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

Maria do Carmo F PASSOS1, Maira Libertad Soligo TAKEMOTO2, Gabriel Cyrillo CORRADINO3 and Luciana S GUEDES3

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.

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. Constipation leads to significant burden for both individuals and society, in terms of reduced quality of life and costs. Chronic idiopathic constipation (CIC) is a functional bowel disorder characterized by difficult, infrequent, and/or incomplete evacuation. 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.

Constipation symptoms are also seen in patients with irritable bowel syndrome (IBS) and those receiving opioid pain management. IBS is a disorder of the gastrointestinal tract characterized by chronic abdominal pain and altered bowel habits in the absence of demonstrable organic disease. 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. 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% and one third of patients need to miss or decrease opioid doses or stop using opioid medication due to gastrointestinal adverse events.

Constipation management strategies usually involve non-pharmacologic measures, such as increased dietary fiber intake or bulk-forming agents, exercises and biofeedback, as well as over-the-counter medications (probiotics, osmotic and stimulant laxatives). 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.
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(19). 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).

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 I² statistics was adopted to evaluate heterogeneity, as implemented by RevMan 5.3 software (Cochrane Library, London, UK). I² >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. but two other studies did not observe a statistically significant difference(19,30). Two of the outcomes addressed in CIC studies...
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=52) or 72 mcg (n=54) | Placebo (n=53) | 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(30) | USA | 237 CIC patients | Lubiprostone 48 mcg (n=119) | Placebo (n=118) | Number of SBMs after 1 week |
|            | Fukudo, 2011(31) | 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(32) | 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) | Lubiprostone 48 mcg (n=769) | Placebo (n=385) | Overall responder rate |
| OIC        | Cryer, 2014(34) | 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(35) | 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(36) | 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 |
|----------|---------|----------------------------------|---------|
| 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 |
| Mean SBM per week (4 weeks) | Barish, 2009 | 5.37 vs 3.46 | 0.0068 |
| Mean SBM per week (1 week) | Christie, 2016 | 5.77 vs 4.78 | NR |
| Change in mean SBM in the first week | Johanson, 2007 | Point estimates NR, higher mean for Lubiprostone (chart) | 0.02 |
| Mean SBM per week (4 weeks) | Johanson, 2008 | 5.69 vs 3.46 | 0.0001 |
| Mean SBM per week (4 weeks) | 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 |
| SBM within 24 hours | Fukudo, 2015 | 3.7 vs 1.3 | 0.001 |
| Weekly full responder rate (≥ 3–4 SBM per week) (4 weeks) | Johanson, 2008(38) | 57.8% vs 27.3% | 0.004 |
| Mean abdominal discomfort score (4 weeks) | Johanson, 2008 | 1.23 vs 1.52 | 0.045 |
| 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 |
|-----------------------------------------|--------------------------|-----------------------------------------|---------|
| 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   |
| Mean improvement in abdominal pain score (month 2) | Drossman, 2009           | Point estimates NR, higher mean for Lubiprostone > 0.05 | 0.028   |
| 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 -0.35                          | 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 |
|-----------------------------------------|--------------------------|-----------------------------------------|---------|
| 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) | Jamal, 2015              | Point estimates NR, higher mean for Lubiprostone (chart) | 0.091   |
|                                         | 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 movements.

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(30).

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).
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.

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. reassessed data from the two pivotal phase three studies reported by Drossman et al. 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 (35).

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 (22-25).

Additionally, lubiprostone has demonstrated a favourable safety profile in individual RCTs, pooled analysis and meta-analysis of both RCTs and extension studies (19-21,23,26-33,36-40). 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 (37).

Two studies presented long-term data about efficacy and safety of lubiprostone for CIC and IBS-C patients and. The IBS-C open-label non-comparative trial enrolled patients from two RCTs who received 8 mg lubiprostone twice daily for at least 36-weeks (43). 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 (43). 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 (43).

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 (40). 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 (44-45). 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 interchangeably 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.

**Orcid**

Maria do Carmo F Passos: 0000-0002-5247-9477.

Maria Libertad Soligo Takemoto: 0000-0002-7016-2879.

Gabriel C Corradino: 0000-0001-6645-4097.

Luciana S Guedes: 0000-0002-8901-2600.

---

**REFERENCES**

1. Magie SM, Benninga MA, Di Lorenzo C. Epidemiology of constipation in children and adults: A systematic review. Best Pract Res Clin Gastroenterol. 2011;25:3-18.

2. Suáres NC, Ford AC. Prevalence of, and risk factors for, chronic idiopathic constipation in the community: systematic review and meta-analysis. Am J Gastroenterol. 2011;106:1582-91.

3. Veiga DR, Mendonça L, Sampaio R, Lopes JC, Azevedo LF. Incidence and health related quality of life of opioid-induced constipation in chronic noncancer pain patients: A Prospective multicentre Cohort Study. Pain Res Treat. 2018;2018:1-11.

4. Mearin F, Caballero AM, Serra J, Brotons C, Tantiñà A, Fort E, et al. A retrospective and prospective 12-month observational study of the socioeconomic burden of moderate to severe irritable bowel syndrome with constipation in Spain. Gastrointest Hepatol. 2019;42:141-9.

5. Brochard C, Chambaz M, Ropert A, L'Héritier AM, Wallenhorst T, Bouguen G, et al. Quality of life in 1870 patients with constipation and/or fecal incontinence: constipation should not be underestimated. Clin Res Gastroenterol Hepatol. 2019;43:682-7.

6. Schmier JK, Miller PE, Levine JA, Perez V, Maki KC, Rains TM, et al. Cost savings of reduced constipation rates attributed to increased dietary fiber intakes: a decision-analytic model. BMC Public Health. 2014;14:374.

7. Raya A, Barrull C, Roset M, Cortes X, Fortea J. Health care cost associated to constipation predominant irritable bowel syndrome in Spain. Value Health. 2011;14(Suppl 1):S78-81.

8. Takemoto MLS, Fernandes RA, Almeida GR, Monteiro RDC, Colombini-Neto M, Bertola-Neto A. Health care resource use and costs in opioid-treated patients with and without constipation in Brazil. Value Health. 2011;14(Suppl 1):S78-81.

9. Black CJ, Ford AC. Chronic idiopathic constipation in adults: epidemiology, pathophysiology, diagnosis and clinical management. Vol. 209, Medical Journal of Australia. Australasian Medical Publishing Co. Ltd. 2018. p. 86-91.

10. Lacy BE. Update on the management of chronic idiopathic constipation. Am J Manag Care. 2019;25(Suppl 8):S55-62.

11. Drewes AM, Munkholm P, Simrén M, Breivik H, Kongsgaard UE, Hatlebakk JG, et al. Definition, diagnosis and treatment strategies for opioid-induced bowel dysfunction—Recommendations of the Nordic Working Group. Scand J Pain. 2016;11:111-22.

12. Lacy BE, Mearin F, Chang L, Chey WD, Lembo AJ, Simren M, et al. Bowel disorders. Gastroenterology. 2016;150:1393-407.e5.

13. Lovell RM, Ford AC. Global Prevalence of and Risk Factors for Irritable Bowel Syndrome: A Meta-analysis. Clin Gastroenterol Hepatol. 2012;10:712-21.e4.

14. Bell TJ, Panchul SJ, Miaskowski C, Bolge SC, Milanova T, Williamson R. The Prevalence, Severity, and Impact of Opioid-Induced Bowel Dysfunction: Results of a US and European Patient Survey (PROBE 1). Pain Med. 2009;10:35-42.

15. Tack J, Müller-Lissner S, Stanghellini V, Boeckxstaens G, Kamm MA, Simren M, et al. Diagnosis and treatment of chronic constipation—a European perspective. Neurogastroenterol Motil. 2011;23:697-710.

16. Solem CT, Patel H, Mehta S, Mody R, Macahilig C, Gao X. Treatment patterns, symptom reduction, quality of life, and resource use associated with lubiprostone in irritable bowel syndrome constipation subtype. Curr Med Res Opin. 2016;32:899-905.

17. Shin JE, Jung H-K, Lee TH, Jo Y, Lee H, Song KH, et al. Guidelines for the Diagnosis and Treatment of Chronic Functional Constipation in Korea, 2015 Revised Edition. J Neurogastroenterol Motil. 2016;22:383-411.
18. Wilson N, Schey R. Lubiprostone in constipation: Clinical evidence and place in therapy. Vol. 6. Therapeutic Advances in Chronic Disease. 2015. p. 40-50.
19. Barish CF, Drossman D, Johanson JF, Ueno R. Efficacy and Safety of Lubiprostone in Patients with Chronic Constipation. Dig Dis Sci. 2010;55:1090-7.
20. 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, dose-finding study. Neurogastroenterol Motil. 2011;23:e54-e60.
21. Cryer B, Katz S, Vallèjo R, Popescu A, Ueno R. A Randomized Study of Lubiprostone for Opioid-Induced Constipation in Patients with Chronic Noncancer Pain. Pain Med. 2014;15:1825-34.
22. Kato T, Honda Y, Kurita Y, Iwasaki A, Sato T, Kessoku T, et al. Lubiprostone improves intestinal permeability in humans, a novel therapy for the leaky gut. A prospective randomized pilot study in healthy volunteers. Green J, editor. PLoS One. 2017;12:e017562.
23. Banerjee R, Chaudhuri H, Shah N, Saravanan A, Tandan M, Reddy DN. Addition of Lubiprostone to polyethylene glycol (PEG) enhances the quality and efficacy of colonoscopy preparation: a randomized, double-blind, placebo-controlled trial. BMC Gastroenterol. 2016;16:133.
24. Sofi AA, Nawras AT, Pai C, Samuels Q, Silverman AL. Lubiprostone Plus PEG Electrolytes Versus Placebo Plus PEG Electrolytes for Outpatient Colonoscopy Preparation. Am J Ther. 2015;22:105-10.
25. 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;91:456-68.
26. Higgins JPT, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
27. Onodo WG, Kenney C, Sullivan K, Davidson A, Hunter C, Janh L, et al. Placebo-controlled trial of lubiprostone for constipation associated with Parkinson disease. Neurology. 2012;78:1650-4.
28. Marciniak CM, Toledo S, Lee J, Jesselson M, Bateman J, Grover B, et al. Lubiprostone vs Sena in postoperative orthopaedic surgery patients with opioid-induced constipation: A double-blind, active-comparator trial. World J Gastroenterol. 2014;20:16723.
29. Johanson JF, Drossman DA, Panas R, Wahle A, Ueno R. Clinical trial: phase 2 study of lubiprostone for irritable bowel syndrome with constipation. Aliment Pharmacol Ther. 2008;27:685-96.
30. Christie J, Shroff S, Shahnazav N, Carter LA, Harrison MS, Dietz-Lindo KA, et al. A Randomized, Double-Blind, Placebo-Controlled Trial to Examine the Effectiveness of Lubiprostone on Constipation Symptoms and Colon Transit Time in Diabetic Patients. Am J Gastroenterol. 2017;112:356-64.
31. 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;13:294-301 e5.
32. Johanson JF, Morton D, Green J, Ueno R. Multicenter, 4-Week, Double-Blind, Randomized, Placebo-Controlled Trial of Lubiprostone, a Locally-Acting Type-2 Chloride Channel Activator, in Patients With Chronic Constipation. Am J Gastroenterol. 2008;103:170-7.
33. Drossman DA, Cryer WD, Johanson JF, Fass R, Scott C, Panas R, et al. Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome - results of two randomized, placebo-controlled studies. Aliment Pharmacol Ther. 2009;29:329-41.
34. Cryer B, Drossman DA, Cryer WD, Webster L, Habibi S, Wang M. Analysis of Nausea in Clinical Studies of Lubiprostone for the Treatment of Constipation Disorders. Dig Dis Sci. 2017;62:3568-78.
35. Spierings ELH, Brewer RP, Rauck RL, Losch-Beridon T, Mareya SM. Lubiprostone for Opioid-Induced Constipation Does Not Interfere with Opioid Analgesia in Patients with Chronic Noncancer Pain. Pain Pract. 2017;17:312-9.
36. Jamal MM, Adams AB, Jansen J-P, Webster LR. A Randomized, Placebo-Controlled Trial of Lubiprostone for Opioid-Induced Constipation in Chronic Noncancer Pain. Am J Gastroenterol. 2015;110:725-32.
37. Chang L, Cryer WD, Drossman D, Losch-Beridon T, Wang M, Lichtleen P, et al. Effects of baseline abdominal pain and bloating on response to lubiprostone in patients with irritable bowel syndrome with constipation. Aliment Pharmacol Ther. 2016;44:1114-22.
38. 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;25:1351-61.
39. Spierings ELH, Drossman DA, Cryer B, Mazen Jamal M, Losch-Beridon T, Mareya SM, et al. Efficacy and Safety of Lubiprostone in Patients with Opioid-Induced Constipation: Phase 3 Study Results and Pooled Analysis of the Effect of Concomitant Methadone Use on Clinical Outcomes Pain Med. 2018;19:1184-94.
40. Li F, Fu T, Tong W-D, Liu B-H, Li C-X, Gao Y, et al. Lubiprostone Is Effective in the Treatment of Chronic Idiopathic Constipation and Irritable Bowel Syndrome. Mayo Clin Proc. 2016;91:456-68.
41. Chey WD, Drossman DA, Johanson JF, Scott C, Panas RM, Ueno R. Safety and patient outcomes with lubiprostone for up to 52 weeks in patients with irritable bowel syndrome with constipation. Aliment Pharmacol Ther. 2012;35:587-99.
42. Lembo AJ, Johanson JF, Parkman HP, Rao SS, Miner PB, Ueno R. Long-Term Safety and Effectiveness of Lubiprostone, a Chloride Channel (CIC-2) Activator, in Patients with Chronic Idiopathic Constipation. Dig Dis Sci. 2011;56:2639-45.
43. Mangera A, Chapple CR, Kopp ZS, Pleshed M. The placebo effect in overactive bladder syndrome. Nat Rev Urol. 2011;8:495-503.
44. Vase L, Wartolowska K. Pain, placebo, and test of treatment efficacy: a narrative review. Br J Anaesth. 2019;123:e254-62.
45. Gu AP, Gu CN, Ahmed AT, Murad MH, Wang Z, Kallmes DF, et al. Sham surgical procedures for pain intervention result in significant improvements in pain: systematic review and meta-analysis. J Clin Epidemiol. 2017;83:18-23.