lubiprostone has been approved by the United States Food and Drug Administration for the treatment of chronic idiopathic constipation, opioid-induced constipation, and irritable bowel syndrome with constipation .The long-term safety of lubiprostone in adults had been investigated and is considered well-tolerated .The most common adverse events were nausea, diarrhea, abdominal distension, and abdominal pain.[17] However, evidence on the efficacy and safety of lubiprostone in PFC is limited and has yet to be summarized .This study aimed to summarize the current evidence of the efficacy and safety of lubiprostone for treating PFC .This evidence will be useful for healthcare providers to decide whether lubiprostone is appropriate in patients with PFC.

Methods

Search strategies and study selection

Three electronic databases, including PubMed, EMBASE, and Cochrane CENTRAL were searched from their inception to August 2022 without any language restriction. Search terms were ("lubiprostone" OR "chloride channel activators") AND ("constipation") AND ("child*" OR "pediatric*").

Clinical studies reporting the efficacy and safety of lubiprostone as a treatment of constipation in children were eligible. The retrieved articles were

de-duplicated using EndNote 20.0. Titles and abstracts were independently reviewed by four review authors (ST, MN, JY, and WD). Any disagreements among authors were discussed and solved by consensus with the other two authors (PS, PD). The protocol was registered in PROSPERO (CRD42023393284).

Data extraction and quality assessment

The standardized data extraction form was developed in Microsoft Excel®. The extracted data consisted of study design, number of participants, participant characteristics, intervention characteristics, comparators, outcomes, and duration of treatment. All full-text articles were independently screened by three review authors (ST, MN, and WD). The data from eligible articles were extracted by the three review authors and verified by the other two authors (PD and PS).

The Cochrane Risk of Bias version 2[18] and the ROBINS-I tool[19] were used to assess the risk of bias for randomized controlled trials and non-randomized studies, respectively. The risk of bias in included studies was independently evaluated by ST, MN, and WD. All disagreements were resolved through discussion with the other two authors (PD and PS).

Outcomes of interest

The efficacy outcome was the number of responders according to spontaneous bowel movement (SBM). Patients with an increase in SBM for one time per week or SBM ≥ 3 times per week were considered as a responder, while patients with no increase or reduced frequency of SBM were defined as a non-responder. The frequency of SBM per week was the secondary efficacy outcome. The number of patients with serious adverse events (SAEs) was the primary safety outcome of interest. The secondary safety outcome was the occurrence of any adverse events (AEs).

Data analysis

According to the limited evidence, only one RCT and two non-RCTs were included. There was not enough data for performing a network meta-analysis without violations of assumptions (as planned). Thus, we decided to summarize the findings using a qualitative approach. Data were summarized by the outcome, doses of lubiprostone, and follow-up time. Relative risk (RR) or mean difference (MD) and its corresponding 95% confidence interval (CI) of each outcome by dose and follow-up for each study were calculated (if not provided).

Results

Search results and study characteristics

A total of 155 articles with 1,264 patients were retrieved after the duplicates were removed (Figure 1).

Of those, only three articles (4 studies)[20-22] were included. One article was a randomized controlled trial (RCT) with an open-label, long-term extension[20] while the other two articles were quasi-experimental studies.[21,22] Two articles[20,22] were conducted to determine the efficacy of lubiprostone for PFC, and all three articles[20-22] determined the adverse events of lubiprostone in patients with PFC. The average age ranged from 5.5-13.9 years old. All patients were diagnosed with PFC based on Rome III criteria with an average SBM frequency at the baseline was 1.4 – 1.6 times a week (Table 1 and Table 2).

Risk of bias in the included studies

The methodology of included studies is summarized in Table 1. For studies determining the treatment effect of lubiprostone, only one RCT[20] for PFC treatment was justified as a low risk of bias, while another quasi-experimental study[22] was justified as a serious risk of bias. For studies determining the safety of lubiprostone, all included non-randomized studies[20-22] were justified as serious risk of bias (Figure 2).

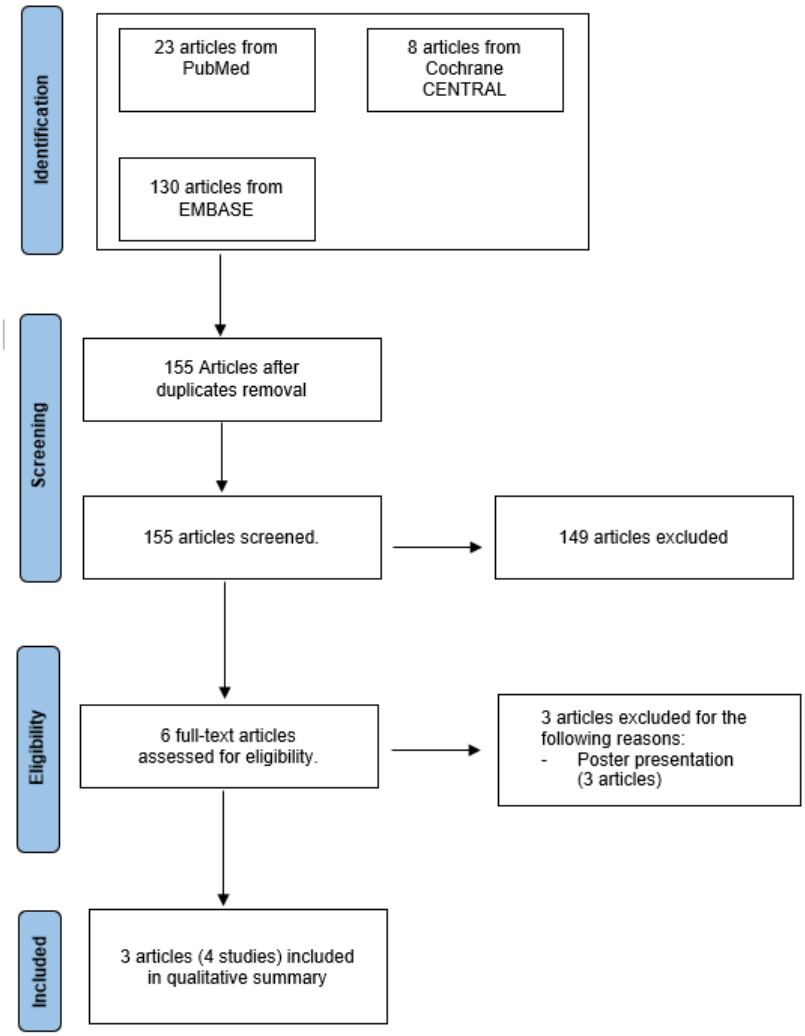

Figure 1 Prisma flow diagram

Table 1 Study and patients' characteristics

Author (Year)	Study design	Country	Patients	Total number of patients	Average age	%Male	Average BMI	Average SBM frequency per week
Benninga 2022[a]	Double-blinded placebo-controlled RCT	USA, Canada, EU	Functional constipation patients aged 6-17 years old (Rome III criteria)	606	11.1 ± 3.2 to 11.2 ± 3.2	45.7 – 45.8%	21.1 ± 5.6 to 21.3 ± 5.5	1.4 ± 0.8 to 1.4 ± 0.9
Benninga 2022[b]	Open-labeled extension study	USA, Canada, EU	Functional constipation patients aged 6-17 years old (Rome III criteria)	444	11.0 ± 3.0	46.0%	NR	1.4 ± 0.8
Hussain 2021	Open-labeled non-RCT	USA	Functional constipation patients aged 6-17 years old (Rome III criteria)	87	8.8 ± 1.8 to 13.2 ± 2.6	43.7%	17.7 ± 2.4 to 26.0 ± 6.4	NR
Hymen 2014	Open-labeled non-RCT	USA	Functional constipation patients aged 6-17 years old (Rome III criteria)	127	5.5 ± 1.7 to 13.9 ± 3.0	52.4%	NR	1.4 ± 0.8 to 1.6 ± 1.0

Abbreviations: BMI :body mass index, EU; the European Union, NR; not report, RCT; randomized controlled trial, SBM; spontaneous bowel movement, USA; the United States of America

Table 2 Intervention and outcomes

Author (Year)	Interventions/ Comparator	Treatment duration	Efficacy outcomes	Efficacy outcomes definition	Safety outcomes	Follow-up time after treatment stopped
Benninga 2022[a]	1. Lubiprostone 12 µg or 24 µg BID (N= 399) 2. Placebo (N= 195)	12 weeks	SBM frequency per week	Increase in SBM ≥ 1 time/week and ≥ 3 times/week for 9 weeks (as responder)	- Gastrointestinal adverse event - Headache - No. of patient withdrawal from TRAE - No. of patients with AE	2 weeks
Benninga 2022[b]	1. Lubiprostone 12 µg BID (N= 157) 2. Lubiprostone 24 µg BID (N= 261)	36 weeks	Not report	NR	- Gastrointestinal adverse event - Headache - No. of patient withdrawal from TRAE - No. of patients with AE	4 weeks
Hussain 2021	1. Lubiprostone 12 µg BID (N= 56) 2. Lubiprostone 24 µg BID (N= 31)	24 weeks	Not report	NR	- Gastrointestinal adverse event - Headache - Upper respiratory tract infection - Chest pain - Blood uric acid - Decreased appetite - No. of patient withdrawal from TRAE - No. of patients with AE	1 week
Hymen 2014	1. Lubiprostone 12 µg BID (N= 65) 2. Lubiprostone 24 µg BID (N= 31) 3. Lubiprostone 12 µg OD (N= 27)	4 weeks	SBM frequency per week	- Average SBM frequency per week - ≥ 3 times/week (as responder)	- Gastrointestinal adverse event - Headache - Upper respiratory tract infection - No. of patient withdrawal from TRAE - No. of patients with AE	2 weeks

Abbreviations: AE; adverse event, BID; twice daily, µg; microgram, OD; once daily, SBM; spontaneous bowel movement, TRAE :treatment-related adverse events, NR; Not report

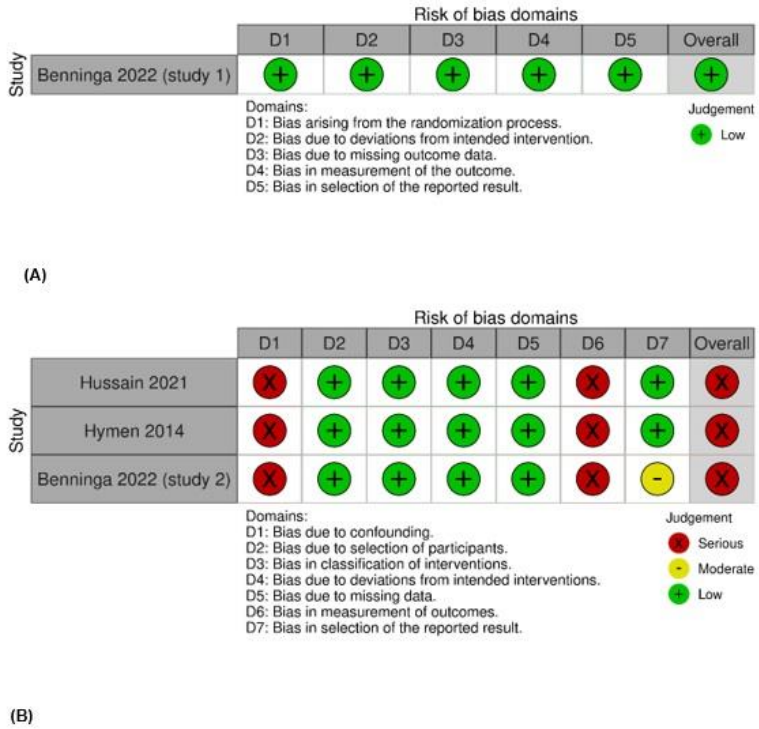

Figure 2 Risk of bias of included studies (A) randomized controlled trial, (B) quasi-experimental study

Efficacy of lubiprostone on PFC

Of those two studies reporting the efficacy of lubiprostone for PFC, one RCT[20] compared two lubiprostone 12 or 24 µg BID to the placebo. Patients weighing <50 kilograms were given lubiprostone 12 µg BID, while patients weighing ≥50 kilograms were given lubiprostone 24 µg BID for 12 weeks. A total of 606 children were included in the study. The author found that 18.5% of patients receiving lubiprostone responded to the medication, while 14.4% of patients receiving a placebo responded to the placebo. However, the difference was not statistically significant (p=0.22) with the RR= 1.32 (95%CI; 0.89 to 1.97). The author performed a subgroup analysis and found that the ratio of responders was significantly higher in patients receiving lubiprostone 12 µg BID compared to the placebo (27.1% VS 14.4%; p=0.007, RR= 1.89 [95%CI; 1.19 to 3.00]), while the ratio was not statistically significant in patients receiving lubiprostone 24 µg BID compared to the placebo (16.1% VS 14.4%; p=0.60, RR= 1.12 [95%CI; 0.73 to 1.72])

Another quasi-experimental study[22] compared the average SBM per week of three lubiprostone regimens (12 µg OD, 12 µg BID, and 24 µg BID) between baseline, weeks 1 – 4. The authors found that lubiprostone 12 µg BID and 24 µg BID had a significantly higher average SBM than their baseline SBM at week 1 and continuously higher through week 4, while lubiprostone 12 µg OD had an insignificant higher average SBM than its baseline SBM at week 1 but it was significant from week 2 – 4.

Compared among different doses, the average SBM frequency per week and treatment response (defined as SBM ≥ 3 times/week) were assessed. The study indicated that the average SBM per week at week 4 for lubiprostone 24 µg BID was minimally higher than lubiprostone 12 µg BID and lubiprostone 12 µg OD, however the differences were not statistically significant. The mean difference between 24 µg BID and 12 µg BID was 0.32 (95%CI; -0.70 to 1.34; p=0.54), while the mean difference between 24 µg BID and 12 µg BID was 0.15 (95%CI; -0.70 to 1.27; p=0.54). On the other hand, the probability of having a response for lubiprostone 24 µg BID was lower than lubiprostone 12 µg BID or lubiprostone 12 µg OD. RRs for lubiprostone 24 µg BID compared to lubiprostone 12 µg BID and lubiprostone 12 µg OD were 0.87 (95%CI; 0.52 to 1.45; p=0.58) and 0.80 (95%CI; 0.44 to 1.45; p=0.47), respectively (Table 3).

The safety of lubiprostone in children

The included studies[20-22] reported several adverse events (AEs) including serious adverse events (SAEs), serious treatment-related adverse events (TRAEs), nausea, vomiting, abdominal pain, headache, and number of patients who withdraw due to AEs. SAEs of lubiprostone ranged from 1.2% - 3.9%, while SAE of the placebo was 3.6%. Serious TRAEs of lubiprostone ranged from 0.0% - 1.7%, while serious TRAE of the placebo was 1.0%. Nausea was the most common AE for lubiprostone. The risk of nausea for lubiprostone ranged from 0.0% - 31.3%, while that for the placebo was 7.2%. The details of selected AEs are presented in Table 4

Discussion

This systematic review summarized the current evidence of efficacy and safety of different lubiprostone regimens for patients with PFC. We found that lubiprostone had a potential efficacy for PFC in terms of treatment responses with a similar risk of serious adverse events compared to the placebo. Some common adverse events, such as nausea, are higher in patients receiving lubiprostone.

The mechanism of action of lubiprostone is different from other laxatives. Lubiprostone increases intestinal secretion through type 2 chloride channel activation in the apical membrane of gastrointestinal epithelium leading to soft stool and improving fecal transition. The amount of lubiprostone is mostly localized in the gastrointestinal tract. Only a small amount of lubiprostone is detected in the systemic

Table 3 Efficacy outcomes

Author (Year)	Intervention	Comparator	Outcomes	Findings	*p*-value
Benninga 2022[a]	LUB 12 µg or 24 µg BID	Placebo	Increase in SBM ≥ 1 time/week and ≥ 3 times/week for 9 weeks	LUB total: 76/399 (18.5%) Placebo: 28/195 (14.4%) Risk ratio: 1.32 (95%CI; 0.89 to 1.97)	*p*=0.22
	LUB 12 µg	Placebo		LUB 12 µg: 29/107 (27.1%) Placebo: 28/195 (14.4%) Risk ratio: 1.89 (95%CI; 1.19 to 3.00)	*p*=0.007
	LUB 24 µg	Placebo		LUB 24 µg: 47/292 (16.1%) Placebo: 28/195 (14.4%) Risk ratio: 1.12 (95%CI; 0.73 to 1.72)	*p*=0.60
Hymen 2014	LUB 24 µg BID	LUB 12 µg BID	Average SBM frequency per week	**At week 1** LUB 12 µg BID: 2.99 ± 2.43 LUB 24 µg BID: 3.82 ± 2.65 Mean difference: 0.83 (95%CI; -0.25 to 1.91) **At week 4** LUB 12 µg BID: 2.65 ± 2.48 LUB 24 µg BID: 2.97 ± 2.08 Mean difference: 0.32 (95%CI; -0.70 to 1.34)	*p*=0.13 *p*=0.54
	LUB 24 µg BID	LUB 12 µg OD		**At week 1** LUB 12 µg OD: 2.45 ± 2.81 LUB 24 µg BID: 3.82 ± 2.65 Mean difference: 1.37 (95%CI; -0.07 to 2.81) **At week 4** LUB 12 µg OD: 2.82 ± 2.17 LUB 24 µg BID: 2.97 ± 2.08 Mean difference: 0.15 (95%CI; -0.97 to 1.27)	*p*=0.06 *p*=0.79
	LUB 12 µg BID	LUB 12 µg OD		**At week 1** LUB 12 µg OD: 2.45 ± 2.81 LUB 12 µg BID: 2.99 ± 2.43 Mean difference: 0.54 (95%CI; -0.62 to 1.70) **At week 4** LUB 12 µg OD: 2.82 ± 2.17 LUB 12 µg BID: 2.65 ± 2.48 Mean difference: -0.17 (95%CI; -1.26 to 0.92)	*p*=0.36 *p*=0.76
	LUB 24 µg BID	LUB 12 µg BID	SBM ≥ 3 times/week	**At week 4** LUB 12 µg BID: 29/65 (45.0%) LUB 24 µg BID: 12/31 (39.0%) Risk ratio: 0.87 (95%CI; 0.52 to 1.45)	*p*=0.58
	LUB 24 µg BID	LUB 12 µg OD		**At week 4** LUB 12 µg OD: 13/27 (48.1%) LUB 24 µg BID: 12/31 (39.0%) Risk ratio: 0.80 (95%CI; 0.44 to 1.45)	*p*=0.47
	LUB 12 µg BID	LUB 12 µg OD		**At week 4** LUB 12 µg OD: 13/27 (48.1%) LUB 12 µg BID: 29/65 (45.0%) Risk ratio: 0.93 (95%CI; 0.58 to 1.49)	*p*=0.76

Abbreviations :BID; twice daily, CI; confidence interval, LUB; lubiprostone, OD; once daily, SBM; spontaneous bowel movement, µg; microgram

Table 4 Reported adverse events from included studies.

Study	Treatment	SAE	Serious TRAE	Number of patients withdraw from AE	Nausea	Vomiting	Abdominal pain	Headache
Benninga 2022[a]	LUB 12 µg BID	9/231 (3.9%)	4/231 (1.7%)	9/231 (3.9%)	32/231 (13.9%)	39/231 (16.9%)	21/231 (9.1%)	15/231 (6.5%)
	LUB 24 µg BID	2/169 (1.2%)	0/169 (0.0%)	8/169 (4.7%)	25/169 (14.8%)	6/169 (3.6%)	21/169 (12.4%)	19/169 (11.2%)
	Placebo	7/195 (3.6%)	2/195 (1.0%)	6/195 (3.1%)	14/195 (7.2%)	12/195 (6.2%)	23/195 (11.8%)	10/195 (5.1%)
Benninga 2022[b]	LUB 12 µg BID	3/157 (1.9%)	2/157 (1.3%)	4/157 (2.5%)	11/157 (7.0%)	18/157 (11.5%)	14/157 (8.9%)	12/157 (7.6%)
	LUB 24 µg BID	10/261 (3.8%)	4/261 (1.5%)	13/261 (5.0%)	25/261 (9.6%)	29/261 (11.1%)	19/261 (7.3%)	21/261 (8.0%)
Hussain 2021	LUB 12 µg BID	NR	NR	NR	4/56 (7.1%)	3/56 (5.4%)	1/56 (1.8%)	3/56 (5.4%)
	LUB 24 µg BID	NR	NR	NR	0/31 (0.0%)	3/31 (5.4%)	1/31 (1.8%)	1/31 (1.8%)
Hymen 2014	LUB 12 µg OD	NR	NR	0/27 (0.0%)	1/27 (3.7%)	4/27 (14.8%)	2/27 (7.4%)	0/27 (0.0%)
	LUB 12 µg BID	NR	NR	3/65 (4.6%)	12/65 (18.5%)	6/65 (9.2%)	4/65 (6.2%)	4/65 (6.2%)
	LUB 24 µg BID	NR	NR	5/32 (15.6%)	10/32 (31.3%)	5/32 (15.6%)	3/32 (9.4%)	3/32 (9.4%)

Abbreviations: AE; adverse event, BID; twice daily, OD; once daily, NR; not report, SAE; serious adverse event, TRAE; treatment-related adverse event, µg; microgram; LUB; Lubiprostone

circulation (< 1%). It results in a predictable, dose-dependent treatment effect, and minimal systemic adverse effects. According to product information, 24 µg BID of lubiprostone has been approved for chronic idiopathic constipation and constipation-predominant irritable bowel syndrome in adults,[23] while there is limited evidence of the use of lubiprostone in children resulting in no recommended dose for PFC.

Our findings showed that at least 12 µg BID of lubiprostone was effective to relieve PFC symptoms compared to the placebo. However, no statistical significance was observed among different doses of lubiprostone.

Based on a recommendation from the Cochrane Reviews,[24] four approaches should be considered to incorporating the risk of bias in analyses including 1) the restriction to studies with low risk of bias, 2) performing stratified analyses, 3) presenting all studies and providing a narrative discussion, and 4) adjust effect estimates of bias. In this study we found only three clinical studies. Therefore, we decided to follow the third approach by presenting all included studies and provide discussion. According to our assessment, the RCT showed a positive treatment effect with a low risk of bias, while the quasi-experimental studies also showed possible treatment effects with a serious risk of bias. These indicated the consistency of the positive treatment effects of lubiprostone for PFC from different levels of evidence. However, because of the limited evidence, the findings should be interpreted with caution. In addition, further large RCTs are warranted.

The efficacy of lubiprostone in children was determined from two studies.[20,22] One RCT reported no statistical difference between lubiprostone 12 or 24 µg BID and the placebo. However, a subgroup analysis indicated that 12 µg BID showed a potential benefit compared to the placebo in terms of treatment response. Although the frequency of SBM for outcome measurement was different between the studies, the similar endpoint was an increase of at least 1 SBM per week compared with baseline which several studies in adults also used this outcome measurement.[25-27] Despite the limited number of participants, patients from a study by Benninga et al.[20] were prone to have more severity of PFC symptoms than Hyman et al.[22] due to the fact that 72% of included participants had a history of treatment failure of PFC. Rescue medication was also assigned to all participants if no response to lubiprostone or the placebo within 3 days. Hyman et al.[22] and Hussain et al.[21] reported the number of patients using rescue therapy as 21.8% and 13.8%, respectively.

Regarding drug dosing for lubiprostone in children, all three included studies using fixed-dose regimens defined by patients' body weight. The studies by Benninga et al. and Hussain et al.[20,22] scheduled a similar dosing regimen as lubiprostone 12 µg BID and 24 µg BID for children weighing < 50 kilograms and ≥ 50 kilograms, respectively. The study by Hyman et al.[22] designed the dosing regimen as lubiprostone 12 µg OD, 12 µg BID and 24 µg BID for children weighing < 24 kilograms, 24 to 35.9 kilograms, and ≥ 36 kilograms, respectively. The differences in drug dosing might result in that some children, who weighed between 36 to 50 kilograms in Hyman et al. study, received a higher dose than those in the study by Benninga et al and Hussain et al.[20,22] The difference of weight-based dosing of lubiprostone in children might affect its effect on SBM, however current studies do not determine which dose according to their body-weight should be used in children.

Although the quasi-experimental studies showed that both lubiprostone 12 µg BID and 24 µg BID had a trend to improve SBM compared to the baseline, only lubiprostone 12 µg BID showed statistically significant improvement of SBM but not for lubiprostone 24 µg BID in the RCT. It might be because the RCT primarily aimed to assess the effect of either lubiprostone 12 µg BID or lubiprostone 24 µg BID on treatment response, which failed to show a positive effect. A possible explanation of the difference in observed treatment effect was the difference in a prior constipation treatment failure which was a proxy of severe PFC. Approximately 74% of patients receiving lubiprostone 24 µg BID failed from previous treatments, while only 68% of patients receiving lubiprostone 12 µg BID failed from previous treatments. Lubiprostone might be more effective in patients with less severe PFC. Further studies are needed to confirm this possibility. Another possible explanation was the difference in the proportion of adolescents included in both groups. The percentage of patients aged 10-17 years old were 74% in the lubiprostone 24 µg BID, only 37 % in the lubiprostone 12 µg BID, and 66% in the placebo group. A previous study evaluating prucalopride showed a high placebo effect in adolescents but not in children[28] which might be possible in the included RCT, leading to the non-significant treatment effect of lubiprostone 24 µg BID group which had a higher proportion of adolescents than the lubiprostone 12 µg BID group.

The safety of lubiprostone in pediatrics was evaluated as a report of adverse events (AEs) from all three included studies[20-22] classified by the Medical Dictionary for Regulatory Activities (MedDRA), system organ class, and preferred term. No significant difference of any AEs; including AEs occurrences, AE-related withdrawal, and serious AEs, between lubiprostone and the placebo was observed. Gastrointestinal AE including nausea, vomiting, and diarrhea was most frequently observed in all included studies. Our results showed the

gastrointestinal adverse events for nausea, diarrhea, and abdominal discomfort which were similar to what was observed in adults.[25,26,29]

Our findings showed that lubiprostone had a potential benefit and was safe for PFC. However, only two studies[20,22] were conducted to determine its efficacy. The larger number of participants and long-term outcome should be further investigated. Even though a protocol of all three studies designated the lubiprostone as monotherapy with rescue medication therapy, it should be considered as an additional therapy for PFC who do not respond to polyethylene glycol (PEG) as recommended by a clinical practice guideline.[10]

Evidence of the optimal duration for lubiprostone for PFC is still lacking .Expert opinion suggested that medication treatment should be maintained for at least two months and PFC should be resolved at least 1 month before medication discontinuation.[10] The longest duration for lubiprostone treatment was assessed by Benninga et al.[20] as a 36-week period with some observed adverse events such as vomiting .However, adverse events should be closely monitored.

Conclusion

Our systematic review indicated that lubiprostone has a potential efficacy in PFC with minimal risks of non-SAEs such as nausea .However, because of the limited RCTs, future large and high-quality RCTs or network meta-analyses comparing all treatments for PFC are warranted to assess the efficacy and safety of lubiprostone and other treatments in children.

Acknowledgments

We would like to thank the Faculty of Pharmacy, Chiang Mai University for its in-kind support.

References

1. Leung AK, Hon KL. Paediatrics: how to manage functional constipation. Drugs Context. 2021;10:2020-11-2.
2. Koppen IJN, Vriesman MH, Saps M, Rajindrajith S, Shi X, van Etten-Jamaludin FS, et al. Prevalence of functional defecation disorders in children: a systematic review and meta-analysis. J Pediatr. 2018;198:121-30.
3. LeLeiko NS, Mayer-Brown S, Cerezo C, Plante W. Constipation. Pediatr Rev. 2020;41(8):379-92.
4. Zeevenhooven J, Koppen IJ, Benninga MA. The new Rome IV criteria for functional gastrointestinal disorders in infants and toddlers. Pediatr Gastroenterol Hepatol Nutr. 2017;20(1):1-13.
5. Levy EI, Lemmens R, Vandenplas Y, Devreker T. Functional constipation in children: challenges and solutions. Pediatric Health Med Ther. 2017;8:19-27.
6. Mulhem E, Khondoker F, Kandiah S. Constipation in children and adolescents: evaluation and treatment. Am Fam Physician. 2022;105(5):469-78.
7. Rajindrajith S, Devanarayana NM. Constipation in children: novel insight into epidemiology, pathophysiology and management. J Neurogastroenterol Motil. 2011;17(1):35-47.
8. Poddar U. Approach to constipation in children. Indian Pediatr. 2016;53:319-27.
9. Hyams JS, Di Lorenzo C, Saps M, Shulman RJ, Staiano A, van Tilburg M. Functional disorders: Children and Adolescents. Gastroenterol. 2016;150:1456-68.
10. Tabbers MM, DiLorenzo C, Berger MY, Faure C, Langendam MW, Nurko S, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. J Pediatr Gastroenterol Nutr. 2014;58(2):258-74.
11. Koppen IJN, Lammers LA, Benninga MA, Tabbers MM. Management of functional constipation in children: therapy in practice. Pediatr Drugs. 2015;17(5):349-60.
12. Rao SSC, Brenner DM. Efficacy and safety of over-the-counter therapies for chronic constipation: an updated systematic review. Am J Gastroenterol. 2021;116(6):1156-81.
13. Nurko S, Zimmerman LA. Evaluation and treatment of constipation in children and adolescents. Am Fam Physician. 2014;90(2):82-90.
14. Pijpers MAM, Bongers MEJ, Benninga MA, Berger MY. Functional constipation in children: a systematic review on prognosis and predictive factors. J Pediatr Gastroenterol Nutr. 2010;50(3).

15. Lacy BE, Levy LC. Lubiprostone: a novel treatment for chronic constipation. Clin Interv Aging. 2008;3(2):357-64.
16. Lacy BE, Hussain Zh Fau - Mearin F, Mearin F. Treatment for constipation: new and old pharmacological strategies. Neurogastroenterol Motil. 2014;26(6):749-63.
17. Lembo AJ, Johanson JF, Parkman HP, Rao SS, Miner PB Jr, Ueno R. Long-term safety and effectiveness of lubiprostone, a chloride channel (ClC-2) activator, in patients with chronic idiopathic constipation. Dig Dis Sci. 2011;56(9):2639-45.
18. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:14898.
19. Sterne JA, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.
20. Benninga MA, Hussain SZ, Sood MR, Nurko S, Hyman P, Clifford RA, et al. Lubiprostone for pediatric functional constipation: randomized, controlled, double-blind study with long-term extension. Clin Gastroenterol Hepatol. 2022;20(3):602-5.
21. Hussain SZ, Labrum B, Mareya S, Stripling S, Clifford R. Safety of lubiprostone in pediatric patients with functional constipation: a nonrandomized, open-label trial. J Pediatr Gastroenterol Nutr. 2021;73(5):572-8.
22. Hyman PE, Di Lorenzo C, Prestridge LL, Youssef NN, Ueno R. Lubiprostone for the treatment of functional constipation in children. J Pediatric Gastroenterol Nutr. 2014;58(3):283-91.
23. McKeage K, Plosker GL, Siddiqui MA. Lubiprostone. Drugs. 2006;66(6):873-9.
24. Boutron I, Page MJ, Higgins JPT, Altman DG, Lundh A, Hrobjartsson A. Chapter 7: Considering bias and conflicts of interest among the included studies. 2022. In: Cochrane Handbook for Systematic Reviews of Interventions version 63 (updated February 2022) [Internet]. Cochrane. Available from: www.training.cochrane.org/handbook.
25. Fukudo S, Hongo M, Kaneko H, Takano M, Ueno R. Lubiprostone increases spontaneous bowel movement frequency and quality of life in patients with chronic idiopathic constipation. Clin Gastroenterol Hepatol. 2015;13(2):294-301.
26. Fukudo S, Hongo M, Kaneko H, Ueno R. Efficacy and safety of oral lubiprostone in constipated patients with or without irritable bowel syndrome: a randomized, placebo-controlled and dose-finding study. Neurogastroenterol Motil. 2011;23(6):544-e205.
27. Li F, Fu T, Tong WD, Liu BH, Li CX, Gao Y, et al. Lubiprostone Is Effective in the treatment of chronic idiopathic constipation and irritable bowel syndrome: a systematic review and meta-analysis of randomized controlled trials. Mayo Clin Proc. 2016;91(4):456-68.
28. Mugie SM, Korczowski B, Bodi P, Green A, Kerstens R, Ausma J, et al. Prucalopride is no more effective than placebo for children with functional constipation. Gastroenterology. 2014;147(6):1285-95.
29. Johanson JF, Ueno R. Lubiprostone, a locally acting chloride channel activator, in adult patients with chronic constipation: a double-blind, placebo-controlled, dose-ranging study to evaluate efficacy and safety. Aliment Pharmacol Ther. 2007;25(11):1351-61.