Prucalopride for Gastroparesis

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Possible Conflicts

Advisory Panels for Gp
- Takeda
- Evoke
- Aeon

Research Grants for Gp
- NIH
- Medtronic
- Takeda
- Vanda

UEG and ESNM Consensus on Gastroparesis

The European consensus defined gastroparesis as the presence of symptoms associated with delayed GE in the absence of mechanical obstruction.

Nausea and vomiting were identified as cardinal symptoms, with often coexisting postprandial distress syndrome symptoms of dyspepsia.

Only dietary therapy, dopamine-2 antagonists and **5-HT_4 receptor agonists** were considered appropriate therapies, in addition to nutritional support in case of severe weight loss.

Schol J, Wauters L, Dickman R, Drug V, Mulak A, Serra J, Enck P, Tack J; ESNM Gastroparesis Consensus Group.
Neurogastroenterol Motil. 2021 Aug;33(8):e14237.

5-HT4 Receptor Agonists

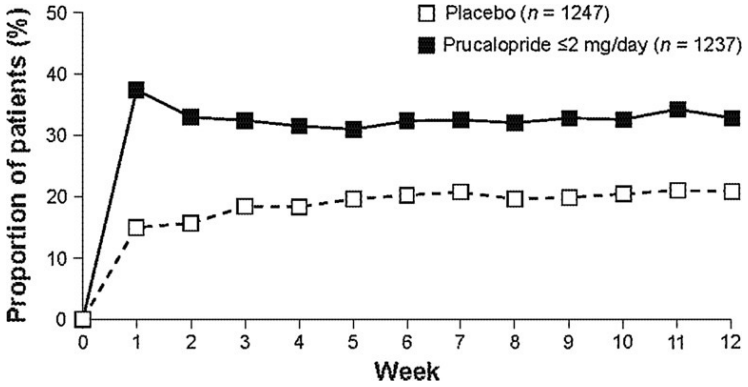
Cisapride	Previously approved for GERD. Used for gastroparesis
Tegaserod	Previously approved for IBS, CIC. Used for gastroparesis
Prucalopride	Approved for chronic constipation Could this be used for gastroparesis?

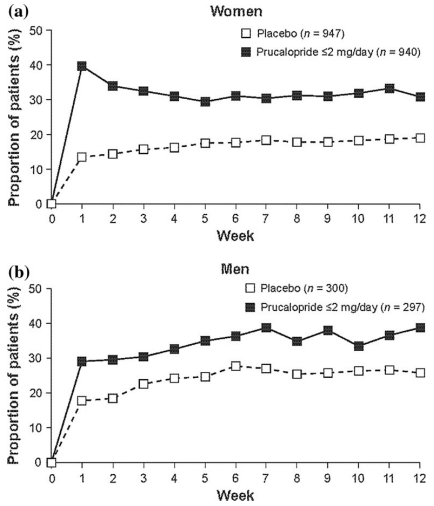
Efficacy and Safety of Prucalopride in Chronic Constipation: An Integrated Analysis of Six Randomized, Controlled Clinical Trials.

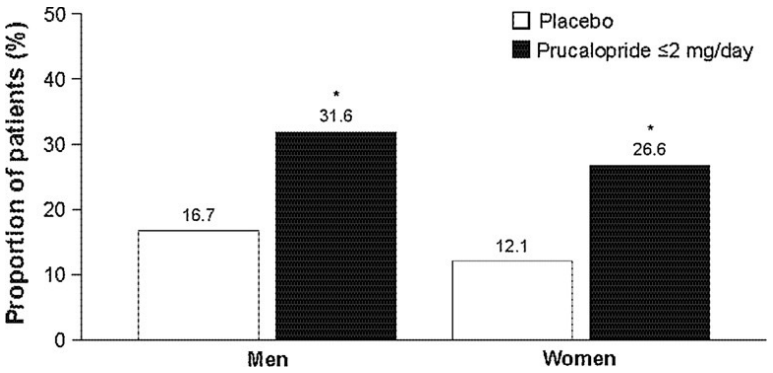
Prucalopride, a selective, high-affinity 5-hydroxytryptamine 4 receptor agonist, stimulates GI and colonic motility and alleviates common symptoms of chronic constipation (CC).

Prucalopride 2 mg daily in CC from 6 randomized, controlled trials.

Primary efficacy endpoint was percentage of patients with mean of ≥3 spontaneous complete bowel movements (SCBMs) per week over 12 weeks of treatment.







Side effects (>5%):
- Nausea
- Diarrhea
- Abdominal pain
- Headache

Cardiovascular effects:
- No EKG changes
- No MI, CVA

Camilleri, Tack, et al.
DDS 2016;61:2157

Prucalopride accelerates gastrointestinal and colonic transit in patients with constipation without a rectal evacuation disorder

Effects of prucalopride on gastrointestinal and colonic transit in patients with constipation.

Gastrointestinal and colonic transit were measured over 48 hours in 40 patients with functional constipation and no evidence of a rectal evacuation disorder.

Randomized to a daily dose of 2 or 4 mg prucalopride or placebo in a double-blind, parallel-group design.

Prucalopride **accelerated overall gastric emptying**, small bowel transit, and overall colonic transit.

Bouras EP, Camilleri M, Burton DD, Thomforde G, McKinzie S, Zinsmeister AR. Gastroenterology. 2001 Feb;120(2):354-60.

AGA FDA Town Hall Meeting: Prucalopride

FDA Submission for approval of prucalopride (Motegrity) 2 mg po qd for chronic idiopathic constipation in adults

Efficacy:

Used European data to supplement application

Side effects:

Cardiovascular: no signal seen

Prucalopride: 1/1545=0.1%; Placebo: 2/2019=0.1%

Suicidal ideation/behavior

Prucalopride: 1 patient suicide in trials; open label 2 pts

Benefit of Prucalopride for Symptom Control and Gastric Emptying Enhancement in Idiopathic Gastroparesis: A Controlled Cross-Over Trial

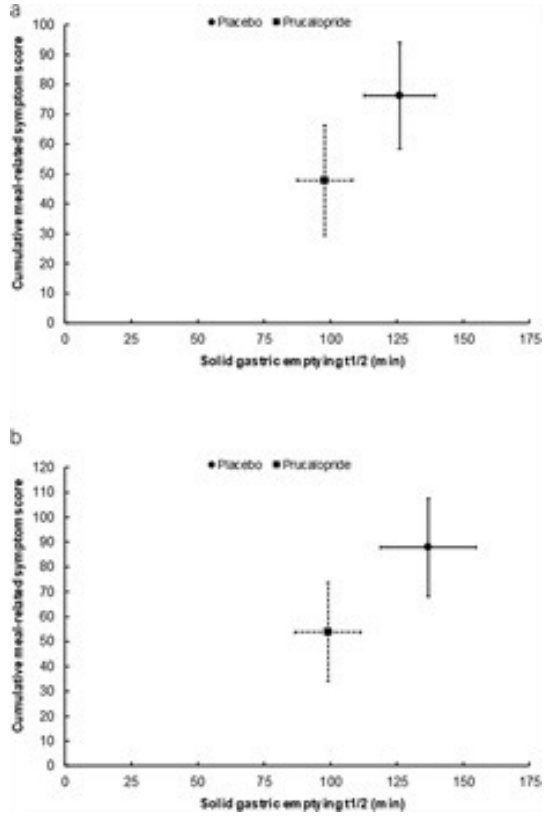
Single center, double-blind, randomized, placebo controlled, crossover study

4 weeks of prucalopride 2 mg po qd versus placebo

28 idiopathic gastroparesis patients. GEBT T1/2, GCSI (0-5)

		Baseline	**Prucalopride**
Gastric emptying (T1/2; min)	128±19	86±13*	141±17
Fullness/satiety	3.2±0.3	2.2±0.2*	3.3±0.3
Nausea/vomiting	1.6±0.2	1.0±0.3*	1.8±0.3
Bloating/distension	2.5±0.3	1.5±0.3*	3.1±0.3
Pain/discomfort	2.9±0.3	1.8±0.3*	2.3±0.3
PAGI-QOL	1.6±0.3	1.2±0.3*	1.9±0.4

No correlation between improvement in GE and symptoms



In idiopathic gastroparesis, 4 weeks prucalopride improved gastric emptying, symptoms and quality of life compared to placebo and to baseline.

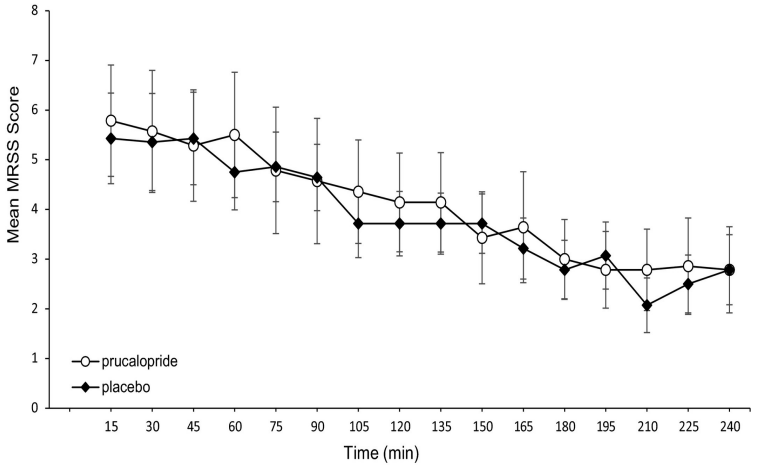
Carbone, Rotondo, Tack.
A J Gastro 2019;114:1265

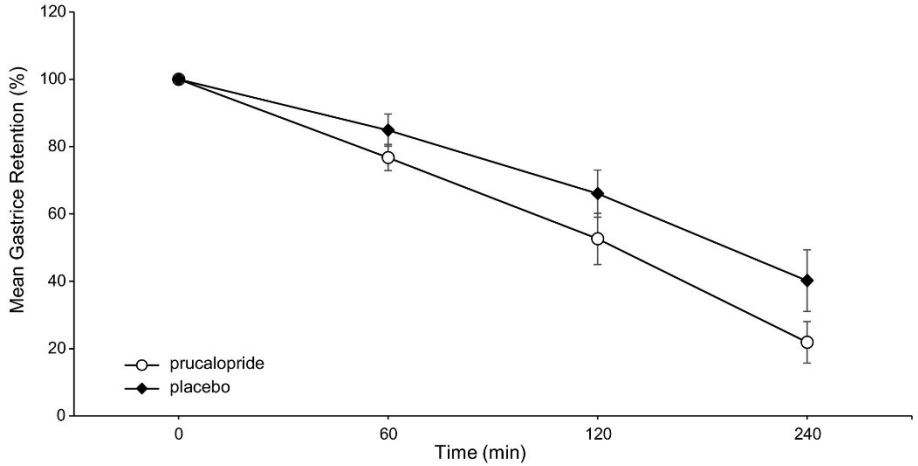
Prucalopride in diabetic and connective tissue disease-related gastroparesis: Randomized placebo-controlled crossover pilot trial

Double-blind crossover trial of four-week treatment periods with prucalopride or placebo divided by two weeks of washout.

Fifteen gastroparesis patients (13 diabetic, 2 CTD) were enrolled.

GCSI scores were lower than baseline but not different between treatment arms.





Weekly BM frequency was higher in prucalopride than placebo periods (10.5 vs 7.5, $p<0.01$

Analysis of diabetic gastroparesis (n = 13) population did not change the conclusions.

Prucalopride 4 mg accelerates gastric emptying and bowel movement frequency but does not appear to reduce gastroparesis or meal-related symptoms.

Andrews CN, Woo M, Buresi M, Curley M, Gupta M, Tack J, Wilsack L, Nasser Y. Neurogastroenterol Motil. 2021 Jan;33(1):e13958.

Prucalopride decreases esophageal acid exposure and accelerates gastric emptying in healthy subjects

Double-blind, placebo-controlled, randomized, crossover study, 21 healthy volunteers received 4 mg prucalopride or placebo per day for 6 days. HRM followed by 120-min HRM-pH-impedance monitoring after a standardized meal, ambulatory 24-h pH-impedance monitoring, and gastric emptying for solids.

Prucalopride decreased total acid exposure time (3.4 vs 1.7 %, p<0.05).

Total number of reflux events was unaffected by prucalopride.

Prucalopride improved acid clearance time (77.5 vs 44.0 s, p<0.05).

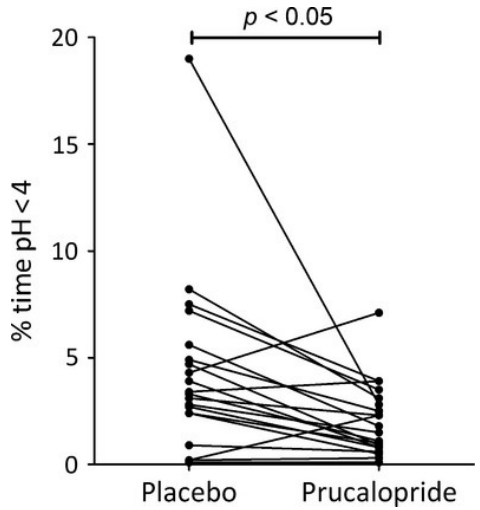
Number of reflux events extending to the proximal esophagus was reduced by prucalopride (15.5 vs 10.5, p<0.05).

Prucalopride did not affect the number of transient lower esophageal sphincter (LES) relaxations or their association with reflux events.

Esophageal motility and basal pressure of LES were not affected by prucalopride.

Prucalopride increased gastric emptying (T1/2 ; 32.7 vs 49.8 min, p<0.05) and decreased residue after 120 min (8.8 [4.4-14.8] vs 2.7 [1.3-5.4] %, p<0.05).

Prucalopride reduces esophageal acid exposure and accelerates gastric emptying in healthy male volunteers. These findings suggest that the drug could be effective for treatment of patients with reflux disease and functional dyspepsia



Kessing BF, Smout AJ, Bennink RJ, Kraaijpoel N, Oors JM, Bredenoord AJ. Neurogastroenterol Motil. 2014 Aug;26(8):1079-86.

Prucalopride reduces the number of reflux episodes and improves subjective symptoms in gastroesophageal reflux disease: Case series

Case presentations: 4 chronically constipated female gastroesophageal reflux disease-patients with reflux symptoms and an increased number of reflux episodes in combined esophageal pH and multichannel impedance monitoring treated with prucalopride (2mg per day). Symptoms were persistent to proton pump inhibitors and ranitidine. Numbers of all reflux episodes as well as non-acid reflux episodes were reduced in all of our patients. The objective findings were concordant with subjective reports of symptom relief. There were no major adverse events during prucalopride Rx.

Conclusion: Prucalopride showed promising results in the treatment of persisting or weakly and/or non-acid reflux episodes in our case series in four constipated patients.

Prucalopride can be regarded as a possible therapeutic option in treatment of standard proton pump inhibitor-persistent reflux in constipated patient.

Nennstiel S, Bajbouj M, Schmid RM, Becker V.J
Med Case Rep. 2014 Feb 5;8:34.

Influence of prucalopride on esophageal secondary peristalsis in reflux patients with ineffective motility

Determine whether prucalopride would augment primary and secondary peristalsis in gastroesophageal reflux disease patients with IEM.

After a baseline recording of primary peristalsis, secondary peristalsis was stimulated by slow and rapid mid-esophageal injections of air in 15 patients with IEM. Two separate sessions with 4-mg oral prucalopride or placebo.

Prucalopride increased primary peristaltic wave amplitude (68.1±10.0 vs 55.5±8.8 mmHg, P=0.02).

Threshold volume for triggering secondary peristalsis was significantly decreased by prucalopride during slow (9.3±0.8 vs 12.0±0.8 mL; P=0.04) and rapid air injection (4.9±0.3 vs 7.1±0.1 mL; P=0.01). Secondary peristalsis was triggered more frequently after application of prucalopride (55%) than placebo (45%) (P=0.008). Prucalopride did not change pressure wave amplitudes during slow air injection (84.6±8.1 vs 57.4±13.8 mmHg; P=0.19) or pressure wave amplitudes during rapid air injection (84.2±8.6 vs 69.5±12.9 mmHg; P=0.09).

Conclusions: Prucalopride enhances primary peristalsis and mechanosensitivity of secondary peristalsis with limited impact on secondary peristaltic activities in IEM patients. Prucalopride appears to be useful in augmenting secondary peristalsis in patients with IEM via sensory modulation of esophageal secondary peristalsis.

Lei WY, Hung JS, Liu TT, Yi CH, Chen CL.
J Gastroenterol Hepatol. 2018 Mar;33(3):650-655.

Prucalopride for Foregut Disorders

Prucalopride can be considered for gastroparesis and refractory GERD.

The studies are small size and at times conflicting.

Appears to improve motility parameters, less so with symptoms.

IGp: improves GE and Sx
DGp: improves GE, not Sx
GERD: improves esophageal contraction amplitude

Prucalopride is approved for chronic idiopathic constipation (ICD-10 K59.04).

Practically, if want to use prucalopride for gastroparesis or GERD, best if chronic constipation is also present.