Review Article

Pharmacologic Treatment for Pediatric Gastroparesis: A Review of the Literature

Emma M. Tillman, PharmD, PhD,[1] Keaton S. Smetana, PharmD,[2] Likeselam Bantu, PharmD,[1] and Merrion G. Buckley, PharmD Candidate[1]

[1]Department of Clinical Pharmacy, The University of Tennessee Health Science Center, Memphis, Tennessee; [2]Department of Pharmacy, University of Kentucky Heathcare, Lexington, Kentucky

There have been a number of agents that have been tried for treatment of gastroparesis over the past 3 decades, with varying levels of success. Guidelines exist for the management of gastroparesis in adults; however, even though the cause of gastroparesis in children is similar to that in adults, no guidelines exist for treating pediatric gastroparesis as studies on the topic are limited. With what little information we have on pediatric gastroparesis, medications used in children's studies do not seem to demonstrate the same results as in adult patients with gastroparesis; thus, future studies of whether certain medications are effective for treating pediatric gastroparesis and at what dose still need to be conducted. Pharmacological treatment options for pediatric gastroparesis do not show a clear correlation of resolving or even maintaining gastroparesis-associated symptoms or disease state. This article reviews the available studies of drugs that have shown some efficacy, with an emphasis on pediatric studies.

INDEX TERMS: drug therapy, gastroparesis, metoclopramide, pediatrics, prokinetic

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INTRODUCTION

Gastroparesis is a debilitating disease that can present with a constellation of symptoms including nausea, vomiting, early satiety, anorexia, weight loss, and epigastric pain. Gastroparesis is defined as the impaired transit of intraluminal contents from the stomach to the duodenum in the absence of mechanical obstruction. Diagnosis of gastroparesis is based on the presentation of gastroparesis-associated symptoms that exist without any gastric outlet obstruction or ulceration and delayed gastric emptying.[1] Delayed gastric emptying is the key diagnostic symptom of gastroparesis resulting from paresis of the stomach, causing its contents to remain in the stomach for a prolonged period of time. Complications associated with gastroparesis may include Mallory-Weiss tears from repeated vomiting, bezoar formation, malnutrition, aspiration pneumonia, and electrolyte disorders.[2]

It may be difficult to assess the cause of gastroparesis, because most adult cases are idiopathic in nature.[3] Presentation of gastroparesis in the pediatric population is seen largely after viral infection or surgical interventions. Patients with long-standing diabetes may be at increased risk of developing gastroparesis due to the development of neuropathies and alterations in vagal innervation.[4] Additionally, gastric motility may be impaired secondary to intestinal surgery, viral infections, neurologic disorders, psychological distress, anticholinergic agents, and overuse of opioids.[2] In general, idiopathic disease tends to be more severe and persistent, whereas post-infectious gastroparesis is self-limiting and may resolve over several months.[5]

Clinical guidelines for management of gastroparesis in adults recommend restoring fluids and electrolytes in patients and providing nutritional support, preferably through oral intake. Pharmacologic therapy is used in conjunction with dietary therapy in attempts to improve gastric emptying and gastroparesis-associated symptoms. Prokinetic medications are most often the first line pharmacological treatment, which work

by increasing gastrointestinal motility; liquid formulation of metoclopramide prescribed at the lowest effective dose is the drug of choice.[1] In patients who do not respond to prokinetic therapy, other pharmacologic recommendations include intravenous erythromycin to improve gastric emptying, antiemetics agents for alleviating associated symptoms of gastroparesis, or tricyclic antidepressants for managing refractory nausea and vomiting. Neither antiemetics nor tricyclic antidepressants improve gastric emptying time and thus are only conditionally recommended as pharmacologic treatment for gastroparesis in adults.[1]

Currently, there are no standardized clinical guidelines for treating gastroparesis in pediatrics. Similar to treatment for adult patients, the first-line recommendation is to restore fluid and electrolytes in the patient while establishing proper nutritional support and/or nutritional counseling. Pharmacologic recommendations are individualized and are intended to increase gastric emptying and manage associated symptoms to improve the patient's lifestyle. Prokinetic therapy is preferred as the first-line medication therapy for gastroparesis as it accelerates intestinal transit; however, studies of medications in this class suggest that they are not as effective in children as they are in adults.

In addition to nutritional management and support, other non-pharmacological options exist for managing gastroparesis in both pediatrics and adults; however, this article reviewed and evaluated the current literature for the pharmacologic treatments of gastroparesis with a focus on pediatric studies where available.

METHODS

Databases PubMed (1975-2014) and Ovid MEDLINE (1975-2014) were searched using terms "gastroparesis," "gastric emptying," and "pediatrics" and combinations of these terms with each of the pharmacologic agents used to treat gastroparesis. Reference lists from all identified studies and reviews were also assessed for relevant papers. Initially, inclusion criteria were limited to pediatric studies; however, this approach yielded a small number of pediatric studies. Because adult studies are relevant to the pediatric population, inclusion criteria were expanded to include both primary and secondary articles on adult and pediatric pharmacotherapy for diseases of gastric dysmotility. Additionally, preclinical studies related to treatment of gastroparesis in pediatrics were included.

REVIEW OF LITERATURE

Metoclopramide

Metoclopramide (MCP) was approved by the U.S. Food and Drug Administration (FDA) in 1979 for gastroparesis and remains the first-line agent for pharmacologic therapy. Favorable prokinetic effects are mediated through antagonism of the dopamine 2 (D_2)-receptor to promote gastric emptying, as well as binding to the 5-hydroxytryptamine receptor 4 (serotonin 5-HT_4) to stimulate cholinergic neural pathways in the stomach.[7] Physiologically, MCP accelerates intestinal transit by increasing the tone and amplitude of gastric contractions as well as relaxing the pyloric sphincter and the duodenal bulb.[8] Additionally, this agent provides antiemetic relief through antagonism of central and peripheral dopamine receptors.[7]

Several studies have compared placebo to MCP in with adult patients and found that MCP improved symptoms and gastric emptying time, assessed by radionuclide scintigraphy. [9-11] Although prokinetic effects have been studied extensively in adults, studies supporting its use in pediatrics are sparse and suggests it may not be as effective. There is some evidence that the underlying cause of gastroparesis may determine the patient's response to therapy. A randomized, controlled study performed by Hyman et al[15] found that MCP is not efficacious in premature and neonatal populations whose primary cause of gastroparesis is prematurity. In light of previous studies linking the lack of efficacy in younger populations to a down-regulation in D_2 receptors[12] and reduced responsiveness to prokinetic therapy in those with mitochondrial disorders,[16] it may be reasonable to predict effectiveness based on age. It has been hypothesized that lower D_2 receptor expression in neonates may be the cause of its reduced effectiveness. Tube feedings that contained 0.2 mg/kg MCP had no effect on promoting gastric motility in low-birth-weight neonates but may be helpful in reducing emesis due to its actions on the chemoreceptor trigger zone.[12-14] The usefulness of MCP in neonates may be due to the centrally acting

antiemetic properties and not the pro-kinetic effects seen through binding of the D_2 receptor in the peripheral nervous system. In preliminary animal studies, Kasirer et al[12] found that neonatal rats that received MCP showed no differences in fundic muscle contraction upon induction with electrical field stimulation. In contrast, MCP was found to have statistically significant differences in electronic field stimulation-induced fundic muscle contraction in juvenile and adult rats. Additionally, the number of D_2 receptors was significantly reduced in the neonatal rat gastric tissues, which may account for the lack of efficacy.[12] Whether this result can be extrapolated to humans is the question.

A retrospective chart review from a single institution evaluated the effectiveness of prokinetic agents in 230 pediatric patients with gastroparesis.[14] Similar to the effects in adult population, post-viral gastroparesis, defined as persistence of symptoms 1 month after onset of viral illness, was a dominant cause. Medication noted in the study included MCP, domperidone, tegaserod, erythromycin, proton pump inhibitors (PPIs), and cyproheptadine. The majority of patients (n = 173; 75%) received MCP as the promotility agent. Dosages ranged from 0.1 to 0.2 mg/kg (maximum of 10 mg/dose) and were given 4 times daily. Mean duration of treatment was 8.6 months. Not only were 80% of patients nonresponsive to MCP therapy, but MCP was associated with the greatest number of adverse effects. Adverse effects such as, headaches, vomiting, behavioral changes, dystonia, movement disorders, drowsiness, dizziness, and galactorrhea were reported by 34 patients (24%). Although a subgroup analysis evaluating efficacy of MCP based on age was not performed, a positive association was noted between promotility agents in children (1-12 years of age) compared to that in adolescents and infants ($p = 0.07$).

Other factors affecting drug absorption and metabolism should be considered when considering an optimal medication regimen. The 2013 adult guidelines for treatment of gastroparesis recommend oral liquid formulation of MCP over tablets due to its preferential absorption profile.[1] In a recent article by Parkman et al,[17] the nasal spray formulation of MCP was preferred over oral tablets for symptom relief from gastroparesis.

Responses to therapy may also be predicted by pharmacogenomic testing. Polymorphisms in the KCNH2 and ADRA1D genes have been linked to better clinical response, whereas the CYP2D6, KCNH2, and HTR4 genes are associated with manifestation of adverse effects.[18]

Although MCP is the only FDA-approved treatment for gastroparesis, it is not a benign drug and its adverse effects ultimately limit its use. There is a "black box" warning for tardive dyskinesia that is associated with the duration of treatment and total cumulative dose. For this reason, use of MCP should be limited to 12 weeks unless therapeutic benefit is thought to outweigh the risk of developing a movement disorder that is often irreversible.[8]

Domperidone

Domperidone (DMP) exerts its prokinetic effects through antagonizing D_2 receptors, which enhances antral-duodenal contraction and leads to improved peristalsis. DMP also has antiemetic properties through its effect on the chemoreceptor trigger zone found outside of the blood-brain barrier in the fourth ventricle. The benefit of using DMP over MCP is that it does not readily cross the blood-brain barrier, resulting in decreased central nervous system adverse effects. Compared to other prokinetic agents, DMP has no cholinergic activity.[19]

In a retrospective review by Rodriguez et al, 33 children (out of 230 total pediatric patients) within the study were put on DMP after a failed trial of a first line agent (either a PPI or MCP). Dosage of DMP was 0.1 to 0.2mg/kg per dose given 4 times daily, with a maximum dose of 10 mg 4 times daily for a mean duration of therapy of 7.6 months. Of 31 patients available for follow-up, 74% of patients taking DMP therapy responded compared to only 20% who were taking MCP and responded to treatement.[14] In that study, DMP produced the highest resolution rate and caused the fewest adverse effects; with 6% of its patients reporting abdominal pain and/or movement disorders as adverse effects. In another trial comparing 0.3 mg/kg DMP with placebo given 3 times a day to 22 preterm infants with gastric dysmotility, the mean gastric emptying time for the treatment arm was significantly reduced: 47 minutes compared to the 68 minutes for the control.[22]

Adult studies have also shown that DMP compared to MCP appears to have a comparable

efficacy but possesses an improved adverse effect profile. A double-blind, multicenter, randomized trial of 93 adult subjects compared adverse effects and efficacy of 20 mg DMP to 10 mg MCP in diabetic gastroparesis. Efficacy was similar between the two groups in reducing the appearance and severity of symptoms such as nausea, vomiting, early satiety, and bloating/distention from baseline. There was, however, a significantly greater reduction in mental acuity in MCP patients at four weeks, as well as non-significant increases in somnolence, akathisia, anxiety, and depression at two and four weeks.[21]

Despite that DMP has been shown to be an effective alternative to MCP in the treatment of gastroparesis, its use is not without risks. Oral DMP has been found to be associated with a mean QTc prolongation of 14 milliseconds in infants at an advanced gestational age of ≥ 32 week of amenorrhea, and in those with a serum potassium level at the upper limit of normal.[23] The proarrhythmic effect of DMP is such a concern that the FDA has not approved it for use in the United States, even outlawing acquisition through compounding pharmacies.[24] Physicians who would like to prescribe DMP for patients with severe gastroparesis or severe gastrointestinal motility disorders that are refractory to standard therapy may only obtain the drug through opening an Investigational New Drug Application.[7]

Although the use of DMP is currently limited, given the lack of a very good prokinetic alternative, DMP is a drug that could enjoy wider use in the future.[25] Pharmacogenetic information about responders, for example, could in future give us an insight into how to best target therapy. Efficacy of therapy has been linked with the potassium channel gene KCNH2 and the drug transporter ABCB1. The adrenoreceptor gene ADRA1D, on the other hand, is thus far the only one associated with adverse effects.[26]

Cisapride

Cisapride promotes acetylcholine release in the myenteric plexus of the gut and indirectly stimulates gastrointestinal motility. Cisapride acts as an agonist at 5-HT_4 receptors and an antagonist at 5-HT_3 receptors, both of which contribute to the release of acetylcholine and subsequent prokinetic effects. It is also noteworthy that, unlike metoclopramide, cisapride is devoid of central nervous system effects because of its lack of antidopaminergic activity.[27]

Although cisapride was first approved by the FDA for treatment of nocturnal heartburn, it had at one time been the preferred agent for conditions of gastric impairment due to promising in vitro and early clinical trial data.[7,27] Evidence for its efficacy in adults, however, was and still is mixed. A few studies have reported that esophageal and gastric emptying of solid and liquid foods was much improved after both a single and repeated doses of cisapride.[28,29] Other trials suggested that observed gastric emptying does not necessarily translate into symptom improvement.[30,31] In some studies, cisapride simply failed to demonstrate a benefit in gastroparesis altogether.[32] The disparity between the trials can possibly be accounted for by methodological variances and heterogeneity in the population studied; however, a clear conclusion still cannot be made.

Data for the pediatric population are even more limited, although what is available does not favor cisapride. In a trial of cisapride efficacy (0.2 mg/kg 3 times daily) in 10 preterm infants, the investigators found that cisapride might in fact delay gastric emptying, as the half gastric emptying time was significantly longer in the cisapride group. The whole gastrointestinal transit time was also longer in the cisapride group but not statistically different from that in the placebo group. Based on their results, the authors advised not using cisapride in preterm infants.[33] Compared to other prokinetic agents, cisapride also fared worse. In a randomized study of 28 insulin-dependent children 6 to 16.9 years of age, cisapride (0.8 mg/kg) was compared with DMP (0.9 mg/kg). At the end of the 8-week period, the DMP group had statistically significant improvements in symptoms as well as reduced gastric emptying time, normalized gastric electrical activity, decreased prevalence of episodes of gastric dysrhythmias, and better glycemic control than the cisapride group.[34]

From a safety standpoint, cisapride initially was shown to have an acceptable adverse effect profile. In a comparison of 10,000 (adult) patients in a phase IV study, and 13,000 patients in a prescription event-monitoring program, the most common adverse events reported were diarrhea, headache, abdominal pain, constipation, and nausea.[35] Later studies, however, suggested something different. In one such study, QTc

prolongation was observed after 3 to 8 weeks of treatment in those children (6 months to 4 years of age) with underlying cardiac disease.[36] In January of 2000, Janssen Pharmaceutica, Inc., warned physicians about the risks and contraindications related to cisapride. From 1993 to 2000, there had been 270 reported cases of serious cardiac arrhythmias such as ventricular tachycardia, ventricular fibrillation, torsades de pointes, and QTc prolongation in patients taking cisapride. Seventy of those reported cases resulted in fatalities. The company also noted that in 85% of those cases the events occurred in patients with known risk factors, including concomitant use of QTc-prolonging drugs, inhibition of CYP 3A4 enzyme, or depletion of serum electrolytes.[37] Finally, on July 14, 2000, Janssen Pharmaceutica, Inc. announced it would stop marketing cisapride in the United States. The drug is now available only through a limited access program for patients who meet specific clinical eligibility criteria.[7]

Macrolide Antibiotics

Macrolide antibiotics at reduced antimicrobial dosages, such as erythromycin oral suspension at 50 to 100 mg 3 to 4 times daily and 30 to 45 minutes prior to meals, promotes gastric motility and improves symptoms of early satiety, fullness, and vomiting.[2] Unlike previous prokinetic agents, which act primarily on the D_2 receptor, these agents act directly on motilin, which is an amino acid peptide synthesized in mucosal endocrine cells. Its name is derived from its ability to stimulate the motility of digestive organs.[38] Although the mechanism of action of motilin on gastric motility is not entirely understood, its activity on its endogenous receptor is believed to regulate phase III of the migrating motor complex (MMC), the presence of which is reflective of peristaltic activity in the antrum and duodenum. The MMC is the motor pattern present during the body's fasting state, with the active phase III responsible for the clearing of debris and indigestible material from the stomach and intestine into the colon.[2]

Erythromycin use in children seems not to have similar results, as a study demonstrated that erythromycin, 3 mg/kg given 4 times daily, up to 10 mg/kg 4 times daily, produced the lowest resolution rate of gastroparesis symptoms in pediatrics with gastroparesis.[14] A study of children (4 to 15 years of age) compared gastric residual volumes with premedication of either erythromycin (0.15 mg/kg) or metoclopramide (1 mg/kg) undergoing a tonsillectomy. The study demonstrated that there were no significant differences between gastric residual volumes, nor were there differences in postoperative nausea and vomiting after pretreatment of either medication. Thus, erythromycin may be as effective as metoclopramide as a prokinetic agent and perhaps preferred due to its absence of the extrapyramidal adverse effects associated with metoclopramide.[42]

In the adult population, erythromycin has demonstrated both effectiveness (compared to placebo) and preferential use compared to other motility agents.[39] A single blind, crossover adult study of 13 patients tested the efficacy of 250-mg erythromycin compared to that of 10-mg MCP, both of which were given 3 times a day for the treatment of diabetic gastroparesis. Upon completion of the 3-week therapy, significant improvements in total scores of gastrointestinal symptoms were observed with both of the drugs, although the half-time of gastric emptying was more pronounced with erythromycin.[38] Similarly, in a systematic analysis of 36 studies with 514 adult patients, erythromycin was found to have the strongest effect on gastric emptying and improvement of symptoms than DMP, cisapride, or metoclopramide. Its availability and efficacy make erythromycin a welcome alternative to metoclopramide.[41] Although studies show that erythromycin effectively treats gastroparesis in adults, studies in pediatrics patients demonstrate that one cannot extrapolate these notions and apply them in pediatric use.

Promising studies on erythromycin in regards to gastric motility in the pediatric population focus mainly on improving feeding tolerance in low-birth-weight and premature infants. Erythromycin (15–30 mg/kg/day) is able to induce antral contractility, though its ability to produce propagated phase!! III MMC activity come with a major caveat.[14, 43-44] Although non-propagating antral activity is present, indicating the presence of motilin receptors, it is not until 32 weeks that premature phase III MMC activity is observed.[45-48] Therefore, pre-term infants <32 weeks gestation might not benefit from erythromycin as much as their older counterparts.[49-50]

It might be possible to improve antroduodenal coordination using combination therapy with

erythromycin and another agent that induces phase III MMC. Sixteen symptomatic pediatric patients (mean age of 8.7 years) were studied in one such trial using adjunctive octreotide. Erythromycin was administered at 1 mg/kg intravenous infusion after 3 hours of fasting, and octreotide (0.5 mcg/kg) was given subcutaneously 1 hour after the erythromycin infusion. Ten patients had spontaneous phase III of the MMC without treatment medications, 12 had phase III after erythromycin, and 15 had phase III after octreotide, all of which originated in the antrum. Sequential use of erythromycin and octreotide in children may therefore be beneficial in treatment of gastric motility disorders, as the combination therapy was found to stimulate both antral and duodenal contractions.[51]

Although erythromycin enjoys the widest use of the motilin agonists in the adult population, it is not the only agent. Azithromycin use as a prokinetic agent has not widely been researched, particularly in the pediatric population, but adult studies shows promise that azithromycin may be an equal alternative to erythromycin and perhaps some advantages.[52] Unlike erythromycin, azithromycin is not extensively metabolized by CYP3A4, which decreases cardiac risk associated with increased blood levels secondary to enzyme inhibition.[53] Also, although 250 mg of erythromycin and azithromycin induce comparable antral activities in adults, higher doses of azithromycin have been shown to significantly increase mean amplitude and duration of antral activity, suggesting dose-dependent effects.[54] Unfortunately, the cardiovascular risk from macrolides remains and arrhythmia-related effects, including QTc-interval prolongation, torsades de pointes and polymorphic ventricular tachycardia, have been observed.[55] Azithromycin's increased duration of action, better adverse effect profile, and lack of CYP450 interaction indicate that it could be a better choice for accelerating gastric emptying time; however, more studies of its potential use and effectiveness in pediatrics and long-term safety in adults need to be conducted.[52]

Concerns with adverse effects, tachyphylaxis with prolonged use, and drug interactions, as well as the possibility of resistance, have prompted research into novel and specific motilin agonists.[2] Although there are several agents in development, only a few have shown promise. In a randomized control trial of 106 patients receiving doses of 10, 20, 30, and 40 mg, mitemcinal accelerated gastric emptying in both diabetic and idiopathic gastroparesis, although it was especially effective in diabetic gastroparesis.[56, 57] Since the early trials looking at mitemcinal efficacy, development appears to have stalled, but the motilin receptor still remains a good target for development of a new agent.

Alternative Contemporary Therapies as Prokinetics

Botulinum toxin A is a purified neurotoxin that inhibits the release of acetylcholine into the neuromuscular synaptic cleft, with subsequent localized reduction in muscle contractility.[58] Pediatric data are limited; however, a retrospective study has looked at endoscopic, submucosal injection of the toxin.[59] The study found botulinum toxin A to be safe and effective for the treatment of intractable pediatric gastroparesis, with older age being an independent predictor of response to treatment. In the study, botulinum toxin A was given at a dose of 6 units/kg, and 30 of 47 participants reported at least mild improvement, with 12 of the 30 participants being asymptomatic. The median duration of effect from the first injection was 3 months in the 30 responders. Of these, 12 patients required only 1 injection. Of those who required subsequent injections, 50% continued to respond to repeated injections. Only 1 patient reported an adverse reaction with exacerbation of vomiting for <1 week.

Baclofen, an antispasmodic and muscle relaxant, is yet another agent that may possibly have clinical benefit in patients with gastroparesis. Although its precise mechanism of action is not well understood, it is thought to have an inhibitory role on the lower esophageal sphincter relaxation through its stimulation of gamma-aminobutyric acid B (GABA) receptors. In a randomized controlled trial of 30 children (2.6-17.4 years of age) with gastroesophageal reflux (GER) refractory to PPIs and H_2-antagonists, investigators studied the effect of baclofen (0.5 mg/kg) on transient lower esophageal sphincter relaxation, GER, and gastric emptying. The mean gastric emptying time for the active group was 61 minutes compared to 114 minutes for the placebo group, showing increased gastric emptying with baclofen. Although the trial was investigating GER specifically, this nevertheless points to efficacy in gastric emptying, if only for a particular population.[60]

Ghrelin is a close relative of motilin, and it is the latest target for drug development treating gastric dysmotility. Endogenous ghrelin is a hormone that serves multiple functions in the body, although of interest to the authors is its ability to stimulate the migrating motor complex, promote stomach emptying, and augment coordination of contraction between the antral and pyloric regions of the stomach.[61] Administration of exogenous ghrelin has been shown to increase gastric emptying both in idiopathic and in diabetic gastroparesis.[62-64] Use of ghrelin itself, however, is not practical because of its short half-life and poor bioavailability.[65] Therefore, synthetic ghrelin receptor agonists are in development. So far 2 agents have reached clinical trial stage. Both TZP-101 and TZP-102 have been shown to improve symptoms, although the phase 2b trial for TZP-102 had to be stopped early for clinical futility.[64-67]

Another potential target is also a gut hormone. Cholecystekinin (CCK) is excreted from duodenal endocrine cells and inhibits gastric motility in response to the presence of lipids. One would therefore expect that a CCK receptor antagonist would counteract the inhibition of gastric motility and promote emptying. In a placebo-controlled trial of 6 patients, an infusion of loxiglumide, 66 µmol/kg/hr, a CCK antagonist, resulted in a mean gastric emptying time of 22 minutes compared to 115 minutes for the placebo.[68] Although this confirms the initial hypothesis, this was a very small trial conducted in adults. Better studies, especially in pediatrics, are sorely lacking. Ultimately, it is also possible these agents will only be useful in gastric dysmotility linked with meals of high lipid content.[69]

Bethanechol is a parasympathomimetic agent that is FDA approved for treatment of urinary retention. Its activity, however, extends beyond the detrusor urinae muscle, as it can also stimulate gastric motility, increase gastric tone, and often restore impaired rhythmic peristalsis.[70] At a dosage of 0.25 mg/kg/dose 30 minutes before breast feeding, bethanechol resolved gastrointestinal symptoms and allowed an increase in daily feeding volume in 2 cases of neonatal congenital myotonic dystrophy believed to be due to maturation arrest of smooth muscle.[71] Compared to MCP, however, bethanechol appears to be less effective. MCP given at 1 mg/kg was compared with 0.075 mg/kg bethanechol and placebo for 3 days in 10 infants, and only MCP exhibited a statistically significant difference in fractional emptying rate and increase in gastric fluid output.[72]

Itopride is a prokinetic benzamide chemically related to cisapride and is not approved in the United States or United Kingdom. It is a D_2 receptor antagonist and anticholinesterase inhibitor, both of which lead to the accumulation of acetylcholine at cholinergic receptor sites. It is through this accumulation that the drug increases the lower esophageal sphincter pressure, accelerates gastric emptying and improves gastroduodenal coordination.[73] An open label, multicenter clinical trial in India investigated the combination of pantoprazole and itopride in the treatment of diabetic gastroparesis over a 3-week period. In 743 patients in the study, there were statistically significant decreases in severity as well as frequency of symptoms such as nausea, vomiting, early satiety, bloating, postprandial fullness, epigastric pain and regurgitation.[74] This suggests that itopride may be an alternative agent for the treatment of gastroparesis, especially as the risk of QTc prolongation appears less compared to cisapride. In a randomized, placebo-controlled, double-blind, crossover study of 10 young adults given 50 mg of itopride 3 times daily, there were no statistical differences in the QTc interval at baseline and following drug administration.[73]

Treatment Management of Gastroparesis

Management of gastroparesis starts with restoration of fluids and electrolytes, adequate nutritional support, and optimization of glycemic control in diabetics. Having small, frequent meals throughout the day is a mainstay in therapy to avoid adverse sequelae such as nausea, vomiting, and early satiety.[1] Another lifestyle modification that has shown to improve gastric emptying is preprandial physical exercise for at least 10 minutes.[6] Inserting a gastrostomy or jejunostomy tube may be necessary if nutritional intake is inadequate. Surgical procedures to assist in improving gastric motility and symptom relief include implanting a gastric pacemaker, gastric bypass, and partial or complete gastrectomy. These invasive surgical procedures have varying degrees of efficacy and may also be accompanied by adverse effects such as gastric pacemaker dysrhythmias, feeding intolerance, and malabsorption.[2]

Another component of the management of gastroparesis, besides inducing gastric motility, is the management of symptoms, particularly nausea and vomiting. In fact there are questions as to whether the benefit seen with certain prokinetic drugs such as MCP or DMP is due to their antiemetic properties more than their prokinetic effects.[75] For example, Schade et al[11] reported that 10 mg of oral MCP acutely enhanced gastric emptying in adult patients, but this effect cannot be demonstrated after chronic administration, even though patients report symptomatic relief. As symptomatic relief often does not appear to be correlated with gastric emptying, antiemetic medications may be useful in symptomatic control of gastroparesis without having a pharmacologic effect on gastric emptying.

The adult guidelines propose a number of agents that could serve as adjunctive antiemetic therapies with prokinetic drugs such as phenothiazines, antihistamines, 5-HT_3-receptor antagonists, aprepitant, dronabinol, and tricyclic antidepressants.[5] Evidence for each is sparse and does not appear to be drawn from reports studying gastroparesis directly. This holds true for pediatric studies as well. One must turn to what few data are available in the treatment of chemotherapy-induced nausea and vomiting, gastroenteritis, or other similar ailments to determine what agents might be useful. For example, a recent Cochrane review of 10 trials examined studies of efficacy of dexamethasone, dimenhydrinate, granisetron, MCP, and ondansetron in acute gastroenteritis in children younger than 18 years of age. The authors concluded there was clear evidence only for ondansetron (0.3 mg/kg) as the agent that does the best in aiding cessation of vomiting, reducing hospital admissions, and reducing the need for intravenous rehydration.[76]

There are other drugs that could come into play during the management of gastroparesis. Proton pump inhibitors such as omeprazole, lansoprazole, pantoprazole and esomeprazole are commonly used in cases of gastrointestinal reflux that results as a complication of gastroparesis.[77] Gastroparesis can also manifest with pain that requires pharmacological management. No specific recommendations are made for management of pain associated with pediatric gastroparesis, although opioids are generally to be avoided because of their possible effect in exacerbation of gastroparesis.[5]

CONCLUSIONS

The prognosis for pediatric gastroparesis is usually good, but this optimistic outcome is often despite current agents that are available for the pharmacological management of this condition. None of the prokinetic agents currently on the market is ideal, particularly for the pediatric population. The Table presents a summary of the various prokinetic agents used in pediatrics along with their evidence for use and limitations. In some agents, their efficacy is in question, whereas in others, their use is associated with serious adverse effects that limit their use; DMP shows promising results for relieving gastroparesis in pediatrics, but its potential adverse effects caused the FDA to limit its use. For those drugs that appear to have some efficacy, there are very few comparison studies to help guide clinicians as to the best agents to use. The trials that are available are fraught with methodological limitations, from small sample sizes to heterogeneity in the various populations studied. When it comes to pediatrics, what little research is available tends to focus on the neonatal population as it relates to feeding intolerance or in the management of symptoms with antiemetics or other agents; therefore, we see most studies try to extrapolate medications and dosing from adult clinical guidelines for the treatment and management of gastroparesis. Unfortunately, medications that show promising results in the treatment of gastroparesis in adults, do not display equally promising results in children.

Although there are new agents are on the horizon, the development is slow going and whether they can be what they are promised to be is in question based on conflicting results in clinical trials. Moving beyond prokinetic medicines, there is very little evidence to guide therapy choice for antiemetics and analgesics. Current evidence reinforces the need for better quality studies examining drug therapy for gastroparesis. On the one hand, factors that affect response to drug therapy and allow us to use current options better need to be investigated. On the other hand, research into newer agents that outperform in both efficacy and safety compared to existing options needs to continue.

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Table 1. Synopsis of Prokinetics Use and Limitations in Pediatrics

Drug	Evidence for Pediatric Use?	Limitations
D-2 Antagonists		
Metoclopramide	Yes. 0.1-0.2 mg/kg (maximum, 10 mg/dose) 4× daily	Cannot use for >12 weeks due to tardive dyskinesia and other adverse effects
Domperidone	Yes; displayed best results. Reduced gastric emptying time with 0.1-0.2 mg/kg (maximum, 10 mg/dose) 4× daily	QTc prolongation; available only through IND due to cardiovascular adverse effects
Itopride	Unknown	Not available in United States
Motilin agonists		
Erythromycin	Mixed. Improved gastric motility in infants at 15-30 mg/kg per day; 3 mg/kg 4× daily did not resolve symptoms in children (4-15 yrs old), but 0.15 mg/kg is effective in reducing post-operative nausea	Antibiotic resistance, arrhythmia, CYP3A4 interactions, tachyphylaxis
Azithromycin	Unknown.	Antibiotic resistance, tachyphylaxis, risk of cardiac arrhythmia
Mitemcinal	Unknown.	Still in development
5HT-4 receptor agonist		
Cisapride	No. 0.2 mg/kg showed to delay gastric emptying time	Available only through compassionate use and IND from manufacturer
Alternative therapies		
Ghrelin agonists	Unknown	Still in development
CCK agonists	Unknown	May be limited to treating dysmotility subsequent to lipid meals
Botulinum toxin	Yes. Symptomatic improvements with 6 units/kg	Data only for refractory gastroesophageal reflux patients; safety studies are lacking
Baclofen	Yes. Reduced gastric emptying time at 0.5 mg/kg	Only trial limited to gastroesophageal reflux patients
Bethanechol	Yes. Dosage of 0.25 mg/kg/dose 30 min prior to breastfeeding resolved symptoms and allowed for increased daily feeding	Less effective than other agents, cholinergic adverse events

5HT-4, 5-hydroxytryptamine receptor 4; IND, investigational new drug

manuscript, including grants, equipment, medications, employment, gifts, and honoraria. All authors had full access to all data and take responsibility for the integrity of the data and accuracy of data analysis.

Abbreviations 5-HT, 5-hydroxytryptamine receptor; CCK, cholecystokinin; DMP, domperidone; D_2, dopamine 2 receptor; FDA, U.S. Food and Drug Administration; GABA, gamma-aminobutyric acid B; GER, gastroesophageal reflux; H_2, histamine receptor; MCP, metoclopramide; MMC, migrating motor complex; PPI, proton pump inhibitors;

Correspondence Emma M. Tillman, PharmD, PhD, BCNSP, Pediatric Clinical Pharmacy Specialist, Pediatric Intensive Care, Riley Hospital for Children, Indiana University Health, 705 Riley Hospital Drive, Indianapolis, IN 46202, email: etillman@iuhealth.org

REFERENCES

1. Camilleri M, Parkman H, Shafi M, Abell TL, et al. Clinical guideline: management of gastroparesis. *Am J Gastroenterol.* 2013;108(1):18-37.
2. Lacy B, Weiser K. Gastric motility, gastroparesis, and gastric stimulation. *Surg Clin North Am.* 2005;85(5):967-987.
3. Soykan I, Sivri B, Sarosiek I, Kiernan B, et al. Demography, clinical characteristics, psychological and abuse profiles, treatment, and long-term follow-up of patients with gastroparesis. *Dig Dis Sci.* 1998;43(11):2398-2404.

4. Undeland KA, Hausken T, Aanderud S, Berstad A. Lower postprandial gastric volume response in diabetic patients with vagal neuropathy. *Neurogastroenterol Motil*. 1997;9(1):19-24.
5. Gariepy C, Mousa H. Clinical management of motility disorders in children. *Semin Pediatr Surg*. 2009;18(4):224-238.
6. Lu CL, Shidler N, and Chen JD. Enhanced postprandial gastric myoelectrical activity after moderate-intensity exercise. *Am J Gastroenterol*. 2000;95(2):425-431.
7. Abell T, Bernstein R, Cutts T, Farrugia G, et al. Treatment of gastroparesis: a multidisciplinary clinical review. *Neurogastroenterol Motil*. 2006;18(4):263-283.
8. Reglan tablets [package insert]. Marietta, GA: Alaven Pharmaceutical LLC; 2010.
9. Perkel M, Moore C, Hersh T, Davidson ED. Metoclopramide therapy in patients with delayed gastric emptying: a randomized, double-blind study. *Dig Dis Sci.* 1979;24(9):662-666.
10. McCallum RW, Ricci DA, Rakatansky H, Behar J, et al. A multicenter placebo-controlled clinical trial of oral metoclopramide in diabetic gastroparesis. *Diabetes Care.* 1983;6(5):463-467.
11. Schade RR, Dugas MC, Lhotsky DM, Gavaler JS, et al. Effect of metoclopramide on gastric liquid emptying in patients with diabetic gastroparesis. *Dig Dis Sci.* 1985;30(1):10-15.
12. Kasirer MY, Welsh C, Pan J, Shifrin Y, et al. Metoclopramide does not increase gastric muscle contractility in newborn rats. *Am J Physiol Gastrointest Liver Physiol.* 2014;306(5):G439–G444.
13. Blumenthal I, Costalos C. The effect of metoclopramide on neonatal gastric emptying. *Br. J. Clin. Pharmac.* 1977;4(2):207-208.
14. Rodriguez L, Irani K, Jiang H, Goldstein AM. Clinical presentation, response to therapy, and outcome of gastroparesis in children. *J Pediatr Gastroenterol Nutr*. 2012;55(2):185-190.
15. Hyman PE, Abrams CE, Dubois A. Gastric emptying in infants: response to metoclopramide depends on the underlying condition. *J Pediatr Gastroenterol Nutr.* 1988;7(2):181-184.
16. Bhardwaj J, Wan DQ, Koenig MK, Liu Y, et al. Impaired gastric emptying and small bowel transit in children with mitochondrial disorders. *J Pediatr Gastroenterol Nutr*. 2012;55(2):194–199.
17. Parkman HP, Carlson, MR, Gonyer D. Metoclopramide nasal spray is effective in symptoms of gastroparesis in diabetics compared to conventional oral tablet. *Neurogastroenterol Motil.* 2014;26(4):521–528.
18. Parkman HP, Misra A, Jacobs M, Pathikonda M, et al. Clinical response and side effects of metoclopramide: associations with clinical, demographic, and pharmacogenetic parameters. *J Clin Gastroenterol*. 2012;46(6):494–503.
19. Reddymasu SC, Soykan I, McCallum RW. Domperidone: review of pharmacology and clinical applications in gastroenterology. *Am J Gastroenterol.* 2007;102(9):2036-2045.
20. Sugumar A, Singh A, Pasricha PJ. A systematic review of the efficacy of domperidone for the treatment of diabetic gastroparesis. *Clin Gastroenterol Hepatol.* 2008;6(7):726-733.
21. Patterson D, Abell T, Rothstein R, Koch K, et al.A double-blind multicenter comparison of domperidone and metoclopramide in the treatment of diabetic patients with symptoms of gastroparesis. *Am J Gastroenterol.* 1999;94(5):1230-1234.
22. Gounaris A, Costalos C, Varchalama E, Kokori F, et al. Gastric emptying of preterm neonates receiving domperidone. *Neonatology.* 2010;97(1):56–60.
23. Djeddi D, Kongolo G, Lefaix C, Mounard J, et al. Effect of domperidone on QT interval in neonates. *J Pediatr.* 2008;153(5):663-666.
24. Silverman S. FDA warning letter on domperidone. 2005.
25. Ahmad N, Keith-Ferris J, Gooden E, Abell T. Making a case for domperidone in the treatment of gastrointestinal motility disorders. *Curr Opin Pharmacol.* 2006;6(6):571-576.
26. Parkman HP, Jacobs MR, Mishra A, Hurdle JA, et al. Domperidone treatment for gastroparesis: demographic and pharmacogenetic characterization of clinical efficacy and side-effects. *Dig Dis Sci.* 2011;56(1):115–124.
27. Quigley, EM. Cisapride: what wan we learn from the rise and fall of a prokinetic? *J Dig Dis.* 2011;12(3):147-156.

28. Horowitz M, Maddox A, Harding PE, et al. Effect of cisapride on gastric and esophageal emptying in insulin-dependent diabetes mellitus. *Gastroenterology.* 1987;92(6):1899-1907.
29. Jian, R, Ducrot F, Piedeloup C, et al. Measurement of gastric emptying in dyspeptic patients: effect of a new gastrokinetic agent (cisapride). *Gut.* 1985;26(4):352-358.
30. Camilleri, M, Malagelada JR, Abell TL, Brown ML, et al.Effect of six weeks of treatment with cisapride in gastroparesis and intestinal pseudoobstruction. *Gastroenterology.* 1989;96(3):704-712.
31. Richards RD, Valenzuela GA, Davenport KG, Fisher KL, et al. Objective and subjective results of a randomized, double-blind, placebo-controlled trial using cisapride to treat gastroparesis. *Dig Dis Sci*. 1993;38(5):811-816.
32. Havelund T, Oster-Jorgensen E, Eshoj O, Larsen ML, et al. Effects of cisapride on gastroparesis in patients with insulin-dependent diabetes mellitus. *Acta Med Scand.* 1987;222(4):339-343.
33. McClure RJ, Kristensen JH, Grauaug A. Randomised controlled trial of cisapride in preterm infants. *Arch Dis Child Fetal Neonatal Ed.* 1999;80(3):F174-F177.
34. Franzese A, Borrelli O, Corrado G, Rea P, et al. Domperidone is more effective than cisapride in children with diabetic gastroparesis. *Aliment Pharmacol Ther.* 2002;16(5):951-957.
35. Wager E, Tooley PJ, Pearce GL, et al. A comparison of two cohort studies evaluating the safety of cisapride: prescription-event monitoring and a large phase IV study. *Eur J Clin Pharmacol*. 1997;52(2):87-94.
36. Levy J, Hayes C, Kern J, Harris J, et al. Does cisapride influence cardiac rhythm? Results of a United States multicenter, double-blind, placebo-controlled pediatric study. *J Pediatr Gastroenterol Nutr.* 2001;32(4):458-463.
37. Gheuens, J. Propulsid (cisapride) dear healthcare professional letter. MedWatch The FDA Safety Information and Adverse Event Reporting Program 2000.
38. Poitras P, Peeters TL. Motilin. *Curr Opin Endocrinol. Diabetes Obes.* 2008;15(1):54-57.
39. Janssens J, Peeters TL, Vantrappen G, Tack J, et al. Improvement of gastric emptying in diabetic gastroparesis by erythromycin preliminary studies. *N Engl J Med.* 1990;322(15):1028-1031.
40. Erbas T, Varoglu E, Erbas B, Tastekin G, Comparison of metoclopramide and erythromycin in the treatment of diabetic gastroparesis. *Diabetes Care.* 1993;16(11):1511-1514.
41. Sturm A, Holtmann G, Goebell H, Gerken G. Prokinetics in patients with gastroparesis: a systematic analysis. *Digestion.* 1999;60(5):422-427.
42. Zatman TF, Hall JE, Harmer M. Gastric residual volume in children: a study comparing efficiency of erythromycin and metoclopramide as prokinetic agents. *Br J Anaesth.* 2001;86(6):869-871.
43. Kubota M, Nakamura T, Motokura T, Mori S, et al. Erythromycin improves gastrointestinal motility in extremely low birthweight infants. *Acta Paediatr Jpn.* 1994;36(2):198-201.
44. Ng PC, Fok TF, Lee CH. Wong W, et al. Erythromycin treatment for gastrointestinal dysmotility in preterm infants. *J Paediatr Child Health.* 1997;33(2):148-50.
45. Curry JI, Lander TD, Stringer MD. Review article: erythromycin as a prokinetic agent in infants and children. *Aliment Pharmacol Ther.* 2001;15(5):595-603.
46. Tomomasa T, Miyazaki M, Koizumi T, Kuroume T. Erythromycin increases gastric antral motility in human premature infants. *Biol Neonate.* 1993;63(6):349-352.
47. Jadcherla SR, Klee G, Berseth CL. Regulation of migrating motor complexes by motilin and pancreatic polypeptide in human infants. *Pediatr Res.* 1997;42(3):365-369.
48. Jadcherla SR, Berseth CL. Effect of erythromycin on gastroduodenal contractile activity in developing neonates. *J Pediatr Gastroenterol Nutr.* 2002;34(1):16-22.
49. Stenson BJ, Middlemist L, Lyon AJ. Influence of erythromycin on establishment of feeding in preterm infants: observations from a randomized controlled trial. *Arch Dis Child Fetal Neonatal Ed.* 1998;79(3):F212-F214.

50. Almonte R, Patole SK, Kadalraja R, Muller R, et al. Erythromycin for feed intolerance in preterm neonate: a randomised, controlled trial. *Pediatric Research* 1999;45(1):276A-276A.
51. Di Lorenzo C, Lucanto C, Flores AF, Idries S, et al. Effect of sequential erythromycin and octreotide on antroduodenal manometry. *J Pediatr Gastroenterol Nutr.* 1999;29(3):293-296.
52. Larson J, Tavakkoli A, Drane W, Toskes P, et al. Advantages of azithromycin over erythromycin in improving the gastric emptying half-time in adult patients with gastroparesis. *J Neurogastroenterol Motil.* 2010;16(4):407-413.
53. Ray WA, Murray KT, Meredith S, et al.Oral erythromycin and the risk of sudden death from cardiac causes. *N Engl J Med*. 2004;351(11):1089-1096.
54. Moshiree B, McDonald R, Hou W, Toskes PP. Comparison of the effect of azithromycin versus erythromycin on antroduodenal pressure profiles of patients with chronic functional gastrointestinal pain and gastroparesis. *Dig Dis Sci*. 2010;55(3):675-683.
55. Matsunaga N, Oki Y, Prigollini A. A case of QT-interval prolongation precipitated by azithromycin. *N Z Med J.* 2003;116(1185): U666.
56. McCallum RW, Cynshi O. Clinical trial: effect of mitemcinal (a motilin agonist) on gastric emptying in patients with gastroparesis—a randomized, multicentre, placebo-controlled study. *Aliment Pharmacol Ther.* 2007;26(8):1121-1130.
57. McCallum RW, Cynshi O. Efficacy of mitemcinal, a motilin agonist, on gastrointestinal symptoms in patients with symptoms suggesting diabetic gastropathy: a randomized, multi-center, placebo-controlled trial. *Aliment Pharmacol Ther.* 2007;26(1):107–116.
58. Galligan JJ, Vanner S. Basic and clinical pharmacology of new motility promoting agents. *Neurogastroenterol Motil*. 2005;17(5):643–653.
59. Botox (botulinum toxin type a) [package insert]. Irvine, CA: Allergan Pharmaceuticals, Inc., 2004.
60. Rodriguez L, Rosen R, Manfredi M, Nurko S. Endoscopic intrapyloric injection of botulinum toxin a in the treatment of children with gastroparesis: a retrospective, open-label study. *Gastrointest Endosc.* 2012;75(2):302-309.
61. Meerveld BG, Kriegsman M, Nelson R. Ghrelin as a target for gastrointestinal motility disorders. *Peptides.* 2011;32(11):2352–2356.
62. Tack J, Depoortere I, Bisschops R, Verbeke K, et al. Influence of ghrelin on gastric emptying and meal-related symptoms in idiopathic gastroparesis. *Aliment Pharmacol Ther.* 2005;22(9):847–853.
63. Binn M, Albert C, Gougeon A, Maerki H, et al. Ghrelin gastrokinetic action in patients with neurogenic gastroparesis. *Peptides.* 2006;27(7):1603–1606.
64. Murray CDR, Martin NM, Patterson M. Taylor SA, et al. Ghrelin enhances gastric emptying in diabetic gastroparesis: a double blind, placebo controlled, crossover study. *Gut*. 2005;54(12):1693–1698.
65. Ejskjaer N, Vestergaard ET, Hellstrom PM, Gormsen LC, et al. Ghrelin receptor agonist (TZP-101) accelerates gastric emptying in adults with diabetes and symptomatic gastroparesis. *Aliment Pharmacol Ther.* 2009;29(11):1179-1187.
66. McCallum RW, Lembo A, Esfandyari T, Bhandari BR, et al. Phase 2b, randomized, double-blind 12-week studies of TZP-102, a ghrelin receptor agonist for diabetic gastroparesis. *Neurogastroenterol Motil*. 2013;25(11):e705-e717.
67. Ejskjaer N, Dimcevski G, Wo J, Hellström PM, et al. Safety and efficacy of ghrelin agonist TZP-101 in relieving symptoms in patients with diabetic gastroparesis: a randomized, placebo-controlled study. *Neurogastroenterol Motil.* 2010;22(10):1069-e281.
68. Ejskjaer N, Wo JM, Esfandyari T, Mazen JM, et al. A phase 2a, randomized, double-blind 28-day study of TZP-102 a ghrelin receptor agonist for diabetic gastroparesis. *Neurogastroenterol Motil* 2013;25(2):e140–e150.

69. Schwizer W, Borovicka J, Kunz P, Fraser R, et al. Role of cholecystokinin in the regulation of liquid gastric emptying and gastric motility in humans: studies with the CCK antagonist loxiglumide. *Gut.* 1997;41(4):500–504.
70. Bethanechol [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc., 2008.
71. Matsui K, Yamashita S, Shibasaki J, Watanabe T. Bethanechol for neonatal transient gastrointestinal dismotility in two cases of congenital myotonic dystrophy. *No To Hattatsu.* 2007;39(4):304-308.
72. Hyman PE, Abrams C, Dubois A. Effect of metoclopramide and bethanechol on gastric emptying in infants. *Pediatr Res.* 1985;19(10):1029-1032.
73. Omari TI, Benninga MA, Sansom L, Butler RN, et al. Effect of baclofen on esophagogastric motility and gastroesophageal reflux in children with gastroesophageal reflux disease: a randomized controlled trial. *J Pediatr*. 2006;149(4):468-474.
74. Gupta S, Kapoor V, Gupta BM, Verma U, et al. Effect of itopride hydrochloride on QT interval in adult healthy volunteers. *JK Pract.* 2005;12(4):207-210.
75. Venkatesh V, Kulkarni KP. Itopride and pantoprazole outcomes in diabetic gastroparesis trial (IPOD trial). *J Indian Med Assoc*. 2008;106(12):814-815.
76. Janssen P, Harris MS, Jones M, Masaoka T, et al. The relation between symptom improvement and gastric emptying in the treatment of diabetic and idiopathic gastroparesis. *Am J Gastroenterol.* 2013;108(9):1382–1391.
77. Carter B, Fedorowicz Z. Antiemetic treatment for acute gastroenteritis in children: an updated cochrane systematic review with meta-analysis and mixed treatment comparison in a Bayesian framework. *BMJ Open*. 2012;2(4):e000622.
78. Saliakellis E, Fotoulaki M. Gastroparesis in children. *Ann Gastroenterology.* 2013;26(3):204-211.