

# Diagnosis and management of chronic idiopathic constipation: a narrative review from a Brazilian expert task force

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Received: 4 October 2021  
Accepted: 21 October 2021

**ABSTRACT – Background** – Chronic idiopathic constipation (CIC) is a condition that widely affects the global population, represents relevant healthcare resource utilization and costs, and impacts the individual's well-being. **Objective** – To review the consensus of expert societies and published guidelines on the diagnosis and treatment of CIC in adults, seeking to assist reasoning and decision-making for medical management of patients with CIC and provide a practical reference material. **Methods** – A Brazilian medical task force searched the scientific literature in the following electronic databases: MEDLINE/PubMed, SciELO, EMBASE and Cochrane, using the following descriptors: chronic constipation, diagnosis, management of chronic constipation. In addition, a review of articles on the mechanism of action, safety, and efficacy of therapeutic options available in Brazil was carried out. **Results** – The diagnostic approach and the understanding of the pathophysiology present in CIC are essential items to indicate the appropriate therapy and to understand the ecosystem of the patient's needs. **Conclusion** – CIC is a common condition in adults, occurring more frequently in the elderly and in women. Proper management is defined by detailed medical history and physical examination, together with appropriate therapeutics, regardless pharmacological or not, and depending on the best moment of indication. This way, the impact on quality of life is also optimized.

**Keywords** – Chronic idiopathic constipation; functional constipation; diagnosis; treatment.

## INTRODUCTION

Chronic constipation (CC) is a common and persistent condition with 14% of global prevalence<sup>(1,2)</sup>. It is often associated with older age, female gender, and lower socioeconomic status<sup>(2-4)</sup>. Characterized by infrequent bowel movements, CC encompasses symptoms such as excessive straining at stool, abdominal pain and bloating, a sense of incomplete evacuation, lengthy (or failed) attempts to defecate, use of digital manoeuvres for evacuation of stool, and hard consistency of stools<sup>(1,5)</sup>. CC results in significant economic burden and substantial healthcare utilization, affects work, productivity, school attendance, and patients may suffer from impaired psychological well-being and poor quality of life (QoL)<sup>(6,7)</sup>. Half of the patients with CC reports symptoms for more than 5 years<sup>(8)</sup>.

After examining secondary causes for CC (organic or systemic diseases, or medications in use), chronic idiopathic constipation (CIC), also called primary constipation, can be divided into three subtypes: a) dyssynergic defecation (DD); b) normal-transit consti-

pation (NTC), the most common subtype, that include functional constipation (FC)<sup>(5)</sup>; and c) slow-transit constipation (STC). These classifications are not mutually exclusive and significant overlap exists. Classification of CC is shown in FIGURE 1<sup>(1)</sup>, and risk factors are presented in BOX 1<sup>(9)</sup>.

Although we recognise that FC often overlaps with irritable bowel syndrome–constipation predominant (IBS-C), the latter would call for a specific material as it has a particular pathophysiology and therapeutic implications. In this article, we aimed to briefly describe the pathophysiology of CIC, with emphasis on FC and its frequent symptoms, diagnostic methods, and current options of treatment to offer a practical reference material.

In this work, we searched the literature in electronic databases such as MEDLINE/PubMed, SciELO, EMBASE and Cochrane, using the following terms: “chronic constipation”, “diagnosis”, “management” and “surgical treatment”. After reviewing the published literature, a Brazilian medical task force, experts in gastroenterology, discussed the findings aiming to briefly describe the pathophysiology of CIC, its frequent symptoms, diagnostic

Declared conflict of interest of all authors: Passos MCF has served as Global Advisory Board Member for Takeda, speaker for Ache, Apsen, EMS and Mantecorp; Alvariz RC has served as speaker for Takeda, Roche, Apsen, Astra Zeneca, Novartis and Bristol-Myers-Squibb; André EA has served as speaker and advisory board for Sanofi and speaker for Takeda; Barbuti RB has served as Global Advisory Board Member for Takeda, Mantecorp, Apsen, Sanofi, Aché and speaker for, Ache, Mantecorp, Takeda, Sanofi, Apsen, Eurofarma; Fillmann HS has served as Advisory Board Member and speaker for Takeda; SMR has served as speaker for Takeda and BK Medical; Rezende Filho J has served as speaker for Takeda; Perrotti M and Guedes L are Takeda Pharmaceuticals Brazil employees.

Disclosure of funding: this work was funded by Takeda Pharmaceuticals.

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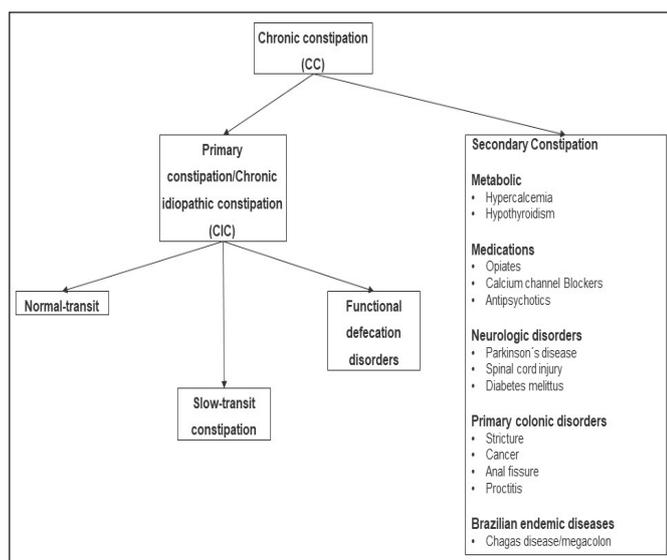


FIGURE 1. Classification of chronic constipation.

#### BOX 1. Risk factors for chronic constipation\*.

- Depression.
- Low calorie intake (high-fiber diet may be protective).
- Low income and low education levels.
- Medications.
- Physical and sexual abuse and inactivity.
- Aging (although, constipation is not necessarily a consequence of normal aging).
- Female sex.
- Inactivity (physical exercise may be protective).

Adapted from Lindberg et al., 2011<sup>(1)</sup>. \*Association with these risk factors is not necessarily causative.

methods, and current options for treatment, to offer a practical reference guiding material with special emphasis in the options available locally. In addition, we reviewed current North American and European guidelines and recommendations to provide a comparison between them, whenever relevant.

#### Normal colonic physiology

To understand CIC, it is worthwhile to consider the normal functioning of the colon. Colonic motility is controlled by the entry of food into the small intestine, and intrinsic somatic movements are the main mechanism of propulsive motility that leads to defaecation<sup>(10)</sup>. Motility of the bowel can be divided, basically, in low- or high-amplitude propagated activity and this latter is mainly related to large amounts of colonic contents and defecation<sup>(11)</sup>. The primary motor pattern associated with these mass movements, which originate from the inhibition of distal haustral segments and contractions of the proximal bowel wall, is called high-amplitude propagating contraction (HAPC), and arise from the contraction of colonic smooth muscle<sup>(12)</sup>. The HAPCs usually occur after meals (there is evidence that fat and carbohydrate may influence the occurrence of HAPC), but they can also be induced by stimulant laxatives (e.g., bisacodyl)<sup>(11,13)</sup>. In turn, peristalsis is mediated by serotonin (5-HT), which is synthesized in enterochromaffin cells in the mucosa, and antagonists of 5-HT receptors can inhibit/block peristalsis, reducing propulsion of contents<sup>(14)</sup>. Contents in the

colon can also move in a retrograde direction, specially following a meal, a mechanism that prevents rapid rectal filling. Though, there is also an increase in the post-prandial colonic motor activity (gastro-colic reflex)<sup>(15)</sup>. The colon also plays an important role in managing fluids and electrolytes, as it reabsorbs approximately 1.5–2 litres of fluid per day, which is important for pharmacological treatment<sup>(16)</sup>.

#### Pathophysiology of chronic idiopathic constipation

The cause of CIC is multifactorial. Motility disturbances of the colon and dysfunctions of the pelvic floor are usually the main causes of CIC, but diet, changes in the microbiome and anatomical issues may also contribute to the condition<sup>(17)</sup>. Life style, behaviour, psychological factors, or medications, may be involved in FC<sup>(18,19)</sup>.

In addition, CIC may be a result of rectal evacuation disorders such as DD (the most common cause of rectal evacuation disorder)<sup>(5)</sup>. When coordination of rectal muscles is impaired, failure of anal relaxation happens or there is an inadequate rectal and abdominal propulsive force, DD may arise<sup>(20)</sup>. DD often results from dysfunctional toilet habits, being considered then a learned behavioural problem<sup>(21)</sup>. History of abuse (physical and sexual) is often present, with 29% of men and 32% of women reporting physical abuse and 22% reporting sexual abuse<sup>(21)</sup>. Rectal evacuation problems may coexist with structural causes (e.g., rectal prolapse, rectal intussusception, rectocele)<sup>(22)</sup>. STC – a delay in the emptying of the proximal colon<sup>(23,24)</sup> and reduction or absence of HAPCs<sup>(24-26)</sup> – may occur concurrently<sup>(27)</sup>.

#### Clinical evaluation of chronic idiopathic constipation

A detailed clinical history should be obtained, including time of symptoms' onset, dietary/fiber intake characteristics as well as history of physical/sexual abuse and obstetric events. According to Rome IV criteria, CIC is diagnosed based on symptoms, such as straining during more than 25% of defecations, sensation of incomplete evacuation more than 25% of defecations and other symptoms<sup>(28)</sup>. Symptoms such as the sense of anal blockage during defecation or a sense of incomplete evacuation after defecation usually suggest DD<sup>(29)</sup>. Abdominal bloating or discomfort, may be associated with abdominal distention, but other symptoms or conditions may also be present (e.g., fatigue, psychosocial distress, fibromyalgia)<sup>(30,31)</sup>. However, the clinician should bear in mind that, generally, symptoms are not a good guide to the pathophysiology of CIC as they are not specific<sup>(9)</sup>.

The Bristol Stool Form Scale (BSFS)<sup>(32)</sup> (FIGURE 2) shows stool form as an indirect measure of colonic transit time, changes in intestinal function and ease of defecation, which are influenced by stool form<sup>(33)</sup>. Frequently, patients misperceive they have constipation because they do not have daily bowel movements<sup>(33)</sup>. Straining to begin defecation is often found in the presence of hard stools, among constipated women<sup>(33)</sup>. Patients with severe DD may have problems to pass even severe soft stools or enema fluids<sup>(34)</sup>.

#### Diagnosis of chronic idiopathic constipation

The diagnosis of CIC can be based mainly on symptoms alone; therefore, a careful medical history is critical and should assess the presence of symptoms, their duration, and progression<sup>(32)</sup>. Johansson et al. (2007) surveyed patients with CC and found that straining (79%), hard stools (71%), abdominal discomfort (62%), bloating (57%), infrequent bowel movements (57%), and feelings of incomplete evacuation after a bowel movement (54%) were the

|               |   |   |
|---------------|---|---|
| <b>Type 1</b> |  | Hard and separate lumps, nuts-like (hard to pass) |
| <b>Type 2</b> |  | Sausage-shaped but lumpy                          |
| <b>Type 3</b> |  | Sausage-shaped, but with cracks on surface        |
| <b>Type 4</b> |  | Sausage or snake-like, smooth and soft            |
| <b>Type 5</b> |  | Soft blobs with clear-cut edges (easy to pass)    |
| <b>Type 6</b> |  | Fluffy pieces with ragged edges and mushy         |
| <b>Type 7</b> |  | Watery (no solid pieces)                          |

FIGURE 2. Bristol Stool Form Scale.

Adapted from Lewis & Heaton, 1997<sup>(2)</sup>.

most frequent symptoms<sup>(35)</sup>. Currently, the criteria most in use for definition of CIC are those of the Rome IV<sup>(36)</sup>. BOX 2 presents the specific diagnostic criteria<sup>(36)</sup>. One of the most important symptoms to differentiate FC from IBS-C is the presence of abdominal pain<sup>(36)</sup>.

| <b>BOX 2. Rome IV diagnostic criteria for functional constipation.</b>  |
|---|
| <ul style="list-style-type: none"> <li>• Must include two or more of the following<sup>b</sup>:                             <ul style="list-style-type: none"> <li>- Straining during more than 25% of defecations.</li> <li>- Lumpy or hard stools (BSFS 1–2) more than 25% of defecations.</li> <li>- Sensation of incomplete evacuation more than 25% of defecations.</li> <li>- Sensation of anorectal obstruction or blockage more than 25% of defecations.</li> <li>- Manual manoeuvres to facilitate more than 25% of defecations.</li> <li>- Fewer than 3 spontaneous bowel movements per week.</li> </ul> </li> <li>• Loose stools are rarely present without the use of laxatives.</li> <li>• Do not meet criteria for irritable bowel syndrome.</li> </ul> |

Adapted from Lacy et al., 2016<sup>(3)</sup>. BSFS: Bristol Stool Form Scale.

<sup>a</sup>Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

<sup>b</sup>For research studies, patients meeting criteria for opioid-induced constipation should not be given a diagnosis of chronic idiopathic constipation because it is difficult to distinguish between opioid side effects and other causes of constipation. However, clinicians recognise that these two conditions might overlap.

Medical history is an important part of the diagnosis and should include: age, family history of colon cancer (or familial polyposis syndromes), frequency of bowel movements, associated symptoms (e.g. abdominal pain, bloating, or distension), an assessment of stool consistency, stool size, and degree of straining during defecation<sup>(37)</sup>. Objective measures such as stool frequency, daily stool weight (<35 g/d), colonic transit, and anorectal function can also be performed and should be done while the patient is not under laxatives<sup>(32)</sup>.

For patients presenting with new onset constipation, causes of secondary constipation such as mechanical obstruction, medica-

tions (BOX 3)<sup>(9)</sup>, and systemic illnesses should be explored<sup>(32,36)</sup>. The presence of alarm features (BOX 4)<sup>(9)</sup>, such as unintentional weight loss (>10% in 3 months) or rectal bleeding (in the absence of bleeding haemorrhoids or anal fissures) among other features, should be investigated<sup>(36)</sup>. When the clinician suspects organic causes of constipation (especially when alarm symptoms are present), objective tests are recommended to guide treatment<sup>(38)</sup>.

| <b>BOX 3. Medications associated with chronic constipation.</b>  |
|--|
| <ul style="list-style-type: none"> <li>• Antacids containing aluminium, calcium.</li> <li>• Antidepressants.</li> <li>• Antidiarrheal agents.</li> <li>• Antiepileptics.</li> <li>• Antihistamines.</li> <li>• Antiparkinsonian drugs.</li> <li>• Antipsychotics.</li> <li>• Antispasmodics.</li> <li>• Calcium and iron supplements.</li> <li>• Calcium channel blockers.</li> <li>• Diuretics.</li> <li>• Monoamine oxidase inhibitors.</li> <li>• Nonsteroidal anti-inflammatory drugs.</li> <li>• Opiates.</li> <li>• Sympathomimetics.</li> <li>• Tricyclic antidepressants.</li> </ul> |

Adapted from Lindberg et al., 2011<sup>(1)</sup>.

| <b>BOX 4. Alarm features.</b>   |
|---|
| <ul style="list-style-type: none"> <li>• Change in stool calibre.</li> <li>• Rectal bleeds.</li> <li>• Rectal prolapse.</li> <li>• Obstructive symptoms.</li> <li>• Loss of weight.</li> <li>• Recent onset constipation.</li> <li>• Heme-positive stool.</li> <li>• Iron-deficiency anaemia.</li> <li>• Patients older than 50 years old with no previous screening for colon cancer.</li> </ul> |

Adapted from Lindberg et al., 2011<sup>(1)</sup>.

Objective testing should be performed if considered necessary to identify underlying pathophysiological mechanisms<sup>(32)</sup>. Diagnosis of DD may be done by specific questionnaires and physical examination, and is important as it may require different treatment strategies<sup>(39,40)</sup>. Central nervous system and spinal lesions can be ruled out by physical examination, and the abdomen should be examined for distension and presence of hard stool or a mass in the colon. Rectal examination is also essential to identify fecal impaction, anal stricture, or rectal mass. It should include examination of the perineum at rest and after strains as inappropriate contractions of the puborectalis muscle and/or anal sphincter when simulating an evacuation is consistent with DD<sup>(28,39,40)</sup>.

Functional evaluation should be performed when DD is suspected or in cases that do not respond to initial treatment with fiber supplementation and/or laxatives<sup>(41,42)</sup>. In addition, anorectal manometry and balloon expulsion tests may help to identify DD<sup>(42)</sup>, as well as defecography may detect anatomic aetiologies that are typical of DD (e.g., intussusception and rectocele with stool retention, or the inability to relax the puborectalis or decrease the

anorectal angle with straining)<sup>(43)</sup>. Electromyography and pudendal nerve latency testing are supporting techniques<sup>(44)</sup>. However, testing for DD is not required for all patients, but for those who do not respond to a reasonable number of attempts of treatment.

Some laboratory studies may be necessary, such as complete blood count, thyroid-stimulating hormone and serum calcium, and a colonoscopy might be indicated in patients aged 45 years or older (though the American Gastroenterological Association [AGA] does not recommend this exam in the absence of alarm symptoms)<sup>(45)</sup>. Radiopaque markers can also be used to evaluate colonic transit<sup>(36,46)</sup>. Below we specify the most used diagnostic methods and when to use them.

### Physical examination

In the evaluation of a patient with CC, it is important to identify diseases that cause constipation and include a detailed physical examination, together with perineal and rectal examination<sup>(39,47)</sup>, which may bring evidence of the presence of haemorrhoids, fissures, scars or skin excoriation as well as some structural abnormalities<sup>(39,48)</sup>. According to the AGA, digital rectal examination should be performed before referral to anorectal manometry, although a normal result does not exclude defecatory disorders<sup>(41)</sup>. In patients with DD, when asked to push or bear down with a normal push manoeuvre, at least one of the following responses are absent: relaxation of the external anal sphincter and/or the puborectalis muscle, together with perineal descent and tightening of abdominal muscles<sup>(39,48)</sup>. Although digital rectal examination is an important part of the diagnosis, showing 75% sensitivity and 87% specificity for detecting DD<sup>(39)</sup>, it is not performed by approximately 50% of the physicians treating constipation<sup>(49)</sup>.

### Stool diary

Bowel habits can provide useful information in the evaluation of patients with CC<sup>(48)</sup>. A stool diary has proven to be a valid instrument<sup>(50)</sup> for assessing patients and findings such as loose or hard stool, stool frequency (which provides information regarding colonic transit time and therapeutic responsiveness such as number of bowel movements per day), stool consistency (as per the BSFS type 1–7), level of straining, use of digital manoeuvres, feeling of incomplete evacuation, presence of pain and bloating<sup>(48,50)</sup>.

### Colonic transit assessment

According to the AGA, colonic transit should be evaluated if anorectal tests do not show defecatory disorders or if after treating them, the symptoms still persist<sup>(45)</sup>. Colonic transit assessment provides useful information on the overall colonic motor function and can be performed by three different methods: a) radiopaque marker test – performed by the oral administration of a radiopaque marker (the patient typically ingests one capsule containing 24 radio-opaque markers five days before or, depending on the technique used, every day) and then performs the abdominal x-ray between 5 and 6 days later, to determine the number of markers remaining. The exam is considered abnormal if more than 5 (>20%) markers are retained in the colon<sup>(51)</sup>; b) colonic scintigraphy – a radiolabelled marker is infused and released in the caecum, and images are made at 24 and 48 hours; c) wireless motility capsule – this method potentially provides information about the whole gut and not only about specific regions. The transit of the capsule is measured by documented normative values<sup>(52)</sup>. DD and STC are conditions that may appear simultaneously, and this test does not

differentiate between them (this requires an anorectal test); however, STC can be found in two-thirds of patients with DD<sup>(21,48,29)</sup>.

### Anorectal structure and function testing

If no alarm symptoms or symptoms suggesting difficulty with defecation are present, the use of empirical trial with laxatives can be considered prior to colorectal tests<sup>(51)</sup>. Symptoms alone do not provide much information on underlying pathophysiology; therefore, diagnostic tests are complementary to clinical assessments<sup>(48)</sup>. However, although several tests are available to define structural morphology and physiology of defecation, no single test can provide a complete picture, so tests and symptoms should be interpreted together with careful consideration<sup>(48)</sup>.

### Anorectal manometry

AGA recommends that anorectal manometry is performed in patients who fail to treatment with laxatives<sup>(45)</sup>. The anorectal manometry assesses sphincter tone in resting and squeeze, rectoanal reflexes, rectal sensations, and changes in pressure during attempt to defecate<sup>(53)</sup>. Most changes found are high anal sphincter pressure during rest and impaired relaxation<sup>(52)</sup>. It is the most reliable test to diagnose DD, especially when the patient is asked to attempt defecation when sitting on a commode<sup>(53)</sup>.

### Balloon expulsion test

The balloon expulsion test is a screening test used to identify patients with DD, and the AGA recommendation is that this test is performed if the patient fails to laxatives<sup>(45)</sup>. Its specificity is high (80–90%), but sensitivity is low (50%)<sup>(54,55)</sup>. This test is performed by placing a balloon filled with warm water (50 mL) in the rectum, and a stop watch is provided to the patient to assess time required for expulsion, which is less than one minute for healthy individuals<sup>(51)</sup>.

### Defecography

In case that anorectal manometry and rectal balloon expulsion tests are inconclusive, the AGA recommends the defecography is performed. Contrast defecography (using barium) or functional magnetic resonance (MR) defecography can provide anorectal imaging. These techniques provide information about anorectal function (e.g., DD) and anatomy (e.g., anal stenosis, rectal intussusception). MR defecography provides additional information about the integrity of anorectal and pelvic floor structures<sup>(6)</sup>.

### Treatment of chronic idiopathic constipation

The treatment options and recommendations presented here are not a consensus, but the result of a literature review combined with best practice and experience of the authors and, therefore, should be used as a guide for clinical practice.

Once the diagnosis is made, the initial management of CIC can be done with a symptomatic approach based on lifestyle and diet changes, an increase in fluid intake, and stopping/reducing medications that may cause constipation. The World Gastroenterology Organization describes as a second step, the addition of osmotic laxatives (polyethylene glycol [PEG] or lactulose), as well as new drugs such as lubiprostone, linaclotide and plecanatide, that treat constipation by increasing fluid secretion into the intestinal lumen through direct action on intestinal epithelial cells<sup>(6)</sup>. Then stimulant laxatives that stimulate colorectal activity (orally or rectally administered), enemas and prokinetic drugs (e.g., prucalopride, which increases the propulsive activity of the colon) can be

alternatives in a next step<sup>(9)</sup>. Other treatment options may include biofeedback (generally effective to treat patients with features of pelvic floor dyssynergia)<sup>(37)</sup> and surgery, that is usually restricted to those refractory cases that fail to respond to aggressive medications and biofeedback treatment<sup>(48)</sup>.

### Changes in lifestyle and diet

Traditionally, changes in lifestyle such as an increase in physical exercises and dietary interventions have been recommended, as well as an increase in fluid intake; however, the European Society of Neurogastroenterology and Motility (ESNM) guidelines for CC points to conflicting evidence regarding the benefits of physical exercise or overall lifestyle modifications<sup>(38)</sup>.

### Fiber

The inclusion of dietary fiber (either ingested as food and/or as medicinal supplement) is recommended by the American College of Gastroenterology (recommendation: strong; quality of evidence: low)<sup>(37)</sup>. The ESNM also recommends a fiber-rich diet as first-line treatment (recommendation: strong; level of evidence: moderate)<sup>(38)</sup>. They are delivered to the colon as they are not digested in the small intestine<sup>(37)</sup>. Depending on how the fiber interacts with water, it is classified as soluble (e.g., psyllium) and insoluble (e.g., bran). Both soluble and insoluble fiber increase the stool frequency in patients with CIC; however, insoluble fiber should be introduced gradually, as it may cause bloating, distension, flatulence, and cramping<sup>(37)</sup>, and with sufficient water intake<sup>(56)</sup>. Low fluid intake has been associated with reductions in stool frequency in women<sup>(57)</sup> and is a better predictor for constipation than a fiber-poor diet<sup>(58)</sup>.

### Other bulk-forming agents

Bulk-forming agents (e.g., polycarbophil, methylcellulose) are natural or medicinal fiber products that help retain water to increase intraluminal volume<sup>(59)</sup>.

### Osmotic laxatives

Patients with constipation frequently present with bloating, which can be due to underlying disorder and/or medications (e.g., fiber and osmotic laxatives). Osmotic laxatives include polyethylene glycol (PEG)-based solutions, products based on magnesium-citrate, sodium phosphate, and non-absorbable carbohydrates<sup>(17)</sup>. Water retention in the colon can be achieved with poorly absorbed ions which create an osmotic gradient, resulting in improved stool consistency and frequency<sup>(52,17)</sup>.

Magnesium hydroxide and other salts are sparingly absorbed and safe; however, they have not been tested in randomized controlled trials. Patients with renal impairment may present with severe hypermagnesemia<sup>(60)</sup>. Among non-absorbable carbohydrates, lactulose, and sorbitol presented similar laxative effects in a randomized crossover study of 30 men, but lactulose was associated with more nausea<sup>(61)</sup>.

Dosing of laxatives prescription varies from patient to patient and from agent to agent. The general goal is to improve symptoms reported by patients. Bacterial metabolism of unabsorbed carbohydrate leads to gas production and abdominal cramping, which can limit long-term use. The American College of Gastroenterology's recommendation is strong for both PEG and lactulose, but for the former the quality of the evidence is high, while for the latter, it is low<sup>(37)</sup> (PEG is also strongly recommended by the ESNM, though lactulose recommendation is weak)<sup>(38)</sup>. Reported adverse events do

not differ from those reported in groups treated with placebo, and include abdominal pain and headache<sup>(37)</sup>.

### Stimulant laxatives

Stimulant laxatives are frequently used on a rescue basis and include diphenylmethane derivatives (e.g., bisacodyl and sodium picosulfate) and anthraquinone derivatives (e.g., senna, aloe, cascara sagrada)<sup>(17)</sup>. Bisacodyl and sodium picosulfate are converted by mucosa deacetylase enzymes and desulfatases of the colonic microbiota, respectively, to bis-(p-hydroxyphenyl)-pyridyl-2-methane, which prevents reabsorption of water and initiates HAPCs in the colon<sup>(62)</sup>. Anthraquinones also increase colonic motility and alter colonic absorption and secretion<sup>(63)</sup>. Sodium picosulfate and bisacodyl are recommended by the American College of Gastroenterology and the ESNM (recommendation: strong; quality of evidence: moderate)<sup>(38)</sup>. The use of these agents is often limited by adverse events (usually abdominal pain and diarrhea)<sup>(17)</sup>. Another stimulant laxative, docusate sodium (an ionic surfactant) decreases the surface tension at the stool oil-water interface and allows water to penetrate the stool. Although it is often recommended, it has few data to support its use<sup>(17)</sup>.

### Prosecretory agents (secretagogues)

Prosecretory agents (e.g., lubiprostone - a bicyclic fatty acid derived from prostaglandin E1 that activates type 2 chloride channels on the apical membrane of epithelial cells) increase secretion of intestinal chloride, stimulate net efflux of ions and water into the intestinal lumen, accelerate transit, and facilitate defecation<sup>(52,17)</sup>. Lubiprostone, linaclotide, and plecanatide have been approved by the Food and Drug Administration for treatment of CIC; however, only lubiprostone is currently approved in Brazil<sup>(64)</sup>. Both lubiprostone and linaclotide are prosecretory agents recommended by the American College of Gastroenterology (recommendation: strong; quality of evidence: high)<sup>(37)</sup>. Nausea, usually mild and well tolerated, is the most common adverse event; therefore, lubiprostone should be taken with food and water (24 mcg twice a day)<sup>(65)</sup>. Linaclotide and plecanatide therapy have similar efficacy and tolerability<sup>(66)</sup>, and diarrhea is the most common adverse event, but fewer than 5% of the patients have been discontinued from clinical trials due to this reaction<sup>(67,68)</sup>.

### Prokinetic drugs

The neurotransmitter serotonin (5-HT) is involved with sensation and motility of the gastrointestinal tract<sup>(56)</sup>. Several agonists of 5-HT receptors have been studied due to their increase in intestinal motility<sup>(56)</sup>. Prucalopride, a highly selective 5-HT<sub>4</sub> agonist, is reported to be well tolerated, although the use has been associated with headache, abdominal pain, nausea and diarrhea. No significant cardiovascular adverse events have been reported with prucalopride use<sup>(17)</sup>. Patients in treatment with prucalopride should be monitored for depression and suicidal thoughts<sup>(56)</sup>. The American College of Gastroenterology recommendation for prucalopride is strong and the quality of evidence is high<sup>(37)</sup>. In Europe, prucalopride has been approved and used for years and is recommended by the ESNM (recommendation: strong and level of evidence: high)<sup>(38)</sup>.

### Probiotics

Although some studies have reported improvement in bowel movements per week with probiotics use, their utility in adults with constipation is unclear<sup>(69)</sup>. An increasing body of evidence shows that changes in the gut microbiota may contribute to the development of functional bowel disorders that are possibly secondary

to dysbiosis of the gut microbiota<sup>(28)</sup>. Possibly, the link between constipation and microbiota is the small intestinal bacterial overgrowth, which has been shown to be associated with prolonged small bowel transit time in methane production microbiota<sup>(69,70)</sup>. More evidence for the effectiveness of specific probiotic strains, and more randomized clinical studies with CIC patients utilizing those well-defined probiotics strains (or combinations) are necessary, as well as education of healthcare professionals on the increased utilisation of probiotics for constipation by the public<sup>(69)</sup>.

### Enemas

Despite lack of studies on the use of enemas in CIC, they continue to be used<sup>(38,70)</sup>. The effect of enemas will depend on the amount of liquid delivered to the rectum (usually between 5–150 mL of glycerine, saline solution, etc.), the intraluminal pressure and the temperature of the enema<sup>(70)</sup>. However, studies are needed to establish the real efficacy of enemas in the treatment of CIC.

### Biofeedback

Biofeedback aims to restore dysfunctional behaviors that may cause constipation, emphasizing appropriate coordination of abdominal and pelvic floor motion during evacuation (although therapy may include Kegel exercises)<sup>(71)</sup>. It may vary in methodological techniques but, in general, biofeedback is effective to treat CIC in patients with DD<sup>(71)</sup>. The patient may learn how to achieve defecation by relaxing the pelvic floor muscles, and to correlate relaxation and pushing during straining<sup>(72)</sup> through visual or auditory feedback of anorectal and pelvic floor muscle activity, which is recorded with surface electromyographic sensors or manometry. Patients practice by expelling a balloon filled with air, and learn how to recognize weaker sensations of rectal filling<sup>(71)</sup>. Biofeedback is underutilized as its benefits are not widely recognized, and the recommendation by the American College of Gastroenterology is weak, with low quality of evidence<sup>(37)</sup>. In addition, the expertise is not widely available. In turn, the ESNM recommendation for biofeedback therapy is strong (level of evidence: moderate)<sup>(38)</sup>.

### Surgery

Surgery is usually reserved for patients with debilitating symptoms and refractory CIC presenting with negative effects on their QoL<sup>(73)</sup>. End sigmoid colostomy may be an option for patients with normal colonic transit and severe refractory pelvic outlet dysfunction constipation<sup>(73)</sup>, but patients with concomitant STC and pelvic dysfunction may consider an ileostomy<sup>(74)</sup>. In patients with STC, a loop ileostomy to assess benefits may be useful before considering a total abdominal colectomy<sup>(73)</sup>. However, a patient should not be referred to surgery before a functional evaluation is carried out, including motility assessment of the upper gastrointestinal tract<sup>(75)</sup>.

### Quality of life

Quality of life (QoL) tools are helpful to measure physical and emotional burden associated with physical, psychological and social stressors that come with CC<sup>(6)</sup>. Different measures of QoL and disease-related QoL have been used in studies reporting impaired QoL in patients with CC. The Well-Being Index has been reported to be lower in individuals with CC<sup>(7)</sup>. Lower QoL scores were reported in a study for patients with constipation who were unemployed or retired than for those who were employed, and symptoms of anxiety and depression were reported risk factors for worse QoL<sup>(76)</sup>. The Medical Outcomes Short-Form Health Survey (SF-36 and SF-12) instruments used in the general population

and in patients in the clinical setting, showed lower physical and mental scores, meaning that individuals with CC had poorer QoL than individuals without constipation<sup>(7)</sup>. Importantly, individuals with constipation in the community had QoL scores similar to those of individuals with stable inflammatory bowel disease (IBD), chronic allergies and dermatitis. In the clinical setting, patients with constipation had QoL scores that were comparable to those of patients with functional dyspepsia or active IBD<sup>(7)</sup>. The Psychological General Well-Being Index (PGWBI) scores were as severe as those associated with untreated conditions such as peptic ulcer disease, gastro-oesophageal reflux disease and mild asthma<sup>(7)</sup>.

### CONCLUSION

Chronic idiopathic constipation is a highly prevalent condition that is probably multifactorial, more prevalent in women, and has a great impact on patient's QoL. The correct approach for diagnosis starts with diving into details of clinical history, the patient's complaints, as well as a careful physical examination, that are basic points for the diagnosis, which will be even more accurate when supported by the well-established Rome IV diagnosis criteria. Alarm symptoms, epidemiological data regarding colorectal cancer surveillance and underlying diseases should also be part of the medical reasoning, so that they can be excluded. Medicine brings new therapeutic innovations and reinforces the most accurate diagnostic methodology possible. Traditional treatment, fluid intake, and a fiber-rich diet greatly helps patients with CIC. The therapeutic options available in Brazil contemplate innovative and traditional molecules (e.g., lubiprostone and prucalopride, respectively) and classic laxatives, but each option should be weighed in relation to efficacy and safety. Prucalopride has been used in refractory cases, and phase III trials have shown lubiprostone as an effective and safe option recently made available locally.

### ACKNOWLEDGEMENTS

We acknowledge Ana Paula A Bueno, a Kantar Health associate for providing medical writing support.

### Authors' contribution

Passos MCF, Alvariz RC, André EA, Barbuti RC, Fillmann HS, Murad-Regadas SM, Rezende Filho J, Perrotti M and Guedes L: conceptualization, data curation, formal analysis, methodology, resources, supervision, validation, visualization and interpretation of data for the work; revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors have approved the final version of the manuscript.

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Passos MCF, Alvariz RC, André EA, Barbuti RC, Fillmann HS, Murad-Regadas SM, Rezende Filho J, Perrotti M, Guedes L. Diagnóstico e abordagem terapêutica da constipação idiopática crônica: uma revisão de especialistas brasileiros. *Arq Gastroenterol.* 2022;59(1):137-44.

**RESUMO – Contexto** – A constipação idiopática crônica (CIC) é uma condição que afeta amplamente a população global, representa um grande custo econômico, causa substancial utilização de recursos em saúde e impacta o bem-estar do indivíduo. **Objetivo** – Revisar os consensos de Sociedades de especialistas e diretrizes publicados sobre o diagnóstico e tratamento da CIC em adultos, buscando auxiliar o raciocínio e a tomada de decisão para a conduta médica frente ao paciente e oferecer um material prático de referência. **Métodos** – Uma força tarefa médica brasileira realizou uma busca na literatura científica nas bases de dados eletrônicos Medline/PubMed, SciELO, Embase e Cochrane, tendo sido utilizados os seguintes descritores: *chronic constipation, diagnosis, management of chronic constipation*. Adicionalmente, foi realizada uma revisão de artigos sobre o mecanismo de ação, segurança e eficácia das opções terapêuticas disponíveis no Brasil. **Resultados** – A abordagem diagnóstica e o entendimento da fisiopatologia presente na CIC são itens fundamentais para que seja indicada a terapêutica apropriada e seja compreendido o ecossistema de necessidades do paciente. **Conclusão** – A CIC é uma condição comum em adultos, ocorrendo com maior frequência em idosos e mulheres. O manejo correto é definido pela anamnese e exame físico detalhados, juntamente com a terapêutica apropriada, independentemente de ser farmacológica ou não, conforme o melhor momento de indicação. Desta forma, o impacto na qualidade de vida também é otimizado.

**Palavras-chave** – Constipação idiopática crônica; constipação funcional; diagnóstico; tratamento.

## REFERENCES

- Sharma A, Rao S. Constipation: Pathophysiology and current therapeutic approaches. *Handb Exp Pharmacol.* 2017;239:59-74. doi: 10.1007/164\_2016\_111.
- Suares NC, Ford AC. Prevalence of, and risk factors for, chronic idiopathic constipation in the community: Systematic review and meta-analysis. *Am J Gastroenterol.* 2011;106:1582-91. doi:10.1038/ajg.2011.164.
- Mugie SM, Benninga MA, Di Lorenzo C. Epidemiology of constipation in children and adults: A systematic review. *Best Pract Res Clin Gastroenterol.* 2011;2:3-18. doi:10.1016/j.bpg.2010.12.010.
- Higgins PDR, Johanson JF. Epidemiology of Constipation in North America: A Systematic Review. *Am J Gastroenterol.* 2004;99:750-9. doi:10.1111/j.1572-0241.2004.04114.x.
- Black CJ, Ford AC. Chronic idiopathic constipation in adults: Epidemiology, pathophysiology, diagnosis and clinical management. *Med J Aust.* 2018;209:86-91. doi:10.5694/mja18.00241.
- Kolar GJ, Camilleri M, Burton D, Nadeau A, Zinsmeister AR. Prevalence of colonic motor or evacuation disorders in patients presenting with chronic nausea and vomiting evaluated by a single gastroenterologist in a tertiary referral practice. *Neurogastroenterol Motil.* 2014;26:131-8. doi:10.1111/nmo.12242.
- Lindberg G, Hamid SS, Malferteiner P, Thomsen OO, Fernandez LB, Garisch J, et al. World gastroenterology organisation global guideline: Constipation - A global perspective. *J Clin Gastroenterol.* 2011;45:483-7. doi:10.1097/MCG.0b013e-31820fb914.
- Holdstock DJ, Misiewicz JJ, Smith T, Rowlands EN. Propulsion (mass movements) in the human colon and its relationship to meals and somatic activity. *Gut.* 1970;11:91-99. doi:10.1136/gut.11.2.91.
- Smith TK, Park KJ, Hennig GW. Colonic migrating motor complexes, high amplitude propagating contractions, neural reflexes and the importance of neuronal and mucosal serotonin. *J Neurogastroenterol Motil.* 2014;20:423-46. doi:10.5056/jnm14092.
- Spencer NJ. Constitutively active 5-HT receptors: An explanation of how 5-HT antagonists inhibit gut motility in species where 5-HT is not an enteric neurotransmitter? *Front Cell Neurosci.* 2015;9:487. doi:10.3389/fncel.2015.00487.
- Lin AY, Du P, Dinning PG, Arkwright JW, Kamp JP, Cheng LK, et al. High-resolution anatomic correlation of cyclic motor patterns in the human colon: Evidence of a rectosigmoid brake. *Am J Physiol Liver Physiol.* 2017;312:G508-G515. doi:10.1152/ajpgi.00021.2017.
- Sandle GI. Salt and water absorption in the human colon: A modern appraisal. *Gut.* 1998;43:294-9. doi:10.1136/gut.43.2.294.
- Camilleri M, Ford AC, Mawe GM, Dinning PG, Rao SS, Chey WD, et al. Chronic constipation. *Nat Rev Dis Prim.* 2017;3:1-19. doi:10.1038/nrdp.2017.95.
- Abrahamsson H, Östlund-Lindqvist AM, Nilsson R, Simrén M, Gillberg PG. Altered bile acid metabolism in patients with constipation-predominant irritable bowel syndrome and functional constipation. *Scand J Gastroenterol.* 2008;43:1483-8. doi:10.1080/0036520802321212.
- Triantafyllou K, Chang C, Pimentel M. Methanogens, methane and gastrointestinal motility. *J Neurogastroenterol Motil.* 2014;20:31-40. doi:10.5056/jnm.2014.20.1.31.
- Parthasarathy G, Chen J, Chen X, Chia N, O'Connor HM, Wolf PG, et al. Relationship between Microbiota of the Colonic Mucosa vs Feces and Symptoms, Colonic Transit, and Methane Production in Female Patients with Chronic Constipation. *Gastroenterology.* 2016;150:367-79.e1. doi:10.1053/j.gastro.2015.10.005.
- Chan AOO, Cheng C, Hui WM, Hu WH-C, Wong N Y-H, Lam K-F, et al. Differing coping mechanisms, stress level and anorectal physiology in patients with functional constipation. *World J Gastroenterol.* 2005;11:5362-6. doi:10.3748/wjg.v11.i34.5362.
- Mazlyn Mena M, Nagarajah Lee HL, Fatimah A, Norimah AK, Goh KL. Stool patterns of Malaysian adults with functional constipation: Association with diet and physical activity. *Malays J Nutr.* 2013;19:53-64.
- Rao SSC, Welcher KD, Leistikow JS. Obstructive defecation: A failure of rectoanal coordination. *Am J Gastroenterol.* 1998;93:1042-50. doi:10.1111/j.1572-0241.1998.00326.x.
- Rao SSC, Tuteja AK, Vellema T, Kempf J, Stessman M. Dyssynergic defecation: Demographics, symptoms, stool patterns, and quality of life. *J Clin Gastroenterol.* 2004;38:680-5. doi:10.1097/01.mcg.0000135929.78074.8c.
- Perniola G, Shek C, Chong CCW, Chew S, Cartmill J, Dietz HP. Defecation proctography and translabial ultrasound in the investigation of defecatory disorders. *Ultrasound Obstet Gynecol.* 2008;31:567-71. doi:10.1002/uog.5337.
- Nullens S, Nelsen T, Camilleri M, Burton D, Eckert D, Iturrino J, et al. Regional colon transit in patients with dys-synergic defaecation or slow transit in patients with constipation. *Gut.* 2012;61:1132-9. doi:10.1136/gutjnl-2011-301181.
- Bassotti G, Gaburri M, Imbimbo BP, Rossi L, Farroni F, Pelli MA, et al. Colonic mass movements in idiopathic chronic constipation. *Gut.* 1988;29:1173-9. doi:10.1136/gut.29.9.1173.
- Dinning PG, Zarate N, Hunt LM, Fuentealba SE, Mohammed SD, Szczesniak MM, et al. Pancolonic spatiotemporal mapping reveals regional deficiencies in, and disorganization of colonic propagating pressure waves in severe constipation. *Neurogastroenterol Motil.* 2010;22. doi:10.1111/j.1365-2982.2010.01597.x.
- Dinning PG, Wiklendt L, Maslen L, Patton V, Lewis H, Arkwright JW, et al. Colonic motor abnormalities in slow transit constipation defined by high resolution, fibre-optic manometry. *Neurogastroenterol Motil.* 2015;27:379-88. doi:10.1111/nmo.12502.
- Bassotti G, Chiarioni G, Vantini I, Betti C, Fusaro C, Pelli MA, et al. Anorectal manometric abnormalities and colonic propulsive impairment in patients with severe chronic idiopathic constipation. *Dig Dis Sci.* 1994;39:1558-64. doi:10.1007/BF02088064.
- Bassotti G, Iantorno G, Fiorella S, Bustos-Fernandez L, Bilder CR. Colonic motility in man: Features in normal subjects and in patients with chronic idiopathic constipation. *Am J Gastroenterol.* 1999;94:1760-70. doi:10.1111/j.1572-0241.1999.01203.x.
- Lyford GL, He CL, Soffer E, Hull TL, Strong SA, Senagore AJ, et al. Pan-colonic decrease in interstitial cells of Cajal in patients with slow transit constipation. *Gut.* 2002;51:496-501. doi:10.1136/gut.51.4.496.
- Tong WD, Liu BH, Zhang LY, Zhang S Ben, Lie Y. Decreased interstitial cells of Cajal in the sigmoid colon of patients with slow transit constipation. *Int J Colorectal Dis.* 2004;19:467-73. doi:10.1007/s00384-003-0577-x.

30. Lacy BE, Mearin F, Chang L, Chey WD, Lembo AJ, Simren M, et al. Bowel disorders. *Gastroenterology*. 2016;150:1393-407.e5. doi:10.1053/j.gastro.2016.02.031.
31. Ravi K, Bharucha AE, Camilleri M, Rhoten D, Bakken T, Zinsmeister AR. Phenotypic Variation of Colonic Motor Functions in Chronic Constipation. *Gastroenterology*. 2010;138:89-97. doi:10.1053/j.gastro.2009.07.057.
32. Bharucha AE, Chakraborty S, Sletten CD. Common Functional Gastroenterological Disorders Associated With Abdominal Pain. *Mayo Clin Proc*. 2016;91:1118-32. doi:10.1016/j.mayocp.2016.06.003.
33. Houghton LA. Bloating in constipation: Relevance of intraluminal gas handling. *Best Pract Res Clin Gastroenterol*. 2011;25:141-50. doi:10.1016/j.bpg.2010.12.009.
34. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol*. 1997;32:920-4. doi:10.3109/00365529709011203.
35. Bharucha AE, Seide BM, Zinsmeister AR, Melton LJ. Insights into normal and disordered bowel habits from bowel diaries. *Am J Gastroenterol*. 2008;103:692-8. doi:10.1111/j.1572-0241.2005.40674.x.
36. Guilera M, Balboa A, Mearin F. Bowel habit subtypes and temporal patterns in irritable bowel syndrome: Systematic review. *Am J Gastroenterol*. 2005;100:1174-84. doi:10.1111/j.1572-0241.2005.40674.x.
37. Johanson JF, Kralstein J. Chronic constipation: A survey of the patient perspective. *Aliment Pharmacol Ther*. 2007;25:599-608. doi:10.1111/j.1365-2036.2006.03238.x.
38. Serra J, Pohl D, Azpiroz F, Chiarioni G, Ducrotté P, Gourcerol G, et al. European society of neurogastroenterology and motility guidelines on functional constipation in adults. *Neurogastroenterol Motil*. 2020;32:e13762. doi:10.1111/nmo.13762.
39. Ford AC, Moayyedi P, Lacy BE, Lembo AJ, Saito YA, Schiller LR, et al. American college of gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. *Am J Gastroenterol*. 2014;109(Suppl.1):S2-26; quiz S27. doi:10.1038/ajg.2014.187.
40. Begtrup LM, Engsbro AL, Kjeldsen J, Larsen PV, Schaffalitzky de Muckadell O, Bytzer P, et al. A positive diagnostic strategy is noninferior to a strategy of exclusion for patients with irritable bowel syndrome. *Clin Gastroenterol Hepatol*. 2013;11:956-62.e1. doi:10.1016/j.cgh.2012.12.038.
41. Tantiphlachiva K, Rao P, Attaluri A, Rao SSC. Digital rectal examination is a useful tool for identifying patients with dyssynergia. *Clin Gastroenterol Hepatol*. 2010;8:955-60. doi:10.1016/j.cgh.2010.06.031.
42. Chiarioni G, Kim SM WW. Dyssynergic Defecation Can Be Diagnosed by Questionnaire and Physical Examination. *Gastroenterology*. 2013;144:S366. doi:10.1016/S0016-5085(13)61347-5.
43. Minguez M, Herreros B, Sanchiz V, Hernandez V, Almela P, Añon R, et al. Predictive Value of the Balloon Expulsion Test for Excluding the Diagnosis of Pelvic Floor Dyssynergia in Constipation. *Gastroenterology*. 2004;126(Suppl.1):57-62. doi:10.1053/j.gastro.2003.10.044.
44. Videlock EJ, Lembo A, Cremonini F. Diagnostic testing for dyssynergic defecation in chronic constipation: Meta-analysis. *Neurogastroenterol Motil*. 2013;25:509-e370. doi:10.1111/nmo.12096.
45. Remes-Troche JM, Rao SS. Neurophysiological testing in anorectal disorders. *Expert Rev Gastroenterol Hepatol*. 2008;2:323-35. doi:10.1586/17474124.2.3.323.
46. Metcalf AM, Phillips SF, Zinsmeister AR, MacCarty RL, Beart RW, Wolff BG. Simplified assessment of segmental colonic transit. *Gastroenterology*. 1987;92:40-7. doi:10.1016/0016-5085(87)90837-7.
47. Orkin BA, Sinykin SB, Lloyd PC. The digital rectal examination scoring system (DRESS). *Dis Colon Rectum*. 2010;53:1656-60. doi:10.1007/DCR.0b013e-3181f23c85.
48. Rao SSC, Rattanakit K, Patcharatrakul T. Diagnosis and management of chronic constipation in adults. *Nat Rev Gastroenterol Hepatol*. 2016;13:295-305. doi:10.1038/nrgastro.2016.53.
49. Törnblom H, Van Oudenhove L, Sadik R, Abrahamsson H, Tack J, Simrén M. Colonic transit time and IBS symptoms: What's the link? *Am J Gastroenterol*. 2012;107:754-60. doi:10.1038/ajg.2012.5.
50. Pannemans J, Masuy I, Tack J. Functional Constipation: Individualising Assessment and Treatment. *Drugs*. 2020;80:947-63. doi:10.1007/s40265-020-01305-z.
51. Remes-Troche JM, Rao SSC. Diagnostic testing in patients with chronic constipation. *Curr Gastroenterol Rep*. 2006;8:416-24. doi:10.1007/s11894-006-0028-2.
52. Rao SSC, Kavlock R, Rao S. Influence of body position and stool characteristics on defecation in humans. *Am J Gastroenterol*. 2006;101:2790-6. doi:10.1111/j.1572-0241.2006.00827.x.
53. Chiarioni G, Kim SM, Vantini I, Whitehead WE. Validation of the Balloon Evacuation Test: Reproducibility and Agreement With Findings From Anorectal Manometry and Electromyography. *Clin Gastroenterol Hepatol*. 2014;12:2049-54. doi:10.1016/j.cgh.2014.03.013.
54. Rao SSC, Ozturk R, Laine L. Clinical utility of diagnostic tests for constipation in adults: A systematic review. *Am J Gastroenterol*. 2005;100:1605-15. doi:10.1111/j.1572-0241.2005.41845.x.
55. Lacy BE. Update on the management of chronic idiopathic constipation. *Am J Manag Care*. 2019;25:S55-S62.
56. Dukas L, Willett WC, Giovannucci EL. Association between physical activity, fiber intake, and other lifestyle variables and constipation in a study of women. *Am J Gastroenterol*. 2003;98:1790-6. doi:10.1111/j.1572-0241.2003.07591.x.
57. Markland AD, Palsson O, Goode PS, Burgio KL, Busby-Whitehead J, Whitehead WE. Association of low dietary intake of fiber and liquids with constipation: Evidence from the national health and nutrition examination survey. *Am J Gastroenterol*. 2013;108:796-803. doi:10.1038/ajg.2013.73.
58. Schiller LR. Chronic constipation: new insights, better outcomes? *Lancet Gastroenterol Hepatol*. 2019;4:873-82. doi:10.1016/S2468-1253(19)30199-2.
59. Bharucha AE, Lacy BE. Mechanisms, Evaluation, and Management of Chronic Constipation. *Gastroenterology*. 2020;158:1232-49.e3. doi:10.1053/j.gastro.2019.12.034.
60. Nyberg C, Hendel J, Nielsen OH. The safety of osmotically acting cathartics in colonic cleansing. *Nat Rev Gastroenterol Hepatol*. 2010;7:557-64. doi:10.1038/nrgastro.2010.136.
61. Lederle FA, Busch DL, Mattox KM, West MJ, Aske DM. Cost-effective treatment of constipation in the elderly: a randomized double-blind comparison of sorbitol and lactulose. *Am J Med*. 1990;89:597-601. doi:10.1016/0002-9343(90)90177-F.
62. Bharucha AE. High amplitude propagated contractions. *Neurogastroenterol Motil*. 2012;24:977-82. doi:10.1111/nmo.12019.
63. Van Gorkom BAP, De Vries EGE, Karrenbeld A, Kleibeuker JH. Review article: Anthranoid laxatives and their potential carcinogenic effects. *Aliment Pharmacol Ther*. 1999;13:443-52. doi:10.1046/j.1365-2036.1999.00468.x.
64. Agência Nacional de Vigilância Sanitária (ANVISA). Diário Oficial da União; Suplemento ANVISA nº227 de 25/11/2019. Published online 2019.
65. Cryer B, Drossman DA, Chey WD, Webster L, Habibi S, Wang M. Analysis of Nausea in Clinical Studies of Lubiprostone for the Treatment of Constipation Disorders. *Dig Dis Sci*. 2017;62:3568-3578. doi:10.1007/s10620-017-4680-1.
66. Shah ED, Kim HM, Schoenfeld P. Efficacy and tolerability of guanylate cyclase-C agonists for irritable bowel syndrome with constipation and chronic idiopathic constipation: A systematic review and meta-analysis. *Am J Gastroenterol*. 2018;113:329-38. doi:10.1038/ajg.2017.495.
67. Lembo AJ, Schneier HA, Shiff SJ, Kurtz CB, MacDougall JE, Jia XD, et al. Two Randomized Trials of Linaclotide for Chronic Constipation. *N Engl J Med*. 2011;365:527-36. doi:10.1056/nejmoa1010863.
68. DeMicco M, Barrow L, Hickey B, Shailubhai K, Griffin P. Randomized clinical trial: efficacy and safety of plecanatide in the treatment of chronic idiopathic constipation. *Therap Adv Gastroenterol*. 2017;10:837-51. doi:10.1177/1756283X17734697.
69. Kaminski M, Skonieczna-Zydecka K, Loniewski I, Koulouozidis A, Marlicz W. Are probiotics useful in the treatment of chronic idiopathic constipation in adults? A review of existing systematic reviews, meta-analyses, and recommendations. *Prz Gastroenterol*. 2020;15:103-18. doi:10.5114/pg.2019.86747.
70. Dembinski A, Warzecha Z, Konturek PJ, Ceranowicz P, Konturek SJ. Influence of capsacin-sensitive afferent neurons and nitric oxide (NO) on cerulein-induced pancreatitis in rats. *Int J Pancreatol*. 1996;19:179-89. doi:10.1016/0016-5085(95)24056-x.
71. Holzer P, Farzi A. Neuropeptides and the microbiota- Gut-brain axis. *Adv Exp Med Biol*. 2014;817:196-219. doi:10.1007/978-1-4939-0897-4\_9.
72. Roland BC, Ciarleglio MM, Clarke JO, Semler JR, Tomakin E, Mullin GE, et al. Small Intestinal Transit Time Is Delayed in Small Intestinal Bacterial Overgrowth. *J Clin Gastroenterol*. 2015;49:571-6. doi:10.1097/MCG.0000000000000257.
73. Quigley EMM. The Spectrum of Small Intestinal Bacterial Overgrowth (SIBO). *Curr Gastroenterol Rep*. 2019;21:3. doi:10.1007/s11894-019-0671-z.
74. Sarosiek I, Bashashati M, Alvarez A, Hall M, Shankar N, Gomez Y, et al. Lubiprostone Accelerates Intestinal Transit and Alleviates Small Intestinal Bacterial Overgrowth in Patients With Chronic Constipation. *Am J Med Sci*. 2016;352:231-8. doi:10.1016/j.amjms.2016.05.012.
75. Remes-Troche JM, Coss-Adame E, Lopéz-Colombo A, Amieva-Balmori M, Carmona Sánchez R, Charúa Guindic L et al. The Mexican consensus on chronic constipation. *Rev Gastroenterol Mex*. 2018;83:168-89. doi:10.1016/j.rgm.2017.12.005.
76. Rao SSC, Seaton K, Miller M, Brown K, Nygaard I, Stumbo P et al. Randomized Controlled Trial of Biofeedback, Sham Feedback, and Standard Therapy for Dyssynergic Defecation. *Clin Gastroenterol Hepatol*. 2007;5:331-8. doi:10.1016/j.cgh.2006.12.023.

