# Serotonin and the GI Tract

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Serotonin (5-hydroxytryptamine, 5-HT) participates in several functions of the gastrointestinal tract. Receptors in seven families (5-$HT_1$–5-$HT_7$) were identified, many of which are present on enterocytes, intrinsic and extrinsic neurons, interstitial cells, and gut myocytes. Most 5-HT is released from enterochromaffin cells in response to physiologic and pathologic stimuli. Roles of 5-HT in health include control of normal gut motor activity, secretion, and sensation, and regulation of food intake and cell growth. Abnormalities of serotonergic function contribute to symptom genesis in functional bowel disorders, inflammatory and infectious diseases of the gut, emetic responses to varied stimuli, obesity, and dysregulation of cell growth. Therapies acting as agonists or antagonists of 5-HT receptors or that modulate 5-HT reuptake play prominent roles in managing these conditions, although use of many agents is hampered by cardiopulmonary complications. Novel agents are in testing, which may exhibit efficacy without significant toxicity.

## Introduction

Serotonin (5-hydroxytryptamine, 5-HT) participates in normal and pathologic functions of the gut, including motility, secretion, visceral perception, and weight maintenance. This article describes serotonin biochemistry, the physiology of gut 5-HT, the role of 5-HT dysregulation in producing clinical disease, and therapies that act on 5-HT receptors or modify 5-HT levels in the intercellular space.

## Biochemistry of Serotonin

5-HT is synthesized from dietary L-tryptophan. Tryptophan initially is converted to 5-hydroxy-L-tryptophan (5-HTP) by tryptophan hydroxylase (TpH). TpH1 is found centrally and expressed in enterochromaffin (EC) cells in gut epithelial crypts, whereas TpH2 is found only in nervous tissues. 5-HTP then undergoes conversion to 5-HT by L-amino acid decarboxylase.

5-HT receptors in seven families (5-$HT_1$-5–$HT_7$) have been characterized (Table 1). An additional peripheral "orphan" receptor (5-$HT_{1P}$) is either the 5-$HT_7$ subtype or a heterodimer of the 5-$HT_{1B/1D}$ receptor with the dopamine D2 receptor [1]. 5-$HT_3$ receptors are ligand-gated $Na^+/K^+$ cation channels. Other subtypes are G-protein coupled. 5-$HT_1$ and 5-$HT_5$ activation reduces cyclic adenosine monophosphate (AMP), whereas 5-$HT_4$, 5-$HT_6$, and 5-$HT_7$ pathways increase cyclic AMP. 5-$HT_2$ activates phospholipase C with subsequent intracellular calcium release. The expression of the distinct 5-HT receptor subtypes in different cells in the gastrointestinal (GI) tract is detailed in Table 1. The clinical relevance of all the 5-HT receptors has not been defined; however, the 5-$HT_{1A}$, 5-$HT_{1B/1D}$, 5-$HT_3$, and 5-$HT_4$ subtypes are the most extensively investigated in the pathogenesis and pharmacologic management of gut disease. 5-$HT_{1A}$ and 5-$HT_{2B}$ receptors are prominent in the stomach, but 5-$HT_3$ and 5-$HT_4$ receptors are dominant in the intestine [2]. Genes (*HTR3A-E*) encoding 5-$HT_3$ subunits (5-$HT_{3A-E}$) were characterized [3]. 5-$HT_4$ and 5-$HT_7$ splice variants were identified.

Ninety-five percent of 5-HT is localized in the GI tract [4•]. Most 5-HT is stored in secretory granules in EC cells; 5-HT also is present in 1% of enteric neurons [4•]. EC cells are numerous in the duodenum and rectum in humans. 5-HT content is highest in the rectum. Mucosal stroking is a potent stimulus of EC cell 5-HT release. This experimental technique closely mimics the physiologic stimulation the gut would experience with local passage of intraluminal fluids or feces. Other stimuli for release in the small intestine include nutrients, low pH, amino acids, hyper- and hypotonic solutions, tastants (caffeine, tyramine, octopamine), and olfactants (thymol, euginol), whereas short-chain fatty acids elicit colonic 5-HT release [5].

Intercellular 5-HT is removed by the serotonin transporter SERT, a 5-HT/$Na^+/Cl^-$ transporter encoded by the gene *SLC6A4* on chromosome 17. SERT immunostaining and mRNA are prominent on the apical and basolateral aspects of epithelial cells and on serotonergic neurons [2]. *SERT* expression is highest in the small intestine [2]. SERT activity is reduced by selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants. A polymorphism (5-HTT–linked promoter region [5-HTT-LPR]) with a 44–base pair insertion/deletion in the *SERT* gene promoter region was characterized. The S (short) allele is associated with reduced SERT activity, whereas the L

**Table 1. Serotonin receptor subtypes in the gut: distribution and proposed function**

| Receptor subtype | GI distribution | Proposed functional roles |
|---|---|---|
| $5\text{-HT}_1$ | | |
| $5\text{-HT}_{1A}$ | Enteric motor neurons, enterocytes | Decrease fundic tone, inhibit gastric and ileal contractions, regulate visceral sensation |
| $5\text{-HT}_{1B}$ | Enteric neurons, smooth muscle, extrinsic nerves | Decrease fundic tone, blunt accommodation, decrease antral contractility, delay gastric emptying |
| $5\text{-HT}_{1D}$ | Enteric neurons, smooth muscle, extrinsic nerves | Decrease fundic tone, blunt accommodation, decrease antral contractility, delay gastric emptying |
| $5\text{-HT}_{1E}$ | Not described | Not described |
| $5\text{-HT}_{1F}$ | Not confirmed | Not confirmed |
| $5\text{-HT}_{1P}$ | Enteric neurons | Participate in peristalsis |
| $5\text{-HT}_2$ | | |
| $5\text{-HT}_{2A}$ | Enteric neurons, smooth muscle, enterocytes | Increase antral and colonic contractions, decrease fundic tone, stimulate secretion |
| $5\text{-HT}_{2B}$ | Enteric neurons, smooth muscle, interstitial cells of Cajal, connective tissue | Increase fundic, ileal, and colonic contractions, regulate visceral sensation, regulate enteric nerve growth |
| $5\text{-HT}_{2C}$ | Not described | Not described |
| $5\text{-HT}_3$ | Enteric neurons, interstitial cells of Cajal, enterocytes, extrinsic nerves, enterochromaffin cells | Increase frequency of small bowel motor complexes, regulate visceral sensation, stimulate secretion |
| $5\text{-HT}_4$ | Enteric neurons, smooth muscle, interstitial cells of Cajal, enterocytes, enterochromaffin cells | Augment peristalsis, relax smooth muscle, (?) regulate visceral sensation, stimulate secretion, enhance neuronal survival |
| $5\text{-HT}_5$ | Not described | Not described |
| $5\text{-HT}_6$ | Not well characterized | Not well characterized |
| $5\text{-HT}_7$ | Enteric neurons, smooth muscle | Relax smooth muscle, regulate visceral sensation |

GI—gastrointestinal; 5-HT—5-hydroxytryptamine.

(long) allele increases *SERT* expression and 5-HT uptake. More than 95% of circulating 5-HT is removed by avid uptake into dense platelet granules. Intracellular monoamine oxidase and aldehyde dehydrogenase convert 5-HT to 5-hydroxyindole acetic acid (5-HIAA). Small amounts of 5-HT are metabolized by glucuronidation and sulfation in several tissues.

Several methods are available to assess 5-HT, its metabolites, and SERT. In general, circulating 5-HT is measured from platelet-poor plasma because more than 95% of 5-HT is bound in platelets and is therefore inactive. Measurement of whole blood containing platelets would give erroneous assessments of active 5-HT, whereas platelet-poor plasma samples provide reliable quantification of active circulating 5-HT. Plasma, tissue, and luminally released 5-HT as well as 5-HIAA commonly are measured using high-performance liquid chromatography or enzyme immunoassay. Tissue 5-HT can be further characterized by immunocytochemical methods. Immunostaining techniques can also define SERT distribution in tissue samples. Immunoblotting is used to measure SERT protein, whereas SERT mRNA can be quantified by reverse transcription polymerase chain reaction techniques.

## Role of Serotonin in GI Physiology

### Gut motor activity

Serotonin participates in physiologic control of gut motor function (Table 1). *SERT* knockout mice exhibit increased colon motility and fecal water output, resulting in diarrhea [6]. In some animals, a bowel pattern of alternating diarrhea and constipation was observed. Destruction of serotonergic neurons with 5,7-dihydroxytryptamine disrupts gut contractions. EC cells exhibit close associations with extrinsic nerves and intrinsic primary afferent neurons (IPANs). Upon stimulation, EC cells release 5-HT, which acts in a paracrine fashion to bind to presynaptic $5\text{-HT}_4$ receptors to augment acetylcholine and calcitonin gene-related peptide release from nerve terminals between IPANs and adjacent interneurons [4•]. Ascending interneurons and excitatory motor neurons are activated to elicit contraction via cholinergic and tachykinin pathways. Simultaneous stimulation of descending interneurons and inhibitory motor neurons evokes relaxation via the actions of nitric oxide, vasoactive intestinal polypeptide, and pituitary adenylate cyclase-activating peptide [4•]. Further 5-HT action as a neurotransmitter on interneuron 5-HT4 pathways enhances peristalsis. Conversely, stimulation of smooth muscle $5\text{-HT}_4$ receptors causes relaxation. $5\text{-HT}_4$

receptor knockout mice exhibit impaired colon motility, supporting a physiologic role for this subtype [4•].

Other 5-HT subtypes modulate gut motor activity (Table 1). 5-$HT_{1A}$ activation inhibits electrical depolarization–evoked gastric and ileal contractions and decreases fundic tone. 5-$HT_{1B/1D}$ agonists reduce fundic tone, blunt accommodation, decrease antral contractility, and delay gastric emptying [7]. 5-$HT_{2A}$ stimulation evokes antral and colonic contraction and fundic relaxation. 5-$HT_{2B}$ activation contracts the fundus, ileum, and colon, and 5-$HT_{2B}$ antagonists blunt colon contractions. 5-$HT_3$ agonists shorten the periodicity of fasting small bowel motor complexes, and 5-$HT_3$ antagonists or 5-$HT_{1B/1D}$ agonists elicit prolongation. 5-$HT_3$ antagonists retard colon transit and blunt gastrocolonic responses to meals; 5-$HT_{2B}$, 5-$HT_3$, and 5-$HT_7$ antagonists inhibit peristalsis in some species [8]. Greater slowing of colon transit with the 5-$HT_3$ antagonist alosetron is observed in patients with the *LL* genotype of the *SERT* promoter polymorphism [9]. 5-$HT_7$ activation of IPANs is excitatory, whereas stimulation of smooth muscle receptors produces relaxation [4•].

### Visceral sensation

Perception of gut stimulation is mediated by 5-HT receptors on intrinsic nerves and extrinsic sensory pathways that project to the nodose and dorsal root ganglia (Table 1). 5-$HT_{1A}$ agonists blunt withdrawal responses to colonic stimulation. 5-$HT_{2B}$ activation increases afferent responses, whereas 5-$HT_{2B}$ antagonists inhibit perception in animal models of visceral pain. 5-$HT_3$ stimulation with 2-methyl-5-HT activates vagal nodose C-fibers, whereas 5-$HT_3$ antagonists reduce sensation of colorectal distention in some animal and human models [4•]. Intrathecal alosetron reduces visceral hypersensitivity evoked by stress. In humans, oral alosetron decreases activation of the limbic system, frontotemporal regions, hypothalamus, amygdala, and cingulate cortex on positron emission tomographic imaging [10]. 5-$HT_3$ antagonists decrease symptoms induced by meals or duodenal lipids without affecting fundic relaxation. The 5-$HT_4$ agonist tegaserod elicits visceral analgesia in animal models of hypersensitivity. In humans, tegaserod blunts the RIII reflex—a measure of spinal sensitivity elicited by rectal distention [11]. However, the actions of tegaserod are not blocked by 5-$HT_4$ antagonists and other 5-$HT_4$ agonists exhibit little antinociceptive effect. Although tegaserod is also a 5-$HT_{2B}$ antagonist, it is unproved that its afferent actions relate to this subtype [4•,12]. 5-$HT_7$ receptors are present in the dorsal horn of the spinal cord; 5-$HT_7$ antagonism increases sensory thresholds for stimulating peristalsis. Prolonged SSRI administration reduces rather than increases sensitivity to luminal distention, possibly reflecting receptor desensitization to continued 5-HT exposure.

### Intestinal secretion

Serotonin pathways regulate intestinal secretion (Table 1). 5-HT increases intestinal $Cl^-$ secretion and decreases $Na^+$ absorption. Activation of 5-$HT_{2A}$ receptors elicits colonic secretion. Likewise, 5-$HT_3$ stimulation evokes chloride secretion, whereas 5-$HT_3$ antagonists blunt 5-HT–mediated colonic secretion in response to cholera toxin, GI pathogens, and corticotropin releasing factor [13,14]. 5-$HT_4$ activation elicits chloride and bicarbonate secretion from intestinal and colonic epithelia. 5-HT released by duodenal acid exposure stimulates bicarbonate secretion partly via 5-$HT_4$ pathways.

### Food intake

Serotonin plays an important role in food intake and control of body weight [15•,16]. 5-HT infusion into the hypothalamic paraventricular nucleus reduces nutrient ingestion, whereas decreased 5-HT activity promotes food intake and weight gain. Destroying serotonin neurons with 5,7-dihydroxytryptamine or impairing 5-HT synthesis with p-chlorophenylalanine increases nutrient consumption, but peripheral 5-HTP decreases food intake. Serotonergic stimulation increases pro-opiomelanocortin (POMC) and decreases neuropeptide Y (NPY) mRNA in the hypothalamus, whereas 5-HT antagonists increase NPY levels. 5-$HT_{2C}$ receptors mediate actions of serotonin on hypothalamic neurons containing POMC and cocaine and amphetamine–regulated transcript (CART). 5-$HT_{1B}$ pathways act on NPY and agouti-related protein (AgRP) neurons [15•]. 5-$HT_{1A}$ agonists elicit consumption, whereas 5-$HT_{1B}$ agonists reduce feeding by inhibiting hypothalamic AgRP and NPY and activating POMC and CART pathways. 5-$HT_{1B}$ and 5-$HT_{2C}$ knockout mice exhibit increased food intake and weight gain [17]. 5-$HT_{2C}$ agonists elicit anorectic effects. 5-$HT_6$ receptors are distributed in the hypothalamic arcuate, paraventricular, and ventromedial nuclei. 5-$HT_6$ antisense oligonucleotide administration promotes weight reduction [18].

### Regulation of cell growth

Serotonin regulates growth of several tissues including pulmonary smooth muscle and fibroblasts, mammary tissues, nerves, and epithelial cells in the intestinal crypts. 5-HTP induces development of epithelial microvilli [19]. Reduced serotonin levels promote increased bone mass in a murine model of osteoporosis [20]. Furthermore, inactivation of gut TpH1 increases bone mass and reduces bone loss occurring as a consequence of oophorectomy. 5-$HT_{1A}$, 5-$HT_{1D}$, 5-$HT_{2B}$, 5-$HT_{2C}$, and 5-$HT_4$ pathways purportedly modulate cell survival. 5-$HT_{2B}$ activation promotes enteric nerve growth and maturation, whereas 5-$HT_4$ agonists enhance neuronal survival and decrease apoptosis (Table 1) [4•,21]. 5-$HT_4$ receptor knockout mice exhibit reduced numbers of neuronal nitric oxide synthase-immunoreactive enteric neurons. The clinical importance of these proliferative effects is not defined.

## Clinical Manifestations of Altered Serotonin Functions

### Inflammatory and infectious diseases of the GI tract

Inflammatory and infectious disorders of the gut show abnormal 5-HT activities. In animal models of colitis

elicited by topical trinitrobenzene sulphonic acid or dextran sodium sulfate (DSS), EC cells and 5-HT content are increased but SERT is reduced. Splanchnic nerve responses to 5-HT are enhanced in DSS-induced colitis. Visceral hypersensitivity after acetic acid–induced colitis in rats is inhibited by 5-$HT_3$ antagonism. EC cells are increased in patients with Crohn's ileitis at sites with and without active inflammation, and ileal myenteric 5-HT immunoreactivity is increased. However, EC populations in inflammatory bowel disease involving the colon show inconsistent abnormalities [22]. EC cells, mucosal 5-HT content, and postprandial 5-HT release are increased and SERT mRNA is reduced in celiac disease [4•,23]. EC cells are increased in radiation colitis, but decreased in acute appendicitis. *SERT* transcripts are reduced in diverticulitis [24]. *Trichinella spiralis* infection in rodents is associated with increased intestinal EC and mast cell populations, and elevated mucosal 5-HT content and release, but decreased *SERT* expression. Persistence of elevated 5-HT content is associated with afferent hypersensitivity. However, in mice with severe combined immunodeficiency, *Trichuris muris* infection decreases EC cells—an effect reversible by adding $CD4^+$ lymphocytes from wild-type animals [25].

**Functional bowel disorders and dysmotility syndromes**

Patients with functional and motor disorders of the gut exhibit prominent disruption of 5-HT function. EC cells and 5-HT–positive enteric nerve fibers are increased in irritable bowel syndrome (IBS) developing after enteric infection with *Campylobacter* or *Shigella* spp [26]. Most, but not all, studies report increased circulating 5-HT levels in platelet-poor plasma in diarrhea-predominant IBS (D-IBS) and postinfectious IBS and functional dyspepsia, whereas 5-HT is reduced in constipation-predominant IBS (C-IBS) [26]. However, the 5-HT to EC number ratio is increased in C-IBS because of a greater decrement in EC cells, reflecting impaired 5-HT release in this IBS subtype [26]. 5-HT–containing colon myenteric neurons are increased, but smooth muscle receptors are decreased in slow-transit constipation. 5-$HT_3$–dependent components of the gastrocolonic response also are impaired in slow-transit constipation [8]. Colon transit is retarded by 5-$HT_3$ and 5-$HT_4$ antagonists in D-IBS, but not in healthy controls, reflecting increases in 5-HT availability. TpH transcription is increased in functional dyspepsia. 5-$HT_{4C}$ splice variant expression is reduced in idiopathic gastroparesis [27].

Studies measuring *SERT* expression in IBS report conflicting results. In one investigation, colonic SERT was reduced in C-IBS, D-IBS, and ulcerative colitis with associated decreases in 5-HT content and TpH1 mRNA [22]. However, intestinal SERT expression was increased in two IBS studies but was no different from controls in another study. *SERT* expression was reduced in another study of functional dyspeptics. The *SS* genotype of the 5-HTTLPR polymorphism was enriched in D-IBS in two studies; however, a meta-analysis did not convincingly confirm the association [28]. Likewise, no association between functional dyspepsia symptoms and *SERT* polymorphisms was observed in another investigation. A different polymorphism (α2c/del322-325) is associated with C-IBS, whereas a mutation of the untranslated region of the *HTR3E* gene is found in D-IBS [29]. *SERT* knockout mice exhibit alternating constipation and diarrhea that mimics symptoms of many IBS patients [6]. Stool inconsistency in these animals may stem from periodic 5-HT receptor desensitization. Further investigation is needed to prove that abnormal *SERT* expression or activity is pathogenic of symptoms in IBS. However, agents that modulate SERT function (including SSRIs and tricyclic antidepressants) relieve symptoms in this disorder, supporting this postulate.

**Secretory diarrhea**

Excess serotonergic activity can cause secretory diarrhea. *Vibrio cholera*, *Escherichia coli*, and *Salmonella typhimurium* toxins promote EC cell 5-HT release. Tumor release of 5-HT underlies the voluminous diarrhea and abdominal discomfort of carcinoid syndrome [4•]. Carcinoid syndrome is the only clinical condition for which measurement of 5-HT or its metabolite 5-HIAA is routinely obtained. The pathogenesis of diarrhea in carcinoid syndrome includes increased intestinal secretion, accelerated intestinal and colonic transit, and elevated colon tone. The increase in tone can be blunted by 5-$HT_3$ antagonist treatment.

**Vomiting**

5-$HT_3$ mechanisms are involved in vomiting after a range of emetic stimuli. Many cancer chemotherapies elicit emesis by stimulating EC cell 5-HT release, which activates 5-$HT_3$ receptors on vagal afferents projecting to the brainstem. 5-$HT_3$ receptors also are present in the area postrema, nucleus tractus solitaritius, and dorsal motor nucleus of the vagus, and may activate during emetic stimulation. Traditionally, 5-HT was considered to elicit only acute chemotherapy-induced emesis; however, studies show 5-HT increases during a delayed period more than 1 day after chemotherapy [30]. Other forms of emesis resulting from 5-HT activation include that induced by radiation therapy and vomiting occurring postoperatively.

**Obesity**

5-HT abnormalities participate in the pathogenesis of obesity. Obese rats exhibit reduced plasma 5-HT with associated reductions in 5-HIAA and loss of normal diurnal serotonin turnover variability in the hypothalamus. Likewise, plasma tryptophan is reduced in obese humans. *SERT* gene knockout mice develop progressive obesity with age, with associated hyperlipidemia, hyperglycemia, and increased circulating leptin.

**Dysregulation of cell growth**

Neoplastic tissue growth is influenced by endogenous 5-HT activity. 5-HT promotes colon cancer growth, possibly by enhancing macrophage-mediated angiogenesis, whereas SSRIs slow growth of colon cancer cell lines [31].

**Table 2. Serotonin-related agents for therapy of gastrointestinal disorders**

| Drug class | Clinically available | Potential clinical applications |
|---|---|---|
| 5-$HT_{1A}$ agonist | Yes (buspirone) | Functional dyspepsia |
| 5-$HT_{1B/1D}$ agonist | Yes (sumatriptan) | Functional dyspepsia, cyclic vomiting, other emesis |
| 5-$HT_{2C}$ agonist | No | Weight reduction |
| 5-$HT_2$ antagonist | Yes (ketanserin) | Carcinoid syndrome |
| 5-$HT_3$ antagonist | Yes (alosetron, ondansetron, granisetron, palonosetron) | D-IBS, carcinoid syndrome, emesis, functional dyspepsia |
| 5-$HT_3$ agonist | No | C-IBS, chronic constipation |
| 5-$HT_4$ agonist | Yes (metoclopramide) | Gastroparesis, functional dyspepsia, C-IBS, chronic constipation, chronic intestinal pseudoobstruction, gastroesophageal reflux, functional heartburn |
| 5-$HT_4$ antagonist | No | D-IBS |
| 5-$HT_6$ partial agonist/ antagonist | No | Weight reduction |
| 5-$HT_7$ antagonist | No | Bloating in IBS |
| Selective serotonin reuptake inhibitor | Yes (fluoxetine, citalopram, sertraline, paroxetine, fluvoxamine) | IBS, weight reduction |
| Combined serotonin/ norepinephrine reuptake inhibitor | Yes (tricyclics, venlafaxine, sibutramine) | IBS, functional dyspepsia, functional vomiting, weight reduction |
| TpH1 inhibitor | No | IBS |
| 5-HT derivative melatonin | Yes (melatonin) | IBS |

5-HT—5-hydroxytryptamine; C-IBS—constipation-predominant irritable bowel syndrome; D-IBS—diarrhea-predominant irritable bowel syndrome; IBS—irritable bowel syndrome.

## Management of GI Disorders by Serotonin Function Modulation

### Functional bowel disorders

Therapies that modulate 5-HT activity are effective in patients with functional bowel disorders by acting as receptor agonists or antagonists or as agents that impair 5-HT uptake (Table 2).

#### *5-$HT_3$ Antagonists*

5-$HT_3$ antagonists retard colon transit, inhibit secretion, enhance colorectal compliance, and increase volumes needed to elicit pain during noxious distention. Older controlled trials reported symptom reductions in IBS and functional dyspepsia with ondansetron. In recent trials, alosetron and cilansetron decreased symptoms in D-IBS [32•]. Alosetron also was reported to produce superior relief of IBS symptoms compared with the antispasmodic agent mebervine in a European trial. Alosetron initially was reported to benefit only women; however, a meta-analysis indicated similar efficacy in men. Alosetron reduced symptoms of functional dyspepsia in a controlled trial. The most common side effect of 5-$HT_3$ antagonists is constipation, which usually develops within 30 days and, in rare cases, mandates hospitalization or surgery.

Alosetron was temporarily withdrawn from the market because of increases in ischemic colitis [33]. Mesenteric ischemia also was reported. Trial and postmarketing surveillance data indicated an incidence rate of ischemic colitis of 0.15% on alosetron versus 0% for placebo. Alosetron was re-released in the United States only on a restricted basis for women with severe D-IBS not responding to other therapies. Although ischemic colitis is still observed on this restricted program, serious sequelae (surgeries, deaths) are substantially reduced. Further investigation of cilansetron was terminated because of ischemic colitis. Mechanisms of 5-$HT_3$-antagonist–induced ischemic colitis are poorly understood. Alosetron has no effects on visceral blood flow. Stercoral ulceration was proposed as a cause in cases with associated constipation. Many women with ischemic colitis also were on hormonal supplements; however, coadministration with alosetron does not appear to promote this complication. Finally, IBS patients exhibit a risk of colonic ischemia irrespective of treatment [33,34•].

#### *5-$HT_4$ Agonists*

Metoclopramide, a 5-$HT_4$ agonist that also acts as a 5-$HT_3$ and dopamine $D_2$ antagonist, treats upper gut disorders (eg, gastroparesis). High-dose metoclopramide prevents chemotherapy-induced emesis, mostly because of its 5-$HT_3$ antagonism. The drug elicits significant neurologic toxicity, including motor disturbances, mood disorders, and sleep disturbances. A warning was placed on metoclopramide by the US Food and Drug Administration because of the risk of irreversible tardive dyskinesia.

In general, tardive dyskinesia and parkinsonian symptoms develop after long-term use and are a consequence of the action of metoclopramide to induce dopamine hypersensitivity in the nigrostriatal pathway in the brain. Clinicians prescribing this agent should observe for tremors or dystonias resulting from short-term use, so that it may be promptly discontinued. Although metoclopramide has become the major prokinetic drug prescribed for upper gut dysmotility syndromes producing nausea and vomiting, other antidopaminergic antiemetic agents without gastrokinetic effects also may cause dystonias and irreversible neurologic disease.

Cisapride was employed as a gastrokinetic agent until its withdrawal in 2000. This 5-$HT_4$ agonist exhibited actions on 5-$HT_{2B}$, 5-$HT_3$, $D_2$, and $\alpha_1$ adrenergic receptors [12]. Cisapride elicited benefits in gastroesophageal reflux and functional dyspepsia, but improved symptoms in only one of four C-IBS trials. Cisapride showed an affinity for the cardiac hERG (human ether-a-go-go) potassium channel that predisposed patients to sudden cardiac death from torsades de pointes cardiac dysrhythmias [35•]. Such events were increased in individuals on other CYP3A4-metabolized medications.

Tegaserod was approved for C-IBS and chronic idiopathic constipation. The drug was a partial 5-$HT_4$ agonist but also served as a 5-$HT_{2B}$ antagonist, inhibited SERT, and bound to 5-$HT_{1A}$, 5-$HT_{1B}$, 5-$HT_{1D}$, 5-$HT_{2A}$, and 5-$HT_7$ receptors [12,35•]. Tegaserod accelerated colon transit times, improved stool frequency, decreased abdominal discomfort, and lowered global symptoms in constipation; it elicited other potential benefits in chronic intestinal pseudoobstruction, gastroparesis, and functional heartburn [35•]. Responses to tegaserod were greater in the *SS* and *SL* genotypes of the *SERT* promoter polymorphism versus the *LL* genotype [36]. Because of cardiovascular adverse events (13 cases of myocardial infarction, angina, and stroke in 11,614 patients vs 1 case in 7031 patients on placebo), tegaserod was withdrawn from the market in 2007. Tegaserod's mechanism of toxicity is uncertain. Tegaserod has little effect on the hERG channel, although an increased rate of electrocardiographic ST segment depression was reported—a phenomenon of uncertain importance [37]. 5-$HT_{1B/1D}$, 5-$HT_{2A}$, 5-$HT_{2B}$, and 5-$HT_7$ pathways mediate vasoactive responses, but their contribution to the complications of tegaserod is unproved. Some question if the association is valid because all affected individuals had prior cardiovascular disease or cardiac risk factors [12,35•].

*Investigational 5-$HT_3$ and 5-$HT_4$ receptor agents*

Novel 5-$HT_4$ and 5-$HT_3$ agonists are under consideration as prokinetic agents. Prucalopride is a 5-$HT_4$ agonist with little 5-$HT_{2C}$ and 5-$HT_3$ binding that accelerates colon transit, increases stool frequency and complete spontaneous bowel movements, decreases stool consistency, reduces straining, and improves quality of life compared with placebo in constipation [38•]. Side effects include diarrhea and headache. Development of prucalopride was temporarily halted because of concerns about carcinogenicity; however, investigations have resumed. TD-5108 is a 5-$HT_4$ agonist that stimulates gut contractions, accelerates colon transit, and shows efficacy in chronic constipation and C-IBS [12]. TD-5108 is selective for 5-$HT_4$ receptors over 5-$HT_{2B}$ and 5-$HT_3$ subtypes and does not affect hERG channels. Renzapride is a 5-$HT_4$ agonist with 5-$HT_3$ antagonist properties that improves stool frequency and consistency, stimulates colonic transit, and reduces symptoms in chronic constipation and IBS [29,39]. Renzapride also enhances liquid gastric emptying in gastroparesis. Minor affinities for 5-$HT_{2A}$, 5-$HT_{2B}$, and 5-$HT_{2C}$ receptors were characterized. Side effects include diarrhea, discomfort, and headache. Affinity of renzapride for the hERG channel is less than with cisapride. Mosapride is a 5-$HT_4$ agonist with a metabolite exhibiting 5-$HT_3$ antagonist properties that accelerates gastric emptying in humans and exhibits prokinetic effects in the colon in animal models [40]. Pumosetrag is a partial 5-$HT_3$ agonist that enhances intestinal motor function and increases stool frequency in chronic constipation and C-IBS [41].

5-$HT_3$ and 5-$HT_4$ antagonists inhibit motor activity and theoretically might be effective in functional diarrheal conditions. DDP-225, a 5-$HT_3$ antagonist with associated norepinephrine uptake inhibition, exhibits efficacy in preliminary studies in D-IBS. The 5-$HT_4$ antagonist piboserod delays orocecal transit and showed trends to reducing symptoms in D-IBS.

*Therapies relating to other 5-HT receptor subtypes*

Other receptor subtypes are possible targets for therapy. The 5-$HT_{1A}$ agonist buspirone reduces fundic tone and improves symptoms in patients with functional dyspepsia. The drug also decreases rectal tone and sensation. The 5-$HT_{1B/1D/1P}$ agonist sumatriptan enhances gastric accommodation by activating nitrergic pathways and decreases perception of distention in functional dyspepsia, but no trials have confirmed its utility [7]. Sumatriptan given systemically or into the brainstem blunts hypersensitivity in visceral pain models [42]. The 5-$HT_2$ and 5-$HT_3$ antagonist mianserin also showed benefits in functional dyspepsia. Newer agents that bind 5-$HT_{1A}$ and 5-$HT_3$ receptors are in development. 5-$HT_7$ antagonists are touted as potential therapies of bloating in patients with functional bowel disorders. The 5-HT derivative melatonin exhibited efficacy in IBS.

*Agents that modulate serotonin uptake and synthesis*

SSRIs and other agents that regulate extracellular serotonin levels are proposed for functional disorders. Paroxetine stimulates intestinal transit and increases fundic accommodation in humans, but retards transit and reduces sensation in animal models [21]. Citalopram increases colon contractions and compliance, but blunts the gastrocolonic response. In IBS trials, citalopram decreased pain and bloating to greater degrees than pla-

cebo, whereas fluoxetine reduced discomfort, decreased bloating, increased stool frequency, and softened stool consistency [12,43]. However, in another study, fluoxetine had no effect on global symptoms in IBS [12]. Tricyclic antidepressants inhibit reuptake of serotonin and norepinephrine and exhibit efficacy in IBS with inconsistent associated reductions in visceral sensation. In a small functional dyspepsia study, amitriptyline reduced symptoms without altering perception of gastric distention. Responses of functional disorders to tricyclics show a weak relation to drug dose, a phenomenon attributed to variable CYP2D6 activity [44]. In general, tricyclic drugs are more often considered for patients with non–C-IBS because of their propensity to slow gut transit. Retardation of transit is most prominent with amitriptyline and is less severe for nortriptyline and desipramine. In such patients, tricyclics may reduce pain and diarrhea. SSRIs (other than paroxetine) tend to accelerate transit and thus may exacerbate symptoms in D-IBS. As a consequence, many clinicians consider SSRIs for individuals with symptoms related to sluggish transit (eg, constipation and bloating). The 5-HT and norepinephrine reuptake inhibitor venlafaxine reduces colonic sensitivity in healthy subjects, but its utility in IBS remains uninvestigated. TpH1 inhibitors are proposed as potential therapies of IBS.

### Vomiting

5-$HT_3$ antagonists prevent and treat emesis induced by cancer chemotherapy, by radiotherapy, and in the postoperative state (Table 2). Such agents also improve quality of life and reduce health care expenditures. 5-$HT_3$ antagonists are best characterized to prevent acute emesis from cancer chemotherapy, and may be given alone for moderately emetogenic agents or in combination with other antiemetics for highly emetogenic drugs (eg, cisplatin). Most 5-$HT_3$ antagonists exhibit little efficacy against delayed emesis (1 to 5 days after chemotherapy); however, a new agent, palonosetron, reduces vomiting during this period because of its increased receptor binding affinity and longer half life [45]. Antiemetic responses to 5-$HT_3$ antagonists are reduced in patients with multiple active *CYP2D6* alleles [45]. Polymorphisms of the gene encoding the *HTR3C* subunit predict responsiveness to 5-$HT_3$ antagonist prophylaxis of chemotherapy-induced emesis.

Therapies relating to other 5-HT activities may reduce nausea and vomiting (Table 2). The 5-$HT_{1A}$ agonist buspirone reduced nausea scores during experimental testing in healthy humans and elicits antiemetic effects in patients with malignancy. The 5-$HT_{1B/1D/1P}$ agonist sumatriptan is proposed to abort emetic episodes in cyclic vomiting syndrome. Tricyclic antidepressants exhibit potent effects to reduce functional vomiting.

### Weight reduction

Agents acting on hypothalamic 5-HT pathways reduce food intake and promote weight reduction (Table 2). L-tryptophan is an appetite suppressant in some countries. Fenfluramine and its enantiomer dexfenfluramine elicited prominent weight reductions in clinical trials [16]. These agents block SERT and inhibit norepinephrine uptake as well. A metabolite of fenfluramine, norfenfluramine is a 5-$HT_{2C}$ agonist. The combination of fenfluramine and phentermine was withdrawn from the market because of complications of pulmonary hypertension and valvular heart disease. In animal and human studies, SSRIs (fluoxetine, sertraline, paroxetine, and fluvoxamine) show some efficacy as weight-reducing therapies [16]. However, tolerance to their anorectic effects limits their long-term utility. The serotonin and norepinephrine reuptake inhibitor sibutramine is the only agent approved for obesity that acts on 5-HT pathways [15•]. In clinical trials, food intake reductions and weight decreases were maintained for at least 10 weeks. The *LS* and *SS* genotypes of the *5-HTT-LPR* polymorphism are associated with greater weight loss than the *LL* genotype.

Several novel 5-HT agents are under investigation as weight-reducing therapies (Table 2). 5-$HT_{2C}$ agonists reduce food intake in animal models. In clinical trials, the 5-$HT_{2C}$ agonist lorcaserin promoted weight reduction in morbid obesity [46]. The 5-$HT_{1B}$ and 5-$HT_{2C}$ agonist mCPP (1,3-chlorophenylpiperazine) reduces hunger and body weight in obese humans [16]. Selective 5-$HT_6$ partial agonists and antagonists affect feeding behavior and elicit weight loss with decreases in fat stores and circulating leptin in animal models of obesity [47].

### Other GI disorders with altered 5-HT function

5-HT–induced symptoms of carcinoid syndrome may be reduced by 5-HT antagonists (ondansetron, ketanserin, and methysergide) or 5-HT synthesis inhibitors (eg, p-chlorophenylalanine), although alosetron showed no effect on colon transit or symptoms in one study. The 5-$HT_2$ antagonist ketanserin reduces flushing, secretory diarrhea, and dyspnea associated with carcinoid syndrome (Table 2). Chronic SSRI use reportedly is associated with a decreased risk of colon cancer, supporting the postulate that 5-HT can promote neoplastic growth [48].

## Conclusions

Serotonin pathways participate in normal functions of the gut and are critical for its communication with the central nervous system. Disorders of motor, sensory, and secretory function, responses to emetic stimuli, and development of obesity all may relate to abnormal 5-HT activities in the gut and brain. Agonists and antagonists of several 5-HT receptor subtypes and agents that prevent 5-HT reuptake have documented benefits in these disorders; however, their utility is hampered by cardiovascular and pulmonary complications, which may or may not relate to their actions on 5-HT receptors. Investigation is ongoing into developing agents that produce clinical improvements without associated toxicity.

## Disclosure

No potential conflict of interest relevant to this article was reported.

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