

# A critical appraisal of lubiprostone in the treatment of chronic constipation in the elderly

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**Abstract:** Chronic constipation is a common disorder in the general population, with higher prevalence in the elderly, and is associated with worse quality of life and with greater health care utilization. Lubiprostone is an intestinal type-2 chloride channel activator that increases intestinal fluid secretion, small intestinal transit, and stool passage. Lubiprostone is currently approved by the US Food and Drug Administration for the treatment of chronic idiopathic constipation and of irritable bowel syndrome with predominant constipation. This review outlines current approaches and limitations in the treatment of chronic constipation in the elderly and discusses the results, limitations, and applicability of randomized, controlled trials of lubiprostone that have been conducted in the general and elderly population, with additional focus on the use of lubiprostone in constipation in Parkinson's disease and in opioid-induced constipation, two clinical entities that can be comorbid in elderly patients.

**Keywords:** irritable bowel syndrome, Parkinson's disease, opioid-induced constipation, chronic constipation

## Introduction

The progressive increase in life expectancy in developed countries has led to a corresponding rise in the proportion of elderly population. In the United States, the population aged 65 and older was 40.2 million in 2010 and is projected to be 88.5 million in 2050.<sup>1</sup> This exponential increase poses a number of challenges, as diseases and conditions that are more prevalent in elderly patients will need a much greater allocation of resources and expertise in health care systems in future years.

Chronic constipation (CC) is a common disorder, with an estimated prevalence of 12%–19% in the general population (depending on the area and the criteria used for the diagnosis).<sup>2</sup> A multinational survey published in 2008 that included 13,879 adults from seven different countries (United States, United Kingdom, Germany, France, Italy, Brazil, and South Korea) found a prevalence of constipation symptoms of 12.3% in the adult population (range 5%–18%), with odds ratios for constipation in women and elderly of 2.43 (95% CI: 2.18–2.71) and 1.5 (95% CI: 1.25–1.73), respectively.<sup>3</sup> This same study reported a prevalence of use of laxatives among those with constipation between 16%–40%. Increasing age, symptom frequency, and lower income and education were individual factors associated with laxative use.

A survey performed in Olmsted (Minnesota, USA), specifically designed for elderly responders ( $\geq 65$  years old, mean age 76), found a constipation prevalence of 40.1% (95% CI: 38.9–44.4). Functional constipation, the most frequent category encountered in this study, had a prevalence of 24.4% (95% CI: 22.0–26.9).<sup>4</sup> In another study, performed using

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face-to-face interviews with frail elderly individuals who were not institutionalized, constipation was spontaneously mentioned by 45% of participants and was considered by 11% to be a major burden to their quality of life.<sup>5</sup> CC affects the majority of long-term patients in hospitals and residents in nursing homes,<sup>6</sup> and often, with exorbitant prevalence (reported up to 50%–79%) in the long-term institutionalized elderly.<sup>7</sup>

Although CC can be seen as a trivial medical problem, its impact on quality of life can be substantial and may result in considerable additional utilization of health care resources, including specialist visits, gastrointestinal diagnostic procedures, and medical treatment modalities.<sup>6,8</sup> Using both disease-specific and generic quality of life measurement instruments, studies suggest constipation is associated with impaired health-related quality of life,<sup>9,10</sup> with CC patients exhibiting lower scores for physical functioning, mental health, general health perception, and bodily pain when compared with individuals without constipation.<sup>11</sup> Medical relief of constipation in a group of 52 CC patients aged 65–89 years resulted in improvement of patient's mood, sexual activity, and quality of life.<sup>12</sup>

In the United States, CC accounts for more than 2.5 million visits to physicians and for laxative sales of several hundred million dollars a year.<sup>13</sup> In England and Wales, constipation generated some 450,000 general practice consultations per year in 1991 and 1992, at an estimated cost of £4.5 million per year.<sup>8</sup> Data from the UK National Survey of morbidity data in general practice showed an age-dependent increase in the consultation rates for constipation, from 75/100,000 person-year for the 45–64 age group, to 400/100,000 person-year for the 77–84 age group.<sup>14</sup>

Lubiprostone (Amitiza<sup>®</sup>, Sucampo Pharmaceuticals) was approved in the United States in 2006 for the treatment of chronic idiopathic constipation (CIC) in men and women, and in 2008 for women with irritable bowel syndrome with predominance of constipation (IBS-C). Since then, several studies focusing on lubiprostone efficacy and use have been published. Aims of this review were: (1) to review the current available treatments of CC in the elderly population; (2) to summarize the pharmacological properties of lubiprostone and data on its effects on constipation, based on studies in the general population; (3) to evaluate the data supporting the use of lubiprostone in the elderly; and (4) to discuss the studies performed using lubiprostone in specific situations occurring more frequently in older people, including Parkinson's disease (PD) and opioid-induced constipation (OIC).

For the purpose of the present review, publications in abstract form and full papers on lubiprostone clinical studies were searched from 1995 to October 2012 on the PubMed

electronic database and from proceedings of gastroenterology international meetings, using combinations of the following keywords: constipation, chronic, idiopathic, elderly, lubiprostone, Amitiza, opioid-induced, and Parkinson's.

## Constipation in the elderly population

### Pathophysiology, onset and clinical features

The underlying mechanisms for CC in older adults include primary slow colonic transit, pelvic floor dysfunction, or a combination of the two. The role of reduced fiber and fluid intake and decreased physical activity is questionable, whereas underlying health problems more prevalent with advanced age (eg, diabetes mellitus, PD, dementia) and the use of medications (ie, calcium supplements, opioids, certain antidepressants) potentially affecting gastrointestinal motility and evacuation of stools are often involved (Table 1). The above factors can intervene, with advancing age, to worsen common underlying disorders already present from a younger age, such as CIC or IBS-C. CC in the elderly, if severe,

**Table 1** Common causes of constipation in elderly patients

Gastrointestinal disorders	Irritable bowel syndrome	
	Anorectal disorders (ie, hemorrhoids, anal fissures)	
	Diverticulitis	
	Hernias	
	Intestinal volvulus	
	Tumors	
	Upper gastrointestinal tract disorders	
	Metabolic disorders	Diabetes mellitus
		Chronic kidney disease
		Hypothyroidism
Hyperparathyroidism		
Neurogenic disorders	Hypercalcemia	
	Panhypopituitarism	
	Cerebrovascular accidents	
	Parkinson's disease	
	Spinal cord injury (ie, spinal canal stenosis)	
Psychogenic causes	Tumors of the central nervous system	
	Trauma to the brain or the medulla	
	Voluntarily ignore or postpone defecation	
Medications	Psychiatric disease	
	Nonsteroidal anti-inflammatory agents	
	Opiates	
	Calcium channel blockers	
	Diuretics (nonpotassium sparing)	
	Iron supplements	
	Antihistamine	
	Anticholinergics	
	Tricyclic antidepressants	
	Antipsychotics	
Antacids containing calcium carbonate or aluminum hydroxide		

entails a substantial rate of complications, with subsequent increase of limitation to independent activities of daily life and hospitalization rate. A wide range of complications can be associated, from anorectal pathology (eg, fissures, hemorrhoids, rectal prolapse, etc) to sigmoid volvulus, fecal impaction, fecal incontinence, and urinary dysfunction.<sup>15</sup>

## Available therapies

Nonpharmacological treatments for constipated patients include lifestyle and dietary measures, such as exercise, modifications to the daily routine, adequate fiber, and water intake. These measures are often difficult to implement in the elderly population, as multiple obstacles ranging from limited mobility to deglutition and mastication problems frequently exist in this group.

In patients with CC and associated pelvic floor dysfunction, pelvic floor retraining using biofeedback techniques has shown to be effective and have durable results.<sup>16,17</sup> The prevalence of pelvic floor dysfunction in CC has been estimated to be 50% or more, in studies in tertiary care centers<sup>18</sup> and is more frequent in patients with history of anorectal surgery or other pelvic floor trauma. A single study of 30 elderly adults with CC showed good response to a combined approach of physiological and psychological therapy.<sup>19</sup> When treating elderly populations, one should bear in mind that biofeedback efficacy may be limited by patients' declining physical or mental abilities.

Pharmacological treatment comprises several types of laxatives, including bulk-forming agents (such as psyllium, calcium polycarbophil, and methylcellulose), stool softeners (such as docusate sodium and docusate calcium), osmotics or salines (such as magnesium hydroxide, lactulose, polyethylene glycol, sorbitol, and glycerin rectal suppositories), and stimulants (such as senna, cascara sagrada, castor oil, and bisacodyl).

Self-medication is common in CC. Laxatives are widely available and remain agents of first choice. It has been reported that up to 16% of individuals aged 65 and above use over-the-counter laxatives, women more often than men.<sup>20-24</sup> The use of laxatives has been associated with a greater number of physician or emergency room visits and more frequent hospitalization, home health services utilization, and prescription drugs use.<sup>21</sup> Among laxatives, the osmotic preparation polyethylene glycol 3350 has been shown to be safe and effective in elderly populations.<sup>25-26</sup> However, clinical trials targeted to the elderly are lacking.

Limited patient compliance, polypharmacy, and patient-provider miscommunication can all contribute to poor

understanding of the laxative dose and mode of administration, resulting in suboptimal results.

In the elderly with CC, prescription agents have been, in general, much less used than over-the-counter laxatives, owing to the limited drug choice, to cost issues, and to potential safety concerns.

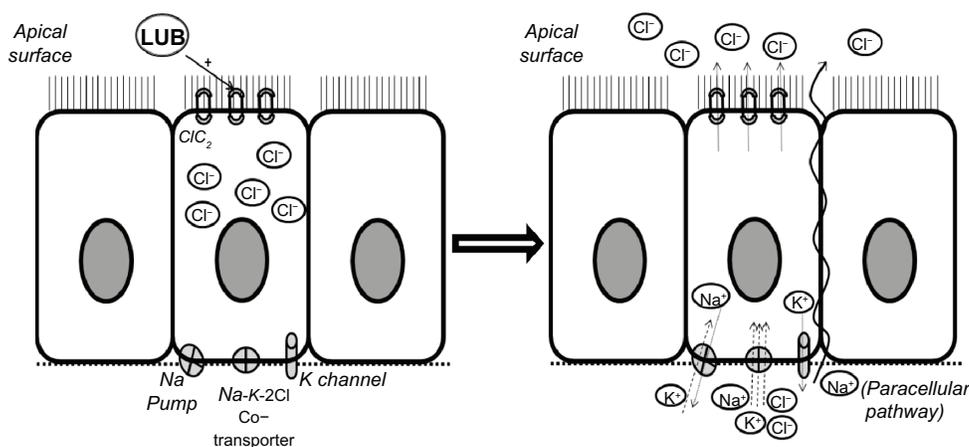
Linaclootide is an agonist of guanylate cyclase 2C that was recently approved by the US Food and Drug Administration (FDA) for treatment of CIC and IBS-C. A 4-week multicenter clinical trial with 310 CIC patients included 30 elderly subjects, who showed similar results in safety and improvement of weekly spontaneous bowel movements (SBMs), stool consistency, straining, abdominal discomfort, and quality of life to the entire study population.<sup>27</sup>

Prucalopride is a 5-HT<sub>4</sub> receptor agonist that was approved in some European countries in 2009 and in Canada in 2011, but not in the US, for the treatment of CIC. A 4-week, placebo-controlled, Phase III trial with 300 elderly patients (mean age of 76.4 ± 0.4 years) showed significant improvement in the number of SBMs/week and quality of life in the treatment group and that the treatment was safe and well tolerated.<sup>28</sup> A 28-day Phase II study of 89 elderly CIC institutionalized patients also showed good treatment tolerability and absence of significant adverse events.<sup>30</sup>

Several reviews discuss clinical trials performed with elderly patients and the current recommendations for treating this population. Regrettably, the guidelines provided are only in part evidence-based, owing to the general lack of large, randomized, controlled trials.<sup>8,10,30</sup> Overall, they call for the need to take into account the patient's specific features (eg, ambulatory versus institutionalized, use of concomitant medications), to individualize the clinical approach. The final goals remain the achievement of acceptable bowel function (associated with better quality of life) and prevention of adverse effects of medications, in this vulnerable population.

## Lubiprostone: pharmacology and physiological effects

Lubiprostone is classified as a prostone, a bicyclic fatty acid compound derived from a metabolite of prostaglandin E1. Lubiprostone acts locally in the small intestinal lumen, inducing secretion of fluid and electrolytes through the activation of the type-2 chloride channels in the intestinal apical cell membrane (Figure 1),<sup>6,31</sup> and thereby accelerates the small bowel and colon transit times. In the upper gut, lubiprostone appears to delay gastric emptying and to increase stomach volumes in the fasting state.<sup>32</sup>



**Figure 1** Summary of the mechanism of action of lubiprostone.

**Notes:** Chloride channels-2, present in the apical membrane of the intestine, are activated, resulting in increased secretion of chloride-rich intestinal fluid. Other channels secondarily act to maintain cellular homeostasis.

**Abbreviations:** LUB, lubiprostone;  $ClC_2$ , chloride channels-2.

## Lubiprostone: clinical data in adults and elderly patients

A summary of results from lubiprostone open-label and placebo-controlled studies of adult and elderly populations with CIC and IBS-C is presented in Tables 2–4.

## Patients with chronic idiopathic constipation

A Phase II, double-blind, dose-ranging study randomized 129 subjects with symptoms of CIC, between 18–75 years old, to four groups receiving placebo or lubiprostone 24, 48, or 72 mcg daily, for 3 weeks.<sup>33</sup> Mean SBMs frequencies were significantly higher for all lubiprostone groups, with better

responses in the groups treated with higher doses. SBMs per week increased after the first 7 days of treatment with 48 and 72 mcg/day, and all three lubiprostone groups presented an increase from fewer than 2 to 5–6 SBMs/week after 2 weeks. Patients also reported an improvement of stool consistency, straining, and abdominal bloating symptoms. However, the percentage of patients using rescue medication during the trial was not significantly different across the four treatment arms and during the 3 weeks. The higher dose also was associated with greater severity of adverse effects, including nausea, headache, and diarrhea and did not appear to provide a clear risk-benefit advantage when compared with lubiprostone 48 mcg/day.

Subsequently, two Phase III trials randomized 479 adults with CIC to placebo or lubiprostone 48 mcg/day

**Table 2** Summary of clinical trials of lubiprostone in adult populations with chronic constipation

Author	Patients	Description	Results
Johanson et al <sup>34</sup>	N = 129 Age 18–75 >84% women	3-week dose ranging study (24 mcg/d, 48 mcg/d and 72 mcg/d doses)	Dose-dependent improvement SBM on day 1, SBMs/week, stool consistency, straining and bloating in lubiprostone arms, accompanied by incremental incidence of adverse events (nausea, headache, and diarrhea).
Johanson et al <sup>2</sup>	N = 242 Age 22–80 90% women	4-week single dose study (24 mcg bid)	Lubiprostone better than placebo on SBM on day 1, SBMs/week after week 1, stool consistency, straining, abdominal bloating, abdominal discomfort, and constipation severity. Nausea more frequent in lubiprostone group (31.7% vs 3.3% in placebo group).
Barish et al <sup>34</sup>	N = 237 88.2% women	4-week single dose study (24 mcg bid)	Lubiprostone better than placebo on SBM on day 1 and SBMs/week after week 1. Stool consistency, straining, and constipation severity. No significant differences in abdominal bloating and discomfort.
Lembo et al <sup>36</sup>	N = 248 Mean age 51 ± 14 83.9% women	48-week open-label, single dose study (24 mcg bid) One subgroup enrolled after a placebo-controlled withdrawal phase	Significant reduction from baseline, in constipation severity, abdominal bloating, and abdominal discomfort.

**Abbreviations:** bid, twice daily; SBM, spontaneous bowel movement.

**Table 3** Summary of clinical trials of lubiprostone in adult populations with IBS and predominant constipation

Author	Patients	Description	Results
Drossman et al <sup>37</sup>	N = 1171 Age 18–85 92% women	Two 12-week Single dose (8 mcg bid) trials	Higher rate of overall responders (subjective rate of relief of IBS symptoms): in lubiprostone group (17.9%) than placebo (10.1%), maintained throughout the study. Improvement in abdominal discomfort/pain, bloating, constipation severity, stool consistency, and straining ( $P < 0.001$ ). Trends in improvement in IBS-QOL measures. Overall subjective rate of relief was 16% after 1 month, 23%–39% after 2–5 months, 37%–44% after 10–13 months of lubiprostone treatment.
Chey et al <sup>38</sup>	N = 520 Age 21–82 93% women	36-week Single dose (8 mcg bid) open-label trials extension of placebo- controlled studies	Increase in SBMs/week after the first month of treatment, maintained at approximately 5 SBMs/week throughout the treatment period, with improvement in abdominal discomfort/pain, abdominal bloating, and stool consistency after the first month and throughout the study ( $P < 0.001$ ). Most common adverse events were nausea and diarrhea (both 11%).

**Abbreviations:** IBS, irritable bowel syndrome; bid, twice daily; QOL, quality of life; SBM, spontaneous bowel movement.

for 4 weeks.<sup>2,34</sup> In the lubiprostone group, a significant increase of SBMs/week was seen starting after the first week of treatment, along with improvement in stool consistency, straining, and constipation severity that was maintained throughout the 4 weeks. The requirement of rescue laxatives was lower in the lubiprostone group, but only in one of the trials was this difference statistically significant.<sup>2</sup> More than 40% of patients in the active treatment groups reported at least one adverse effect during the studies, which led to the withdrawal of the drug in approximately 7% of patients overall. Nausea was the side effect reported most commonly (24%–32%).

A meta-analysis on lubiprostone data from 610 patients with CIC,<sup>35</sup> using self-reported relief of symptoms by patients as the main outcome measure, concluded that treatment during 3 or 4 weeks with lubiprostone 48 mcg/day was more effective than placebo (55% vs 33.1% of responders). The calculated number needed to treat was 5 (95% CI: 3–7). Adverse events, mostly diarrhea and nausea, were also overall more frequent in the lubiprostone-treated patients (60% vs 34% taking placebo).

A long-term, prospective, multicenter, open-label trial included 248 CIC patients to be treated with lubiprostone 48 mcg/day versus placebo, during 48 weeks.<sup>36</sup> Lubiprostone was more effective at reducing constipation severity, abdominal bloating, and discomfort. To minimize the impact of side effects occurrence on treatment withdrawals, the study

design allowed dose reduction of lubiprostone when side effects occurred, at the discretion of the investigators, and redosing was performed in 17% of patients. Most lubiprostone-related adverse effects were mild (50%) or moderate (44%), and the most frequent were nausea (19.8%) and diarrhea (9.7%). Other adverse effects included abdominal distension, headache, abdominal pain, and vomiting. Overall, 13.3% of patients withdrew from the study due to adverse effects.

### Patients with irritable bowel syndrome with predominant constipation

A combined analysis of two Phase III randomized trials involving 1171 patients who met Rome II criteria for IBS-C was performed comparing lubiprostone 16 mcg/day with placebo, for 12 weeks.<sup>37</sup> The patients were predominantly female (91.6%), 18–85 years old. The total number of overall responders (response was defined as moderate to significant IBS symptom relief, according to an electronic diary) was significantly higher in the lubiprostone group (17.9% versus 10.1%). Symptoms of abdominal discomfort or pain, bloating, constipation severity, straining, or stool consistency also improved significantly. The most frequent adverse effects were related to the gastrointestinal tract (ie, nausea, diarrhea, and abdominal distension) and had similar incidence in both groups.

**Table 4** Summary of clinical trials of lubiprostone in elderly adults

Author	Patients	Description	Results
Ueno et al <sup>39</sup>	N = 57 Age $\geq 65$	Subanalysis of 3 pooled placebo-controlled single dose (24 mcg bid) clinical trials of 3–4 weeks duration	Significant improvement in lubiprostone group, in weeks 1, 3, and 4, of SBMs rates stool consistency, and bowel straining rates. Lesser adverse events in the lubiprostone group.
Ueno et al <sup>40</sup>	N = 878 (N = 163, age $\geq 65$ , N = 715 age 18–64)	Subanalysis of 3 pooled 48-week single dose (24 mcg bid) placebo-controlled trials	Significant improvement, in elderly and nonelderly groups, of constipation severity, abdominal bloating, and discomfort. Incidence of nausea: 17.8% in elderly vs 29.4% in nonelderly patients.

**Abbreviations:** bid, twice daily; SBM, spontaneous bowel movement.

An extension of this study was performed in 520 patients, mostly female (92.9%), with an age range of 21–82 years, for a total of 52 weeks.<sup>38</sup> Patients were randomized to three groups, according to the previous treatment, and received sequential treatment with placebo-lubiprostone, lubiprostone-lubiprostone, or lubiprostone-placebo-lubiprostone. The response rates to lubiprostone tended to improve over time, from 16% after 1 month, 32%–35% at 6–9 months, to 37%–44% after 10–13 months of treatment. Individually, symptoms of abdominal discomfort and pain, abdominal bloating, and stool consistency were significantly improved throughout the study. Rescue medication was required by 31.5% patients overall. Nausea and diarrhea were the most common treatment-related adverse effects, and 10.4% of patients discontinued treatment or experienced a dose reduction due to one of these adverse events.

## Elderly patients

Generally, extrapolation of the results of clinical trials performed in the overall adult population to elderly patients must be done with caution. Data from three open-label clinical trials were combined to obtain a pool of elderly patients with CIC. These analyses were published as abstracts, with the available data assessing a limited range of outcomes.

A group of 57 patients aged  $\geq 65$  years was randomized to placebo or lubiprostone 48 mcg/day and followed for 4 weeks. In the lubiprostone group, a significant improvement in SBMs frequency (4.6–5.4 additional SBMs/week compared with 1.29–2.27 in the placebo group) and stool consistency was seen at week 4. Fewer patients in the lubiprostone arm experienced related adverse effects than those receiving placebo (46.2% vs 61.3%).<sup>39</sup>

Another group of 163 elderly constipated patients was compared with a group of 715 nonelderly lubiprostone trial participants. Tolerability and efficacy of lubiprostone 48 mcg/day was assessed for 6 to 12 months. There was a significant improvement in constipation severity, abdominal bloating, and abdominal discomfort, at all postbaseline time points from week 1 to week 48, for both groups. Constipation severity appeared consistently improved throughout the study. The incidence rate for nausea, the most common adverse effect, was markedly less frequent in elderly subjects when compared to their nonelderly counterparts (17.8% vs 29.4%).<sup>40</sup> In a separate subanalysis, nausea occurred in only 18.8% of elderly patients, when the overall rate of nausea was 31.1%.<sup>41</sup>

Although these results are encouraging, additional studies, with more patients, are required before confirming the efficacy and safety of the treatment in elderly patients.

## Approved use of lubiprostone in CIC and IBS-C

Based upon the results of these pivotal studies, the FDA approved lubiprostone use for the treatment of adult men and women with CIC (at the dose of 24 mcg, twice daily) and for the treatment of adult women with IBS-C (at the dose of 8 mcg, twice daily).

The incidence of adverse effects appears to be dose-related, improving after the discontinuation of the treatment. These effects include diarrhea, nausea, abdominal pain or discomfort, and bloating and, less frequently, extraintestinal complaints, including stomatitis, headache, dyspnea, vertigo, or palpitations.<sup>6,31,33</sup> No alterations in the electrocardiogram were reported in one study performed on 177 patients with CIC and 68 healthy volunteers.<sup>42</sup>

## Lubiprostone: clinical data in specific situations

### Parkinson's disease

PD is the second most common neurodegenerative disease in the United States, after Alzheimer's disease, with a point prevalence of at least one million affected individuals and about 50,000–60,000 new cases diagnosed annually. Incidence and prevalence of PD increase with age, with average disease onset at 60 years of age. Greater disease severity and higher doses of dopaminergic medications seem closely related to patients' age and to more severe autonomic problems in PD. Autonomic dysfunction affects activities of daily life and health-related quality of life in PD.<sup>43</sup> Constipation is among the most common symptoms related to autonomic dysfunction in PD. Severe constipation in PD may eventually lead to megacolon, intestinal pseudo-obstruction, volvulus, and bowel perforation.<sup>43</sup> Its mechanisms include delayed gastric emptying, small intestine, and colonic transit time, difficulties with the volitional defecation process, and medication side effects. These digestive abnormalities are in part secondary to the early involvement in PD of the dorsal motor nucleus, which controls the majority of parasympathetic innervation to the gut; the loss of dopaminergic neurons and deposition of  $\alpha$ -synuclein in the myenteric ganglia and in the abdominopelvic autonomic plexus also likely play a role, resulting in dysregulation of the enteric nervous system.<sup>43–45</sup> Derangement of the volitional defecation process manifests clinically as impaired stool evacuation and is commonly the result of lack of coordination between the muscles in the pelvic floor and between these and the muscle groups involved in change of intra-abdominal pressure.<sup>44</sup>

Although levodopa is generally not very effective in the treatment of gastrointestinal symptoms in PD patients,<sup>43</sup> its intrajejunal continuous infusion in patients with advanced PD showed improvement in constipation, in a study of 22 patients.<sup>46</sup> There are a few trials evaluating the use of bulk-ing agents, such as dietary fibers, psyllium, and polycarbo-phil, performed with a small number of PD patients.<sup>47-49</sup> Fiber supplementation seems to improve stool consistency and frequency, but not colonic transit, and also enhances the delivery of dopaminergic agents, which may allow better control of symptoms.<sup>47-50</sup> The efficacy and safety of poly-ethylene glycol was evaluated in an 8-week, double-blind, placebo-controlled study of 57 PD patients, with significant improvement in SBMs frequency and stool consistency.<sup>51</sup> Pyridostigmine bromide, a reversible cholinesterase inhibitor, might have a possible beneficial effect and has been proposed as a safe option in case reports.<sup>52</sup> Cisapride, a 5-HT<sub>4</sub> receptor agonist prokinetic, now withdrawn from the US market, was associated with faster colonic transit in a small, open-label PD study.<sup>53</sup> The selective 5-HT<sub>4</sub> receptor agonist and partial 5-HT<sub>3</sub> antagonist mosapride was also found to accelerate colonic transit time and improve evacuation, in another open-label, 3-month study of PD patients. Lastly, *botulinum* toxin injections have been proposed as treatment in cases of focal dystonia of the puborectalis muscle in PD patients; however, controlled data are lacking to support this.<sup>54</sup>

In a double-blind, placebo-controlled study of 54 patients with CC and PD, mean age 67.0 ± 10.1 years,<sup>44</sup> treatment with lubiprostone 48 mcg/day over 4 weeks was well tolerated, increased stools per day, and improved subjective rating of constipation by visual analog scale score and questionnaires. The most commonly reported side effect was the occurrence of loose stools, in 48% of the lubiprostone-treated patients versus 3.7% in the placebo group. These were of mild severity and did not lead to treatment discontinuation. Of note, no patient receiving lubiprostone reported nausea. The duration of the study was limited; however, it suggests that use of lubiprostone in PD might be beneficial, without posing additional safety concerns.

## Opioid-induced constipation

Opioid narcotics are commonly prescribed in the United States for both cancer and noncancer pain. It is estimated that 90% of patients presenting to pain centers and receiving treatment in such facilities are managed with opioids.<sup>55</sup> In elderly patients, chronic pain is highly prevalent, with 45%–85% of elderly patients reporting pain in moderate to severe degree,<sup>56</sup> and with the *de facto* common use of opioid narcotics, such as morphine, fentanyl, or oxycodone, despite the overall lack of

clinical data to support the effectiveness and safety of these drugs in the elderly population.<sup>57</sup> Alongside their analgesic properties, opioids carry the burden of inducing cognitive impairment, cough depression, addiction, and sensory and motor dysfunction throughout the bowel, and are associated with a wide range of gastrointestinal manifestations.<sup>58</sup> Constipation is the most common gastrointestinal adverse effect of opioid narcotics, with an incidence about 40%.<sup>59,60</sup>

Alvimopan and methylnaltrexone, two peripherally acting antagonists of the  $\mu$ -opioid receptors with restricted ability to cross the blood-brain barrier, have demonstrated efficacy and safety in the treatment of OIC, without reversing the central effects of analgesia.<sup>61,62</sup> Alvimopan has been approved by the FDA as a short-term treatment to accelerate the time of upper and lower gastrointestinal recovery after bowel resection.<sup>63</sup> Methylnaltrexone has been approved to treat OIC in patients with advanced illness receiving palliative care, when the response to laxatives has been insufficient.<sup>64</sup> Additional pharmacodynamic and clinical data suggest methylnaltrexone has potential effects on gastric emptying, on relief of nausea and vomiting, and on reduction of episodes of airway aspiration.<sup>65</sup>

Lubiprostone has been a potential candidate in OIC treatment. Studies performed on animal<sup>66</sup> and human intestinal tissues<sup>67</sup> suggested lubiprostone has the potential to counteract the inhibition by morphine of secretomotor neurons in the enteric nervous system of the small intestine. Four double-blind, Phase III clinical trials, one of them an extension of two previous ones, were performed in Europe, Canada, and the United States. They compared lubiprostone 48 mcg/day to placebo, in adults with OIC secondary to treatment with a full-agonist opioid for chronic, noncancer-related pain. Two of these have been published as abstracts.<sup>68,69</sup>

One 12-week trial (NCT00595946) included 443 subjects. The lubiprostone-treated group showed significant improvement in SBMs/week, constipation severity, stool consistency, abdominal discomfort, and straining. This range of effects was not observed in patients on methadone.<sup>68</sup> A second 12-week trial (NCT01298219) enrolled 439 patients, excluding patients treated with methadone.<sup>69</sup> The lubiprostone-treated group reported significantly higher response in terms of SBMs compared with patients receiving placebo (26.9% vs 18.6%). Straining, stool consistency, abdominal discomfort, and constipation severity were also significantly improved. In a separate trial (NCT00597428), however, conducted in 420 adults over 12 weeks, lubiprostone did not show significant difference in the improvement of SBMs/week compared with placebo, although a significant improvement was found in the secondary end points of stool consistency, abdominal

discomfort, constipation severity, and straining. As seen in the previous studies, the subgroup of patients on methadone treatment showed lower response rates.<sup>70</sup>

A Phase III extension of NCT00595946 and NCT00597428 was later performed in the United States. It included 439 adults that were followed for 36 weeks. According to data filed by the drug manufacturer, a maintained improvement of SBM compared with baseline was observed, while remaining on lubiprostone.<sup>71</sup>

The most common adverse effects in these trials were diarrhea, nausea, and abdominal pain or discomfort, which were reported by less than 10% of patients, but without affecting analgesia.

OIC is not an FDA-approved indication for treatment with lubiprostone. While lubiprostone might represent an additional option in OIC, it is unclear how its efficacy would compare with that of selective, peripheral opioid reversal agents available and in clinical development, and additional studies might be needed.

## Conclusion

CC is highly prevalent in the general population and especially among elderly patients. It can worsen quality of life and significantly impair activities of daily living. There is an unmet need for safe and effective CC treatments in the elderly. Lubiprostone is approved for the treatment of CC and IBS-C in the general population. Lubiprostone has also shown efficacy in smaller studies of constipation in the context of PD and seems promising as a treatment modality for OIC, two situations found more frequently in elderly populations. Lubiprostone use is limited by the incidence of gastrointestinal side effects, most notably nausea, which can only in part be modulated by dose reduction.

Few data are available on lubiprostone use for CC in elderly patients. These data seem to support a comparable range of efficacy to that described in other adult populations and do not show a high incidence of nausea, although the statistical power of this elderly patient sample is likely limited. The available evidence supports, with the limitations discussed above, the efficacy and safety of lubiprostone for CC treatment in the elderly.

## Disclosure

The authors report no conflicts of interest in this work.

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