Gastrointestinal Motility Disorders: An Update

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Key Words

Motility disorders · Achalasia · Dyspepsia ·
Gastroparesis · Constipation · Irritable bowel
syndrome · Chronic intestinal pseudo-obstruction

Abstract

Gastrointestinal motility disorders encompass a wide array of signs and symptoms that can occur anywhere throughout the luminal gastrointestinal tract. Motility disorders are often chronic in nature and dramatically affect patients' quality of life. These prevalent disorders cause a tremendous impact both to the individual patient and to society as a whole. Significant progress has been made over the last 5 years in understanding the etiology and pathophysiology of gastrointestinal motility disorders. This clinical update will focus on seven of the most common gastrointestinal motility disorders (achalasia, non-achalasia esophageal motility disorders, dyspepsia, gastroparesis, chronic intestinal pseudo-obstruction, irritable bowel syndrome, and chronic constipation) with an emphasis on current treatment options and new therapeutic modalities.

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Introduction

Gastrointestinal (GI) motility disorders are highly prevalent, produce an extensive array of symptoms, and occur anywhere throughout the lumen of the GI tract.

Patients with motility disorders have a reduced quality of life [1–4]. As well, these disorders impose a significant economic burden to both the individual patient and to society as a whole [5–7]. In this section of the journal, we will provide a summary of advances in the field of GI motility disorders over the last 5 years, with an emphasis on advances in treatment.

Methods

Ovid MEDLINE and PubMed databases were used to search the published literature. In the interest of providing an update, rather than providing a comprehensive review, our search was limited to the last 6 years. For Ovid MEDLINE (2000 to September 2005, English language only) 14 primary search terms (achalasia, esophagus, esophageal motility disorders, esophageal dysmotility, stomach, dyspepsia, gastroparesis, small intestine, chronic intestinal pseudoobstruction, colon, irritable bowel syndrome, constipation, motility disorders, diarrhea) were individually combined with a larger number of secondary search terms, including but not limited to (in alphabetical order): ABT229, alosetron, alternative medicine, alvimopan, antibiotics, biofeedback, botulinum toxin, buspirone, cilansetron, cisapride, complementary medicine, domperidone, erythromycin, gastric pacing, gastric stimulation, GM-611, itopride, levosulpiride, lubiprostone, medications, metoclopramide, mosapride, motilin, neostigmine, neurokinin, octreotide, pelvic floor, prucalopride, renzapride, sildenafil, suma-

triptan, surgery, tachykinins, technology, tegaserod, therapies, treatment, tricyclic antidepressants. A similar search process was followed for PubMed (2000 to September 2005). All identified articles were then manually searched for other relevant studies. Abstracts were generally not included, except in limited circumstances.

Achalasia

Achalasia is the classic motility disorder of the esophagus. The annual incidence of achalasia is estimated at 1/100,000 persons [8]. Clinically, achalasia is characterized by dysphagia, chest pain, and bland regurgitation. Manometrically, achalasia is defined by incomplete relaxation of the lower esophageal sphincter (LES) in combination with aperistalsis of the body of the esophagus. Pathophysiologically, achalasia develops as a result of denervation of the intrinsic nervous system of the esophagus, with loss of nitric-oxide containing neurons [9].

Current treatment options for achalasia include pneumatic dilation, surgery, or botulinum toxin injection (BTX). Although all three treatments can improve symptoms, none of these treatments restore esophageal peristalsis or normalize LES function. In the last 5 years, new data has emerged regarding methods to assess esophageal emptying, the efficacy and long-term outcome of standard treatments, and the use of new treatments.

The timed barium swallow (or timed barium esophagram) provides objective evidence of esophageal emptying [10]. Patients drink as much barium sulfate as they can over a 30- to 45-second period. Upright radiographs are taken 1, 2, and 5 min after the last swallow of barium. The distance from the gastroesophageal junction to the top of the barium column is then measured, along with the width of the esophagus at the widest point. This study is repeated after treatment and compared to baseline. This test provides an objective measure of therapeutic response, in contrast to a subjective response based on symptom scores.

A recent study evaluated the long-term results of pneumatic dilation in 249 patients with achalasia [11]. 125 patients completed the questionnaire (58%), with an average follow-up of 12 years. A median of 4 dilations was required, and the long-term success rate was estimated at only 40–50%. These interesting results are in contrast to earlier studies (see below), and may indicate the need for earlier surgical referral. For example, Katz et al. [12] reported that after a mean follow-up of 6.5 years, 85% of their patients noted an improvement in symptoms after

pneumatic dilation. A recent analysis of 232 achalasia patients treated at the Cleveland Clinic found that 86% of 111 patients had symptomatic improvement after pneumatic dilation [13]. Heller myotomy led to symptomatic improvement in 89% of 72 patients, while BTX injection of the LES improved symptoms in only 57% of patients, with benefits lasting 6 months on average.

Sildenafil, a phosphodiesterase-5 inhibitor, is a potent smooth muscle relaxant. In normal volunteers, sildenafil reduces LES resting pressure and the amplitude of contractions in the distal esophagus [14, 15]. Similar findings were reported in two studies of patients with achalasia using 50 mg of sildenafil [15, 16].

Non-Achalasia Esophageal Motility Disorders

The primary esophageal motility disorders include diffuse esophageal spasm (DES), nutcracker esophagus (NE), isolated hypertensive LES, idiopathic hypotensive LES, and ineffective esophageal motility (IEM) [17]. As a group, these disorders are associated with a number of non-specific symptoms, which include chest pain, dysphagia, and heartburn symptoms. Pathophysiologically, symptoms may develop due to abnormalities in either excitatory or inhibitory innervation to either the LES or the esophageal body. As an example, unopposed excitatory innervation to the body of the esophagus is associated with high-amplitude contractions that characterize NE and DES [18]. Although the exact incidence and prevalence of these disorders is not known, several studies have estimated that 11.4–33% of patients referred for esophageal manometry have one of these disorders [19, 20].

The treatment of non-achalasia motility disorders includes medical therapy, endoscopic therapy, and surgery. Previous studies have shown that neither metoclopramide nor domperidone effectively stimulate esophageal body motility, although both agents increase LES resting pressure in healthy volunteers [21, 22]. Although several studies initially reported that cisapride increased both LES pressure and the amplitude of contractions in the distal esophagus [23–25], a number of other studies failed to confirm any direct prokinetic effects of cisapride on the esophagus [20, 26]. No studies evaluating the effects of metoclopramide, domperidone, or cisapride on esophageal motor function have been published in the last 5 years.

Erythromycin acts as a motilin agonist and has well-documented gastrokinetic effects (see below). The effects of intravenous erythromycin (200 mg) on esophageal mo-

tility were assessed in 18 healthy volunteers in a double-blinded, randomized study [27]. Compared to placebo, erythromycin significantly increased the amplitude of contractions in the distal esophagus, increased the duration of esophageal peristalsis, and increased the resting pressure of the LES. These effects were felt to be due to stimulation of cholinergic pathways, since they could be blocked by pretreatment with atropine. Similar findings were demonstrated in a study of 15 patients with gastroesophageal reflux disease (GERD) [28]. In a study of 45 patients with non-insulin-dependent diabetes mellitus, oral erythromycin (250 mg p.o., q.a.c.) shortened mean transit time in the esophagus and accelerated gastric emptying [29]. In a similar manner, intravenous clarithromycin was shown to increase LES tone, and both the amplitude and duration of esophageal contractions, in a double-blind, placebo-controlled study of 15 normal volunteers [30]. In a randomized, double-blind, placebo-controlled trial, ABT-229, a motilin agonist, did not affect LES tone, esophageal motility, or the incidence of transient LES relaxations (TLESRs) in 24 GERD patients [31].

Baclofen, a selective γ -aminobutyric acid agonist, reduced the number of TLESRs in patients with GERD [32]. A double-blind, placebo-controlled, cross-over study of 37 patients with GERD confirmed that baclofen reduces the incidence of reflux episodes by inhibiting TLESRs [31]. Baclofen did not affect LES pressure or esophageal clearance.

Previous studies in healthy volunteers revealed that 6 mg of subcutaneous sumatriptan, a 5-HT₁ agonist, increased LES tone and the amplitude of contractions in the distal esophagus [33]. Sumatriptan also affects the frequency of post-prandial TLESRs [34]. A double-blind, randomized, cross-over trial of 10 patients with IEM found that 6 mg of subcutaneous sumatriptan increased the number of swallows and the number of primary esophageal motor waves. In contrast to healthy volunteers, however, sumatriptan did not influence LES tone or the amplitude of contractions [35].

Tegaserod, a specific 5-HT₄ receptor partial agonist, initiates gut peristalsis, stimulates chloride secretion in the small intestine, and alters visceral sensation [36]. A prospective, double-blinded trial of 19 patients compared four different doses of tegaserod to placebo over separate 2-week trial periods [37]. Low-dose tegaserod (1 mg/day) reduced post-prandial esophageal acid exposure and decreased the number of post-prandial reflux episodes. No significant changes were identified in LES resting pressure or in the amplitude of distal esophageal contractions.

Mosapride, a benzisoxazole derivative, is a selective 5-HT₄ agonist; its main metabolite is a 5-HT₃ antagonist [38]. A prospective, randomized, blinded, cross-over study of 41 patients with GERD compared mosapride to cisapride [39]. Mosapride (30 mg p.o. t.i.d.) improved several parameters of acid reflux (duration of longest episode of reflux, reflux fraction time), and slightly increased the amplitude of contractions in the lower esophageal body. LES function was not reported in this study. Mosapride increased the rate of esophageal bolus transit, measured by multichannel intraluminal impedance manometry, in a study of 20 healthy volunteers using a double-blinded, placebo-controlled, cross-over design [40]. No changes were noted, however, in LES pressure or amplitude, duration, and velocity of esophageal body contractions.

Two separate studies found that sildenafil (50 mg) reduces elevated LES tone and the amplitude of contractions in the distal esophageal body in patients with isolated hypertensive LES [41, 42]. A recent study of patients with hypercontractile motility disorders demonstrated that sildenafil reduced the amplitude of contractions by more than 70% in both healthy volunteers and patients, although improvement in symptoms occurred in only 36% of subjects, and 50% of these patients had significant side effects [43].

Itopride, a benzamide derivative shown to stimulate gastric motility [44], has primarily been evaluated in dyspepsia and gastroparesis (see below). The utility of itopride was assessed in a study of 26 patients with mild acid reflux disease [45]. Patients with mild esophagitis (Savary-Miller Grade I or II) were randomized to either 50 or 100 mg of itopride t.i.d. for 4 weeks. Compared to placebo, patients treated with either dose of itopride noted a significant improvement in reflux symptoms compared to baseline. Patients treated with 300 mg of itopride daily also had a statistically significant improvement in pH measurements compared to baseline. Esophageal motility was not assessed in this study, and thus the mechanism of reduced acid exposure remains unclear.

In an interesting use of theophylline, Rao et al. [46] demonstrated in an open-label trial that this adenosine antagonist increased the sensory threshold for distention induced chest pain. No changes in motor function were noted, and a placebo-controlled, blinded study has yet to be performed.

The beneficial effects of BTX in patients with achalasia led to its use in other motility disorders of the esophagus. BTX of the LES relieved symptoms, and normalized manometric abnormalities, in a patient with hyper-

tensive LES [47]. Nine patients with DES were treated with multiple intraesophageal injections of BTX (100 U total) [48]. Eight of 9 patients had a significant reduction in total symptom score (chest pain, dysphagia, regurgitation) at 4 weeks, and these effects persisted for 6 months. Twenty-nine patients with spastic disorders of the esophagus (DES, hypertensive LES, IEM, NE) were enrolled in an open-label trial to evaluate the efficacy of BTX injection of the LES for the treatment of chest pain [49]. Twenty-one patients (72%) responded with at least a 50% reduction in their chest pain score. The type of underlying motility disorder did not predict response to therapy, although women generally responded better than men.

The role of surgery for patients with esophageal motility disorders remains controversial. In a retrospective review of a prospectively collected database, Patti et al. [19] reported on the results of myotomy in 397 patients with esophageal motility disorders. Of 19 patients with DES, 80–86% noted an improvement in dysphagia, while 65–80% noted an improvement in complaints of chest pain. Of 12 patients with NE, 60–83% reported an improvement in dysphagia, while 40–50% reported a good or excellent response for their symptoms of chest pain. A smaller study of 16 patients with spastic disorders of the esophagus found that resting pressure and relaxation of the LES improved after long myotomy, although peristalsis did not [50]. In general, patients with a diverticulum and localized manometric abnormalities did better than patients with a diffuse pattern of disordered motility.

Antireflux surgery is now one of the most commonly performed elective surgeries. During pre-operative evaluation most patients undergo esophageal manometry, and many are identified as having a motility disorder of the esophagus. Of 239 patients referred for antireflux surgery, 57 (24%) were identified as having a non-specific motility disorder of the esophagus [51]. In this study, all named esophageal motility disorders (achalasia, DES, NE, hypertensive LES) were excluded from further analysis. The majority of patients underwent laparoscopic Nissen fundoplication; median follow-up was 30 months. Overall, patients with non-specific motility disorders were found to do as well post-operatively as patients with normal pre-operative esophageal manometry. In a similar light, Heider et al. [52] reported that 48 of 262 patients referred for antireflux surgery had IEM. Nineteen of these patients agreed to perform follow-up manometry after surgery, and only 1 had a worsening of esophageal motility. These data, combined with previously published studies, support the concept that complete fundoplication

is unlikely to produce significant dysphagia or chest pain in patients with minor or mild disorders of esophageal motility.

Gastric banding is now frequently performed for morbid obesity. A recent study found that gastric banding reduced the amplitude of contractions in the distal esophagus, although LES tone was not affected [53]. This raises the question of whether morbidly obese patients identified pre-operatively with IEM and acid reflux should be referred for an alternative procedure, such as a Roux-en-Y gastric bypass.

Finally, electrical acupoint stimulation was recently evaluated to determine its effect on TLESRs in a study of 14 healthy volunteers [54]. Electric acupoint stimulation inhibited the frequency of TLESRs compared to sham stimulation, although it did not change LES pressure, esophageal motility, or the duration of TLESRs.

Dyspepsia

Dyspepsia is defined as discomfort or pain centered in the upper abdomen, often associated with negative symptoms of fullness, bloating or early satiety [55, 56]. Symptoms tend to wax and wane, and relapse is common. Dyspepsia is categorized into two large groups: organic and functional dyspepsia. Once investigated, the majority of patients are diagnosed with functional dyspepsia [57]. Functional dyspepsia (FD) is defined as at least a 3-month history of dyspeptic symptoms for which no definite structural or biochemical explanation can be found [58]. Patients with classic symptoms of heartburn are excluded from the formal definition of dyspepsia.

The optimal initial evaluation and management of dyspepsia continues to be debated [59–61]. Options include: prompt endoscopy; empiric therapy with an antisecretory or a prokinetic agent, or a 'test-and-treat' strategy for *Helicobacter pylori* [62]. Up-front endoscopy reduces patient anxiety, with an improvement in patient sense of well-being within the first week of endoscopy [63]. In patients with uninvestigated dyspepsia, endoscopy led to improved patient satisfaction regardless of the findings [64]. The cost-effectiveness of prompt endoscopy, especially in the younger patient, has been questioned [65].

Empiric treatment with an antisecretory agent is commonly employed since many dyspeptic patients have increased acid sensitivity [66]. Concerns with empiric therapy focus on the likelihood of missing an organic lesion. However, recent studies suggest improved patient satis-

faction and outcome with prompt endoscopy and test-and-treat strategy, as discussed below.

The role of *H. pylori* in FD continues to evolve. Several trials have demonstrated that test-and-treat strategies have outcomes similar to prompt endoscopy, and are more effective than a short course of PPI alone [67–69]. At present, no clear association exists between *H. pylori* and symptoms of FD, and the benefit of *H. pylori* therapy on symptoms continues to be debated [70–73]. A recent meta-analysis of 17 randomized controlled trials found that there was an 8% relative risk reduction in the eradication group and the number needed to treat to cure 1 case of dyspepsia was 18 [74]. Thus, eradication of *H. pylori* appears to have a small, but statistically significant effect in FD.

Lifestyle modifications are often prescribed for the treatment of dyspepsia, although no studies have been published on this subject in the last 5 years. As such, antisecretory agents such as H₂RAs and PPIs are a mainstay of therapy for FD. The efficacy of these treatments remains unclear, however, due to flawed study designs with failure to exclude patients with peptic ulcer disease and predominant GERD. A meta-analysis on the use of H₂RAs found that these agents had little or no benefit when compared to placebo [75], although famotidine has demonstrated some promise in the treatment of FD [76–78]. A randomized, placebo-controlled trial comparing omeprazole, ranitidine, cisapride and placebo demonstrated superior symptom relief with omeprazole [79].

Prokinetic therapy is often employed in the treatment of FD, since nearly 40% of patients demonstrate a mild to moderate delay in gastric emptying [80]. Although metoclopramide is commonly used, its efficacy has been questioned in a recent meta-analysis [81]. On the other hand, another meta-analysis of 8 studies found domperidone to be more effective than placebo at improving global symptoms, with an odds ratio of 7.0 [82].

Tegaserod, a partial selective 5-HT₄ agonist, has been shown to accelerate gastric emptying [83]. Preliminary studies demonstrate improved upper GI symptoms in female patients with FD [84]. Mosapride, another 5-HT₄ receptor agonist, has also improved some symptoms of FD in an early clinical trial [85].

Itopride hydrochloride is a benzamide derivative and acts as a dopamine antagonist. In an open-label, non-comparative study, itopride (50 mg t.i.d) was well tolerated and relieved symptoms of dyspepsia [86]. Another study found itopride to be comparable to domperidone in providing symptom relief [87].

Levosulpiride, another dopamine antagonist, decreases the perception of gastric distention [88]. In FD patients, levosulpiride was found to be as effective as cisapride [89] at providing symptom relief.

The chronic abdominal pain of FD can be difficult to treat. Tricyclic antidepressants have been used with modest success [90, 91]. Fluoxetine did not lead to any improvement in FD patients, as evaluated by electrogastrography [92]. Alosetron, a 5-HT₃ receptor antagonist has also shown potential benefit in decreasing upper abdominal pain [93].

Fundic relaxation may be impaired in patients with FD, leading to symptoms of post-prandial pain, discomfort, and nausea. 5-HT₁ agonists such as sumatriptan and buspirone should theoretically increase gastric accommodation and improve symptoms in a subset of FD patients. Large controlled trials have not yet been performed, however. Clonidine, an α -adrenergic receptor agonist, may also decrease pain perception with gastric distention [94].

A number of non-conventional therapies have been used in the treatment of dyspepsia, including ginger, peppermint oil, caraway oil, red pepper (capsaicin) and Iberogast (combination of 9 different herbs). One small randomized study showed some benefit of capsaicin compared to placebo [95]. A meta-analysis found Iberogast to be more effective at relieving symptoms than placebo [96]. Artichoke leaf extract may also improve some symptoms of dyspepsia [97, 98].

Psychotherapy, behavioral therapy and hypnotherapy all may have a role in the treatment of dyspepsia, although their efficacy has not been clearly established [99–103]. It appears that symptom pattern and psychological characteristics are independent predictors of treatment response, with patients having high scores for reflux-like symptoms and high scores for somatization demonstrating greater response to acid suppressants [104].

Gastroparesis

Gastroparesis is defined as the impaired transit of intraluminal contents from the stomach to the duodenum in the absence of mechanical obstruction. Diabetes accounts for 25% of cases, while idiopathic gastroparesis accounts for nearly 50% [105].

The goals of treatment include relief of symptoms, improved nutrition, and the prevention of complications, such as bezoar formation. Therapeutic intervention is often multidimensional, including diet, lifestyle changes,

and medications. If a patient is unable to maintain adequate nutritional status, total parenteral nutrition or a jejunostomy feeding tube may be required [106].

Small, frequent meals are an essential component of therapy. Meals should be low in fiber, to prevent bezoar formation, and low in fat, as fat delays gastric emptying. Liquids should be emphasized over solid foods. A recent study found that walking after eating increases the normal 3-cpm activity in the stomach and thus may improve gastric emptying in some patients [107].

A large number of antiemetic agents are now available to treat nausea in gastroparetic patients [108]. The most commonly used agents include phenothiazines and 5-HT₃ receptor antagonists. Antihistamines exhibit central antiemetic effects and, though well established for use of motion sickness, the efficacy in gastroparesis is not well described [109]. Other agents that have been used include benzodiazepines and cannabinoids. Given the refractory nature of nausea, patients frequently require multiple agents, usually one each from different chemical classes.

Prokinetic agents used in the treatment of gastroparesis include metoclopramide, erythromycin, domperidone and tegaserod. Metoclopramide has both prokinetic and antiemetic properties [110]. No studies evaluating the utility of metoclopramide in gastroparetic patients have been published in the last 5 years. Erythromycin is a potent gastrokinetic [111–115], although its efficacy in relieving symptoms has not been clearly demonstrated [116]. GM-611, a motilin agonist, is under development. Preliminary animal studies have shown that this agent accelerates gastric emptying; its effects in the human GI tract have not been characterized.

Domperidone, another dopamine antagonist, improves symptoms and quality of life in patients with diabetic gastroparesis, although this medication is not readily obtainable in the USA [117–119].

Tegaserod, a selective 5-HT₄, increases gastric emptying in diabetic mice, increases gastric emptying in patients with dyspepsia and delayed gastric emptying, and increases orocecal transit time in women with constipation [36, 120, 121]. Tegaserod has also been shown to accelerate gastric emptying, small intestinal transit and colonic transit in healthy male subjects [122]. In a small case series, tegaserod was successfully used as a prokinetic agent in critically ill patients with impaired gastric motility [123]. Tegaserod is not yet approved by the FDA for use in gastroparetic patients.

Cisapride, a mixed 5-HT₄ agonist/5-HT₃ antagonist, is available only under limited use. No studies have been

published in the last 5 years on the efficacy of cisapride in gastroparesis.

Preliminary studies have shown that mosapride has prokinetic effects on many areas of the GI tract [124, 125]. In one study, mosapride improved gastric motility in diabetic gastropathy and also improved glycemic control with a corresponding decrease in HgA1C [126, 127].

Other new prokinetic agents under investigation include the dopamine receptor antagonist levosulpiride and the cholecystokinin receptor antagonist loxiglumide [128, 129]. In animal studies, itopride increases gastric motility through its antidopaminergic and antiacetylcholinesterase actions [130].

In patients with refractory gastroparesis, psychotropic medications such as tricyclic antidepressants may provide relief of nausea, vomiting and associated abdominal pain [131, 132]. Alternative therapies include ginger [133], acupuncture with stimulation of the PC6 point on the wrist [134, 135], or the ST36 (Zusanli) point below the patella [136].

Endoscopic and surgical interventions are now available for gastroparetic patients with refractory symptoms. Endoscopically, BTX injection into the pylorus inhibits the release of acetylcholine from synaptic vesicles at the synaptic junction, thereby inducing a state of transient muscle paralysis. Efficacy of BTX has been demonstrated in diabetic gastroparesis as well as idiopathic gastroparesis. Long-term outcomes have not been determined to date [137, 138].

Surgical options include gastric resection and gastric electrical stimulation. In general, gastric resection appears to be of limited benefit and should only be used as a last resort for patients with profound symptoms and gastric stasis [139, 140]. Gastric electrical stimulation (GES) uses an implantable neurostimulator that delivers a high-frequency, low-energy signal with short pulses. An initial study showed a decrease in nausea and vomiting in 20 of 26 patients at 3 and 6 months after implantation [141]. A second study of the implantable neurostimulator involved a double-blind sham stimulation-controlled trial for 2 months followed by activation of all devices for 1 year [142]. The study consisted of 33 patients with either diabetic or idiopathic gastroparesis. Of 33 patients, 21 preferred having the stimulator in the 'on' mode. In phase 2 of the trial, all devices were turned on. Follow-up at the end of 1 year showed a relative decrease in vomiting frequency from 25 to 6 times per week with associated improvements in quality of life, primarily in the diabetic gastroparesis subgroup. A subset of 12 patients in

the Gastric Electromechanical Stimulation (GEMS) Study Group was extensively evaluated with regards to nutritional parameters before and after stimulator implantation. GES improved symptoms in addition to body weight, body mass index and serum albumin at 3 and 6 months [143]. A small study of diabetic patients with drug-refractory gastroparesis showed symptom improvement after GES implantation and also improved glycemic control at 6 and 12 months [144]. Despite significant cost of the device and its implantation, in the long term, GES may be more cost effective than intensive medical therapy [145].

Chronic Intestinal Pseudo-Obstruction

Chronic intestinal pseudo-obstruction (CIP) is characterized by signs and symptoms (present for at least 6 months) which suggest mechanical obstruction of the intestinal tract. While the clinical symptoms of CIP are usually indistinguishable from mechanical obstruction, the etiology, pathology and treatment are quite different. First identified in 1958, it is estimated that approximately 100 infants are born each year in the USA with congenital pseudo-obstruction. CIP may be categorized as primary (neuropathic, myopathic, or mesenchymopathic), secondary (collagen vascular disease, endocrine, neoplastic, neurologic), or idiopathic in nature [146, 147]. The most common symptoms of CIP are abdominal pain, vomiting, bloating, constipation, and diarrhea. Additional symptoms may include dysphagia, reflux, early satiety, and genitourinary symptoms, such as difficulty voiding. Treatment options for CIP are limited, and focus on correcting nutritional deficiencies, minimizing symptoms, and preventing weight loss and malnutrition. Previous treatments have included cisapride, domperidone, metoclopramide, and octreotide – although none have been uniformly successful [146].

A recent study evaluated the effects of oral erythromycin (500 mg t.i.d. or q.i.d.) in 15 consecutive patients with CIP who had failed standard medical therapy [148]. Six patients (40%) responded with a decrease in nausea, vomiting, and abdominal pain. Men appeared to respond better than women, and responders were less likely than non-responders to be taking long-term narcotics.

Neostigmine, an acetylcholinesterase inhibitor, is used to treat acute colonic pseudo-obstruction [149]. A recent case report describes the daily use of neostigmine (2 mg i.v. q 6 h) for several months in a hospitalized patient with chronic colonic pseudo-obstruction [150]. To

date, neostigmine has not been studied in a controlled manner in patients with CIP. No formal trials have been conducted to date using tegaserod, mosapride, renzapride, or levosulpiride; although all of these prokinetic agents theoretically could improve symptoms in patients with CIP.

Surgery is generally avoided in patients with CIP, for fear of precipitating an acute episode. However, intestinal transplantation may be a viable treatment for patients with severe CIP who cannot be maintained on parenteral nutrition. Six patients with CIP underwent intestinal transplantation (isolated small bowel in 5, and stomach, duodenum, pancreas, and small bowel in 1) after medical management had failed [151]. Mean follow-up was 25 months. All 5 patients who underwent isolated small bowel transplant survived, and 3 were able to stop parenteral nutrition; the 1 patient who underwent a more extensive graft died from hemolytic-uremic syndrome. Multivisceral transplantation has been described in pediatric patients (median age 4 years) with severe CIP [152]. Ten patients survived after 2 years; all were off parenteral nutrition and were tolerating enteral feedings.

Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is characterized by abdominal pain with disturbed defecation [153]. IBS is highly prevalent and is associated with a significant reduction in quality of life [154]. A large number of clinical studies have been published over the last 5 years in the field of IBS. For patients with IBS and constipation, fiber supplementation may improve symptoms of constipation, although abdominal pain is unlikely to improve [155–157]. Tegaserod, a 5-HT₄ agonist, improves global symptoms of IBS and constipation in women with constipation-predominant IBS [158, 159]. Renzapride, a mixed 5-HT₄ receptor agonist/5-HT₃ receptor antagonist, accelerates colonic transit in constipation-predominant IBS patients [160]. Based on animal studies, mosapride, another 5-HT₄ receptor agonist, may have a role in the treatment of constipation-predominant IBS [124, 125].

For diarrhea-predominant IBS, loperamide can reduce loose stools, urgency and fecal soiling [161, 162]. Alosetron, a 5-HT₃ receptor antagonist, was shown to improve diarrhea and urgency in women [163, 164]. Alosetron was removed from the market by the FDA due to concerns over an association with ischemic colitis. Re-

cently, patients with IBS have been shown to have a two-to-fourfold increased risk of ischemic colitis, so the actual medication risk of alosetron is unclear [164, 165]. Preliminary data on cilansetron, another 5-HT₃ receptor antagonist, shows that this medication may improve symptoms of IBS and diarrhea in both men and women. A review by the FDA in the spring of 2005 did not lead to a letter of approval, however, and further clinical trials were requested.

Smooth muscle antispasmodics alleviate symptoms of abdominal pain and bloating in some patients with IBS. In one meta-analysis, 5 drugs showed efficacy over placebo (cimetropium bromide, pinaverium bromide, octylonium bromide, trimebutine, and mebeverine) [166]. Although commonly used in the clinical setting, this meta-analysis did not show that dicyclomine and hyoscyamine were effective. Tricyclic antidepressants (TCAs) and serotonin reuptake inhibitors (SSRIs) have been shown to alter visceral sensitivity, reduce central pain perception, and treat concurrent psychiatric co-morbidities. It is thought that TCAs work centrally rather than peripherally to reduce pain [167]. A recent Cochrane database review found that, in IBS patients, the relative response to TCAs was 1.34 and the number needed to treat was 6. Low-dose TCAs may be helpful if pain is constant in nature, rather than intermittent. SSRIs may improve visceral hypersensitivity, particularly in constipation-predominant IBS, although the efficacy of this class of medications continues to be debated [168, 169]. Finally, SSRIs have been shown to improve patients' sense of well-being, even in non-depressed patients [170].

In addition to medical therapy, a number of different psychological interventions have been evaluated. In a randomized trial in the primary care setting, cognitive behavior therapy, in addition to antispasmodic treatment, showed additional benefits when compared to medication therapy alone at 6 months, although the effects had waned by 12 months [171]. Overall, the efficacy of psychological intervention remains unclear [172, 173].

Probiotics are a potential new therapy for the treatment of IBS [174]. It is believed that probiotics act to normalize the ratio of anti-inflammatory to pro-inflammatory cytokines in the gut, thereby alleviating symptoms. A recent trial showed improvement in cytokine balance with associated improved QOL assessments in patients taking *Bifidobacterium* (*B. infantis* 35624) in a malted milk drink [175].

Newer agents under current investigation, all of which require further study, include CCK1 receptor antagonists

and tachykinins. Asimadoline, a κ -opioid agonist, showed decreased overall perception of pain with colonic distention in a study of female patients with IBS [176].

Alternative therapies are commonly used by patients with IBS. Dried turmeric extracts improved IBS symptoms when compared to placebo in a partially blinded randomized pilot study [177]. Two small pilot studies in diarrhea-predominant IBS patients suggest that transcutaneous electrical acustimulation at ST36 and P6, but not sham stimulation, increased the threshold of rectal sensation of gas, desire to defecate and pain [178, 179]. Finally, hypnosis has been reported to improve global IBS symptoms in a recent study and review [180, 181].

Chronic Constipation

Chronic constipation is not a single disorder, but instead represents a number of different pathophysiologic processes, including colonic inertia, normal transit constipation, and pelvic floor dyssynergia [182, 183]. Many patients suffer from two of these processes at the same time (i.e., both colonic inertia and pelvic floor dysfunction). The data presented below is thus for a heterogeneous group of patients, rather than for a pure population of patients with only one pathophysiologic abnormality.

The prevalence of chronic constipation is estimated at 12–19%, while the incidence is estimated at 4 per 100 person-years of follow-up [184, 185]. Although studies are limited, chronic constipation can both reduce patients' quality of life and impose a substantial economic burden [186].

Lactulose, a non-absorbable synthetic disaccharide, has been used to treat constipation for over 20 years. Only one study using lactulose in patients with chronic constipation has been published since 2000. This study employed a parallel-group, multicenter, randomized design and compared lactulose (33 patients) to polyethylene glycol (PEG) (32 patients). No significant difference was found between the groups with regard to stool frequency, stool consistency, or straining [187]. A recent systematic review found that lactulose was less effective than PEG or bulk laxatives at relieving symptoms of constipation [188].

PEG is a large, non-absorbable, chemically inert polymer which acts as an osmotic agent to retain water in the stool. Cleveland et al. [189] conducted a randomized, double-blind, cross-over study in 23 patients and compared PEG (17 g/day) to placebo over a 2-week trial period. PEG was found to improve stool frequency and

stool consistency; no discontinuations were reported. Di-Palma et al. [190] randomized 151 patients to either PEG (17 g/day) or placebo in a double-blinded, multicenter study which lasted 10 days. No significant adverse events were reported in the 135 patients who completed the study. PEG was found to be statistically superior to placebo in regards to stool frequency and stool passage. Similar results on the efficacy of PEG have been reported elsewhere [191].

Two large randomized, placebo-controlled trials have been performed to evaluate the efficacy and safety of tegaserod in the treatment of chronic constipation. Kamm et al. [192] compared tegaserod (2 or 6 mg) to placebo in 1,264 women and men over a 12-week trial period. The primary efficacy variable was the responder rate for complete spontaneous bowel movements during the first 4 weeks of treatment. Both the 6- and 2-mg dose, given b.i.d., were more effective than placebo ($p < 0.0001$ and $p < 0.01$, respectively). In another randomized, double-blind, placebo-controlled of 1,348 men and women with chronic constipation, Johanson et al. [193] found that both 2 mg and 6 mg b.i.d. were more effective than placebo at increasing the number of complete spontaneous bowel movements.

Prucalopride, a 5-HT₄ agonist, has been shown to accelerate GI transit and improve symptoms of constipation in several different studies. In a double-blind, parallel-group design of 40 patients with functional constipation but without evidence of a rectal evacuation disorder, 4 mg of prucalopride accelerated gastric, small bowel, and colonic transit [194]. Emmanuel et al. [195], in a double-blind, placebo-controlled trial of 74 patients, found that 1 mg of prucalopride daily accelerated orocecal transit, increased stool frequency, and improved symptoms of constipation. A 4-week, double-blind, placebo-controlled trial found that 4 mg of prucalopride daily improved whole gut transit, reduced straining, and reduced time to first stool in 53 patients with chronic constipation [196]. Finally, prucalopride (either 1 or 2 mg) was shown to improve symptoms of constipation and reduced mean colonic transit time in a double-blind, placebo-controlled, cross-over study of 28 patients with chronic constipation [197]. Concerns over possible cardiac arrhythmias with prucalopride use have halted further studies for now.

Neurotrophin-3 (NT-3) is a neurotrophic growth factor that enhances the growth and development of neurons, especially those of the enteric nervous system. A double-blind, randomized, placebo-controlled, multicenter study was performed using NT-3 in 107 patients with functional constipation (Rome II criteria). Patients

were randomized to placebo, 3 mg, or 9 mg of NT-3 given subcutaneously either weekly or three times weekly [198]. Colon transit time and stool frequency were the primary endpoints measured. Weekly dosing of NT-3 was not effective, although 9 mg of NT-3 given three times weekly led to a significant improvement in stool frequency, stool consistency, and straining. In addition, colonic transit was accelerated. The clinical utility of this agent will likely be limited by the fact that patients will require an injection, and also by the fact that 33–50% of the patients who received NT-3 had injection site reactions.

Lubiprostone is a bicyclic fatty acid that acts to open specific chloride channels (ClC-2) within the GI tract, thereby enhancing fluid secretion. It is not presently known whether this agent acts with greater affinity or specificity in one portion of the GI tract compared to another. Although clinical data is limited and still mostly in abstract form, it appears that this oral medication does not appear to alter electrolyte levels in either normal volunteers or patients. A multicenter, randomized, double-blinded study showed that 24 µg b.i.d. of lubiprostone was more effective than placebo with regards to improving stool frequency, stool consistency, and straining [199]. Several studies involving lubiprostone and patients with chronic constipation were recently presented at the annual meeting of the American College of Gastroenterology in October 2005. Lubiprostone (24 µg b.i.d.) was compared to placebo in a multicenter, parallel-group, 4-week, double-blind study of 237 patients with idiopathic constipation [200]. More patients treated with lubiprostone noted a spontaneous bowel movement within the first 24 h, compared to placebo ($p < 0.001$). Stool frequency over the 4-week trial period was significantly improved for the lubiprostone group compared to placebo ($p < 0.05$). One concern from these studies, however, is that lubiprostone has been associated with a significant incidence of nausea – up to 31.7% of all subjects in one study. Publication of the data in full manuscript form is eagerly awaited.

Mosapride, a 5-HT₄ agonist with 5-HT₃ antagonist properties, has been evaluated in an open-label study of 14 Parkinsonian patients with constipation [201]. Both subjective (straining, difficulty with evacuation), and objective (frequency) measurements of constipation and colon motility (colonic transit time and rectoanal videomanometry) were recorded at baseline and after 3 months of treatment with 15 mg/day. Mosapride improved symptoms of constipation (frequency and straining) and also improved colonic transit time, particularly in the left co-

lon. Mosapride also resulted in larger amplitude of rectal contractions.

Alvimopan is a novel orally active μ -opioid receptor antagonist [202]. Early studies have focused on the role of alvimopan on reversing narcotic-induced constipation and improving post-operative ileus. A recent abstract reported that alvimopan improves whole bowel transit time in adults with chronic constipation [203].

Biofeedback has been evaluated in a number of studies of patients with chronic constipation due to pelvic floor dysfunction. However, no placebo or sham controlled trials have been performed in adults. A recent study of 52 patients confirms the clinical view that biofeedback is effective at treating symptoms of constipation due to pelvic floor dyssynergia, although it is not effective at treating constipation due to slow transit constipation [204]. For further details, the reader is referred to a recent comprehensive review that nicely summarizes studies performed to date for biofeedback and functional anorectal disorders [205].

Conclusions

Motility disorders of the GI tract are highly prevalent in the clinical setting and are now readily diagnosed in the motility laboratory. In the last 5 years, several advances have taken place, notably the development of multichannel impedance, increasing use of electrogastrography, and greater clinical use of gastric stimulation. A number of new therapies are now available to treat symptoms of GI dysmotility. Many of these target the serotonin system, which has been recognized as playing a critical role in normal gut pathophysiology. However, due to ever increasing concerns over safety, future studies of medications will need to be performed for longer periods of time, involve more patients, include an extended investigation time. Finally, although at least 35% of adults routinely use some form of alternative or complementary medication, there are few well-designed trials evaluating the efficacy and safety of these agents. These will be required if these agents are to become accepted by the clinician.

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