

Serotonin and Its Role in Colonic Function and in Gastrointestinal Disorders

Meagan M. Costedio, M.D.,¹ Neil Hyman, M.D.,¹ Gary M. Mawe, Ph.D.²

¹ *Department of Surgery, University of Vermont College of Medicine, Burlington, Vermont*

² *Department of Anatomy and Neurobiology, University of Vermont College of Medicine, Burlington, Vermont*

Serotonin (5-HT) is most commonly thought of as a neurotransmitter in the central nervous system. However, the predominant site of serotonin synthesis, storage, and release is the enterochromaffin cells of the intestinal mucosa. Within the intestinal mucosa, serotonin released from enterochromaffin cells activates neural reflexes associated with intestinal secretion, motility, and sensation. Two important receptors for serotonin that are located in the neural circuitry of the intestines are the 5-HT₃ and 5-HT₄ receptors; these are the targets of drugs designed to treat gastrointestinal disorders. 5-HT₃ receptor antagonists are used to treat nausea and emesis associated with chemotherapy and for functional disorders associated with diarrhea. 5-HT₄ receptor agonists are used as promotility agents to promote gastric emptying and to alleviate constipation. Because of the importance of serotonin in normal gut function and sensation, a number of studies have investigated potential changes in mucosal serotonin signaling in pathologic conditions. Despite the inconsistencies in the current literature, changes in serotonin signaling have now been demonstrated in inflammatory bowel disease, irritable bowel syndrome, postinfectious irritable bowel syndrome, and idiopathic constipation. Emerging evidence has led to many contradictory theories regarding serotonin signaling and its roles in the pathology of gut disorders. This review summarizes the current medications affecting serotonin signaling and provides an overview of our current knowledge

of the changes in serotonin that occur in pathologic conditions. [Key words: Irritable bowel syndrome; Constipation; Enterochromaffin cells; 5-HT₃ and 5-HT₄ receptors]

SEROTONIN AND THE COLON

Over one hundred years ago, Bayliss and Starling noted that the bowel is capable of generating complex motor patterns independent of the central nervous system (CNS) when stimulated by stretch, pH alterations, or nutrients. These factors incite a propulsive wave of coordinated contractions and relaxations we now refer to as peristalsis.¹⁻³ The cellular components and signaling molecules that are responsible for this coordinated reflex continue to be actively investigated and better defined.

Serotonin was discovered in the 1930s by Vittorio Erspamer, who named the substance “enteramine” because it was extracted from the intestine.^{4,5} The same substance was independently extracted from blood samples in 1948 by Page and Rapport in their search for circulating constricting factors that could cause hypertension.^{6,7} Unaware that they were working with “enteramine,” Page and Rapport called the compound serotonin, because of its vasoconstrictive action, and subsequently identified its structure as 5-hydroxytryptamine (5-HT). Bulbring and Crema first implicated 5-HT as an important enteric neurotransmitter in the late 1950s. It is now clear that 5-HT is a critical signaling molecule in the gut.^{3,8,9}

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Correspondence to: Gary M. Mawe, Ph.D., Department of Anatomy and Neurobiology, University of Vermont College of Medicine, D403A Given Building, Burlington, Vermont 05401, e-mail: gary.mawe@uvm.edu

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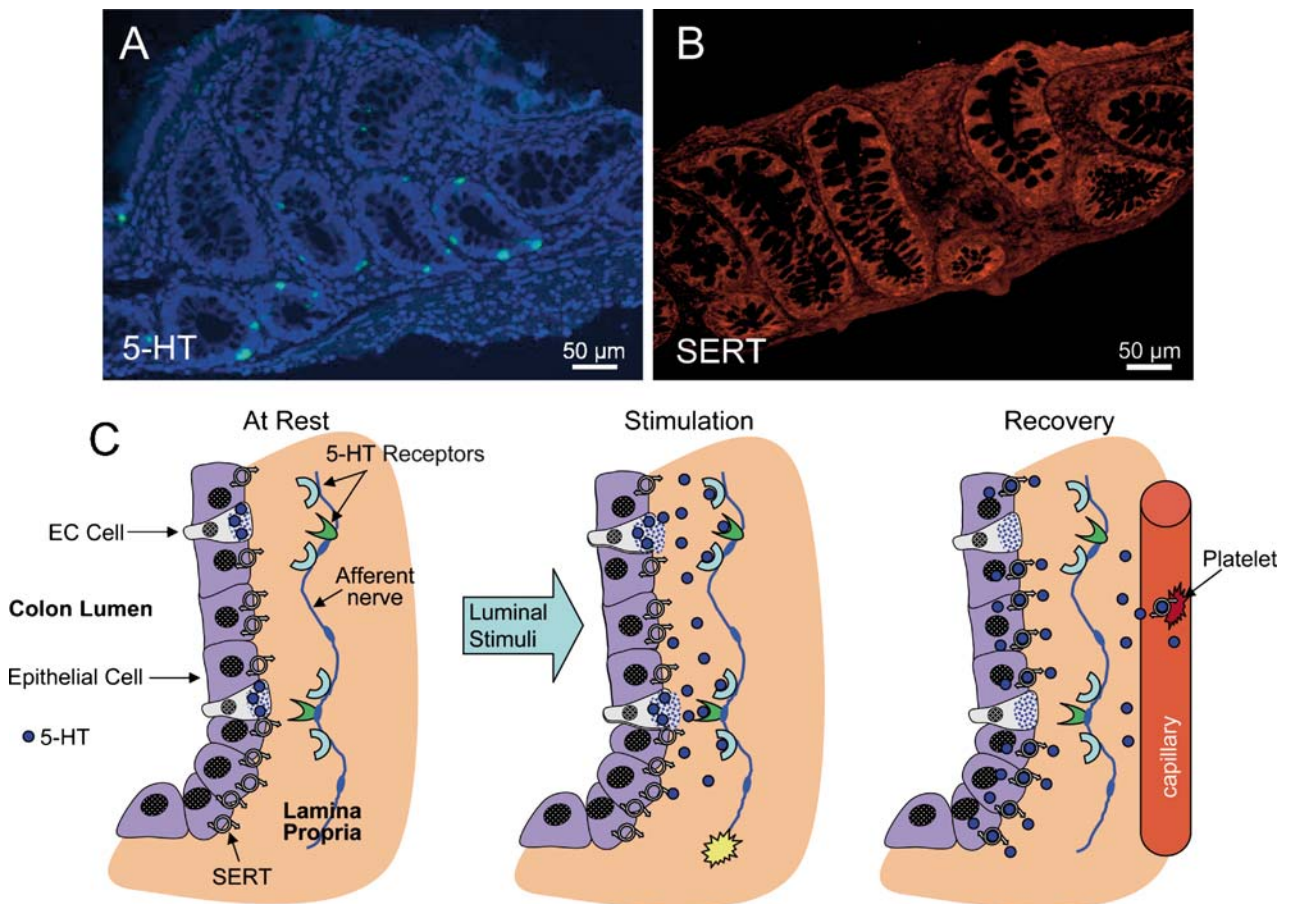


Figure 1. A. Photomicrograph of EC (enterochromaffin) cells in the mucosa of the human sigmoid colon. This specimen was immunostained with antisera directed against human 5-HT (serotonin), and the EC cells are depicted in green. EC cells are the primary site of 5-HT synthesis, storage, and release in the body. B. SERT (serotonin-selective reuptake transporter) immunoreactivity in colonic glands of the human colon. Note that all of the epithelial cells are SERT-immunoreactive and that the immunofluorescence is particularly intense in the basal half of the cells. C. Schematic diagram depicting the sequence of events in mucosal 5-HT signaling. At rest, 5-HT (depicted as blue circles) is stored in secretory vesicles at the basal half of EC cells. Following mucosal stimulation, 5-HT is released from EC cells and activates 5-HT receptors on nearby afferent nerve fibers. 5-HT signaling is terminated by the removal of 5-HT from the interstitial space. Most of the 5-HT is transported into epithelial cells, all of which express SERT. The remainder of the 5-HT enters the blood stream and is taken up into platelets, which also express the serotonin transporter.

Recent evidence suggests that altered 5-HT signaling may play a fundamental role in the pathophysiology of many common gastrointestinal disorders.

SEROTONIN SIGNALING

Enterochromaffin (EC) cells, found primarily at the base of the crypts in the gastrointestinal tract, contain appropriate enzymes for the synthesis of 5-HT from the amino acid tryptophan (Fig. 1A). The 5-HT is then stored in secretory granules at the base of the EC cell.^{10,11} Release of 5-HT into the lamina propria beneath the crypt epithelium leads to the activation of multiple types of 5-HT receptors on the axons of

sensory neurons (Fig. 1C). Some of these primary sensory neurons that project to the lamina propria reside in the submucosal and myenteric ganglia of the enteric nervous system (ENS) and are referred to as intrinsic sensory nerves. Others, referred to as extrinsic sensory nerves, have processes that project to the gut from spinal and nodose ganglia. The stimulation of intrinsic primary afferent neurons (IPANs) activates cholinergic excitatory motor neurons and nitergic inhibitory motor neurons *via* ascending and descending interneurons, respectively.^{12–16} The local reflex activity leads to an oral contraction of the smooth muscle and a coordinated aboral relaxation generating a pressure gradient and

peristalsis.^{17,18} Serotonin also participates in extrinsic afferent reflex pathways relating to nausea and vomiting *via* vagal afferents and conduction of signals leading to perceptions of discomfort and pain in the gastrointestinal tract by way of the spinal afferents.^{19,20} This latter pathway is less well defined but may underlie the promising effects that 5-HT receptor ligand medications have on the symptoms of discomfort in those with irritable bowel syndrome (IBS).²¹ Responses of 5-HT are terminated by the removal of 5-HT from the interstitial space. Most of the 5-HT is taken up into the epithelial cells by the serotonin-selective reuptake transporter (SERT), which is the same transporter that sequesters 5-HT in the brain and is the target of serotonin-selective reuptake inhibitors (SSRIs) (Figs. 1B and C). The remainder of the 5-HT enters the bloodstream where it is rapidly taken into platelets which express SERT on their membranes.^{16,22,23}

SEROTONIN RECEPTORS AND TARGETING MEDICATIONS

Serotonin can elicit a number of actions on cells and tissues in the gut, including epithelial secretion, direct smooth muscle activation or relaxation, stimulation of extrinsic and intrinsic sensory neurons, and activation of cholinergic neurons that contract smooth muscle.^{3,8,12,24,25} A number of subtypes of 5-HT receptors, with specific distributions in the intestines, are responsible for the multitude of actions that can be elicited by 5-HT. Serotonin receptors that have been identified to date include 5-HT_{1A-E}, 5-HT_{2A,B,C}, 5-HT₃, 5-HT₄, 5-HT₅, 5-HT₆, and 5-HT₇.¹⁶ The 5-HT₃ and 5-HT₄ receptors are the most thoroughly understood subtypes with regard to gut function, and at this point they are the primary pharmacotherapeutic targets for the treatment of gastrointestinal disorders. Several medications that affect these receptors have been approved for the treatment of nausea, vomiting, pain, discomfort, and increased or decreased gastrointestinal motility; therefore, these receptors, and the compounds that act on them, are discussed in further detail below (Table 1).

5-HT₃ Receptors

The 5-HT₃ receptor is a ligand-gated ion channel that causes a rapid and transient excitatory response when activated by 5-HT. Like most ligand-gated ion channels, 5-HT₃ receptors quickly desensitize with

continuous exposure to an agonist. Within the ENS, 5-HT₃ receptors are located on the processes of intrinsic and extrinsic sensory neurons and on the cell bodies of most enteric neurons.^{16,58-61} Therefore, 5-HT₃ receptor activation of intrinsic afferent fibers can initiate peristalsis, secretion, and vasodilation in the gut, while extrinsic afferent nerve fiber activation can trigger homeostatic, emetic, and nociceptive reflexes. The wide variety of effects that 5-HT₃ receptors have explains why so much effort has been expended to develop selective and effective 5-HT₃ receptor antagonists for the treatment of nausea and vomiting associated with chemotherapy and the symptoms of irritable bowel syndrome with diarrheal predominance (IBS-D).

5-HT₃ Receptor Agonists

Because of the location of 5-HT₃ receptors in the enteric reflex circuitry, it is plausible that 5-HT₃ receptor agonists could act as prokinetics. However, to avoid tachyphylaxis as a result of the rapidly desensitizing property of this receptor and the nausea and vomiting that typically occur in response to vagal afferent stimulation, it is likely that only partial agonists would be effective pharmacotherapeutic agents. The effects of the partial 5-HT₃ agonist MKC-733 have been tested in a gastric emptying assay,²⁶ but data are lacking with regard to colonic function and sensitivity. This medication is not currently FDA approved.

5-HT₃ Receptors Antagonists

Chemotherapeutic agents are known to elicit an abnormal 5-HT release in the gut, and 5-HT₃ antagonists work, in part, by blocking 5-HT₃ receptors on intestinal afferent fibers.²⁷ A number of 5-HT₃ antagonists have been approved by the FDA to decrease the sensation of nausea associated with chemotherapy, including ondansetron, granisetron, dolasetron, and ramosetron.³⁵ These agents also decrease postprandial motility and visceral sensitivity,^{62,63} therefore, 5-HT₃ receptor antagonists have been investigated for use in IBS-D.

Alosetron is a 5-HT₃ receptor antagonist that is ten times more potent than ondansetron and was developed specifically for IBS-D.⁴² This drug prolongs colonic transit but has minimal effect on colonic visceral sensation in healthy volunteers.³⁰ Four large randomized, double-blind, placebo-controlled trials

Table 1.
Overview of Medications Affecting 5-HT₃ and 5-HT₄ Receptors

Class/Medication	Receptor Target/Action	Effect
5-HT ₃ receptor agonists MKC-733 ²⁶	5-HT ₃ receptor/agonist	Increased upper GI motility
5-HT ₃ receptor antagonists Ondansetron ^{a26,27}	Block 5-HT ₃ receptors/antagonist	Decreased nausea, vomiting, nociception, and motility
Granisetron ^{a26,27}	Block 5-HT ₃ receptors/antagonist	Decreased nausea, vomiting, nociception, and motility
Dolasetron ^{a26,27}	Block 5-HT ₃ receptors/antagonist	Decreased nausea, vomiting, nociception, and motility
Palonosetron ^{a26,27}	Block 5-HT ₃ receptors/antagonist	Decreased nausea, vomiting, nociception, and motility
Ramosetron ^{26,27}	Block 5-HT ₃ receptors/antagonist	Decreased nausea, vomiting, nociception, and motility
Alosetron ^{b28–32}	Block 5-HT ₃ receptors/antagonist	Decreased nociception and colonic motility, enhanced GI absorption
Cilansetron ^{28,33}	Block 5-HT ₃ receptors/antagonist	Expected decreased nociception and colonic motility
5-HT ₄ receptor agonists Tegaserod ^{c34–40}	5-HT ₄ receptor/agonist	Increased motility and secretion, decreased nociception
Cisapride ^{35,41–43}	5-HT ₄ receptor/agonist & weak 5-HT ₃ receptor/antagonist	Increased upper > lower GI motility
Prucalopride ^{26,42,44–48}	5-HT ₄ receptor/agonist	Increased GI motility
5-HT ₄ receptor antagonists Piboserod ^{35,49–52}	5-HT ₄ receptor/antagonist	Decreased GI motility and secretions
Mixed activity medications Renzapride ^{d35,53–55}	5-HT ₄ receptor/partial agonist and 5-HT ₁ ,5-HT ₃ receptor/antagonist	Increased gastroduodenal motility and secretion
Mosapride ^{56,57}	5-HT ₄ receptor/partial agonist, metabolite = 5-HT ₃ receptor/antagonist	Increased upper GI motility

5-HT = serotonin; GI = gastrointestinal; IBS-D = diarrhea-predominant irritable bowel syndrome; IBS-C = constipation-predominant irritable bowel syndrome; FDA = Food and Drug Administration.

^a FDA-approved for chemotherapy-induced nausea and vomiting.

^b FDA-approved for females with severe IBS-D.

^c FDA-approved for chronic constipation and IBS-C in females.

^d Currently in phase III trials for IBS-C.

have demonstrated that alosetron is associated with a significant improvement in stool frequency, consistency, and abdominal discomfort in women with IBS-D.^{29,31,32,64,65} The most common side effect of alosetron is constipation, but of greater concern is an increased incidence of ischemic colitis (0.15 percent) compared with placebo (0 percent), leading to temporary withdrawal of the drug in 2000 by GlaxoWellcome.⁴² Further investigation demonstrated that the increase in the incidence of ischemic colitis did not correspond with an increase in mortality, and alosetron was reapproved by the FDA on a restricted basis for refractory cases of IBS-D in female patients.

Cilansetron is a second 5-HT₃ receptor antagonist with a mechanism much like alosetron, but it is not

currently FDA-approved. Cilansetron has similar efficacy to alosetron in the female IBS-D subgroup, but the same concern exists with regard to the development of ischemic colitis.^{28,33} Cilansetron did not receive FDA approval and development has been discontinued by Solvay.

5-HT₄ Receptors

The 5-HT₄ receptor is a guanine nucleotide-binding (G) protein-coupled receptor that leads to protein kinase A (PKA) activation resulting in a prolonged excitatory response.^{54,66} The precise distributions of 5-HT₄ receptors in the gastrointestinal tract have not been definitively resolved, but they are clearly located on nerve terminals throughout the

intrinsic reflex circuitry of the gut^{67,68} and may be located on sensory nerve terminals in the lamina propria.⁶⁹ Activation of presynaptic 5-HT₄ receptors results in the facilitation of transmitter release and an augmentation of reflex activity. Thus, stimulation does not initiate motor activity but rather enhances motor function in the intestine.^{70,71} If 5-HT₄ receptors are located on the processes of sensory neurons in the lamina propria, they would contribute to the initiation of reflex activity in response to 5-HT release from EC cells. Therefore, 5-HT₄ receptor agonists are believed to increase gastrointestinal motility in response to intraluminal stimuli, whereas antagonists suppress motor activity.

5-HT₄ Agonists

Tegaserod, an aminoguanidine indole, is a selective partial agonist of 5-HT₄ receptors that has been developed for disorders of slow transit.^{35,38} It is unlikely that tegaserod produces receptor desensitization with prolonged use because it is a partial agonist and, consistent with this, has demonstrated sustained clinical benefit.³⁶ *In vivo*, tegaserod increases the maximum stimulation of peristalsis, to a lesser extent than that seen with 5-HT stimulation, as expected of a partial agonist.^{54,72,73} Placebo-controlled clinical trials of tegaserod have shown promise, demonstrating an increase in the overall number of bowel movements and a decrease in the numbers of days without bowel movements.^{36,37,39} This effect reached significance only in females and there was no significant improvement of abdominal pain. There has been no documented increase in ischemic colitis, gallbladder disorders, or cardiac arrhythmias with the use of tegaserod.^{36,40} Tegaserod is currently FDA-approved for treatment of IBS with constipation predominance (IBS-C) in females and has a Grade A recommendation by the American College of Gastroenterology for chronic constipation in patients under the age of 65.³⁴ There has been some indication that tegaserod may be useful in chronic colonic pseudo-obstruction; however, data remain insufficient to support this use.^{54,74}

Prucalopride is a benzofuran-derived 5-HT₄ receptor agonist that stimulates stomach and ascending colonic emptying in healthy volunteers.^{26,46} Randomized, double-blind, placebo-controlled studies have demonstrated an increase in the number of spontaneous bowel movements in response to prucalopride.^{44,45,47,48} At present, drug development has been halted second-

ary to reports of cardiac arrhythmias and concerns regarding carcinogenicity in animal studies.^{26,42}

Cisapride is a substituted piperidinyl benzamide derivative and is a 5-HT₄ receptor agonist with weak 5-HT₃ receptor antagonist properties.^{35,42} It was developed with the intention of treating both upper and lower gastrointestinal dysfunction. Randomized double-blind, placebo-controlled trials produced mixed results. Overall, only one of four studies was able to show an improvement in IBS-C patients taking cisapride when compared with placebo.^{41,43} Cisapride has been removed from the United States market secondary to the risk of arrhythmias in those with predisposing conditions.^{42,75} In light of the well-documented cardiac risks, cisapride is no longer an alternative for the typical IBS-C patient.

5-HT₄ Receptor Antagonists

The 5-HT₄ receptor antagonist piboserod decreased motility in patients with IBS-D in a small randomized, double-blind, placebo-controlled trial.^{35,49,50} Overall, animal and human studies have shown that 5-HT₄ receptor antagonists have a minimal effect on normal healthy volunteers, but do ameliorate the effects of administered 5-HT or 5-HT₄ receptor agonists.^{49,51} These data suggest that piboserod works in disorders of excess 5-HT but not in the healthy population. There is concern that piboserod may cause atrial fibrillation because of its effects on atrial 5-HT₄ receptors.⁵² As the understanding of gastrointestinal motility disorders expands, there will likely be further development of this class of antagonists because they counteract only the effect of increased serotonin and do not appear to cause secondary gastrointestinal side effects of their own accord.

Mixed-Activity Medications

Renzapride is a mixed 5-HT₁ and 5-HT₃ receptor antagonist and a 5-HT₄ receptor partial agonist.³⁵ Its properties are very similar to those of cisapride, but it has a much less potent effect on potassium channels, which is thought to be the cause of cardiac arrhythmias with cisapride.⁵⁵ One small clinical trial suggested a statistically significant increase in colonic transit and bowel function scores in females with IBS-C.⁵³ Renzapride is currently in a phase III trial for IBS-C, and phase II trials have been completed for IBS with alternating symptoms.

Mosapride is a new 5-HT₄ receptor partial agonist whose metabolite is a 5-HT₃ receptor antagonist. Interestingly, mosapride promotes gastric emptying but has little effect on colonic motility, and there are no reports to date of the same cardiac effects as cisapride.⁵⁶

COLONIC DISORDERS OF ALTERED MOTILITY

Serotonin is an initiator of motor and secretory reflexes and signaler to the CNS. This knowledge has led to a number of investigations of potential changes in 5-HT signaling in enteric disorders that are associated with changes in gut function and/or sensation. Although the cause-and-effect relationship is not yet clearly understood, it is apparent that mucosal 5-HT availability is altered in a variety of intestinal disorders (Table 2).

Inflammatory Bowel Disease (IBD)

Data from animal and human studies indicate that inflammation results in changes in various aspects of mucosal serotonin signaling. Animal studies involving a number of different species and various inflammatory models indicate that inflammation leads to changes in 5-HT content, EC cell numbers, 5-HT release and 5-HT reuptake (Table 2).⁷⁶⁻⁸⁰ Some of these alterations have also been noted in patients with ulcerative colitis or Crohn's disease, although a number of inconsistencies exist.⁸¹⁻⁸⁴ Approximately 50 percent of patients with IBD in long-standing remission have IBS-like symptoms, which may be related to these inflammation-induced alterations in 5-HT signaling.⁹³ These data support the notion that inflammation alters the normal 5-HT signaling cascade producing chronic IBS-like symptoms in addition to the direct effects of the inflammatory response.

Postinfectious IBS (PI-IBS)

Approximately 25 percent of patients who suffer from an acute infectious gastrointestinal illness continue to have symptoms of IBS for months after cessation of the acute disease, most commonly after *Campylobacter jejuni* infection.⁹⁴ The acute infection incites an inflammatory response that is evident in biopsies up to three months after the initial infection. These inflammatory changes are accompanied by an increase in EC cell numbers in those with symptoms

suggestive of PI-IBS. IBS and PI-IBS are two disorders that have a strong resemblance and appear to have similar effects on 5-HT signaling. PI-IBS mimics IBS-D but has a clear inciting illness, and the symptoms may involve the well-established inflammatory effects on 5-HT signaling noted in animal models (Table 2). At present, there are no data on the use of 5-HT₃ receptor antagonists in PI-IBS.

IBS

Irritable bowel syndrome (IBS) has historically been a frustrating disease to both patients and health care professionals because of the lack of objective diagnostic criteria and limited therapeutic options. IBS is a collection of disorders involving diarrhea (IBS-D), constipation (IBS-C), or alternating symptoms and in which pain and discomfort are predominant complaints. This disorder affects up to 15 percent of the population worldwide, but continues to be poorly understood despite its prevalence.⁹⁵ A number of theories exist regarding the etiology of IBS, including mucosal immune activation and associated neuropathic changes, altered perception of visceral stimuli at the level of the CNS, psychological factors, genetic factors, and dysmotility secondary to changes in bowel flora and/or altered serotonin signaling.⁹⁶⁻¹⁰¹ It is likely that combinations of these factors contribute to the pathophysiology of IBS, considering its varied clinical nature, but this review will focus on the data surrounding 5-HT signaling.

Various aspects of 5-HT signaling have been evaluated in relation to IBS, including EC cell numbers, TpH message levels, 5-HT content, 5-HT release, SERT immunoreactivity, SERT message levels, platelet-free serum 5-HT levels, serum 5-HIAA levels, and platelet 5-HT (Table 2).^{81,86-88} Changes in 5-HT signaling have been reported in all of these investigations; however, the results are inconsistent.

Based on findings from animal and human studies, it is possible that altered 5-HT signaling could result in IBS-like symptoms. For example, transgenic mice that lack 5-HT₄ receptors show behavioral changes and decreased colonic motility.¹⁰¹ Furthermore, SERT knockout mice exhibit diarrhea, constipation, or an alternating pattern.¹⁰² A recent study that administered the SSRI paroxetine to mice demonstrated a significant decrease in upper gastrointestinal transit and a significant decrease in stool output.¹⁰³ Many of the medications that act on serotonin receptors de-

Table 2.
Overview of Changes in Mucosal 5-HT Signaling That Have Been Reported in Animal Models and in Human Gastrointestinal Disorders

Model	5-HT Content	EC Cells	5-HT Release	Serum [5-HT]	5-[HIAA]	SERT Expression	Platelet 5-HT
1. Guinea pig							
TNBS colitis Linden <i>et al.</i> ⁷⁶	↑	↑	↑ ^a			↓	
TNBS ileitis O'Hara <i>et al.</i> ⁷⁷	↑	↑	↑			↓	
2. Mouse							
TNBS colitis Linden <i>et al.</i> ⁷⁸	↑ ^b	↔	↔			↓	
<i>T. spiralis</i> ileitis		↑				↓	
Wheatcroft <i>et al.</i> ⁷⁹						↓	
<i>Citrobacter</i> infection	↓	↓	↑			↓	
O'Hara <i>et al.</i> ⁸⁰							
3. Human							
a. Ulcerative colitis							
Coates <i>et al.</i> ⁸¹	↓	↓	↔			↓	
Ahonen <i>et al.</i> ⁸²		↓					
b. Inflammatory bowel disease							
Magro <i>et al.</i> ⁸³	↓						
El Salhy <i>et al.</i> ⁸⁴		↑ ^c					
c. IBS-D							
Coates <i>et al.</i> ⁸¹	↓	↔	↔			↓	
Bearcroft <i>et al.</i> ⁸⁵				↑	↔		
Miwa <i>et al.</i> ⁸⁶	↔				↔		
Atkinson ⁸⁷				↑	↑		↔
d. IBS-C							
Coates <i>et al.</i> ⁸¹	↓	↔	↔			↓	
Miwa <i>et al.</i> ⁸⁶	↑				↔		
Dunlop <i>et al.</i> ⁸⁸	↔	↔		↓	↓		
Atkinson <i>et al.</i> ⁸⁷				↓	↓		↑
e. PI-IBS with diarrheal symptoms							
Spiller <i>et al.</i> ⁸⁹		↑					
Dunlop <i>et al.</i> ⁹⁰		↑					
Dunlop <i>et al.</i> ⁸⁸	↔	↔		↑	↓		
f. Chronic constipation							
Lincoln <i>et al.</i> ⁹¹	↑						
El Salhy <i>et al.</i> ⁸⁴		↓					
Zhao <i>et al.</i> ⁹²		↑					

5-HT = serotonin; 5-[HIAA] = 5-hydroxyindoleacetic acid; EC = enterochromaffin; SERT = serotonin-selective reuptake transporter; TNBS = trinitrobenzene sulfonic acid; IBS = irritable bowel syndrome; -D = diarrhea predominant; -C = constipation predominant; PI = postinfectious.

↓ decrease; ↑ increase; ↔ no change.

^aIncrease in stimulation-induced release may actually reflect a decrease in reuptake, based on the differences detected with and without a SERT blocker present.

^bIncrease in 5-HT content in the mouse may be a result of an increase in mast cells, which contain 5-HT in the mouse.

^cMeasured area rather than EC cell number.

scribed earlier significantly affect colonic motility in patients with IBS-C and D types. Importantly, 5-HT₄ and 5-HT₃ receptor antagonists only decrease colonic transit in patients with IBS-D when compared to healthy controls, which is consistent with the concept that 5-HT availability is increased in IBS-D.^{49,104,105} In summary, there is uncertainty about the nature of how 5-HT is related to the symptoms of IBS, but evidence implicating altered 5-HT signaling in

functional disorders of the gastrointestinal tract is mounting.

Chronic Constipation

Constipation is a common disorder that affects up to 34 percent of the population.^{106,107} Constipation persists in a contingent of these patients and chronic constipation can be divided into three subsets: pelvic

floor dysfunction, slow-transit constipation, and idiopathic constipation. Unfortunately, patients with a diagnosis of chronic constipation commonly fail to respond to medical therapy.¹⁰⁸

The etiology of this disorder is poorly understood and recent investigations have focused on neural mechanisms, including a decrease in interstitial cells of Cajal.^{109,110} Investigators have also evaluated other potential mechanisms, including proto-oncogenes, tyrosine kinase C, autonomic neuropathy, overexpression of progesterone receptors, infectious agents, autoimmunity, medications, as well as gut hormones.^{111–120}

A number of studies suggest that alterations in 5-HT signaling may contribute to the symptoms of chronic constipation, but again, inconsistencies exist among these investigations (Table 2).^{84,91,92,121} Overall, there appears to be a link between serotonin and chronic constipation, but it is not yet clear whether there is decreased serotonin availability at the receptors or a decrease in receptor density and function.

Currently there is a Grade A Recommendation from the American College of Gastroenterology for the clinical use of the 5-HT₄ receptor agonist tegaserod for chronic constipation. Two randomized placebo-controlled, double-blind clinical trials have shown a statistically significant increase in the number of complete spontaneous bowel movements in individuals receiving tegaserod.^{34,38,122}

Colectomy improves symptoms in the subset of patients with slow transit constipation, but most patients continue to have persistent gastrointestinal dysfunction.^{106,123} Subtotal colectomy undoubtedly increases bowel-movement frequency but may not affect abdominal pain and may cause incontinence and diarrhea that adversely affect quality-of-life scores.¹²⁴ A better understanding of this disorder may lead to less invasive treatments with fewer adverse effects.

Colonic Pseudo-Obstruction

Colonic pseudo-obstruction is characterized by dilation of the colon without a demonstrable mechanical obstruction.¹²⁵ The etiology of acute colonic pseudo-obstruction (ACPO) is poorly understood but is thought to be secondary to alterations in autonomic function associated with a predisposing condition (*i.e.*, surgery, trauma, infection, heart failure, neurologic).^{125,126}

The mainstay of pharmacologic treatment for ACPO is acetylcholinesterase inhibitors (*i.e.*, neostigmine). Several studies have demonstrated the efficacy of neostigmine in decompressing the colon in

patients with ACPO.^{127–130} MacColl *et al.*¹³¹ presented a case report of colonic decompression using cisapride. Subsequently, Pelckmans and colleagues¹³² published a report of two patients with no effect after treatment with cisapride. There have been no studies to further elucidate any connection between serotonin and ACPO.

CONCLUSION

The role of serotonin in ENS reflex activity and in the physiology and pathophysiology of the gut continues to be a controversial topic. Despite the inconsistencies in the literature regarding the specific alterations in 5-HT signaling and how they affect functional gastrointestinal disorders, it is becoming increasingly clear that 5-HT plays a pivotal role in altered motility. Changes in serotonin signaling appear to be initiated by mucosal inflammation. This suggests a role for medications that target 5-HT receptors in inflammatory disorders to ameliorate concomitant or lingering symptoms from disordered motility.

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REFERENCES

1. Bayliss WM, Starling EH. The movements and innervation of the small intestine. *J Physiol* 1899;24:99–143.
2. Bayliss WM, Starling EH. The movements and innervation of the small intestine. *J Physiol* 1900;26:107–38.
3. Bulbring E, Crema A. The release of 5-hydroxytryptamine in relation to pressure exerted on the intestinal mucosa. *J Physiol* 1959;146:18–28.
4. Erspamer V, Vialli M. Ricerche sul secreto delle cellule enterocromaffini. *Boll Soc Med Chir Pavia* 1937;51:357–363.
5. Whitaker-Azmitia PM. The discovery of serotonin and its role in neuroscience. *Neuropsychopharmacology* 1999; 21:2S–8S.
6. Page IH. The vascular action of natural serotonin, 5- and 7-hydroxytryptamine and tryptamine. *J Pharmacol Exp Ther* 1952;105:58–73.
7. Page IH. Serotonin (5-hydroxytryptamine). *Physiol Rev* 1954;34:563–88.
8. Bulbring E, Crema A. The action of 5-hydroxytryptamine, 5-hydroxytryptophan and reserpine on intestinal peristalsis in anaesthetized guinea-pigs. *J Physiol* 1959;146:29–53.

9. Bulbring E, Lin RC. The effect of intraluminal application of 5-hydroxytryptamine and 5-hydroxytryptophan on peristalsis; the local production of 5-HT and its release in relation to intraluminal pressure and propulsive activity. *J Physiol* 1958;140:381–407.
10. Racke K, Reimann A, Schworer H, Kilbinger H. Regulation of 5-HT release from enterochromaffin cells. *Behav Brain Res* 1996;73:83–7.
11. Racke K, Schworer H. Regulation of serotonin release from the intestinal mucosa. *Pharmacol Res* 1991; 23:13–25.
12. Gaddum JH, Picarelli ZP. Two kinds of tryptamine receptor. *Br J Pharmacol Chemother* 1957;12:323–8.
13. Gershon MD. Serotonin and the motility of the gastrointestinal tract. *Gastroenterology* 1968;54:453–6.
14. Kim DY, Camilleri M. Serotonin: A mediator of the brain-gut connection. *Am J Gastroenterol* 2000; 95:2698–709.
15. Gershon RR, Vlahov D, Kelen G, Conrad B, Murphy L. Review of accidents/injuries among emergency medical services workers in Baltimore, Maryland. *Prehospital Disaster Med* 1995;10:14–8.
16. Gershon MD. Review article: Serotonin receptors and transporters-roles in normal and abnormal gastrointestinal motility. *Aliment Pharmacol Ther* 2004;20 (Suppl 7), 3–14.
17. Crowell MD, Shetzline MA, Moses PL, Mawe GM, Talley NJ. Enterochromaffin cells and 5-HT signaling in the pathophysiology of disorders of gastrointestinal function. *Curr Opin Investig Drugs* 2004;5:55–60.
18. Goyal RK, Hirano I. The enteric nervous system. *N Engl J Med* 1996;334:1106–15.
19. Bulbring E, Gershon MD. 5-hydroxytryptamine participation in the vagal inhibitory innervation of the stomach. *J Physiol* 1967;192:823–46.
20. Grundy D. Towards a reduction of rectal pain?. *Neurogastroenterol Motil* 2002;14:217–9.
21. Kirkup AJ, Brunsdon AM, Grundy D. Receptors and transmission in the brain-gut axis: Potential for novel therapies. I. Receptors on visceral afferents. *Am J Physiol Gastrointest Liver Physiol* 2001;280:G787–94.
22. Fuller RW, Wong DT. Serotonin uptake and serotonin uptake inhibition. *Ann N Y Acad Sci* 1990;600:68–80.
23. Da Prada M, Tranzer JP, Pletscher A. Storage of 5-hydroxytryptamine in human blood platelets. *Experientia* 1972;28:1328–9.
24. Gershon MD. Serotonin: Its role and receptors in enteric neurotransmission. *Adv Exp Med Biol* 1991; 294:221–30.
25. Wallis DI, Stansfeld CE, Nash HL. Depolarizing responses recorded from nodose ganglion cells of the rabbit evoked by 5-hydroxytryptamine and other substances. *Neuropharmacology* 1982;21:31–40.
26. Cash BD, Chey WD. Review article: The role of serotonergic agents in the treatment of patients with primary chronic constipation. *Aliment Pharmacol Ther* 2005;22:1047–60.
27. Hargreaves AC, Lummis SC, Taylor CW. Ca²⁺ permeability of cloned and native 5-hydroxytryptamine type 3 receptors. *Mol Pharmacol* 1994;46:1120–8.
28. Camilleri M. Treating irritable bowel syndrome: Overview, perspective and future therapies. *Br J Pharmacol* 2004;141:1237–48.
29. Cremonini F, Delgado-Aros S, Camilleri M. Efficacy of alosetron in irritable bowel syndrome: A meta-analysis of randomized controlled trials. *Neurogastroenterol Motil* 2003;15:79–86.
30. Delvaux M, Louvel D, Mamet JP, Campos-Oriola R, Frexinos J. Effect of alosetron on responses to colonic distension in patients with irritable bowel syndrome. *Aliment Pharmacol Ther* 1998;12:849–55.
31. Jones RH, Holtmann G, Rodrigo L, *et al.* Alosetron relieves pain and improves bowel function compared with mebeverine in female nonconstipated irritable bowel syndrome patients. *Aliment Pharmacol Ther* 1999;13:1419–27.
32. Lembo T, Wright RA, Bagby B, *et al.* Alosetron controls bowel urgency and provides global symptom improvement in women with diarrhea-predominant irritable bowel syndrome. *Am J Gastroenterol* 2001; 96:2662–70.
33. Olden KW, Crowell MD. Cilansetron. *Drugs Today (Barc)* 2005;41:661–6.
34. Brandt LJ, Prather CM, Quigley EM, Schiller LR, Schoenfeld P, Talley NJ. Systematic review on the management of chronic constipation in north america. *Am J Gastroenterol* 2005;100 (Suppl 1), S5–21.
35. Callahan MJ. Irritable bowel syndrome neuropharmacology. A review of approved and investigational compounds. *J Clin Gastroenterol* 2002;35:S58–67.
36. Camilleri M. Review article: Tegaserod. *Aliment Pharmacol Ther* 2001;15:277–89.
37. Evans BW, Clark WK, Moore DJ, Whorwell PJ. Tegaserod for the treatment of irritable bowel syndrome. *Cochrane Database Syst Rev* 2004; CD003960.
38. Kamm MA, Muller-Lissner S, Talley NJ, *et al.* Tegaserod for the treatment of chronic constipation: A randomized, double-blind, placebo-controlled multinational study. *Am J Gastroenterol* 2005;100:362–72.
39. Muller-Lissner SA, Fumagalli I, Bardhan KD, *et al.* Tegaserod, a 5-HT₄ receptor partial agonist, relieves symptoms in irritable bowel syndrome patients with abdominal pain, bloating and constipation. *Aliment Pharmacol Ther* 2001;15:1655–66.
40. Nyhlin H, Bang C, Elsborg L, *et al.* A double-blind, placebo-controlled, randomized study to evaluate the efficacy, safety and tolerability of tegaserod in patients with irritable bowel syndrome. *Scand J Gastroenterol* 2004;39:119–26.

41. Jaiwala J, Imperiale TF, Kroenke K. Pharmacologic treatment of the irritable bowel syndrome: A systematic review of randomized, controlled trials. *Ann Intern Med* 2000;133:136–47.
42. Kamm MA. Review article: The complexity of drug development for irritable bowel syndrome. *Aliment Pharmacol Ther* 2002;16:343–51.
43. Ziegenhagen DJ, Kruis W. Cisapride treatment of constipation-predominant irritable bowel syndrome is not superior to placebo. *J Gastroenterol Hepatol* 2004; 19:744–9.
44. Bouras EP, Camilleri M, Burton DD, Thomforde G, McKinzie S, Zinsmeister AR. Prucalopride accelerates gastrointestinal and colonic transit in patients with constipation without a rectal evacuation disorder. *Gastroenterology* 2001;120:354–60.
45. Coremans G, Kerstens R, De Pauw M, Stevens M. Prucalopride is effective in patients with severe chronic constipation in whom laxatives fail to provide adequate relief. Results of a double-blind, placebo-controlled clinical trial. *Digestion* 2003;67:82–9.
46. De Schryver AM, Andriessse GI, Samsom M, Smout AJ, Gooszen HG, Akkermans LM. The effects of the specific 5HT₄ receptor agonist, prucalopride, on colonic motility in healthy volunteers. *Aliment Pharmacol Ther* 2002;16:603–12.
47. Emmanuel AV, Roy AJ, Nicholls TJ, Kamm MA. Prucalopride, a systemic enterokinetic, for the treatment of constipation. *Aliment Pharmacol Ther* 2002; 16:1347–56.
48. Sloots CE, Poen AC, Kerstens R, *et al.* Effects of prucalopride on colonic transit, anorectal function and bowel habits in patients with chronic constipation. *Aliment Pharmacol Ther* 2002;16:759–67.
49. Bharucha AE, Camilleri M, Haydock S, *et al.* Effects of a serotonin 5-HT₄ receptor antagonist sb-207266 on gastrointestinal motor and sensory function in humans. *Gut* 2000;47:667–74.
50. Houghton LA, Jackson NA, Whorwell PJ, Cooper SM. 5-HT₄ receptor antagonism in irritable bowel syndrome: Effect of sb-207266-a on rectal sensitivity and small bowel transit. *Aliment Pharmacol Ther* 1999; 13:1437–44.
51. Sanger GJ, Banner SE, Smith MI, Wardle KA. Sb-207266: 5-HT₄ receptor antagonism in human isolated gut and prevention of 5-HT-evoked sensitization of peristalsis and increased defaecation in animal models. *Neurogastroenterol Motil* 1998;10:271–9.
52. Tonini M, De Ponti F, Di Nucci A, Crema F. Review article: Cardiac adverse effects of gastrointestinal prokinetics. *Aliment Pharmacol Ther* 1999;13:1585–91.
53. Camilleri M, McKinzie S, Fox J, *et al.* Effect of renzapride on transit in constipation-predominant irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2004;2:895–904.
54. Galligan JJ, Vanner S. Basic and clinical pharmacology of new motility promoting agents. *Neurogastroenterol Motil* 2005;17:643–53.
55. Potet F, Bouyssou T, Escande D, Baro I. Gastrointestinal prokinetic drugs have different affinity for the human cardiac human ether-a-gogo k(+) channel. *J Pharmacol Exp Ther* 2001;299:1007–12.
56. Carlsson L, Amos GJ, Andersson B, Drews L, Duker G, Wadstedt G. Electrophysiological characterization of the prokinetic agents cisapride and mosapride *in vivo* and *in vitro*: Implications for proarrhythmic potential? *J Pharmacol Exp Ther* 282:220–7.
57. Mine Y, Yoshikawa T, Oku S, Nagai R, Yoshida N, Hosoki K. Comparison of effect of mosapride citrate and existing 5-HT₄ receptor agonists on gastrointestinal motility *in vivo* and *in vitro*. *J Pharmacol Exp Ther* 1997;283:1000–8.
58. Bertrand PP, Kunze WA, Furness JB, Bornstein JC. The terminals of myenteric intrinsic primary afferent neurons of the guinea-pig ileum are excited by 5-hydroxytryptamine acting at 5-hydroxytryptamine-3 receptors. *Neuroscience* 2000;101:459–69.
59. Galligan JJ. Electrophysiological studies of 5-hydroxytryptamine receptors on enteric neurons. *Behav Brain Res* 1996;73:199–201.
60. Galligan JJ. Pharmacology of synaptic transmission in the enteric nervous system. *Curr Opin Pharmacol* 2002; 2:623–9.
61. Costall B, Naylor RJ. 5-HT₃ receptors. *Curr Drug Targets CNS Neurol Disord* 2004;3:27–37.
62. Talley NJ, Phillips SF, Haddad A, *et al.* Gr 38032f (ondansetron), a selective 5HT₃ receptor antagonist, slows colonic transit in healthy man. *Dig Dis Sci* 1990; 35:477–80.
63. von der Ohe MR, Hanson RB, Camilleri M. Serotonergic mediation of postprandial colonic tonic and phasic responses in humans. *Gut* 1994;35:536–41.
64. Camilleri M, Chey WY, Mayer EA, *et al.* A randomized controlled clinical trial of the serotonin type 3 receptor antagonist alosetron in women with diarrhea-predominant irritable bowel syndrome. *Arch Intern Med* 2001;161:1733–40.
65. Camilleri M, Northcutt AR, Kong S, Dukes GE, McSorley D, Mangel AW. Efficacy and safety of alosetron in women with irritable bowel syndrome: A randomised, placebo-controlled trial. *Lancet* 2000; 355:1035–40.
66. Bockaert J, Claeysen S, Compan V, Dumuis A. 5-HT₄ receptors. *Curr Drug Targets CNS Neurol Disord* 2004; 3:39–51.
67. Foxx-Orenstein AE, Jin JG, Grider JR. 5-HT₄ receptor agonists and delta-opioid receptor antagonists act synergistically to stimulate colonic propulsion. *Am J Physiol* 1998;275:G979–83.
68. Liu M, Geddis MS, Wen Y, Setlik W, Gershon MD.

- Expression and function of 5-HT₄ receptors in the mouse enteric nervous system. *Am J Physiol Gastrointest Liver Physiol* 2005;289:G1148–63.
69. Grider JR. Desensitization of the peristaltic reflex induced by mucosal stimulation with the selective 5-HT₄ agonist tegaserod. *Am J Physiol Gastrointest Liver Physiol* 2006;290:G319–27.
 70. Galligan JJ, Pan H, Messori E. Signalling mechanism coupled to 5-hydroxytryptamine₄ receptor-mediated facilitation of fast synaptic transmission in the guinea-pig ileum myenteric plexus. *Neurogastroenterol Motil* 2003;15:523–9.
 71. Pan H, Galligan JJ. 5-HT_{1a} and 5-HT₄ receptors mediate inhibition and facilitation of fast synaptic transmission in enteric neurons. *Am J Physiol* 1994; 266:G230–8.
 72. Grider JR, Foxx-Orenstein AE, Jin JG. 5-Hydroxytryptamine₄ receptor agonists initiate the peristaltic reflex in human, rat, and guinea pig intestine. *Gastroenterology* 1998;115:370–80.
 73. Jin JG, Foxx-Orenstein AE, Grider JR. Propulsion in guinea pig colon induced by 5-hydroxytryptamine (HT) via 5-HT₄ and 5-HT₃ receptors. *J Pharmacol Exp Ther* 1999;288:93–7.
 74. Lyford G, Foxx-Orenstein A. Chronic intestinal pseudoobstruction. *Curr Treat Options Gastroenterol* 2004; 7:317–25.
 75. Ferriman A. UK licence for cisapride suspended. *BMJ* 2000;321:259.
 76. Linden DR, Chen JX, Gershon MD, Sharkey KA, Mawe GM. Serotonin availability is increased in mucosa of guinea pigs with tnbs-induced colitis. *Am J Physiol Gastrointest Liver Physiol* 2003;285:G207–16.
 77. O'Hara JR, Ho W, Linden DR, Mawe GM, Sharkey KA. Enteroendocrine cells and 5-HT availability are altered in mucosa of guinea pigs with TNBS ileitis. *Am J Physiol Gastrointest Liver Physiol* 2004;287: G998–1007.
 78. Linden DR, Foley KF, McQuoid C, Simpson J, Sharkey KA, Mawe GM. Serotonin transporter function and expression are reduced in mice with TNBS-induced colitis. *Neurogastroenterol Motil* 2005;17: 565–74.
 79. Wheatcroft J, Wakelin D, Smith A, Mahoney CR, Mawe G, Spiller R. Enterochromaffin cell hyperplasia and decreased serotonin transporter in a mouse model of postinfectious bowel dysfunction. *Neurogastroenterol Motil* 2005;17:863–70.
 80. O'Hara JR, Skinn AC, MacNaughton WK, Sherman PM, Sharkey KA. Consequences of *Citrobacter rodentium* infection on enteroendocrine cells and the enteric nervous system in the mouse colon. *Cell Microbiol* 2006; 8:646–60.
 81. Coates MD, Mahoney CR, Linden DR, *et al.* Molecular defects in mucosal serotonin content and decreased serotonin reuptake transporter in ulcerative colitis and irritable bowel syndrome. *Gastroenterology* 2004; 126:1657–64.
 82. Ahonen A, Kyosola K, Penttila O. Enterochromaffin cells in macrophages in ulcerative colitis and irritable colon. *Ann Clin Res* 1976;8:1–7.
 83. Magro F, Vieira-Coelho MA, Fraga S, *et al.* Impaired synthesis or cellular storage of norepinephrine, dopamine, and 5-hydroxytryptamine in human inflammatory bowel disease. *Dig Dis Sci* 2002;47:216–24.
 84. El-Salhy M, Danielsson A, Stenling R, Grimelius L. Colonic endocrine cells in inflammatory bowel disease. *J Intern Med* 1997;242:413–9.
 85. Bearcroft CP, Perrett D, Farthing MJ. Postprandial plasma 5-hydroxytryptamine in diarrhoea predominant irritable bowel syndrome: A pilot study. *Gut* 1998; 42:42–6.
 86. Miwa J, Echizen H, Matsueda K, Umeda N. Patients with constipation-predominant irritable bowel syndrome (IBS) may have elevated serotonin concentrations in colonic mucosa as compared with diarrhea-predominant patients and subjects with normal bowel habits. *Digestion* 2001;63:188–94.
 87. Atkinson W, Lockhart S, Whorwell PJ, Keevil B, Houghton LA. Altered 5-hydroxytryptamine signaling in patients with constipation- and diarrhea-predominant irritable bowel syndrome. *Gastroenterology* 2006; 130:34–43.
 88. Dunlop SP, Coleman NS, Blackshaw E, *et al.* Abnormalities of 5-hydroxytryptamine metabolism in irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2005; 3:349–57.
 89. Spiller RC, Jenkins D, Thornley JP, *et al.* Increased rectal mucosal enteroendocrine cells, T lymphocytes, and increased gut permeability following acute *Campylobacter enteritis* and in post-dysenteric irritable bowel syndrome. *Gut* 2000;47:804–11.
 90. Dunlop SP, Jenkins D, Neal KR, Spiller RC. Relative importance of enterochromaffin cell hyperplasia, anxiety, and depression in postinfectious IBS. *Gastroenterology* 2003;125:1651–9.
 91. Lincoln J, Crowe R, Kamm MA, Burnstock G, Lennard-Jones JE. Serotonin and 5-hydroxyindoleacetic acid are increased in the sigmoid colon in severe idiopathic constipation. *Gastroenterology* 1990;98: 1219–25.
 92. Zhao R, Baig MK, Wexner SD, *et al.* Enterochromaffin and serotonin cells are abnormal for patients with colonic inertia. *Dis Colon Rectum* 2000;43:858–63.
 93. Simren M, Axelsson J, Gillberg R, Abrahamsson H, Svedlund J, Bjornsson ES. Quality of life in inflammatory bowel disease in remission: The impact of IBS-like symptoms and associated psychological factors. *Am J Gastroenterol* 2002;97:389–96.
 94. Neal KR, Hebden J, Spiller R. Prevalence of gastroin-

- testinal symptoms six months after bacterial gastroenteritis and risk factors for development of the irritable bowel syndrome: Postal survey of patients. *BMJ* 1997; 314:779–82.
95. Drossman DA, Whitehead WE, Camilleri M. Irritable bowel syndrome: A technical review for practice guideline development. *Gastroenterology* 1997;112: 2120–37.
 96. Chadwick VS, Chen W, Shu D, *et al.* Activation of the mucosal immune system in irritable bowel syndrome. *Gastroenterology* 2002;122:1778–83.
 97. Tornblom H, Lindberg G, Nyberg B, Veress B. Full-thickness biopsy of the jejunum reveals inflammation and enteric neuropathy in irritable bowel syndrome. *Gastroenterology* 2002;123:1972–9.
 98. Mertz H, Morgan V, Tanner G, *et al.* Regional cerebral activation in irritable bowel syndrome and control subjects with painful and nonpainful rectal distention. *Gastroenterology* 2000;118:842–8.
 99. Locke GR, 3rd, Zinsmeister AR, Talley NJ, Fett SL, Melton LJ, 3rd. Familial association in adults with functional gastrointestinal disorders. *Mayo Clin Proc* 2000;75:907–12.
 100. Nobaek S, Johansson ML, Molin G, Ahrne S, Jeppsson B. Alteration of intestinal microflora is associated with reduction in abdominal bloating and pain in patients with irritable bowel syndrome. *Am J Gastroenterol* 2000;95:1231–8.
 101. Gershon MD. Nerves, reflexes, and the enteric nervous system: Pathogenesis of the irritable bowel syndrome. *J Clin Gastroenterol* 2005;39:S184–93.
 102. Chen JJ, Li Z, Pan H, *et al.* Maintenance of serotonin in the intestinal mucosa and ganglia of mice that lack the high-affinity serotonin transporter: Abnormal intestinal motility and the expression of cation transporters. *J Neurosci* 2001;21:6348–61.
 103. Coates MD, Johnson AC, Greenwood-Van Meerveld B, Mawe GM. Effects of serotonin transporter inhibition on gastrointestinal motility and colonic sensitivity in the mouse. *Neurogastroenterol Motil* 2006;18:464–71.
 104. Camilleri M, Mayer EA, Drossman DA, *et al.* Improvement in pain and bowel function in female irritable bowel patients with alosetron, a 5-HT₃ receptor antagonist. *Aliment Pharmacol Ther* 1999;13:1149–59.
 105. De Ponti F, Tonini M. Irritable bowel syndrome: New agents targeting serotonin receptor subtypes. *Drugs* 2001;61:317–32.
 106. Knowles CH, Scott M, Lunniss PJ. Outcome of colectomy for slow transit constipation. *Ann Surg* 1999; 230:627–38.
 107. Sonnenberg A, Koch TR. Epidemiology of constipation in the United States. *Dis Colon Rectum* 1989; 32:1–8.
 108. Voderholzer WA, Schatke W, Muhldorfer BE, Klausner AG, Birkner B, Muller-Lissner SA. Clinical response to dietary fiber treatment of chronic constipation. *Am J Gastroenterol* 1997;92:95–8.
 109. He CL, Burgart L, Wang L, *et al.* Decreased interstitial cell of Cajal volume in patients with slow-transit constipation. *Gastroenterology* 2000;118:14–21.
 110. Tong WD, Liu BH, Zhang LY, Zhang SB, Lei Y. Decreased interstitial cells of Cajal in the sigmoid colon of patients with slow transit constipation. *Int J Colorectal Dis* 2004;19:467–73.
 111. Facer P, Knowles CH, Thomas PK, Tam PK, Williams NS, Anand P. Decreased tyrosine kinase C expression may reflect developmental abnormalities in Hirschsprung's disease and idiopathic slow-transit constipation. *Br J Surg* 2001;88:545–52.
 112. Knowles CH, Gayther SA, Scott M, *et al.* Idiopathic slow-transit constipation is not associated with mutations of the ret proto-oncogene or GDNF. *Dis Colon Rectum* 2000;43:851–7.
 113. Altomare DF, Portincasa P, Rinaldi M, *et al.* Slow-transit constipation: Solitary symptom of a systemic gastrointestinal disease. *Dis Colon Rectum* 1999;42: 231–40.
 114. Xiao ZL, Pricolo V, Biancani P, Behar J. Role of progesterone signaling in the regulation of g-protein levels in female chronic constipation. *Gastroenterology* 2005;128:667–75.
 115. Bueno L, Fioramonti J. Action of opiates on gastrointestinal function. *Baillieres Clin Gastroenterol* 1988; 2:123–39.
 116. Fotherby KJ, Hunter JO. Idiopathic slow-transit constipation: Whole gut transit times, measured by a new simplified method, are not shortened by opioid antagonists. *Aliment Pharmacol Ther* 1987;1:331–8.
 117. Sonsino E, Mouy R, Foucaud P, *et al.* Intestinal pseudo-obstruction related to cytomegalovirus infection of myenteric plexus. *N Engl J Med* 1984;311: 196–7.
 118. Sykes NP. Oral naloxone in opioid-associated constipation. *Lancet* 1991;337:1475.
 119. Vassallo M, Camilleri M, Caron BL, Low PA. Gastrointestinal motor dysfunction in acquired selective cholinergic dysautonomia associated with infectious mononucleosis. *Gastroenterology* 1991;100:252–8.
 120. Knowles CH, Martin JE. Slow transit constipation: A model of human gut dysmotility. Review of possible aetiologies. *Neurogastroenterol Motil* 2000;12:181–96.
 121. Zhao RH, Baig MK, Thaler KJ, *et al.* Reduced expression of serotonin receptor(s) in the left colon of patients with colonic inertia. *Dis Colon Rectum* 2003;46:81–6.
 122. Johanson JF, Wald A, Tougas G, *et al.* Effect of tegaserod in chronic constipation: A randomized, dou-

- ble-blind, controlled trial. *Clin Gastroenterol Hepatol* 2004;2:796–805.
123. Piccirillo MF, Reissman P, Wexner SD. Colectomy as treatment for constipation in selected patients. *Br J Surg* 1995;82:898–901.
124. FitzHarris GP, Garcia-Aguilar J, Parker SC, *et al*. Quality of life after subtotal colectomy for slow-transit constipation: Both quality and quantity count. *Dis Colon Rectum* 2003;46:433–40.
125. Saunders MD, Kimmey MB. Systematic review: Acute colonic pseudo-obstruction. *Aliment Pharmacol Ther* 2005;22:917–25.
126. De Giorgio R, Barbara G, Stanghellini V, *et al*. Review article: The pharmacological treatment of acute colonic pseudo-obstruction. *Aliment Pharmacol Ther* 2001;15:1717–27.
127. Paran H, Silverberg D, Mayo A, Shwartz I, Neufeld D, Freund U. Treatment of acute colonic pseudo-obstruction with neostigmine. *J Am Coll Surg* 2000;190:315–8.
128. Ponc RJ, Saunders MD, Kimmey MB. Neostigmine for the treatment of acute colonic pseudo-obstruction. *N Engl J Med* 1999;341:137–41.
129. Stephenson BM, Morgan AR, Salaman JR, Wheeler MH. Ogilvie's syndrome: A new approach to an old problem. *Dis Colon Rectum* 1995;38:424–7.
130. Trevisani GT, Hyman NH, Church JM. Neostigmine: Safe and effective treatment for acute colonic pseudo-obstruction. *Dis Colon Rectum* 2000;43:599–603.
131. MacColl C, MacCannell KL, Baylis B, Lee SS. Treatment of acute colonic pseudo-obstruction (Ogilvie's syndrome) with cisapride. *Gastroenterology* 1990;98:773–6.
132. Pelckmans PA, Michielsen PP, Jorens PG, Van Maercke YM. Cisapride in Ogilvie's syndrome. *Gastroenterology* 1990;99:1194–5.