

# TREATMENT OF AUTONOMIC NEUROPATHY

## TREATMENT OF AUTONOMIC DYSFUNCTION OF THE GASTROINTESTINAL TRACT (Part Three)

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The autonomic control of the gastrointestinal tract is mediated by the extrinsic parasympathetic and sympathetic nervous systems and the intrinsic enteric nervous system. The parasympathetic input to the gut originates from the vagus and pelvic nerves from second through fourth sacral segments. The post-synaptic cholinergic neurons provide excitatory input to the gastrointestinal tract. The sympathetic nervous system provides inhibitory input to the gastrointestinal tract. Extrinsic sympathetic efferents arising in the intermediolateral grey column synapse in the celiac, superior, and inferior mesenteric ganglia and ramify throughout the gastrointestinal tract in the distribution of their respective arterial trunks. The upper gastrointestinal tract is innervated by the greater splanchnic nerve which synapses in the celiac ganglion and travels with the celiac artery; the small intestine (mid-gut) is innervated by the lesser splanchnic nerve which synapses in the superior mesenteric ganglion and travels with the superior mesenteric artery; and the large intestine is innervated by the lumbar splanchnic nerve which synapses in the inferior mesenteric ganglion and travels with the inferior mesenteric ganglion.<sup>1-3</sup>

The enteric nervous system is comprised of a myenteric plexus located between the inner-circular and outer-longitudinal smooth muscle layers (Auerbach's plexus) and a submucosal plexus (Meissner's plexus). At least five types of intrinsic enteric neuron have been identified, and any individual neuron may contain multiple neuropeptides.<sup>2</sup> Motor excitation is mediated by the cholinergic-substance P neurons and inhibition is mediated by the dynorphin-vasoactive intestinal polypeptide neurons. Even in the absence of extrinsic autonomic nervous system influences, the enteric nervous system governs basic gut functions.<sup>2</sup> The myoelectrical activity of gastrointestinal smooth muscle thus may be influenced by neural input intrinsic to the gut (the enteric nervous system), by extrinsic parasympathetic and sympathetic pathways, and by gastrointestinal neuropeptides acting either as neurotransmitters or as circulating hormones.

The "extrinsic" autonomic nervous system appears to integrate functions in anatomically discrete areas of the gastrointestinal tract. For example, the internal anal sphincter is under autonomic control, particularly tonic sympathetic excitation while the striated muscle sphincters, both at the anus (external anal sphincter) and at the level of the esophagus, are also subject to extrinsic autonomic nervous system influences.

## **Disorders of bowel motility and peripheral neuropathy**

Peripheral autonomic neuropathy may affect motility at any level of the gastrointestinal tract. Diabetic neuropathy is the most common of the peripheral dysautonomias; and, given its various gastrointestinal manifestations, it is not surprising that a great experience has accrued in its management, and that therapies in diabetics have become paradigms for trials in other diseases. Feldman reported that 76% of a random sampling of diabetic outpatients reported one or more gastrointestinal symptoms, of which constipation was the most common.<sup>4</sup> Among asymptomatic patients, radiologic evidence for gastric retention was observed in 22% in one prospective study.<sup>5</sup>

Gastric emptying is delayed in 30–50% of both type I and type II diabetics.<sup>6, 7</sup> The term gastroparesis diabeticorum was first introduced by Kassander to describe the altered gastrointestinal motility in diabetics.<sup>5</sup> Food residue is retained in the stomach due to absent or decreased gastric peristalsis compounded by lower intestinal dysmotility.<sup>8</sup> Diabetic gastroparesis may manifest as nausea, post-prandial vomiting, bloating, abdominal distension and pain, belching, loss of appetite, and early satiety. Many patients, however, are asymptomatic despite impaired gastric motility.<sup>7</sup> A gastric splash may be elicited on clinical examination. Gastroparesis is also associated with the development of bezoars<sup>9</sup> and bacterial overgrowth of stomach and small intestine, esophagitis, gastric ulcers, and gastritis.<sup>10</sup> Gastroparesis may impair the establishment of adequate glycemic control by mismatching plasma glucose and insulin levels. The absorption of orally administered drugs may also be affected.<sup>5, 11</sup>

Impaired gastric emptying is frequently associated with cardiovagal neuropathy and small-fiber dysfunction.<sup>12</sup> Morphological changes in the vagus nerve are reported in some,<sup>13, 14</sup> but not all studies.<sup>15</sup> Recent studies have implicated hyperglycemia as a cause of impaired gastric and small intestinal motility during fasting and after food intake. Hyperglycemia, delays gastric emptying in healthy and diabetic subjects.<sup>16–19</sup>

Diarrhea and other lower gastrointestinal tract symptoms may also occur. Diabetic diarrhea manifests as a profuse, watery, typically nocturnal diarrhea, which can last for hours or days and frequently alternates with constipation.<sup>20–22</sup> Abdominal discomfort is commonly associated. The pathogenesis of diabetic diarrhea includes reduced gastrointestinal motility<sup>23</sup> abnormalities in gut transit time<sup>24, 25</sup> reduced alpha-2 adrenergic receptor mediated fluid absorption<sup>26</sup> bacterial overgrowth<sup>27</sup> pancreatic insufficiency, co-existent celiac disease<sup>28</sup> and abnormalities in bile salt metabolism.<sup>29</sup> Fecal incontinence, due to anal sphincter incompetence or reduced rectal sensation is another manifestation of diabetic intestinal neuropathy.<sup>26, 30</sup> Incontinence is often exacerbated by diarrhea.

Constipation is the most frequently reported gastrointestinal autonomic symptom and is found in up to 60% of diabetics.<sup>4</sup> The pathophysiology of diabetic constipation is poorly understood but may reflect intestinal denervation and loss of the post-prandial gastrocolic reflex.<sup>31</sup>

### **Pharmacotherapy of bowel hypomotility**

An increase in dietary fibre (up to 25 g/day), with water (10 ounces four times per day) and exercise is the first line of therapy for most patients. The use of psyllium (up to 30 g/day) or methylcellulose (up to 6 g/day) with a concomitant increase in fluid intake will further increase stool bulk. Appropriate caution must be exercised with these agents for example high fiber may be disadvantageous in diabetic gastroparesis, because of distension and cramping pain that can be associated with its use or because of the potential of bezoar formation.

Stool softeners (e.g. docusate sodium 100–500 mg/day) or lubricants (e.g. mineral oil) together with an osmotic laxative (e.g. lactulose 15–60 ml/day) may be used if the above measures are ineffective. Glycerin suppositories or sodium phosphate enemas stimulate evacuation by promoting fluid retention in the rectum. (See Table 1)

The contact cathartics such as the diphenylmethane derivatives (phenolphthalein and bisacodyl), the anthraquinones (senna and cascara) should be used sparingly – although the use of these agents cannot be avoided in patients with constipation due to autonomic failure. Extensive use of these agents may damage the myenteric plexus producing cathartic bowel.

One or more of three general mechanisms of action have been described for the laxatives a group. First, a given drug may increase intestinal bulk because of its hydrophilic or osmotic properties; second, it may decrease the net absorption of electrolytes and water by the intestinal mucosa by damaging the enterocytes or weakening intercellular junctions; third, it may have its effects by enhancing intestinal motility and thus reducing fluid and electrolyte absorption.

The individual agents may be classified by their response latency and clinical effects. Softening of feces over one to three days occurs with the bulk forming preparations and docusates; a semifluid stool may be induced over six to eight hours by diphenylmethane and anthraquinone laxatives; and a watery evacuation in one to three hours occurs with the saline cathartics, such as magnesium citrate and milk of magnesia.<sup>32–38</sup>

The benzamide, metoclopramide (5–20 mg orally, 30 minutes before meals and at bedtime), accelerates gastric emptying and has a central antiemetic action. Metoclopramide action is inhibited by atropine and is not affected by vagotomy, suggesting that its mode of action, which is primarily on antral motor activity, involves release of acetylcholine from intramural cholinergic neurons or direct stimulation of antral muscle by intact postganglionic cholinergic neurons.<sup>39–43</sup> A dopaminergic mechanism has been inferred from studies demonstrating that levodopa-related inhibition of gastric emptying is reversed by metoclopramide.<sup>41,44</sup>

In diabetics with concurrent gastroparesis and constipation, metoclopramide was associated with improvement in both symptoms.<sup>42</sup> Battle, et al.<sup>45</sup> have observed that metoclopramide has a dose-related stimulatory effect on colonic myoelectrical and

motor activity in normal and diabetic patients, although other authors have noted no major effect on colonic motility.<sup>39, 46</sup>

Tolerance to metoclopramide therapy has been described.<sup>44</sup> Patients maintained in the long term on metoclopramide theoretically may be at risk for the development of tardive dyskinesia and other dopamine–antagonist–related side effects. Concurrent renal failure may increase risk for acute toxicity.<sup>47</sup> The cholinomimetic bethanecol has been used in combination with metoclopramide and in cases of metoclopramide resistance.<sup>4, 48</sup>

Erythromycin and related macrolide compounds exhibit strong in vitro affinity for motilin receptors and have agonist properties that mimic the prokinetic action of exogenous motilin, a gastrointestinal polypeptide.<sup>49, 50</sup> Infusions of motilin in diabetics with gastroparesis result in accelerated gastric emptying, but therapeutic use of the agent is limited by its need for intravenous administration and by its short half–life.<sup>51</sup> In human studies<sup>52</sup> single intravenous doses of erythromycin shortened post–prandial, gastric–emptying time for both liquids and solids to normal levels in diabetics with gastroparesis. After four weeks of treatment with oral erythromycin (250 mg three times per day), gastric emptying continued to exhibit improvement, though not to the degree noted after a single parenteral administration.

Cisapride is a cholinomimetic agent which increases motility in esophagus, stomach, and bowel by enhancing release of acetylcholine from neurons of the myenteric plexus. In contrast to metoclopramide, cisapride lacks dopamine blocking activity. It has been tried with some success in several clinical conditions including idiopathic gastric stasis<sup>53</sup> intestinal pseudo–obstruction<sup>54–56</sup> chronic constipation associated with laxative use<sup>57</sup> in diabetics with constipation<sup>58</sup> and in diabetic gastroparesis.<sup>59</sup> In a comparison of intravenously administered doses of cisapride and metoclopramide, cisapride accelerated post–prandial emptying to a slightly greater degree.<sup>59</sup> Unfortunately, due to an increased incidence of ventricular arrhythmias, this agent is no longer available for general use.<sup>60</sup>

The somatostatin analogue, octreotide, may stimulate intestinal motor complexes and this agent has been used to treat sclerodermatous pseudo–obstruction.<sup>61</sup> Somatostatin, however, is known to impair motor responses to feeding<sup>62</sup> and treatment with octreotide in other conditions has been associated with hypomotility and bacterial overgrowth.<sup>63</sup> Clinical experience to date with octreotide suggests that its various side effects may potentially limit therapeutic use. Nausea and abdominal cramping pain occur with administration of the medication. Fat malabsorption and cholelithiasis have been described with chronic use.<sup>63</sup>

Domperidone, a peripheral antidopaminergic agent, may provide symptomatic relief in patients with gastroparesis<sup>64–66</sup> although it is not clear that the medication improves objective measures of gastric emptying.<sup>67, 68</sup> Koch<sup>69</sup> observed that gastric "dysrhythmias," as determined by electrogastrogram, normalized in six patients treated with domperidone over six months, although only minimal improvement was noted in gastric emptying over the same period.

The synthetic prostaglandin E1 analog, misoprostol, enhances intestinal motility and affects intestinal fluid and electrolyte secretion. Preliminary studies suggest that this agent may be of benefit in refractory constipation.<sup>70</sup>

Rare patients who do not respond to medical therapy may require colonic surgery. Such patients should have documented slow colonic transit time and intact rectal sphincter function.

### **Pharmacotherapy of bowel hypermotility**

Diabetic diarrhea best exemplifies the diagnostic subtleties that are involved in the evaluation and treatment of neurogenic diarrheal conditions. Prior to the diagnosis of neurogenic diarrhea, other causes must systematically be excluded. Diarrhea as a result of bacterial overgrowth has been a subject of some controversy. One theory regarding the pathogenesis of diabetic diarrhea holds that gastric and small bowel hypomotility may predispose to the proliferation of bacteria, which deconjugate bile salts and thus inhibit micelle formation. Steatorrhea and diarrhea result indirectly as a consequence of neurogenic dysmotility.<sup>4</sup>

A trial of antibiotic therapy (tetracyclines, metronidazole, or cephalosporin) is therefore conducted in most patients with unexplained chronic diarrhea, especially when steatorrhea is present. Bile acid malabsorption may be treated with cholestyramine. Treatment with prokinetic agents (see above) may also improve diarrhea. Should these measures fail, opioid agonists should be used. These agents decrease peristalsis and increase rectal sphincter tone. The synthetic opioids (diphenoxylate and loperamide) are preferable to alcohol solutions of opium. In the individual case, empiric management with antibiotics, opiates, prokinetic agents, psyllium, anticholinergics, and others is often required.<sup>32</sup>

An alternative theory implicates a dysregulation of alpha-2 adrenoreceptor mediated intestinal ion transport in diabetic diarrhea. Clonidine, a specific alpha-2-adrenergic receptor agonist, may be used to treat diarrhea in doses of up to 1.2 mg per day.<sup>26</sup>

The somatostatin analogue, octreotide, has been studied as a potential antidiarrheal agent in small numbers of patients with various conditions.<sup>71</sup> As noted above, it may have a prokinetic action, but somatostatin has also been shown to inhibit stimulated water secretion in gut.<sup>4</sup>

### **Fecal incontinence**

Studies of idiopathic fecal incontinence have found delayed conduction in pudendal nerves supplying the external sphincter and denervation changes in pelvic muscles. Impaired rectal sensation may be responsible for incontinence in such cases, since detecting the presence of stool in the anal canal is essential to normal continence. Other authors have argued that the neuropathy is secondary to prolonged straining at stool and traction on pudendal nerves.

Medical treatments generally attempt to rectify conditions that are either associated with or predispose to fecal incontinence. Use of high-fiber diets and bulking agents may be beneficial, since a semi-formed stool is more easily controlled than liquid feces. Fecal disimpaction is indicated in some cases. Daily tap water enemas aid in clearing residua in the rectum between evacuations and may allow for functional continence. Antidiarrheal agents may benefit patients for whom incontinence and diarrhea coexist. Biofeedback based on the patient's perception of a distensible balloon in the rectum and training to increase external sphincter pressure has met with success in some reports, although the response to biofeedback is likely dependent on the state of afferent pathways from the rectum.

A majority of patients who undergo surgical sphincter repair may regain continence for solid stool, although the presence of pelvic floor neuropathy is associated with poorer outcome. Other surgical interventions, including colostomy, artificial anal sphincters, and creation of a reconstructed with muscle grafts may be necessary in treatment-resistant cases.<sup>30, 72</sup>

**TABLE 1**

**Pharmacotherapy of bowel hypomotility**

**Bulk Agents**

Bran  
Psyllium  
Methylcellulose

**Laxatives and Cathartics:**

Osmotic Laxatives and Cathartics  
Lactulose  
Sorbitol  
Magnesium Salts  
Sodium Phosphate  
Polyethylene glycol–saline solutions  
Glycerin suppositories  
Contact Cathartics  
Diphenylmethane derivatives  
Phenolphthalein  
Bisacodyl tablets or suppositories  
Anthraquinone derivatives  
Senna  
Cascara  
Ricinoleic acid (Castor oil)

**Stool Softeners and Lubricants:**

Mineral Oil  
Docusates

**Prokinetic Agents**

Metoclopramide  
Cisapride  
Domperidone  
Erythromycin  
Cholinomimetics  
Bethanechol  
Acetyl–cholinesterase inhibitors  
Opioid antagonists  
Misoprostol

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