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## Status of Pharmacologic Management of Gastroparesis: 2014



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**Gastroparesis is characterized by delayed gastric emptying without mechanical obstruction of the gastric outlet or small intestine. The main etiologies are diabetes, idiopathic and post-gastric and esophageal surgical settings. The management of gastroparesis is challenging due to a limited number of medications and patients often have symptoms, which are refractory to available medications. This article reviews current treatment options for gastroparesis including adverse events and limitations as well as future directions in pharmacologic research.**

### INTRODUCTION

**G**astroparesis is a syndrome characterized by delayed emptying of gastric contents without mechanical obstruction of the stomach, pylorus or small bowel. Patients can present with nausea, vomiting, postprandial fullness, early satiety, pressure, fullness and abdominal distension. In addition, abdominal pain located in the epigastrium, and distinguished from the term discomfort, is increasingly being recognized as an important symptom. The main etiologies of gastroparesis are diabetes, idiopathic, and post gastric and esophageal surgeries.<sup>1</sup> Hospitalizations from

documented gastroparesis are increasing.<sup>2</sup> Physicians have both medical and surgical approaches for these patients (See Figure 1). Medical therapy includes both prokinetics and antiemetics (See Table 1 and Table 2).

The gastroparesis population will grow as diabetes increases and new therapies will be required. What do we know about the size of the gastroparetic population? According to a study from the Mayo Clinic group surveying Olmsted County in Minnesota, the risk of gastroparesis in Type 1 diabetes mellitus was significantly greater than for Type 2. The cumulative proportions developing gastroparesis over a ten year time period was 5.2% in Type 1 and 1.0% in Type 2, compared to 0.2% in controls. They concluded that gastroparesis is a relatively uncommon complication of diabetes.<sup>3</sup> However in recent studies utilizing a more “real world” population of diverse cultures and socioeconomic status, not represented in Olmsted County, there is a very different result. This new

*(continued on page 22)*

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(continued from page 20)

study concluded that approximately 165,000 Type 1 diabetes mellitus (14% of US patients with Type 1 diabetes) and 2.1 million Type 2 diabetes mellitus (9.4%) patients are currently seeking medical therapy for diabetic gastroparesis symptoms and had moderate to severe symptoms of diabetic gastroparesis within the previous seven days of being in the survey.<sup>4</sup> The prevalence of diabetic gastroparesis is thus higher than previously reported and is significantly underdiagnosed and undertreated. The greater standardization and acceptance of radionuclide four hour gastric emptying and the SmartPill (wireless motility capsule) will facilitate more confidence in the evaluation of gastric emptying and with better recognition the full breadth of gastroparesis will be better appreciated as a relatively common and severe complication of Diabetes Mellitus. The predicted number with diabetic gastroparesis in the US is 4 million and combined with other etiologies of gastroparesis the overall figure approaches or exceeds ten million patients in the USA. This is essentially 3% of the population. Put in perspective, hepatitis C and celiac sprue are now both thought to be present in approximately 1% of the population.

## Prokinetics

### Metoclopramide

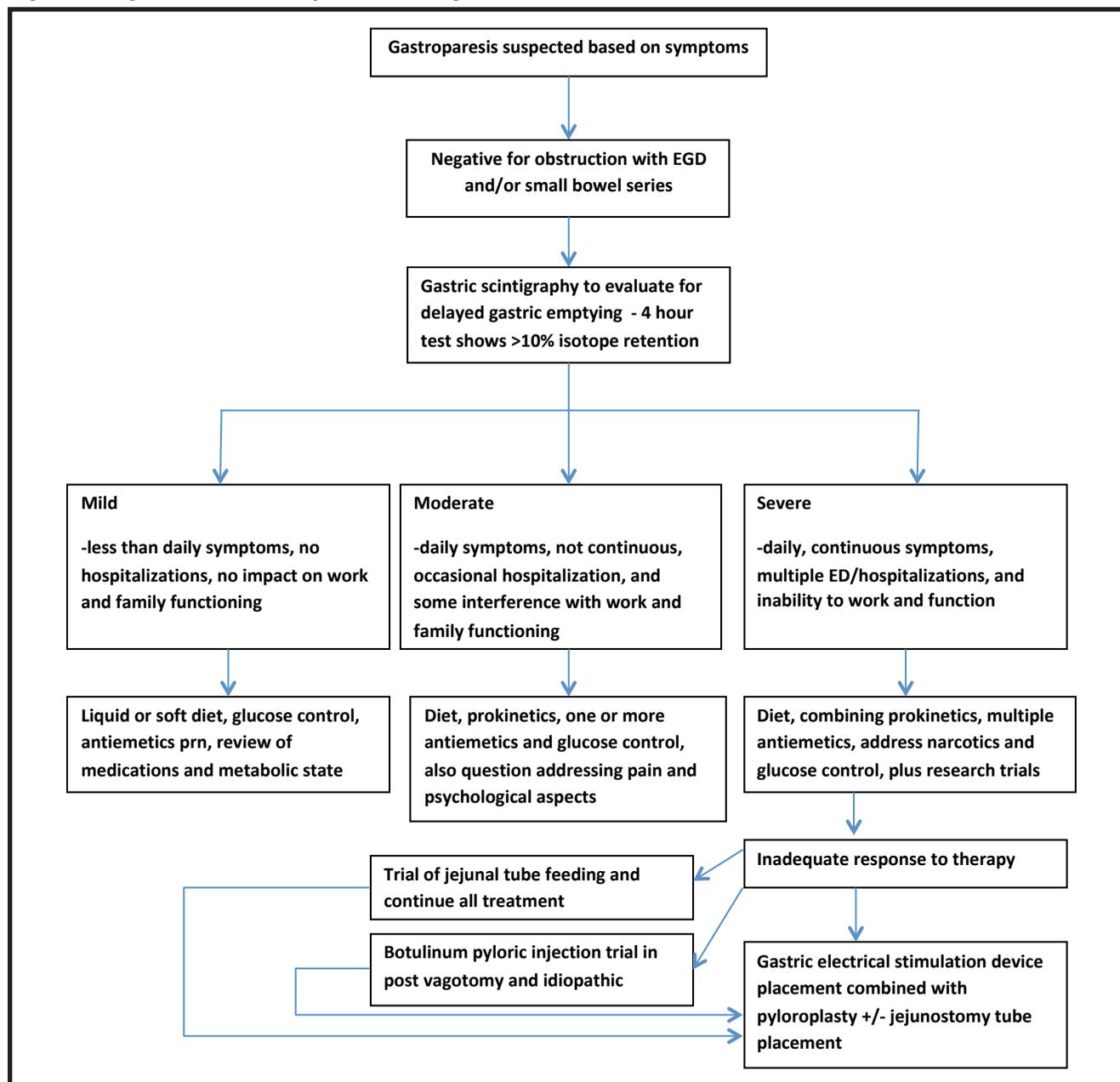
Approved by the FDA in 1979, metoclopramide is the only gastric prokinetic registered in the United States. Metoclopramide blocks dopamine D<sub>2</sub> receptors in the upper gastrointestinal tract as well as stimulates 5-HT<sub>4</sub> receptors resulting in augmented acetylcholine release which promotes gastric motility by affecting pre-synaptic and post-synaptic receptors in the gut wall. Overall, the medication leads to increased lower esophageal sphincter pressure, gastric tone, intragastric pressure, as well as coordinates antroduodenal motility with relaxation of the pylorus, resulting in faster gastric emptying. Dopamine inhibits lower oesophageal sphincter pressure and gastroduodenal motility.<sup>5</sup> Levodopa was shown to increase gastric retention of a technetium labelled meal compared to placebo. Administration of metoclopramide with levodopa returned gastric emptying toward normal. This study demonstrated the inhibitory effect of dopamine receptors on gastric motility.<sup>6</sup> Metoclopramide also provides antiemetic relief through inhibiting D<sub>2</sub> dopamine within the chemoreceptor trigger zone of the brain as well as some antagonism of 5-HT<sub>3</sub> receptors.<sup>7</sup>

Most of the research with metoclopramide occurred as long as thirty years ago. A multi-center placebo controlled trial in 1983 using a dose of 10 mg orally four times a day showed improved symptom outcomes and gastric emptying time in patients with diabetic gastroparesis.<sup>8</sup> Two trials with a total of twenty three diabetic gastroparesis patients showed improvement in gastric emptying and symptoms over placebo.<sup>9,10</sup> Patients did have symptom improvement as far as nausea, vomiting, constipation, fullness and bloating; however, gastric emptying did not improve and did not correlate with symptom improvement in either study. Therefore, metoclopramide's clinical efficacy is provided by a combination of pro-kinetic effects peripherally and antiemetic properties centrally.<sup>8,9</sup>

Metoclopramide is available in oral, suppository, and injectable routes of administration. Oral formulations include tablet, liquid and dissolvable tablets. A trial of ten patients showed that subcutaneous metoclopramide (2 cc=10 mg) administration can lead to improvement in gastric emptying and symptoms. In the outpatient setting, subcutaneous metoclopramide in doses of 10 to 40 mg per day can be used as an adjunct to the patient's oral medications since the plasma levels achieved are 80% of the intravenous levels thus overcoming the limitations of erratic absorption in the setting of gastroparesis and vomiting.<sup>11</sup> This subcutaneous self administration essentially equates to IV use in the emergency department. The newly released metoclopramide ODT (Metozolv ODT) is an orally dissolvable tablet available in 5 mg and 10 mg, which facilitates patient compliance. The absorption occurs in the small bowel and not through the buccal mucosa. An intranasal route of administration is also being developed to address the challenges of gastroparesis by providing a continuous plasma level for the agent.

Adverse events are a significant detraction for metoclopramide. The United States Food and Drug Administration released a warning for metoclopramide in 2009 stating the medications risk of tardive dyskinesia, specifically with patients taking the medications for greater than three months.<sup>12</sup> Overall, approximately thirty percent of patients cannot maintain long term use. The medication can cross the blood-brain barrier leading to inhibition of central D<sub>2</sub> receptors involved in movement pathways such as the basal ganglion, manifesting in a wide array of involuntary movement disorders. An acute dystonic reaction can occur within the first few hours typically when given parenterally,

Figure 1. Algorithm for Gastroparesis Management



which will resolve with discontinuation. Within the first few weeks and months, akathisia, anxiety, tremor, drug-induced Parkinsonism and depression can develop. These can be reversible within a few days to a few months after drug discontinuation or tapering of the dose, and sometimes adding carbidopa briefly. Also, benadryl is an antidote to reduce the anxiety and restlessness. Tardive dyskinesia is an irreversible movement disorder defined by disfiguring and involuntary movements. The reported incidence of tardive dyskinesia with metoclopramide has a large range from 0.1% to 29%.

The length of treatment prior to symptom development was also variable from 14 to 20 months.<sup>3</sup> Careful follow up of patients on chronic metoclopramide with actual office visits and not refilling prescriptions without seeing patients will prevent this possibility.

### Domperidone

Domperidone is a dopamine receptor antagonist, which has both central antiemetic and peripheral prokinetic properties in the upper GI tract. However,

*(continued on page 29)*

(continued from page 23)

the important distinction from metoclopramide is that it only minimally crosses the blood brain barrier. This leads to really no concerns about central nervous system side effects. Another distinction is domperidone is not a 5-HT<sub>4</sub> agonist. Unfortunately, domperidone is not easily available in the United States since the FDA withheld approval in 1989 due to borderline statistical significance related to sample size enrolled in the controlled clinical trials. The pharmaceutical company, Janssen, subsequently withdrew their application without pursuing further trials. To obtain domperidone, clinicians can request the medication through an Investigational New Drug Application through the FDA. Serum potassium and EKG should be performed on initial and subsequent evaluations, because of concerns about possible prolongation of the QT interval.<sup>13</sup> In an extensive experience by the author

in over 500 patients using high dose domperidone 80 to 120 mg per day, compared to usual European dosing of 40 mg per day, cardiac events have not been evident and QT prolongation is infrequent.<sup>14</sup> The only side effects may be due to increased levels of prolactin resulting in gynecomastia, breast tenderness, galactorrhea and menstrual irregularities. Prolactin release occurs from stimulation of the pituitary gland. Both the pituitary and the chemoreceptor trigger zone emetic areas are regarded as being outside the blood brain barrier consistent with domperidone's lack of CNS side effects. Chronic therapy does not appear to lead to decreased efficacy. The starting standard dose has been listed at 10 mg oral four times a day in other countries but clinical trials in the United States have used 20 mg four times a day and in clinical practice 30 mg four times a day can be used while also monitoring ECG at regular visits. The maximum dose recommended is 120 mg orally per

**Table 1. Prokinetic Medication Classes**

Prokinetic Class	Available Agents	Under Investigation
Dopamine receptor antagonists	Metoclopramide Domperidone(*)	Itopride Levosulpride
Motilin receptor agonists	Erythromycin Azithromycin Clarithromycin	
Serotonin 5-HT <sub>4</sub> agonists		Prucalopride Renzapride Mosapride
Ghrelin agonists		Ghrelin EX-1314 BIM-28131 TZP-101, TZP-102 Rm - 131 (Rhythm)
Cholinesterase inhibitor	Neostigmine Physostigmine Nizatidine	Acotiamide Itopride
Opiate receptor antagonists	Methylnaltrexone	
GABA B receptor agonist	Baclofen	

(\*) Not available in the United States.

This table summarizes the current gastric prokinetics available based on their mechanism of action and agents under investigation.

day. We recommend a trial of domperidone in doses of 80 to 120 mg per day for up to 3 months as our current practice before patients can be considered as medical treatment failures.<sup>15</sup> This approach results in 72% of patients achieving satisfactory control of symptoms.<sup>16</sup>

### Motilin Receptor Agonists

The macrolides class of agents are motilin receptor agonists of a particular chemical structure, which promote motility in the stomach and small bowel.<sup>17</sup> Their unique molecular structure permits them to occupy the motilin receptor in the antrum of the stomach. The distinction of a “particular channel structure” differentiates this class from small molecule motilin receptor agonists that are currently under development eg GSK 962040. In addition, another evolving motilin agonist is RQ-00201894, a small non-peptide motilin agonist shown to induce contractions in an animal model.<sup>18</sup> The macrolide class includes erythromycin and azithromycin. Erythromycin lactobionate is well studied as a prokinetic. It can be given IV at up to 3 mg/kg every six to eight hours in the hospital setting to facilitate gastric and small bowel tube placement and decrease gastric residuals with tube feeding as well as treat post-operative ileus and as a preparation for performing upper GI endoscopy in the setting of GI bleeding. Based on a meta-analysis of oral prokinetics, erythromycin has better acute outcomes than domperidone, cisapride, and metoclopramide for both gastric emptying and gastrointestinal symptoms.<sup>19</sup> Orally this medication has been determined to have limited long term efficacy because of concerns for tachyphylaxis after a few weeks. Both the liquid and tablet forms of erythromycin have been noted to increase gastrointestinal motility.<sup>20</sup> Hence using a low oral dosing of 150 mg to 250 mg twice to three times a day is recommended to reduce “saturation” of receptors.<sup>21</sup> At this dose, erythromycin is not being used at an antibiotic dose so there are no concerns regarding patients developing bacterial resistance when the agent is being used frequently. Among patients with diabetic and idiopathic gastroparesis, erythromycin was shown to decrease symptoms and gastric emptying time with both oral and intravenous forms.<sup>21</sup> Patients given intravenous erythromycin for post-vagotomy-antrectomy gastroparesis had improvement in initial phase of solid meal gastric emptying<sup>22</sup> indicating that there are motilin receptors in the fundus of the stomach. QT prolongation is a possible side effect of macrolides, and erythromycin carries the greatest risk.<sup>23</sup> Combined

use of calcium channel blockers and macrolides can lead to hypotension and shock.<sup>24</sup> In an experimental model of proarrhythmia, erythromycin and azithromycin lead to similar prolongation of repolarization but erythromycin has greater proarrhythmic potential than azithromycin.<sup>25</sup> There are rare reports of erythromycin being associated with sudden cardiac death from QT prolongation due to P450 iso-enzyme inhibition. Azithromycin in a 500 mg dose intravenously was shown to be equally effective as erythromycin 200 mg intravenously in accelerating emptying time during nuclear studies<sup>26</sup> but recent concerns have also been raised regarding cardiac aspects of azithromycin. Azithromycin in clinically relevant doses was shown to activate recombinant human motilin receptors similarly to erythromycin.<sup>27</sup>

### 5-HT<sub>4</sub> Receptor Agonists

Serotonin, also identified as 5-hydroxytryptamine (5-HT), has seven receptor subtypes. Enterochromaffin cells of the gastrointestinal mucosa secrete 5-HT after a meal, which stimulates adenylyl cyclase and increases cellular cyclic AMP. 5-HT<sub>4</sub> receptor activation of efferent myenteric cholinergic excitatory neurons results in acetylcholine release leading to increase smooth muscle activity. Metoclopramide is both a 5-HT<sub>4</sub> receptor agonist and dopamine D<sub>2</sub> receptor antagonist. Cisapride is a 5-HT<sub>4</sub> receptor agonist with no D<sub>2</sub> receptor antagonism. Tegaserod is a 5-HT<sub>4</sub> receptor agonist with minimal 5HT<sub>3</sub> effects but is also a 5-HT<sub>2B</sub> receptor antagonist.<sup>28</sup> Although tegaserod and cisapride were available for several years, they were withdrawn from the market due to increased cardiovascular side effects related to hERG K(+) cardiac channels.<sup>29</sup>

The 5-HT<sub>4</sub> receptor agonists still being actively investigated are prucalopride and velusetrag, although they are being initially studied for constipation. Prucalopride does not affect the hERG potassium channel. Prucalopride showed no difference between placebo for corrected QT intervals or incidence of supraventricular or ventricular arrhythmias in a phase II trial among elderly patients with constipation.<sup>30</sup> Being a selective, high-affinity 5-HT<sub>4</sub> receptor agonist,<sup>31</sup> it was shown to improve spontaneous complete bowel movements in a randomized, placebo controlled double-blind trial of 713 patients with constipation in Europe where it is now approved.<sup>32</sup> It is also being considered for investigation for gastroparesis and dyspepsia in the USA. Velusetrag is a selective serotonin 5-HT<sub>4</sub> receptor

*(continued on page 32)*

(continued from page 30)

agonist, and it was shown to accelerate gastric emptying after multiple doses in a study for chronic constipation.<sup>33</sup> Another novel 5-HT<sub>4</sub> agonist, naronapride, has demonstrated acceleration of gastric emptying following single and multiple oral administration to healthy human subjects in a randomized double-blind, placebo-controlled trial.<sup>34</sup> Further phase 2 trials are being planned for gastroparesis.

### Acetylcholinesterase Inhibitors

Acotiamide has been proposed as a gastroprokinetic agent with a mechanism of action related to inhibiting acetylcholinesterase activity in the stomach. Hence, this agent facilitates acetylcholine release from cholinergic nerve terminals by blocking muscarinic autoreceptors, both M1 and M2, which regulate the release of acetylcholine. The mode of acetylcholinesterase inhibitory actions was found to be selective and reversible. There has been no affinity demonstrated for dopamine or 5-HT receptors distinguishing acotiamide from mosapride, a 5-HT<sub>4</sub> agonist, and itopride, an agent with both dopamine affinity and inhibition of acetylcholinesterase activity. It has an accompanying excellent safety profile and future studies and trials are required outside of Asia, where it has been mainly studied and is approved for “functional dyspepsia”.

Itopride was studied in Asia with some promise but its role has not evolved. It combined central antidopamine with peripheral cholinesterase activity, which augmented cholinergic function. Nizatidine (an H<sub>2</sub> blocker) is also a partial prokinetic beyond its acid-inhibitory properties, based on cholinesterase inhibitor mechanisms.

### Ghrelin Receptor Agonists

Ghrelin is released by neuroendocrine cells in the gastric fundus and duodenum. Endogenous ghrelin rises before and falls after a meal. The appetite stimulating signal appears to travel through the vagal afferent pathway, and this pathway could be impaired in diabetic gastroparesis. Intravenous ghrelin administration increases gastric emptying and ghrelin receptor agonists could become novel treatments for gastroparesis.<sup>35</sup> In a rat model, intravenous ghrelin was shown to accelerate gastric emptying.<sup>36</sup> Intravenous ghrelin has been shown to improve gastric emptying and meal related symptoms in idiopathic gastroparesis<sup>37</sup> and it has also been shown to increase gastric emptying in diabetic gastroparesis.<sup>38</sup>

TZP-101 is synthetic selective ghrelin receptor agonist in clinical development. Intravenous administration daily for four days improved gastroparesis symptoms in a randomized, placebo-controlled study of 57 patients with diabetic gastroparesis.<sup>39</sup> Among ten patients with diabetic gastroparesis, TZP-101 produced significant reductions in radiolabelled solid meal half-emptying.<sup>40</sup> A recent phase 2a randomized, double-blind trial 92 patients receiving TZP-102, an oral ghrelin receptor agonist, showed no significant improvement in gastric emptying but did provide symptomatic relief.<sup>41</sup> However, a subsequent phase 2b 12 week placebo controlled trial using 10 and 20 mg doses once per day for twelve weeks was not able to show any clinical efficacy versus placebo and subsequently pursuing TZP-102 in gastroparesis was abandoned by the company (Tranzyme).

RM-131 is a promising synthetic ghrelin receptor agonist under development demonstrating greater potency than human ghrelin in animal experiments. RM-131 was shown to improve early phase gastric emptying of solids and reduce upper gastrointestinal symptoms in type 1 diabetes mellitus patients with delayed gastric emptying in randomized, placebo-controlled, single-dose, two-period, crossover study.<sup>42</sup>

A Phase 2 clinical trial was designed to evaluate the effect of relamorelin (Rm-131) on gastrointestinal (GI) motility, the symptoms of gastroparesis, and safety in patients with diabetic gastroparesis. The randomized, double-blind, placebo-controlled, adaptive, parallel-group study assessed relamorelin 10 mcg administered once daily, twice daily, or placebo-administered daily to patients with diabetic gastroparesis over a period of one month. The study was submitted and presented at DDW 2014. Relamorelin is effective in significantly accelerating gastric emptying in patients with diabetic gastroparesis and resulted in clinically important, significant improvements in vomiting. Vomiting episodes were reduced by 60% vs. placebo (p=0.033). In a large subgroup of patients who had vomiting at baseline (~60% of patients), relamorelin significantly improved a composite endpoint including the other subjective symptoms of diabetic gastroparesis—nausea, abdominal pain, bloating, and early satiety—vs. placebo, in addition to improving gastric emptying and vomiting (post hoc analysis). For the overall study group, there was a strong placebo effect for the subjective diabetic gastroparesis symptoms (nausea, abdominal pain, bloating, and early satiety), and relamorelin was

associated with only numerical improvements vs. placebo that did not reach statistical significance.<sup>43</sup> This positive initial result is being followed by further clinical trials of this agent in gastroparesis.

### Baclofen

$\gamma$ -Aminobutyric acid (GABA) is an important inhibitory neurotransmitter and is located throughout the gastrointestinal tract.<sup>44</sup> Baclofen is a GABA-B receptor agonist shown to increase lower esophageal sphincter pressure and decrease transient lower esophageal sphincter relaxation. It has been used to treat patients with refractory GERD.<sup>45</sup> The standard dose is 10 mg four times a day. The most common side effect of oral baclofen is drowsiness; it's also noted to cause confusion, dizziness and fatigue. Baclofen was noted to accelerate gastric emptying time in a trial of thirty children with GERD.<sup>46</sup> Animal models have shown improved liquid and solid gastric emptying with baclofen.<sup>47</sup> However, randomized trials are lacking for gastroparesis.

### Opioid Receptor Antagonists

Opiates such as morphine can delay gastric emptying and intestinal transit.<sup>48</sup> Gastroparesis patients may develop worsening symptoms if they are placed on narcotics either for back pain, peripheral neuropathy, or abdominal pain. Methylnaltrexone is mu-opioid receptor antagonist, which does not cross the blood brain barrier. The subcutaneous form has been shown in a randomized study of 133 patients to induce defecation rapidly without reversing the central analgesic effects of opioids.<sup>49</sup> In a randomized, double-blind, crossover placebo-controlled study, patients given morphine had a delay of gastric emptying, which was reversed when given methylnaltrexone.<sup>50</sup> However, methylnaltrexone was not shown to prevent post-operative nausea and vomiting in a prospective double-blind trial.<sup>51</sup> In pre-marketing clinical trials, the most common side effects were abdominal pain, diarrhea, flatulence, and nausea. Randomized trials for methylnaltrexone in gastroparesis are lacking.

### Antiemetics

Antiemetics should be used in combination with prokinetics to maximize symptom control in gastroparesis (see Table 2). Each antiemetic has its own mechanism of action based on blocking specific receptors in the chemoreceptor emetic center. For a

given gastroparesis patient, it is difficult to know which antiemetic will be the most efficacious. Hence a series of antiemetics may be required to be used alone or in combination in an attempt to gain control of nausea and vomiting through antagonizing one or more receptors in the chemoreceptor trigger zone.

### Phenothiazines

Phenothiazines are mainly dopamine and cholinergic receptor antagonists with the predominant site of action in the area postrema in the medulla oblongata. Examples includes prochlorperazine, promethazine, and trimethobenzamide. Sedation and extrapyramidal side effects such as slurred speech and dystonia are possible.<sup>51</sup>

Promethazine can be given by intravenous, intramuscular, oral, and rectal suppository routes. However, the intravenous route can cause injury related to phlebitis and even amputations have been reported with intravenous administration. It should be avoided in small veins such as the hand.<sup>53</sup>

### Muscarinic Receptor Antagonist

Patients with erratic drug absorption because of vomiting and gastroparesis benefit from transdermal medications. Scopolamine is a selective competitive antagonist of muscarinic cholinergic receptors. Sustained serum levels can produce antiemetic effects. Scopolamine is available as a 1.5 mg patch for three days. It is typically placed behind the ear to maximize absorption through that site with minimal subcutaneous fat. In postoperative patients, it was noticed to significantly decrease the risk of vomiting and nausea.<sup>54</sup> It is particularly attractive in the setting of gastroparesis where absorption can be unpredictable or oral medications not possible with active vomiting. The patch guarantees a sustained blood level over a 3 day duration. There is no evidence that the anticholinergic content in muscarinic receptor antagonists effects or delays gastric emptying.

### 5-HT<sub>3</sub> Antagonists

Ondansetron, granisetron, and dolasetron inhibit 5-HT<sub>3</sub> receptors in the area postrema. They also have peripheral effects via efferent fibers of the vagus nerve. They are antiemetics for chemotherapy and postoperative vomiting but now are also used for gastroparesis by oral or parenteral administration. Ondansetron orally dissolvable tablets are also available to facilitate absorption in very nauseated patients.

**Table 2. Antiemetic Agents for Gastroparesis**

Prokinetic agents with antiemetic properties (antagonize dopamine receptors - (D <sub>2</sub> ))	Metoclopramide (Reglan) Domperidone (Motilium)
Phenothiazine derivatives (antagonize dopamine receptors in area postrema)	Prochlorperazine (Compazine) Trimethobenzamide (Tigan)
Anticholinergic agents	Scopolamine patch
Antihistamines (H <sub>1</sub> receptor antagonists)	Diphenhydramine (Benadryl) Promethazine (Phenegran) Meclizine (Antivert)
Antiserotonergic (5-HT <sub>3</sub> receptor antagonists)	Ondansetron (Zofran) Granisetron (Kytril) (Sancuso Patch) Dolasetron (Anzemet) Palonosetron (Aloxi)
Tricyclic Antidepressants	Amitriptyline Nortriptyline
Substance P / Neurokinin-1 Receptor Antagonists	Aprepitant (Emend)
Tetrahydrocannabinol (THC) (CB1 receptor agonist)	Dronabinol (Marinol)

This table summarizes the current antiemetic agents based on their mechanism of action and also providing specific agents in each category.

Side effects are minimal although mild constipation has been reported. A generic version of ondansetron has increased accessibility to this drug class. However there are no controlled trials of 5HT<sub>3</sub> antagonists in gastroparesis. Diabetic gastroparesis patients treated with ondansetron did not have improvements in gastric emptying.<sup>55</sup> Among 14 healthy volunteers, ondansetron did not affect the gastric emptying of solids.<sup>56</sup>

Unfortunately, ondansetron can also interact with the hERG K(+) channel found in the heart leading to prolongation of cardiac repolarization.<sup>57</sup> In a study of inpatients for acute coronary syndrome or heart failure, ondansetron exposure led to a prolonged QTc in 31% and 46% respectively. In the heart failure group, QTc was prolonged by 18.3 +/- 20 msec.<sup>58</sup> Due to the risk of Torsades de Pointes, a potentially fatal heart rhythm, the FDA has removed the 32 mg intravenous single dose vial from the market.<sup>59</sup> These data are for IV administration and oral blood levels that are achieved are clearly much lower.

Granisetron is also available as a patch (Sancuso) providing plasma blood levels for up to seven days. In a double-blind, phase III, non-inferiority study, the patch controlled nausea and vomiting in 60% versus 65% for

oral granisetron in the patient setting of chemotherapy.<sup>60</sup> An open label study of the granisetron patch was moderately effective in reducing nausea and/or vomiting in 83% of gastroparesis patients.<sup>61</sup> Recent reports in gastroparesis have been promising and a double-blind trial is being planned by the pharmaceutical company (ProStrakan).

### NK-1 Receptor Antagonists

High levels of substance P have been found in the area postrema and the vagal afferents from animal models.<sup>62,63</sup> Direct administration of substance P into the area of the nucleus tractus solitarii of the hindbrain induces emesis.<sup>64</sup> The action of substance P in these centers is controlled by the neurokinin-1 receptor (NK-1) and antagonism of NK-1 receptor has shown antiemetic activity in animals given cisplatin.<sup>65</sup> A NK-1 receptor antagonist was an effective antiemetic against a variety of provoking agents including radiation, morphine, and copper sulfate in an animal model.<sup>66</sup>

Aprepitant is a selective, oral nonpeptide antagonist of the NK1 receptor with the ability to penetrate the central nervous system. The earliest clinical trials

*(continued on page 37)*

(continued from page 34)

were for patients receiving chemotherapy, specifically cisplatin. In a randomized, double-blind, placebo-controlled phase III study of 520 patients, 72.7% of group of patients receiving aprepitant, 5-HT<sub>3</sub> antagonists and steroids had complete response (no emesis and no rescue therapy) versus 52.3% in the standard therapy group receiving 5-HT<sub>3</sub> antagonist and steroids.<sup>67</sup> Based on retrospective data for chemotherapy patients, 42 patients treated with aprepitant and granisetron had a higher rate of complete response than 40 patients treated only with granisetron without significant difference in adverse drug events.<sup>68</sup> Aprepitant (Emend) is available in the United States for nausea and vomiting associated with chemotherapy and surgery. However, it has been adopted for use by gastroenterologists. Two case reports are available for the use of aprepitant for gastroparesis. One patient with refractory idiopathic gastroparesis responded to aprepitant 40 mg daily.<sup>69</sup> Another patient with refractory diabetic gastroparesis was able to tolerate aprepitant for four months prior to gastric electrical stimulation device placement.<sup>70</sup> A randomized, double-blind clinical trial is now being conducted by the NIH funded Gastroparesis Consortium utilizing a dose of 125 mg for the efficacy of aprepitant in gastroparesis and results are expected in 2015.

### Cannabinoids

Cannabinoids are agonists of CB1 receptors in the brain and gut. They are both antiemetics and appetite stimulants. They can be used for patients who are refractory to other treatments. It should be noted that cannabinoids delay gastric emptying in healthy subjects.<sup>71</sup> Chronic daily smoking of marijuana for greater than five years can lead to cannabis hyperemesis syndrome in a subset of subjects with genetically predisposed cannabinoid receptor sensitivity. This entity is characterized by unexplained recurrent nausea and vomiting, compulsive bathing in hot baths and showers, and abdominal pain. The majority of patients who stopped using marijuana had symptom improvement.<sup>72</sup>

The earliest studies of cannabinoids were from the 1980s. In 1985, nabilone was compared to prochlorperazine for chemotherapy related emesis and was shown to be significantly superior in reducing vomiting episodes.<sup>73</sup> More recently, dronabinol was compared to ondansetron for delayed chemotherapy-induced nausea and vomiting in 2007. Among 61 patients, dronabinol and ondansetron were equally

effective by themselves and combination therapy was not superior.<sup>74</sup> Dronabinol (Marinol) is available in the United States and the recommended antiemetic dosing is 5 mg orally three times a day ranging up to 10 mg three times a day. There are a subset of gastroparesis patients who definitely respond to this medication. In the few states in America where marijuana has been legalized, it can be an effective therapy when utilized on an “as needed” basis for nausea and vomiting of different etiologies, including in gastroparesis patients. This is an entirely different method of use than chronic daily smoking for greater than five years, which leads to the episodes of “cyclic vomiting” or “cannabis hyperemesis syndrome”.

### Tricyclic Antidepressants

In one hypothesis, gastroparesis symptoms of nausea and abdominal pain could be explained by neuropathic changes in sensory vagal and spinal nerves. In a study of vagal nerve integrity using sham feedings, impaired pancreatic polypeptide response was noted in diabetic gastroparesis but not idiopathic gastroparesis.<sup>75</sup> Nortriptyline, amitriptyline, and doxepin are available tricyclic antidepressants (TCAs). A chart review of 37 patients with functional nausea and vomiting showed an 84% response rate to TCAs with complete remission in 51%.<sup>76</sup> A randomized cross-over study of amitriptyline and placebo among functional abdominal pain patients showed improvement in symptoms after four weeks. The symptom improvement was not associated with a normalization of the perceptual responses to gastric distension.<sup>77</sup>

Prospective, randomized and adequately powered trials have been lacking for tricyclics in gastroparesis. In a two year follow-up open labeled study, eighty-eight percent of patients treated for cyclic vomiting syndrome had improved clinical status by subjective global assessment.<sup>78</sup> Thirty-six chemotherapy patients in a double-blind, randomized, crossover study showed reduced emetic episodes when using a combination of intravenous metoclopramide and oral nortriptyline versus intravenous metoclopramide alone.<sup>79</sup>

Nortriptyline did not differ in overall symptomatic improvement versus placebo for idiopathic gastroparesis in a just completed 12 week multicenter, randomized, double-masked, placebo-controlled dose escalation trial which was well powered and conducted by the NIH Gastroparesis Consortium.<sup>80</sup> However, nausea showed improvement in the first few weeks at low

doses of nortriptyline (25 mg) while abdominal pain and early satiety improved in the latter part of the trial when doses were averaging 50 mg at night. In another retrospective study, the majority of 24 diabetic patients with nausea and vomiting who failed prokinetics had symptomatic improvement after treatment with tricyclic antidepressants.<sup>81</sup>

Clearly the tricyclics and other neuromodulators need to be further studied in all etiologies of gastroparesis and also with specific symptoms.

### Transcutaneous Stimulation

Transcutaneous stimulation of acupuncture sites for nausea and vomiting is an alternative form of therapy and has shown improved rates of gastric emptying and reduction of symptoms. This utilizes the nausea and vomiting acupuncture sites of PC6 near the wrist and ST36 on the leg as sites for cutaneous electrical stimulation.

Multiple trials have demonstrated the effectiveness of transcutaneous stimulation on nausea and vomiting. Twenty three women with significant nausea and vomiting in the first 14 weeks of pregnancy were enrolled in a randomized, crossover study between a sensory affect stimulation unit and an inactive placebo unit; twenty one experienced improvement with a sensory affect stimulation delivered through the volar surface of the wrist.<sup>82</sup> More than 75% of over 100 patients with chemotherapy-induced sickness not adequately controlled with antiemetics alone had improvement with the addition transcutaneous electrical stimulation of the P6 antiemetic point.<sup>83</sup> Electrical stimulation of acupuncture points significantly increased the percentage of regular slow waves on electrogastrography in healthy humans.<sup>84</sup> A recently completed placebo-controlled multicenter clinical trial using a microstimulator developed by Transtimulation Research Incorporated showed improvement in gastroparesis symptoms after 4 weeks of use<sup>85</sup> and more trials are anticipated. One mechanism of action is a change in vagal ratio indicating possible motor and sensory benefits attributed to peripheral and central vagal actions.

### Expert Commentary on the Field

Combination therapy of antiemetics and prokinetics is our recommendation for symptomatic control in gastroparesis. Metoclopramide should be started at 5-10 mg three times a day before meals and at night

time. If tolerated (in 60% or more of patients), doses can be increased up to 20 mg before meals and at night time plus or minus adjunctive role for subcutaneous administration. Scopolamine 1.5 mg patch behind the ear, replaced every 72 hours can overcome the limitations of nausea control by orally administered agents in settings of vomiting and gastroparesis and should be utilized in all patients particularly since it is well tolerated. Dissolvable ondansetron or phenergan are other options to be given on a scheduled regimen up to three times a day since nausea needs to be aggressively inhibited and not prescribed "as needed". Subcutaneous metoclopramide can be added for intermittent "rescue" medication to avoid emergency room visits. If metoclopramide cannot be tolerated, then substitute domperidone 20 to 30 mg before meals and at night time. Marinol and granisetron (administered by a sustained 5 day patch, Sancuso) are other possibilities as degrees of intolerance and/or refractoriness are encountered.

The model of central emetic action combined with peripheral prokinetic activity is a very attractive approach to gastroparesis. Unfortunately this class is limited to metoclopramide and domperidone. Itopride was studied in Asia with some promise but its role has not evolved. It combined central antidopamine with peripheral cholinesterase activity, which augmented cholinergic function. There is also discussion about modifying metoclopramide by a polymerization method to limit its penetration of the blood-brain barrier thus overcoming its central nervous system side effects. In addition, there is an IND pending for a new dopamine-2/dopamine-3 antagonist compound, which will overcome the past adverse event problems.

Gastroparesis remains a challenging syndrome to treat. Patients can be refractory to a limited field of currently available medications. As far as research in progress, ghrelin receptor agonists show the most promise. Despite promising results with double-blind randomized trials with TZP-102 indicating efficacy in the diabetic gastroparesis population, two recent trials failed to show efficacy versus placebo. The new ghrelin agonist relamorelin (RM-131) is a synthetic ghrelin agonist over 100 times more potent as a ghrelin agonist than TZP-102. Analysis of the data from 204 patients with diabetic gastroparesis indicates that relamorelin administered twice daily for four weeks in these patients with moderate to severe gastroparesis significantly improved gastric emptying, significantly

reduced vomiting, and in a large (~60%) subgroup of the patients with vomiting at baseline, significantly improved a composite symptom score comprising nausea, abdominal pain, bloating, and early satiety.

Motilin agonists are still topical and despite setbacks in balancing dosing, half-life and timing of administration, there are ongoing studies of motilin agonists in Phase 1 and 2 levels of development.

5HT<sub>4</sub> receptor agonists have run into many difficulties with cardiac side effects but there is continued interest in this class and prucalopride as a survivor with no cardiac side effects is still being investigated and velusetrag is another selective 5HT<sub>4</sub> receptor agonist. Both agents have great potential to evolve into gastroparesis following focus initially on constipation.

There are important contributions forthcoming from the NIH funded Gastroparesis Consortium. The following pharmacological goals have been identified through histological and molecular structures in the gastric muscularis propria: 1.) Targeting nNOS/Nitric oxide with precursor medications in settings where nNOS/NO are depleted. BH4 precursors such as Seprapterm have been used in animal models; 2.) Targeting interstitial cells of Cajal (ICC) epigenomics stem cells; 3.) Targeting the heme oxidase pathways with agents such as Hemin, or IL-10 which induce Hemin resulting in less reduction in heme oxygenase and loss of ICC in diabetic gastroparesis.

In the meantime, gastric electrical stimulation remains the mainstay of therapy for the 20-25% of patients failing all medical approaches. The recent modification of this approach by adding a pyloroplasty during the surgery ensures accelerated gastric emptying while at the same time the electrical stimulation is acting centrally to reduce nausea and vomiting via afferent pathways to the chemoreceptor trigger zone and augmenting vagal function to help gastric tone. ■

## Article Highlights

1. An up to date summary of the established and putative gastric prokinetic agents and their mechanisms of action.
2. A major emphasis on the crucial contributions of antiemetics in the symptomatic control of gastroparesis patients - based on the fact that physicians do not recognize nausea as a dominant, under-appreciated and debilitating daily symptom.
3. Explores new antiemetic horizons involving

transcutaneous electrical stimulation of acupuncture sites for nausea and vomiting.

4. Future advances in therapy will be based on knowledge gained from histological and cellular analysis of smooth muscle tissue specifically how to prevent loss of the Interstitial Cells of Cajal, inflammatory changes of interstitial neurons, and decreases in heme-oxygenase and nitric oxide synthase with a new spectrum of pharmacologic agents treating gastroparesis by addressing these abnormalities.

## Authors' Declaration of Personal Interests

Richard W. McCallum has been on the Advisory Board of Smart Pill Corporation and Prostrakan Pharm. He has been a consultant for Tranzyme, Inc., Evoke, Rhythm and Medtronic Corporation. He has received research funding from Tranzyme, Takada, Salix, Novartis, Red Hill Pharma and Rhythm as well as current National Institutes of Health (NIH) funding from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) – Gastroparesis Consortium.

Joseph Sunny has no declaration of personal interests.

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(continued on page 42)

(continued from page 40)

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