Treatment of Gastroparesis: An Update

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Abstract
Gastroparesis is a chronic disorder of gastric motility that is characterized by delayed emptying of either solids or liquids from the stomach in the absence of any mechanical obstruction. Nausea, vomiting, early satiety and bloating are some of the manifestations of gastroparesis. Idiopathic, diabetes mellitus and postsurgical states account for the majority of cases. Gastroparesis is a difficult condition to treat. Prokinetic drugs like metoclopramide and erythromycin form the mainstay of therapy but are less than ideal. Some patients may benefit from endoscopic botulinum toxin injection. Gastric electrical stimulation, though promising, is not ready for prime time yet.

Etiology
The etiology of gastroparesis is diverse with the idiopathic variety constituting the largest group in one study [6]. Diabetes accounted for 29% of patients in that same report with postsurgical causes making up 13%. These 3 causes (idiopathic, diabetes and postsurgical) account for a majority of all cases. Other causes of gastroparesis include neurological conditions like Parkinsonism, collagen vascular diseases, Chagas disease, hypothyroidism, hyperparathyroidism and hypoparathyroidism.

Clinical Manifestations and Diagnosis
Present studies indicate that the majority of those with delayed gastric emptying are women and the mean age of onset is 34 years [6]. Gastroparesis manifests itself through a combination of symptoms. Most symptoms are nonspecific and overlap with common gastrointestinal disorders like peptic ulcer disease and nonulcer dyspepsia. Nausea/vomiting,
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postprandial fullness/early satiety and bloating are the commonest manifestations. Nausea is the most consistent symptom found in over 90% of patients [6, 7]. Bloating and early satiety are present to a lesser degree, being found in 75% and 60%, respectively, in one study [6].

Abdominal pain may be present in 46–89% of patients but is unlikely to be the predominant symptom [6, 7].

As the symptoms are nonspecific with a significant degree of overlap with other gastric disorders, the initial work-up should include an upper endoscopy, even if gastroparesis is strongly suspected. This is necessary to rule out any mechanical obstruction and other common disorders like peptic ulcer diseases and nonulcer dyspepsia.

When an upper endoscopy does not reveal any organic obstruction and the endoscopic findings do not adequately explain the patient’s symptoms, a definitive test to diagnose gastroparesis such as gastric scintigraphy must be done.

Assessment of Severity

Assessment of severity is important for appropriate management. One method is the Gastroparesis Cardinal Symptom Index (GCSI), which is a sum, total of 3 subscales (ranging from 1–3) for the 3 main symptom complexes: postprandial fullness/early satiety, nausea/vomiting and bloating [8].

Another simple gradation of severity is outlined in table 1 [9]. Grade 1 usually includes patients with mild intermittent symptoms that are controlled with diet modification and avoidance of exacerbating agents. Grade 2 patients have moderately severe symptoms but no weight loss and require prokinetic drugs plus antiemetic agents for control. In Grade 3, patients are refractory to medication, unable to maintain oral nutrition and require frequent emergency room visits. These patients require intravenous fluids, medications, enteral or parenteral nutrition and endoscopic or surgical therapy.

Treatment

A wide array of therapeutic interventions is available to treat gastroparesis. Diet modification, pharmacological agents, endoscopic techniques, surgery and psychological counseling are some of the modalities employed.

General and Dietary Measures

While there are no controlled trials testing the efficacy of diet modification in the therapy of gastroparesis, some dietary recommendations may prove helpful in patients with milder forms of the disease. Multiple small meals a day as opposed to 2 or 3 large meals facilitate gastric emptying. Generous intake of fluids during a meal may aid gastric emptying, as liquids empty more rapidly than solids. An overall reduction in the solid food content is also advised. A diet low in fats decreases the inhibitory effect of lipids on gastric emptying. Patients should be told to avoid a high fiber diet to prevent phytobezoar formation.

Proper mastication and postprandial walking are additional factors that may facilitate the gastric emptying process.
Medicines that decrease gastric motility should be discontinued if possible (table 2). Identification and correction of the underlying cause of gastroparesis may be helpful in some cases. In diabetics, aggressive control of blood sugar is advocated as it is thought to facilitate the action of other therapeutic measures.

**Prokinetic Agents**

There are 3 broad classes of prokinetic agents used in the treatment of gastroparesis: dopamine receptor antagonists, motilin receptor agonists and 5-HT4 receptor agonists (table 3).

**Dopamine Receptor Antagonists**

*Metaclopramide.* Metaclopramide is a 5-HT4 agonist, a dopamine D2 receptor antagonist and a direct stimulant of smooth muscle, all of which contributes to its prokinetic effect [1]. In addition to accelerating gastric motility, metaclopramide has an independent antiemetic effect. Metaclopramide can be administered intravenously, subcutaneously or through the oral route. A liquid preparation is also available.

Although there are several studies [10–18] that have attempted to document the efficacy of metoclopramide in gastroparesis, most of them suffer from significant design flaws or insufficient numbers. Some of the more acceptable trials are listed in table 4. The overall conclusion that can be drawn from these trials is that a minority of patients may experience symptom benefit from metoclopramide therapy. However, there appears to be poor correlation between the improvement in gastric emptying and reduction of symptoms.

When compared to erythromycin, metoclopramide proved to be inferior in terms of symptom relief in one study [16]. Other studies [17, 18] have shown that metoclopramide may be equally effective or marginally inferior to domperidone in efficacy.

Patients may develop tolerance over time and uncomfortable side effects may limit its use in up to 30% of patients. Irreversible tardive dyskinesia is a serious side effect that occurs in 1–10% of patients treated for more than 3 months [19]. Therefore, it is not advisable to maintain patients on metoclopramide for a prolonged period. When initiating therapy, the side effects should be discussed and documented in the patient record.

*Domperidone.* Domperidone is a peripheral dopamine D2 receptor antagonist with prokinetic properties and a potent antiemetic effect. As it does not cross the blood-brain barrier, its central nervous system side effects are minimal.

In clinical trials, the efficacy of domperidone matches that of metoclopramide and cisapride [18]. However, its effect on solid-phase gastric emptying is lost by 6 weeks [20]. The drug is not approved in the United States by the FDA but can be made available through special application for patients with refractory gastroparesis.

**Motilin Receptor Agonists**

*Erythromycin.* Erythromycin exerts its prokinetic effect by stimulating the motilin receptors on smooth muscles and neurons in the gastroduodenal area [21]. How-
ever, unlike metaclopramide, erythromycin has no independent antiemetic effect.

Most published trials [22–26] reporting on the efficacy of erythromycin in gastroparesis have been open labeled, had inadequate numbers or lacked strict definitions [22]. A few representative studies are outlined in table 5. The conclusion gleaned from these reports is that though erythromycin improves gastric emptying, it benefits only a minority of patients with regard to symptom amelioration.

Erythromycin can be administered intravenously in hospitalized patients or provided in liquid form or oral tablets to outpatients. Its most potent effect is seen when injected intravenously [27]. The oral route (125–250 mg, 3–4 times daily) is less efficacious. Tolerance is known to occur with chronic use. An increased incidence of sudden cardiac death in patients using erythromycin has been reported [28].

Other Motilin Receptor Agonists. Mitemcinal, a new motilin agonist, which can be administered orally, has shown promise in initial trials [29]. Ghrelin, an endogenous neurohumoral mediator, is currently under study [30].

5-HT_4 Receptor Agonists

tegaserod and Cisapride are 5-HT_4 receptor agonists, which have been used to treat gastroparesis in the past. Both agents were withdrawn from use in the United States owing to serious cardiovascular complications [1].

Symptomatic Therapy

Antiemetic drugs have been used successfully in clinical practice to treat the symptoms of gastroparesis although hard evidence for this rationale in the form of scientific studies is minimal. The most commonly used antiemetic drugs are the phenothiazines (for example prochlorperazine and thiethylperazine) and they can be used in conjunction with prokinetic agents [9].

Low-dose tricyclic antidepressants may provide relief of symptoms in patients with gastroparesis [31].

Pain may be a prominent symptom in some patients. Nonsteroidal agents, selective serotonin reuptake inhibitors and opiates have been used with varying degrees of success [9].

Endoscopic Treatment

In some patients with gastroparesis, pylorospasm may contribute to a delay in gastric emptying. Endoscopic therapy involves the injection of botulinum toxin (100–200 units in a circumferential pattern; 4 injections around

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Design</th>
<th>Route</th>
<th>Symptom reduction</th>
<th>GE improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richards et al. [25]</td>
<td>10</td>
<td>OL</td>
<td>PO, IV</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Ramirez et al. [24]</td>
<td>16</td>
<td>OL</td>
<td>PO, IV</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Fiorucci et al. [23]</td>
<td>12</td>
<td>OL</td>
<td>IV</td>
<td>not stated</td>
<td>yes</td>
</tr>
<tr>
<td>Samsom et al. [26]</td>
<td>12</td>
<td>DBC</td>
<td>PO</td>
<td>unclear</td>
<td>not done</td>
</tr>
</tbody>
</table>

GE = Gastric emptying; OL = open label; PO = per os; IV = intravenous; DBC = double-blind controlled.

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose</th>
<th>Follow-up</th>
<th>Symptom reduction</th>
<th>GE improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ezzedine et al. [33]</td>
<td>6</td>
<td>100 IU</td>
<td>6 weeks</td>
<td>55% 52%</td>
</tr>
<tr>
<td>Miller et al. [34]</td>
<td>10</td>
<td>100 IU</td>
<td>4 weeks</td>
<td>38% 48%</td>
</tr>
<tr>
<td>Arts et al. [36]</td>
<td>20</td>
<td>100 IU</td>
<td>1 month</td>
<td>29% 35%</td>
</tr>
<tr>
<td>Lacy et al. [35]</td>
<td>8</td>
<td>200 IU</td>
<td>12 weeks</td>
<td>55% 33%</td>
</tr>
<tr>
<td>Bromer et al. [32]</td>
<td>63</td>
<td>200 IU</td>
<td>2 months</td>
<td>43% NS</td>
</tr>
</tbody>
</table>

Randomized placebo-controlled trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose</th>
<th>Follow-up</th>
<th>Symptom reduction</th>
<th>GE improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arts et al. [38]</td>
<td>23</td>
<td>100 IU</td>
<td>1 month</td>
<td>none</td>
</tr>
<tr>
<td>Friedenberg et al. [39]</td>
<td>16</td>
<td>200 IU</td>
<td>1 month</td>
<td>none</td>
</tr>
</tbody>
</table>

GE = Gastric emptying; NS = not significant.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>n</th>
<th>Duration</th>
<th>Symptom improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEMS [42]</td>
<td>open</td>
<td>33</td>
<td>12</td>
<td>yes</td>
</tr>
<tr>
<td>WAVESS [43]</td>
<td>DBS</td>
<td>33</td>
<td>2</td>
<td>yes</td>
</tr>
<tr>
<td>Forster et al. [40]</td>
<td>open</td>
<td>25</td>
<td>12</td>
<td>improved at 3 months sustained at 12 months</td>
</tr>
<tr>
<td>Forster et al. [44]</td>
<td>open</td>
<td>55</td>
<td>12</td>
<td>improved at 6 months not sustained at 12 months</td>
</tr>
<tr>
<td>Lin et al. [45]</td>
<td>open</td>
<td>55</td>
<td>36</td>
<td>improved at 1 year sustained for 3 year</td>
</tr>
<tr>
<td>Anand et al. [46]</td>
<td>open</td>
<td>214</td>
<td>48</td>
<td>improved at 4 year</td>
</tr>
</tbody>
</table>

DBS = Double-blind sham.
the pylorus) into the pyloric area, which is thought to decrease pylorospasm and accelerate gastric emptying. Several open-labeled studies [32–37] indicated a good symptomatic response (Table 6) with symptom scores falling by 29–55%. Gastric emptying rates also registered a marked improvement (33–52%) and correlated well with symptom reduction. The effect of botulinum toxin lasted up to 5 months in one study [32].

However, the results from 2 randomized, placebo-controlled trials [38, 39] have not been encouraging. Arts et al. [38] failed to demonstrate any beneficial effect on either gastric emptying or symptoms over placebo. In the study by Friedenberg et al. [39], gastric emptying rates improved, but provided no symptom benefit. More studies are required before reaching a final verdict on botulinum toxin injection therapy.

Dilation of the pylorus may produce the same benefit as botulinum injection [1].

**Gastric Electrical Stimulation**

Using exogenous electrical current to stimulate the stomach in patients with gastroparesis is a logical and attractive concept. Initial methods involved external leads, which were too large for implantation and unwieldy [40]. Recently, the FDA has given limited approval on humanitarian grounds for a gastric electrical stimulator with a pulse generator that can be implanted into the abdominal wall (Enterra gastric electrical stimulation system). The pulse generator delivers low-energy, high-frequency stimuli and has a battery life of 6–8 years [41]. This method is, at present, limited to a few centers.

Initial experience with gastric stimulators was obtained through 2 multicenter trials, the Gastric Electrical Mechanical Stimulation Study (GEMS) [42] and the Worldwide Anti-Vomiting Electrical Stimulation Study (WAVESS) [43]. GEMS was a multicenter open-labeled trial that documented improvement in nausea and vomiting in gastroparetic patients. WAVESS was a controlled double-blind sham stimulation trial that reaffirmed the efficacy of gastric stimulation and paved the way for FDA approval of the Enterra system.

All trials [40, 44–46] have produced encouraging results with patients experiencing 75–80% reduction in symptoms (Table 7). While some initial studies showed conflicting results with regard to sustenance of improvement [40, 44], two subsequent studies have indicated long-term benefits lasting 3 and 4 years, respectively [45, 46]. Cutts et al. [47] were able to demonstrate that gastric stimulation therapy is superior to intensive medical treatment.

About 10% of patients, however, develop complications like infection, which invariably warrants removal of the device. Other adverse events noted include: lead dislodgement, wire breakage, penetration of the stomach and intestinal obstruction, all of which require surgical intervention [41].

New methods that involve electrodes that can be placed orally by endoscopy or through a percutaneous endoscopic gastrostomy [48] or by percutaneous techniques [49] are also being explored.

Gastric electric stimulation is not ready for prime time yet. Available devices need to undergo further refinement

### Treatment of Gastroparesis

**Table 8. Consensus recommendations for the treatment of gastroparesis**

<table>
<thead>
<tr>
<th>Psychological measures</th>
<th>Glycemic control</th>
<th>Nutritional care</th>
<th>Prokinetic medications</th>
<th>Antiemetic therapy</th>
<th>Pain control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empathy and education</td>
<td>Twice daily long-acting insulin plus periprandial short-acting insulin</td>
<td>Small, frequent meals, low in fat and fiber</td>
<td>Metoclopramide or erythromycin PRN</td>
<td>Phenothiazine or dopamine receptor antagonist PRN</td>
<td>Acetaminophen or nonsteroidal agents</td>
</tr>
<tr>
<td>Patient support groups</td>
<td>Primarily liquid diet</td>
<td>Liquid nutrient supplements</td>
<td>Metoclopramide or erythromycin scheduled dosing</td>
<td>Muscarinic receptor antagonist PRN</td>
<td>Tramadol or propoxyphene</td>
</tr>
<tr>
<td>Behavioral or relaxation therapy</td>
<td>Enteral feedings</td>
<td>Central or peripheral parenteral nutrition short term</td>
<td>Domperidone or tegaserod</td>
<td>Tricyclic agents</td>
<td>Tricyclic agents</td>
</tr>
<tr>
<td>Hypnosis</td>
<td>Pyloric botulinum toxin</td>
<td></td>
<td>Pyloric botulinum toxin</td>
<td>Tetrahydrocannabinol,lorazepam or alternative therapies</td>
<td>Newer antidepressants</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TCAs, SNRIs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fentanyl patch or methadone</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Referral for pain specialist</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nerve block</td>
</tr>
</tbody>
</table>

A stepped care approach in a top-down vertical manner is recommended which is dependent on the severity of gastroparesis. Treatment from different categories (columns) is often used in combination. TCA = Tricyclic antidepressant agent; SNRI = selective norepinephrine reuptake inhibitor. Reproduced from Abel et al. [9].

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For references, please consult the original source.
and easier electrode implantation techniques that obviate the need for surgery are required. Long-term controlled studies involving larger numbers will be necessary for gastric electrical stimulation to be accepted as standard therapy [50, 51].

Surgery
Extreme cases may require surgical intervention, and operations like partial gastrectomy and pyloroplasty have been performed to treat resistant gastroparesis. The results are uns proven so far.

Rarely, a venting gastrostomy may be placed to release the discomfort from gas and liquids [1].

Enteral and Parenteral Nutrition
Some patients with severe refractory gastroparesis may need enteral or parenteral modes of nutritional support. Enteral nutrition is usually indicated in patients with significant malnutrition (>10% weight loss over 6 months), evidence of mineral deficiencies and electrolyte imbalance and in those who require frequent hospitalizations [1].

Total parenteral nutrition may be necessary in patients who have concomitant intestinal motility.

Psychological Support
Anxiety, depression and somatization are increasingly found in patients with severe gastroparesis and appropriate psychological support is necessary to improve the overall well-being of the patient. Psychotherapeutic measures like relaxation techniques have been useful. Some patients benefit from hypnosis and biofeedback [9].

Conclusion
Most therapeutic measures available to treat gastroparesis are less than ideal and patients may require a combination of measures depending on the severity of their condition. Table 8 summarizes the overall approach to the treatment of gastroparesis.

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