Pharmacologic treatment of gastroparesis: What is (still) on the horizon?

Schweckendiek, Daniel ; Pohl, D

Abstract: Gastroparesis is a neuromuscular disorder of the upper gastrointestinal tract. Patients typically complain about early satiety, postprandial fullness, nausea and vomiting. Etiology is multifactorial. Treatment strategies include nutritional support, pharmacologic agents or surgery for refractory cases. Metoclopramide is the first and only FDA approved pharmacologic agent for (diabetic) Gastroparesis. A couple of compounds are currently in clinical testing. Some beacons of hope have failed recently, however. Here we present an update on possible future treatment options.

DOI: https://doi.org/10.1016/j.coph.2023.102395

Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Pharmacology

Pharmacologic treatment of gastroparesis: What is (still) on the horizon?

D. Schweckendiek and D. Pohl

Abstract

Gastroparesis is a neuromuscular disorder of the upper gastrointestinal tract. Patients typically complain about early satiety, postprandial fullness, nausea and vomiting. Etiology is multifactorial. Treatment strategies include nutritional support, pharmacologic agents or surgery for refractory cases. Metoclopramide is the first and only FDA approved pharmacologic agent for (diabetic) Gastroparesis. A couple of compounds are currently in clinical testing. Some beacons of hope have failed recently, however. Here we present an update on possible future treatment options.

Addresses

University Hospital Zürich Switzerland, Department of Gastroenterology and Hepatology, Raemistrasse 100, 8091, Zurich, Switzerland

Corresponding author: Pohl, D. (Daniel.Pohl@usz.ch)

Current Opinion in Pharmacology 2023, **72:**102395

This review comes from a themed issue on **Gastrointestinal (2022)**

Edited by **Tim Vanuytsel** and **Daniel Pohl**

For complete overview about the section, refer Gastrointestinal (2022)

Available online 26 August 2023

https://doi.org/10.1016/j.coph.2023.102395

Introduction and pathophysiology

Gastroparesis (GP) is a neuromuscular disorder of the upper gastrointestinal tract defined by delayed gastric emptying and the presence of characteristic upper abdominal symptoms in the absence of a mechanical obstruction [1]. The pathophysiology is multifactorial. Loss of nerve cell bodies and affection of interstitial cells of Cajal as well as immune processes with autoantibodies targeting gastric myenteric ganglions play a role [2,3]. As a result, irrespective of etiology, patients complain of early satiety and/or postprandial fullness/bloating, nausea, vomiting and pain [1–4]. Gold standard technique for diagnosing and defining GP is a gastric scintigraphy study using a validated 4-h T99 labeled solid meal technique [5]. GP and associated symptoms have a high impact on the quality of life. Socioeconomic burden is enormous with overall healthcare expenditure in the USA alone of approximately 3.5 billion USD [3].

Risk factors and symptom assessment

Risk factors for GP include all states that affect the nerve fibers descending from the prefrontal cerebral cortex. Among them are diabetes mellitus (Diabetic gastroparesis DG), (viral) infections, surgery with vagal injury, connective tissue disease, myopathies, neurodegenerative disease (especially Parkinson's disease), metabolic disorders and substances that inhibit or slow gastrointestinal propulsion (opioids and anticholinergics) [3]. However, in most of the cases GP is idiopathic (IG) [6]. Symptoms can be quantified with different validated questionnaires. Widely used are the Patient Assessment of upper Gastrointestinal Symptoms Severity Index (PAGI-SYM) and the Gastroparesis Cardinal Symptom Index (GCSI) as well as the GCSI-Daily Diary (GCS-DD) from the American Neurogastroenterology and Motility Society.

Intra-disease specific differences and very subjective burden of disease find their expression also in recommendations from the FDA when it comes to clinical trial design. Sponsors should test new drugs separately in DG and IG. While both types share the same symptoms, pain, for example, is more prevalent in IG. On the other hand, in DG agents used to control blood sugar levels can potentially interact with the pharmacokinetics of the tested agent.

In both subtypes they propose to use the change in the five core symptoms, nausea, vomiting, postprandial fullness, early satiety and abdominal pain, as endpoints in the absence of a unique parameter that comprises all of those. Ideally, studies should include a treatment of at least 12 weeks and patient reports in form of a daily diary. Gastric emptying time should not be used as a primary end-point as changes in gastric-emptying time are not associated with changes in GP symptoms [7].

Management of gastroparesis

Management is stepwise, starting with dietary modification (small-particle (<2 mm), low-fat and low-fiber diet, adequate hydration) [1–3,8]. The only Food and

Given the role as Guest Editor, Daniel Pohl had no involvement in the peer review of the article and has no access to information regarding its peer-review. Full responsibility for the editorial process of this article was delegated to Tim Vanuystel.

Drug Administration (FDA) approved prokinetic agent to treat (diabetic) GP is the dopamine D2 receptor antagonist metoclopramide. Dopamine inhibits acetylcholine release, thereby slowing down muscle contraction and propulsion. Unfortunately, metoclopramide crosses the blood–brain barrier and can also act centrally in an unfavorable manner. This feature resulted in a black-box warning for extrapyramidal symptoms (EPMS, involuntary movements). Another dopamine (D2/3) receptor antagonist, domperidone, is available for prescription only through the FDA's program for Expanded Access to Investigational Drugs [2]. In the European Union it is approved for the treatment of nausea and vomiting for short term use (usually no longer that 7 days) [9]. It does not cross the blood-brain-barrier. However, cardiac dysrhythmias due to interaction with the hERG potassium channel as an off-target effect are a matter of concern [2]. Besides, it is not recommended in patients with medications that are also metabolized via the CYP 450 enzymes due to the use of the same pathway [2,9].

Off-label in use are inhibitors of the acetylcholinesterase such as neostigmine (short half-life, for intravenous use only in the hospital setting), as well as pyridostigmine and Motilin receptor agonists (i.e. erythromycin, a macrolide antibiotic). Unwanted side effects such as EPMS, tardive dyskinesia and tachyphylaxis underline the need for additional options for patients suffering from GP [2,3,7,9]. In this short review, we consider registered trials on clinicaltrials.gov and the European Union's clinical trial registry EudraCT registered active and ongoing as of January 2023 (Table 1). We present an update on compounds that are currently still in clinical testing and where results are expected in the mid-to-near future (Figure 1).

Phase I

In a small, open label trial Pioglitazone is tested in patients with IG. Pioglitazone is an already approved oral antidiabetic agent. This member of the glitazone family acts as an insulin sensitizer that increases glucose uptake in the fat, muscle and liver. It does so by acting as an agonist at the nuclear peroxisome proliferator-activated receptor-γ (PPAR-y). This receptor regulates genes that are involved in glucose and lipid metabolism. The therapy rational for its application in GP is an expected effect on restoring the gastrointestinal neuronal nitric oxide synthase (nNOS) activity through improved glycemic control. An impaired NO pathway in the myenteric plexus and loss of neurons due to oxidative stress is assumed to contribute to GP symptoms, at least in DG [2,10]. Furthermore, as acute hyperglycemia can potentially slow gastric emptying reduction of postprandial glucose peaks might be beneficial [10].

Phase II

Recently completed but without published results is the MOMENTUM study of PCS12852 (formerly YH 12852). The compound is a novel, potent and highly selective 5-hydroxytryptamine-4 (5-HT4) receptor agonist [11]. The 5-HT4 receptors belong to the group of the G-protein family coupled receptors. They are widely expressed in the gastrointestinal tract [2,4]. In a prior phase I/II study it was compared to placebo and active control prucalopride. PCS12852 was shown to increase stool frequency with faster onset than those who received prucalopride. Also the gastric emptying rate in constipated patients was increased [12].

Another trial is looking at the safety and efficacy of oral phenothiazine metopimazine (NG101) compared to placebo. NG101 is a highly selective and potent dopamine D2/3 receptor antagonist [13]. In certain parts of the world it is an already approved antiemetic and marketed under different brands names. It is said to have a more favorable safety profile as it does not cross the blood-brain-barrier. Besides, it does not inhibit the hERG channel [14,15].

Currently, another trial investigates the use of oral Cannabidiol in the treatment of GP. In patients with functional dyspepsia (FD, without delayed gastric emptying) no significant difference was seen in gastric emptying time and different patient reported outcomes compared to placebo [16]. Up to a certain extent the trial reflects already real-life as one study found use of cannabinoids in one third of patients for treatment of their chronic GP symptoms. Most of them reported improvements of their symptoms with cannabidiol [17]. In a smaller, open-label observation an improvement of abdominal pain was seen in patients that were refractory to standard therapies for GP [18]. In a recent review however authors warned that cannabis-based agents should not be used first-line. They raise the fear that they could even worsen gastrointestinal symptoms if used on a chronic basis. They also criticize published data from uncontrolled trials [19]. Another review that was looking on the general effect of cannabinoids in pain reduction found a high placebo effect supported by positive media attention and trial participants' high expectations [20]. This placebo effect could possibly be also responsible for the improvements observed in GP.

Also studied in GP is the gut-selective antibiotic rifaximine. Supposed rationale is that the reduction of oxidative stress, as in poorly controlled diabetes, and reactive oxygen species caused by bacterial dysbalance, is beneficial to the function of interstitial cells of Cajal and, ultimately, gastric motility [21].

Another study evaluates the orally taken compound CIN-102 vs. placebo. CIN-102 is a deuterium-containing, peripherally selective dopamine D2/D3 receptor antagonist (deu-domperidone), a modified-version of domperidone. Therapeutic and supra-therapeutic concentrations of deu-domperidone had

no effect on the QT/QTc interval, suggesting an acceptable cardiovascular safety [22].

Results are awaited also for the recently completed BESST trial. Here buspirone, a 5-hydroxytryptamine (5-HT) 1a receptor agonist and D2 receptor antagonist, was tested against placebo in GP patients. Buspirone is already approved as an anxiolytic drug (Buspar™/Vanspar™) in the US. Its mechanism of action is not yet fully understood. It is said to interact with the 5-HT1a-receptor in a way that it limits serotonin release initially, but overall serotonin supply increases over time due to compensatory mechanisms. Finally, higher serotonin levels should lead to an improvement of intestinal motility. Buspirone has been shown to promote fundic relaxation and increase gastric accommodation in animal models and to alleviate dyspeptic symptoms in functional dyspepsia in humans [23].

Finally, Prucalopride, another selective 5-HT4 receptor agonist and approved prokinetic agent (Resolor™) for the treatment of chronic constipation is currently tested in GP, too. A small study (prucalopride 4 mg versus placebo) found accelerated gastric emptying and increased bowel movement frequency but did not appear to ameliorate gastroparesis or meal-related symptoms [24]. In another small study four weeks of prucalopride treatment significantly improved symptoms (GCSI) as well as quality of life and enhanced gastric emptying compared with placebo [25]. Overall, it has a favorable safety profile with no known cardiac affects [26].

Finally, for naronapride (formerly ATI-7505), a 5-HT4 receptor stimulator and D2 receptor antagonist a phase 2 dose finding study was initiated during the review process of this manuscript. Naronapride has been studied in chronic constipation before [27].

Uncertain fate/late stage failure

Other beacons of hope have an uncertain fate or recently failed in late stage clinical testing.

Tradipitant (VLY-686) is an antagonist of at the tachykinin receptor 1 (TACR1), also called neurokinin 1 receptor (NK1R) or substance P receptor (SPR). While effective in a phase 2 study in a placebo-controlled phase 3 trial (NCT04028492), reported in February 2022, it missed its primary endpoint (change of the average severity of nausea from GCS - DD at week 12 vs. baseline) [28,29]. Besides, a partial clinical hold on tradipitant protocols of longer than 12 weeks duration makes it unlikely that this agent will advance to registration soon [30]. One year after completion according to publicly available information the sponsor has still not asked for approval.

Ghrelin on the other hand is a peptide hormone released from gastric mucosal endocrine cells that docks to receptors in the enteral nervous system. Ghrelin stimulates directly the gastrointestinal motility via vagal signaling and via Central Nervous System [3]. Various synthetic selective Ghrelin receptor agonist development programs (RM-131/relamorelin, TZP-101/ulimorelin, TZP-102) seem to be abandoned. The relamorelin program e.g. was terminated for business reasons [31]. For ulimorelin since five years there is no active clinical study listed. None of the former or current sponsors still lists the compound as active in their clinical pipelines.

Other compounds such as Velusetrag (TD-5108) and Felcisetrag (TAK-954), Sepiapterin (CNSA-001) as well as some Motilin receptor agonists and Granisetron seem to share the same fate.

Velusetrag and Felcisetrag, both are selective 5-HT4 receptor agonists. In a short (7 days of treatment) and small study in patients with DG or IG Velusetrag accelerated gastric emptying time versus placebo [32]. However, only the 5 mg showed significant efficacy in another dose ascending study [33]. Five years after study completion no confirmatory phase 3 trial for this compound has been initiated. Development therefore seemed to have been stopped.

Despite showing significant acceleration in small bowel and colonic transit as well as accelerated gastric emptying time in a small study Felcisetrags necessity of intravenous application could be a competitive disadvantage that hinders further development [34]. Currently, it is not listed anymore for the indication GP on the sponsors pipeline chart [35].

Sepiapterin (CNSA-001/PTC 923) is a naturally occurring precursor of tetrahydrobiopterin (BH4). Nerves in the GI-tract express the nitric oxide synthase (nNOS). BH4 is a critical enzymatic cofactor for the proper function of the nNOS. NO is a key regulator for motility in the GI. Sepiapterin was investigated under the assumption, that it increases BH4 concentrations, improving nNOS with positive effects on gastric accommodation and emptying. Primary endpoint (change in gastric accommodation) was met, but no change in gastric emptying or symptoms were shown [36]. Currently, the sonsor is following only an approval path for a use in rare disease (phenylketonuria) instead of GP [37].

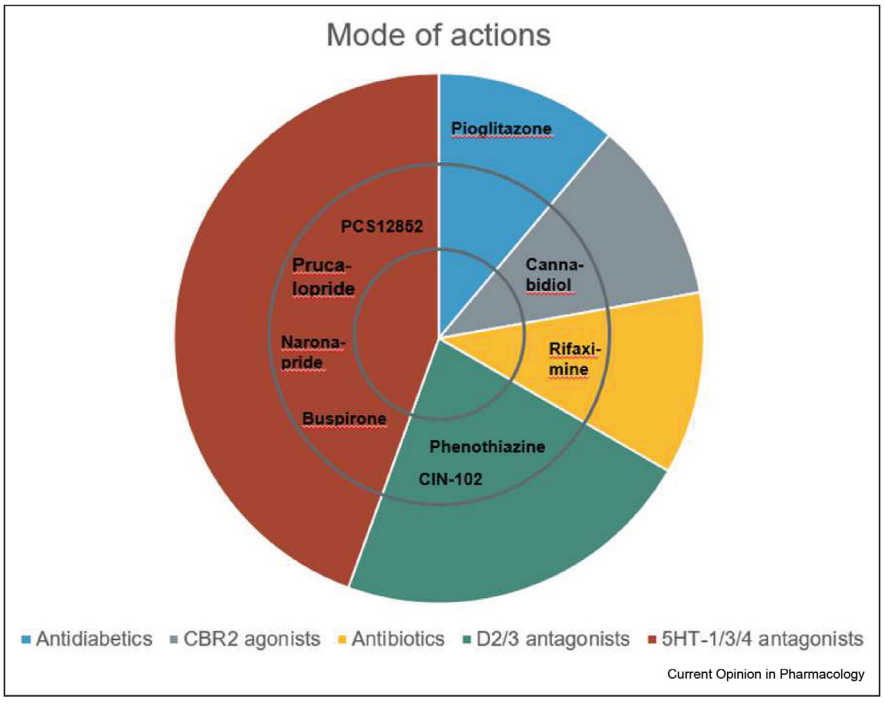
Motilin is a peptide secreted by M-cells in the duodenum and jejunum. It regulates gastrointestinal motility via action on the Motilin receptor (GPR38) in the stomach and duodenum. The macrolide antibiotic erythromycin acts as an agonist on this receptor, too. Without giving details according to company information the macrolides analogue (motilid) compounds GSK 962040 and GSK1322888 will not be studied further [38]. However, there are new non-macrolide GR38

Table 1

Ongoing active/recently finished clinical trials in GP (results given where significant).

Agent (Brand™), Mode of action	Phase	Population (n)	Primary endpoint(s)
Pioglitazone (Actos™) PPAR-y Agonist	Phase I (NCT04300127) (PIOGAS)	n = 10 IG	Change in GCSI-DD baseline and after 8 weeks
PCS12852 5-HT4- receptor agonist	Phase II (NCT05270460) (MOMENTUM)	n = 24 IG + DG	Change in Gastric Emptying Rate Assessed by 13C Spirulina gastric emptying breath test baseline and after 4 weeks Compound plasma concentration over time
Phenothiazine Metopimazine mesylate (Nortrip™, Vogalen™) Dopamine D2/3 receptor antagonist	Phase II (NCT04303195).	n = 280 IG + DG	Change in nausea severity from baseline and after 12 weeks (measured by patients Daily Diary) Incidence and severity of Adverse Events
Cannabidiol (Epidiolex™, Cesamet™, Syndros™ and Marinol™) for different indications CBR2 agonist	Phase II (NCT03941288)	n = 96 GP or functional dyspepsia (FD)	Change (baseline and after 4 weeks) in GP: - fasting gastric and accommodation Volumes (measured by SPECT) - Satiation (measured via Volume to fullness (VTF, mL) on satiation test) - Gastric emptying (measured via Gastric emptying T1/2 of solids on scintigraphy in minutes) - Average weekly GCSI-DD in FD: Change in postprandial distress score via Nepean Dyspepsia Index (every 2 weeks)
Rifaximin Rifamycin derivative (Xifaxan™) Gut Selective Antibiotic	Phase II (NCT04254549)	n = 40 DG	Change in self-reported bloating vs. placebo baseline and after 2 weeks
CIN-102 Dopamine D2/D3 receptor antagonist	Phase II (NCT04026997).	n = 73 IG + DG or documented delayed gastric emptying	Change in gastric emptying time vs placebo baseline and after 2 weeks
Buspirone (Buspar™/Vanspar™) 5-HT 1a receptor agonist	Phase II (NCT03587142) (BEST)	n = 96 IG + DG	Change in the 4-item post-prandial fullness/early satiety sub-score GCSI baseline and after 4 weeks
Prucalopride (Resolor™) 5-HT4 receptor agonist	Phase II (NCT02031081) Phase II (NCT02510976)	n = 15 (DG) n = 31 IG + DG	Change in Cumulative Meal-related symptoms and gastric emptying baseline and after 4 weeks Gastric emptying mean 4-h meal retention 22 ± 6% in PRU vs 40 ± 9% placebo (P = 0.05) Weekly Bowel movement frequency prucalopride vs. placebo period (10.5 ± 1.8 vs 7.5 ± 0.8, P < 0.0001) Change in GCI baseline and after 4 weeks Gastroparesis Cardinal Symptom Index (1.65 ± 0.19 vs 2.28 ± 0.20, P < 0.0001)
Naronapride 5 -HT4 receptor agonist/D2 antagonist	Phase II (NCT05621811) (MOVE-IT)	n = 320 IG + DG	Change in GCSI - Daily Diary baseline and after 12 weeks

Figure 1



Clinical trial pipeline in GP therapeutics. Outer ring: Phase 1, Middle ring: Phase 2, Inner circle: phase 3.

agonists underway (e.g. DS3801B) that have been developed through chemical engineering [39]. They could provide a future option.

Another once promising agent is the approved anti-emetic granisetron. This 5-HT3 antagonist applied via a transdermal patch was studied in an open-label registry prescription study. An improvement in nausea and vomiting (assessed with CPGAS at 2 weeks, 2.28 ± 2.53; $P < 0.05$) as well as other GP related GI symptoms was seen [40]. Another larger study listed as status "withdrawn" however for unknown reasons during the review process of this manuscript [41]. By label its use is currently limited to prevent nausea and vomiting in adults receiving anti-cancer (chemo-therapy) treatment.

Summary

We note a scarcity of new compounds for the treatment of GP. Some tested compounds are already approved for other indications (pioglitazone, rifaximine, cannabidiol, prucalopride, buspirone). Maybe we will see a re-purposing of these drugs in the future. Currently, besides PCS12852 only CIN-102 and naronapride seem to be on a path forward. With the help of FDA's guidance for sponsors it will probably be easier to compare trial results of different agents in the future. However, so far, despite the better understanding of the role of different cell types, no cell-directed/targeted therapies are in clinical testing. Due to the role of loss of interstitial cells of Cajal in pathogenesis of GP future approaches will likely target the restoration or conservation of these cells [2,3].

CRediT authorship contribution statement

D. Schweckendiek: Conceptualization, Investigation, Writing – review & editing. **D. Pohl:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

References

Papers of particular interest, published within the period of review, have been highlighted as:

** of outstanding interest

1. Stanculete MF, Chiarioni G, Dumitrascu DL, *et al.*: **Disorders of the brain-gut interaction and eating disorders**. *World J Gastroenterol* 2021, **27**:3668–3681.

2. Camilleri M, Sanders KM: **Gastroparesis**. *Gastroenterology* 2022, **162**:68–87.e1.
**
The authors give a good overview on the current state of knowledge in gastroparesis. Special focus is on potential cellular mechanisms such

as inflammation and oxidative stress. This is important since these mechanisms represent potential therapeutic targets.

3. Mekaroonkamol P, Tiankanon K, Rerknimitr R: **A new paradigm shift in gastroparesis management**. *Gut Liver* 2022, https://doi.org/10.5009/gnl210309.
** The authors give an update on three factors that possibly influence the future management of gastroparesis. These factors include improved understanding of the gastric pacemaker cells, advanced diagnostic modalities and invasive treatment approaches such as endoscopic pyloromyotomy.

4. Hong SW, Chun J, Kim J, *et al.*: **Efficacy and safety of Ghrelin agonists in patients with diabetic gastroparesis: a systematic review and meta-analysis**. *Gut Liver* 2020, **14**:589–600.

5. Keller J, Hammer HF, Afolabi PR, *et al.*: **European guideline on indications, performance and clinical impact of 13 C-breath tests in adult and pediatric patients: an EAGEN, ESNM, and ESPGHAN consensus, supported by EPC**. *United European Gastroenterol J* 2021 Jun, **9**:598–625.

6. Karamanolis G, Caenepeel P, Arts J, *et al.*: **Determinants of symptom pattern in idiopathic severely delayed gastric emptying: gastric emptying rate or proximal stomach dysfunction?** *Gut* 2007, **56**:29–36.

7. https://fda.gov/regulatory-information/search-fda-guidance-documents/gastroparesis-clinical-evaluation-drugs-treatment-guidance-industry. Accessed 7 March 2023.

8. Fonseca Mora MC, Milla Matute CA, Alemán R, *et al.*: **Medical and surgical management of gastroparesis: a systematic review**. *Surg Obes Relat Dis* 2021 Apr, **17**:799–814.

9. https://www.emea.ma.europa.eu/en/medicines/human/referrals/domperidone-containing-medicines. Accessed 13 August 2022.

10. Avalos DJ, Sarosiek I, Loganathan P, *et al.*: **Diabetic gastroparesis: current challenges and future prospects**. *Clin Exp Gastroenterol* 2018, **11**:347–363.

11. https://www.processapharmaceuticals.com/product-pipeline/pcs12852. Accessed 14 August 2022.

12. Lee HA, Ju Moon S, Yoo H, *et al.*: **YH12852, a potent and selective receptor agonist of 5-hydroxytryptamine, increased gastrointestinal motility in healthy volunteers and patients with functional constipation**. *Clin Transl Sci* 2021, **14**:625–634.

13. https://neurogastrx.com/pipeline/. Accessed 13 August 2022.

14. Heckroth M, Luckett RT, Moser C, *et al.*: **Nausea and vomiting in 2021. A comprehensive update**. *J Clin Gastroenterol* 2021 Apr 1, **55**:279–299.
** The authors give a comprehensive overview and update on two key symptoms of gastroparesis, nausea and vomiting. They especially look at patho-physiology and recent advances in the pharmacotherapy.

15. Vabre C, Araujo M, Damase-Michel C, *et al.*: **Initial data on the safety of metopimazine during pregnancy and the risk of major birth defects and pregnancy loss - an observational study using the EFEMERIS database**. *Therapie* 2021. S0040-5957(21)00203-1.

16. Atieh J, Maselli D, Breen-Lyles M, *et al.*: **Cannabidiol for functional dyspepsia with normal gastric emptying: a randomized controlled trial**. *Am J Gastroenterol* 2022, **117**:1296–1304.

17. Jehangir A, Parkman HP: **Cannabinoid use in patients with gastroparesis and related disorders: prevalence and benefit**. *Am J Gastroenterol* 2019 Jun, **114**:945–953.

18. Barbash B, Mehta D, Siddiqui MT, *et al.*: **Impact of cannabinoids on symptoms of refractory gastroparesis: a single-center experience**. *Cureus* 2019 Dec 20, **11**, e6430.

19. Nasser Y, Woo M, Andrews CN: **Cannabis in gastroenterology: watch your head! A review of use in inflammatory bowel disease, functional gut disorders, and gut-related adverse effects**. *Curr Treat Options Gastroenterol* 2020, **18**:519–530.
** The use of cannabinoids and cannabis for medical purposes is on the rise. The authors give a review on the use in gastrointestinal disorders. Among them is gastroparesis. A special focus is also on adverse effects.

20. Gedin F, Blomé S, Pontén M, *et al.*: **Placebo response and media attention in randomized clinical trials assessing cannabis-based therapies for pain: a systematic review and meta-analysis**. *JAMA Netw Open* 2022, **1**:5.

21. Roland BC, Ciarleglio MM, Clarke JO, *et al.*: **Small intestinal transit time is delayed in small intestinal bacterial overgrowth**. *J Clin Gastroenterol* 2015, **49**:571–576.

22. https://cindome.com/cin-102. Accessed 13 August 2022.

23. Radetic M, Gabbard S: **Buspirone for the management of functional dyspepsia with rapid gastric emptying**. *ACG Case Rep J* 2019 Nov 26, **6**, e00280.

24. Andrews CN, Woo M, Buresi M, *et al.*: **Prucalopride in diabetic and connective tissue disease-related gastroparesis: randomized placebo-controlled crossover pilot trial**. *Neuro Gastroenterol Motil* 2021, **33**, e13958.

25. Carbone F, Van den Houte K, Clevers E, *et al.*: **Prucalopride in gastroparesis: a randomized placebo-controlled crossover study**. *Am J Gastroenterol* 2019, **114**:1265–1274.

26. Ali H, Pamarthy R, Sarfraz S: **Role of prucalopride in treating functional constipation and gastroparesis: a systemic review**. *Cureus* 2021, **13**, e14306.

27. Palme M, Milner PG, Ellis DJ, *et al.*: **A novel gastrointestinal prokinetic, ATI-7505, increased spontaneous bowel movements (Sbms) in a phase II, randomized, placebo-controlled study of patients with chronic idiopathic constipation (CIC)**. *Gastroenterology* 2010, **138**:S128–S129.

28. Carlin JL, Lieberman VR, Dahal A, *et al.*: **Efficacy and safety of tradipitant in patients with diabetic and idiopathic gastroparesis in a randomized, placebo-controlled trial**. *Gastroenterology* 2021, **160**:76–87.

29. https://vandapharmaceuticals.com/pdfs/vanda_corporate_presentation_may_2022.pdf. Accessed 13 March 2023.

30. https://vandapharmaceuticalsinc.gcs-web.com/node/14786/pdf. Accessed 13 August 2022.

31. https://clinicaltrials.gov/ct2/show/NCT03786380?cond=relamorelin&draw=3&rank=13. Accessed 13 August 2022.

32. Kuo B, Barnes CN, Nguyen DD, *et al.*: **Velusetrag accelerates gastric emptying in subjects with gastroparesis: a multicentre, double-blind, randomised, placebo-controlled, phase 2 study**. *Aliment Pharmacol Ther* 2021, **53**:1090–1097.

33. Abell TL, Kuo B, Esfandyari T, *et al.*: **A randomized, double-blind, placebo-controlled, phase 2b study of the efficacy and safety of velusetrag in subjects with diabetic or idiopathic gastroparesis**. *Neuro Gastroenterol Motil* 2023, **00**, e14523.

34. Chedid V, Brandler J, Arndt K, *et al.*: **Randomised study: effects of the 5-HT4 receptor agonist felcisetrag vs placebo on gut transit in patients with gastroparesis**. *Aliment Pharmacol Ther* 2021, **53**:1010–1020.

35. https://www.takeda.com/what-we-do/research-and-development/our-pipeline/. Accessed 13 August 2022.

36. Abell TL, Garcia LM, Wiener GJ, *et al.*: **Effect of Oral CNSA-001 (sepiapterin, PTC923) on gastric accommodation in women with diabetic gastroparesis: a randomized, placebo-controlled, Phase 2 trial**. *J Diabet Complicat* 2021, **35**, 107961.

37. https://www.ptcbio.com/2020/06/01/expanding-areas-of-therapeutic-focus-phenylketonuria-pku/. Accessed 13 August 2022.

38. Personal communication via e-mail to the author on request from Glaxo Smith Kline, Medical Information Services, received September 2022.

39. Toda N, Shida T, Takano R, *et al.*: **Discovery of DS-3801b, a non-macrolide GPR38 agonist with N-methylanilide structure**. *Bioorg Med Chem Lett* 2022, **1**, 128554.

40. Midani D, Parkman HP: **Granisetron transdermal System for treatment of symptoms of gastroparesis: a prescription registry study**. *J of Neurogastroenterol and Motility* 2016, **22**:650–655.

41. https://clinicaltrials.gov/ct2/show/NCT04501211?term=granisetron&cond=Gastroparesis&draw=2&rank=2. Accessed 27 February 2023.