Neurogastroenterol Motil (2006) **18,** 263–283 doi: 10.1111/j.1365-2982.2006.00760.x

REVIEW ARTICLE

Treatment of gastroparesis: a multidisciplinary clinical review

The American Motility Society Task Force on Gastroparesis (members in alphabetical order)

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Abstract *This clinical review on the treatment of patients with gastroparesis is a consensus document developed by the American Motility Society Task Force on Gastroparesis. It is a multidisciplinary effort with input from gastroenterologists and other specialists who are involved in the care of patients with gastroparesis. To provide practical guidelines for treatment, this document covers results of published research studies in the literature and areas developed by consensus agreement where clinical research trials remain lacking in the field of gastroparesis.*

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Received: 29 August 2005
Accepted for publication: 14 December 2005

Keywords *gastroparesis, gastric emptying, prokinetic agents, antiemetic agents, botulinum toxin.*

INTRODUCTION

This consensus document reviews the current treatment options for management of gastroparesis. The paper was conceived by gastroenterologists with input from nutrition, diabetology, surgery, pain management and psychology specialists who are involved in the care of patients with gastroparesis. To provide practical therapeutic guidelines, the authors reviewed research studies published in the literature from 1966 to 2005. Abstract data presented at meetings of national and international societies of gastroenterology and gastrointestinal (GI) motility where appropriate are discussed to complement the published findings. Finally, in areas where clinical trials have not been performed, consensus opinions were formulated by the authors to facilitate management.

CLINICAL PRESENTATION

Symptoms

Gastroparesis is a disorder characterized by symptoms of and evidence for gastric retention in the absence of mechanical obstruction.[1] Gastroparesis typically affects patients, mostly women, and has significant impact on quality of life.[2–4] The true prevalence of gastroparesis is not known; however, it has been estimated that up to 4% of the population experiences symptomatic manifestations of this condition. Diabetes mellitus is the most common systemic disease associated with gastroparesis. A similar number of patients present with gastroparesis of an idiopathic nature. Postsurgical gastroparesis, often with vagotomy or damage to the vagus nerve, represents the third most common aetiology of gastroparesis. The most frequently reported symptoms of gastroparesis include nausea, vomiting, early satiety and postprandial fullness.[2] Abdominal discomfort and pain also are noted by many affected patients and represent challenging symptoms to treat.[5] Weight loss, malnutrition and dehydration may be prominent in severe cases. In diabetics, gastroparesis may adversely affect glycaemic control. Gastroparesis may also be part of a larger problem of motor function in generalized dysmotility syndromes such as chronic intestinal pseudo-obstruction. There is some overlap between gastroparesis and functional dyspepsia as both symptoms and gastric emptying test results may meet definitions for both in a subset of patients.[1,6] As a consequence, some patients with mild abdominal pain, nausea, vomiting and evidence of delayed emptying are considered to have functional dyspepsia by some clinicians and gastroparesis by others. Patients with marked delay in gastric emptying should be diagnosed with gastroparesis not functional dyspepsia. In general, predominant abdominal pain with lesser degrees of nausea is more consistent with a diagnosis of functional dyspepsia, whereas predominant nausea and vomiting with lesser degrees of abdominal pain is more characteristic of gastroparesis.

Gastric emptying testing

A variety of methods have been advocated for the measurement of gastric emptying of nutritive and inert meals. The best accepted technique is scintigraphy involving ingestion of an egg meal cooked with a technetium radiolabel. The diagnosis of gastroparesis is made when a delay in gastric emptying is present and laboratory studies to rule out metabolic causes of symptoms and endoscopic and radiographic testing to exclude luminal blockage have been performed.[1] It has been a common assumption that the GI symptoms can be attributed to delays in gastric emptying; however, most investigations have observed only weak correlations between symptom severity and the degree of gastric stasis. In diabetics, the correlation between global gastric symptoms and rates of gastric emptying is poor.[7] When individual symptoms have been examined, only postprandial fullness appears to associated with delayed emptying of solid food.[8] In functional dyspepsia, symptoms of early satiety, postprandial fullness, nausea and vomiting are more prevalent in individuals with delayed gastric emptying than those with normal emptying.[9,10] However, in this condition, these symptoms exhibit a relatively poor accuracy in predicting the rate of gastric emptying. More recent studies confirm an association of delayed gastric emptying with postprandial symptoms in functional dyspepsia; however, some symptomatic patients can exhibit accelerated rather than delayed emptying in the early postprandial period.[11] These observations suggest that, while delayed gastric emptying of triturated food may participate in the genesis of symptoms in patients with gastroparesis, other factors likely to have important roles as well. This conclusion factors into the approach to the management of gastroparesis, which should not only include therapies, which promote gastric emptying but also therapies that act through other mechanisms.

TREATMENT OVERVIEW

Therapeutic targets

For rational therapy of gastroparesis, it is important to attempt to understand the pathogenesis of the disorder. Delays in gastric emptying may result from a variety of deficits of neuromuscular function. Distinct regional motor abnormalities of the stomach may have selective effects on global emptying and symptoms. Furthermore, symptomatic manifestations of gastroparesis require the involvement of the peripheral and the central nervous systems. Indeed, the act of emesis with gastroparesis mandates participation of a number of linked brainstem nuclei. Effective management of gastroparesis relies on the design of therapies that act on one or more of these sites.

The different symptoms of gastroparesis may have their basis from regional abnormalities within the stomach. Manometric studies have characterized increases in tonic and phasic motor activity of the pylorus in subsets of gastroparesis patients.[12] This, along with antral hypomotility, may be the cause of

delays in gastric emptying in individuals with gastroparesis.[13] Alterations in compliance and accommodation of the proximal stomach may explain symptoms such as early satiety and postprandial fullness and discomfort.[14–16] Heightened perception of gastric distention has been described in diabetic patients with upper GI symptoms suggesting a possible contribution from visceral afferent hypersensitivity to symptoms such as nausea and pain. Further, many patients have associated dysmotility of the small bowel whose contribution to the clinical syndrome has not been well-defined.[13] Potentially, each of these regional abnormalities represents a distinct and useful therapeutic target.

Assessment of disease severity

Many therapies of gastroparesis relieve symptoms only in subsets of gastroparesis patients or are associated with significant side-effects. Recent investigations have focused on the quantification of disease severity both for research purposes and to assist in the delineation of which patients are likely to benefit from the different modes of treating gastroparesis. A symptom questionnaire, the Gastroparesis Cardinal Symptom Index (GCSI), has been developed and validated in university-based clinical practices for quantifying symptoms in gastroparesis.[17] The GCSI is based on three subscales (postprandial fullness/early satiety, nausea/vomiting and bloating) and represents a subset of the longer Patient Assessment of Upper Gastrointestinal Disorders-Symptoms (PAGI-SYM). In addition, a simple clinical severity grading scale was proposed in 2003 but has yet to validated (Table 1). Future investigations will determine if the use of such scoring systems for patient stratification will improve care.

The general principles for treating symptomatic gastroparesis are to: (i) correct and prevent fluid, electrolyte and nutritional deficiencies; (ii) reduce symptoms and (iii) identify and rectify the underlying cause of gastroparesis, if possible.[1] Care of patients generally relies on dietary modification, medications that stimulate gastric motor activity and antiemetic drug therapy. Although in most cases, rigorous investigations have not assessed therapeutic responses as a function of symptom severity, a number of basic recommendations can be made. For mild symptoms (grade 1), dietary modifications should be tried. When possible, patients should avoid the use of medications that delay gastric emptying. If needed, low doses of antiemetic or prokinetic medications can be taken on an as needed basis. Diabetic patients should strive for optimal glycaemic control to minimize effects of hyperglycaemia on gastric function. For individuals with compensated gastroparesis (grade 2), treatment recommendations commonly involve a combination of antiemetic and prokinetic medications given at regularly scheduled intervals to relieve more chronic symptoms of nausea, vomiting, fullness and bloating. These agents frequently have no effect on the pain and discomfort that may be associated with gastroparesis. In these patients, measures which are directed to pain control but which do not exacerbate the other manifestations of gastroparesis must be designed. For patients with severe gastroparesis (grade 3), more aggressive treatments including hospitalization for i.v. hydration, insulin administration and i.v. administration of antiemetic and prokinetic agents are considered. Chronic care of these individuals may include enteral or parenteral nutritional support with endoscopic and/or surgical intervention.

Table 1 Proposed classification of gastroparesis severity

Grade 1: Mild gastroparesis
Symptoms relatively easily controlled
Able to maintain weight and nutrition on a regular diet or minor dietary modifications
Grade 2: Compensated gastroparesis
Moderate symptoms with partial control with pharmacological agents
Able to maintain nutrition with dietary and lifestyle adjustments
Rare hospital admissions
Grade 3: Gastroparesis with gastric failure
Refractory symptoms despite medical therapy
Inability to maintain nutrition via oral route
Frequent emergency room visits or hospitalizations

DIETARY AND NUTRITIONAL RECOMMENDATIONS

There have been no published controlled trials examining the effects of dietary interventions on clinical outcomes in patients with gastroparesis. Nevertheless, a number of dietary recommendations can be made based on our understanding of the physiology of gastric emptying of foods of different physical properties and different nutrient classes.[18] Such dietary recommendations are likely to be of greatest benefit to those with mild disease (grade 1), but should also be offered to patients with more severe gastroparesis (grades 2 and 3) to complement pharmaceutical and non-pharmaceutical therapies.

A careful patient history can identify intolerances to specific foods, such as dairy products or red meats, which can be addressed during design of a diet programme for the patient with gastroparesis. The physical examination should include attention to

dentition. Impaired mastication resulting in consumption of poorly chewed food could compound the defect in antral trituration. Reducing meal size and increasing the number of meals to 4–6 per day are reasonable initial recommendations to minimize postprandial gastric distention. Patients are instructed to chew food well, to avoid foods that cannot be chewed easily, to take fluids throughout the course of the meal and to sit or walk for 1–2 h after meals. A diet low in indigestible, insoluble fibre is advocated as fibre delays gastric emptying and can contribute to bezoar formation in those with profound gastric stasis.[19] Likewise, fibre supplements for treatment of constipation should be discontinued if possible. Fatty foods should be restricted as lipids delay emptying. However, fat-containing liquids may be tolerated and provide needed calories. A daily multivitamin/mineral supplement can be taken if dietary intake is inadequate.

If these measures are ineffective, the patient may be advised to consume the bulk of their calories as liquid because gastric emptying of liquids often is preserved in gastroparesis. To meet the nutritional needs of the patient, it may be necessary to supplement the diet with a commercially available liquid nutrient preparation that is low in fat and fibre. Homogenized solid meal supplements such as blenderized foods may be used as a liquid nutrient source. Poor tolerance of a liquid diet is predictive of a future poor success with more solid food, even if pureed.

PROKINETIC MEDICATION THERAPY

Prokinetic medications enhance contractility of the GI tract and promote the movement of luminal contents in an antegrade direction (Table 2). There has been little in the way of controlled investigations directly comparing the different prokinetic medications. A meta-analysis assessing benefits of four different drugs in 514 patients in 36 clinical trials reported that the macrolide antibiotic erythromycin is the most potent stimulant of gastric emptying, while erythromycin and the dopamine receptor antagonist domperidone are best at reducing symptoms of gastroparesis.[20] However, as for all meta-analyses, concerns can be raised regarding publication bias in which negative studies are not reported and marked differences in study design that can invalidate comparisons of the different drugs. Thus, several factors must be considered when choosing a prokinetic drug for the patient with gastroparesis including efficacy, toxicity, regional availability and cost.

Dopamine receptor antagonists

Dopamine is an inhibitor of motor activity of the stomach. Two agents, which act as dopamine receptor antagonists, metoclopramide and domperidone, are commonly used in patients with gastroparesis. Both agents act to counteract the inhibitory effects of endogenous dopamine on gastric emptying. They further act as antiemetic agents by virtue of their blockade of dopamine receptor-mediated pathways in the brainstem. Metoclopramide also acts as a serotonin 5-HT_4-receptor agonist to stimulate cholinergic neural pathways in the stomach and a weak 5-HT_3-receptor antagonist.

Metoclopramide has been approved for short-term use (4–12 weeks) since 1979. Several studies have evaluated the efficacy of metoclopramide for the treatment of gastroparesis. In one 3 week double-blind trial, metoclopramide produced greater symptom improvement and acceleration of gastric emptying than placebo.[21] Similar results were observed in other placebo-controlled crossover studies; however, individual improvements in gastric emptying correlated poorly with reductions in nausea and vomiting emphasizing that symptom benefits may not result from the

Table 2 Prokinetic medication classes for treatment of gastroparesis

Class of agent	Presently available	Available under special circumstances	Under study
Dopamine D_2-receptor antagonists	Metoclopramide	Domperidone*	Itopride
Motilin receptor agonists	Erythromycin, clarithromycin, azithromycin		Mitemcinal
5-HT_4-receptor agonists	Tegaserod	Cisapride†	Renzapride, mosapride
Muscarinic receptor agonists	Bethanechol		
Acetylcholinesterase inhibitors	Physostigmine, neostigmine		
CCK receptor antagonists			Loxiglumide, dexloxiglumide

*Via FDA IND and IRB approval.
†Under strict compassionate use protocol approved by pharmaceutical company and IRB.
FDA, Food and Drug Administration; IND, investigational new drug; IRB, Institutional Review Board; CCK, cholecystokinin.

prokinetic actions of the drug and that antiemetic mechanisms may be important for clinical efficacy.[22,23] One additional possible mechanism of action of metoclopramide is to normalize gastric slow wave dysrhythmias.[24]

Metoclopramide is generally begun at a oral dose of 5–10 mg 30 min before meals and at bedtime, which can be increased to 20 mg four times daily if necessary and if there are no side-effects. For patients who may not efficiently empty pills from the stomach for absorption, metoclopramide is available in a liquid formulation. An orally disintegrating preparation may soon be available. For individuals with more refractory nausea and vomiting and unable to retain oral medications, subcutaneous injections of metoclopramide have shown symptomatic efficacy in patients.[25] Finally, i.v. metoclopramide is often used in inpatient care of the patient with gastroparesis.

Most of the severe side-effects of metoclopramide result from its ability to easily cross the blood–brain barrier. Up to 30% of patients cannot tolerate metoclopramide due either to drowsiness and fatigue or to restlessness and irritability. Acute dystonic reactions develop in approximately 1% of patients, often within 24–48 h of initiating treatment. Prolonged treatment infrequently may produce Parkinsonian-like symptoms. Tardive dyskinesia, characterized by involuntary movement of the face, tongue, or extremities, is an infrequent adverse effect of prolonged use of metoclopramide that may not reverse upon discontinuing the medication. The prevalence of tardive dyskinesia ranges from 1% to 10% when taking metoclopramide for at least 3 months.[26,27] Doctors should discuss the risk of tardive dyskinesia with their patients and document this discussion in their medical record. Some clinicians have patients sign an informed consent to document communicating the risks of metoclopramide. Other common side-effects of metoclopramide relate to its actions to stimulate prolactin secretion from the pituitary and include breast tenderness, galactorrhoea and menstrual irregularities.

Domperidone, a peripheral dopamine receptor antagonist, has been studied most extensively in diabetic gastroparesis. The drug stimulates both liquid- and solid-phase gastric emptying; however, the symptom benefits of domperidone do not clearly relate to its motor stimulatory actions but may instead stem from its antiemetic properties.[28] In a trial of diabetics with symptoms suggestive of gastroparesis, 260 patients initially received domperidone at 20 mg four times a day for 4 weeks.[29] Eighty percentage of these individuals responded to therapy, defined as more than 30% reduction in symptoms. Responders were randomized to double-blind continuation of domperidone *vs* withdrawal on placebo. Those maintained on domperidone reported significantly greater persistence of symptom benefit compared with those withdrawn from active drug regardless of the results of gastric emptying testing. In a small study of six patients with diabetic gastroparesis, symptom improvement on domperidone was associated with resolution of gastric slow wave dysrhythmias suggestive of a possible gastric antidysrhythmic effect of this agent.[30]

Domperidone is generally started at 10 mg four times a day. If symptoms persist, the dose is increased to 20–30 mg four times daily. A trial of 80–120 mg day^{-1} for up to 1 month is considered the time needed to assess its efficacy. Because it does not cross the blood–brain barrier, domperidone has a more favourable side-effect profile compared with metoclopramide. Dystonias and other movement disorders are exceedingly uncommon with this agent. Domperidone is often used in patients whom have had side-effects to metoclopramide. Domperidone is especially useful in gastroparetic patients with Parkinson's disease in whom it can improve gastric emptying without blocking the central dopaminergic actions of treatment for Parkinson's disease.[31] The anterior pituitary lies outside of the blood–brain barrier; hyperprolactinaemic effects represent the major adverse effects of domperidone therapy. An i.v. form of domperidone was withdrawn in the 1980s due to rare reports of fatal cardiac dysrhythmias.

In the United States, domperidone is not approved by the Food and Drug Administration (FDA) and cannot be obtained by routine prescription or covered by healthcare plans. Traditionally, domperidone has been obtainable from other countries, from Internet websites, or from compounding pharmacies within the USA. These practices have been discouraged by the FDA. Domperidone can be obtained through a FDA investigational new drug application (IND) with local Institutional Review Board (IRB) approval. Using this mechanism, patients sign an informed consent document and purchase domperidone from an FDA-approved pharmacy.

Other dopamine receptor antagonists are in development. Itopride, an agent with dopamine antagonist and acetylcholinesterase inhibitory properties, accelerates gastric emptying in patients with diabetic gastroparesis and is used in Asia as a therapy for functional dyspepsia.[32,33] In North America, itopride is currently in phase III clinical trials.

Motilin receptor agonists

Motilin, an endogenous peptide hormone released by the duodenal mucosa, elicits antroduodenal contrac-

tions via activation of smooth muscle L-type calcium-channels after occupation of motilin receptors on enteric neurones and smooth muscle tissue.[34] A number of macrolide antibiotics act as motilin receptor agonists to promote upper gut transit, including erythromycin, clarithromycin and azithromycin.[35,36] When given i.v., erythromycin is the most potent stimulant of gastric emptying among the available prokinetic drugs.[37] The regional actions of erythromycin include stimulation of cholinergic nerves in the antrum which elicit co-ordinated phasic contractions and activation of inhibitory nerves in the pylorus which promote pyloric relaxation.[38–40]

A number of controlled and open trials have reported clinical benefits of erythromycin therapy in patients with gastroparesis. Symptom improvement has been noted in 43% of patients treated with oral erythromycin.[41] However, the utility of chronic oral erythromycin therapy may be limited by development of tachyphylaxis as a consequence of motilin receptor downregulation which can develop within days of initiating treatment.[42] When given chronically, erythromycin is usually started in low doses (125 mg two to four times daily) in liquid form to facilitate its absorption. Dosing can be titrated as needed for clinical effect. Side-effects of erythromycin therapy are common and include nausea, vomiting and abdominal pain that may occur more prominently at higher doses. Recently, a review of a large Medicaid cohort observed approximately a twofold increased risk of sudden cardiac death in individuals on erythromycin therapy.[43] This risk was further increased by concomitant use of cytochrome P-450 (CYP-3A) inhibitors such as verapamil or diltiazam. Azithromycin does not have the cardiac risk and has been proposed as an alternative, although long-term data are not available.[36]

A recent focus of pharmaceutical investigation has been the development of motilin receptor agonists exhibiting prokinetic capabilities but without antimicrobial properties. An early motilin agonist, ABT-229, actually worsened symptoms in diabetics with nausea and vomiting compared with placebo and showed no benefits in functional dyspepsia.[44,45] A newer agent, mitemcinal, exhibits potent prokinetic action in the stomach and early results in diabetic gastroparesis show good effects.[46] Ghrelin, a neurohumoral transmitter secreted by the stomach, is believed to play a physiological role as a stimulant of food intake. Recent preliminary investigations show a prokinetic action of ghrelin with stimulation of gastric emptying in patients with diabetic and idiopathic gastroparesis.[47,48]

5-HT_4-receptor agonists

Cisapride is the best characterized 5-HT_4-receptor agonist with prokinetic properties in the GI tract. Cisapride activation of 5-HT_4-receptors facilitates release of acetylcholine from myenteric cholinergic nerves throughout the gut. The functional consequences of this action are to stimulate antral contractions, improve antroduodenal co-ordination and accelerate gastric emptying.[49,50] Cisapride initially was approved by the FDA for treatment of nocturnal heartburn in patients with gastro-oesophageal reflux disease. Studies demonstrated symptom benefits in patients with gastroparesis which lasted for at least 1 year.[51] As a result, cisapride became a drug of choice for management of gastroparesis. In prolonged post-marketing surveillance, a number of cases of sudden death from cardiac dysrhythmias were attributed to cisapride use.[52] Subsequent investigations implicated a direct action of cisapride on cardiac potassium-channels, which promoted QT interval prolongation and predisposed patients to development of ventricular dysrhythmias including Torsades de pointes. Patients with underlying cardiac disease, especially of the conduction system, and those on medications known to prolong the QT interval are the main groups at risk. Because of this adverse effect, cisapride was withdrawn from the USA market in 2000. Currently, the drug is available in the United States through a compassionate use/limited-access programme through Janssen Pharmaceutica (Titusville, NJ, USA) with strict patient monitoring.[52] Cisapride also can be obtained from Internet websites and in various geographic sites worldwide. However, its use is discouraged by the authors of this consensus paper.

Tegaserod, a 5-HT_4-receptor agonist, is approved for treatment of constipation-predominant irritable bowel syndrome and chronic constipation. Although its prokinetic actions appear to be greatest in the small intestine and proximal colon, tegaserod given at a dose of 6 mg twice daily accelerates gastric emptying in healthy volunteers.[53,54] In an abstract publication of 163 patients with gastroparesis, tegaserod was shown to accelerate solid-phase gastric emptying which was most pronounced at doses higher than those commonly used to treat constipation (6 mg three times daily and 12 mg twice daily).[55] The effect of tegaserod on symptoms was not reported. Because of this prokinetic effect, tegaserod has been used on an off-label basis for the treatment of gastroparesis. Studies are ongoing to determine if the prokinetic actions of tegaserod produce clinically meaningful symptom improvements in diabetics with

gastroparesis. Tegaserod has no effects on the cardiac QT interval.[56]

Other 5-HT_4-receptor agonists have been developed and show efficacy in gastroparesis. Mosapride accelerates gastric emptying in healthy volunteers and patients with diabetic gastroparesis.[57,58] Furthermore, the drug may improve glycaemic control in diabetics with delayed gastric emptying.[58] In contrast to cisapride, mosapride has little effect on potassium-channel activity and appears to exhibit a significantly lesser cardiac dysrhythmogenic potential.[59] Renzapride is a combined 5-HT_4-receptor agonist and 5-HT_3-receptor antagonist. Future studies are needed to determine if renzapride exhibits efficacy in gastroparesis.

Other prokinetic medications

Other agents have been proposed as motor stimulatory treatments in gastroparesis. The cholinergic muscarinic receptor agonist bethanechol increases phasic antral motor activity; however, the elicited contractions are not peristaltic and do not facilitate gastric emptying.[60–62] Bethanechol also produces significant side-effects including flushing, diaphoresis, nausea and abdominal discomfort. As a consequence, bethanechol is rarely used alone for treating gastroparesis. Some clinicians employ the medication in low doses in combination with other prokinetic agents; however, this practice has not been subjected to a clinical trial. Acetylcholinesterase inhibitors, such as physostigmine and neostigmine, stimulate gut motor activity by increasing acetylcholine levels with subsequent muscarinic receptor activation. As with bethanechol, anticholinesterase agents do not improve antroduodenal co-ordination and have inconsistent effects on gastric emptying.[63] Some H_2-receptor antagonists, such as nizatidine, exhibit anticholinesterase activity and stimulate gastric emptying but their efficacy in long-term treatment of gastroparesis is unknown.[64,65] The α-adrenoceptor receptor agonist clonidine was reported to accelerate gastric emptying in a small study of patients with diabetic gastroparesis, but delayed gastric emptying in another trial.[66,67] Cholecystokinin receptor antagonists accelerate gastric emptying in some studies. The utility of such agents in gastroparesis remains to be determined.

ANTIEMETIC MEDICATION THERAPY

As stated above, it is likely that a component of the clinical benefits observed with some of the available prokinetic drugs, such as metoclopramide and domperidone, stem from antiemetic actions on brainstem nuclei (Table 3). Use of antiemetic medications without prokinetic potential to reduce nausea and vomiting associated with gastroparesis is common clinical practice. However, there is very limited literature on the use of antiemetic agents in gastroparesis. Indeed, a careful Medline search revealed only a single case study reporting on the use of the non-prokinetic dopamine receptor antagonist thiethylperazine in gastroparesis.[68] Most of the standard antiemetic agents have no effect on gastric motor function; some may delay stomach emptying. It is the consensus opinion of the authors that use of antiemetic medications may be beneficial in cases in which prokinetic drug therapy is ineffective or produces unacceptable toxicity. Indeed, it is possible that some cases of gastroparesis may show superior responses to antiemetics. In refractory patients of gastroparesis (grade 3), both prokinetics and antiemetics are often used in combination to address control of symptoms. Although pharmacoge-

Table 3 Antiemetic medication classes

Class of agent	Examples
Dopamine D_2-receptor antagonists	
With prokinetic activity	Metoclopramide, domperidone
Without prokinetic activity	Prochlorperazine, trimethobenzamide, thiethylperazine
Serotonin 5-HT_3-receptor antagonists	Ondansetron, granisetron, dolasetron, tropisetron
Tricyclic antidepressants	Desipramine, nortriptyline, amitriptyline
Muscarinic M_1-receptor antagonists	Scopolamine, hyoscyamine, clinidium
Histamine H_1-receptor antagonists	Dimenhydrinate, meclizine, promethazine
Cannabinoids	Tetrahydrocannabinol
Benzodiazepines	Lorazepam
Neurokinin NK_1-receptor antagonists	Aprepitant

The H_1, D_2 and M_1 receptor antagonists have overlap. The classification reflects the predominant activity.

nomics related to phase I reactions are relevant to the combination of prokinetics and antiemetics, there is no evidence to suggests that adding an antiemetic agent adversely affects the clinical course of patients.

Antiemetic medications reduce vomiting by action on a diverse range of receptor subtypes in the peripheral and central nervous systems (Table 3). When considering antiemetic drug use in gastroparesis, the clinician should take into account factors such as side-effects, interactions with other medications, development of tolerance and cost. The most commonly prescribed traditional antiemetic drugs are the phenothiazines, which act as both dopamine and cholinergic receptor antagonists. These agents include prochlorperazine and thiethylperazine, which are believed to act primarily in the area postrema. Cholinergic muscarinic M_1-receptor antagonists are commonly employed for disorders involving vestibular pathways, including motion sickness. Transdermal scopolamine is occasionally used to treat nausea and vomiting in gastroparesis,[69] although there is no published data to support this practice. Muscarinic antagonists such as hyoscyamine and clidinium delay gastric emptying.[70,71] Histamine H_1-receptor antagonists exhibit the greatest benefit in conditions that activate vestibular pathways, such as motion sickness and labyrinthitis, and some cases of postoperative emesis.[72,73] Pure H_1 antagonists include dimenhydrinate and meclizine, whereas promethazine has mixed actions on other receptor subtypes. Many of these agents have a mild inhibitory effect on gastric emptying.[74] The serotonin 5-HT_3-receptor antagonists have efficacy in chemotherapy-induced emesis, postoperative emesis and radiation therapy-induced vomiting. An abstract reported that ondansetron produced small but statistically significant reductions in nausea, vomiting and abdominal pain in 17 patients with refractory unexplained nausea and vomiting.[75] Ondansetron has no effect on gastric emptying in healthy volunteers and patients with gastroparesis,[76,77] although one investigation observed inhibition of gastric activity with tropesitron.[78] Cannabinoids exhibit potency equal to or slightly greater than dopamine receptor antagonist antiemetic drugs in chemotherapy-induced emesis, and may have additional appetite stimulatory effects.[79] Benzodiazepines are useful in the management of anticipatory nausea and vomiting prior to chemotherapy administration, in large part because of their anxiolytic and tranquilizing effects. Benzodiazepines do not affect gastric emptying and may be useful in i.v. form for inpatients with gastroparesis by virtue of their sedating actions.[80] The most recently introduced antiemetics are the neurokinin NK_1-receptor antagonists, which are available for prophylaxis and treatment of chemotherapy-evoked nausea and vomiting.[81,82] The utility of these agents in reducing symptoms in patients with gastroparesis must be subjected to controlled investigation.

One group of medications with antiemetic properties, the tricyclic antidepressant agents, may warrant special attention as a potential therapy for certain patients with gastroparesis. Low-dose tricyclic drugs are commonly prescribed by gastroenterologists for refractory functional bowel diseases such as irritable bowel syndrome. In a recent retrospective evaluation, tricyclic drugs given for a mean of 5 months produced moderate to complete symptom reductions in the majority of patients with functional vomiting.[83] In a preliminary abstract on the retrospective analysis of 24 diabetics with nausea and vomiting unresponsive to prokinetic drugs, 88% experienced symptom reductions on tricyclic medications at a median dose of 50 mg day^{-1} and one-third of patients reported symptom remission.[84] Nearly one-third of patients had a pre-existing delay in gastric emptying, suggesting that tricyclics may be effective in some cases of gastroparesis even though this drug class traditionally has been considered to delay gastric emptying. Future prospective controlled trials will define the role of this group of medications in the management of gastroparesis.

Complementary and alternative medicine therapies often are given for treatment of nausea and vomiting. Ginger, a traditional Chinese antiemetic agent, exhibits weak 5-HT_3-receptor antagonist properties and has gastric slow wave antidysrhythmic effects in humans.[85,86] Acupressure and electrical acustimulation on the P6 acupuncture point (the Relief Band) have shown variable success for postoperative emesis, chemotherapy-induced vomiting and nausea of pregnancy.[87] One study has reported benefits of acupuncture in 35 gastroparesis patients.[88]

MEDICATIONS FOR PAIN CONTROL

In some patients with gastroparesis, pain represents a prominent symptom and can produce significant morbidity and utilization of healthcare resources.[2,5] The pathogenesis of pain in gastroparesis is poorly understood and treatments for this symptom largely are unsatisfactory. In diabetics with gastroparesis, pain has been considered to be a consequence of autonomic neuropathy. However, one small study found that more severe forms of visceral afferent neuropathy were associated with fewer rather than more symptoms.[89] To date, there have been no studies to specifically address the effectiveness of any therapy of abdominal pain in patients with gastroparesis.

The approach to dealing with pain in these patients begins with an empathetic understanding by the doctor with recognition that pain is a valid component of the gastroparesis symptom complex. The role of pharmacotherapy in the management of pain with gastroparesis is complicated by potential drug toxicities and drug properties, which can delay emptying and/or worsen symptoms thereby counteracting the benefits of prokinetic and antiemetic medications. Several medication classes offer theoretical benefits for reducing pain in the gastroparesis patient. Non-steroidal anti-inflammatory agents ameliorate gastric slow wave dysrhythmias in several healthy human models.[90] Furthermore, oral indomethacin and i.v. ketorolac have been reported to resolve slow wave abnormalities in diabetics and patients with dyspeptic symptoms.[91,92] However, non-steroidal agents are potentially ulcerogenic and may worsen renal function in some diabetics. Thus, their routine use cannot be advocated by the authors of this consensus document although selected patients can be considered for these drugs. In addition to their potential utility as antiemetics, tricyclic medications in low doses may reduce pain associated with gastroparesis much as they do in other forms of neuropathic pain.[93] Other antidepressant classes including selective serotonin reuptake inhibitors (SSRIs), selective noradrenaline reuptake inhibitors and combined serotonin/noradrenaline reuptake inhibitors (such as the novel agent, duloxetine, which was recently approved for diabetic neuropathy) may have benefits as well; however, there are no data on their actions on visceral nerve function.[94] Among SSRIs, paroxetine may selectively accelerate small intestinal transit.[95,96] Other agents with efficacy in peripheral neuropathic pain such as gabapentin and topiramate have unknown actions in patients with pain associated with gastroparesis.[97,98] The α-adrenoceptor receptor agonist clonidine exhibits visceral antinociceptive effects, but its effects on pain with gastroparesis are uncertain.[99]

Unfortunately many patients with severe pain do not respond to more conservative therapies and are given intermittent or chronic therapy with opiate agents for pain control. Although narcotic agents produce generalized analgesia, their efficacy in gastroparesis is unproved. Furthermore, opiates exert potent inhibitory effects on GI transit inhibiting gastric emptying and colonic transit.[100] Finally, chronic narcotic use may result in tolerance to its analgesic effects, physical dependence and addiction. Thus, the routine use of opiate agents for the management of pain with gastroparesis is not advocated by the authors. If narcotics are to be considered, milder agents such as tramadol, an opioid with less impact on μ-opiate receptors, may produce fewer side-effects.[100] Longer acting compounds such as methadone or continuous release preparations such as transdermal fentanyl may elicit less constipation than other narcotics.[101,102] A current area of drug development is the generation of peripheral opioid receptor antagonists which block peripheral effects of narcotic drugs but preserve the central analgesic effects.[103,104] However, a study of the novel peripheral μ-opiate receptor antagonist alvimopan observed reversal of the inhibitory effects of codeine on the small intestine and colon but not the stomach.[105]

PSYCHOLOGICAL SUPPORT

Unrelenting nausea and vomiting, often with associated pain, frequently combine to produce significant psychological consequences. Virtually all studies examining psychological aspects of gastroparesis and functional dyspepsia show impaired quality of life and increased levels of anxiety, depression and somatization.[2,106,107] Furthermore, one study has reported that measures of psychological dysfunction correlated better with gastropathic symptoms in diabetics than do measures of neuropathy and gastric emptying.[108]

Patients with gastroparesis need an empathetic doctor who recognizes the emotional disruptions caused by their GI illness. Instilling hope, addressing pain and increasing self-management of their chronic illness are important. Conceptualizing the psychophysiological aspects of the disease helps the patient focus on what he/she can control and decreases viewing the disease as 'psychiatric' in nature.[109] Management of severe gastroparesis may be enhanced by the active participation of a team of providers who communicate together and collaborate effectively.[110] The clinical psychologist can be an important member of the 'gastroparesis team' to help the patient develop a game plan for coping with symptoms. Efforts to facilitate psychosocial support and rehabilitation, including encouraging education and the support of family and friends, are important.[109,111] Psychotherapeutic interventions can be helpful as adjunctive measures. Simple measures such as relaxation techniques, cognitive restructuring and distraction help promote a sense of control on the part of the patient. Other techniques such as hypnosis and biofeedback may benefit some patients.[112]

SPECIAL CONSIDERATIONS IN THE DIABETIC PATIENT

In tertiary care centres, up to 50% of patients with long-standing (>5 years) type 1 (insulin-dependent) or type 2 (non-insulin-dependent) diabetes may have

delayed gastric emptying.[113] The prevalence of GI symptoms in diabetics in the primary care setting appears to be lower. A population-based survey reported that 18% of diabetics experience frequent dysmotility type, upper GI symptoms, a rate greater than in non-diabetics.[114] Moreover, this survey observed a trend to an increase in frequency of symptoms in those with poor glycaemic control. Conversely in a US epidemiological study, the prevalence of most GI symptoms was similar in persons with or without diabetes.[115] The presence of impaired motor function of the stomach in patients with diabetes does not always lead to development of gastric symptoms. In one investigation, only 50% of diabetic patients with delayed gastric emptying reported typical symptoms of gastroparesis.[116] Additionally, diabetics with normal gastric emptying may have a symptom constellation indistinguishable from those with delayed gastric emptying.[117] It is a common clinical observation that diabetic patients with gastroparesis may also exhibit erratic postprandial blood sugar values. Indeed, loss of good glycaemic control in a previously well-regulated diabetic should raise concern for gastroparesis. Gastric stasis impairs delivery of nutrients and oral hypoglycaemic medications to the small intestine for absorption. Postprandial hypoglycaemia or hyperglycaemia may develop depending on how the delivery of nutrients corresponds with the peak absorption of the medication.

Hyperglycaemia and gastric emptying

A number of studies have demonstrated a relationship between blood glucose levels and parameters of gastric function both in diabetic patients and in healthy volunteers.[118,119] In patients with type 1 diabetes, acute hyperglycaemia to blood glucose levels of 288–360 mg dL^{-1} elicits delays in both liquid and solid gastric emptying.[118] Other investigations in diabetics have demonstrated hyperglycaemia-evoked impairment of postprandial phasic antral contractions and induction of tachygastria, providing possible mechanisms for the retarding effects on gastric emptying of high glucose levels.[120] Conversely in some type 2 diabetics, liquid-phase gastric emptying may be accelerated during hyperglycaemia.[121] Investigations in healthy volunteers observe that acute increases in blood glucose can abolish phasic antral motor activity, stimulate pyloric contractions, evoke tachygastria and enhance fundic compliance, indicating that the degree of glycaemic control itself can influence gastric function independently of the presence of underlying neuropathy.[122,123] The relation of the actions of hyperglycaemia on gastric function to its impact on symptoms is less clear. However, one study has observed a significant correlation between the degree of hyperglycaemia and the severity of postprandial fullness in diabetic patients.[124] All studies to date have examined the functional consequences of acute elevations in blood glucose. The impact of chronic, long-term hyperglycaemia on gastric dysfunction in persons with diabetes is less clear; there are no long-term controlled studies confirming the importance of good glycaemic control in reducing symptoms in diabetic gastroparesis. However, observations from physiological studies suggest that high blood glucose levels can adversely affect responses to therapy. In both type 1 diabetic patients and healthy volunteers, induction of acute hyperglycaemia markedly attenuates the motor stimulatory effects of the prokinetic drug erythromycin on the stomach.[125,126]

Glycaemic control in diabetic gastroparesis

Because of the consistent observations from physiological studies that high serum glucose levels adversely affect gastric function, it is the consensus opinion of the authors that intensification of therapies to correct hyperglycaemia may facilitate the actions of and increase the benefits of other treatments in managing the patient with diabetic gastroparesis. Measures that are likely to be effective include more aggressive glucose monitoring with frequent dosing of short-acting insulin preparations to prevent profound postprandial hyperglycaemia. Prevention of wide fluctuations in serum glucose levels may be more important than maintenance of a given steady-state blood sugar value from a gastric emptying perspective.[127] To this end, monitoring 2-h postprandial blood glucose levels may be useful. Conversely, there is little convincing evidence to suggests that prokinetic treatment of delayed gastric emptying can reliably improve glycaemic control.[128]

Glucose control in the type 2 diabetic patient with gastroparesis can represent a significant challenge. In many type 2 diabetics, oral hypoglycaemic medications often are ineffective and can contribute to swings in blood glucose levels because of the temporal mismatch between nutrient absorption and medication. The addition of basal insulin therapy to oral therapy may be valuable in achieving glycaemic control in the type 2 diabetic patient. Furthermore, use of a long-acting insulin preparation with a 24 h profile that mimics normal pancreatic basal secretion may improve overall regulation of blood glucose levels. Newer insulin analogues such as insulin glargine limit

the number and severity of isolated insulin peaks and are associated with fewer hypoglycaemic episodes. Addition of basal insulin glargine or neutral protamine Hagedorn (NPH) to target a mean fasting plasma glucose concentration of ≤100 mg dL^{-1} facilitates attainment of glycosylated haemoglobin (HbA_{1c}) values of <7% in patients who were inadequately controlled with oral hypoglycaemic agents.[129] Patients on insulin glargine are more likely to reach this goal without nocturnal hypoglycaemia compared with those on NPH insulin.

Patients with type 1 diabetes are especially prone to wide variations in blood glucose levels. The use of a premixed formulation with both short- and long-acting insulin requires relatively strict adherence to meal timing and composition, and assumes that nutrients will be available within a given time frame to avoid hypoglycaemia. Because of these restrictions, premixed insulin may be a poor choice for individuals with delayed or unpredictable gastric emptying. For many type 1 diabetic patients, a long-acting preparation such as insulin glargine may be administered twice daily with preprandial injections of regular insulin formulas. However, in those with gastroparesis, postprandial hypoglycaemic episodes can occur when the glucose-lowering effects of preprandial short-acting insulin precede delivery of nutrients into the small intestine for digestion and absorption. As a consequence, some persons with delayed emptying may need regular insulin dosing during or even after meal ingestion. Postprandial administration also allows the patient to reduce the insulin dose if vomiting prevented consumption of the entire meal. Some patients benefit from use of improved insulin pumps which can be set to provide a constant basal insulin infusion 24 h a day. These individuals then administer bolus regular insulin injections prior to, during, or after meals. In selected cases, jejunostomy feedings may minimize extreme glycaemic fluctuations. Additional insulin may be needed for those receiving nocturnal enteral nutrition to correct for the additional calories and to prevent overnight hyperglycaemia.

ENTERAL OR PARENTERAL NUTRITIONAL SUPPORT

Patients with chronic symptoms of gastroparesis may develop dehydration, electrolyte abnormalities and/or extreme malnutrition. Such individuals warrant careful nutritional assessment and consideration to initiate supplemental enteral nutrition, or as a last resort, parenteral nutrition.

Nutritional assessment

Determining the degree of nutritional compromise involves assessment of symptoms, diet history, bodyweight (bw) and disease course. The conventional nutritional laboratory assessments of serum albumin and prealbumin levels are affected by a variety of factors in gastroparesis and may not be reliable measures of nutritional status. Unintentional weight loss over time is probably the most important, non-invasive parameter for assessing the degree of malnutrition. A 10% loss of weight over 6 months is consistent with current definitions of significant malnutrition.[130] One should compare the patient's current actual weight to his or her usual bw as opposed to the ideal bw, which can result in overestimation or underestimation of true weight loss. The subset of diabetic patients with chronic renal failure requiring haemodialysis requires careful scrutiny as progressive falls in weight may reflect either development of gastroparesis or excessive fluid withdrawal during dialysis. Essential nutrient and mineral deficiencies, particularly those resulting in anaemia and metabolic bone disease, require ongoing monitoring and supplementation if needed. Laboratory studies should include: (i) electrolytes including magnesium, as hypokalaemia and hypomagnesaemia can exacerbate delay in gastric emptying; (ii) serum glucose and HbA_{1c} in diabetic patients; (iii) iron and ferritin levels particularly for partial gastrectomy settings; (iv) vitamin B_{12} and (v) 25-OH vitamin D especially in those with long-standing gastroparesis or gastroparesis occurring after partial gastrectomy.

Enteral nutrition

Initiation of enteral feedings is indicated if oral nutrition fails to meet the caloric and fluid needs of the patient with gastroparesis. Enteral nutrition is preferable to total parenteral nutrition (TPN) in most individuals, because of issues related to infectious complications, thrombosis, i.v. access problems, hepatobiliary consequences, administration and cost. Furthermore, TPN rarely is necessary in the patient with gastroparesis unless there is profound dysmotility also involving the small intestine as in chronic intestinal pseudo-obstruction. However, some severely malnourished gastroparetic patients may benefit from a brief course of TPN to provide supplemental caloric support and to gain glycaemic control. For these individuals, 30–40 units of regular insulin may need to be added to each litre of TPN, depending on the patient's prior insulin requirements and TPN contents (1 unit regular insulin per 5 g carbohydrate or 15 g protein).

Criteria for initiation of enteral nutrition have been proposed which relate to symptom severity, nutritional consequences of disease and complications of gastroparesis (Table 4).[131] The recommendation to place enteral access may not initially be accepted by the patient. Management goals such as desired weight, reductions in hospitalizations and improved glycaemic control should be discussed with the patient, such that the decision to begin enteral feedings is made rationally. Several options for enteral access and feeding are available (Table 5). There are no data favouring one approach over another and the choice of access is often determined by the expertise of the individual centre. However, infusion of liquid meals into the stomach via a nasogastric tube or gastrostomy is not advocated because of the likelihood of symptom exacerbation and the risk of pulmonary aspiration resulting from the impairment of gastric emptying. Short-term nasojejunal feeding is often used to help determine if the patient will tolerate chronic small bowel feedings through a permanent enteral access. Jejunostomies are most commonly placed by laparotomy or laparoscopy. Direct percutaneous endoscopic jejunostomy placement is performed in some centres. Jejunostomy extension tubes can be passed through pre-existing gastrostomies for delivery of enteral feedings in patients who are not candidates for direct jejunostomy access or in whom such access is not desired for other reasons. In some individuals, a button device may improve quality of life and personal appearance. Enteral feedings are usually initiated 24 h after jejunostomy tube placement. Standard polymeric formulas with caloric density of 1.0–1.5 cal mL^{-1} (e.g. Jevity 1.5, Nutren 1.5 unflavoured, Promote, or Isosource HN) are begun at low infusion rates of 25–50 mL h^{-1} and advanced by 10–25 mL h^{-1}

Table 4 Criteria for initiation of enteral nutrition supplementation

Severe weight loss, e.g. unintentional weight loss >5–10% of usual bodyweight over 3–6 months
Repeated hospitalizations for refractory gastroparesis requiring i.v. hydration and/or i.v. medication
Inability to meet weight goals set by doctor, dietician and patient
Patient would benefit from gastric decompression
Patient would benefit from a way to absorb medications everyday to gain therapeutic levels when vomiting prevents this
Patient has maintained usual bodyweight, but experiences significant clinical manifestations
Diabetic ketoacidosis
Cyclic nausea and vomiting
Overall poor quality of life due to gastroparesis symptoms

Used with permission from the University of Virginia Health System Nutrition Support Traineeship Syllabus (87).

Table 5 Forms of enteral access for nutrition supplementation

Type of access	Usefulness	Disadvantages
Nasogastric tube	Gastric decompression in acute management	Not meant for long-term use Large tube size often causes is comfort Is a poor choice for feeding due to delayed gastric emptying Significant gastro-oesophageal reflux can occur
Nasoduodenal/ nasojejunal tube	Used to give trial feedings to determine if jejunal feedings are tolerated May be acceptable if there are no other options	Not for long-term use Vomiting may expel the tube into the stomach
Gastrostomy tubes	May be used for venting of secretions to decrease vomiting and fullness	Poor choice for feeding due to delayed gastric emptying May prevent proper electrode placement for gastric electrical stimulation
PEG-J or Jet-PEG	Allows the patient to vent gastric secretions to decrease/prevent persistent emesis Provides jejunal feedings New PEG-Js have distal feeding ports to reduce duodenogastric reflux	Migration of the J-tube extension into stomach Pyloric obstruction from J-tube May prevent proper electrode placement for gastric electrical stimulation
Jejunostomy (surgical, endoscopic, radiographic)	Stable access for reliable jejunal nutrient delivery Avoids gastric penetration which would interfere with proper electrode placement for gastric electrical stimulation	Cannot vent stomach
Dual gastrostomy and jejunostomy	Two sites – one for venting and one for enteral nutrition	Increased risk of leakage, infection Cosmetic issues

every 4–12 h until the desired daily caloric intake is achieved. Liquid formulations of medications can be given though the jejunostomy followed by low volume water flushes.[131] Individuals should avoid oral intake during the initial 48–72 h after starting enteral infusions to facilitate determination of patient tolerance of tube feedings. When first administering enteral nutrition, jejunal feedings should be delivered continuously 24 h a day. Over time, this can be converted to nocturnal infusions to free up the daytime hours for optional oral intake and to participate in normal daily activities. High calorie formulas (1.5–2.0 cal mL^{-1}) can reduce volumes and times of infusion; however, supplemental hydration may be needed. In those with considerable weight loss, enteral feedings should be initiated more slowly to avoid refeeding problems such as respiratory failure and congestive heart failure.[132] Prevention of complications from jejunostomy tubes include regular flushing after use and routine skin care. Some centres advocate tube replacements every 3–6 months to avoid problems such as tube decomposition and skin infection whereas other institutions recommend intervention only when adverse issues arise.

ENDOSCOPIC THERAPY

Some patients with documented gastroparesis exhibit prolonged periods of increased phasic and tonic motor activity of the pylorus.[12] This phenomenon, termed pylorospasm, has been postulated to contribute to the delay in gastric emptying by producing a functional gastric outlet obstruction.[12] In theory, use of a therapy to reduce pylorospasm might have beneficial actions in gastroparesis. Botulinum toxin binds to presynaptic acetylcholine terminals and produces blockade at the level of the neuromuscular junction thereby preventing cholinergic transmission and promoting muscle relaxation. Endoscopic injection of botulinum toxin into the pylorus has been shown to reduce fasting and postprandial phasic and tonic pyloric contractions in patients with gastroparesis.[133,134] In several small open-label series, acceleration of gastric emptying and modest reductions in symptoms have been observed 1–3 months after pyloric injection of botulinum toxin.[134–138] Doses have ranged from 80 to 200 units delivered in circumferential fashion at 4–5 sites into the pylorus.

More recent retrospective analyses of larger numbers of patients have provided additional information on the utility of pyloric botulinum toxin injection.[139,140] In one study of 63 patients in clinical practice, the response rate was 43% – lower than many of the initial enthusiastic reports – and the average duration of response was 5 months.[139] In an abstract report of 78 patients, percentages of patients experiencing symptom reductions after pyloric injection of botulinum toxin were similar in patients with diabetic (55%), idiopathic (51%) and postsurgical gastroparesis (44%).[140] Prior response to botulinum injection predicted a favourable response to subsequent injection. Higher doses of botulinum toxin (150–200 units) were more likely to produce reductions in nausea and vomiting compared with doses ≤100 units.

Results of these uncontrolled trials have served as the impetus for the conduct of placebo-controlled trials of pyloric injection of botulinum toxin in gastroparesis. Preliminary results of one investigation reported an increase of gastric emptying without symptom improvement.[141] However, this preliminary report of 12 patients was underpowered to detect an effect of the drug. Until appropriate studies are performed, the authors feel it is appropriate to consider pyloric injection of botulinum toxin when other accepted medication therapies have failed or produce unacceptable side-effects. To date, few adverse effects have been reported with botulinum toxin injections thus the major limiting factors relate to issues of insurance coverage and the inconvenience of undergoing endoscopy.

The therapeutic endoscopist also may offer other treatment options to individuals with refractory gastroparesis. Endoscopic placement of a venting gastrostomy may allow the patient with severe postprandial fullness or discomfort to release gas and fluid intermittently to reduce symptoms.[142,143] In theory, dilation of the pylorus may produce similar benefits as pyloric injection of botulinum toxin; however, no studies have been performed to test this method.

GASTRIC ELECTRICAL STIMULATION

Development of practical gastric electrical stimulation techniques for the treatment of gastroparesis have been a focus of research over the past decade. Studies using a gastric pacemaker that delivered high energy depolarizing stimuli to the stomach just above the physiological slow wave frequency (3.3 cpm) showed promise in promoting gastric emptying and reducing symptoms of gastroparesis.[144] However, this system proved unwieldy because of the large external current source required to drive the stomach through pacing electrodes that penetrated the abdominal wall and sewn to the gastric serosa. In 2000, the FDA-granted humanitarian device exemption approval for the Enterra gastric electrical stimulator (Medtronic, Inc.;

Shoreview, MN, USA) for patients with refractory diabetic or idiopathic gastroparesis. This system consists of a pair of electrodes sutured to the muscular layer of the anterior wall of the stomach, which are connected to a pulse generator implanted in a subcutaneous pocket in the abdominal wall. The pulse generator delivers low energy 0.1 s trains of pulses at a frequency of 12 cycles per minute. Within each pulse train, individual pulses oscillate at a frequency of 14 cycles per second.

Clinical outcomes

Two multicentre trials have been conducted to evaluate the efficacy of the gastric electrical stimulator in patients with diabetic and idiopathic gastroparesis. In an open-label study, 35 of 38 patients (mostly with idiopathic gastroparesis) experienced >80% reductions in nausea and vomiting which persisted for the duration of the observation period (3–15 months) associated with significant weight gain.[145] Although many individuals were able to discontinue enteral or parenteral nutrition, one quarter of patients needed to undergo additional surgeries including subtotal gastrectomy for symptom control and device removal for complications. The second multicentre investigation represents the only sham-stimulation controlled study to date.[146] In this trial, 33 gastroparesis patients (16 idiopathic, 17 diabetic) were randomized to sham *vs* active stimulation for 1 month each in double-blind, crossover fashion followed by an open-label stimulation period to 12 months. During the blinded phase, vomiting frequencies were 14% lower when the device was ON compared with times when the device was deactivated – a difference reported to be statistically significant. Furthermore, patients preferred the ON period over the OFF period by a threefold margin. However, the benefits of treatment were predominantly, if not exclusively, experienced by the diabetic group. During the open phase of the study, electrical stimulation produced a 76% reduction in vomiting at 12 months. Approximately 15% of patients required device explant or revision because of complications. In other open-label, single centre studies, electrical stimulation has been reported to improve nutritional status, limit the need for prokinetic and antiemetic medications, reduce the need for supplemental nutrition, decrease health-related costs and improve HbA_{1c} values in diabetics.[110,147–149] In an abstract with long-term patient follow-up, investigators have observed 26% and 44% reductions in nausea and vomiting, respectively, persisting for up to 10 years after device implantation.[150] Most recently, the gastric electrical stimulator has shown efficacy in reducing symptoms in postsurgical gastroparesis – an unapproved indication.[151,152] The most common complication of this form of therapy is infection of the subcutaneous stimulator pocket, which occurs in 5–10% of patients and nearly always requires surgical removal of the device. Other complications include wire breakage, electrode dislodgement or penetration of the stomach, and intestinal obstruction. Patients should not undergo magnetic resonance imaging and should avoid certain metal detecting security devices after stimulator implantation.

While the results of these investigations are encouraging, the clinical benefits of gastric electric stimulation have not been unequivocally demonstrated or the site of action. A larger, longer duration, sham-stimulation controlled, multicentre trial of gastric electrical stimulation is ongoing in patients with gastroparesis. Optimal pulse parameters need to be defined and predictors of clinical improvement must be characterized. Endoscopic placement may offer a much more attractive lead placement method. A recently reported method of temporary gastric electrical stimulation via endoscopically placed electrodes offers a potential means to preoperatively predict potential response to surgery.[153]

Mode of action

The mechanism(s) underlying the clinical benefits of the gastric electrical stimulator are not fully understood. Most investigations observed only minimal acceleration of gastric emptying.[145,146,148,149] Those studies reporting acceleration of emptying are composed largely of patients with idiopathic gastroparesis, a condition which can show progressive spontaneous improvement. Furthermore, this device does not entrain slow waves or reverse underlying slow wave dysrhythmias.[154] Recent reports indicate that electrical stimulation can modulate gastric biomechanical properties, enhance postprandial proximal gastric accommodation and reduce sensitivity to gastric distension.[155,156] An investigation employing cerebral imaging methods suggests that gastric electrical stimulation has inhibitory actions on afferent pathways projecting to different regions in the brain.[157] Others have suggested that the benefits of the device may stem from action on vagal pathways.[147,154] However, if the findings from case series reporting responses in patients with postvagotomy gastroparesis are reproduced, mediation by vagal pathways cannot represent the sole mechanism of action of gastric electrical stimulation.[152]

Practical considerations

Because of the restrictions imposed by its humanitarian device status, the Enterra gastric electrical stimulator cannot be implanted at any given institution until its use has been approved by the local IRB. Although patients with refractory symptoms have embraced the availability of this device, this special status has been used by some third party insurance carriers to deny coverage. Candidates for implantation of the gastric electrical stimulator include patients with chronic diabetic or idiopathic gastroparesis with relentless nausea and vomiting who are not responding to appropriate diet and medication therapy. There is a special need in diabetics being considered for renal and/or pancreas transplantation where it is important that the immunosuppressive agents will be absorbed. Conversely, individuals without nausea and vomiting but with other manifestations of gastroparesis (fullness, early satiety, anorexia, pain) have not been shown to predictably respond to gastric stimulation. Patients being considered for enteral or parenteral nutritional support may be given particular consideration for this treatment option. However, one group has reported in an abstract that aggressive medical therapy with combination drug therapy (antiemetics and prokinetics in adequate doses) and pyloric injections of botulinum toxin produces adequate symptom responses that avoid the need for surgery in up to two-thirds of patients referred for consideration of gastric electrical stimulation.[158] Contraindications may include generalized dysmotility syndromes also involving the small bowel including chronic intestinal pseudo-obstruction and collagen vascular diseases such as scleroderma and prior gastric resections. Although chronic narcotic analgesic use may reduce the symptomatic benefits of gastric electrical stimulation, the need for opiates should be evaluated on an individual basis and does not necessarily represent an exclusion criterion.[159] Insertion of a jejunostomy tube during implantation of the gastric electrical stimulator should be considered in patients who may have difficulty meeting their nutritional and hydration needs.

OTHER SURGICAL OPTIONS

In selected instances, other surgical procedures may be considered for control of refractory symptoms in patients with gastroparesis.[143] The range of surgical options includes drainage procedures such as pyloromyotomy or pyloroplasty and partial or total gastric resections to bypass a non-emptying stomach and

Table 6 Consensus recommendations for the treatment of gastroparesis

Psychological measures	Glycemic control	Nutritional care	Prokinetic medications	Antiemetic therapies	Pain control
Empathy and education	Twice daily long-acting insulin plus periprandial short-acting insulin	Small, frequent meals, low in fat and fibre	Metoclopramide or erythromycin PRN	Phenothiazine or dopamine receptor antagonist PRN	Acetaminophen or non-steroidal agents
Patient support groups	Insulin pump	Primarily liquid diet Liquid nutrient supplements	Metoclopramide or erythromycin scheduled dosing	Muscarinic receptor antagonist or 5-HT_3 antagonist	Tramadol or propoxyphene
Behavioural or relaxation therapy	Pancreas transplant	Enteral feedings	Domperidone or tegaserod	Tricyclic agents	Tricyclic agents
Hypnosis		Central or peripheral parenteral nutrition short term	Pyloric botulinum toxin	Tetrahydrocannabinol, lorazepam, or alternative therapies	Newer antidepressants TCAs, SNRIs
				Gastric electrical stimulation	Fentanyl patch or methadone
					Referral for pain specialist Nerve block

A stepped care approach in a top–down vertical manner is recommended which is dependent on the severity of gastroparesis. Treatments from different categories (columns) are often used in combination.
TCA, tricyclic antidepressant agent; SNRI, selective norepinephrine reuptake inhibitor.

decrease symptoms. Most published studies are uncontrolled and report disappointing responses to operative resection.[143] Of seven patients who underwent partial (subtotal) gastrectomy with Roux-en-Y gastrojejunostomy, six reported reduced vomiting.[160] However, three individuals developed renal failure and two died within 5 months of surgery. More impressive results have been observed in some studies in which total (completion) gastric resection was performed for postsurgical gastroparesis.[161–163] Results from these uncontrolled, retrospective case series observed symptom reductions in approximately two-thirds of patients after this drastic surgical option. However, a more recent study of completion gastrectomy for severe postsurgical gastric stasis reported successful outcomes in only 43% of patients.[164] In diabetic patients, pancreatic transplantation has been shown to halt progression or even partly reverse peripheral polyneuropathy.[165] However, no consistent benefits of pancreas transplantation on symptoms or gastric emptying have been reported in patients with diabetic gastroparesis.[166,167]

CONCLUSIONS

The treatment of gastroparesis includes dietary modifications, prokinetic and antiemetic medications, measures to control pain and address psychological issues, and endoscopic or surgical options in selected instances. Table 6 lists the consensus opinions of the authors of this document regarding the organized approach to treating this challenging condition. The different therapeutic modalities may be offered alone or in different combinations as dictated by the needs of the individual patient. Goals of therapy include relief of symptoms, normalization of nutrition and hydration status, improvement of glycaemic control in diabetics, and improvement of gastric emptying when appropriate. Effective management of the patient with gastroparesis may mandate involvement of a team of specialists including the primary doctor, gastroenterologist, endocrinologist, dietician, psychologist, interventional radiologist and surgeon.

ACKNOWLEDGMENTS

The authors are appreciative of Jeanne Keith-Ferris of the patient support group Gastroparesis and Dysmotility Association (GPDA) who helped organize the conferences held to discuss the topics contained in this report of the American Motility Society Workshop on Consensus Guidelines for the Treatment of Gastroparesis.

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