Differences in efficacy and safety of lubiprostone used for idiopathic vs opioid-induced constipation: meta-analysis of East Asian and Western populations

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(Rceived 29 November, 2019; Accepted 4 December, 2019)

Several secretagogues, such as lubiprostone, have been developed for the treatment of constipation in the last 10 years. It is unclear whether the efficacy of lubiprostone for spontaneous bowel movement (SBM) and the adverse events are similar between idiopathic and opioid-induced constipation and between East-Asian and Western populations. We conducted a meta-analysis to compare efficacy and safety of lubiprostone in two populations with idiopathic vs opioid-induced constipation. The PubMed and Cochrane databases were searched for relevant randomized control trials (RCTs) investigating the efficacy and safety that were published in English up to March 2019. Compared with the placebo groups in idiopathic and opioid-induced constipation, the lubiprostone groups significantly improved in 24-h SBM frequency [relative risk: 1.28, 95% confidence interval, 1.11–1.49, and 1.23, 1.14–1.32] and weekly frequency >3 SBM/week (1.68, 1.41–2.01, and 1.43, 1.01–2.04), respectively. Although the incidence of adverse events was similar between idiopathic and opioid-induced constipation, the incidence of nausea in Western populations with idiopathic constipation was significantly higher (29.2%) than that in East-Asian populations (10.0%, p<0.001). In conclusion, lubiprostone effectively improved SBM frequency, irrespective of the etiology of constipation and population. The incidence of nausea was significantly higher in Western populations.

Key Words: lubiprostone, constipation, opioid, secretagogues

Chronic constipation, including idiopathic functional constipation and opioid-induced constipation, is one of the most common gastrointestinal disorders in the world, with an estimated global prevalence of 14%. Functional constipation by the Rome IV criteria was defined as the presence of ≥2 of the following symptoms for at least 3 months: straining during at least 25% of defecations, passage of hard lumpy stool in at least 25% of defecations, sensation of incomplete evacuation for at least 25% of defecations, sensation of anal rectal obstruction/blockage for at least 25% of defecations, and manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor). In general, the pathophysiology of chronic constipation is characteristically heterogeneous. Therefore, although it is necessary to select an appropriate treatment method for each patient according to the different individual’s pathophysiology of chronic constipation, many chronic constipation patients are refractory to multiple pharmacological treatments. Because chronic constipation is associated with impaired quality of life, increased risk of colorectal cancer, and is responsible for a substantial economic health service burden, further treatment options, such as dietary manipulation, interventions that modify the microbiota, and biofeedback have been used in these patients.

Opioid-containing substances are used for management of moderate-to-severe chronic pain. Opioid-induced constipation is a common problem among these patients. The Rome IV criteria defined opioid-induced constipation as new, or escalating, symptoms of constipation when initiating, changing, or increasing opioid therapy with further clinical features, such as the sensation of incomplete evacuation and <3 spontaneous bowel movements (SBMs) per week. Opioid-induced constipation is the most common subtype of opioid-induced gastrointestinal dysfunction (i.e., nausea, vomiting, bloating, and gastroesophageal reflux-related symptoms) that occurs in 51–87% of cancer patients receiving opioids. Opioids adversely impact the sensorimotor function of the gastrointestinal tract, acting as exogenous agonists on the enteric nervous system.

Global guidelines for treatment of chronic constipation are available in the UK, America, Europe, and Japan. In the guidelines of the American College of Gastroenterology (ACG), the use of secretagogues, fiber supplements, polyethylene glycol, lactulose, sodium picosulfate, bisacodyl, and prucalopride are mentioned as possible treatments for chronic constipation. In the Japanese guideline for chronic constipation, although magnesium oxide is recommended to use as first-line drug to treat constipation, due to the ability of magnesium oxide to improve bowel movement by drawing water into the large intestine. However, patients taking magnesium oxide are required to pay attention for increase of serum magnesium level. Several secretagogues have been developed for the treatment of chronic constipation in the last 10 years, and their efficacy has been shown to be superior to placebo in increasing the frequency of SBMs. The guidelines of ACG state that “secretagogues (linaclotide and lubiprostone) are effective in the treatment of chronic idiopathic constipation,” and strongly recommend them based on high-quality evidence. Of several secretagogues, lubiprostone is an orally active prostane that locally and selectively activates chloride channel type 2 (CIC-2) on the apical surface of intestinal epithelium and enhances intestinal fluid secretion without altering serum electrolyte levels. The resulting chloride and water influx into the intestinal lumen is associated with a substantial economic health service burden. Further treatment options, such as dietary manipulation, interventions that modify the microbiota, and biofeedback have been used in these patients.

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Advance Publication
results in faster transit through the small intestine and colon. Lubiprostone increases the frequency of SBMs, decreases colonic transit time, and improves quality of life compared with placebo. Many clinical trials have shown that lubiprostone improves abnormal bowel habits in patients with either idiopathic or opioid-induced constipation.\(^{(13-21)}\) Due to the small sample size in each report, however, it remains unclear whether efficacy and safety of lubiprostone are similar between the two diseases, or among different populations (Asian and Western) with different risks for chronic constipation (i.e., food, life-style and microbiota).\(^{(22,23)}\) We aimed to perform a meta-analysis to compare the efficacy and safety of lubiprostone between patients with idiopathic and opioid-induced constipation.

**Methods**

**Search strategy and inclusion criteria.** For a meta-analysis to investigate the efficacy and safety of lubiprostone in patients with idiopathic and opioid-induced constipation, we conducted a search of randomized controlled trials (RCTs). Three researchers (MS, MM, and HM) independently searched both the PubMed and Cochrane databases using the terms “lubiprostone” and “constipation,” and reviewed titles and abstracts for all studies (Fig. 1). The inclusion criteria were: (1) RCTs published in English up to March 2019; (2) studies comparing idiopathic and opioid-induced constipation patients receiving lubiprostone with those receiving placebo with respect to improvement of SBM frequency and incidence of treatment-related adverse events. Bowel habits were evaluated in terms of SBM frequency over 24 h, 48 h, and >3 SBMs/week. The full texts of potential studies were then screened to select studies meeting the inclusion criteria, and duplicated studies and multiple versions of the same study were excluded. The exclusion criteria were (1) single-arm studies without a non-treatment control group, (2) studies of irritable bowel syndrome patients, and (3) non-RCT.

Authors, publication year, country where the study was conducted, population demographics, study design, numbers of patients, follow-up periods after treatment, patient demographics (sex and age), doses of lubiprostone, dosing times of lubiprostone, definition of constipation, bowel habits, and incidence of treatment-related adverse events were extracted from each study.

**Statistical analysis.** Subgroup analyses were conducted with regard to kinds of constipation (i.e., idiopathic and opioid-induced constipation) and where the study was conducted (i.e., East Asian and Western populations). Publication bias in each study was evaluated by funnel plots and Egger’s test. Heterogeneity was evaluated by I\(^2\) value and Cochran’s Q. All meta-analyses were conducted using open-source statistical software (Review Manager ver. 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). All \(p\) values are two-sided, and \(p<0.05\) was considered statistically significant. Calculations were performed using commercial software (SPSS ver. 20, IBM Inc; Armonk NY).
Table 1. Characteristics of the randomized control trials

| Authors (year)         | Country            | Disease                | Follow-up periods (weeks) | Number of patients/control (n) | Age (years) | Sex (male/female) | Dose of lubiprostone per day |
|------------------------|--------------------|------------------------|---------------------------|-------------------------------|-------------|------------------|------------------------------|
| Johnson JF, et al. (2007)<sup>13</sup> | USA                | Chronic idiopathic constipation | 3                         | 94/33                         | 48.8        | 10/84            | 24 g (24 g od), 48 g (24 g bid), 72 g (24 g tid) |
| Johnson JF, et al. (2008)<sup>14</sup> | USA                | Chronic idiopathic constipation | 4                         | 120/122                       | 48.02 ± 12.28 | 13/107          | 48 g (24 g bid)               |
| Barish CF, et al. (2010)<sup>15</sup>  | USA                | Chronic idiopathic constipation | 4                         | 119/118                       | 46.2 ± 12.13 | 15/104           | 48 g (24 g bid)               |
| Fukudo S, et al. (2011)<sup>16</sup>  | Japan              | Chronic idiopathic constipation | 2                         | 128/42                        | 39.9        | 13/115           | 16 g (8 g bid), 32 g (16 g bid), 48 g (24 g bid) |
| Fukudo S, et al. (2015)<sup>17</sup> | Japan              | Chronic idiopathic constipation | 4                         | 62/62                         | 42.7 ± 16.4 | 6/56             | 48 g (24 g bid)               |
| Christie J, et al. (2017)<sup>18</sup> | USA                | Chronic idiopathic constipation + DM | 8                         | 37/39                         | 56.9 ± 9.1 | 14/23            | 48 g (24 g bid)               |
| Cryer B, et al. (2014)<sup>19</sup>  | USA/Canada         | Opioid-induced constipation | 12                        | 210/208                       | 50.5 ± 9.7  | 78/132           | 48 g (24 g bid)               |
| Mazen Jamal M, et al. (2015)<sup>20</sup> | USA/Europe         | Opioid-induced constipation | 12                        | 214/217                       | 51.9 ± 9.1  | 80/134           | 48 g (24 g bid)               |
| Spiering ELH, et al. (2018)<sup>21</sup> | USA/Canada | Opioid-induced constipation | 12                        | 223/212                       | 48.9 ± 9    | 83/140           | 48 g (24 g bid)               |

bid, twice-daily dosing; DM, diabetes mellitus; IBS, irritable bowel syndrome; od, once-daily dosing; tid, three-times daily dosing.

**Results**

**Literature search and data extraction.** The search strategy yielded 261 potentially eligible studies from the PubMed and Cochrane databases and 12 studies by hand-search through other sources and papers (Fig. 1). Twenty-five studies were selected from the extracted studies. Of those, four RCTs for irritable bowel syndrome, 1 RCT for Parkinson disease-induced constipation, nine reviews, and two data-not-available studies were excluded. Thus, nine studies were included in the meta-analysis (Fig. 1).<sup>13–21</sup> Six RCTs in patients with idiopathic constipation and 3 RCTs in patients with opioid-induced constipation were investigated for efficacy (achievement of SBM within 24 h, 48 h, and >3 SBMs/week) and safety (incidence of treatment-related adverse events).

Ultimately, a total of 2,234 patients with chronic constipation (950 patients with idiopathic constipation and 1,284 patients with opioid-induced constipation) were included in this analysis (Table 1). The mean or median follow-up period after treatment ranged from 2–12 weeks, and the mean or median age of patients ranged from 39.9–56.9 years (Table 1). The ratio of females was 62.2–90.3%. Dosing of lubiprostone ranged from 16 µg/day (8 µg bid) to 72 µg/day (24 µg tid). In all three studies investigating patients with opioid-induced constipation, the daily dose of lubiprostone was 48 µg/day (24 µg bid).

**Meta-analysis for improvement in SBM after lubiprostone.**

In patients with chronic constipation of both types, 571 (48.8%) among 1,170 patients who received lubiprostone achieved an SBM within 24 h, and 324 (32.0%) of 1,014 patients on placebo achieved the same (Fig. 2A). The relative risk (RR) for achievement of an SBM within 24 h with the lubiprostone group was 1.55 (95% CI: 1.32–1.83) (<0.00001). In all patients with both types, 671 (70.1%) among 957 lubiprostone patients achieved an SBM within 48 h, and 491 (56.9%) among 863 patients on placebo achieved (Fig. 2D). The RR for achievement of an SBM within 48 h with the treatment group vs controls was 1.23 (95% CI: 1.14–1.32) (<0.00001). Achievement of >3 SBMs/week was experienced by 46.1% (281/609) patients after treatment with lubiprostone, and by 27.7% (153/552) patients on placebo (Fig. 3A). The RR for achievement of a >3 SBMs/week with the treatment group was 1.63 (95% CI: 1.39–1.91) (<0.00001).

**Subgroup analysis between different baseline diseases and between different doses of lubiprostone.** We divided chronic constipation patients into idiopathic and opioid-induced constipation subgroups (Fig. 2B, C, E and F). For idiopathic constipation, RRs for SBMs within 24 and 48 h with the lubiprostone group vs placebo were 1.83 (95% CI: 1.54–2.16) and 1.32 (1.17–1.49), respectively (<0.00001). Achievement of >3 SBMs/week was 56.5% (223/395) after lubiprostone, and 33.4% (112/335) in the placebo group (Fig. 3B). The RR for achievement of a >3 SBMs/week with the lubiprostone group vs placebo was 1.68 (95% CI: 1.41–2.01) (<0.00001).

For opioid-induced constipation patients, achievement of an SBM within 24 and 48 h in the lubiprostone group was higher than those in the placebo group (Fig. 2C and F). The RRs for achievement of an SBM within 24 and 48 h with the lubiprostone group was 1.28 (95% CI: 1.11–1.49) and 1.18 (1.08–1.29), respectively (<0.0007 and 0.0003). There was only one study showing achievement of >3 SBMs/week for opioid-induced constipation (Fig. 3C).<sup>20</sup>

Johanson and Ueno<sup>13</sup> and Fukudo et al.<sup>16</sup> evaluated the efficacy of lubiprostone at different doses in patients with idiopathic constipation. In both studies, the bowel habits (SBM within 24 h, 48 h, and >3 SBMs/week) improved (Table 2) in a dose-dependent fashion. SBMs within 24 h with 16, 24, 32, 48 and 72 µg/day were 53.7% (22/41), 44.8% (13/29), 53.5% (23/43), 61.5% (23/377), 63.6% (21/33), respectively (<0.320).

**Meta-analysis of adverse effects during treatment.**

The incidence rate of treatment-related adverse events after dosing of lubiprostone was 24.2–50.8% in idiopathic constipation and 23.1–36.5% in opioid-induced constipation, which was higher than those in the control groups (Table 3 and Fig. 4A–C). The RRs for incident of treatment-related adverse events in all patients with chronic constipation, idiopathic and opioid-induced constipation after treatment were 1.91 (95% CI: 1.49–2.43), 2.32 (1.80–2.99) and 1.78 (1.18–2.69), respectively, compared to controls (p = 0.00001). The incidence rate of nausea as a major adverse event in patients with idiopathic constipation (22.9%, 128/560) was higher than that in patients with opioid-induced constipation (12.9%, 83/643) (Fig. 5B and C), (p = 0.03 and p<0.0001, respectively).

When divided into Western and East Asian populations, although lubiprostone increased the risk of treatment-related adverse events including nausea, the incidence of nausea in Western populations with idiopathic constipation was significantly higher (29.2%) than that in East Asian population (10.0%) (<0.0001) (Fig. 5D and E). There was no study investigating the adverse effects of lubiprostone for patients with opioid-induced constipation.
A All patients: An SBM within 24 h

| Study or Subgroup | Experimental Events | Control Events | Risk Ratio M-H, Random, 95% CI | Year |
|-------------------|---------------------|----------------|-----------------------------|------|
| Johanson JF (2007) | 53 | 94 | 9 | 33 | 6.1% | 2.07 [1.15, 3.71] | 2007 |
| Johanson JF (2008) | 68 | 120 | 45 | 122 | 15.0% | 1.54 [1.16, 2.03] | 2008 |
| Barkin CF (2010)  | 73 | 119 | 37 | 118 | 14.0% | 1.96 [1.45, 2.65] | 2010 |
| Fukudo S (2011)   | 78 | 128 | 11 | 42 | 7.1% | 2.33 [1.37, 3.94] | 2011 |
| Cryer B (2014)    | 81 | 210 | 58 | 208 | 15.1% | 1.38 [1.05, 1.83] | 2014 |
| Fukudo S (2015)   | 36 | 62 | 19 | 62 | 9.4% | 1.89 [1.33, 2.61] | 2015 |
| Mazen Jamal M (2015) | 108 | 214 | 81 | 217 | 18.1% | 1.35 [1.09, 1.68] | 2015 |
| Spiering ELH (2018) | 74 | 223 | 64 | 212 | 15.2% | 1.10 [0.83, 1.45] | 2018 |

Total (95% CI) | 1,170 | 2,014 | 1,000.00% | 1.55 [1.32, 1.83] |

Total events | 571 | 324 |
Heterogeneity: Tau²=0.03; Chi²=14.02, df=7 (p=0.05); P=50% |
Test for overall effect: Z=5.26 (p<0.00001)

B Idiopathic constipation: An SBM within 24 h

| Study or Subgroup | Experimental Events | Control Events | Risk Ratio M-H, Random, 95% CI | Year |
|-------------------|---------------------|----------------|-----------------------------|------|
| Johanson JF (2007) | 53 | 94 | 9 | 33 | 6.2% | 2.07 [1.15, 3.71] | 2007 |
| Johanson JF (2008) | 68 | 120 | 45 | 122 | 35.8% | 1.54 [1.16, 2.03] | 2008 |
| Barkin CF (2010)  | 73 | 119 | 37 | 118 | 30.6% | 1.96 [1.45, 2.65] | 2010 |
| Fukudo S (2011)   | 78 | 128 | 11 | 42 | 10.1% | 2.33 [1.37, 3.94] | 2011 |
| Fukudo S (2015)   | 36 | 62 | 19 | 62 | 15.2% | 1.89 [1.23, 2.91] | 2015 |

Total (95% CI) | 523 | 377 | 100.00% | 1.83 [1.54, 2.16] |

Total events | 308 | 121 |
Heterogeneity: Tau²=0.00; Chi²=2.73, df=4 (p=0.60); P=0% |
Test for overall effect: Z=7.04 (p<0.00001)

C Opioid-induced constipation: An SBM within 24 h

| Study or Subgroup | Experimental Events | Control Events | Risk Ratio M-H, Random, 95% CI | Year |
|-------------------|---------------------|----------------|-----------------------------|------|
| Cryer B (2014)    | 81 | 210 | 58 | 208 | 27.6% | 1.38 [1.05, 1.83] | 2014 |
| Mazen Jamal M (2015) | 108 | 214 | 81 | 217 | 44.4% | 1.35 [1.09, 1.68] | 2015 |
| Spiering ELH (2018) | 74 | 223 | 64 | 212 | 27.7% | 1.10 [0.83, 1.45] | 2018 |

Total (95% CI) | 647 | 637 | 100.00% | 1.28 [1.11, 1.49] |

Total events | 263 | 203 |
Heterogeneity: Tau²=0.00; Chi²=1.71, df=2 (p=0.43); P=0% |
Test for overall effect: Z=3.37 (p<0.00007)

D All patients: An SBM within 48 h

| Study or Subgroup | Experimental Events | Control Events | Risk Ratio M-H, Random, 95% CI | Year |
|-------------------|---------------------|----------------|-----------------------------|------|
| Johanson JF (2008) | 96 | 120 | 74 | 122 | 18.1% | 1.32 [1.11, 1.56] | 2008 |
| Fukudo S (2011)   | 105 | 128 | 24 | 42 | 6.6% | 1.44 [1.09, 1.89] | 2011 |
| Cryer B (2014)    | 129 | 210 | 108 | 208 | 18.0% | 1.18 [1.00, 1.40] | 2014 |
| Fukudo S (2015)   | 50 | 62 | 40 | 62 | 10.5% | 1.25 [1.00, 1.56] | 2015 |
| Mazen Jamal M (2015) | 155 | 214 | 127 | 217 | 26.0% | 1.24 [1.08, 1.42] | 2015 |
| Spiering ELH (2018) | 136 | 223 | 118 | 212 | 20.2% | 1.10 [0.93, 1.29] | 2018 |

Total (95% CI) | 957 | 863 | 100.00% | 1.23 [1.14, 1.32] |

Total events | 671 | 491 |
Heterogeneity: Tau²=0.00; Chi²=4.14, df=5 (p=0.53); P=0% |
Test for overall effect: Z=5.56 (p<0.00001)

E Idiopathic constipation: An SBM within 48 h

| Study or Subgroup | Experimental Events | Control Events | Risk Ratio M-H, Random, 95% CI | Year |
|-------------------|---------------------|----------------|-----------------------------|------|
| Johanson JF (2008) | 96 | 120 | 74 | 122 | 51.0% | 1.32 [1.11, 1.56] | 2008 |
| Fukudo S (2011)   | 105 | 128 | 24 | 42 | 19.3% | 1.44 [1.09, 1.89] | 2011 |
| Fukudo S (2015)   | 50 | 62 | 40 | 62 | 29.6% | 1.25 [1.00, 1.56] | 2015 |

Total (95% CI) | 310 | 226 | 100.00% | 1.32 [1.17, 1.49] |

Total events | 351 | 138 |
Heterogeneity: Tau²=0.00; Chi²=0.61, df=2 (p=0.74); P=0% |
Test for overall effect: Z=4.51 (p<0.00001)

F Opioid-induced constipation: An SBM within 48 h

| Study or Subgroup | Experimental Events | Control Events | Risk Ratio M-H, Random, 95% CI | Year |
|-------------------|---------------------|----------------|-----------------------------|------|
| Cryer B (2014)    | 129 | 210 | 108 | 208 | 27.8% | 1.18 [1.00, 1.40] | 2014 |
| Mazen Jamal M (2015) | 155 | 214 | 127 | 217 | 41.0% | 1.24 [1.00, 1.42] | 2015 |
| Spiering ELH (2018) | 136 | 223 | 118 | 212 | 23.2% | 1.10 [0.93, 1.29] | 2018 |

Total (95% CI) | 647 | 637 | 100.00% | 1.18 [1.08, 1.29] |

Total events | 420 | 353 |
Heterogeneity: Tau²=0.00; Chi²=1.28, df=2 (p=0.53); P=0% |
Test for overall effect: Z=3.58 (p<0.00003)

Fig. 2. Forest plot of the improvement of SBM rate over 24 h between the lubiprostone group and a control group in 8 randomized control studies (RCTs) with all 8 studies (A), the studies investigating chronic idiopathic constipation (B) and the studies investigating opioid-induced constipation (C). The forest plots for the improvement of SBM rate over 48 h between the lubiprostone group and a control group in 6 studies (D), and the studies investigating chronic idiopathic constipation (E) and opioid-induced constipation (F).
In this meta-analysis, we evaluated whether lubiprostone effectively improved abnormal bowel habits in patients with either chronic idiopathic or opioid-induced constipation. This meta-analysis of nine RCTs (six studies investigating idiopathic constipation and three investigating opioid-induced constipation) showed that lubiprostone was associated with significant improvement for an SBM within 24h, within 48h, and for >3 SBMs/week, irrespective of different populations (i.e., Western or East Asian population) or etiology of constipation (i.e., idiopathic or opioid-induced constipation). Our observations suggest that lubiprostone is helpful in patients with chronic constipation, either idiopathic or opioid-induced, to improve bowel habits and quality of life (QOL).

**Lubiprostone-induced adverse events among different populations.** Nine RCTs consisting of 2,234 patients provided lubiprostone-induced adverse event data. Among the lubiprostone-induced adverse events, chronic constipation patients who received lubiprostone were significantly more likely to experience diarrhea, abdominal pain, and nausea/vomiting compared with placebo, irrespective of constipation etiology. However, the frequencies for these events were relatively low, around 10%, in the lubiprostone-treated groups (10.0% and 5.5% for diarrhea and abdominal pain in patients with idiopathic constipation and 3.9% and 4.5% in opioid-induced constipation) and the severity of adverse events in most cases was mild–moderate. Therefore, these adverse effects were tolerated due to the high efficacy of improvement in abnormal bowel habits, suggesting that the use of lubiprostone for chronic constipation has merit to improve bowel habits with acceptable overall safety.

However, nausea, which was the most common adverse effect of lubiprostone, can limit patient compliance with drug intake. The incidence of nausea with lubiprostone may be considered the major problem for use of this drug. In fact, the incidence rate of nausea in lubiprostone was higher than that in other secretagogues, such as linaclotide. RCTs investigating efficacy and safety of linaclotide in patients with chronic constipation did not experience nausea as an adverse event. Although lubiprostone-induced nausea was not dose-dependent and typically did not lead to discontinuation of the medication, this meta-analysis showed that the incidence rate of nausea/vomiting was 23.8% in patients with idiopathic constipation and 14.9% in opioid-induced constipation. The physiological mechanism of this is unclear. In a recent study using mouse models, lubiprostone affected gastrointestinal motility by increasing gastrointestinal circular muscle contraction, but not longitudinal small intestinal smooth muscles. Gastric distention from decreased pyloric outflow and increased gastric secretion may produce nausea, especially in those with decreased compliance of the gastric wall. Surprisingly, in this study, we showed that when we divided constipation patients into Western and East Asian populations, the incidence rate of nausea in the Western population was significantly higher (29.2%) than that in East Asian (10.0%, p<0.001). The pathophysiology of idiopathic constipation is heterogeneous, and this observation might be considered to be cause by different lifestyles, genetic factors, kinds of food, and microbiota among different populations. The influence of lubiprostone on gastrointestinal motility and sensation might differ among different populations. In general, lubiprostone is well tolerated with overall high compliance due to improvement in constipation symptoms with relatively mild and self-limited nausea and there were relatively few cases of severe nausea leading to medication discontinuation. Therefore, this drug might be acceptable for patients with chronic constipation, especially in East Asian populations.

This study showed that the incidence rate of nausea/vomiting...
Table 2. Bowel habit and outcome after administration of lubiprostone

| Authors (year) | Definition of constipation | Treatment | Frequency of SBMs at baseline, % (n/n) | SBM within 24 h, % (n/n) | SBM within 48 h, % (n/n) | >3 SBMs/week, % (n/n) | Complete evacuation, % (n/n) |
|---------------|---------------------------|-----------|----------------------------------------|--------------------------|--------------------------|------------------------|---------------------------|
| Johanson JF, et al. (2007) | A history of constipation (<3 SBMs/week) and a current clinical diagnosis of constipation | Control | NA | 27.3 (9/33) | NA | 30.1 (10/33) | NA |
| | Patients had symptoms of abdominal bloating or discomfort and one or more constipation-related symptoms | 24 µg (24 µg od) | NA | 44.8 (13/29) | NA | 44.8 (13/29) | NA |
| | | 48 µg (24 µg bid) | NA | 59.3 (19/32) | NA | 43.8 (14/32) | NA |
| Johanson JF, et al. (2008) | A history of chronic constipation (an average of <3 SBMs/week) over >6 months | Control | 1.47 ± 1.33 | 36.9 (45/122) | 61.7 (74/122) | 27.9 (34/122) | NA |
| | >1 symptom associated with >25% of BM: very hard to hard stools, a sensation of incomplete evacuation, or straining at defecation | 48 µg (24 µg bid) | 1.37 ± 0.87 | 56.7 (68/120) | 80.0 (96/120) | 57.5 (69/120) | NA |
| Barish CF, et al. (2010) | <3 defecations per week during a 2-week period | Control | 1.5 ± 0.8 | 31.4 (37/118) | NA | 39.0 (46/118) | NA |
| | >1 symptom (>25% of BMs: very hard to hard stools, a sensation of incomplete evacuation, or straining at defecation) | 48 µg (24 µg bid) | 1.3 ± 0.88 | 61.3 (73/119) | NA | 59.7 (71/119) | NA |
| Fukudo S, et al. (2011) | A history of chronic constipation (<3 SBMs per week) over >6 months | Control | NA | 26.2 (11/42) | 57.1 (24/42) | NA | NA |
| | >1 symptom (lumpy or hard stools in >25% of defecations, sensation of incomplete evacuation for >25% of defecations, straining during >25% of defecations) | 16 µg (8 µg bid) | NA | 53.7 (22/41) | 73.2 (30/41) | NA | NA |
| | | 32 µg (16 µg bid) | NA | 53.5 (23/43) | 74.4 (32/43) | NA | NA |
| | | 48 µg (24 µg bid) | NA | 75.0 (33/44) | 97.7 (43/44) | NA | NA |
| Fukudo S, et al. (2015) | <3 defecations per week during a 2-week baseline/screening period | Control | 1.68 ± 0.77 | 30.6 (19/62) | 64.5 (40/62) | 35.5 (22/62) | NA |
| Christie J, et al. (2017) | Patients with constipation as defined by the Rome III criteria and with DM | Control | 1.65 ± 0.78 | 58.1 (36/62) | 80.6 (50/62) | 51.6 (32/62) | NA |
| Cryer B, et al. (2018) | <3 defecations per week during the screening period | 48 µg (24 µg bid) | 2.33 ± 2.14 | 27.9 (58/208) | 51.9 (108/208) | NA | NA |
| | >1 symptom (>25% of bowel movements: very hard or hard stools, a sensation of incomplete evacuation, or moderate to very severe straining) | 48 µg (24 µg bid) | 1.4 ± 1.1 | 38.6 (81/210) | 61.4 (129/210) | NA | NA |
| Mazen Jamal M, et al. (2019) | <3 defecations per week without the use of a laxative or stool softener during the last 2 weeks of the screening period | Control | 1.4 ± 0.8 | 37.3 (81/217) | 58.5 (127/217) | 18.9 (41/217) | NA |
| | >1 symptom (>25% of bowel movements: hard or very hard stools, sensation of incomplete evacuation, or moderate straining) | 48 µg (24 µg bid) | 1.3 ± 0.8 | 51.4 (108/214) | 72.4 (155/214) | 27.1 (58/214) | NA |
| Spiering ELH, et al. (2018) | <3 defecations per week | Control | 1.6 ± 1.3 | 30.2 (64/212) | 55.7 (118/212) | NA | NA |
| | >1 symptom (>25% of bowel movements: hard or very hard stools, sensation of incomplete evacuation, or moderate to very severe straining) | 48 µg (24 µg bid) | 1.6 ± 1.3 | 33.2 (74/223) | 61.0 (136/223) | NA | NA |

bid, twice-daily dosing; DM, diabetes mellitus; NA, not available; od, once daily dosing; SBM, spontaneous bowel movement; tid, three-times daily dosing.

in patients with idiopathic constipation was significantly higher than that in opioid-induced constipation. Because most cancer patients using opioids receive antiemetic drugs, it is unclear whether this caused the difference in the incidence rate of nausea between patients with idiopathic constipation and opioid-induced constipation.

### Lubiprostone-induced improvement of constipation

Among Japanese populations <70 years, the prevalence of functional constipation according to the Rome III criteria was 8.76% and the frequency was higher in females than in males. Several new drugs have been developed for the treatment of chronic constipation in the last 20 years and were shown to increase the number of SBMs as well as decrease colonic transit time and improve QOL. In fact, the numbers needed to treat (NNT), estimated from placebo-controlled trials comparing these drugs with placebo in idiopathic constipation, were NNT 3 (95% CI: 2 to 4) for osmotic and stimulant laxatives, NNT 4 (95% CI: 3 to 7) for lubiprostone, NNT 6 (95% CI: 5 to 9) for prucalopride and NNT 6 (95% CI: 5 to 8) for linaclotide. In this meta-analysis, 72.8, 81.0 and 56.5% of idiopathic constipation patients who received lubiprostone achieved an SBM within 24 and 48 h and achieved >3 SBMs/week, and its efficacy was similar between different baseline diseases and between different populations. However, because the absence of direct comparisons between different drug classes limits comparisons of efficacy, head-to-head trials of different secretagogues and among secretagogues, other drugs (fibers supplements, polyethylene glycol, lactulose, sodium picosulfate and bisacodyl, and prucalopride) and foods (carnitine and yogurt) will be necessary to determine the appropriate selection of pharmacological agents for patients with chronic constipation.

In general, abdominal symptoms of chronic constipation are subjective. Although chronic constipation can arise from various physiological and psychological causes, its pathophysiology is not fully understood. Recently, the profile of the gut microbiota has been focused upon as an important factor in chronic constipation. The findings suggested that alteration of the gut microbiota has potential as a new treatment target for chronic constipation. Sarosiek et al. recently demonstrated improvement in small intestinal bacterial overgrowth (SIBO) with the use of lubiprostone in chronic constipation patients, potentially because of the increased foregut fluid secretion and subsequent hypothetical cleansing effect of lubiprostone in the small intestine. Previously, we demonstrated that successful eradication of *Helicobacter pylori* improved abdominal symptoms of constipation, especially in patients with mild gastric atrophy and with moderate–severe symptoms before eradication therapy, suggesting...
Table 3. Averse events

| Authors (year) | Treatment | Incidence of adverse events, % (n/n) | Treatment-related adverse events, % (n/n) | Diarrhea/ Loose stool, % (n/n) | Nausea, % (n/n) | Vomit, % (n/n) | Abdominal pain, % (n/n) | Abdominal distention, % (n/n) | Dyspepsia, % (n/n) | Abdominal cramp, % (n/n) |
|----------------|-----------|--------------------------------------|------------------------------------------|-----------------------------|----------------|--------------|----------------------|--------------------------|-----------------|---------------------|
| Johanson JF, et al. (2007) | 24 µg (24 µg qd) | 34.5 (10/29) | 10.3 (3/29) | 17.2 (5/29) | 0 (0/29) | 0 (0/29) | 0.8 (1/122) | 16 (1/122) | 0 (0/29) | 3.4 (1/29) |
| Johanson JF, et al. (2008) | 24 µg (24 µg bid) | 50.0 (16/32) | 6.3 (2/32) | 43.8 (14/32) | 3.1 (1/32) | 9.3 (3/32) | 9.3 (3/32) | 3.1 (1/32) | 6.1 (2/33) |
| Barish CF, et al. (2010) | | 50.8 (61/120) | 8.3 (10/120) | 31.7 (38/120) | 5.0 (6/120) | 2.5 (3/120) | 2.5 (3/120) |
| Johanson JF, et al. (2008) | 24 µg (24 µg bid) | 50.8 (61/120) | 8.3 (10/120) | 31.7 (38/120) | 5.0 (6/120) | 2.5 (3/120) | 2.5 (3/120) |
| Fukudo S, et al. (2011) | 24 mg (24 mg qd) | 62.1 (18/29) | 34.5 (10/29) | 17.2 (5/29) | 0 (0/29) | 0 (0/29) | 0.8 (1/122) | 16 (1/122) | 0 (0/29) | 3.4 (1/29) |
| Fukudo S, et al. (2015) | 24 mg (24 mg bid) | 50.8 (61/120) | 8.3 (10/120) | 31.7 (38/120) | 5.0 (6/120) | 2.5 (3/120) | 2.5 (3/120) |
| Christie J, et al. (2017) | 24 mg (24 mg bid) | 62.1 (18/29) | 34.5 (10/29) | 17.2 (5/29) | 0 (0/29) | 0 (0/29) | 0.8 (1/122) | 16 (1/122) | 0 (0/29) | 3.4 (1/29) |
| Cryer B, et al. (2014) | 24 mg (24 mg bid) | 62.1 (18/29) | 34.5 (10/29) | 17.2 (5/29) | 0 (0/29) | 0 (0/29) | 0.8 (1/122) | 16 (1/122) | 0 (0/29) | 3.4 (1/29) |
| Mazen Jamal M, et al. (2015) | 24 mg (24 mg bid) | 62.1 (18/29) | 34.5 (10/29) | 17.2 (5/29) | 0 (0/29) | 0 (0/29) | 0.8 (1/122) | 16 (1/122) | 0 (0/29) | 3.4 (1/29) |
| Spiering ELH, et al. (2018) | 24 mg (24 mg bid) | 62.1 (18/29) | 34.5 (10/29) | 17.2 (5/29) | 0 (0/29) | 0 (0/29) | 0.8 (1/122) | 16 (1/122) | 0 (0/29) | 3.4 (1/29) |

Fig. 4. Forest plots for the incidence rate of treatment-related adverse events between lubiprostone group and control group in randomized control studies with all studies (A), in the studies investigating chronic idiopathic constipation (B), and in the studies investigating opioid-induced constipation (C).
that the eradication of specific gut microbiota may be one factor responsible for the improvement in symptoms of chronic constipation.\(^{(34)}\) In the near future, an association between microbiota and lubiprostone may be a breakthrough in clinical practice.\(^{(33)}\)

**Limitation.** There are limitations to this meta-analysis. We meta-analyzed studies of patients with idiopathic and opioid-induced constipation, not with irritable bowel syndrome (IBS). It is not clear if the efficacy of lubiprostone applies to all populations with chronic constipation. Most studies investigating efficacy in IBS focused upon whether lubiprostone improved disease-specific abdominal symptoms, and not improvement in bowel habits. It will be required to clarify the efficacy of lubiprostone in all patients with constipation using the same comparative criteria. In addition, this meta-analysis is insufficient to investigate the efficacy of the other secretagogues. Because there have been no comparative studies among them, such studies will be necessary.

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**Fig. 5.** Forest plots for the incidence rate of nausea as a treatment-related adverse event between lubiprostone group and control groups in all studies (A), in the studies investigating chronic idiopathic constipation (B) and in the studies investigating opioid-induced constipation (C). Forest plots for the incidence rate of nausea in Western populations (D) and East Asian populations (E).
Conclusion

In conclusion, this meta-analysis strengthens the evidence for the potential of lubiprostone to effectively improve abnormal bowel habits, irrespective of chronic idiopathic vs opioid-induced constipation etiologies, and irrespective of different populations (Western or East Asian). In addition, we showed that the incidence rate of lubiprostone-induced adverse events differed among different populations, especially in regard to nausea, which is the most common adverse effect of lubiprostone. Further large studies of lubiprostone in primary care are required, ideally with head-to-head comparisons of efficacy among different kinds of anti-constipation drugs.

Acknowledgments

We thank Libby Cone, MD, MA, from DMC Corp. (www.dmed.co.jp) for editing drafts of this manuscript.

Conflict of Interest

No potential conflicts of interest were disclosed.

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