

Pathophysiology of Idiopathic Gastroparesis and Implications for Therapy

Mattis Bekkelund^{1,2}, Dag A. Sangnes^{2,3,4}, Jan Gunnar Hatlebakk^{2,3,4}, Lars Aabakken^{1,5}

¹Faculty of Medicine, Department of Clinical Medicine, University of Oslo, Oslo, Norway;

²National Centre for Functional Gastrointestinal Disorders, Department of Medicine,

Haukeland University Hospital, Bergen, Norway; ³Department of Medicine, Haukeland

University Hospital, Bergen, Norway; ⁴Clinical institute 1, University of Bergen, Bergen,

Norway; ⁵Department of Transplantation Medicine, Section for Gastroenterology, Oslo

University Hospital, Oslo, Norway

Corresponding Author:

Mattis Bekkelund

Faculty of Medicine, Department of Clinical Medicine, University of Oslo, Oslo, Norway

Haakon den godes vei 29

0373, Oslo

Tel: +47 48186897

Email: mattis.bekkelund@studmed.uio.no

Word count: 4314 words

Abstract

Objectives

Idiopathic gastroparesis is a gastric motility disorder characterized by chronic upper gastrointestinal symptoms and delayed gastric emptying without an identifiable underlying condition. This review summarizes recent understanding of the pathophysiology and treatment of idiopathic gastroparesis

Materials and methods

Structured literature search in the PubMed, Embase and ClinicalTrials.gov databases

Results

Idiopathic gastroparesis involves several alterations in gastric motility and sensation, including delayed gastric emptying, altered myoelectrical activity, impaired fundic accommodation, visceral hypersensitivity and disturbances in antropyloroduodenal motility and coordination. Multiple cellular changes have been identified, including depletion of interstitial cells of Cajal (ICC) and enteric nerves, as well as stromal fibrosis. The underlying cause of these changes is not fully understood, but may be an immune imbalance, including loss of anti-inflammatory heme-oxygenase-1 positive (HO-1) macrophages. There is currently no causal therapy for idiopathic gastroparesis. The treatment ladder consists of dietary measures, prokinetic and antiemetic medications, and varying surgical or endoscopic interventions, including the promising pyloric therapies. There are ongoing trials with several novel medications, raising hopes for future treatment.

Conclusions

Patients with idiopathic gastroparesis presents several pathophysiological alterations in the stomach, where depletion of ICC is of special importance. Treatment is currently focused on alleviating symptoms through dietary adjustments, medication or surgical or endoscopic interventions.

Keywords: Gastroparesis; idiopathic gastroparesis; gastric emptying; gastric accommodation; interstitial cells of Cajal; gastric dysrhythmia

Introduction

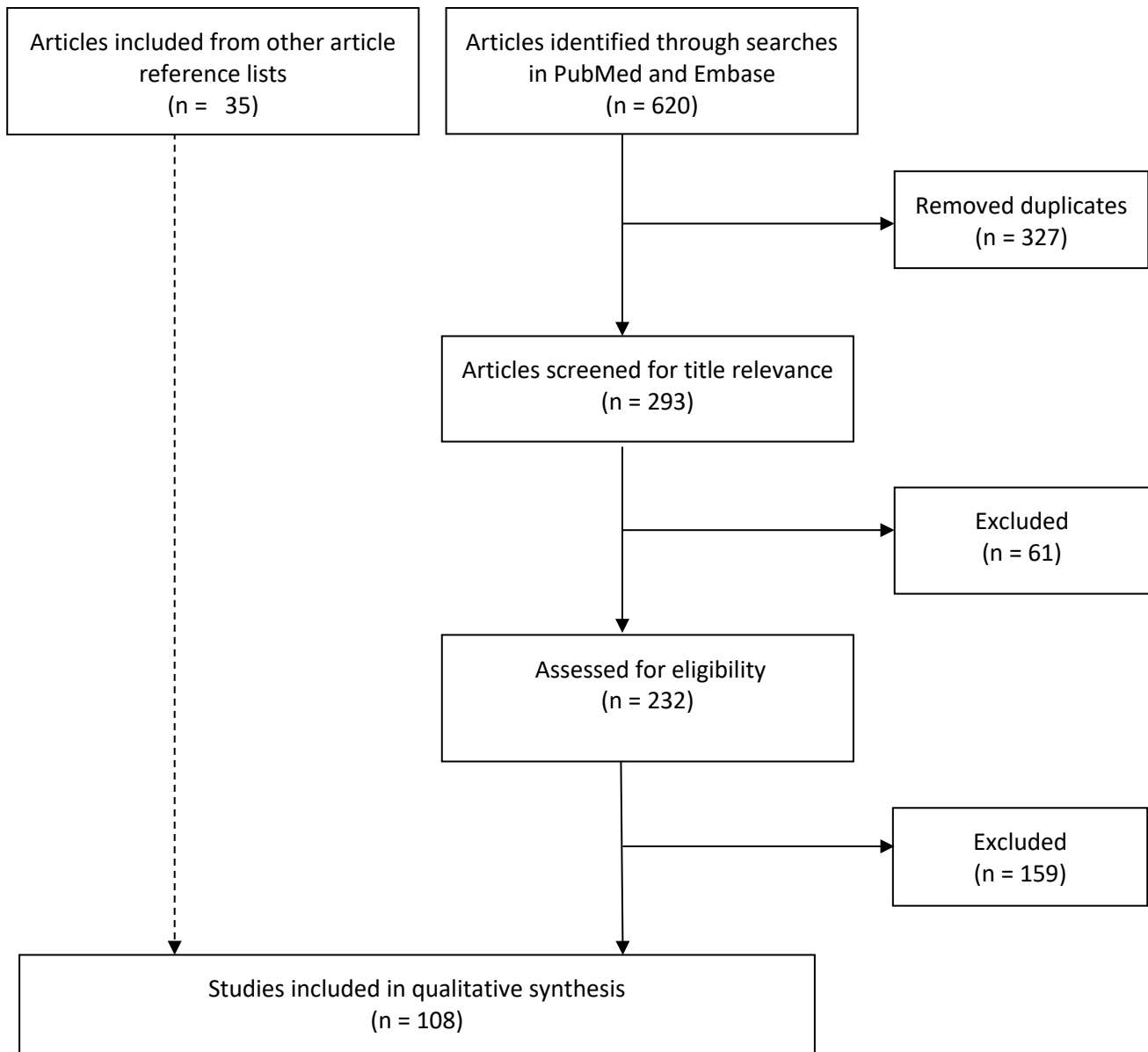
Gastroparesis is a chronic disorder in which gastric emptying is delayed without mechanical obstruction or other underlying conditions [1, 2]. The main subsets of gastroparesis are idiopathic gastroparesis, diabetic gastroparesis and iatrogenic gastroparesis due to surgery or medication [1]. Idiopathic gastroparesis is assumed to be a heterogeneous group of hitherto not defined etiologies, and the diagnosis can be made when no other underlying cause of gastroparesis is identified. Idiopathic gastroparesis makes up 36-65% of patients with gastroparesis; however, estimates are uncertain [3-5]. Significantly more women than men are affected, and female gender has been linked to increased symptom severity [3, 4, 6].

The onset of gastroparesis symptoms may be acute or insidious, and symptoms may progress in different patterns: Stable, intermittent exacerbations or gradually worsening symptom load [5, 6]. Early satiety, postprandial fullness, bloating, nausea, and vomiting are considered the cardinal symptoms of gastroparesis [7]. Other symptoms such as upper or lower abdominal pain, gastroesophageal reflux symptoms, anorexia, constipation and diarrhea are also common [3-6, 8, 9]. No single symptom or symptom cluster reliably differentiates the different subsets of gastroparesis, and the association between gastric retention and symptom severity in gastroparesis is weak [10]. The demarcation of idiopathic gastroparesis in relation to functional dyspepsia is also unclear, as there is a substantial overlap in symptoms and gastric motility dysfunctions, including delayed gastric emptying.

The pathophysiology of idiopathic gastroparesis remains poorly understood and as a consequence, development of new therapeutic modalities has been slow. However, an increased interest in gastroparesis combined with new technologies for assessing gastrointestinal motility, has led to increased insight into the topic. In this article, we review the literature on the pathophysiology of idiopathic gastroparesis, and its potential therapeutic implications.

Materials and methods

Two structured searches in the databases of PubMed and Embase was performed using the search strings '(idiopathic gastroparesis) AND (pathophysiology OR pathology OR symptoms)' and '(idiopathic gastroparesis) AND (therapy OR treatment)'. The first search yielded 245 hits in PubMed and 97 hits in Embase. The second search yielded 199 hits in PubMed and 79 hits in Embase. Only review articles and original articles were included in the search. The search was not time-limited and ended 16.8.18. After removal of duplicates, articles were initially evaluated based on title relevance. The full text of the remaining articles was then assessed, and articles deemed not relevant for this review were excluded. 34 articles were included from other article reference lists. This left us with 107 articles included in this review. See flow chart in Figure 1 for further details on article selection. To get an overview of ongoing therapeutic trials, we also performed a structured search in the ClinicalTrials.gov database using the search string "idiopathic gastroparesis". The search was performed on October 2, 2018 and yielded 172 hits. Of these, 8 clinical trials were deemed relevant for this article.



Results

Cellular pathology

Insight in the cellular pathology of idiopathic gastroparesis is crucial to understand the pathophysiology behind impaired gastric motility, symptom generation and for the development of new therapies. However, as full-thickness biopsies of the stomach are mainly acquired laparoscopically during insertion of a gastric electrical stimulator, results are currently applicable only to patients with severe symptoms refractory to medical therapy. Therefore, the cellular pathology of mild and moderate gastroparesis is largely unknown.

Histopathological studies of gastric full-thickness biopsies have consistently revealed a loss of interstitial cells of Cajal (ICC) in the gastric body, antrum and pylorus in patients with refractory idiopathic gastroparesis [11-18]. Further, in transmission electron microscopy (TEM) studies, ICCs show marked morphological changes indicative of injury such as few or swollen mitochondria, and a loss of contact with nerves and smooth muscle cells and adjacent ICCs [13, 19]. Given the physiological role of ICCs in mechanotransduction and initiation and propagation of slow waves, absence of ICCs could be central in the pathophysiology of idiopathic gastroparesis [20]. Still, it is not fully understood whether depletion of ICCs correlates with symptom severity in idiopathic gastroparesis [11, 12, 14].

Another prominent ultrastructural feature in idiopathic gastroparesis is the presence of fibrosis in the stroma, which is significantly increased in comparison with diabetic gastroparesis [19]. Fibrillary sheaths encase smooth muscle cells, ICCs and particularly nerve endings [13, 19]. It has been speculated that these fibrillary sheets may impair smooth muscle metabolism and as such cause cell damage [19]. The nerve structures themselves also have pathological features. On examination with TEM, both nerve endings and neuronal bodies seem to have altered morphology with abnormal mitochondria, chaotically arranged neurofilaments and

nerve endings empty of granulae, indicating a loss of neurotransmitter [13, 19]. Additionally, some studies by light microscopy, hematoxylin and eosin-staining and immunohistochemistry have found a loss of enteric nerve bodies and fibers [13, 15, 16, 21]. Patients with idiopathic gastroparesis may also have decreased levels of neurotransmitters such as NO and Substance P [13, 16]. However, these results are uncertain and in one study, NOS1-expression was found to be higher than in controls [22].

In studies of antral full-thickness biopsies, patients with idiopathic gastroparesis show a loss of M2-like macrophages with an anti-inflammatory phenotype within the muscular wall [23]. Macrophages are thought to play a central role in diabetic gastroparesis, in which a loss of anti-inflammatory heme-oxygenase-1 (HO-1) positive macrophages leads to decreased protection against oxidative stress, resulting in damage to ICCs and delayed gastric emptying in diabetic mice [24-27]. A role for macrophages and HO-1 in idiopathic gastroparesis is now starting to emerge. Longer alleles of repeat polymorphisms of the gene coding for HO-1 has been found to be associated with nausea severity [28]. Further, expression of HMOX1, a marker for HO-1 is decreased in the gastric muscularis externa [22]. An increase in expression of genes associated with inflammatory M1-like macrophages along with other immune imbalances has also been found by Grover et al [29]. As such, a loss of HO-1 expressing M2-like macrophages could be a mechanism leading to the oxidative damage seen in idiopathic gastroparesis.

Abnormalities in smooth muscle cell contractile elements and markers of contractility has been demonstrated in idiopathic gastroparesis, suggesting that in a subset of patients, impaired motility may stem from impaired contractility of smooth musculature [22]. However, the majority of smooth muscle cells show no pathological alterations on TEM [19]. As such, the role of smooth muscle cells in idiopathic gastroparesis is not fully understood.

Other cell types that may be of importance also seem to be altered in idiopathic gastroparesis. On examination with TEM, enteric glial cells show signs of pathological alterations and the cytoplasm is filled with lysosomes, lipofuscin bodies and vacuoles [13, 19]. This may be another distinguishing feature of idiopathic gastroparesis, as enteric glial cell damage has not been observed in diabetic gastroparesis. Telocytes (Platelet-derived growth factor receptor α + fibroblast-like cells), a recently identified cell type believed to play a role in slow wave conduction, neural transduction and gastric pacemaker activity, may also play a part in idiopathic gastroparesis. No changes in telocyte number has been found when examined by immunolabelling [30]. However, one study examining transcriptional changes in idiopathic gastroparesis found a loss of mRNA encoding for PDGFR α in all samples, suggesting a loss of telocytes in idiopathic gastroparesis [22]. This was associated with a loss of platelet-derived growth factor-B (PDGFB), a ligand for PDGFR α , implicating a role for PDGFB in the maintenance of the gastric telocyte-population and an impairment of this mechanism in idiopathic gastroparesis.

Gastric myoelectrical activity

Altered gastric myoelectrical activity seems to be a common feature in idiopathic gastroparesis when measured by electrogastrography (EGG) [31-33] and serosal recording techniques [31, 34].

Using a dense array of serosal electrodes able to detect alterations in spatial coordination and propagation of slow waves, O'Grady and colleagues discovered multiple novel types of dysrhythmias in patients with idiopathic gastroparesis [34]. An important finding was that patients with apparently normal slow wave frequency also have altered myoelectrical activity. Feelings of nausea have been linked to EGG alterations and such alterations have been proposed as an objective marker of nausea [35]. As such, gastric

dysrhythmia may be a mechanism specifically related to nausea and thereby a central feature of idiopathic gastroparesis. Further, successful medical therapy for idiopathic gastroparesis was associated with normalization of EGG parameters in one study [36].

The underlying mechanisms leading to aberrant slow-wave activity in gastroparesis is not well understood. However, a low ICC-count is associated with dysrhythmia in gastroparesis and its physiological roles in slow wave initiation and conduction makes ICCs likely to be central in the pathogenesis of dysrhythmias [12, 34]. Given the role of fibrosis in cardiac arrhythmias, the fibrosis seen in idiopathic gastroparesis may play a similar role.

Motility disturbances

Delayed gastric emptying

Delayed gastric emptying is mandatory for the diagnosis of gastroparesis [1]. However, the pathophysiological mechanisms behind delayed gastric emptying in idiopathic gastroparesis is not clear. In a study assessing the reproducibility of gastric emptying scintigraphy (GES) in patients with upper gastrointestinal symptoms, delayed gastric emptying of solids seem to be a relatively stable parameter, though the authors noted that for mild gastroparesis, repeated testing may be necessary to confirm delayed gastric emptying [37].

There is consensus that gastric emptying scintigraphy of solids is the most accurate method to diagnose gastroparesis [38]. However, in a subset of patients, gastric emptying of solids may be normal whilst gastric emptying of liquids is impaired [39-41]. Isolated delayed liquid emptying may be more common in non-diabetic gastroparesis [39].

The association between the degree of gastric retention and loss of ICCs in the gastric body is uncertain [12, 14, 15, 23]. However, pyloric fibrosis and ICC-loss may be more common in gastroparesis than in the so-called gastroparesis-like syndrome, in which the

patient experiences symptoms of gastroparesis but without delayed gastric emptying [18]. As such, pyloric fibrosis and ICC-loss may be a mechanism behind delayed gastric emptying.

The relationship between delayed gastric emptying of solids and symptom generation in idiopathic gastroparesis is uncertain. No specific symptoms have been found to consistently correlate with the severity of gastric retention [6, 42-44]. However, in a multicenter study of 243 patients with idiopathic gastroparesis, severe gastric retention (>35%) after 4 hour GES was associated with a higher score on the global Gastroparesis Cardinal Symptom Index [6, 7].

Interdigestive motor activity

Gastric emptying time (GET) may be assessed by a wireless motility capsule (SmartPill®, Medtronic, Minneapolis, USA) measuring pH, pressure and temperature throughout the gastrointestinal tract. Being a non-digestible capsule, one assumes that expulsion of the SmartPill from the stomach is caused by interdigestive phase III contractions [45]. As such, GET differs from GES in the mechanism of gastric emptying that is measured. When measured with SmartPill, a subset of patients with idiopathic gastroparesis appears to have a delayed interdigestive phase III, with migrating motor complexes re-appearing 5 hours or more postprandially [46-49]. Though scarcely studied, impaired motilin release may be associated with the delay or absence of interdigestive phase III contractions in idiopathic gastroparesis [50].

Impaired fundic accommodation

In impaired fundic accommodation (FA), the gastric fundus fails to exert its reservoir function after the ingestion of food or drink. Impaired gastric accommodation has been reported to be associated with early satiety and anorexia [44, 51]. The gold standard for measuring fundic

accommodation is currently the gastric barostat: An infinitely compliant balloon which is placed in the proximal stomach to measure changes in the volume of the fundus after a liquid meal. Using the gastric barostat, Tack and colleagues found that 43% of patients with medically refractory idiopathic gastroparesis had impaired FA [44]. In another study, scintigraphy of a solid meal was used to show that only 12% of patients in a mixed gastroparesis group had impaired FA [51]. However, impaired FA was found to be associated with non-diabetic gastroparesis.

Visceral hypersensitivity

A lowered threshold for sensing a mechanical or chemical stimulus (hypersensitivity), sensing the stimulus as painful at a lower threshold (hyperalgesia) or sensing an otherwise non-painful stimulus as painful (allodynia) is termed visceral hypersensitivity. The mechanisms behind visceral hypersensitivity is not fully understood. However, the vanilloid 1 receptor (TRPV1), an ion channel involved in a wide range of sensory functions, is assumed to play a central role in this process. In medically refractory idiopathic gastroparesis, Tack et al found visceral hypersensitivity to be present in 29% of the study subjects and this was associated with early satiety, abdominal pain and anorexia [44].

Antropyloroduodenal motility and coordination

A general antral hypomotility may be present in patients with idiopathic gastroparesis, in which frequency, velocity and amplitude of antral contractions is blunted and this may be one of the mechanisms leading to delayed gastric emptying [47, 52].

The endoluminal functional lumen imaging probe (EndoFLIP®, Crospon Ltd, Galway, Éire) uses impedance planimetry to measure multiple physiological characteristics of the pylorus, including its diameter, pressure and distensibility. Compared to healthy volunteers,

distensibility seems to be decreased and pyloric pressure increased in a subset of idiopathic gastroparesis, though it is uncertain whether these parameters are associated with degree of gastric retention [53-55].

Other motility dysfunctions

Extragastric motility dysfunction appear to be a relatively common feature in idiopathic gastroparesis. Esophageal dysmotility and dysphagia may be predictive of delayed gastric emptying, and the two motility disorders seem to correlate with each other [56, 57]. Impaired small bowel and colonic motility has also been demonstrated in patients with idiopathic gastroparesis [47, 48, 58].

Post-infectious gastroparesis

A subgroup of patients with idiopathic gastroparesis has an onset of symptoms after a prior infection. Multiple infectious agents are assumed to be able to cause post-infectious gastroparesis including Epstein-Barr virus, cytomegalovirus and enterovirus [4, 59, 60]. An infectious prodrome with symptoms of food poisoning, gastroenteritis or upper respiratory infection is common [6]. Patients with post-infectious gastroparesis have been suggested to be associated with dysautonomia [60]. However, this has not been systematically studied. Clinically, post-infectious gastroparesis is similar to other patients with idiopathic gastroparesis but is associated with an acute onset of symptoms [4, 6]. Identifying patients with a presumed viral prodrome is important, as this may be associated with long term clinical improvement [4, 59, 61-63].

Implications for therapy

Treatment ladder in idiopathic gastroparesis	
Dietary recommendations	Food should be of small particle size, or easy to process into small particles. Small, frequent meals accompanied by liquids to ease gastric emptying. Avoid meals containing high amounts of fats, fiber or other components known to slow gastric emptying. Dietary guidance may be needed, as nutritional deficiencies are common.
Prokinetic and anti-emetic medications	Metoclopramide (10 mg, 10-15 minutes before a meal, preferably liquid formulation). Domperidone (10-20 mg x 3). Erythromycin (100-250 mg x 3, preferably liquid formulation). Ondansetron (4-8 mg before breakfast and optionally 4-8 mg before bedtime).
Endoscopic and surgical interventions	In cases refractory to medical therapy, one can consider placing a gastrostomy tube for decompression and a jejunostomy tube for enteral nutrition. In carefully selected patients, consider performing a pyloroplasty. As a last resort, total/subtotal gastrectomy may be performed. Gastric electrical stimulation is currently not advised for patients with idiopathic gastroparesis.

Conventional therapies

There is a general lack of treatment studies specifically addressing patients with idiopathic gastroparesis. Therefore, treatment recommendations are largely based on the general principles of treatment of gastroparesis in general. Treatment involving minimal risk of side effects should be tried before more invasive options are considered, as shown in Table 1.

In a prospective study of 262 gastroparesis patients (177 idiopathic), only one third responded with a modest symptomatic improvement after 48 weeks of standard care, which included medications (anti-emetics, prokinetics, proton pump inhibitors), total parenteral nutrition in

26 patients and gastric electrical stimulation in 18 patients [63]. Symptomatic improvement has been found to be associated with male sex, initial infectious prodrome and age 50 years or older, while a lack of symptomatic improvement was associated with abdominal pain, 4-hour gastric retention greater than 20%, severe GERD, obesity and moderate to severe depression [63]. Tricyclic antidepressive medications may not have a place in the treatment of idiopathic gastroparesis, as in a placebo-controlled, double masked, randomized clinical trial, nortriptyline was not found to be superior to placebo [64].

Gastric electrical stimulation

In gastroparesis patients refractory to medical treatment, some centers offer treatment with gastric electrical stimulation (GS) [65]. In a long-term study of both diabetic and idiopathic subjects, GS has been shown to near normalize serosal EGG parameters [66]. Though varying in the effect on gastric emptying, the device has shown efficacy in open label studies [65, 67-76], but failed to show significant symptomatic improvement in idiopathic gastroparesis in double blinded, placebo-controlled studies [77, 78]. Most centers now only offers GS for patients with diabetic gastroparesis.

Pyloric therapies

As the pyloric muscle is believed to play a role in the pathophysiology of gastroparesis, multiple therapies targeting the pyloric sphincter have been developed. Injections with botulinum toxin A into the pyloric sphincter has shown mixed results on symptoms and gastric emptying in open label trials [79-81]. In randomized double blinded placebo-controlled studies of patients with mixed etiology of gastroparesis, the effect was not superior to placebo [82, 83].

Laparoscopic pyloroplasty is a safe and effective therapy to reduce gastric retention in patients with gastroparesis and seems to be effective in reducing symptoms [84]. Gastric per oral endoscopic myotomy (POP) is another promising treatment which can be used to cleave the pylorus [85]. In retrospective open label studies of mixed etiology gastroparesis cohorts, POP is safe and effective at reducing 4-hour GES and most symptoms of gastroparesis [85-89]. In one study, POP was as effective as laparoscopic pyloroplasty (PP) at reducing symptoms and gastric emptying time, but resulted in less complications, a shorter length of hospital stay and had a shorter operation time [87]. As such, POP is a minimally invasive alternative to PP. However, as POP is a relatively new technique, long-term data on efficacy, side-effects and complications are not available. Further, randomized double blinded placebo-controlled studies specifically targeting idiopathic gastroparesis are needed.

Pyloric therapies in combination with GS may be more efficient than either therapy alone. In two studies of patients with gastroparesis, PP in combination with GES significantly improved symptoms better than patients only receiving GS or PP regardless of etiology [90, 91]. However, both studies are limited by small sample size and a retrospective design.

Individualized treatment

GS for idiopathic gastroparesis is currently not recommended [2]. However, a novel approach to patient selection could be to utilize the knowledge of response to GS. Nausea/vomiting as a primary symptom seems to predict the best response to GS, while abdominal pain and bloating seem to be associated with poor symptomatic improvement [65, 70, 92, 93]. Severe ICC-depletion seems to be predictive of a negative symptomatic response to GS [12, 94]. In another study, response to GS was inversely correlated with number of ganglia per high-power field [15]. However, endoscopic minimally invasive techniques for harvesting full-

thickness gastric wall biopsies need to be developed before this can be utilized in clinical practice.

Since a subgroup of patients with idiopathic gastroparesis show objective signs of pathology in the pyloric sphincter, this could possibly be used to select patients for pyloric interventions. In one study, low pyloric distensibility was used as selection criteria for pyloric balloon dilation [55]. Low pyloric distensibility ($< 9.2 \text{ mm}^2/\text{mmHg}$) was also found to be predictive of clinical efficacy of POP in a pilot study, though only 4 of 20 patients had idiopathic gastroparesis [95]. Patients with normal slow wave activity on EGG may also be more responsive to pyloric botulinum toxin A injection or pyloric balloon dilation [96]. However, further studies are needed to identify parameters for use in such treatment algorithms.

Novel medical treatment

Intravenous immunoglobulin therapy (IVIg)

Gastroparesis from autoimmune disorders may be considered one subgroup of idiopathic gastroparesis. In one case series, 14 patients with symptoms of gastroparesis refractory to medical and GS therapy were identified with immunological abnormalities on full-thickness gastric biopsies and on an autoimmune serological panel [97]. The study subjects were then treated with IVIg for 12 weeks, resulting in a clinically significant symptom reduction.

Anti-viral therapy

In one case study, 9 of 11 patients with post-infectious gastroparesis, an active enterovirus infection was observed in gastric biopsies [60]. Eight of these were treated with anti-viral

medications and/or immune therapies such as IVIG with most of the patients experiencing symptom improvement, supporting post-infectious gastroparesis as a separate therapeutic entity.

5-HT₄ agonists

Although serotonin has been shown to play a role in the motor and sensory functions of the upper gastrointestinal tract, only minor serotonergic alterations has been found in idiopathic gastroparesis [98]. However, as the now withdrawn 5-HT₄ agonist cisapride was shown to increase gastric emptying [99], there is a search for new, equally effective 5-HT₄ agonists. Prucalopride is a 5-HT₄ agonist, which is approved for the treatment of chronic constipation in most countries and is used in the treatment of gastroparesis at some centers. The effect of this agent in idiopathic gastroparesis has been assessed in a completed double-blinded cross-over study, but results await publication [100]. Other agents under investigation includes velusetrag, which has completed phase I and phase II studies [101, 102], and TAK-954 [103].

Ghrelin agonists

Ghrelin is a peptide hormone mainly involved in appetite regulation. Amongst several mechanisms, it can act as a stimulant on gastrointestinal motility. The ghrelin agonist relamorelin is a promising new drug shown to be safe and effective at reducing gastroparesis symptoms in a randomized, placebo-controlled study of 393 diabetic gastroparesis patients [104]. However, the effect of ghrelin agonists on idiopathic gastroparesis has not been extensively studied in a systematic manner. An exception is one double-blinded, placebo-controlled study of 6 patients, in which 40 µg ghrelin was infused intravenously at the start of a meal [105]. The study subjects experienced improvement in the cumulative meal-related symptom score, fullness and pain. Liquid gastric emptying was also significantly enhanced

and tended to correlate with improvement in bloating ($P=0.06$). This could be of importance, as a delay in liquid gastric emptying may be more common in non-diabetic than diabetic gastroparesis. As ghrelin-release in response to sham feeding seem to be normal in idiopathic gastroparesis, the manner through which ghrelin mediates improvement in motility and symptoms is unclear [106]. However, the authors suggests that one mechanism may be through increased fundic accommodation as this is shown in healthy subjects given ghrelin. As impaired fundic accommodation is found in a subset of patients with idiopathic gastroparesis, ghrelin analogues could represent a new treatment alternative in idiopathic gastroparesis, but this demands confirmation in larger studies.

Anti-emetics

Symptoms of nausea and vomiting in gastroparesis can be treated with anti-emetics, as listed in table 1. However, prolonged use of metoclopramide may lead to irreversible tardive dyskinesia. Domperidone use bears a risk of cardiac arrhythmia and sudden cardiac death, while the effect of ondansetron on nausea in gastroparesis has not been studied specifically. As such, there is a need for new anti-emetic medications for patients with gastroparesis.

The neurokinin 1 (NK1) receptor is central in both the acute and delayed emetic process and distributed both peripherally in the gastrointestinal tract and centrally in the vomiting center in the brainstem. As such, NK-1 antagonists have been developed for the treatment of delayed emesis in chemotherapy-induced nausea and vomiting. NK1-antagonists may have a role in the treatment of idiopathic gastroparesis, as in a double-blind, placebo-controlled study of patients with gastroparesis or associated conditions, the NK1-antagonist aprepitant was found to have moderate effects on nausea, vomiting and overall symptoms [107]. However, the primary aim of the study, to decrease nausea 25 mm or more on a 100 mm visual analogue scale, was not met.

TAK-906, a peripheral dopamine D2/D3 receptor antagonist, likely ameliorates nausea and vomiting in a similar manner as domperidone, but hopefully without the cardiac side effects. Phase I is completed, while phase II-studies are ongoing [103, 108].

Systematically studied medications for the treatment of gastroparesis exacerbations is also lacking. However, in a double-blind study, Haloperidol, a dopamine receptor antagonist antipsychotic drug, was more effective than placebo as an adjunctive therapy to treat gastroparesis exacerbations in an emergency department [109].

Olanzapine is another antipsychotic medication that may be effective in the treatment of gastroparesis. In an ongoing pilot study, it is hypothesized to have an anti-emetic and prokinetic effect on gut motility, partially through increased ghrelin levels [110].

Others

Trials utilizing vagal stimulation are ongoing in mixed gastroparesis cohorts. Though largely unexplored in gastroparesis, low vagal tone may lead to inflammation and gastrointestinal dysmotility. Therefore, vagal stimulation may be a novel way of increasing gastric emptying and perhaps shifting the gastric muscularis macrophage population to a phenotypically anti-inflammatory one [111, 112].

As multiple motility dysfunctions and symptoms of idiopathic gastroparesis are shared with functional dyspepsia, medication such as acotiamide used to treat functional dyspepsia should be tested on patients with idiopathic gastroparesis [113].

Conclusion

In addition to delayed gastric emptying, patients with idiopathic gastroparesis can suffer from multiple other motility dysfunctions, gastric dysrhythmia and visceral hypersensitivity. All of

these may stem from underlying cellular alterations. Current treatment is limited to alleviating symptoms, but as novel pathophysiological features are uncovered, development of new treatment modalities should aim to normalize or modulate immune alterations, sensory pathways, gastric myoelectrical activity and the affected cell types involved. In addition, there are need for further research to better select patients to existing advanced treatments such as gastric neurostimulation or pyloric interventions.

Declaration of interests: The authors have no competing interests.

Authors contributions: MB wrote the manuscript. DS, JH and LA contributed with critical revision of the manuscript and has approved the final version.

1. Parkman HP, Hasler WL, Fisher RS, et al. American Gastroenterological Association technical review on the diagnosis and treatment of gastroparesis. *Gastroenterology*. 2004 Nov;127(5):1592-622.
2. Camilleri M, Parkman HP, Shafi MA, et al. Clinical guideline: management of gastroparesis. *Am J Gastroenterol*. 2013 Jan;108(1):18-37; quiz 38. doi: 10.1038/ajg.2012.373.
3. Jung HK, Choung RS, Locke GR, 3rd, et al. The incidence, prevalence, and outcomes of patients with gastroparesis in Olmsted County, Minnesota, from 1996 to 2006. *Gastroenterology*. 2009 Apr;136(4):1225-33. doi: 10.1053/j.gastro.2008.12.047.
4. Soykan I, Sivri B, Sarosiek I, et al. Demography, clinical characteristics, psychological and abuse profiles, treatment, and long-term follow-up of patients with gastroparesis. *Dig Dis Sci*. 1998 Nov;43(11):2398-404.
5. Parkman HP, Yates K, Hasler WL, et al. Similarities and differences between diabetic and idiopathic gastroparesis. *Clin Gastroenterol Hepatol*. 2011 Dec;9(12):1056-64; quiz e133-4. doi: 10.1016/j.cgh.2011.08.013.
6. Parkman HP, Yates K, Hasler WL, et al. Clinical features of idiopathic gastroparesis vary with sex, body mass, symptom onset, delay in gastric emptying, and gastroparesis severity. *Gastroenterology*. 2011 Jan;140(1):101-15. doi: 10.1053/j.gastro.2010.10.015.
7. Revicki DA, Rentz AM, Dubois D, et al. Development and validation of a patient-assessed gastroparesis symptom severity measure: the Gastroparesis Cardinal Symptom Index. *Aliment Pharmacol Ther*. 2003 Jul 01;18(1):141-50.
8. Cherian D, Sachdeva P, Fisher RS, et al. Abdominal pain is a frequent symptom of gastroparesis. *Clin Gastroenterol Hepatol*. 2010 Aug;8(8):676-81. doi: 10.1016/j.cgh.2010.04.027.
9. Hoogerwerf WA, Pasricha PJ, Kalloo AN, et al. Pain: the overlooked symptom in gastroparesis. *Am J Gastroenterol*. 1999 Apr;94(4):1029-33. doi: 10.1111/j.1572-0241.1999.01008.x.
10. Nguyen LA, Snape WJ, Jr. Clinical presentation and pathophysiology of gastroparesis. *Gastroenterol Clin North Am*. 2015 Mar;44(1):21-30. doi: 10.1016/j.gtc.2014.11.003.

11. Forster J, Damjanov I, Lin Z, et al. Absence of the interstitial cells of Cajal in patients with gastroparesis and correlation with clinical findings. *J Gastrointest Surg*. 2005 Jan;9(1):102-8. doi: 10.1016/j.gassur.2004.10.001.
12. Lin Z, Sarosiek I, Forster J, et al. Association of the status of interstitial cells of Cajal and electrogastrogram parameters, gastric emptying and symptoms in patients with gastroparesis. *Neurogastroenterol Motil*. 2010 Jan;22(1):56-61, e10. doi: 10.1111/j.1365-2982.2009.01365.x.
13. Grover M, Farrugia G, Lurken MS, et al. Cellular changes in diabetic and idiopathic gastroparesis. *Gastroenterology*. 2011 May;140(5):1575-85 e8. doi: 10.1053/j.gastro.2011.01.046.
14. Grover M, Bernard CE, Pasricha PJ, et al. Clinical-histological associations in gastroparesis: results from the Gastroparesis Clinical Research Consortium. *Neurogastroenterol Motil*. 2012 Jun;24(6):531-9, e249. doi: 10.1111/j.1365-2982.2012.01894.x.
15. Heckert J, Thomas RM, Parkman HP. Gastric neuromuscular histology in patients with refractory gastroparesis: Relationships to etiology, gastric emptying, and response to gastric electric stimulation. *Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society*. 2017 Aug;29(8). doi: 10.1111/nmo.13068.
16. Harberson J, Thomas RM, Harbison SP, et al. Gastric neuromuscular pathology in gastroparesis: analysis of full-thickness antral biopsies. *Dig Dis Sci*. 2010 Feb;55(2):359-70. doi: 10.1007/s10620-009-1071-2.
17. Moraveji S, Bashashati M, Elhanafi S, et al. Depleted interstitial cells of Cajal and fibrosis in the pylorus: Novel features of gastroparesis. *Neurogastroenterol Motil*. 2016 Jul;28(7):1048-54. doi: 10.1111/nmo.12806.
18. Bashashati M, Moraveji S, Torabi A, et al. Pathological Findings of the Antral and Pyloric Smooth Muscle in Patients with Gastroparesis-Like Syndrome Compared to Gastroparesis: Similarities and Differences. *Dig Dis Sci*. 2017 Oct;62(10):2828-2833. doi: 10.1007/s10620-017-4629-4.
19. Faussone-Pellegrini MS, Grover M, Pasricha PJ, et al. Ultrastructural differences between diabetic and idiopathic gastroparesis. *J Cell Mol Med*. 2012 Jul;16(7):1573-81. doi: 10.1111/j.1582-4934.2011.01451.x.
20. Farrugia G. Interstitial cells of Cajal in health and disease. *Neurogastroenterol Motil*. 2008 May;20 Suppl 1:54-63. doi: 10.1111/j.1365-2982.2008.01109.x.
21. Lahr CJ, Griffith J, Subramony C, et al. Gastric electrical stimulation for abdominal pain in patients with symptoms of gastroparesis. *Am Surg*. 2013 May;79(5):457-64.
22. Herring BP, Hoggatt AM, Gupta A, et al. Idiopathic gastroparesis is associated with specific transcriptional changes in the gastric muscularis externa. *Neurogastroenterol Motil*. 2018 Apr;30(4):e13230. doi: 10.1111/nmo.13230.
23. Grover M, Bernard CE, Pasricha PJ, et al. Diabetic and idiopathic gastroparesis is associated with loss of CD206-positive macrophages in the gastric antrum. *Neurogastroenterol Motil*. 2017 Jun;29(6). doi: 10.1111/nmo.13018.
24. Choi KM, Kashyap PC, Dutta N, et al. CD206-positive M2 macrophages that express heme oxygenase-1 protect against diabetic gastroparesis in mice. *Gastroenterology*. 2010 Jun;138(7):2399-409, 2409 e1. doi: 10.1053/j.gastro.2010.02.014.
25. Cipriani G, Gibbons SJ, Miller KE, et al. Change in Populations of Macrophages Promotes Development of Delayed Gastric Emptying in Mice. *Gastroenterology*. 2018 Feb 28. doi: 10.1053/j.gastro.2018.02.027.
26. Choi KM, Gibbons SJ, Nguyen TV, et al. Heme oxygenase-1 protects interstitial cells of Cajal from oxidative stress and reverses diabetic gastroparesis. *Gastroenterology*. 2008 Dec;135(6):2055-64, 2064 e1-2. doi: 10.1053/j.gastro.2008.09.003.
27. Choi KM, Gibbons SJ, Sha L, et al. Interleukin 10 Restores Gastric Emptying, Electrical Activity, and Interstitial Cells of Cajal Networks in Diabetic Mice. *Cell Mol Gastroenterol Hepatol*. 2016 Jul;2(4):454-467. doi: 10.1016/j.jcmgh.2016.04.006.
28. Gibbons SJ, Grover M, Choi KM, et al. Repeat polymorphisms in the Homo sapiens heme oxygenase-1 gene in diabetic and idiopathic gastroparesis. *PLoS One*. 2017;12(11):e0187772. doi: 10.1371/journal.pone.0187772.

29. Grover M, Gibbons SJ, Nair AA, et al. Transcriptomic signatures reveal immune dysregulation in human diabetic and idiopathic gastroparesis. *BMC Med Genomics*. 2018 Aug 7;11(1):62. doi: 10.1186/s12920-018-0379-1.
30. Grover M, Bernard CE, Pasricha PJ, et al. Platelet-derived growth factor receptor alpha (PDGFRalpha)-expressing "fibroblast-like cells" in diabetic and idiopathic gastroparesis of humans. *Neurogastroenterol Motil*. 2012 Sep;24(9):844-52. doi: 10.1111/j.1365-2982.2012.01944.x.
31. Chen JD, Schirmer BD, McCallum RW. Serosal and cutaneous recordings of gastric myoelectrical activity in patients with gastroparesis. *Am J Physiol*. 1994 Jan;266(1 Pt 1):G90-8. doi: 10.1152/ajpgi.1994.266.1.G90.
32. Chen JD, Lin Z, Pan J, et al. Abnormal gastric myoelectrical activity and delayed gastric emptying in patients with symptoms suggestive of gastroparesis. *Dig Dis Sci*. 1996 Aug;41(8):1538-45.
33. Brzana RJ, Koch KL, Bingaman S. Gastric myoelectrical activity in patients with gastric outlet obstruction and idiopathic gastroparesis. *Am J Gastroenterol*. 1998 Oct;93(10):1803-9. doi: 10.1111/j.1572-0241.1998.00524.x.
34. O'Grady G, Angeli TR, Du P, et al. Abnormal initiation and conduction of slow-wave activity in gastroparesis, defined by high-resolution electrical mapping. *Gastroenterology*. 2012 Sep;143(3):589-598 e3. doi: 10.1053/j.gastro.2012.05.036.
35. Koch KL. Gastric dysrhythmias: a potential objective measure of nausea. *Exp Brain Res*. 2014 Aug;232(8):2553-61. doi: 10.1007/s00221-014-4007-9.
36. Rothstein RD, Alavi A, Reynolds JC. Electrogastrography in patients with gastroparesis and effect of long-term cisapride. *Dig Dis Sci*. 1993 Aug;38(8):1518-24.
37. Desai A, O'Connor M, Neja B, et al. Reproducibility of gastric emptying assessed with scintigraphy in patients with upper GI symptoms. *Neurogastroenterol Motil*. 2018 May 2:e13365. doi: 10.1111/nmo.13365.
38. Abell TL, Camilleri M, Donohoe K, et al. Consensus recommendations for gastric emptying scintigraphy: a joint report of the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine. *J Nucl Med Technol*. 2008 Mar;36(1):44-54. doi: 10.2967/jnmt.107.048116.
39. Sachdeva P, Malhotra N, Pathikonda M, et al. Gastric emptying of solids and liquids for evaluation for gastroparesis. *Dig Dis Sci*. 2011 Apr;56(4):1138-46. doi: 10.1007/s10620-011-1635-9.
40. Ziessman HA, Chander A, Clarke JO, et al. The added diagnostic value of liquid gastric emptying compared with solid emptying alone. *J Nucl Med*. 2009 May;50(5):726-31. doi: 10.2967/jnumed.108.059790.
41. Ziessman HA, Okolo PI, Mullin GE, et al. Liquid gastric emptying is often abnormal when solid emptying is normal. *J Clin Gastroenterol*. 2009 Aug;43(7):639-43.
42. Parkman HP, Hallinan EK, Hasler WL, et al. Early satiety and postprandial fullness in gastroparesis correlate with gastroparesis severity, gastric emptying, and water load testing. *Neurogastroenterol Motil*. 2017 Apr;29(4). doi: 10.1111/nmo.12981.
43. Cassilly DW, Wang YR, FriedenberG FK, et al. Symptoms of gastroparesis: use of the gastroparesis cardinal symptom index in symptomatic patients referred for gastric emptying scintigraphy. *Digestion*. 2008;78(2-3):144-51. doi: 10.1159/000175836.
44. 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 Jan;56(1):29-36. doi: 10.1136/gut.2005.089508.
45. Brun R, Michalek W, Surjanhata BC, et al. Comparative analysis of phase III migrating motor complexes in stomach and small bowel using wireless motility capsule and antroduodenal manometry. *Neurogastroenterol Motil*. 2012 Apr;24(4):332-e165. doi: 10.1111/j.1365-2982.2011.01862.x.
46. Kuo B, McCallum RW, Koch KL, et al. Comparison of gastric emptying of a nondigestible capsule to a radio-labelled meal in healthy and gastroparetic subjects. *Aliment Pharmacol Ther*. 2008 Jan 15;27(2):186-96. doi: 10.1111/j.1365-2036.2007.03564.x.

47. Hasler WL, May KP, Wilson LA, et al. Relating gastric scintigraphy and symptoms to motility capsule transit and pressure findings in suspected gastroparesis. *Neurogastroenterol Motil.* 2018 Feb;30(2). doi: 10.1111/nmo.13196.
48. Lee A, Wilding G, Kuo B. Variable abnormal physiological motility in the proximal upper gastrointestinal tract in gastroparesis. *Neurogastroenterol Motil.* 2012 Jul;24(7):652-7, e276. doi: 10.1111/j.1365-2982.2012.01905.x.
49. Sarosiek I, Selover KH, Katz LA, et al. The assessment of regional gut transit times in healthy controls and patients with gastroparesis using wireless motility technology. *Aliment Pharmacol Ther.* 2010 Jan 15;31(2):313-22. doi: 10.1111/j.1365-2036.2009.04162.x.
50. Labo G, Bortolotti M, Vezzadini P, et al. Interdigestive gastroduodenal motility and serum motilin levels in patients with idiopathic delay in gastric emptying. *Gastroenterology.* 1986 Jan;90(1):20-6.
51. Orthey P, Yu D, Van Natta ML, et al. Intra-gastric Meal Distribution During Gastric Emptying Scintigraphy for Assessment of Fundic Accommodation: Correlation with Symptoms of Gastroparesis. *J Nucl Med.* 2018 Apr;59(4):691-697. doi: 10.2967/jnumed.117.197053.
52. Ajaj W, Goehde SC, Papanikolaou N, et al. Real time high resolution magnetic resonance imaging for the assessment of gastric motility disorders. *Gut.* 2004 Sep;53(9):1256-61. doi: 10.1136/gut.2003.038588.
53. Malik Z, Sankineni A, Parkman HP. Assessing pyloric sphincter pathophysiology using EndoFLIP in patients with gastroparesis. *Neurogastroenterol Motil.* 2015 Apr;27(4):524-31. doi: 10.1111/nmo.12522.
54. Snape WJ, Lin MS, Agarwal N, et al. Evaluation of the pylorus with concurrent intraluminal pressure and EndoFLIP in patients with nausea and vomiting. *Neurogastroenterol Motil.* 2016 May;28(5):758-64. doi: 10.1111/nmo.12772.
55. Gourcerol G, Tissier F, Melchior C, et al. Impaired fasting pyloric compliance in gastroparesis and the therapeutic response to pyloric dilatation. *Aliment Pharmacol Ther.* 2015 Feb;41(4):360-7. doi: 10.1111/apt.13053.
56. Zikos TA, Clarke JO, Triadafilopoulos G, et al. A Positive Correlation Between Gastric and Esophageal Dysmotility Suggests Common Causality. *Dig Dis Sci.* 2018 Jun 26. doi: 10.1007/s10620-018-5175-4.
57. Boltin D, Zvidi I, Steinmetz A, et al. Vomiting and dysphagia predict delayed gastric emptying in diabetic and nondiabetic subjects. *J Diabetes Res.* 2014;2014:294032. doi: 10.1155/2014/294032.
58. Surjanhata B, Brun R, Wilding G, et al. Small bowel fed response as measured by wireless motility capsule: Comparative analysis in healthy, gastroparetic, and constipated subjects. *Neurogastroenterol Motil.* 2018 May;30(5):e13268. doi: 10.1111/nmo.13268.
59. Oh JJ, Kim CH. Gastroparesis after a presumed viral illness: clinical and laboratory features and natural history. *Mayo Clin Proc.* 1990 May;65(5):636-42.
60. Barkin JA, Czul F, Barkin JS, et al. Gastric Enterovirus Infection: A Possible Causative Etiology of Gastroparesis. *Dig Dis Sci.* 2016 Aug;61(8):2344-50. doi: 10.1007/s10620-016-4227-x.
61. Naftali T, Yishai R, Zangen T, et al. Post-infectious gastroparesis: clinical and electrogastrographic aspects. *J Gastroenterol Hepatol.* 2007 Sep;22(9):1423-8. doi: 10.1111/j.1440-1746.2006.04738.x.
62. Bityutskiy LP, Soykan I, McCallum RW. Viral gastroparesis: a subgroup of idiopathic gastroparesis--clinical characteristics and long-term outcomes. *Am J Gastroenterol.* 1997 Sep;92(9):1501-4.
63. Pasricha PJ, Yates KP, Nguyen L, et al. Outcomes and Factors Associated With Reduced Symptoms in Patients With Gastroparesis. *Gastroenterology.* 2015 Dec;149(7):1762-1774.e4. doi: 10.1053/j.gastro.2015.08.008.
64. Parkman HP, Van Natta ML, Abell TL, et al. Effect of nortriptyline on symptoms of idiopathic gastroparesis: the NORIG randomized clinical trial. *JAMA.* 2013 Dec 25;310(24):2640-9. doi: 10.1001/jama.2013.282833.

65. Heckert J, Sankineni A, Hughes WB, et al. Gastric Electric Stimulation for Refractory Gastroparesis: A Prospective Analysis of 151 Patients at a Single Center. *Dig Dis Sci*. 2016 Jan;61(1):168-75. doi: 10.1007/s10620-015-3837-z.
66. Williams PA, Nikitina Y, Kedar A, et al. Long-term effects of gastric stimulation on gastric electrical physiology. *J Gastrointest Surg*. 2013 Jan;17(1):50-5; discussion p 55-6. doi: 10.1007/s11605-012-2020-5.
67. Richmond B, Chong B, Modak A, et al. Gastric electrical stimulation for refractory gastroparesis: predictors of response and redefining a successful outcome. *Am Surg*. 2015 May;81(5):467-71.
68. Anand C, Al-Juburi A, FAMILONI B, et al. Gastric electrical stimulation is safe and effective: a long-term study in patients with drug-refractory gastroparesis in three regional centers. *Digestion*. 2007;75(2-3):83-9. doi: 10.1159/000102961.
69. McCallum RW, Lin Z, Forster J, et al. Gastric electrical stimulation improves outcomes of patients with gastroparesis for up to 10 years. *Clin Gastroenterol Hepatol*. 2011 Apr;9(4):314-319 e1. doi: 10.1016/j.cgh.2010.12.013.
70. Velanovich V. Quality of life and symptomatic response to gastric neurostimulation for gastroparesis. *J Gastrointest Surg*. 2008 Oct;12(10):1656-62; discussion 1662-3. doi: 10.1007/s11605-008-0655-z.
71. Brody F, Vaziri K, Saddler A, et al. Gastric electrical stimulation for gastroparesis. *J Am Coll Surg*. 2008 Oct;207(4):533-8. doi: 10.1016/j.jamcollsurg.2008.04.032.
72. Mason RJ, Lipham J, Eckerling G, et al. Gastric electrical stimulation: an alternative surgical therapy for patients with gastroparesis. *Arch Surg*. 2005 Sep;140(9):841-6; discussion 847-8. doi: 10.1001/archsurg.140.9.841.
73. Abell T, Lou J, Tabbaa M, et al. Gastric electrical stimulation for gastroparesis improves nutritional parameters at short, intermediate, and long-term follow-up. *JPEN J Parenter Enteral Nutr*. 2003 Jul-Aug;27(4):277-81. doi: 10.1177/0148607103027004277.
74. Forster J, Sarosiek I, Lin Z, et al. Further experience with gastric stimulation to treat drug refractory gastroparesis. *Am J Surg*. 2003 Dec;186(6):690-5.
75. McKenna D, Beverstein G, Reichelderfer M, et al. Gastric electrical stimulation is an effective and safe treatment for medically refractory gastroparesis. *Surgery*. 2008 Oct;144(4):566-72; discussion 572-4. doi: 10.1016/j.surg.2008.06.024.
76. Timratana P, El-Hayek K, Shimizu H, et al. Laparoscopic gastric electrical stimulation for medically refractory diabetic and idiopathic gastroparesis. *J Gastrointest Surg*. 2013 Mar;17(3):461-70. doi: 10.1007/s11605-012-2128-7.
77. Abell T, McCallum R, Hocking M, et al. Gastric electrical stimulation for medically refractory gastroparesis. *Gastroenterology*. 2003 Aug;125(2):421-8.
78. McCallum RW, Sarosiek I, Parkman HP, et al. Gastric electrical stimulation with Enterra therapy improves symptoms of idiopathic gastroparesis. *Neurogastroenterol Motil*. 2013 Oct;25(10):815-e636. doi: 10.1111/nmo.12185.
79. Bromer MQ, Friedenberg F, Miller LS, et al. Endoscopic pyloric injection of botulinum toxin A for the treatment of refractory gastroparesis. *Gastrointestinal endoscopy*. 2005 Jun;61(7):833-9.
80. Arts J, van Gool S, Caenepeel P, et al. Influence of intrapyloric botulinum toxin injection on gastric emptying and meal-related symptoms in gastroparesis patients. *Aliment Pharmacol Ther*. 2006 Aug 15;24(4):661-7. doi: 10.1111/j.1365-2036.2006.03019.x.
81. Miller LS, Szych GA, Kantor SB, et al. Treatment of idiopathic gastroparesis with injection of botulinum toxin into the pyloric sphincter muscle. *Am J Gastroenterol*. 2002 Jul;97(7):1653-60. doi: 10.1111/j.1572-0241.2002.05823.x.
82. Friedenberg FK, Palit A, Parkman HP, et al. Botulinum toxin A for the treatment of delayed gastric emptying. *Am J Gastroenterol*. 2008 Feb;103(2):416-23. doi: 10.1111/j.1572-0241.2007.01676.x.
83. Arts J, Holvoet L, Caenepeel P, et al. Clinical trial: a randomized-controlled crossover study of intrapyloric injection of botulinum toxin in gastroparesis. *Aliment Pharmacol Ther*. 2007 Nov 1;26(9):1251-8. doi: 10.1111/j.1365-2036.2007.03467.x.

84. Shada AL, Dunst CM, Pescarus R, et al. Laparoscopic pyloroplasty is a safe and effective first-line surgical therapy for refractory gastroparesis. *Surg Endosc.* 2016 Apr;30(4):1326-32. doi: 10.1007/s00464-015-4385-5.
85. Khashab MA, Ngamruengphong S, Carr-Locke D, et al. Gastric per-oral endoscopic myotomy for refractory gastroparesis: results from the first multicenter study on endoscopic pyloromyotomy (with video). *Gastrointestinal endoscopy.* 2017 Jan;85(1):123-128. doi: 10.1016/j.gie.2016.06.048.
86. Malik Z, Kataria R, Modayil R, et al. Gastric Per Oral Endoscopic Myotomy (G-POEM) for the Treatment of Refractory Gastroparesis: Early Experience. *Dig Dis Sci.* 2018 Feb 22. doi: 10.1007/s10620-018-4976-9.
87. Landreneau JP, Strong AT, El-Hayek K, et al. Laparoscopic pyloroplasty versus endoscopic per-oral pyloromyotomy for the treatment of gastroparesis. *Surg Endosc.* 2018 Jul 17. doi: 10.1007/s00464-018-6342-6.
88. Rodriguez JH, Haskins IN, Strong AT, et al. Per oral endoscopic pyloromyotomy for refractory gastroparesis: initial results from a single institution. *Surg Endosc.* 2017 Dec;31(12):5381-5388. doi: 10.1007/s00464-017-5619-5.
89. Rodriguez J, Strong AT, Haskins IN, et al. Per-oral Pyloromyotomy (POP) for Medically Refractory Gastroparesis: Short Term Results From the First 100 Patients at a High Volume Center. *Ann Surg.* 2018 Sep;268(3):421-430. doi: 10.1097/SLA.0000000000002927.
90. Sarosiek I, Forster J, Lin Z, et al. The addition of pyloroplasty as a new surgical approach to enhance effectiveness of gastric electrical stimulation therapy in patients with gastroparesis. *Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society.* 2013 Feb;25(2):134-e80. doi: 10.1111/nmo.12032.
91. Arthur LE, Slattery L, Richardson W. Tailored approach to gastroparesis significantly improves symptoms. *Surg Endosc.* 2018 Feb;32(2):977-982. doi: 10.1007/s00464-017-5775-7.
92. Musunuru S, Beverstein G, Gould J. Preoperative predictors of significant symptomatic response after 1 year of gastric electrical stimulation for gastroparesis. *World J Surg.* 2010 Aug;34(8):1853-8. doi: 10.1007/s00268-010-0586-1.
93. Maranki JL, Lytes V, Meilahn JE, et al. Predictive factors for clinical improvement with Enterra gastric electric stimulation treatment for refractory gastroparesis. *Dig Dis Sci.* 2008 Aug;53(8):2072-8. doi: 10.1007/s10620-007-0124-7.
94. Omer E, Kedar A, Nagarajarao HS, et al. Cajal Cell Counts are Important Predictors of Outcomes in Drug Refractory Gastroparesis Patients With Neurostimulation. *J Clin Gastroenterol.* 2018 Apr 18. doi: 10.1097/MCG.0000000000001025.
95. Jacques J, Pagnon L, Hure F, et al. Peroral endoscopic pyloromyotomy is efficacious and safe for refractory gastroparesis: prospective trial with assessment of pyloric function. *Endoscopy.* 2018 Jun 12. doi: 10.1055/a-0628-6639.
96. Wellington J, Scott B, Kundu S, et al. Effect of endoscopic pyloric therapies for patients with nausea and vomiting and functional obstructive gastroparesis. *Autonomic neuroscience : basic & clinical.* 2017 Jan;202:56-61. doi: 10.1016/j.autneu.2016.07.004.
97. Ashat M, Lewis A, Liaquat H, et al. Intravenous immunoglobulin in drug and device refractory patients with the symptoms of gastroparesis-an open-label study. *Neurogastroenterol Motil.* 2018 Mar;30(3). doi: 10.1111/nmo.13256.
98. van Lelyveld N, Ter Linde J, Schipper M, et al. Serotonergic signalling in the stomach and duodenum of patients with gastroparesis. *Neurogastroenterol Motil.* 2008 May;20(5):448-55. doi: 10.1111/j.1365-2982.2007.01068.x.
99. Richards RD, Valenzuela GA, Davenport KG, et al. Objective and subjective results of a randomized, double-blind, placebo-controlled trial using cisapride to treat gastroparesis. *Dig Dis Sci.* 1993 May;38(5):811-6.
100. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 - . Identifier NCT02510976, Prucalopride Versus Placebo in Gastroparesis; 2015 Jul 29 [cited 2018 2018 Oct 10]; [about 5 screens]. Available from: <https://ClinicalTrials.gov/show/NCT02510976>

101. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 - . Identifier NCT02267525, The Diabetic and Idiopathic Gastroparesis Efficacy, Safety, and Tolerability (DIGEST) Study; 2014 Oct 17 [cited 2018 Oct 10]; about 5 screens]. Available from: <https://ClinicalTrials.gov/show/NCT02267525>
102. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 - . Identifier NCT01718938, Phase 2 Study of Velusetrag in Diabetic or Idiopathic Gastroparesis; 2012 Nov 1 [cited 2018 Oct 10]; About [6 screens]. Available from: <https://ClinicalTrials.gov/show/NCT01718938>
103. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 - . Identifier NCT03281577, Effect of TAK-954 on Gastrointestinal and Colonic Transit in Diabetic or Idiopathic Gastroparesis Participants; 2017 sept 13 [cited 2018 Oct 10]; About 6 screens] Available from: <https://ClinicalTrials.gov/show/NCT03281577>
104. Camilleri M, McCallum RW, Tack J, et al. Efficacy and Safety of Relamorelin in Diabetics With Symptoms of Gastroparesis: A Randomized, Placebo-Controlled Study. *Gastroenterology*. 2017 Nov;153(5):1240-1250 e2. doi: 10.1053/j.gastro.2017.07.035.
105. Tack J, Depoortere I, Bisschops R, et al. Influence of ghrelin on gastric emptying and meal-related symptoms in idiopathic gastroparesis. *Aliment Pharmacol Ther*. 2005 Nov 1;22(9):847-53. doi: 10.1111/j.1365-2036.2005.02658.x.
106. Gaddipati KV, Simonian HP, Kresge KM, et al. Abnormal ghrelin and pancreatic polypeptide responses in gastroparesis. *Dig Dis Sci*. 2006 Aug;51(8):1339-46. doi: 10.1007/s10620-005-9022-z.
107. Pasricha PJ, Yates KP, Sarosiek I, et al. Aprepitant Has Mixed Effects on Nausea and Reduces Other Symptoms in Patients With Gastroparesis and Related Disorders. *Gastroenterology*. 2018 Jan;154(1):65-76 e11. doi: 10.1053/j.gastro.2017.08.033.
108. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 - . Identifier NCT03268941, A Study to Evaluate the Safety, Pharmacokinetics (PK) and Pharmacodynamics (PD) for TAK-906 in Participants With Diabetes Mellitus and Gastroparesis (DG) or With Idiopathic Gastroparesis (IG); 2017 Aug 31 [cited 2018 Oct 10]; [About 8 screens]. Available from: <https://ClinicalTrials.gov/show/NCT03268941>
109. Roldan CJ, Chambers KA, Paniagua L, et al. Randomized Controlled Double-blind Trial Comparing Haloperidol Combined With Conventional Therapy to Conventional Therapy Alone in Patients With Symptomatic Gastroparesis. *Acad Emerg Med*. 2017 Nov;24(11):1307-1314. doi: 10.1111/acem.13245.
110. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 - . Identifier NCT01625923, A Pilot Study on the Efficacy and Safety of Olanzapine in Gastroparesis; 2012 Jul 22 [cited 2018 Oct 10]; [About 6 screens]. Available from: <https://ClinicalTrials.gov/show/NCT01625923>
111. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 - . Identifier NCT03120325, Vagal Nerve Stimulation for Gastroparesis; 2017 Apr 19 [cited 2018 Oct 10]; [About 5 screens]. Available from: <https://ClinicalTrials.gov/show/NCT03120325>
112. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 - . Identifier NCT03603730, Vagal Nerve Stimulation for Functional Dyspepsia and Gastroparesis; 2018 Jul 27 [cited 2018 Oct 10]; [About 7 screens]. Available from: <https://clinicaltrials.gov/ct2/show/NCT03603730>
113. Tack J, Pokrotnieks J, Urbonas G, et al. Long-term safety and efficacy of acotiamide in functional dyspepsia (postprandial distress syndrome)-results from the European phase 3 open-label safety trial. *Neurogastroenterol Motil*. 2018 Jun;30(6):e13284. doi: 10.1111/nmo.13284.
114. Sangnes DA, Softeland E, Biermann M, et al. [Gastroparesis - causes, diagnosis and treatment]. *Tidsskr Nor Laegeforen*. 2016 May;136(9):822-6. doi: 10.4045/tidsskr.15.0503.
115. Olausson EA, Storsrud S, Grundin H, et al. A small particle size diet reduces upper gastrointestinal symptoms in patients with diabetic gastroparesis: a randomized controlled trial. *Am J Gastroenterol*. 2014 Mar;109(3):375-85. doi: 10.1038/ajg.2013.453.