

Irritable bowel syndrome: treatment options

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Practice Points

- Nonpharmacological approaches can be sufficient in patients with mild irritable bowel syndrome symptoms.
- Information and reassurance, dietary guidance, regular exercise and probiotic intake individually and in combination reduces symptoms and improves quality of life.
- The information and reassurance should be provided by the patient's doctor.
- Intake of probiotics increases the patient's tolerance to fermentable oligosaccharides, disaccharides, monosaccharides and polyols.
- In addition to nonpharmacological treatment, a drug directed to the main symptom that troubles patients can be used.
- Irritable bowel syndrome patients that do respond to nonpharmacological and pharmacological treatment are candidates for gut-directed hypnotherapy.

SUMMARY Irritable bowel syndrome is a common gastrointestinal disorder that considerably reduces the patient's quality of life and represents an economic burden to society due to the high consumption of healthcare resources and the nonproductivity of irritable bowel syndrome patients. The options for the treatment of irritable bowel syndrome are nonpharmacological and pharmacological. The nonpharmacological approach includes: information and reassurance, dietary guidance, regular exercise, probiotic intake, hypnotherapy and cognitive therapy, psychodynamic interpersonal therapies and relaxation training. There is still some uncertainty regarding the role of cognitive behavior, psychodynamic interpersonal therapies and relaxation training in managing irritable bowel syndrome. This is due to significant challenges in terms of study design, patient selection and the interpretation of results.

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Pharmacological treatment mainly includes laxatives, antidiarrheal drugs, antispasmodic drugs, antidepressants and anti-anxiety drugs. Patient confidence is higher for the nonpharmacological approach than medication. The nonpharmacological approach is also more effective than medication.

Irritable bowel syndrome (IBS) is a chronic functional disorder of the gut. Patients with IBS suffer from abdominal pain/discomfort, bloating, abdominal distension and diarrhea alternating with constipation. The intensity of symptoms varies in different patients from mild to severe. Some patients complain of daily symptoms, while others report intermittent symptoms at intervals of weeks/months. The prevalence of IBS is from 5 to 10% of the world's population and the annual incidence is approximately 200 per 100,000 [1–3]. IBS is more common in women than in men, and is more commonly diagnosed in patients younger than 50 years of age [1]. IBS reduces quality of life with the same degree of impairment as major chronic diseases such as diabetes, congestive heart failure, renal insufficiency, hepatic cirrhosis and inflammatory bowel diseases [4–6]. IBS is not known, however, to be associated with the development of serious disease or with excess mortality.

IBS patients visit physicians more often than other patients with common somatic diseases such as diabetes, hypertension or asthma, and they represent 12–14% of primary care patient visits and 28% of referrals to gastroenterologists [1]. IBS represents an economic burden to society in the form of direct and indirect costs. The direct costs are caused by overconsuming medications, diagnostic tests and being hospitalized frequently [1,7,8]. The indirect costs are brought about by the lower work productivity of IBS patients [1,7,8].

There is no biochemical, histopathological or radiological diagnostic test for IBS. Rather, the diagnosis of IBS is based on symptom assessment. Thus, Rome III criteria have been established (Box 1), where elaborated, detailed, accurate and clinically useful definitions of the syndrome are used [9]. In addition to these criteria, warning symptoms (red flags) such as age >50 years, short history of symptoms, nocturnal symptoms, weight loss, rectal bleeding, anemia and the presence of markers for inflammation or infections should be excluded. IBS patients are subgrouped on the basis of differences in predominant bowel pattern as diarrhea-predominant (IBS-D),

constipation-predominant (IBS-C) or a mixture of both diarrhea and constipation (IBS-M), and unsubtyped IBS in patients with insufficient abnormality of stool consistency to meet criteria for IBS-C, D or a mixture of both diarrhea and constipation. The division is useful for clinical practice and symptomatic treatment. In clinical practice, however, it is common for IBS patients to switch from one subtype to another over time. These patients are now called 'alternators'. More than 75% of IBS patients change to either of the other two subtypes at least once over a 1-year period [10]. In clinical practice, few clinicians in primary and secondary care use the Rome criteria systematically, but instead rely more on a holistic approach [11–14].

Treatment options

The treatment options for IBS include nonpharmacological and pharmacological options [1].

The nonpharmacological approach comprises: information, reassurance, dietary guidance, regular exercise, probiotic intake, hypnotherapy and cognitive therapy, amongst others [1]. Pharmacological treatment mainly includes laxatives, antidiarrheal drugs, antispasmodic drugs, antidepressants and anti-anxiety drugs [1]. The use of nonpharmacological treatments and pharmacological drugs in primary healthcare and by gastroenterologists is almost the same [1]. Patient confidence is higher for the nonpharmacological approach than medication, and the nonpharmacological approach is also more effective than medication [1].

Nonpharmacological approaches

■ Information & reassurance

Approximately 52% of IBS patients believe that IBS is caused by a lack of digestive enzymes, 42.8% believe that IBS is a form of colitis, 47.9% believe it will worsen with age and 43% believe it can develop into colitis, 37.7% into malnutrition and 21.4% into cancer [15]. The IBS patients are interested in learning about which foods to avoid (63.3%), the causes of IBS (62%), coping strategies (59.4%) and medications (55.2%); they are also interested in finding out whether

Box 1. Rome III criteria for the diagnosis of irritable bowel syndrome.

Recurrent abdominal pain or discomfort with onset at least 6 months prior to diagnosis, associated with two or more of the following, at least 3 days/month in the last 3 months:

- Improvement with defecation
- Onset associated with change in frequency of stool
- Onset associated with change in form (appearance) of stool

Symptoms that cumulatively support the diagnosis are:

- Abnormal stool frequency (greater than three bowel movements per day or less than three bowel movements per week)
- Abnormal stool form (lump/hard or loose/watery stool)
- Abnormal stool passage (straining, urgency or feeling of incomplete evacuation)
- Passage of mucus
- Bloating or feeling of abdominal distension

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or not they would have to live with IBS for life (51.6%) and in reading research studies (48.6%) [16]. The qualities in healthcare providers desired by the IBS patients are the ability to provide comprehensive information, the ability to listen and answer their questions, and to provide support and hope [1]. The majority of the IBS patients stated that they prefer to get information from a doctor in person [1]. An effective physician–patient relationship that provides both reassurance and a thorough explanation of the IBS disorder has been found to reduce the use of healthcare resources, the fear of cancer and self-perceptions of impairment in daily functioning [1].

We believe that information and reassurance should be provided by the patient's doctor simply because this is what the patients prefer (Box 2). Moreover, this is important in establishing patient–doctor relationships. Consequently, these patients need longer consultations than normal. Dedicated longer time slots may be an appropriate way to manage the disorder rather than repeated brief consultations. The arguments that are given in favor of providing information to a small group of patients (IBS school) instead of providing information individually are that it is less time-consuming and that patient education in a group setting offers an opportunity to share experiences with others in the same situation, which can contribute to improvements in coping strategies. Actually providing information for a group of patients does not save a doctor time as 2 h of a gastroenterologist's time are used to inform a group of five to ten patients [16,17]. Modeling, according to the self-efficacy theory, is a process of comparing oneself with someone else. When people

see someone succeeding at something, their self-efficacy is more likely to increase, whereas when they see people failing, their self-efficacy is more likely to decrease. This process is more effective when a person sees him- or herself as being similar to his or her own model. Regarding this matter, the IBS patients who attended the IBS school apparently failed to cope with IBS; according to the modeling, seeing failed people is more likely to decrease self-efficacy.

Optimal consultation techniques designed to elicit a therapeutic alliance between patients and physicians are especially important in consultations with IBS patients. The patients should be allowed to tell their story in their own words in order to feel that the doctor has understood their concerns. This becomes even more important when previous consultations may have been unsatisfactory in this respect. Furthermore, the first consultation should include a thorough physical examination and some blood tests to exclude infection/inflammation, anemia, diabetes, or thyroidal, liver or kidney diseases. An educational booklet containing the same information provided should be freely available at the end of the consultation, along with the opportunity for patients to discuss their concerns again once they have read this material.

■ Dietary guidance & regular exercise

Diet seems to play an important role in the manifestation of IBS symptoms. The mechanisms thought to lie behind this have been discussed elsewhere [1]. Fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) are short-chain carbohydrates that are poorly absorbed so that a significant portion of the ingested carbohydrates enters the distal small

Box 2. The contents of the information provided to irritable bowel syndrome patients.

- IBS is recognized as a common illness in the population and there is some evidence to show that it could be hereditary
- IBS is not known to be associated with the development of serious disease, cancer or with excess mortality
- IBS is a chronic condition and the intensity of symptoms fluctuate, in that there will be good days and bad days
- A clear knowledgeable explanation of the known pathophysiology and the pathogenesis of IBS
- The possible coexistence of other gastrointestinal and extragastrointestinal symptoms in patients with IBS
- There is no miracle cure for IBS. An explanation of the treatment options and the fact that a nonpharmacological approach could be sufficient and could be combined with pharmacological treatment on bad days
- A thorough explanation regarding the fact that a physical examination, blood tests, gastroscopy and colonoscopy can exclude other diseases that the patients fear. In patients who have already undergone gastroscopy and colonoscopy, an explanation should be offered as to what these tests have excluded
- Intensive research is being carried out on IBS worldwide and our understanding of this disorder increases every day, which will hopefully offer new treatment possibilities. In other words, there will be light at the end of the tunnel

IBS: Irritable bowel syndrome.

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bowel and colon. There they increase the osmotic pressure and provide a substrate for bacterial fermentation with the production of gas, distension of the large intestine and abdominal discomfort or pain. A restricted intake of FODMAPs has been shown to reduce symptoms of IBS [18,19]. An increased consumption of dietary fiber is thought to accelerate oro–anal transit time and decrease intracolonic pressure, therefore playing a role in the management of IBS symptoms, particularly regarding constipation [20]. However, more recent studies where dietary fiber was considered as a whole entity, yielded controversial results [1]. In studies that distinguished between insoluble and soluble fiber, soluble fiber tended to improve symptoms whereas insoluble fiber worsened them [21]. Moreover, a recent, randomized, double-blind, placebo-controlled trial of soluble fibers showed a significant reduction in the intensity of abdominal pain, constipation and diarrhea, as well as an improvement in the performance of daily activities [22]. A lower intake of FODMAPs should be recommended to IBS patients, as well as increasing their intake of foods rich in water soluble fibers (Box 3).

In the clinic, tolerance to FODMAPs and insoluble fibers varies between different patients with IBS. This wide variation could be owing to differences in intestinal flora between patients. Furthermore, consuming food supplemented with probiotics increases a patient's tolerance to FODMAPs and insoluble fibers. IBS patients received two sessions, 1 h each, of individual dietary guidance recommending that they increase their daily intake of dairy products and food items supplemented with probiotics. They subsequently increased their intake of β -carotene, retinol equivalents, riboflavin,

calcium, magnesium and phosphorus [23]. Furthermore, they reported a better quality of life and improved symptoms [23]. In addition to general dietary advice, individual dietary guidance is also required.

Regular exercise has been found to reduce symptoms and improve the quality of life in patients with IBS [1]. Based on clinical experience and circumstantial evidence physicians recommended exercise for IBS patients. Physical activity effects on IBS patients have previously been attributed to promoting overall well being. However, physical activity has been found to increase gastrointestinal transit [24,25]. The increased gastrointestinal motility has been attributed to vagus stimulation and/or decreased blood flow to the gut, which leads to an increase in important gastrointestinal hormones [25,26].

■ Probiotics

Probiotics are live microorganisms that, when administered in adequate amounts, confer health benefits to the host. The most commonly used probiotics include bacteria or yeasts from the genera *Lactobacillus*, *Bifidobacteria* and *Saccharomyces*. Commercially available probiotics contain either single strains or a mixture of strains and are available in capsules, powders, yoghurts and fermented milks. Probiotics must be well tolerated for human consumption, they must survive transit through the gastrointestinal tract and they must have some physiological impact. Some of the beneficial effects attributed to probiotics are enhancement of the host's anti-inflammatory and immune response and the stimulation of anti-inflammatory cytokines, improving the epithelial cell barrier, inhibiting bacterial translocation and growth, inhibiting

the adhesion of viruses and inactivating bile acids [27,28]. In animal models, probiotics have been found to reduce hypermotility and visceral hypersensitivity [29,30]. Controlled clinical trials of a single probiotic preparation and a probiotic mixture demonstrated that IBS symptoms are improved depending on the preparation used, and that some products appear to be more effective than others [1,31–34]. The bacteria that have been proven to be effective in this aspect are *Bifidobacterium infantis* 35624, *Bifidobacterium lactis* DN–173–010, *Lactobacillus plantrum*, *Lactobacillus GG*, *Lactobacillus acidophilus* and *Saccharomyces faecium*. The mechanism by which these bacteria exert their effects is attributed to the ability of these bacteria to reduce the number of sulphite-reducing *Clostridia* spp., which is known to produce gas upon the fermentation of nutrients. This could contribute to improvements in flatulence, bloating and abdominal distension in IBS patients [28]. Although probiotics have beneficial effects in some patients with IBS, they are not potent enough to be used alone, especially in patients with severe symptoms [28]. In clinical practice, a relapse of IBS symptoms was observed in some patients as soon as they stopped taking the probiotics [1].

■ Combined program

A health program combining of reassurance and information, dietary management, probiotic intake and regular exercise was followed by 143 IBS patients, who were followed up over 2 years [35]. The patients who followed this program reported improved quality of life and reduced symptoms throughout the follow-up period [35]. These findings are in favor of the additive effect of combining several nonpharmacological approaches in a short health program.

■ Psychological treatment

There is still some uncertainty regarding the role of cognitive behavior, psychodynamic interpersonal therapies and relaxation training in managing IBS [1]. This is due to significant challenges in terms of study design, patient selection and the interpretation of results.

Gut-directed hypnotherapy requires six to 12 sessions, 30–60 min each, spread over several months [36–39]. The goal of this therapy is to make IBS patients independent of healthcare in managing their symptoms. The rationale of

gut-directed hypnotherapy is to use hypnotic induction, progressive relaxation and imagery directed to the control of gut function [36–39].

The dropout rates in patients with refractory IBS are relatively high [39]. This therapy has been shown to be effective not only in improving IBS symptoms but also in improving many of the features of the condition, including quality of life and psychological status [38–41]. The beneficial effects appear to be sustained over time [35].

Box 3. General food advice to irritable bowel syndrome patients.

Food allowed:

- Meat
- Fish
- Chicken
- Milk
- Fat and oils
- Rice
- Potatoes
- Carrot
- Apple and pear (peeled)
- Citrus
- Banana
- Raspberry blueberry and strawberry
- Honeydew melon
- Kiwifruit and passionfruit
- Tomato
- Coffee and tea
- Chocolate
- Alcohol
- Probiotic supplemented
- Spelt and spelt products

Food advised to avoid:

- Onion
- Garlic
- Light products (food containing artificial sweeteners)
- Paprika
- Beans
- Peas
- Cabbage and rutabaga
- Carbonated beverages (soda)
- Avocado
- Artichokes
- Broccoli
- Cabbage
- Watermelon
- Flour and flour products

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This form of treatment should be restricted to specialist centers caring for more severe forms of IBS (refractory IBS) [34].

Gut-directed hypnotherapy normalizes visceral sensation, reduces colonic phasic contractions and reverses the negative thoughts that patients often have regarding their condition [42–44]. It has been proposed that the action of hypnotherapy is probably owing to the activation of certain areas of the brain, especially the anterior cingulate, which is supported by the finding that the hypnotic reduction of somatic pain is associated with a reduction in the activation of this brain region [44].

Pharmacological approaches

■ Symptomatic treatment

Pharmacological treatments for the relief of IBS symptoms have been presented in detail in recent comprehensive reviews [45–49]. Drug treatment is chosen based on the main symptoms that trouble patients; thus, pharmacological drugs against abdominal pain and/or bloating, diarrhea and constipation are most commonly used (Table 1).

Several treatment options are available for the symptomatic relief of constipation in IBS patients [1]. Soluble fibers and bulking agents are most frequently used as the first-line treatment; conventional bulking agents include psyllium, methylcellulose and calcium polycarboxylate. Bulking agents containing insoluble fibers often

have the adverse effects of bloating and flatulence. Psyllium preparations have been proven to be effective and free from the side effects of other bulking agents [50–53]. Osmotic laxatives, such as polyethylene glycol and lactulose, are used for constipation in IBS, although lactulose is associated with bloating and abdominal pain and is not suitable for chronic use [54]. Stimulant laxatives as bisacodyl and senna are effective but are associated with abdominal cramping, electrolyte depletion and diarrhea, and consequently should not be used for long periods [1].

Diarrhea in IBS patients can be treated with loperamide or diphenoxylate. Loperamide is an opiate μ -agonist that does not cross the blood–brain barrier. It is widely used in clinical practice because it is effective for urgent loose stools and it is safe, well tolerated and inexpensive [55]. Loperamide stimulates absorption, inhibits secretion and slows intestinal transit. However, it is not effective in abdominal pain [56].

Several tricyclic antidepressants are used to treat IBS patients, especially those with diarrhea as the predominant symptom. These have anticholinergic and antiselective serotonin reuptake inhibitor effects. These drugs may alter pain perception independent of their antidepressant or anxiety effects. However, even treatment with low doses of these drugs can cause side effects such as a dry mouth, constipation, fatigue and drowsiness in over a

Table 1. Pharmacological options for the treatment of irritable bowel syndrome patients.

Target symptom	Drug class	Generic name	Dose
Diarrhea	Opiate μ -agonist	Loperamide	2 mg with each loose stool, up to a maximum of 16 mg daily
Diarrhea, abdominal distension and pain	Tricyclic antidepressants	Desipramide	10–150 mg at night
		Amitriptyline	10–150 mg at night
		Nortriptyline	10–150 mg at night
Global benefit without benefit to bowel symptoms	Selective serotonin reuptake inhibitors	Paroxetine	20–50 mg daily
		Fluoxetine	10–40 mg daily
Global improvement of symptoms and improvement in bloating and distension	Antibiotics	Rifaximin	400–550 mg three-times daily over 7–10 days
		Neomycin	1 g daily over 10 days
		Metronidazole	400 mg twice daily over 15 days
Improve straining and hard stools	Bulking agents	Psyllium	2.5–30 g daily in divided doses
		Ispaghula	3.5 g one to three-times daily
	Osmotic laxative	Polyethylene glycol	17 g in 237 ml solution daily
Limited proven efficacy	Emollient laxative	Mineral oil	5–10 cm ³ daily
		Antispasmodics	Hycocamine sulfate
			Dicyclomine

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third of patients. Selective serotonin reuptake inhibitors inhibit the reuptake of serotonin by blocking the serotonin transporter protein at presynaptic nerve endings and increasing synaptic exposure to a high concentration of serotonin [57]. A standard dose of selective serotonin reuptake inhibitors has been shown to lead to a significant improvement in the health-related quality of life in patients with chronic or treatment-resistant IBS [58]. These drugs confer global benefits without significant changes in bowel symptoms or pain [1]. These drugs are better tolerated by patients than tricyclic antidepressants.

The rationale for using antibiotics in the treatment of IBS is based on the assumption that IBS symptoms could be caused by small intestinal bacterial overgrowth and the presence of inflammatory mediators and/or inflammatory cells in the mucosa of some IBS patients. Clinical trials with antibiotics have shown global relief of IBS symptoms and bloating [1].

In randomized, double-blind, placebo-controlled studies, administration of melatonin 3 mg at bedtime attenuated abdominal pain and reduced rectal pain sensitivity. This treatment had no effect on sleep disturbances or psychological stress suggesting that the beneficial effects of melatonin are independent of its action on sleep disturbances or psychological profiles [59,60]. The rationale behind the use of an antispasmodic agent is to attenuate the heightened baseline and postprandial contractility observed in IBS patients; however, the efficacy of these agents in the treatment of IBS is limited [1].

■ The use of gut neuroendocrine peptides/amines in the treatment of IBS

The neuroendocrine peptides/amines of the gut have the potential to be used in the treatment of IBS; this could be considered as the correction of a pre-existing abnormality in the neuroendocrine system of the gut or through the use of the pharmacological actions of gut hormones. The neuroendocrine peptides/amines of the gut have broad physiological/pharmacological effects: they can often bind to and activate several receptors with independent actions. Thus, in order to be able to target these bioactive substances, receptor-specific agonists or antagonists should be developed. Both serotonin agonists and antagonists have been proven to be useful in clinical practice.

Ondansetron, granisetron, alosetron and cilansetron are 5-HT₃ receptor antagonists [1]. These antagonists have been found to decrease small intestinal secretion, small and large intestinal motility and nausea, as well as reducing colonic hypersensitivity [1]. Alosetron was approved for the treatment of IBS-D in female patients, but it was later withdrawn from the market because of its side effects [1,61]. Other 5-HT₃ receptor antagonists, especially cilansetron, have been investigated or are still under development for the treatment of IBS-D patients [1].

The 5-HT₄ receptors are located on afferent neurones in the myenteric plexus, smooth muscles and enterochromaffin cells [57,58]. These receptors mediate the release of the colonic neurotransmitters acetylcholine, substance P, vasoactive intestinal polypeptide and calcitonin gene-related peptide, which stimulate the peristaltic reflex [1]. Furthermore, 5-HT₄ receptor activation induces small bowel and colonic fluid secretion [1]. Tegaserod, prucalopride, renzapride and cisapride are 5-HT₄ receptor agonists. Tegaserod has been shown to promote small intestinal transit time and to enhance proximal colonic emptying in IBS-C patients [59]. In healthy humans, tegaserod stimulates intestinal secretion and promotes the evacuation of jejunal gas [1]. Tegaserod has been used to treat IBS-C, but it was withdrawn from the market because of its side effects. Prucalopride has also been reported to decrease colonic transit time [1,62–64].

Other treatment options

■ Acupuncture

Acupuncture is an ancient traditional Chinese medical practice based on the theory that energy or the life force 'qi' runs through the body in channels, or 'meridians'. Qi is essential for health and any disruption of its flow causes symptoms and disease. This disruption is believed to be corrected by acupuncture at identifiable anatomical locations called 'acupoints'. The effect of acupuncture on IBS is believed to be caused by altering visceral sensation and motility by stimulating the somatic nervous system and vagus nerve [1].

Acupuncture intervention in a randomized controlled pilot study showed significant improvements in IBS symptoms. In another two large, randomized controlled studies, no difference was found in the global outcome

measurements between patients who received real or sham acupuncture [65,66]. However, improvements were found in IBS symptoms and quality of life in patients who received real and sham acupuncture compared with baseline values and IBS patients on the waiting list [65,66]. These findings suggest that the observed effect of acupuncture may have been due to the placebo effect.

■ **Herbal therapy**

In traditional Chinese medical theory IBS is a syndrome of stagnated liver energy and a dysfunction of the spleen. Thus, Chinese herbal treatments for IBS were developed to relieve suppressed liver functioning and to replenish the energy of the spleen. There are several Chinese herbal formulations for IBS, such as Tong Yao Fang (the essential formula for abdominal pain and diarrhea), which contains up to 20 herbal ingredients, and the Tibetan herbal formulation Padma Lax. Studies on the beneficial effects of herbal treatments have shown conflicting results and the efficacy of this type of treatment remains controversial [1,67].

Extracts from the peppermint plant (*Mentha piperita*, Lamiaceae) are believed to have a spasmolytic effect on the smooth muscles of the gut causing a relief in IBS symptoms.

Most trials support the effectiveness of peppermint oil in improving IBS symptoms; however, further studies are needed to elucidate the beneficial effects of such a treatment [1].

Conclusion & future perspective

The available options for the treatment of IBS are nonpharmacological and pharmacological. The nonpharmacological approaches are sufficient in treatment of patients mild IBS, which constitutes the majority of IBS patients. Gut-directed hypnotherapy is effective in patients with refractory IBS. Pharmacological treatment is by far symptomatic. There is ongoing intensive research on the role of intestinal flora in IBS, which may result in expanding our knowledge in this area and might improve the use of probiotics in nonpharmacological treatment of IBS. Four neuroendocrine peptides/amines are candidates for pharmacological treatment of IBS, namely serotonin, ghrelin, peptide YY and cholecystokinin. Receptor specific agonists and agonists for these neuroendocrine peptides/amines are under development, and new serotonin agonists and antagonists are actually on their way to the clinic.

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