

Current Opinion on Prucalopride in Gastroparesis and Chronic Constipation Treatment: A Focus on Patient Selection and Safety

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Abstract: Prucalopride is a third-generation, highly selective 5-hydroxytryptamine 4 (5-HT₄) receptor agonist. Many recent studies indicate prucalopride may play an important role in various motility disorders. The aim of this study was to investigate safety and patient selection considerations when using prucalopride as gastroparesis and chronic constipation treatment. We systematically searched PubMed, Embase, the Cochrane Central Register and ClinicalTrials.gov, and we reviewed all studies that evaluated prucalopride for the treatment of gastroparesis and chronic idiopathic constipation in adults. Prucalopride is an effective and safe option based on all the studies currently conducted. Thus, it may be the first-line treatment in the future. Prucalopride has the potential to be useful in the treatment of functional constipation and other forms of gastrointestinal diseases (eg, gastroparesis). Through the research on this potential, prucalopride is expected to be a useful and versatile option for treating gastrointestinal diseases in the future.

Keywords: prucalopride, gastroparesis, constipation, safety

Introduction

Prucalopride is a third-generation, highly selective 5-hydroxytryptamine 4 (5-HT₄) receptor agonist. Prucalopride stimulates colonic transit and is the underlying principle of action for chronic constipation.^{1,2} Thus, prucalopride provided clinicians with an option that could help treat conventional laxative refractory constipation. Many recent studies indicate prucalopride may play an important role in various motility disorders such as gastroparesis, which is often treated with prokinetic drugs. Moreover, symptom improvements can be expected by stimulating gastric motility and increasing the gastric emptying rate. However, these treatments are often ineffective for severe gastroparesis. Approved prokinetics are also limited in use due to significant side effects (central, extrapyramidal, anticholinergic, and cardiac arrhythmia, and so on). New prokinetic agents that are effective and safe are necessary to treat gastroparesis. Prucalopride improves gastric transit in canine models and healthy subjects as well as in patients with chronic constipation.²⁻⁴ Thus, studies are being conducted to determine the effect of prucalopride on gastroparesis treatment. Currently, available evidence suggests that using prucalopride may help, especially in patients suffering from both gastroparesis and chronic constipation. This study aims to investigate safety and patient selection considerations when using prucalopride as gastroparesis and chronic constipation treatment.

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The Use of Prucalopride for Chronic Constipation and Potential for Gastroenterology

Lifestyle modifications, fiber supplementation, or bulk-forming agents are common treatments for chronic constipation. Basic osmotic laxatives (eg, polyethylene glycol (PEG)-based laxatives and lactulose) can be administered if the response is insufficient.⁵ Stimulant laxatives (eg, bisacodyl or senna) can be used if other treatments are ineffective. However, none of these treatments is sufficient for laxative refractory chronic constipation. Therefore, intestinal secretagogues (eg, lubiprostone and linaclotide) or prokinetic agents targeting 5-HT₄ and motilin receptors have been considered as new therapeutic approaches.

The 5-HT₄ receptors are members of the G-protein family coupled receptors that are widely expressed throughout the gastrointestinal tract of smooth muscle cells and intestinal neurons.^{6,7} Therefore, many studies have been conducted on these receptors as targets for prokinetic drugs. The activation of these receptors promotes gastrointestinal motility and mucosal secretion through inhibitory circular smooth muscle relaxation and cholinergic transmission enhancement acetylcholine release.^{8,9} Several types of 5-HT₄ agonists were developed for the prokinetic treatment of multiple dysmotility diseases. Each agent had different degrees of affinity and selectivity for the 5-HT₄ receptor.

Early 5-HT₄ receptor agonists, represented by cisapride and tegaserod, were withdrawn from the market due to serious side effects (eg, cardiovascular and QT prolongation).^{10,11} These side effects are due to the effect on the human ether-à-go-go-related gene (hERG)-encoding potassium channel and not only 5-HT₄ but also unrelated 5-HT₁ or 5-HT₂ receptors. This is because selectivity for only 5-HT₄ receptors is insufficient.^{6,12} Unlike these drugs, the new highly selective 5-HT₄ receptor agonists, including prucalopride, velusetrag, and naranapride, are known to be relatively safe. It did not show effects on the 5-HT receptor or hERG-encoding potassium channels known to be associated with QT prolongation and cardiovascular side effects.^{6,13,14}

Chronic constipation is often alone or overlapped with functional gastrointestinal disorders (eg, irritable bowel syndrome, gastroesophageal reflux disease, and dyspepsia). Also, gastroparesis and chronic constipation seem to occur in the same patient frequently. An analysis of 206 patients by Zikos et al showed that patients with

gastroparesis were more likely to have slow colon transit than patients with dyspeptic symptoms but normal gastric emptying. Moreover, patients with slow colon transit were more likely to have delayed gastric emptying.¹⁵ According to Hasler's report, >40% of the 209 patients with suspected gastroparesis reported an extra gastric passage delay.¹⁶ Prucalopride showed a decrease in esophageal acid exposure and accelerated gastric emptying in healthy adult male volunteers, although whether the decrease in esophageal acid exposure is a secondary finding due to the improvement of esophageal movement is unclear.⁴ In gastro reflux patients with ineffective esophageal motility, prucalopride promoted the frequency of esophageal secondary peristalsis and significantly increased primary peristaltic wave amplitude.¹⁷ Prucalopride also accelerated gastrointestinal transit in patients with chronic constipation without a rectal evacuation disorder.² Therefore, the effect on gastric emptying and reduction of esophageal acid exposure suggests that prucalopride may be effective in treating gastroparesis or reflux esophagitis. Thus, prucalopride may play an important role in several motor disorders, especially gastroparesis, and impaired esophageal motility. However, research on these diseases is officially lacking, and more studies are needed. Therefore, it is necessary to examine the subjects and the effects and side effects of prucalopride from the studies published to date.

Previous studies, including large randomized controlled trials, assessed the efficacy, tolerability, safety, and impact on prucalopride's quality of life.¹⁸ In general, prucalopride reportedly had allowable safety and tolerability, especially regarding cardiovascular risks, and electrocardiography parameters. Commonly reported side effects are abdominal pain, diarrhea, nausea, and headache.^{19–23} Most of these side effects occurred in the study group within the first 24 h after initiation of prucalopride therapy, and the duration of side effects was relatively short.²³ While using prucalopride for 24 months, gastrointestinal symptoms, and headache occurred in 3.3% and 1.0%, respectively.²⁴ In the first 3 months, 2.5% of patients stopped using prucalopride due to side effects (ie, abdominal pain, diarrhea, nausea, and headache).²⁴ Moreover, prucalopride showed relatively safe results, did not affect the QT interval, and did not show any association with adverse cardiovascular side effects.^{22,25}

Prucalopride does not affect the P glycoprotein or cytochrome P450 functions and is not widely metabolized in the body. Thus, few clinically significant interactions

with other drugs (eg, oral contraceptive bioavailability) exist.²¹ Prucalopride is also not significantly metabolized in the human body, does not significantly change, and is mainly excreted in the urine.^{26,27} Therefore, drug clearance can be reduced significantly in patients with severe renal impairment. Thus, dose reduction is required. Furthermore, it should not be used in patients on dialysis or with drug sensitization, intestinal obstruction, or toxic megacolon.²⁸ Although liver metabolism is minimal, patients with advanced liver disease need similar dose reductions.²⁷ Even in patients with constipation >65 years old, prucalopride was equally effective and safe when 1 or 2–4 mg was taken.²⁹ Therefore, 2-mg prucalopride is recommended for once-a-day administration. However, 1-mg prucalopride is recommended for the elderly (>65 years old) patients, patients with severe liver impairment (Child–Pugh class C) or severe renal impairment (glomerular filtration rate, <30 mL/min/1.73 m²). It is also not recommended for use during lactation or pregnancy (category C drug).³⁰ Several case reports exist on serious neuropsychiatric events or acute tubular necrosis. However, they do not appear to have a clear causal relationship.^{31,32}

Patient Perspectives Focusing on the Critical Safety of Patients with Gastroparesis and Chronic Constipation

Gastroparesis

Gastroparesis refers to delayed gastric emptying without mechanical obstruction.³³ It is caused by diabetes complications and can be defined as idiopathic cases occurring without a specific cause. Gastroparesis can be considered a pan-gastroenteric disorder due to various causes (eg, visceral hypersensitivity, impaired accommodation of gastric fundus/body, impaired pyloric relaxation, as well as lowering of gastric emptying).³⁴ Prokinetics are generally considered as a gastroparesis treatment, but evidence for effectiveness is lacking.³⁵ Furthermore, prokinetics cause gastric emptying too quickly and can cause gastric fundus/body accommodation dysregulation and other symptoms.^{35,36} It can be difficult to find a physiologically optimal point where gastric emptying is neither too fast nor too slow because the severity of the patient's symptoms, the cause of gastroparesis, and the rate of gastric emptying are all different. Diabetic gastroparesis may respond differently

to prokinetics compared to idiopathic gastroparesis. Due to these various factors, there is no consensus on the optimal access to treatment for gastroparesis.

The diagnosis of gastroparesis requires two conditions to be fulfilled: the identification of delayed gastric emptying using appropriate tools and the recognition of the cardinal symptoms. For symptom evaluation, a validated questionnaire (ie, PGI-SYM-based Gastroparesis Cardinal Symptom Index [GCSI] and the recently revised GCSI-Daily Diary score) was developed to quantify the severity of gastroparesis and other digestive symptoms.^{37,38} In particular, two validated patient-reported outcomes for gastroparesis (the American Neurogastroenterology and Motility Society, GCSI daily diary, and Diabetic Gastroparesis Symptom Severity Diary) are being used in ongoing clinical trials.^{39,40} To measure GE, various measurement methods such as stable isotope breath testing and wireless motility capsule are available, but scintigraphic gastric emptying is the current gold standard.^{41,42}

Prucalopride, as a novel and investigational medication, has been studied. For gastroparesis, a small number of small, randomized placebo-controlled crossover studies have been conducted in each patient with predominantly female idiopathic or diabetic gastroparesis to date. Therefore, summarizing the research and results, examining the adaptation of prucalopride to gastroparesis, and planning future research directions will be important.

Summary of Completed Research

Two randomized placebo-controlled crossover pilot trials are available to date (Table 1). In a study of 34 gastroparesis patients (28 idiopathic and 6 diabetics), Carbone et al reported significant improvement in the daily 2-mg prucalopride 4-week treatment group compared with the placebo group. Gastric half-emptying time ($p < 0.050$) and the severity of symptoms assessed with GCSI were significantly reduced (bloating/distension, $p < 0.001$; nausea/vomiting, $p = 0.010$; and fullness/satiety, $p < 0.001$) compared with the placebo group.⁴³ Moreover, in Andrews' study of 15 gastroparesis patients [13 diabetics and 2 connective tissue disease (CTD)], 4 mg of prucalopride accelerates gastric emptying and stool frequency, but does not appear to improve gastroparesis or diet-related symptoms.⁴⁴

Research Subject Analysis

The few pilot studies conducted to date have shown improved gastric emptying in idiopathic, diabetic, and CTD gastroparesis.^{43,44} Also, 2-mg daily prucalopride in the idiopathic group improved patient symptoms and quality

Table 1 Characteristics of the Randomized Placebo-Controlled Crossover Pilot Trials About the Effect of Prucalopride on Gastroparesis

Author	Study Groups	Sample Size	Age (Year)	Gender (M/F)	Intervention	Efficacy on Gastroparesis Symptoms	Efficacy of Gastric Emptying	Safety and Adverse Effects (n)
Carbone ⁴³	Canada, 1 site	34 (28: I 6: D)	43.5 ± 2.3 (I: 42.3 ± 2.6 D: 49.0 ± 4.0)	8/26 (I: 7/ 21 D: 1/ 5)	P 2 mg daily 4 weeks	Improved nausea/vomiting, fullness/satiety, and bloating/distention (GCSI) (total, 1) Improved upper abdominal pain and reflux symptoms (PAGI-SYM questionnaire) Improved overall QOL and the subscale of clothing	Improved solid gastric emptying rate	Dropout cases SAE: small bowel volvulus (1) AE: Diarrhea (1) headache (1) Transient AE cases AE: diarrhea (9) headache (8) Abdominal cramps (1) Cystitis (1) Respiratory infection (1)
Andrews ⁴⁴	Canada, 1 site	15 (13: D 2: connective tissue disease)	46 ± 3	6/9	P 4 mg daily 4 weeks	No improvement in symptoms	Enhancing effects on gastric emptying and colonic transit	Abdominal cramping, pain (1) (dose reduction) Headache (5) abdominal cramping (5), and diarrhea (1) (transient, resolved)

Abbreviations: I, idiopathic; D, diabetic; GCSI, Gastroparesis Cardinal Symptom Index; PAGI-SYM, Patient Assessment of Upper Gastrointestinal Disorders Symptoms Questionnaire; QOL, quality of life; SAE, serious adverse event; AE, adverse event; P, prucalopride.

of life. However, there was no association between symptom improvement and the gastric emptying rate.⁴³ The correlation between symptoms and delayed gastric emptying in diabetes and idiopathic gastroparesis remains the subject of ongoing debate. In several studies, the relationship between symptom improvement and gastric half-emptying time was not good and did not show a significant correlation.^{35,45} This may be because gastric half-emptying time measurements cannot reflect all of these in evaluating response to treatment and postprandial motor function.

A recent report states that an optimal gastric emptying measurement for at least 3 h via scintigraphy or breathing tests shows the best correlation.⁴¹ Another study that analyzed the relationship between improved simultaneously measured symptoms and changes in gastric emptying rate after using prokinetics agents revealed no correlation between the two in the analysis of eight clinical trials, even in the closest apposition. The observed symptoms' significant benefit may be attributable to effects other than enhanced gastric emptying.⁴⁶ This result has been the subject of debate

for some time.⁴⁷ Therefore, other mechanisms may be involved in prucalopride's therapeutic effect that is unrelated to the prokinetic effect. Prucalopride, which has an antinociceptive effect, may also improve symptoms by reducing the perception of luminal distension by gas.⁴⁸ Thus, additional analysis, research on other measurements, or new methods is needed to confirm the therapeutic effect of prucalopride on symptoms.^{49–52} In Andrews' study, the symptoms did not improve in the diabetic group. Too few CTD groups allow meaningful analysis to be performed.⁴⁴ Moreover, patients with diabetic gastroparesis may have sensory neuropathy, which may confuse symptom evaluation, and more large-scale studies may need to be performed.^{33,53,54}

It is unclear whether the studies to date, mainly targeting patients in tertiary care centers, can be applied to patients receiving different care levels. Similarly, the effect on gastroparesis is unclear because there have been no studies on patients with organic or drug-induced gastroparesis.

The Carbone et al and multicenter studies using velusetrag showed fewer symptom improvements than the placebo in a subset of diabetic patients, suggesting that idiopathic may have a better response than diabetic gastroparesis.^{43,55} Therefore, based on the studies to date, it is expected that gastroparesis, especially idiopathic gastroparesis, with symptoms that are being cared for in tertiary care centers can be used as an off-label. However, more studies are needed.

Capacity Analysis

The effective prucalopride dose for gastroparesis is currently unclear. Prokinetics increase gastric emptying through stimulation of gastric contractility. However, prokinetics may cause symptoms due to rapid food discharge by reducing fundic accommodation.^{35,36} The lack of correlation between changes in gastric emptying rates and symptomatic benefits of prucalopride suggests that enhanced gastric emptying is not necessarily the mechanism responsible for the majority of symptom improvement. Therefore, finding the optimal dose for which gastric emptying is neither too fast nor too slow and should be evaluated and studied differently according to gastroparesis etiology and symptom severity. A lower starting dose may be preferable in the off-label use for gastroparesis because the current diabetic group did not show symptom improvement in the 4-mg dose.⁴⁴ Similarly,

daily 2-mg prucalopride in the idiopathic group showed improved symptoms and quality of life.⁴³

Analysis of Complications That Occurred

Both studies reported the side effects were diarrhea, headache, abdominal cramps, cystitis, and respiratory infection. Most of the side effects were temporary. In a study by Carbone et al, three patients in the prucalopride group dropped out due to small bowel volvulus, diarrhea, and headache (3/17). In Andrews' study, abdominal cramping required dose reduction in one patient (1/15). In a study by Carbone et al, one serious side effect, small bowel volvulus, occurred.⁴³ Therefore, more research is needed. However, caution may be exercised for use in patients with risk factors for volvulus (eg, enlarged colon or abdominal adhesions).⁵⁶ Moreover, consideration should be given to the volvulus if any suspicious symptoms are noted during use.

Chronic Constipation

Table 2 shows seven Phase II studies, ten Phase III studies, and one Phase IV study. Table 2 summarizes the total, severe, and serious adverse events (AEs) and withdrawal rates from all Phase II, III, and IV trials in constipation. In particular, we have summarized the prucalopride stability in a specific population, cardiovascular safety, and side effects depending on the dose.

Summary of Research Completed

Safety During Phase II Studies

Treatment-associated AEs were reported in 50–88% of the patients due to the safety assessment of phase II randomized controlled trial comparing the placebo group and the 0.5, 1, 2, or 4 mg prucalopride-treated group. The most common treatment-associated AEs were headache, nausea, abdominal pain, and diarrhea. Most AEs were transient and arose within the first 24 h of prucalopride treatment. Discontinuation rates due to AEs were reported in the placebo (10.6%) and the prucalopride treatment (4–50%) groups. Many discontinuations were the consequence of abdominal pain and discomfort, diarrhea, vomiting, headache, atypical chest discomfort, fecal incontinence, back pain, nausea, flatulence, malaise, edema sensation, dizziness, dysphagia, palpitations, insomnia, dry skin, and increased micturition frequency. No consistent, clinically relevant, or treatment-related differences were reported

Table 2 Characteristics and Safety Outcomes of the Randomized Placebo-Controlled Trials About the Effect of Prucalopride on the Constipation (Phase 2, 3, 4)

Table 2A Characteristics in Phase 2 Trials

Author	Condition	Age/Sex (n)	Group (n)	Intervention	Duration
Bouras ²	Functional constipation	41 ± 3/M (4):F (36)	P 2 mg (13)/P 4 mg (11)/ Placebo (14)	P 2, 4 mg/day	1 week
Krogh ⁸⁸	Chronic constipation after spinal cord injury	≥18 years/M (16):F (6)	P 1 mg (8)/P 2 mg (7)/Placebo (7)	P 1, 2 mg/day	4 weeks
Emmanuel ⁸⁹	Chronic idiopathic constipation	≥18 years/F (74)	P (37)/Placebo (36)	P 1 mg/day	4 weeks
Sloots ⁹⁰	Chronic functional constipation	18–70 years/M (3):F (25)	P 1 mg (12)/P 2 mg (16)	P 1, 2 mg/day	2 weeks
Camilleri ²²	Elderly patients with constipation residing in a nursing facility	Elderly patients (range: 65–98 years)/M (24):F (65)	P 0.5 mg (21)/P 1 mg (24)/P 2 mg (26)/Placebo (18)	P 0.5, 1, 2 mg/day	4 weeks
Coremans ⁹¹	Chronic constipation	18–75 years/M (1):F (52)	P (27)/Placebo (26)	P 4 mg/day	4 weeks
Sloots ⁷⁰	Opioid-induced constipation	≥18 years/NA	P 2 mg (66)/P 4 mg (64)/ Placebo (66)	P 2, 4 mg/day	4 weeks

Table 2B Characteristics in Phase 3 Trials

Author	Condition	Age (Mean ± SD)/Gender (n)	Group (n)	Intervention	Duration
Camilleri ⁵⁷	Chronic constipation	48.3 ± 0.6/M (75):F (545)	P 2 mg (207)/P 4 mg (204)/ Placebo (209)	P 2, 4 mg/day	12 weeks
Tack ¹⁹	Chronic constipation	43.9 ± 0.57/M (66):F (650)	P 2 mg (238)/P 4 mg (238)/ Placebo (240)	P 2, 4 mg/day	12 weeks
Quigley ⁵⁸	Chronic constipation	47.9 ± 0.54/M (86):F (555)	P 2 mg (214)/P 4 mg (215)/ Placebo (212)	P 2, 4 mg/day	12 weeks
Muller-Lissner ²⁹	Chronic constipation	Elderly patients (range: 64–95 years)/M (91):F (212)	P (231)/Placebo (72)	P 1, 2, 4 mg/day	4 weeks
Ke ⁶⁴	Chronic constipation	41.6 ± 12.89/M (51):F (450)	P (249)/Placebo (252)	P 2 mg/day	12 weeks
Cinca ⁶¹	Chronic constipation	18–75 years/F (240)	P (120)/PEG 3350 + electrolytes (120)	P 1, 2 mg/day	4 weeks
Yiannakou ⁶³	Chronic constipation	≥18 years/M (370)	P (184)/Placebo (186)	P 1, 2 mg/day	12 weeks
Camilleri ²⁴	Chronic constipation	46.7 (range: 18–86 years)/M (143):F (1312)	P (960)/Placebo (495)	P 2, 4 mg/day	12 weeks
Mugie ⁶⁰	Children with functional constipation	Children (P 8.3 ± 4.54 Placebo 8.2 ± 4.69)/M (95):F (118)	P (106)/Placebo (107)	≤50 kg: 0.04 mg/kg >50 kg: 2 mg	8 weeks
Tack ²⁰	Chronic constipation	P 46.3 ± 0.57 Placebo 46.1 ± 0.54/M (144):F (1176)	P (659)/Placebo (661)	P 2 mg/day	12 weeks

Table 2C Characteristics in Phase 4 Trials

Author	Condition	Age/Gender (n)	Group (n)	Intervention	Duration
Piessevaux ⁹²	Chronic constipation	48.9 ± 16.0/M (53):F (308)	P (181)/Placebo (180)	Prucalopride 1–2 mg/day	24 weeks

Abbreviations: P, prucalopride; M, male; F, female; NA, not available.

Table 2D Safety Outcomes in Phase 2 Trials

Author	AE [n, Percentage]	Most Common AE	Severe AE	Serious AE	Treatment Withdrawals Due to AEs [n/Total Participants (Percentage)]
Bouras ²	P 2 mg (24)/P 4 mg (24)/Placebo (3)	GI (diarrhea, flatulence), Non-GI (headache)	No	No	P 2 mg 1/13 (7.7%) (n = 1: atypical chest discomfort), P 4 mg 1/11 (9.1%) (n = 1: diarrhea, vomiting, and abdominal discomfort)
Krogh ⁸⁸	P 1 mg 7/8 (87.5%)/P 2 mg 6/8 (75.0%)/Placebo 6/7 (85.7%) PDAE: P 1 mg 5/8 (18 events)/P 2 mg 5/8 (13 events)/Placebo 1/7 (1 events)	GI (flatulence, abdominal pain, and diarrhea)	NA	No	Placebo 1/7 (14.3%) (n = 1: fecal incontinence) P 2 mg 4/8 (50%) (n = 1: pressure sore in the gluteal region, n = 2: abdominal pain, headache, n = 1: diarrhea, headache)
Emmanuel ⁸⁹	P 28/37 (77%)/Placebo 24/36 (66%)	GI [diarrhea (10%), flatulence (21%), Non-GI [headache (49%)]	P 36%/Placebo 34%	No	P 3/37 (8.1%) (n = 1: back pain, nausea, n = 1: abdominal pain, diarrhea, n = 1: diarrhea, vomiting)
Sloots ⁹⁰	Group 1 (P 1 mg): P (8)/Placebo (8) Group 2 (P 2 mg): P (14)/Placebo (2)	GI (abdominal pain, nausea, diarrhea and flatulence) Non-GI [headache (25–27%)]	NA	No	P 2 mg 3/16 (18.8%) [n = 1: diarrhea and headache; n = 1: abdominal pain, diarrhea, flatulence, malaise, and nausea; n = 1: headache and sensation of edema (swollen hands, feet, and face)]
Camilleri ²²	P 0.5 mg 18/21 (85.7%)/P 1 mg 17/24 (70.8%)/P 2 mg 18/26 (69.2%)/Placebo 9/18 (50%) PDAE: 40/215 events (18.6%) (89 patients)	GI (diarrhea, and abdominal pain) Non-GI (urinary tract infection, injury, fall, anemia, headache)	P 0.5 mg 2/21 (9.5%)/P 1 mg 2/24 (8.3%)/P 2 mg 1/26 (3.8%)/Placebo 2/18 (11%)	P 0.5 mg (n = 2)* Two expiry*	P 0.5 mg 3/21 (14.3%)/P 1 mg 1/24 (4.2%)
Coremans ⁹¹	P 24/27 (88.9%) (84 events)/Placebo 12/26 (46.2%) (30 events)	GI (headache), Non-GI (nausea)	Approximately one-third	No	P 3/24 (12.5%) (n = 1: dizziness and headache; n = 1: abdominal pain and headache; n = 1: dysphagia, palpitations, insomnia, dry skin, and increased micturition frequency)
Sloots ⁷⁰	TEAE: P 2 mg 38/66 (50.0%)/P 4 mg 32/64 (50.0%)/Placebo 32/66 (48.5%)	Abdominal pain (P 4 mg 16/64, 25.0%/P 2 mg 8/66, 12.1%/Placebo 9/66, 9.1%) and nausea Headache [P 2 mg, 4/66 (6.1%)/P 4 mg, 5/64 (7.8%)/Placebo 3/66 (4.5%)]	P 2 mg 11/66 (16.7%)/P 4 mg 14/64 (21.9%)/Placebo 13/66 (19.7%) PDAE: P 2 mg 9/66 P 4 mg 9/64 Placebo 7/66	P 2 mg 4/66 Placebo 4/66	Placebo 7/66 (10.6%)/P 2 mg 3/66 (4.5%)/P 4 mg 5/64 (7.8%) (m/c: abdominal pain)

Notes: *Prucalopride 0.5 mg n = 1 (moderate diarrhea, melana, colitis, and diverticulitis all considered possibly related). n = 1 (urinary tract infection and skin ulceration; not related to study medication). *Neither was considered related to study medication by the site investigator.

Abbreviations: P, prucalopride; NA, not available; AE, adverse event; GI, gastrointestinal; TEAE, treatment-emergent AEs; PDAE, possibly drug related AEs.

regarding PR, QT, QTcB, or QTcF intervals. A randomized controlled trial was conducted in elderly patients aged ≥ 65 years to investigate prucalopride's safety

compared to the placebo group and the 0.5, 1, or 2 mg daily prucalopride-treated group.²² Of the patients included in this study, 78% were being treated for

Table 2E Safety Outcomes in Phase 3 Trials

Author	AE (n/Total Participants, Percentage)	Most Common AE	Severe AE	Serious AE	Treatment Withdrawals Due to AEs (n/Total Participants, Percentage)
Camilleri ⁵⁷	TEAE: P 2 mg 166/207 (80.2%)/P 4 mg 160/204 (78.4%)/ Placebo 149/209 (71.3%)	GI (nausea, abdominal pain, and diarrhea), Non-GI (headache)	NA	P 2 mg 3/207 (1.4%)*/P 4 mg 7/ 204 (3.4%)/Placebo 8/209 (3.8%)	P 2 mg 17/207 (8.2%)/P 4 mg 16/204 (7.8%) Placebo 4/209 (1.9%)
Tack ¹⁹	TEAE: P 2 mg 170/238 (71.4%)/P 4 mg 178/238 (74.8%)/ Placebo 161/240 (67.1%)	GI (nausea, abdominal pain, diarrhea), Non-GI (headache)	Severe diarrhea: P 2 mg (0.8%)/P 4 mg (3.4%)/ Placebo (2.1%)	No	P 2 mg 15/238 (6.3%)/P 4 mg 36/238 (15.1%) Placebo 16/240 (6.7%)
Quigley ⁵⁸	TEAE: P 2 mg 173/214 (81%)/P 4 mg 163/215 (76%)/ Placebo 140/212 (66%)	GI (nausea, abdominal pain, diarrhea and flatulence), Non-GI (headache)	P 2 mg 33/214 (15%)/P 4 mg 45/ 215 (21%)/Placebo 21/212 (10%)	P 2 mg 4/214 (1.9%)/P 4 mg 5/ 215 (2.3%)/Placebo 5/212 (2.4%)	P 2 mg 9/214 (4%)/P 4 mg 12/215 (6%) Placebo 4/212 (2%)
Muller-Lissner ²⁹	TEAE: P 1 mg 37/76 (48.7%)/P 2 mg 29/75 (38.7%)/P 4 mg 38/80 (47.5%)/Placebo 32/ 72 (44.4%)	GI (nausea, abdominal pain, diarrhea), Non-GI (headache)	P 1 mg (3.9%)/P 2 mg (6.7%)/P 4 mg (6.3%)/Placebo (6.9%)	Placebo (n = 1) [*] P 1 mg (n = 1) [*] P 4 mg (n = 1) [*]	m/c GI disorders: P 1 mg 2/76 (2.6%)/P 2 mg 4/75 (5.3%)/P 4 mg 7/80 (8.8%)/Placebo 3/72 (4.2%)
Ke ⁶⁴	TEAE: P 142/249 (57%)/Placebo 92/252 (36.5%) PDAE: P 90/249 (36.1%)/Placebo 33/252 (13.1%)	GI (nausea, abdominal pain, and diarrhea), Non-GI (headache)	NA	P 3/249 (1.2%) [¥] / Placebo 5/252 (2.0%) [€]	P 8/249 (3.2%): m/c diarrhea Placebo 3/252 (1.2%)
Cinca ⁶¹	TEAE: P 1–2 mg 82/120 (68.3%)/ PEG 3350 + electrolytes 102/120 (85.0%) PDAE: P 1–2 mg (14.3%)/ PEG (5.3%)	GI (nausea, vomiting, and abdominal pain), Non-GI (headache, dysmenorrhea, pharyngitis)	P 1–2 mg 3/187 events (1.6%)/PEG 8/280 events (2.9%)	P 1 mg (n = 1) [°]	P 3/120 (2.5%)
Yiannakou ⁶³	TEAE: P 78/184 (42.4%)/Placebo 64/186 (34.4%) PDAE: P 42/186 (22.8%)/Placebo 25/186 (13.4%)	GI (nausea, abdominal pain, and diarrhea), Non-GI (headache)	P 3/186 (1.6%)/ Placebo 3/186 (1.6%)	Placebo (n = 4) [#] P (n = 1) [#]	P 6/184 (3.3%): diarrhea, nausea, headache, and dizziness Placebo 7/186 (3.8%)
Camilleri ²⁴	NA	GI (abdominal pain, diarrhea, and nausea), Non- GI (headache)	NA	NA	Month 3 P 24/961 (2.5%) Placebo 34/494 (6.9%)
Mugie ⁶⁰	TEAE: P 74/106 (69.8%)/Placebo 65/107 (60.7%)	Headache (P: 13.2%; placebo: 0.9%)	No	Placebo n = 2 (3 events) P n = 5 (9 events) PDAE: 5/12 events	P 1/106 Placebo 1/107

(Continued)

Table 2E (Continued).

Author	AE (n/Total Participants, Percentage)	Most Common AE	Severe AE	Serious AE	Treatment Withdrawals Due to AEs (n/Total Participants, Percentage)
Tack ²⁰	P 2 mg 509/659 (77.2%)/ Placebo 450/661 (68.1%)	GI (nausea, abdominal pain, and diarrhea), Non-GI (headache)	NA	1–3%	P 41/659 (6.2%) Placebo 25/661 (3.8%)

Notes: *One patient with known mitral-valve prolapse and a history of supraventricular tachycardia. [†]Prucalopride n = 1 (ECG signs of myocardial ischemia considered possibly related to study drug). [‡]Placebo n = 1 (intrauterine death considered possibly related to study drug) n = 1 (erysipelas considered doubtfully related to study drug). [§]Placebo n = 1 (arrhythmia, myocardial infarction considered not related to the study drug; the patient expired). Prucalopride 1 mg n = 1 (mild drug abuse considered doubtfully related and accidentally reported). Prucalopride 4 mg n = 1 (fracture of the left forearm reported as moderate and not related to study medication). [¶]Prucalopride 1 mg n = 1 (GI disorder and vertigo considered severe and possibly related to study medication). ^{‡‡}Placebo n = 4 (myocardial ischemia, lower limb fracture, glottis carcinoma, and atelectasis considered not related to the study drug). Prucalopride n = 1 (atrial fibrillation considered not related to the study drug)

Abbreviations: P, prucalopride; NA, not available; AE, adverse event; GI, gastrointestinal; TEAE, treatment-emergent AEs; PDAE, possibly drug related AEs.

cardiovascular disease, and 88% had a history of cardiovascular disease in the past. No group experienced life-threatening arrhythmias. Prolongation of QTc interval (QTcF of >450 and >470 ms in males and females, respectively) was reported in about 5% of the placebo, 0.5 mg prucalopride and 1 mg prucalopride groups. There were no differences between the groups. Severe AEs (eg, moderate diarrhea, melaena, colitis, and diverticulitis), all of which occurred in one patient in the prucalopride 0.5 mg group, were reported to be drug related. However, the side effects of most of the current phase II studies have been mild to moderate. Therefore, the phase II study results showed that the overall use of prucalopride was safe across the therapeutic dose range.

Safety in Phase III Trials

The most common treatment-associated AEs were headache followed by nausea, abdominal pain, and diarrhea at 25%–30%, 12%–24%, 16%–23%, and 12%–19%, respectively, in the prucalopride group and 12%–17%, 8%–14%, 11%–19%, and 3%–5%, respectively, in the placebo group.^{19,22,25,57–59}

Most AEs were of mild to moderate severity, transient, and occurred within the first 24 h of prucalopride treatment. Excluding AEs reported on day 1, the difference between prucalopride and placebo recipients in the incidence of these AEs was weak.^{19,57,58,60} Discontinuation rates due to AEs were reported in the placebo (1.2–6.9%) and prucalopride treatment (2.5–15.1%) groups. Among the serious side effects reported related to the drug were GI disorder and vertigo that occurred in the 1-mg prucalopride group, which was severe and possibly related to study medication.⁶¹ Moreover, diarrhea was reported in 6–14% of patients in the daily 2- or 4-mg prucalopride-treated group. The Asian Pacific study cohorts were reported to have higher diarrhea occurrence (22.1%). In the prucalopride group, changes in QTcF from baseline were not significant. Similarly, the occurrence of the prolonged QT interval was not significant compared with the placebo group.^{19,25,29,57,61–64}

Research Subject Analysis

Cardiovascular risks of prucalopride have been carefully examined for the safe use of prucalopride in chronic

Table 2F Safety Outcomes in Phase 4 Trials

Author	AE (n/Total Participants, Percentage)	Most Common AE	Severe AE	Serious AE	Treatment Withdrawals Due to AEs (n/Total Participants, Percentage)
Piessevaux ⁹²	PDAE: P 35/180 (19.4%)/ Placebo 48/181 (26.5%)	GI (nausea and abdominal pain) Non-GI (headache)	P [4/181 (2.2%)]/ Placebo [4/180 (2.2%)]	Placebo n = 4 [¶] P n = 4 [¶]	(Diarrhea, nausea, headache, abdominal pain, and dizziness) P 14/181 (7.7%)/Placebo 9/180 (5.0%)

Notes: [¶]Placebo n = 4 (ischemic colitis, chronic cholecystitis, vestibular neuronitis, ischemic stroke, and orthostatic hypotension). Prucalopride n = 4 (gastric obstruction, decreased blood pressure, prolonged QT interval, cerebrovascular accident, and abnormal behavior).

Abbreviations: P, prucalopride; AE, adverse event; GI, gastrointestinal; PDAE, possibly drug related AEs.

constipation patients, including cardiologically vulnerable patients (eg, elderly patients), especially because of concerns over the negative effects of 5-HT₄ on the cardiovascular system. Additional safety, tolerability, and clinical effectiveness assessments in elderly patients are required for the routine use of prucalopride in conventional laxative-resistant chronic constipation patients.

Elderly Population

Although prucalopride's efficacy and safety have been demonstrated in several randomized clinical trials, trials in elderly populations with generally associated heart, kidney, liver, and lung comorbidities and prevalent incidence of chronic constipation are lacking. However, based on the current research results, prucalopride was shown to be safe in elderly patients.^{22,29} A previous study investigated a 0.5–2 mg dose escalation of prucalopride. This study had 89 participants in a nursing home. History of cardiovascular disease was reported in 89% of the participants. Headache and diarrhea were the most common adverse effects of the escalation and any electrocardiographic changes or cardiac events were not reported.²²

Male

Prucalopride use was recommended for women because 87% of the patients in this study were women. Thus, the effect in men was not sufficiently reviewed.⁶⁵ From the clinical experience of real experts and the results of a randomized controlled study, the use of prucalopride can be used effectively and safely to treat male constipation.⁶³ In a phase III trial with 370 men, the occurrence of at least one treatment-emergent AE (TEAE) was not significantly higher in the prucalopride (42.4%) than the placebo group (34.4%). The most common TEAEs regarding prucalopride were diarrhea, nausea, abdominal pain, and headache. One and four serious TEAEs were reported in the prucalopride and placebo groups, respectively. Moreover, mild or moderate TEAEs are the majority. Treatment discontinuation due to AEs was similar between the two groups at 3.3% and 3.8% in the prucalopride and placebo groups, respectively. One and two cardiovascular AEs were reported in the prucalopride (coronary artery occlusion) and placebo (one angina and one myocardial ischemia) groups showing low cardiovascular AE occurrence in both groups, respectively. One patient in the prucalopride group had prolonged QT at week 4 but it normalized at week 12. Prucalopride treatment was continued subsequently.

Asian and Non-Asian

In the integrated analysis of phase III clinical trials regarding prucalopride, the Asian and non-Asian subgroups of the prucalopride group showed a significant difference in the number of patients reporting at least one TEAE ($p < 0.001$). More patients in the Asian subgroup experienced diarrhea, but other TEAEs, including headache, dizziness, abdominal pain, upper abdominal pain, flatulence, nausea, and vomiting, were lower than the non-Asian subgroup.^{23,59} Numeric differences regarding efficacy and TEAEs were found among the Asian and non-Asian subgroups. The differences are thought to result partly from the concurrence of the functional gastrointestinal disorders in the non-Asian subgroup.

Application Depending on Constipation Type

Prucalopride was effective in patients with a defecatory disorder or constipation-predominant irritable bowel syndrome and slow-transit constipation.⁶⁶ In addition to typical constipation symptoms (eg, straining, residual stool, and hard stool), abdominal symptoms (eg, bloating and discomfort) were improved.⁶⁷ Therefore, prucalopride can be used in patients with chronic constipation of various subtypes if no response to traditional laxatives is noted.

Opioid-Induced Constipation. Chronic opioid therapy could commonly cause opioid-induced constipation (OIC) in patients suffering from cancer- or noncancer-related pain.⁶⁸ OIC is defined in Rome IV criteria as an atypical change in bowel habits after beginning opioid therapy with any of the following characteristics: bowel frequency reduction, development or exacerbation of tension at stools, incomplete evacuation sensation, or a patient's feeling of discomfort regarding bowel habits.⁶⁹ New OIC treatments have been approved by the Food and Drug Administration including methylnaltrexone, naloxegol, and naloxone with the recent approval of naldemedine and lubiprostone. In the case of prucalopride, two placebo-controlled double-blind trials have been conducted for the efficacy in OIC patients.^{70,71} However, one trial was discontinued prematurely due to the safety of unrelated business decision priority of the sponsor.⁷² The primary endpoint was set as the percentage of patients with >1 CSBM/week increase from the baseline. The prucalopride group showed modest results compared with the placebo group in these trials (RR = 0.74; 95% confidence interval (CI), 0.58–0.96; NNTT = 6).⁷³ However, the therapeutic value, compared with the placebo, was lower in the prucalopride trial than in the methylnaltrexone

and naloxegol trials.⁷⁴ The total scores of Patient Assessment of Constipation-Symptom and Patient Assessment of Constipation-Quality of Life were improved in the prucalopride trial.⁷⁰ The patients who remained constipated with active treatment were lower in the prucalopride trial (31%) compared with the methylal-trexone trials (42%) and significant AEs were not reported.^{70,75}

Constipation-Predominant Irritable Bowel Syndrome. No published prucalopride trial is believed to exist regarding constipation-predominant IBS (IBS-C) even though the European Agency of Medicinal Products approved prucalopride as the treatment for laxative-resistant chronic constipation. An integrated data analysis from three double-blind trials, consisting of 936 constipated female patients, demonstrated favorable outcomes of prucalopride regarding typical IBS abdominal symptoms (eg, bloating, abdominal discomfort, and abdominal pain in these patients).⁶⁷ A recent study⁴⁸ using an intestinal gas transit test reported that prucalopride decreased the perception of abdominal symptoms in a small number of IBS-C patients (mean score, 2.3 ± 0.5) compared with the placebo group (mean score, 3.5 ± 0.3 ; $p = 0.045$) with no modification in the gas evacuation rate from the bowel. These results justify the conduct of a new trial investigating the use of prucalopride in IBS-C patients. However, no randomized controlled trial regarding prucalopride use in IBS-C patients is yet published. Since the stimulation of 5-HT₄ receptors leads to visceral antinociceptive effects and prucalopride decreases abdominal symptoms (eg, abdominal pain and discomfort) without accelerating gas transit and modifying gas retention, the efficacy of prucalopride in IBS-C patients is expected.^{48,67} Moreover, prucalopride was reportedly used rather frequently in clinical practice among Canadian and Italian gastroenterologists for IBS-C patients in two recently conducted surveys.^{76,77} Further studies regarding this crucial clinical issue are required.

Analysis of Complications That Occurred

Cardiovascular Safety

The first-generation 5-HT₄ receptor agonist's cisapride and tegaserod were removed from the market due to associated cardiovascular risk. Arrhythmia was thought to be associated with QTc prolongation by cisapride, and an ischemic event of uncertain was caused by tegaserod. However, prucalopride works selectively only on 5-HT₄ receptors, unlike cisapride and tegaserod. Thus, no risk of

cardiovascular side effects was noted.⁷⁸ The QT interval was not affected even when prucalopride was administered at a therapeutic dose (2 mg) and a dose exceeding the treatment dose (10 mg) in healthy volunteers.⁷⁹ Palpitations have been reported during the first 2 days of taking prucalopride. However, the incidence is low, the incidence of other cardiovascular complications is very low, and no statistically significant difference exists compared with the placebo group.^{24,80} According to a multinational population-based cohort study by Gilseman et al, the pooled adjusted incidence rate ratio of major adverse cardiovascular events in patients with chronic constipation using prucalopride was 0.64 when compared to PEG (95% CI, 0.36–1.14).⁸¹ In the post hoc analysis of major adverse cardiac events (MACE) from prucalopride's clinical studies, 19 double-blind, placebo-controlled studies and 9 open-label studies for chronic idiopathic constipation (CIC) patients were noted. Moreover, the number of MACE in clinical trials with prucalopride in adults with CIC was low and similar to that for placebo.⁸² Therefore, attention should focus on using prucalopride in patients at risk of cardiovascular disease. However, the incidence of significant complications is very low. Thus, it can relatively be used safely.

Analysis of Side Effects According to Dose

A meta-analysis by Sajid showed an increasing trend in the number of patients with side effects after using 4 and 2 mg compared with 1 mg prucalopride. In patients with chronic constipation, the side effects of profiles identified by the OR of 1, 2, and 4 mg doses of prucalopride were 2.02, 1.76, and 1.52, respectively, indicating an increased prucalopride effect without increasing the side effects. However, the generally recommended dosage of prucalopride is 2 mg once daily.⁸³ Exceeding a prucalopride dosage of 2 mg once daily is not expected to increase efficacy. The results of the Sajid study are only for a group of patients who have failed basic laxative treatments, lifestyle modifications, and potent laxative treatments. Therefore, generalizing and applying the conclusions to a group of patients for which all types of constipation and early treatment were not optimally tested is not possible.

Expert Opinion

In summary, it seems likely that prucalopride may help, especially in patients suffering from both gastroparesis and chronic constipation. According to a recent post hoc

analysis analyzing six phases 3 and 4 randomized, double-blind, placebo-controlled studies of patients with significant abdominal bloating by Lembo et al, treatment with prucalopride improved symptoms compared with placebo, irrespective of baseline bloating severity, and was most effective in women and patients <65 years old with CIC.⁸⁴ Thus, prucalopride had a beneficial effect on bloating, and the only item in the Carbone study that significantly improved in terms of quality of life was how patients' clothing fit. Bloating is also often associated with lower gastrointestinal disorders and may originate from something other than the upper GI origin. Large effect sizes (>0.8) were seen on bloating and incomplete bowel movements according to a study by Tack et al.⁶⁷ Thus, the clinical benefit of prucalopride in gastroparesis may be primarily related to a decrease in the perception of bloating, not as a result of a more intuitive prokinetic effect. In future clinical trials, a study investigating the increase of the therapeutic effect in patients with concurrent gastroparesis and chronic constipation may be conducted.

The long-term effectiveness of prucalopride is yet undisclosed.⁸⁵ Prucalopride reportedly lost its efficacy gradually after the first few weeks of favorable and beneficial response in some patients. Tachyphylaxis, the development of tolerance, could cause this incomprehensible phenomenon, leading to drug dose escalation of reaching the same result. This often reversible mechanism could result either from an acceleration of the drug catabolism (inactivation) or reduced pharmacological activity due to receptor desensitization, which is more likely with prucalopride. The escalation of the prucalopride dose (up to 4 mg/day) does not provide sufficient efficacy in patients with tachyphylaxis. However, 2–4 weeks of delay followed by subsequent readministration of the previous effective dose of prucalopride seems to be more advantageous.

Prucalopride is currently recommended for use after failure of common laxatives, according to the guidelines. Moreover, prucalopride is not a first-line drug due to its relatively high price.^{86,87} The gradual decrease of previous laxatives, rather than abrupt stops, was recommended while waiting for the advent of prucalopride's effect. Consequently, the gastroenterologist could adjust the therapeutic prucalopride scheme as needed without compromising the clinical efficacy because the drug's efficacy is dose-dependent, and the drug may partially show its efficacy even below the commonly recommended dose. After the desired therapeutic response is achieved, the prucalopride administration

schedule can be adjusted to determine each patient's minimum effective dose. Even though no studies yet investigate the efficacy of the therapeutic schemes of prucalopride other than the daily 2 mg administration, this study could observe at least in some patients from the experience of this study that the therapeutic efficacy was maintained at a daily dose of 1 mg or with the administration of every other day or even with greater intervals. These therapeutic schemes may benefit the patients with minor AEs.

Conclusion: Analyzing the Data Presented in the Review

Prucalopride is an effective and safe option based on all the studies currently conducted. Its side effects are usually found on the first day of administration and are usually self-limiting and mostly mild to moderate. Its high selectivity for 5-HT₄ receptor has a very favorable stability profile, and no concern exists for cardiovascular problems. Thus, it may be the first-line treatment for constipation or other gastrointestinal diseases in the future. Where possible, prucalopride should be considered when managing adult patients with constipation who have not obtained relief from laxatives, regardless of subtype or symptom pattern.⁶⁶ Prucalopride also has the potential to be useful in the treatment of functional constipation and other forms of gastrointestinal diseases (eg, gastroparesis). Through the research on this potential, prucalopride is expected to be a useful and versatile option for treating gastrointestinal diseases in the future.

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