

# Lubiprostone in the treatment of chronic idiopathic constipation: an update on health-related quality of life and patient-reported outcomes

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**Abstract:** Chronic idiopathic constipation, if inadequately treated, can be bothersome with a detrimental effect on patients' quality of life (QOL). This may also result in frequent health care visits, increasing the burden of this ailment's medical cost. Management strategies, focused on lifestyle changes, include increased exercise, a high-fiber diet, and toilet training. Pharmacologic options include fiber supplementation, laxatives, serotonergic agents, and prosecretory agents such as lubiprostone. In this review, we were able to conclude that lubiprostone, when used for chronic idiopathic constipation, has a significantly beneficial effect on both patients' symptoms and their QOL. In multiple randomized controlled trials, it has been found to have increased the number of spontaneous bowel movements at different time endpoints. Corresponding improvements were also observed for abdominal bloating, discomfort, stool frequency, and straining symptoms among patients.

**Keywords:** functional, gastrointestinal disorders, spontaneous bowel movements, secretory agents, abdominal pain, cost-effectiveness

## Introduction

Lubiprostone is regarded to be a safe drug for short-term use with minimal side effects; however, its long-term safety profile is yet to be determined.

Unfortunately, despite lubiprostone's efficacy and great safety profile, it is currently underutilized in medical setting, with its high cost being the major limiting factor. Due to a lack of comparison with standard treatment modalities for severe constipation, its role in guideline-directed therapy is yet to be determined.

Constipation is one of the most common ambulatory gastrointestinal (GI) conditions, with around 3.1–5.7 million outpatient clinic visits per year.<sup>1,2</sup> Constipation is more common in women and in populations from lower socioeconomic classes.<sup>3</sup> Chronic idiopathic constipation (CIC) is defined as pain, difficulty, or lack of periodicity in defecation, without an identifiable organic cause.<sup>4</sup> The pooled prevalence of CIC is reported to be around 10%–15%.<sup>3,5</sup>

About 70% of these patients have symptoms of constipation for >2 years.<sup>6</sup> In one study, 89% of patients reported little or no improvement in their condition over a 12- to 20-month period.<sup>7</sup> The three most prevalent symptoms are straining, hard stool, and bloating.<sup>6</sup> Around 50% of patients reported that their quality of life (QOL) was affected by chronic constipation and expressed dissatisfaction with their current management.<sup>6</sup>

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Given the chronicity and suboptimal treatment of this ailment, the symptoms can often be debilitating and limiting.<sup>8</sup> These patients may present repeatedly for evaluation of their constipation symptoms over prolonged periods of time. A population-based case-control study compared the outpatient cost of CIC patients over 2 years to be significantly higher than that of controls, when adjusted for comorbidities, age, and sex (US\$6,284 vs US\$5,254, respectively).<sup>1</sup>

Given the significant impact of CIC on patients' QOL, along with the economic burden on patients and the health care system, the efficacy and cost-effectiveness of various treatment methods should be evaluated. Treatment options include dietary changes, lifestyle modifications, and pharmacologic interventions. Pharmacologic treatment approaches for CIC include fiber supplementation, laxatives (eg, polyethylene glycol, lactulose, sodium picosulfate), serotonergic agents (eg, prucalopride), and prosecretory agents such as linaclotide or lubiprostone.<sup>5</sup> Long-term effects of lubiprostone include an increased number of spontaneous bowel movements (SBMs) and improvement in the QOL of patients with CIC.<sup>9</sup> In this article, we will review the role of lubiprostone in further detail.

## Mechanism of action

Lubiprostone was approved by the Food and Drug Administration in 2006 to help treat chronic constipation in adults.<sup>10</sup> This agent is a prostone analog and a selective type two chloride channel activator.<sup>11</sup> It works on the apical surface of the intestinal epithelium to activate the chloride channel to allow luminal influx of chloride and water.<sup>5</sup> This results in an increase in intestinal water and chloride content, in turn increasing the intestinal and colonic motility and stool passage.<sup>11,12</sup>

## Efficacy of lubiprostone

We have summarized all published randomized controlled trials (RCTs) involving lubiprostone in Table 1. Its effect on SBM, disease-specific QOL, global QOL, GI symptoms (discomfort and bloating), and common adverse events are discussed below.

## Spontaneous bowel movements

An RCT showed that patients treated with lubiprostone experienced more SBMs at week 1 compared with placebo (5.89 vs 3.99,  $P=0.0001$ ).<sup>13</sup> The number of SBMs observed in the first 24 hours was significantly greater than was observed with placebo (61.3% vs 31.4%,  $P<0.0001$ ).<sup>13</sup> At each assessment, SBM frequency and percentages of full

responders ( $\geq 4$  SBMs per week) were significantly greater among lubiprostone-treated patients than among those treated with placebo ( $P\leq 0.0171$ ).<sup>13</sup> Patients in the treatment group reported sustained improvement in frequency, consistency, and other constipation symptoms over 4 weeks of treatment and improvement in abdominal bloating as early as 1 week.<sup>13</sup> They also reported increased effectiveness of their treatment at 4 weeks when compared with placebo ( $P<0.0004$ ).<sup>13</sup> GI-related disorders were the most common adverse events in both treatment groups.<sup>13</sup>

In another double-blinded RCT, mean SBM frequencies were again observed to be higher for lubiprostone groups (5.1–6.1) vs placebo (3.8;  $P<0.05$ ).<sup>14</sup> Most patients taking lubiprostone (at 48 and 72  $\mu\text{g}/\text{day}$ ) had an SBM within the first 24 hours ( $P\leq 0.009$ ).<sup>14</sup> A comparison of the doses showed that SBM frequencies at the end of 1 week were higher for doses 48 or 72  $\mu\text{g}/\text{day}$  ( $P\leq 0.003$ ); at the end of week 2, all three lubiprostone doses (ie, 24, 48, or 72  $\mu\text{g}/\text{day}$ ) yielded significantly higher SBM rates than did placebo ( $P\leq 0.020$ ).<sup>14</sup> The most commonly reported side effects were nausea, headache, and diarrhea.<sup>14</sup>

Another multicenter RCT by the same investigators reported a significant increase in SBMs at week 1 (5.69 vs 3.46,  $P=0.0001$ ), with progressively increasing SBMs also reported at weeks 2, 3, and 4 ( $P\leq 0.002$ ).<sup>15</sup> Fifty-four percent more patients given lubiprostone experienced an SBM within 24 hours and 32% more patients within 48 hours of their first dose.<sup>15</sup> In addition, fewer patients in the lubiprostone subgroup needed alternative rescue medications during each treatment week. Corresponding improvements were observed for abdominal bloating, discomfort, stool frequency, and straining ( $P\leq 0.0003$ ).<sup>15</sup> The two most common treatment-related adverse events were nausea (31.7%) and headache (11.7%).<sup>15</sup>

Similar results were reported by researchers in Japan. They reported that daily intake of lubiprostone induced an increase in the weekly average number of SBMs at week 1 (increase of  $3.7\pm 2.8$ ), compared with placebo (increase of  $1.3\pm 1.8$ ;  $P<0.001$ ).<sup>16</sup>

A randomized controlled Phase 3 trial was conducted across multiple centers in Japan.<sup>17</sup> The findings revealed that the number of SBMs in 1 week increased with increasing doses of lubiprostone (placebo,  $1.5\pm 0.4$ ; 16  $\mu\text{g}$ ,  $2.3\pm 0.4$ ; 32  $\mu\text{g}$ ,  $3.5\pm 0.5$ ; 48  $\mu\text{g}$ ,  $6.8\pm 1$  mean  $\pm$  standard error per week;  $P<0.0001$ ).<sup>17</sup> These primary endpoint results applied to patients with or without irritable bowel syndrome (IBS). Dose dependency was also seen for the secondary efficacy endpoints. Only 19.4% of patients reported one or more minimal side effects.<sup>17</sup>

**Table 1** Summary of evidence from RCT for SBM, disease-specific QOL, global QOL, GI symptoms (discomfort and bloating), and common adverse events

Reference study	Study design	Number (n)	Study duration	Dosage/day	SBM within 24 and/or 48 hours	SBM/week	Disease-specific QOL	Global QOL	Abdominal discomfort severity score (0–4)	Bloating severity score (0–4)	Common adverse events
Johanson and Ueno, 2007 <sup>14</sup>	DB-RCT, parallel group, placebo controlled	129	3 weeks	24 µg 48 µg 72 µg placebo	Higher 44.8% 59.4% 63.6% 27.3% P=0.008	Higher Week 1 (P=0.006) Week 2 (P=0.014) Week 3 (P=0.046)	N/A	N/A	No significant difference	1.4 (72 µg) vs 1.9 (placebo) (P=0.006)	Nausea (n=33) Diarrhea (n=10)
Johanson et al, 2008 <sup>15</sup>	Multicenter, DB-RCT, parallel group, placebo controlled	242	4 weeks	48 µg	Higher 56.7% vs 36.9% P=0.0024	(5.59–6.02) vs (3.5–3.7) P<0.002	N/A	N/A	1.23 vs 1.52 P<0.045	1.49 vs 1.75 P<0.031	Nausea (n=38) Headache (n=14)
Barish et al, 2010 <sup>13</sup>	Multicenter, Phase 3, DB-RCT, parallel group, placebo controlled	237	4 weeks	48 µg	Higher 61.3% vs 31.4% P<0.001	Mean SBM/week 5.89 vs 3.99 P<0.001	N/A	N/A	No significant difference	1.71 vs 1.44 P=0.03 (only significant for week 1)	Nausea (n=25) Abdominal pain (n=8) Flatulence (n=7)
Fukudo et al, 2011 <sup>17</sup>	Multicenter, Phase 2, DB-RCT, parallel group, placebo controlled	170	2 weeks	Placebo 16 µg 32 µg 48 µg	Higher 57.1% 73.2% 74.4% 97.7% (P<0.0001 at 48 hours only)	Higher 1.5 2.3 3.5 6.8 (CIC only P<0.0001)	No significant difference	No significant difference	N/A	N/A	Diarrhea (n=12) Nausea (n=10)
Fukudo et al, 2015 <sup>16</sup> Study 1 and 2	Multicenter Phase 3, DB-RCT, parallel group, placebo controlled 48-week observational	124	4 weeks	48 µg 24 µg	Higher 58.1% vs 30.6% P<0.04	Higher 3.7 vs 1.3 P<0.01 (at the end of week 1)	Improved P<0.0001	Improved in some domains only <sup>a</sup>	N/A	N/A	Diarrhea (n=9) Nausea (n=9)

**Note:** <sup>a</sup>Domains included bodily pain, physical function, general health, role emotional, and vitality (at 24 weeks only).

**Abbreviations:** DB-RCT, double-blind randomized controlled trial; GI, gastrointestinal; N/A, not applicable; SBM, spontaneous bowel movements QOL, quality of life.

A meta-analysis of three RCTs<sup>13–15</sup> concluded that 45.1% of patients receiving lubiprostone failed to respond to therapy compared to 66.9% of patients receiving placebo, with a number needed to treat of 4 and a relative risk (RR) of 0.67 (95% CI)<sup>18</sup> with no significant heterogeneity between studies ( $I^2=30\%$ ,  $P=0.24$ ).<sup>18</sup> Total number of adverse events were significantly higher with lubiprostone (RR =1.79, 95% CI [1.21, 2.65], number needed to harm [NNH] =4, 95% CI [3, 6]), with the more frequent side effects being nausea and diarrhea.<sup>18</sup> There was no significant difference in the rates of abdominal pain or headaches among patients.<sup>18</sup>

Another meta-analysis assessed the effect on SBM in patients on lubiprostone compared to placebo.<sup>19</sup> It demonstrated no difference in the frequency of SBM (combined standardized difference in mean change, 0.137; 95% CI 0.127, 0.400;  $P=0.34$ ) with the caveat that heterogeneity between studies was large ( $I^2=67.0\%$ ;  $P=0.05$ ).<sup>19</sup>

## Quality of life

Fukudo et al evaluated the effect on QOL as part of the double-blind placebo-controlled RCT arm and the observational arm of the study.<sup>16</sup> Short Form-36 (SF-36) health survey and IBS-QOL were used to assess the difference between lubiprostone and placebo. The SF-36 score is based on points assessing mental health, physical functioning, pain control, general health, social performance, vitality, and role limitations due to emotional or physical problems. The IBS-QOL is a patient-reported, point-based questionnaire revolving around QOL measures, which helps assess the impact of symptoms and treatment on patients' daily life.

The trial arm failed to show significant differences in SF-36 and IBS-QOL scores when compared to placebo at baseline.<sup>16</sup> Interestingly, the observational part of the study showed an improvement of IBS-QOL scores at both weeks 24 and 48 of lubiprostone treatment when compared to baseline QOL scores ( $P<0.0001$  for both at weeks 24 and 48).<sup>16</sup> Statistically significant outcomes were also observed in only some subscales of general QOL when measured by SF-36 health survey, both at 24 and 48 weeks, respectively. These domains included physical functioning ( $P=0.0010$  and  $P=0.0019$ ), bodily pain ( $P=0.021$  and  $P<0.0001$ ), general health ( $P=0.0136$  and  $P=0.0001$ ), vitality at 24 weeks only ( $P=0.0192$ ), and role emotional domain ( $P=0.0008$  and  $P=0.0301$ ).<sup>16</sup>

## Abdominal pain and bloating

A recent systematic review and meta-analysis demonstrated a significant difference in the degree of abdominal pain

after 1 week of treatment (standardized difference in mean change, 0.547; 95% CI 0.185, 0.909;  $P=0.003$ ). The difference, however, was not seen at 1- and 3-month intervals.<sup>20</sup> It is important to note that sustained improvement in abdominal bloating was shown at the end of 3 months.<sup>20</sup>

## Safety profile of lubiprostone

Nausea is the most commonly reported side effect of lubiprostone.<sup>21</sup> The incidence of nausea in lubiprostone-treated patients ranged from 11.4% to 31.1%.<sup>21</sup> Patients reported mild to moderate severity of nausea, which was most commonly observed within the first 5 days of treatment.<sup>21</sup>

Based on the results of the abovementioned trials, the most commonly reported side effects were minor to moderate in intensity. Diarrhea (RR =4.46; 95% CI [1.28, 15.48]) and nausea (RR =7.27; 95% CI [3.76, 14.06]) occurred significantly more frequently with lubiprostone (RR =1.79; 95% CI [1.21, 2.65], NNH =4; 95% CI [3, 6]), but no significant difference in the rates of abdominal pain or headache was detected.<sup>18</sup>

Johanson et al reported that 66% of patients receiving lubiprostone experienced adverse events, compared with 58% of patients receiving placebo.<sup>22</sup> In addition, 17% of patients taking lubiprostone complained of nausea, compared with 4% of patients taking placebo. These differences were not statistically significant.<sup>22</sup> Diarrhea was the only adverse event that occurred more frequently among those receiving lubiprostone (NNH =10, 95% CI [5, 25]).<sup>22</sup>

Another study using pooled data stated that 50% of patients receiving lubiprostone reported at least one adverse event.<sup>23</sup> Interestingly, 51% of patients in the placebo group also reported at least one adverse event.<sup>23</sup> Diarrhea occurred in 6% of lubiprostone-treated patients compared with 4% of placebo-treated patients.<sup>23</sup> Nausea was reported by 8% of those treated with lubiprostone and 4% of those treated with placebo.<sup>23</sup>

## Cost-effectiveness

Lubiprostone's availability and utility is limited by its high costs. A decade-long study in the UK was designed to evaluate the cost-effectiveness of lubiprostone in comparison to prucalopride, placebo, and immediate referral to secondary care in CIC in an economic model that was used by the UK National Institute for Health and Care Excellence.<sup>24</sup> The researchers concluded that lubiprostone was more effective, but also costlier, than placebo and immediate referral to secondary care. They compared the incremental cost-effectiveness ratios of £58,979 and £21,152, respectively.<sup>24</sup>

Huang et al also concluded that linaclotide was cheaper in comparison to lubiprostone with regard to comparable response based on global assessment tool (US\$946 vs US\$1,015, respectively) and SBM frequency (US\$727 vs US\$737, respectively).<sup>19</sup>

## Conclusion

Based on the current literature, the prosecretory agent lubiprostone is effective in the treatment of CIC with benefit seen with short-term treatment. Long-term treatment still requires critical evaluation. Due to a lack of comparison with standard treatment modalities for severe constipation, however, its role in guideline-directed therapy is yet to be determined. Although lubiprostone has been deemed to be a safe drug for short-term use with minimal side effects, its long-term safety profile is yet to be determined. The high cost of lubiprostone may be a serious limiting factor.

## Disclosure

The authors report no conflicts of interest in this work.

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