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Novel Therapeutic Agents in Neurogastroenterology: Advances in the Past Year

Michael Camilleri, M.D.

Clinical Enteric Neuroscience Translational and Epidemiological Research (C.E.N.T.E.R.) and
#Division of Biomedical Statistics and Informatics, Department of Health Sciences Research
Mayo Clinic, Rochester, Minnesota

Introduction

There are significant advances in the pharmacological therapy of patients with neurogastroenterological disorders including irritable bowel syndrome (IBS) and functional abdominal pain, functional diarrhea, chronic constipation, gastroparesis, and functional dyspepsia. This article focuses on information from peer-reviewed articles or prominent preliminary communications presented in the past year; conditions other than functional disorders or gastroparesis are not covered here. These medications are reviewed under two main categories: established classes of medications and new classes of medications. In each class of medications, the mechanistic basis is briefly reviewed with particular emphasis on recently published basic or translational science as proof of concept before the clinical trial data are assessed.

Established Classes of Medications

Tricyclic Agents

Two large, randomized, controlled trials appraised the efficacy of nortriptyline compared to placebo in gastroparesis or in functional dyspepsia, the latter in a comparison of two antidepressant classes (tricyclic and serotonin reuptake inhibitor).

In a multicenter, NIH consortium study of the effect of nortriptyline (in a standard dose-escalation approach) in 130 patients with *idiopathic gastroparesis* (1) who were selected with stringent eligibility criteria at seven U.S. academic medical centers, 65 were randomized to each group, and >95% received at least two weeks of treatment. Inclusion criteria included delayed gastric emptying demonstrated by scintigraphy (retention of a low-fat, egg-white meal at 4 hours averaged 26%) and symptom scores of 21 or greater on the 9-symptom Gastroparesis Cardinal Symptom Index (GCSI, range of possible scores: 0–45 points). Over a 15-week period, there were no significant differences between the two treatment groups in the changes from baseline in Gastrointestinal Symptom Rating Scale (GSRS) Scores for nausea, fullness (or early satiety), bloating or total score. Treatment was

Address for correspondence: Michael Camilleri, M.D. Mayo Clinic 200 First St. S.W. Charlton Bldg., Rm. 8-110 Rochester, MN 55905 Tele: 507-266-2305 camilleri.michael@mayo.edu.

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stopped more often, and there was greater severity of dry mouth and urinary retention in the nortriptyline group than in the placebo group.

A randomized, double-blind, placebo-controlled trial of placebo, 50 mg amitriptyline, or 10 mg escitalopram conducted at eight North American sites involved patients meeting Rome II criteria for *functional dyspepsia* (FD) and absence of current depression and antidepressant use. Of the 292 subjects, 75% were females, and 70% had dysmotility-like FD and 30% had ulcer-like FD. There was a borderline treatment effect in the proportion of responders with “adequate relief”: 40% placebo, 53% on amitriptyline, and 38% on escitalopram. Patients with ulcer-like FD receiving amitriptyline had increased odds for reporting adequate relief compared to placebo (OR=3.1; 95% CI: 1.1-9.0). Patients with delayed gastric emptying had decreased odds for reporting adequate relief in response to the antidepressant class compared to placebo, in contrast to responsiveness in subjects with normal gastric emptying (OR=0.4; 95% CI: 0.2-0.8). No treatment-related differences in gastric emptying or meal-induced satiety were observed (2).

5-HT₃ Receptor Antagonists

5-HT₃ receptor antagonists reduce visceral sensation, retard colonic transit, and reduce the contractile and tonic responses to meal ingestion (3,4); multiple large trials and strong meta-analyses demonstrated benefit of 5-HT₃ receptor antagonists as a class of medications in patients with in diarrhea-predominant IBS (IBS-D) (5), including work productivity (6).

The relatively novel 5-HT₃ receptor antagonist, *ramosetron*, has been associated with efficacy on stool consistency in 296 male IBS-D patients recruited across 52 centers in Japan (7). Current data suggest there is lower risk of ischemic colitis and complications of constipation than with other drugs in this class (8).

A resurgence of interest in an older 5-HT₃ receptor antagonist, *ondansetron*, suggests that this may also be efficacious in IBS-D, especially for improved stool consistency, reduced stool frequency, lower urgency, and slower colonic transit, but non-significant effects on pain and bloating (9).

5-HT₄ Receptor Agonists

Mawe and Hofmann (10) summarized the conventional functions of 5-HT in mediating intrinsic reflexes (e.g., stimulation of propulsive and segmentation motility, epithelial secretion and vasodilation). The 5-HT₄ receptor agonists activate the release of acetylcholine from intrinsic cholinergic neurons to generally stimulate smooth muscle contraction in the gastrointestinal tract. There is evidence that mucosal 5-HT₄ receptor activation can mediate the prokinetic and antinociceptive actions of 5-HT₄ receptor agonists (11). There is a new generation of 5-HT₄ receptor agonists that have lower risk of cardiac arrhythmias compared to older agents in this class (12).

A meta-analysis of randomized, controlled trials of recently introduced selective 5-HT₄ receptor agonists in adults with chronic constipation with a maximum of 12 weeks' therapy reviewed 13 trials (11 *prucalopride*, 1 *velusetrag*, 1 *narlapride*) that demonstrated superiority of treatment to placebo for all outcomes: mean 3 spontaneous complete bowel

movements (SCBM)/week (RR=1.85; 95% CI 1.23–2.79); mean 1 SCBM over baseline (RR=1.57; 95% CI 1.19, 2.06); 1 point improvement in PAC-QOL and PAC-SYM scores. The conclusion of the meta-analysis was that the demonstration of efficacy on patient-important outcomes and a favorable safety profile support the continued use and development of highly selective 5-HT₄ receptor agonists for the treatment of chronic constipation (13).

In a trial of 57 patients with functional constipation, the effects of 10, 20, or 30mg of a new 5-HT₄ receptor agonist, *YKP10811*, on GI and colonic transit and bowel function, safety and tolerability was tested. YKP10811 significantly accelerates gastric, small bowel, and colonic transit, improves stool consistency, and shortens time to first bowel movement in patients with functional constipation (14).

Guanylate Cyclase C Agonist

In addition to the secretagogue agents, lubiprostone and linaclotide, recently marketed for chronic constipation and constipation-predominant IBS (IBS-C) (15-17), a new guanylate cyclase C agonist, *plecanatide*, appears to show similar efficacy to the marketed medication, linaclotide, in patients with functional constipation. Plecanatide loosens stool consistency in healthy volunteers (18). In a 12-week, multicenter trial of 951 patients with chronic idiopathic constipation, a dose response study showed that the 3mg dose significantly increased responders (defined as >3 SCBMs/week and an increase of >1 SCBM from baseline for 9 of the 12 weeks, including 3 of the last 4 weeks of treatment) (19).

Interesting mechanistic data support reduction of pain with linaclotide in IBS-C through inhibition of colonic nociceptors via actions of guanylate cyclase C and extracellular cGMP; this results in reduced activation demonstrated in dorsal horn neurons, suggesting an effect on visceral afferents (20).

New Classes of Drugs

Glutamine

Patients with IBS-D have increased permeability (21). A subset of patients with IBS (42% in one study) had increased intestinal membrane permeability and decreased glutamine synthetase expression compared to patients with IBS with normal membrane permeability (22). In a placebo-controlled trial of glutamine (10g t.i.d.) in 61 IBS-D patients with high intestinal permeability and reduced expression of the tight junction protein, claudin-1, in intestinal biopsies (23), the glutamine treatment arm was associated with significantly improved abdominal pain, bloating, and diarrhea, as well as restored intestinal permeability compared with placebo.

Farnesoid X Receptor Agonist

The farnesoid X receptor (FXR) is a nuclear receptor located in enterocytes and hepatocytes. Bile acids are preferentially absorbed into enterocytes through active transport mechanism in the distal ileum called apical sodium-coupled transporter (ASBT), also called ileal bile acid transporter (IBAT) or solute carrier family 10 member two (SLC10A2). In the ileal

enterocytes, bile acids are agonists for FXR and, thereby, activate the gene transcription to synthesize fibroblast growth factor-19 (FGF-19). FGF-19, released into the portal circulation, activates FGF receptor 4 in hepatocytes to downregulate cholesterol 7 α -hydroxylase (CYP7A1) and synthesis of the primary bile acids, such as cholic acid and chenodeoxycholic acid (CDCA).

Obeticholic acid (OCA), or 6-ethyl CDCA, is a semi-synthetic derivative of CDCA with approximately 70-fold greater FXR agonist potency compared to an equimolar CDCA concentration (24). In 10 patients with primary bile acid diarrhea with less than 10% ⁷⁵SeHCAT retention at 7 days (median 4.8%), 25mg/day of obeticholic acid resulted in clinical improvements in all patients, with significantly reduced stool frequency and improved stool consistency on Bristol stool form scale, and numerically lower (but not significant) abdominal pain, urgency and bloating scores. As expected for an FXR agonist, obeticholic acid increased fasting FGF-19 and reduced fasting and postprandial serum bile acid concentrations, and these biochemical perturbations correlated significantly with reduction in stool frequency (25).

Histamine H₁ Receptor Antagonist

There is evidence of increased histamine release (from mast cells) in descending colon mucosal biopsy material from patients with IBS, and supernatants from such biopsies excite mesenteric afferents and sensitize dorsal root ganglion (DRG) neurons and submucous plexus neurons (reviewed in ref. 26). The effects on afferents were generally blocked by histamine H₁ receptor antagonist, but not by H₃ receptor antagonist (27).

A 12-week trial of the histamine H₁ receptor antagonist, ebastin, for the treatment of visceral pain associated with IBS, randomized 28 patients to ebastin and 27 to placebo (28). Visual analog scale (VAS) pain score of symptoms evoked by rectal distensions was the primary pharmacodynamics endpoint. The study was powered to demonstrate a reduction of >15 points on the VAS scale during 21mmHg distension over baseline operating pressure (BOP). Other distension pressures were also tested (+3 and +9mmHg over BOP). The primary endpoint was not significantly influenced by treatment group; however, overall sensation ratings over the three distensions were significantly lowered in patients with rectal hypersensitive treated with ebastin compared to placebo. Moreover, treatment over 12 weeks was associated with at least considerable relief of symptoms in 46% of the ebastin group and 12% of placebo group, and there were lower average abdominal pain scores with ebastin. The clinical secondary endpoints were not different in the subgroups of IBS patients with hypersensitivity or normal sensitivity.

Tachykinin NK-2 Receptor Antagonist

Substance P-containing enteroendocrine cells are overexpressed in colonoscopic mucosal biopsies from patients with IBS-D compared to controls (29); however, another recent study failed to show increased mucosal concentration of substance P in IBS compared to healthy controls (30).

Experimental data suggest that tachykinin NK-2 receptors may affect both motor and sensory mechanisms in mammalian colon. Tachykinin NK-2 receptor is a major factor in

tachykinin-induced smooth muscle contraction in human colon smooth muscle in vitro; the response consists of an excitatory component via direct action on the smooth muscle and an inhibitory component, possibly via nitrergic neurons (31). In a rabbit model of intracolonic zymosan-induced visceral hypersensitivity, the tachykinin NK-2 receptor antagonist, TAK-480, markedly inhibited the visceromotor response to colorectal distension (32), suggesting a reduction in visceral sensitivity.

Ibodutant is a selective tachykinin NK-2 receptor antagonist which reduced intestinal hypermotility and hyperalgesia in disease animal models. Oral ibodutant (1, 3, and 10mg, once per day) was compared with placebo for 8 weeks in 559 patients (333 females and 229 males) with IBS-D (Rome III criteria). The trial showed a significant effect with the 10mg/day dose on the satisfactory relief response in at least 6 out of 8 weeks in females, but not in males (33). These data contrast with studies of other neurokinin receptor antagonists such as talnetant which was not efficacious in modulating human rectal sensation (34). Overall the data available suggest that tachykinin NK-2 receptors may be optimal targets for visceral pain and diarrhea (33).

Combined μ -Opioid Agonist and δ -Antagonist

The most prevalent opioid receptors (OR) in the gastrointestinal tract are μ , δ , and κ receptors; they reduce neuronal excitability and neurotransmitter release (acetylcholine) (35) in non-sphincteric muscle, increase tone in gastrointestinal sphincters such as the pylorus and ileocecal region and inhibit transit (36). Their cellular targets are enteric motor and secretomotor neurons, extrinsic primary afferent neurons, and immune cells (37).

Eluxadoline is a locally active, mixed μ -OR agonist / δ -OR antagonist with low oral bioavailability; it reduced contractility in intestinal tissue, inhibited neurogenic secretion in vitro, and normalized stress-induced acceleration of colonic transit in vivo (38). However, in an animal model of visceral hypersensitivity, it had no effect on the abdominal wall electromyogram recordings in response to repetitive rectal distension. In a clinical trial involving 807 patients randomized to receive twice daily oral placebo or 5, 25, 100, or 200mg oral eluxadoline for 12 weeks, the 100mg and 200mg doses improved global symptoms, bowel movement consistency, frequency and urgency, quality of life, and adequate relief in patients with IBS-D. Although abdominal pain as an individual symptom did not appear to respond to medication compared to placebo, the global and adequate relief responses are encouraging and suggest overall benefit with the medication at 100 and 200mg doses (39). Preliminary data from 2 phase III, placebo-controlled randomized controlled trials testing 75 and 100mg doses have appraised the efficacy of eluxadoline on the endpoints recommended by regulatory agencies. Thus, with the FDA composite endpoint in IBS (that is >50% days from week 1-12, with daily stool consistency <5 (BSFS) or absence of a bowel movement and improvement in the worst abdominal pain in the past 24h by >30% compared to baseline) the two trials showed consistently higher proportion of responders compared to placebo (40). In addition, both studies documented numerical improvement in stool consistency (both trials, $p<0.01$), but not in pain response rates ($p=0.12$ and $p=0.28$).

Peripherally Active μ -Opiate Receptor Antagonists (PAMORA)

This class of medication is designed to poorly penetrate the blood brain barrier; this allows preservation of the central analgesic effects of the μ -opioid agonist, while antagonizing the peripheral effects of the analgesic medication on the gastrointestinal adverse effects, typically constipation. Naloxegol and TD-1211 are prototypes in the PAMORA class, for which phase IIB or III studies have been presented in the last year. The chloride channel activator, lubiprostone (24 μ g, b.i.d.), is an alternative that is also efficacious and approved for the treatment of opioid-induced constipation (OIC, see below), though it does not inhibit the effects of the μ -opioid receptor agonist.

Naloxegol is an oral PEGylated conjugate of naloxone, an antagonist at μ - (highest affinity), κ -, and δ -OR. It is rapidly absorbed, antagonizes the opioid receptor agonist peripherally and, since it has low central nervous system penetration, it does not inhibit the analgesic actions. Three randomized, controlled trials in OIC showed that 12.5 or 25mg/day of naloxegol significantly increased numbers of spontaneous bowel movements (SBMs), and there were more symptom responders among OIC patients over 12 weeks based on a rigorous, composite, FDA-sanctioned endpoint (3 SBM/week, with 1 SBM/week increase over baseline for at least 9 of 12 weeks and at least 3 of the last 4 weeks of the trial). There was no evidence of opioid withdrawal or reversal of analgesia with treatment with naloxegol (41,42,43).

TD-1211 is a PAMORA with high affinity for human μ - and δ -opioid receptors, and its *in vitro* receptor selectivity was $\mu \approx \kappa > \delta$ (44). TD-1211 reverses opiate-induced inhibition of colonic motility without reversing the central or analgesic effects of the μ -opioid analgesic (45). In a phase IIB, 3 dose level, placebo-controlled study consisting of a 1-week baseline and a 4-week treatment phase conducted in 217 chronic non-cancer pain patients with OIC, TD-1211 (10 and 15mg) significantly increased SBMs and complete SBMs per week, and increased the proportion of patients with response on a constipation symptom global assessment compared to placebo (46).

Whereas, neither of these PAMORAs are currently marketed, the chloride secretagogue, lubiprostone (a prostaglandin E1-derived bicyclic fatty acid), is approved by the FDA at a dose of 24 μ g, 2 times per day, for the treatment of OIC related to non-cancer pain, based on three phase IIB or III trials (47,48). In vitro studies suggest that lubiprostone may not be effective in reversing OIC caused by methadone treatment (49).

Ghrelin Agonist

Ghrelin belongs to a family of peptides that includes acyl-ghrelin and des-acyl ghrelin, which have opposite effects on gastric motility and appetite (increased with acyl-ghrelin). The enzyme, ghrelin-o-acyl transferase (GOAT), is essential for acylation of ghrelin, and the growth hormone secretagogue receptor (GHSR) is essential for the binding of ghrelin, and for the various actions of ghrelin on the gastrointestinal tract (50). Prior studies showed that ghrelin promotes gastric motility in animal models and, in humans, it accelerates gastric emptying and reduces gastric accommodation without inducing dyspepsia (reviewed in ref. 51). At infusion rates that mimic physiological concentrations of native ghrelin, the

synthetic formulation of human ghrelin did not accelerate gastric emptying in healthy normal weight or obese humans (52). Recent experience with ghrelin receptor agonists that have a macrocycle structure (TZP-101, TZP-102) has not confirmed earlier promising results (53); however, there is little evidence that ghrelin receptors downregulate with repeated treatment, and therefore stimulation of ghrelin receptors could still be potentially effective in accelerating gastric emptying (54).

RM-131 (relamorelin) is a synthetic pentapeptide ghrelin receptor agonist with similar characteristics as native ghrelin, but with a 100-fold greater potency in reversing gastric ileus in animal models and a longer plasma $T_{1/2}$. RM-131 (100µg/day, s.q.) accelerated gastric emptying in patients with type 1 or 2 diabetes who had upper gastrointestinal symptoms (55,56). In a phase 2, randomized, double-blind, placebo-controlled trial of 10µg RM-131 in 204 patients with diabetic gastroparesis (12% T1DM, 88% T2DM) consisting of a 28-day treatment period after a 1-week, single-blinded, placebo run-in, RM-131 enhanced gastric emptying and reduced vomiting episodes and vomiting severity. In the 58.3% of patients with vomiting at baseline, all three endpoints also improved and, in addition, there was reduction in composite score of nausea, abdominal pain, bloating and early satiety (each measured on a 0-10 scale) (57).

Ghrelin receptors are identified throughout the gastrointestinal tract, including the colon (58). Ghrelin hyperpolarized resting membrane potential of human colon circular smooth muscle cells (59), suggesting that it has also functional effects on colonic motility.

In a phase IIa pharmacodynamics study, RM-131 (100µg/day, s.q.) accelerated gastric, small bowel, and colonic transit, and improved stool consistency in patients with functional constipation (60). The acceleration of colonic transit appears to be centered on the region of the colon beyond the ascending region. This suggests that conditions that cause constipation and have impaired parasympathetic supply to the left colon (such as spinal cord injury or central neurological disorders) might be appropriate groups for RM-131 therapy.

Conclusion

There is a highly promising pipeline of medications for conditions in the field of neurogastroenterology. For many mediations discussed here, there is sufficient proof of concept to warrant further drug development. It is hoped that advances in defining appropriate endpoints for regulatory approval (already available for disorders associated with constipation and IBS) will facilitate the development of medications in areas with high unmet need, such as gastroparesis. For example, advances in validation, performance and understanding of the American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index endpoint based on a daily diary (61) augur well for patients with gastroparesis, based on extensive collaboration between academia and the Food and Drug Administration.

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Figure 1.

Pharmacological agents impacting neurogastroenterology: Obeticholic acid is an FXR agonist that reduces bile acid synthesis by hepatocytes. Multiple mechanisms alter secretory function (guanylate cyclase C agonist and chloride channel activator), motility and secretion (μ opioid agonist and δ antagonist and PAMORA, 5-HT₄ agonist), sensation (5-HT₃ antagonist NK₂ antagonist), immune function (H₁ antagonist and NK₂ antagonist) and mucosal barrier function (glutamine).