New and Emerging Treatment Options for Chronic Constipation

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Chronic constipation remains a therapeutic challenge for today’s physicians. Traditional approaches include use of fiber, osmotic laxatives, stimulant laxatives, prokinetic agents, biofeedback training, and surgery. These often are tried sequentially and episodically and have little evidence of long-term efficacy. Patients often report inadequate relief of symptoms. There is room for improvement, therefore, in the therapy of chronic constipation. Future advances largely will be based on insights into the enteric nervous system (ENS), the structure and function of which is being revealed in great detail. Manipulating the ENS pharmacologically offers the opportunity to reprogram this key control system to improve bowel function. For example, interneurons in the ENS display 5-HT4 receptors, activation of which enhances the peristaltic reflex. Prokinetic agents that stimulate those receptors, such as tegaserod and prucalopride, have demonstrated efficacy as investigational agents for the treatment of chronic constipation in large studies. Less well studied investigational drugs with presumed activity in the ENS include opiate antagonists and the nerve growth factor neurotrophin-3. Both of these types of agents have been shown to be effective in small groups of patients with constipation. Another approach under development is to stimulate colonic fluid secretion by opening chloride channels in the epithelium pharmacologically. Existing non-pharmacological treatments that can be improved include biofeedback training for pelvic floor dysfunction and surgery. Future developments include investigation of electrical stimulation of the colon and use of stem cells to repopulate degenerated populations of neurons, interstitial cells of Cajal, or smooth muscle cells.

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Current approaches to chronic constipation often fail to control the patient’s symptoms adequately, produce problematic side effects, or lose effectiveness with time; thus new therapies are needed.
Most available and approved drugs for constipation have been passed down from antiquity and have not been tested in modern, well-designed studies; their use depends more on custom than on science.¹ Physicians often prescribe drugs for constipation with which they are familiar and comfortable without regard to the underlying pathophysiology. In part this is due to the fact that available drugs are not precisely targeted and, in many cases, anything will do. When patients do not respond adequately to these empiric treatments—as is often the case—the need for better treatments becomes evident.

Nonpharmacological treatments for constipation, such as pelvic floor biofeedback training and surgery, are employed more selectively by physicians but often fail, probably due to defects in the selection of patients for these treatments. Improvements in these modalities also are needed.

It is the author’s belief that progress in the treatment of constipation will come as its pathophysiology is unraveled, particularly defects in the enteric nervous system (ENS), which seem to underlie most cases of slow-transit constipation and problems with the control mechanisms of the muscles of the pelvic floor, which are the basis for pelvic floor dyssynergia.² Of course, new drugs and techniques that can correct these defects will need to be developed before targeted therapy is feasible.

This review will briefly consider some of the drugs and techniques that are being developed for patients with chronic constipation and how they may be used in the future.

### Potential Pharmacological Targets in the ENS

Over the last 20 years the neuroanatomy, neurochemistry, and electrical properties of the ENS have been defined with unprecedented precision.⁶⁻⁻¹⁰ The role of the interstitial cells of Cajal as intermediaries between the ENS and smooth muscle also has been sorted out.¹¹ It has become clear that the ENS has all the functionality of a complete neural system with sensory, integrative, and motor neurons. Although the ENS is connected to the central nervous system by the autonomic nerves, much of the activity of the gut is regulated locally.¹²

Peristalsis is an excellent example of a function of the gut that is integrated locally.⁸⁻⁻¹³ As outlined in Figure 1, the intrinsic primary afferent neuron (IPAN) has dendrites in the vicinity of the epithelium that have receptors for a variety of substances and can respond to a number of inputs.¹⁶ For example, 5-HT₁p receptors on the dendrites depolarize the IPAN in response to serotonin (5-HT) released by enterochromaffin cells interspersed in the mucosa.¹⁷ These enterochromaffin cells have microvilli and can sense changes in luminal contents. They also release 5-HT in response to mechanical stimulation and in response to bacterial toxins, such as cholera toxin.¹⁸ Activation of the IPAN causes release of calcitonin gene-related peptide from the axonal terminals, which then activates interneurons in the myenteric plexus. This release is facilitated by 5-HT₄ receptors on the axon.¹⁹ The interneurons run proximally and distally in the gut. The chain of interneurons uses several different neurotransmitters, including acetylcholine, met-enkephalin, and somatostatin, to eventually cause proximal circular muscle contraction.

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**Figure 1. Schematic diagram of the enteric nervous system.** Serotonin (5-HT) released from the enterochromaffin cells in the mucosa in response to physical or chemical stimuli diffuses to the dendrite of the intrinsic primary afferent neuron where it interacts with 5-HT₁p receptors to depolarize the neuron. This in turn releases calcitonin gene-related peptide (CGRP) at the axon terminal, which activates the chain of interneurons and ultimately results in contraction of the proximal circular smooth muscle and relaxation of the distal circular smooth muscle—the peristaltic reflex—which can propel intraluminal material distally. Ach, acetylcholine; SP, substance P; VIP, vasoactive intestinal polypeptide; NO, nitric oxide; GI, gastrointestinal. Adapted with permission from Grider JR et al. Gastroenterology. 1998;115:370-380⁰ and Gershon MD. Rev Gastroenterol Disord. 2003;3(suppl 2):S25-S34.¹⁴
mediated by motor neurons secreting acetylcholine and tachykinins (eg, substance P), and distal circular muscle relaxation mediated by motor neurons secreting vasoactive intestinal polypeptide and nitric oxide. The longitudinal muscle is regulated reciprocally, and relaxes proximally and contracts distally. Each of the receptors in this chain is a potential target for pharmacological intervention with agonists or antagonists. Although reasonable predictions can be made about the effect of these agents on gut motor function in normal individuals, less can be said about the effects of drugs in patients in whom the enteric nervous system may be damaged.

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in patients in whom the ENS may be damaged. If neurons are lost due to infection or degeneration, their receptors are no longer present to interact with drugs, and so the effects of medications may be less pronounced. In the future some assessment of the damage to the ENS may allow better targeting of drug therapy.

The functional anatomy of the ENS also explains why some agents that would seem to have a rational place in the therapy of constipation have not been all that effective. For example, in many patients with slow-transit constipation the amplitude of contractions is low. Increasing the intensity of contractions with a muscarinic agonist drug would seem to be useful, yet use of muscarinic drugs, such as bethanechol, is generally disappointing. This may be because coordinated contraction and relaxation (ie, peristalsis)—not just stronger contractions—is what is needed to propel luminal contents forward in chronic constipation. Neostigmine, which increases acetylcholine levels at all cholinergic synapses (including those in the myenteric plexus with M1 receptors), enhances coordinated colonic propulsion. This may account for its success in the management of acute colonic pseudo-obstruction.  

Peripheral 5-HT4-Receptor Agonists

Because of the role of 5-HT4 receptors in enhancing the peristaltic reflex, researchers have designed agents with agonist activity for use in patients with chronic constipation. Two of these drugs, prucalopride and tegaserod, have been studied in large groups of patients with chronic constipation. Prucalopride is a member of a novel class of drugs known as benzofuran-2-carboxamides and is a full agonist at 5-HT4 receptors (Figure 2). It was thought that this drug would be an improved version of cisapride, a benzamide prokinetic agent that occasionally caused cardiac arrhythmias due to blockade of potassium channels in the heart (due to its chemical structure, not its 5-HT4-agonist activity). Preliminary studies showed that prucalopride sped colonic transit in normal subjects and constipated patients.

Two large randomized, controlled trials including more than 1200 patients were then mounted and confirmed that prucalopride in doses of 2 or 4 mg daily increased the number of complete, spontaneous bowel movements over 12 weeks of therapy as compared to placebo. Prucalopride did not help everyone in the studies; only 29% of patients treated with prucalopride had 3 or more complete, spontaneous bowel movements per week, but this was a significantly greater proportion than those patients treated with placebo (13%, P < .003). The absolute treatment benefit was therefore 16% and the number needed to treat was 6. Considering the fact that more than half of the study subjects assessed themselves as having “severe” or “very severe” constipation and had a median of zero complete spontaneous bowel movements before treatment, these modest results suggest that the drug provided an important benefit to some of the patients. Many subjects experienced enough benefit to want to continue the drug chronically beyond the 12-week study period.

Despite these results, studies with prucalopride were suspended when safety concerns about cardiac arrhythmias were raised. Although not fully worked out, it is likely that this side effect is due to the chemical structure of the drug and not 5-HT4-receptor agonist activity (Figure 2). As of this
writing, it is unlikely that prucalo-pride will ever be marketed for constipation or any other indication. Nevertheless, its efficacy in treating constipation is proof of the principle that 5-HT₄-receptor stimulation can be useful clinically.

A more feasible approach to stimulation of peripheral 5-HT₄ receptors may be use of the drug tegaserod. This partial 5-HT₄ agonist has been approved by the US Food and Drug Administration for the treatment of irritable bowel syndrome with constipation and has compiled an admirable safety record in clinical trials and general use.³¹-³⁵

Tegaserod is designed to mimic the molecular structure of serotonin, but has been modified by addition of a hydrophilic tail that prevents easy passage across the blood-brain barrier, effectively limiting its action to the peripheral nervous system (Figure 3). It is the first drug in a new chemical category, the aminoguanidine indoles.³⁶-³⁸ This class of drugs does not block cardiac potassium channels and would not be expected to cause cardiac arrhythmias. This expectation has been confirmed in clinical trials involving more than 1600 patients given therapeutic doses and in a small study in healthy volunteers given up to three times the usual dose.²⁹ In both of these settings there was no effect on the electrocardiogram.

Two large well-designed, randomized, placebo-controlled studies with tegaserod have been completed in patients with chronic constipation, one done mainly in North and South America and one done mainly in Europe and Africa.⁴⁰ Patients were included if they had fewer than three complete, spontaneous bowel movements weekly and additional evidence of difficulty with evacuation at least 25% of the time (hard or very hard stools, sensation of incomplete evacuation, straining with defecation). Those with known systemic or local causes of constipation were excluded. Each study randomized more than 1000 patients who were divided into three groups taking tegaserod 2 mg or 6 mg or placebo twice daily before meals. Patients of the North and South American study 43% of the higher dose tegaserod group but only 25% of the placebo group successfully met the primary outcome variable of an increase of one or more complete, spontaneous bowel movements per week (Figure 4). This statistically significant improvement was mirrored in the European and African trial. The absolute benefit was 18%, making the number needed to treat equal to 6. This benefit was sustained over the 12 weeks of the trials (Figure 5).

Significant improvements also were noted in secondary outcome variables, including the number of complete, spontaneous bowel movements, time to first bowel movement, straining with defecation, distention and bloating, abdominal discomfort or pain, satisfaction with bowel habits, and bothersome constipation.

As important as the efficacy data, tegaserod again proved to be very safe during these studies. The main reported side effects were diarrhea and headache. Discontinuation of study drug because of side effects was uncommon.

In both studies women outnumbered men by about 9 to 1. The number of complete, spontaneous bowel movements, time to first bowel movement, straining with defecation, distention and bloating, abdominal discomfort or pain, satisfaction with bowel habits, and bothersome constipation.

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tegaserod for constipation. It is likely that the initial approval for this indication will be restricted to women as with irritable bowel syndrome with constipation.

The official labeling for tegaserod has been altered recently to reflect post-marketing reports of adverse events. Doctors have been advised to look out for severe diarrhea and for intestinal ischemia in patients treated with tegaserod. It is not known whether or not these conditions are causally related to use of the drug, but the conservative approach would be to stop the drug in patients treated with tegaserod who present with dehydrating diarrhea, new onset abdominal pain, or rectal bleeding until they can be evaluated further.

Opiate Antagonists

Another important signaling system in the ENS involves neurons secreting endogenous opiates and δ-opiate receptors. Release of endogenous opiates and their interaction with postsynaptic receptors slows peristalsis. This is the mechanism co-opted by exogenous opiates that commonly causes constipation. Although a case report published 20 years ago suggested that naloxone, an opiate antagonist, could improve symptoms of chronic idiopathic constipation not associated with opiate therapy, most attention has been focused on using opiate antagonists to reverse opiate-induced constipation.

The problem in employing these agents clinically has been that available opiate antagonists penetrate the blood–brain barrier and affect opiate receptors in the central nervous system. Thus one might mitigate opiate-induced constipation by administering an opiate antagonist, but at the price of reducing the opiate’s effectiveness as an analgesic. Trials of two opiate antagonists that cannot cross the blood–brain barrier, methylnaltrexone and alvimopan, have commenced and suggest that peripheral opiate antagonists may be efficacious in opiate-induced constipation and postoperative ileus. Because animal studies and experience with intrathecal opiate infusion in patients suggest that administration of opiates centrally may still cause constipation, additional proof-of-concept studies are needed.

Endogenous opiates also inhibit fluid and electrolyte secretion from the lumen by direct and indirect effects on enterocytes mediated via δ-opiate receptors. Increasing secretion by blockade of this mechanism would result in more fluid retention intraluminally and might mitigate constipation. Measurement of the...
effect of a δ-opiate receptor antagonist on intestinal fluid and electrolyte absorption in patients with constipation could address the significance of that mechanism and might suggest another therapeutic approach to chronic constipation.

**Neurotrophin-3**

Molecular biology has identified many cellular growth factors that stimulate the growth of cells and their maintenance by interacting with receptors on the cell surface. One of these is neurotrophin-3 (NT-3), a peptide that enhances the development of neurons in vitro. Diseases like Parkinson’s disease and Alzheimer’s disease involve loss of functioning neurons and so attempts were made to treat patients who had these conditions with injections of NT-3 in hope of growing new neurons and synapses to replace those lost. Although there was no demonstrable improvement in neurological function during clinical trials, diarrhea was a prominent side effect and so a study was mounted to see if injected recombinant methionyl-human NT-3 could help patients with constipation. NT-3 accelerated colonic emptying and stool frequency in a group of 8 patients with constipation.

Larger randomized, double-blind, placebo-controlled dose-ranging study was then conducted. Although many of the patients included in the study had end-stage constipation and were laxative- or enema-dependent, NT-3 in a dose of 9 mg three times a week subcutaneously increased the frequency of bowel movements from an average of one per week to five per week (P < .001) (Figure 6). Side effects were minimal.

It is unclear what the mechanism of action was. Because the response occurred so rapidly, it is unlikely that any new neurons were created. Although neurons in the ENS have receptors for growth factors, the effect of NT-3 on the electrophysiology of the enteric neurons is unexplored as yet. One paper found no effect of NT-3 on colonic motility or propulsion and speculated that the effect of NT-3 in patients with constipation is due to stimulation of fluid and electrolyte secretion.

**Chloride-Channel Activators**

One class of investigational drugs that doubtless has an effect on mucosal transport are agents that open mucosal chloride channels. Fluid secretion by the gut is dependent upon chloride secretion, which is mediated by chloride channels in the apical membrane of the enterocyte. This is the mechanism co-opted by many bacterial toxins to cause secretory diarrhea. Drugs that could open chloride channels theoretically might be very effective anti-constipation agents.

One such drug, RU-0211, has been subjected to two clinical trials in patients with constipation and had a salutary effect each time. In a dose-ranging study bowel movement frequency improved significantly with 48 or 72 µg doses and subjects had adequate relief of global constipation symptoms with the drug. The main drug-associated side effect was nausea, but only a few patients withdrew because of this and no patient developed dehydrating diarrhea. A follow-up, phase III trial of 242 patients again demonstrated a statistically significant increase in bowel movement frequency (an increase in weekly spontaneous bowel movement frequency from a range of 2.8–3.5 in the placebo group to a range of 5.1–5.7 in the RU-0211 group, P < .002) with a dose of 24 µg twice daily. Again, straining, stool consistency, and global assessment of efficacy improved significantly with the active drug. Only 9 subjects withdrew because of adverse events. Further reports are awaited with interest.

**Nonpharmacological Therapies**

Two nonpharmacological therapies are used with some frequency today: biofeedback training and subtotal colectomy with ileorectal anastomosis. Both treatments—while effective...
in selected patients—could be improved substantially.

Biofeedback training is used in patients with outlet obstruction constipation (dyschezia) due to incoordination of the skeletal muscles of the pelvic floor and external anal sphincter during defecation.\textsuperscript{61,62} These patients do not open the rectal outlet fully and therefore have difficulty expelling stool. They are identified by a constellation of symptoms (inability to expel stool that is in the rectum, incomplete evacuation, need for digital manipulation to facilitate defecation) and usually have abnormalities on one or more functional tests, including anorectal manometry, balloon expulsion, electromyography, or defecography.

Patients with this problem are taught proper defecation techniques and practice relaxation of the pelvic floor muscles and external sphincter to facilitate defecation. The biofeedback part is to relay information about the contractile state of those muscles by means of manometry or electromyography so that patients can understand what they are doing and perfect it.

Although good results have been reported from many centers (usually case-series or other uncontrolled observations), it has been difficult to get consistently good results in many centers and so the availability of biofeedback training for constipation is limited.\textsuperscript{62} It is not known whether the inconsistent results in different centers are due to variation in technique, personnel, or patients. Simplification and shortening of the process would also be useful. Better criteria for patient selection need to be evaluated.

Patient selection is also an issue for surgery. Subtotal colectomy with ileorectal anastomosis is reserved for patients with refractory symptoms and should be a rare operation at most centers.\textsuperscript{63-65} Bad results can occur in patients with concomitant, unrecognized functional outlet obstruction or small-bowel dysmotility, and those with substantial abdominal pain who have a high rate of postoperative bowel obstruction. It is essential that better criteria for patient selection be developed to avoid unfortunate results.

**Colonic Electrical Stimulation**

Because gastrointestinal smooth muscle contracts in response to changes in the transmembrane electrical potential, researchers have long sought to develop “pacemaker” devices for conditions like ileus and gastroparesis. The only device to make the jump from the laboratory to the clinic is a gastric electrical stimulator.\textsuperscript{66} However, this device does not “pace” the stomach in the sense that it makes gastric muscles contract. To do so would require high currents that are sensed as painful and can cause contractions of the abdominal wall as well as the stomach. Instead, the currently available device uses a high-frequency, low-voltage stimulus that cannot entrain gastric smooth muscle contraction but reduces nausea and vomiting, presumably by stimulating the ENS or elements of the autonomic nerves that innervate the stomach.

Three different approaches to elec-

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**Main Points**

- Current approaches to chronic constipation, including use of fiber, osmotic laxatives, stimulant laxatives, prokinetic agents, biofeedback training, and surgery, often fail to control the patient’s symptoms adequately, produce problematic side effects, or lose effectiveness with time.

- Progress in the treatment of constipation will come as its pathophysiology is unraveled, particularly defects in the enteric nervous system, which seem to underlie most cases of slow-transit constipation, and problems with the control mechanisms of the muscles of the pelvic floor, which are the basis for pelvic floor dysynergia.

- Because of the role of 5-HT\textsubscript{4} receptors in enhancing the peristaltic reflex, researchers have designed agents with agonist activity for use in patients with chronic constipation.

- Tegaserod, which is already approved by the FDA for the treatment of irritable bowel syndrome with constipation, has been shown to be safe in clinical trials and general use. Results from several large studies in patients with chronic constipation have been encouraging.

- Trials of two opiate antagonists that cannot cross the blood–brain barrier, methylnaltrexone and alvimopan, have commenced and suggest that peripheral opiate antagonists may be efficacious in opiate-induced constipation and postoperative ileus without reducing the opiate’s effectiveness as an analgesic.

- Two nonpharmacological therapies used with some frequency, biofeedback training and subtotal colectomy with ileorectal anastomosis, often show disappointing results.
Clinical stimulation are being investigated for treatment of constipation. In one approach patients with impaired rectal sensation have been selected to receive the same sort of sacral nerve electrical stimulation used to treat urinary or fecal incontinence. The sensory threshold for desire to defecate and the frequency of the sensation of the need to defecate increased from baseline after stimulation. Studies in animals suggest that propagated contractions can be stimulated that are similar to those occurring with spontaneous defecation. Another approach is designed to induce peristalsis in the colon by use of microprocessor-controlled sequential electrical stimulation and has only been tried in a canine model of constipation (dogs receiving diphenoxylate/atropine). Colon transit improved without gross evidence of discomfort during stimulation. Development of a device suitable for use in human beings is underway. A third approach has been tried in patients with spinal cord injury and involves electrical stimulation of the abdominal wall muscles to facilitate defecation. Stimulating these muscles halved the time necessary to have an initial bowel movement and significantly reduced the time required for bowel care.

The Future

Since slow-transit constipation seems to be due to problems with the ENS, interstitial cells of Cajal, or smooth muscle cells, replacement of the missing or defective cells would be an attractive way of treating constipation at a fundamental level. Taking advantage of the rapidly evolving technology of stem cells to grow precursors to these cells should be easy; distribution of the cells to their proper locations in the gut and getting them properly wired are the hurdles that must be surmounted. Yet one cannot be anything but optimistic that this can be achieved in time as we better understand the embryological mechanisms that create the colon—and its nervous system—in the first place.

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