REVIEW

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Systematic review with meta-analysis: lubiprostone efficacy on the treatment of patients with constipation

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ABSTRACT – **Background** – Lubiprostone is a type 2 chloride channel activator that has been shown to be efficacious and safe in the treatment for chronic constipation. **Objective** – To systematically review randomized clinical trials (RCTs) assessing efficacy of lubiprostone for patients with chronic idiopathic constipation (CIC), irritable bowel syndrome with predominant constipation (IBS-C) and opioid-induced constipation (OIC). **Methods** – Searches were conducted in PubMed, LILACS, Cochrane Collaboration Database, and Centre for Reviews and Dissemination. Lubiprostone RCTs reporting outcomes of spontaneous bowel movements (SBM) and abdominal pain or discomfort were deemed eligible. Meta-analysis was performed calculating risk ratios and 95% confidence intervals, using the Mantel-Haenszel method and random effects model. **Results** – Searches yielded 109 records representing 93 non-duplicate publications, and 11 RCTs (978 CIC, 1,366 IBS-C, 1,300 OIC, total = 3,644) met inclusion criteria. Qualitative synthesis showed that for CIC patients, lubiprostone is superior to placebo in terms of SBM outcomes. Meta-analysis for CIC was feasible for full responder and SBM within 24h rates, indicating superiority of lubiprostone over placebo. For IBS-C, lubiprostone was significantly superior for all SBM outcomes in follow-ups ranging from 1 week-3 months. In terms of abdominal pain, lubiprostone provided significantly better symptoms relief, particularly after 1 month of treatment. For OIC, lubiprostone was more effective than placebo for both SBM and discomfort measures. **Conclusion** – Our findings demonstrated that lubiprostone is superior to placebo in terms of SBM frequency for CIC, IBS-C and OIC. In terms of abdominal symptoms, the most pronounced effect was seen for abdominal pain in IBS-C patients.

HEADINGS – Lubiprostone. Constipation. Irritable bowel syndrome. Opioid-induced constipation.

INTRODUCTION

Chronic constipation is one of the most common gastrointestinal disorders presenting to primary care physicians or subspecialty physicians. Quantitative data synthesis of chronic constipation prevalence in these analyses seems consistently around 15%, with female gender, elderly, lower socioeconomic status and educational level documented as risk factors[1,2]. Constipation leads to significant burden for both individuals and society, in terms of reduced quality of life[3-5] and costs[6-8].

Chronic idiopathic constipation (CIC) is a functional bowel disorder characterized by difficult, infrequent, and/or incomplete defecation[9]. Patients with CIC should not have an underlying anatomic or structural abnormality as the cause of their symptoms. There are three subtypes of CIC: dyssynergic defecation, slow transit constipation and normal transit constipation, which is the most common subtype[10].

Constipation symptoms are also seen in patients with irritable bowel syndrome (IBS) and those receiving opioid pain management[11]. IBS is a disorder of the gastrointestinal tract characterized by chronic abdominal pain and altered bowel habits in the absence of demonstrable organic disease[12]. A meta-analysis of 81 studies assessing 260,960 subjects indicated an IBS global prevalence of 11.2% and the IBS subtype with predominance of constipation (IBS-C) represents approximately 35.0% of these cases[13]. Opioid-induced constipation (OIC) is a common problem in patients on chronic opioid therapy and impacts the patients' quality of life. For instance, the prevalence of OIC in non-cancer patients with chronic opioid use ranges from 41–57%[11] and one third of patients need to miss or decrease opioid doses or stop using opioid medication due to gastrointestinal adverse events[14].

Constipation management strategies usually involve non-pharmacologic measures, such as increased dietary fiber intake or bulking agents, exercises and biofeedback, as well as over-the-counter medications (probiotics, osmotic and stimulant laxatives)[15]. These approaches appear to be well-tolerated and effective for some constipated patients, but patients with more moderate to severe constipation usually require more specific treatment[15-17].

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Takemoto MLS has served as Consultant Epidemiologist for Takeda, Abbvie, Astrazeneca, Biogen, and Novartis.
Corradino GC is an employee of Takeda Pharmaceuticals Brazil (Clinical Research Analyst)
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Therapeutic approaches with distinctive options and variable mode of actions (all of which increase intestinal secretion of chloride and water) have been developed over the past 10 years[18]. In this context, lubiprostone is a type 2 chloride channel activator that acts increasing the secretion of chloride-rich intestinal fluid and accelerates colonic transit. US FDA granted approval for lubiprostone and since its first clinical data, lubiprostone efficacy and safety have been addressed in clinical trials enrolling patients with chronic idiopathic constipation (CIC), IBS-C and opioid-induced constipation (OIC)[19-21], as well as colonoscopy preparation and leaky gut[22-24]. A previous systematic review with meta-analysis conducted by Fan et al. 2016 addressed the efficacy and safety of lubiprostone for CIC and IBS-C[25], but an analysis comprising all three indications is still lacking.

Thus, the main objective of this study is to answer the following question: *Among patients with chronic idiopathic constipation, opioid-induced constipation and irritable bowel syndrome with predominant constipation (IBS-C), what is the overall efficacy of lubiprostone versus comparators in terms of spontaneous bowel movements and abdominal pain or discomfort outcomes?*

METHODS

Search strategy

A systematic search was performed using MEDLINE via PubMed, LILACS (Latin American and Caribbean Health Sciences Literature), Cochrane Collaboration Database, and Centre for Reviews and Dissemination, to identify randomized clinical trials (RCTs) investigating the efficacy of lubiprostone in the management of CIC, IBS-C, and OIC (from inception to July 1st 2019). Search strategies using a combination of controlled vocabulary (MeSH and DeCs keywords, for PubMed and Lilacs, respectively) and text words were adopted, as described in FIGURE 1.

After applying the search strategies, resulting records were screened by two independent reviewers using the following inclusion criteria: i) randomized clinical trials; ii) enrolling patients with CIC, IBS-C and/or OIC; iii) reporting spontaneous bowel movements and abdominal pain or discomfort outcomes; and iii) papers reported in English, French, Portuguese, and Spanish only. No limits related to publication date were included. The definition of CIC, IBS-C and OIC adopted in the present review was the one stated in the original studies, given that it was clearly described in the publication. Studies were excluded if they had any of following exclusion criteria: i) observational studies or non-comparative clinical trials; ii) publications reporting studies previously included as pooled analysis or similar (duplicates).

Database	Search strategy
PubMed	(lubiprostone [tiab] OR lubiprostone [mesh] OR Amitiza [tiab]) AND ((irritable bowel syndrome [mesh] OR "irritable colon" [tiab] OR "irritable bowel" [tiab] OR "functional colonic disease" [tiab] OR "colon irritable" [tiab] OR "IBS" [tiab] OR "functional bowel disease" [tiab]) OR ("constipation" [mesh] OR constipat*[tiab] OR "slow transit" [tiab])) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [mh] NOT humans [mh])
Lilacs	lubiprostone OR lubiprostona
Cochrane collaboration	lubiprostone
Centre for reviews and dissemination	lubiprostone [all fields]

FIGURE 1. Search strategies.

In cases of disagreement between the two main reviewers, it was planned that a third reviewer would be the responsible for the final inclusion/exclusion decision. No disagreements were identified in the review process; therefore, this strategy was not employed. Data extraction was performed using a data collection tool specifically designed for this review. Variables abstracted from individual RCTs were: author, year, sample size and characteristics, disease (CIC, IBS-C or OIC), primary endpoints, spontaneous bowel movements and pain or discomfort outcomes results. Assessment of bias was based on the Cochrane Collaboration Risk of Bias Tool[26].

Outcomes measures

The efficacy outcome measures were defined as: (i) frequency of passage of spontaneous bowel movements (SBM), assessed as mean change from baseline, mean frequency, proportion of patients presenting a SBM within 24 hours of first dose; (ii) full responder rate, defined as the proportion of patients presenting ≥3–4 SBM in a given week; (iii) degree of abdominal pain or discomfort, assessed as mean score and also as rate of patients presenting the symptom. SBM were defined as any spontaneous bowel movement occurring 24 hours or more after the use of rescue medication (natural origin only). Abdominal pain and discomfort were rated using a 0 to 4 scale, with 0 indicating "absent", 1 "mild", 2 "moderate", 3 "severe", and 4 "very severe". Abdominal pain scores were selected as outcomes in IBS-C studies and abdominal discomfort scores in CIC and OIC trials, due to clinical manifestations usually seen in these conditions.

Data synthesis

Outcomes were selected for meta-analysis based on the availability of complete data (number of events for dichotomous variables and means and dispersion measures for continuous variables) within studies with similar methods. Pooled effects were estimated by calculating risk ratios (RR) and their 95% confidence intervals (95% CI) for dichotomous events, using the Mantel-Haenszel method (M-H) and a random effects model. Studies did not provide sufficient information for pooling results of continuous outcomes (median time to first SBM, pain and discomfort scales), thus weighted mean difference was not used in the present analysis. Higgins I^2 statistics was adopted to evaluate heterogeneity, as implemented by RevMan 5.3 software (Cochrane Library, London, UK). I^2 >50% and *P*-value of 0.1 were adopted as significance levels for heterogeneity. Probability value of <0.05 was considered statistically significant.

RESULTS

Study selection

The search strategy yielded 109 records that represented 93 non-duplicate publications, of which 11 RCTs (involving 978 CIC patients, 1,366 IBS-C patients, 1,300 OIC patients, total n=3,644)

published between 2007 and 2017 met inclusion criteria for this review (FIGURE 2). Two studies were excluded after full-text screening and the reasons are presented in FIGURE 2[27,28].

Study characteristics

TABLE 1 presents characteristics of included studies. All studies were double-blind placebo-controlled randomized trials and oral lubiprostone doses varied from 16 to 72 mcg daily, with most studies providing patients with 48 mcg daily (24 mcg bid). Only outcomes related to the 48 mcg daily scheme were abstracted for the purposes of this analysis, once this is the current established dosage for the medication. Follow-up of patients varied from 3 to 12 weeks. One study was a pooling analysis of two RCTs that were not published separately, thus the pooling analysis is presented here. All studies except one adopted primary efficacy endpoints related to SBM frequency, although outcome definition markedly varied in each study. Only Johanson (IBS-C) adopted a pain score as the primary endpoint in a study involving patients with IBS-C[29]. In terms of patients characteristics, one trial enrolled patients with constipation with or without IBS and we opted for including it under the CIC subgroup of studies[20]. Christie et al. enrolled only diabetic patients but the eligibility criteria clearly stated that patients had idiopathic constipation and an organic cause was not present[30].

Risk of bias

Risk of bias of included studies was overall low in all domains, once only double-blinded placebo-controlled prospective randomized trials were deemed eligible.

Data synthesis

Qualitative synthesis of all selected outcomes for each of the included studies grouped by the underlying condition is presented in TABLES 2, 3 and 4. Only published data was analysed.

Among CIC studies (TABLE 2), lubiprostone was significantly superior to placebo for all SBM-related outcomes except for full responder rate in the Fukudo et al. (P=0.066)[31]. Lubiprostone demonstrated a better efficacy profile in follow-up durations ranging from 1 to 8 weeks in CIC studies. In terms of abdominal discomfort endpoints, lubiprostone-treated patients had significantly lower scores 4 weeks after treatment initiation in the Johanson et al.[32] but two other studies did not observe a statistically significant difference[19,30]. Two of the outcomes addressed in CIC studies

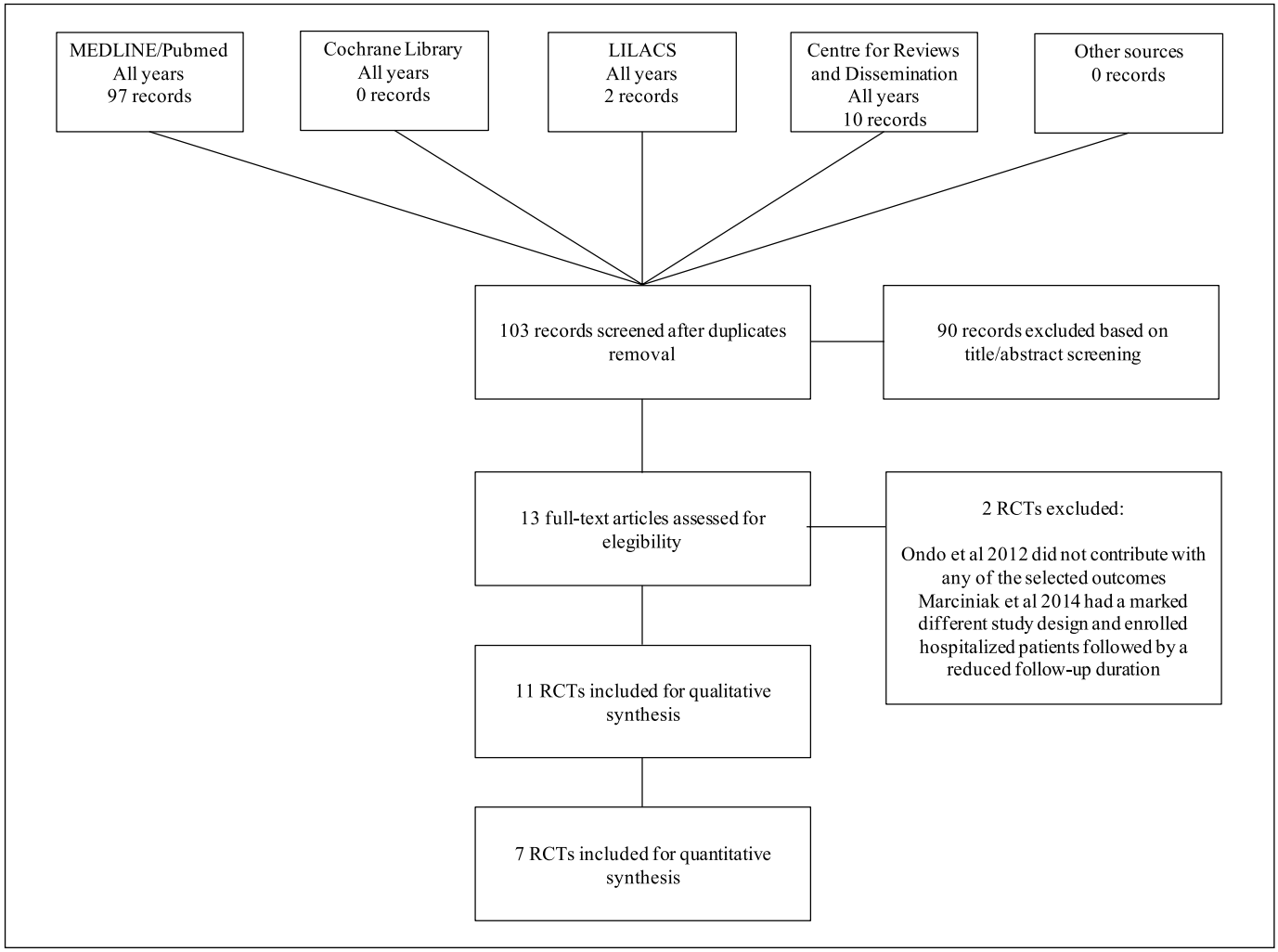

FIGURE 2. PRISMA flowchart.

TABLE 1. Characteristics of included studies.

Population	Author, year	Country	Sample size	Intervention	Comparator	Outcomes
CIC	Johanson, 2007[38]	USA	129 CIC patients	Lubiprostone 24 (n=30), 48 (n=32) or 72 mcg (n=34)	Placebo (n=33)	Mean number of SBMs per week
	Johanson, 2008[32]	USA	242 CIC patients	Lubiprostone 48 mcg (n=120)	Placebo (n=122)	Number of SBMs after 1 week
	Barish, 2009[19]	USA	237 CIC patients	Lubiprostone 48 mcg (n=119)	Placebo (n=118)	Number of SBMs after 1 week
	Fukudo, 2011[20]	Japan	170 constipation patients with or without IBS	Lubiprostone 16 (n=41), 32 (n=43) or 48 mcg (n=44)	Placebo (n-42)	Change from baseline in the weekly average number of SBMs at week 1
	Fukudo, 2015[31]	Japan	124 CIC patients	Lubiprostone 48 mcg (n=62)	Placebo (n=62)	Change from baseline in the weekly mean number of SBMs after 1 week
	Christie, 2016[30]	USA	76 CIC patients	Lubiprostone 48 mcg (n=37)	Placebo (n=39)	Difference in number of SBMs per week from baseline
IBS-C	Johanson, 2008[29]	USA	195 IBS-C patients	Lubiprostone 16 (n=51), 32 (n=49) or 48 mcg (n=45)	Placebo (n=48)	Change from baseline in mean abdominal pain score (1 month)
	Drossman, 2009[33]	USA	1171 Rome II IBS-C patients (pooled results of 2 RCTs) Study 0431 n=590 Study 0432 n=581	Lubiprostone 48 mcg (n=769)	Placebo (n=385)	Overall responder rate
OIC	Cryer, 2014[21]	USA and Canada	418 chronic noncancer pain patients	Lubiprostone 48 mcg (n=210)	Placebo (n=208)	Change from baseline in the frequency of SBMs at week 8
	Jamal, 2015[36]	USA and EU	431 chronic noncancer pain patients using non-methadone opioid	Lubiprostone 48 mcg (n=214)	Placebo (n=217)	Overall SBM response rate
	Spierings, 2017[39]	USA	451 chronic noncancer pain patients	Lubiprostone 48 mcg (n=224)	Placebo (n=213)	Change from baseline in frequency of SBMs at week 8

CIC: chronic idiopathic constipation; IBS-C: constipation-predominant irritable bowel syndrome; OIC: opioid-induced constipation; RCT: randomized clinical trial; SBM, spontaneous bowel movements.

TABLE 2. Main findings in CIC Lubiprostone studies.

	Outcomes	Studies	Results (lubiprostone vs placebo)	*P*-value
CIC	Mean change in the number of SBMs from baseline (4 weeks)	Fukudo, 2015	2.56 vs 1.62	0.042
	Mean SBM per week (8 weeks)	Christie, 2016	7.00 vs 5.27	0.02
	Mean SBM per week (4 weeks)	Johanson, 2008	5.30 vs 2.91	0.002
		Barish, 2009	5.37 vs 3.46	0.0068
		Christie, 2016	5.77 vs 4.78	NR
	Mean SBM per week (1 week)	Johanson, 2007	Point estimates NR, higher mean for Lubiprostone (chart)	0.02
		Johanson, 2008	5.69 vs 3.46	0.0001
		Barish, 2009	5.89 vs 3.99	0.0001
	Change in mean SBM in the first week	Fukudo, 2011	6.8 vs 1.5	0.0001
		Fukudo, 2015	3.7 vs 1.3	0.001
	SBM within 24 hours	Johanson, 2007	59.4% vs 27.3%	0.009
		Johanson, 2008	56.7% vs 36.9%	0.0024
		Barish, 2009	61.3% vs 31.4%	0.0001
		Fukudo, 2011	75.0% vs 26.2%	0.0001
		Fukudo, 2015	58.1% vs 34.6%	0.004
	Weekly full responder rate (≥ 3-4 SBM per week) (4 weeks)	Johanson, 2008†	57.8% vs 27.9%	0.004
		Barish, 2009	60.0% vs 39.0%	0.0022
		Fukudo, 2015	54.2% vs 36.7%	0.066
	Mean abdominal discomfort score (4 weeks)	Johanson, 2008	1.23 vs 1.52	0.045
		Barish, 2009	1.24 vs 1.47	0.1383
	Mean abdominal discomfort rate (4 weeks)	Christie, 2016	53.0% vs 67.0%	0.86
	Mean abdominal discomfort rate (8 weeks)	Christie, 2016	50.0% vs 52.0%	0.86

CIC: chronic idiopathic constipation; NR: not reported; SBM: spontaneous bowel movements; †definition of full-responder = ≥ 3 SBM per week.

TABLE 3. Main findings in IBS-C Lubiprostone studies.

	Outcomes	Studies	Results (lubiprostone vs placebo)	*P*-value
IBS-C	Overall responder rate†	Drossman, 2009	17.9% vs 10.1%	0.001
	Monthly responder rate (month 3)	Study 0431 in Drossman, 2009	21.3% vs 14.5%	0.026
		Study 0432 in Drossman, 2009	22.7% vs 14.6%	0.026
		Drossman, 2009 (pooled results)	22.0% vs 14.5%	0.003
	Weekly responder rate (weeks 2, 4, 5, 6, 10 and 12)	Drossman, 2009	Point estimates NR, higher rate for Lubiprostone (chart)	0.030
	Mean change from baseline in weekly SBM rate (month 3)	Johanson, 2008b	Point estimates NR, higher rate for Lubiprostone (chart)	0.033
	Mean improvement in abdominal pain score (month 1)	Johanson, 2008b	Point estimates NR, higher mean for Lubiprostone (chart)	0.023
		Drossman, 2009	Point estimates NR, higher mean for Lubiprostone	> 0.05
	Mean improvement in abdominal pain score (month 2)	Johanson, 2008b	Point estimates NR, higher mean for Lubiprostone (chart)	0.028
		Drossman, 2009	-0.43 vs -0.35	0.039
	Mean improvement in abdominal pain score (month 3)	Johanson, 2008b	Point estimates NR, higher mean for Lubiprostone (chart)	0.260
		Drossman, 2009	-0.45 vs -0.36	0.028

IBS-C: constipation-predominant irritable bowel syndrome; NR: not reported; SBM: spontaneous bowel movements; †responder rate was defined as patients achieving ≥ 3-4 SBM per week.

TABLE 4. Main findings in OIC Lubiprostone studies.

	Outcomes	Studies	Results (lubiprostone vs placebo)	*P*-value
OIC	Mean change from baseline in SBM frequency (week 8)	Cryer, 2014	3.3 vs 2.4	0.005
		Spierings, 2017	2.6 vs 2.4	0.842
	Mean change from baseline in SBM frequency (week 12)	Cryer, 2014	Point estimates NR, higher mean for Lubiprostone (chart)	0.091
		Jamal, 2015	Point estimates NR, higher mean for Lubiprostone (chart)	0.040
		Spierings, 2017	2.5 vs 2.6	0.956
	Mean change from baseline in SBM frequency (overall)	Cryer, 2014	2.2 vs 1.6	0.004
		Jamal, 2015	3.2 vs 2.4	0.001
		Spierings, 2017	2.6 vs 2.3	0.224
	SBM within 24 hours	Cryer, 2014	38.8% vs 27.8%	0.018
		Jamal, 2015	50.9% vs 38.2%	0.008
		Spierings, 2017	33.2% vs 30.2%	0.502
	Overall responder rate	Jamal, 2015	27.1% vs 18.9%	0.030
	Median time to first SBM	Cryer, 2014	28.5 vs 46.0 hours	0.053
		Jamal, 2015	23.5 vs 37.7 hours	0.004
	Mean improvement in abdominal discomfort scales (overall)	Cryer, 2014	Point estimates NR, higher mean for Lubiprostone (chart)	0.047
		Jamal, 2015	Point estimates NR, higher mean for Lubiprostone (chart)	0.127
		Spierings, 2017	-0.5 vs -0.4	0.027

NR: not reported; OIC: opioid-induced constipation; SBM: spontaneous bowel movement.

provided sufficient data for meta-analysis (weekly responder rate assessed in three studies and rate of SBM within 24 hours of first dose in five studies), as presented in FIGURE 3 A and B. Lubiprostone increased the likelihood of a patient achieve a full-responder status by 1.67 (95% CI 1.36–2.06) and present a SBM in 24 hours of 1.90 (1.56–2.31).

In the IBS-C studies (TABLE 4), all selected SBM-related outcomes were significantly better among lubiprostone patients, even in longer follow-ups (up to 3 months). For abdominal pain measures, three RCTs assessed mean scores in 1, 2 and 3 months after treatment initiation. Johanson et al. observed a higher mean improvement from baseline in abdominal pain score after 1 and 2 months of lubiprostone therapy[29]. Patients enrolled in the Drossman et al. trial presented better improvement in abdominal pain after 2 and 3 months of lubiprostone as compared to patients receiving placebo[33].

Findings from OIC RCTs were less consistent for each of the selected outcomes (TABLE 4). Statistically significant differences in favour of lubiprostone were seen for mean change from baseline in SBM frequency at week 8 (1 out of 2 RCTs), week 12 (1 out of 3 RCTs), and overall (2 out of 3 RCTs); SBM within 24 hours (2 out of 3 RCTs); overall responder rate (1 RCT); median time to first SBM (1 out of 2 RCTs); and mean improvement in abdominal discomfort scales (overall, two out of three studies). For the SBM within 24 hours rate, meta-analysis was feasible for 2 out of 3 studies (FIGURE 4, without statistical significance)[34,35]. Jamal et al. 2015 did not provide absolute number of events or patients for each time cut-off, thus the inclusion of its data on meta-analysis was not feasible[36].

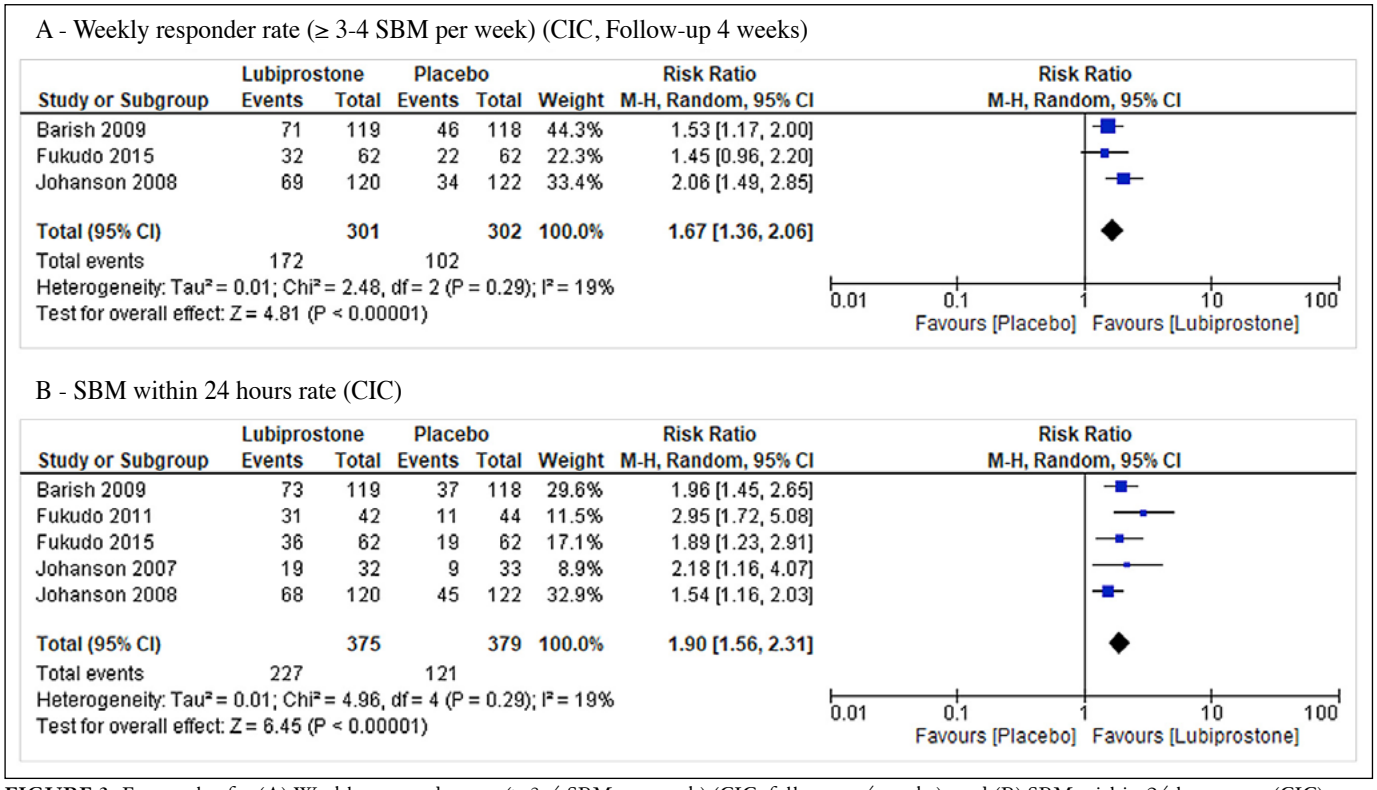

FIGURE 3. Forest plot for (A) Weekly responder rate (≥ 3-4 SBM per week) (CIC, follow-up 4 weeks), and (B) SBM within 24 hours rate (CIC).

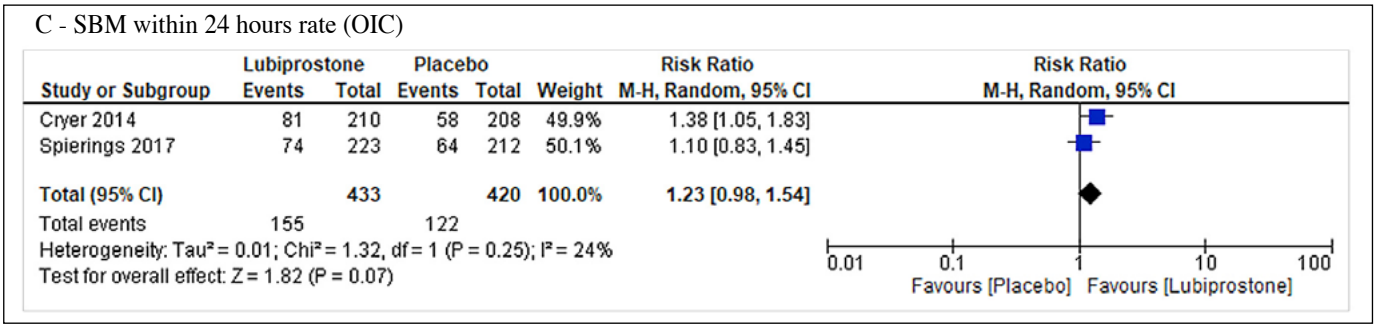

FIGURE 4. Forest plot for SBM within 24 hours rate (OIC).

DISCUSSION

The objective of this study was to assess the efficacy of lubiprostone in patients with CIC, IBS-C and OIC in terms of SBM and abdominal pain and discomfort outcomes, through a systematic review and meta-analysis of randomized clinical trials. Overall, significant clinical heterogeneity was found between included studies, particularly in terms of outcomes definition and duration of follow-up, but the risk of bias was assessed as low once only placebo-controlled double-blind randomized clinical trials were included. The systematic review showed that for CIC patients, lubiprostone efficacy is generally superior to placebo in terms of SBM outcomes. Meta-analysis of CIC studies was feasible only for full responder and SBM within 24-hour rates, indicating superiority of lubiprostone over placebo. Unfortunately, discomfort outcomes in CIC RCTs were assessed using different measures precluding meta-analysis and the relatively small sample size in each individual study may be the reason why statistically significant differences were not observed. It is worth mentioning that the results observed by Christie et al. 2016 indicate a positive effect of lubiprostone in diabetic patients with CIC, as previously described for CIC patients without diabetes. Once outcome measures adopted by Christie et al. 2016 differ from the ones used in other included CIC studies, direct comparability is impaired[30].

For IBS-C patients, lubiprostone was associated with significantly superior results for all SBM-related outcomes in follow-up durations ranging from 1 week to 3 months. In terms of abdominal pain measures, lubiprostone seems to provide significantly better relief of symptoms, particularly after 1 month of treatment, as demonstrated in the qualitative data synthesis. A post hoc analysis published by Chang et al.[37] reassessed data from the two pivotal phase three studies reported by Drossman et al.[33] using the 2012 FDA recommended eligibility criteria and a composite endpoint combining both abdominal pain and stool frequency in the

same measure. In this analysis, 325 lubiprostone-treated and 180 placebo-treated patients were included. Responders according to the FDA composite endpoint (improved pain and stool frequency) were 26.3% vs 15.3% in the lubiprostone and placebo groups, respectively (P=0.008). The composite endpoint of bloating and stool frequency improvement also showed statistically significant differences in favour of lubiprostone (23.8% vs 12.6%; P=0.012). These additional findings reinforce that IBS-C patients treated with lubiprostone present better clinically relevant outcomes than placebo[37].

OIC RCTs also presented marked differences in methods adopted to assess lubiprostone and placebo efficacy and meta-analysis was feasible only for the SBM within 24-hour rate. The systematic review and qualitative data synthesis identified that lubiprostone was more effective than placebo for most assessed outcomes in the included studies (both SBM and discomfort-related measures). Our findings for lubiprostone versus placebo were in agreement with previous systematic reviews with or without meta-analysis using similar methods[22,23].

Additionally, lubiprostone has demonstrated a favourable safety profile in individual RCTs, pooled analysis and meta-analysis of both RCTs and extension studies[19-21,23,29-33,36,38-40]. Gastrointestinal adverse events such as nausea, vomiting or diarrhoea were the most common across the studies[40]. Regarding nausea (the most frequent adverse event in lubiprostone trials), Cryer et al.[34] conducted a pooled analysis of data from RCTs and long term observational studies of lubiprostone for CIC, IBS-C and OIC to address the frequency of nausea among lubiprostone-treated patients. The authors analysed three RCTs and three long-term open-label studies for CIC analysis and IBS-C and OIC analysis included three 12-week placebo-controlled studies and one 36-week open-label extension study each. Pooled data indicate that nausea incidence ranges from 11.4 to 31.1%, higher among CIC patients (who receive a higher dose of lubiprostone – 24 mcg bid), and most patients had mild or moderate severity (96.5–99.1%, all studies) and only one nausea event (83.6–88.7%), particularly in the first 5 days of treatment[34].

Also, in terms of safety, a pooled analysis of OIC studies specifically addressed the potential influence of lubiprostone in pain control among noncancer patients. The Brief Pain Inventory short form (BPI-SF) scores and opioid use records (expressed as morphine-equivalent daily dose, MEDD) were assessed. This analysis included 1,300 patients and the MEDD was 97.5 mg in placebo-treated patients and 112.5 mg in lubiprostone at baseline and modifications from baseline were not significantly different for both MEDD and BPI-SF in any of the follow-up durations, suggesting that lubiprostone does not interfere with the analgesic action of opioids[35].

Two studies presented long-term data about efficacy and safety of lubiprostone for CIC and IBS-C patients[41,42]. The IBS-C open-label non-comparative trial enrolled patients from two RCTs who received 8mcg lubiprostone twice daily for at least 36-weeks[41]. Overall monthly responder rate increased from 16.0% after 1 month of lubiprostone treatment to 37.0–44.0% of patients after 10–13 months of treatment. SBM frequency per week also gradually improved with lubiprostone treatment, remaining stable at approximately 5 SBMs/week (P≤0.002 for most months compared to baseline). The same pattern was observed for discomfort and pain with significant improvements from baseline in each of the assessed months[41]. The lubiprostone adverse event profile was similar to the one reported in phase three clinical trials with incidence of diarrhoea, nausea, urinary tract infection, sinusitis and abdominal distention of 11.0%; 11.0%; 9.0%; 9.0%; and 5.8%, respectively. Severe adverse events reported in the study were not considered treatment-related and only 17 out of 520 patients discontinued lubiprostone due to treatment-related adverse events[41].

Lembo et al. also conducted a prospective, multicentre, open-label trial that enrolled 248 patients with CIC to receive lubiprostone 24 mcg BID as needed for 48 weeks[42]. Overall, lubiprostone treatment significantly improved patient-reported constipation severity, abdominal bloating, and abdominal discomfort when compared to baseline (P<0.0001). Dose reduction was observed in 17.0% of patients and the most common treatment-related adverse events were nausea (19.8%), diarrhoea (9.7%), abdominal distension (6.9%), headache (6.9%), and abdominal pain (5.2%). Only one treatment-related serious adverse event was reported.

Thus, besides the short-term efficacy demonstrated in our systematic review and meta-analysis, lubiprostone safety and efficacy have also been reported for longer follow-ups reaching 48 to 52 weeks in open-label studies[41,42].

Another relevant aspect evidenced by our systematic review and meta-analysis is the efficacy observed among placebo-treated patients. For example, the weekly responder rate estimated in the meta-analysis for the placebo group in CIC studies was 33.8% (102 out of 302 patients), while the SBM within 24 hours rate was 31.9% (121 out of 379) (FIGURE 3). Among OIC patients included in the meta-analysis, the SBM within 24 hours rate was 29.0%, not statistically different than the rate observed for lubiprostone (35.8%). Placebo effect was also observed for other SBM-related outcomes as well as for pain and discomfort measures in studies included in the systematic review. Response to placebo has been widely described for functional gastrointestinal disorders as well as for patient-reported outcomes and pain measures[43-45]. The exact mechanisms involved in placebo effect is not fully understood, but psychological and neurobiological factors probably play major role[44]. In terms of real-world application of these findings, in clinical practice, it is relevant to highlight that placebo response in clinical trials should not be considered interchangeable with the evolution of non-treated patients. Therefore, it is reasonable to hypothesize that the benefit associated with lubiprostone over placebo in RCTs could be even more pronounced as compared to real-world settings once constipated patients are likely to not receive effective pharmacological therapy.

Limitations of our study can be related to the significant clinical and methodological heterogeneity of included RCTs, precluding meta-analysis for most outcomes and indications but also impairing the comparability of results across trials. Other limitations in our analysis are the variability in the follow-up duration and the absence of detailed assessment of all efficacy and safety outcomes. Due to the large availability of endpoints with different follow-up durations, it was not feasible to address all of them in a single analysis. The majority of RCTs included in the meta-analysis had shorter follow-up durations with only a small part assessing patients for at least 3 months. This aspect limits our ability to derive robust conclusions about long-term efficacy of lubiprostone within the scope of our systematic review.

Evidence from open-label non-comparative trials has demonstrated similar efficacy and safety patterns in longer follow-ups (48–52 weeks). Future research is needed to better address the efficacy and safety of lubiprostone versus standard of care, once

placebo response rates correlate with frequency of the intervention and with overall treatment effects in chronic constipation clinical studies. In a similar manner, head-to-head trials with active comparators would also provide relevant data to help selecting treatment approaches.

In conclusion, the results of our systematic review and meta-analysis demonstrated that lubiprostone is superior to placebo in terms of spontaneous bowel movements frequency for patients with CIC, IBS-C and OIC. In terms of abdominal discomfort, CIC and OIC patients seems to have better results while receiving lubiprostone as compared to placebo, but the most pronounced effect was seen for abdominal pain in IBS-C patients.

Authors' contribution

All authors contributed equally to conceptual planning of this analysis and interpretation of study findings; critically revised and modified the manuscript for relevant intellectual content; and approved the final version to be published. MLST conducted data analysis and wrote the preliminary version of the manuscript.

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RESUMO – **Contexto** – Lubiprostona é um ativador de canal de cloreto tipo 2 que tem se demonstrado eficaz e seguro no tratamento da constipação crônica. **Objetivo** – Revisar sistematicamente ensaios clínicos randomizados (ECRs) avaliando a eficácia da lubiprostona para pacientes com constipação idiopática crônica (CIC), síndrome do intestino irritável com constipação predominante (IBS-C) e constipação induzida por opioide (OIC). **Métodos** – Buscas foram conduzidas no PubMed, LILACS, Cochrane Collaboration Database e Centre for Reviews and Dissemination. ECRs de lubiprostona relatando desfechos de movimentos intestinais espontâneos (SBM) e dor ou desconforto abdominal foram considerados elegíveis. Metanálise foi realizada calculando razão de riscos e intervalos de confiança de 95%, utilizando o método de Mantel-Haenszel e modelo de efeitos aleatórios. **Resultados** – As buscas identificaram 109 registros representando 93 publicações não-duplicadas e 11 ECRs (978 pacientes de CIC, 1366 de IBS-C e 1300 OIC, total = 3644) preencheram os critérios de inclusão. Síntese qualitativa mostrou que, para pacientes com CIC, a lubiprostona foi superior ao placebo em termos de desfechos SBM. Metanálise para CIC foi possível para os desfechos de responder completo e taxa de SBM em 24 horas, indicando superioridade da lubiprostona sobre o placebo. Para IBS-C, lubiprostona foi significativamente superior para todos os desfechos de SBM em tempos de seguimento variando de 1 semana a 3 meses. Em termos de dor abdominal, lubiprostona proporciono alívio dos sintomas significativamente melhor, particularmente após 1 mês de tratamento. Para OIC, lubiprostona foi mais efetiva do que placebo tanto para medidas de SBM quando de desconforto abdominal. **Conclusão** – Nossos achados demonstraram que lubiprostona é superior ao placebo em termos de frequência de SBM para CIC, IBS-C e OIC. Em termos de sintomas abdominais, o efeito mais pronunciado foi visto para dor abdominal em pacientes com IBS-C.

DESCRITORES – Lubiprostona. Constipação intestinal. Síndrome do intestino irritável. Constipação induzida por opioides.

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