



## MONOGRAPH ON CONSTIPATION

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## INTRODUCTION

**Definition**

Constipation is defined as "Infrequent stools (typically fewer than three per week), hard stools, the need for excessive straining, a sense of incomplete bowel evacuation, and excessive time spent on the toilet or in unsuccessful defecation".<sup>[1]</sup>

*The patient's view.* Different patients have different perceptions of symptoms. Some patients regard constipation as straining (52%), while for others, it means hard, pellet-like stools (44%) or an inability to defecate when desired (34%), or infrequent defecation (33%).<sup>[1,2]</sup>

**1. Adults**

Two or more of the following for at least 12 weeks (not necessarily consecutive)

In the preceding 12 months.<sup>[3]</sup>

- Straining during >25% of bowel movements
- Lumpy or hard stools for >25% of bowel movements
- Sensation of incomplete evacuation for >25% of bowel movements
- Sensation of anorectal blockage for >25% of bowel movements
- Manual maneuvers to facilitate >25% of bowel movements (e.g., digital evacuation or support of the pelvic floor)
- Less than 3 Bowel movements per week
- Loose stools not present and insufficient criteria for irritable bowel syndrome.<sup>[3]</sup>

**2. Infants and children**

Pebble-like, hard stools for a majority of bowel movements for at least 2 weeks

- Firm stools  $\leq 2$  times per week for at least 2 weeks
- No evidence of structural, endocrine, or metabolic disease.<sup>[4]</sup>

**Etiology**

Constipation can be classified into three broad categories

1. Normal-transit constipation.
2. Slow-transit constipation.
3. Disorders of defecatory or rectal evacuation.

**Normal-transit constipation**

- In patients with this disorder, stool traverses at a normal rate through the colon and the stool frequency is normal, yet patients believe they are constipated.
- In this group of patients, constipation is likely to be due to a perceived difficulty with evacuation or the presence of hard stools.<sup>[5]</sup>
- The patients may experience bloating and abdominal pain or discomfort, and they may exhibit increased psychosocial distress.<sup>[6]</sup>
- Some may have increased rectal compliance, reduced rectal sensation, or both.
- Symptoms of constipation typically respond to therapy with dietary fiber alone or with the addition of an osmotic laxative.<sup>[7]</sup>

**Slow-transit constipation**

Slow-transit constipation occurs most commonly in young women who have infrequent bowel movements (once a week or fewer). The condition often starts at puberty. Associated symptoms are an infrequent urge to defecate, bloating, and abdominal pain or discomfort.

- In patients with a minimal delay in colonic transit dietary and cultural factors contribute to symptoms.
- In these patients, a high-fiber diet may increase stool weight, decrease colon-transit time,
- And relieve constipation.
- Patients with more severe slow-transit constipation have a poor response to dietary **fiber and laxatives**.<sup>[7]</sup>

**Defecatory disorder**

Defecatory disorders are most commonly due to dysfunction of the pelvic floor or anal sphincter.

- Other terms used to describe defecatory disorders include anismus, pelvic-floor dyssynergia, paradoxical pelvic-floor contraction, obstructed

constipation, functional rectosigmoid obstruction, the spastic pelvic floor syndrome, and functional fecal retention in childhood.

- Functional fecal retention in children may result in secondary encopresis due to leakage of liquid stool around impacted stool, which can lead to an initial misdiagnosis of diarrhea.<sup>[7]</sup>

### Pathophysiologic Mechanisms of Constipation

Two mechanisms explain the pathophysiology of constipation.<sup>[8,9]</sup> Colonic motility dysfunction, or dysmotility, is failure of coordinated motor activity to move stool through the colon. It is sometimes associated with: dietary factors, medications that can alter motility; or systemic disease (e.g. neurologic, metabolic, or endocrine disorders). Others exhibit abnormalities of the enteric nerves, such as decreased volume of interstitial cells of Cajal (ICC) and other neural elements.<sup>[10]</sup> The second mechanism involves pelvic floor dysfunction, or disorders of the anorectum and pelvic floor, which result in outlet dysfunction and an inability to adequately, evacuate rectal contents. Functional constipation may occur as a result of disordered movement through the sigmoid colon and/or anorectum. Both mechanisms coexist in some patients,<sup>[9]</sup> making it difficult to determine the exact underlying mechanisms for constipation.

### Physiology of dysmotility

Dysmotility results in colonic delay (i.e. abnormally prolonged colonic transit time). Three types of colonic delay have been identified: right colonic (colonic inertia), left colonic, and rectosigmoid. Additionally, delay can occur in patients with no colonic dysmotility.<sup>[11]</sup> Mechanisms of delay include: dysfunction of the autonomic nervous system, disruption in the ENS,<sup>[12]</sup> disruptions in the neuroendocrine system,<sup>[13,14]</sup> and/or colonic myopathy.<sup>[15,16]</sup> Impaired colonic propulsive activity may represent a major mechanism for colonic dysmotility. In patients with constipation (n = 45), there were fewer mass movements segmental contractions.<sup>[17]</sup> No differences in post awakening values were found in patients with chronic constipation, which suggests that the brain-gut control of fundamental mechanisms governing colonic motility is preserved.<sup>[18]</sup> A disorder of the ICC may have a role in the development of diminished or absent colonic motor activity.<sup>[19]</sup> In patients with STC, the number of ICC was significantly decreased in all layers of the colonic wall,<sup>[10]</sup> including the external muscle layer.<sup>[20]</sup> Thus, constipation in patients with colonic inertia is attributable to weak or absent electric activity. When compared with healthy controls, patients with STC exhibit reduced daytime colonic pressure waves and a higher frequency of periodic rectal motor activity (PRMA) that were unrelated to proximal colonic activity. Their findings suggest that excessive and uncoordinated phasic rectal activity may further impede stool transport and contribute to STC.<sup>[21]</sup>

### Changes in physiology associated with disease states

Disease states that alter slowly wave patterns or spike responses will alter contraction and motility.<sup>[22]</sup> Abnormalities in colonic motility seen in diabetic patients with constipation are due in part to altered autonomic neural control manifested as an abnormal gastrocolonic response. Slow wave patterns appear unaltered in healthy participants compared to patients with constipation and diabetes. Minimal spike potential activity is seen in both healthy and diabetic patients during fasting. Following a meal, spike potential activity quickly increases during the first 10 min and is sustained for 30 min in healthy participants. This activity is inhibited by the pre-administration of an anticholinergic drug, which suggests that the postprandial response is mediated through the cholinergic nervous system. In diabetic patients without constipation, the response to a meal is the same as in controls. In chronic insulin dependent diabetic patients with constipation, the normal postprandial increase in spike potential is not present. The lack of spike potential leads to abnormal postprandial motor activity in the colon, which results in constipation.<sup>[23,24]</sup>

### Pelvic floor dysfunction

The second major mechanism for constipation is pelvic floor dysfunction, which results in disordered defecation. It is most commonly due to dysfunction of the pelvic floor muscles or anal sphincters.<sup>[25]</sup> Different terms that are used to describe these disorders include anismus, pelvic floor dyssynergia, paradoxical pelvic floor contraction, obstructed defecation, functional rectosigmoid obstruction, and functional fecal retention in childhood.<sup>[26]</sup> The pathophysiology of these disorders is not completely understood.

### Physiology of pelvic floor dysfunction

When constipation is accompanied by an immobile perineum, patients have impaired balloon expulsion, impaired and delayed artificial stool expulsion, decreased straightening of the anorectal angle, decreased descent of the pelvic floor with defecation, and prolonged rectosigmoid transit times. All are thought to be signs of pelvic floor dysfunction rather than delayed transit time.<sup>[27]</sup> When compared to healthy controls, patients with obstructed defecation demonstrate lower intrarectal pressure and defecation indices and higher anal residual pressures on anorectal manometry recordings during straining. Impaired rectal contraction, paradoxical anal contraction, or inadequate anal relaxation seen in patients with obstructed defecation suggests that rectoanal coordination is impaired.<sup>[28]</sup>

### Neural influences on pelvic floor dysfunction

Parasympathetic afferent nerves are stimulated by both slow or cumulative and fast or intermittent distention of the rectum, whereas sympathetic afferent nerves are only stimulated by fast distention. In a study that examined the role of sympathetic afferent nerves in the mediation of rectal filling sensations, women with obstructed

defecation were found to have either blunted or absent rectal sensory perception.<sup>[29]</sup> Participants experienced a nonspecific sensation in the pelvis or lower abdomen with fast distention, which suggested that sympathetic efferents were deficient. In spite of this, rectal wall compliance was normal in the patients with obstructed defecation.<sup>[30]</sup> The gastrocolic reflex has been evaluated in patients with obstructed defecation. It was found to be absent or prolonged in patients with obstructive defecation in whom transit time is prolonged. The gastrocolic reflex was found to be intact if slow transit was absent.<sup>[31,32]</sup>

### Diagnostic Tests for Constipation

As there is no gold standard, self-reported symptoms are necessary, but unreliable for the evaluation of constipation. It is important to be systematic for the evaluation of patient with constipation which includes history taking, physical examination and diagnostic tests.<sup>[33]</sup>

### History Taking

A detailed medical, surgical, dietary and drug history can facilitate the recognition of common constipation. It includes questions about constipation such as

1. How often you have a bowel movement.
2. How long you have had suffered symptoms.
3. What your stool look like
4. Eating habits.
5. Level of physical activity.
6. Medicines being used.<sup>[34]</sup>

It also includes

1. Checking for Rome criteria.
2. Checking of neurological disorders (spinal cord injury, multiple sclerosis).
3. Checking for psychiatric conditions (sexual abuse, trauma, eating disorders, and depression).
4. Check for age of onset (sudden or gradual).
5. Is urge present or not: Yes- outlet obstruction.

No- colonic inertia.

- Is there a family history of constipation?

### Physical Examination

A comprehensive physical examination includes detailed neurological and abdominal examination which helps to recognize systemic diseases. The abdomen must be carefully examined for the presence of stool, particularly in the left quadrant. It is important to exclude a gastrointestinal mass although, patients may commonly have a normal physical examination.<sup>[35,36]</sup>

It includes Percussion (check for gas), Palpable feces (loaded colon), Rectal touch – consistency, Presence of non-fecal masses, Presence of blood, Sphincter tone.<sup>[33]</sup>

Physical examination also include digital rectal examination which is very important as it is the revealing part of the clinical evaluation. Abnormalities such as

thrombosed external haemorrhoids, rectal prolapse, anal fissure, anal warts and excoriation can be easily appreciated on anorectal inspection.<sup>[38]</sup>

### Diagnostic Tests

A complete blood count, biochemical profile, serum calcium, glucose levels, thyroid function tests are usually an underlying metabolic or pathologic disorders. If there is high index of suspicion serum protein electrophoresis, urine porphyrins, serum parathyroid hormone, serum cortisol levels may be requested. However there are no studies done to assess the clinical value of routine use of the test alone and hence there is no evidence to either support or reject the utility of these tests.<sup>[40]</sup>

### Radiographic Tests

**Plain Abdominal Radiograph:** It is inexpensive and frequently used to complement clinical history and physical examination in patients with suspicion of constipation.<sup>[40]</sup> Furthermore, in addition to considerable inter-observer variation in radiological assessment of fecal loading, there was very poor correlation with colonic transit. This suggests that plain abdominal radiographs may not be a reliable method to assess for fecal loading in constipation.<sup>[41]</sup>

**Barium Enema:** It is used to identify anatomic abnormalities such as redundant sigmoid colon, mega colon, mega rectum, extrinsic compression and intra luminal masses. However, there are limited studies evaluating its clinical utility.<sup>[39,42]</sup> Both studies concluded that barium enema could not evaluate organic disease. Hirschsprung disease can be detected by barium enema, although manometry and histology are essential.<sup>[43,44]</sup>

**Defecography:** It involves imaging the rectum with contrast and observation of process, rate and complications of rectal evacuation using fluoroscopic techniques. It gives information about anatomical and functional change of anorectum. It is performed by infusing 150 mL of contrast into the patient's rectum, and having the subject squeeze, cough, and expel the barium. The most common findings are poor activation of levator any muscles, prolonged retention or inability to expel the barium, absence of a stripping wave in the rectum, mucosal intussusceptions, and / or rectocele.<sup>[45,46]</sup> Though there are some advantages, its drawbacks include radiation exposure, embarrassment, interobserver bias, and inconsistent methodology. Hence, defecography is recommended as an adjunct to clinical and manometric assessment.

### Magnetic Resonance Imaging

MRI and dynamic pelvis MRI can be useful for assessment of anorectal disorders.<sup>[46]</sup>

- **Endoanal MRI:** reveals change in external anal sphincter.
- **MRI Fluoroscopy:** directly shows pelvic floor and viscera during rectal evacuation and squeeze maneuvers.

- **Dynamic Pelvis MRI:** useful in diagnosis of rectal intussusception and also provides information on movements of whole pelvic floor.<sup>[47,48]</sup>

**Endoscopy:** It is indicated in patients with

- Over 50 years with no colorectal cancer.
- Change in stool caliber.
- Before surgery for constipation.
- Iron deficiency anemia.
- Obstructive symptoms.
- Recent onset of constipation.
- Rectal bleeding.
- Rectal prolapsed.
- Weight loss.<sup>[50]</sup>

**Colonoscopy** It provides direct visualization of colon and is indicated in selected patients to exclude mucosal lesions. A colonoscopy is recommended in constipated patients if they have alarming features such as rectal bleeding, heme positive stool, iron deficiency anemia, weight loss, obstructive symptoms, recent onset of symptoms, rectal prolapsed, or change in stool caliber, and in subjects older than 50 years who have not previously had colon cancer screening. In younger patients, a flexible sigmoidoscopy may be sufficient to exclude distal colonic disease.<sup>[51]</sup>

Tests to be performed in patients whose constipation is refractory to laxatives and dietary changes and in those with suspected evacuation disorder.

#### Colonis Transit Study

It helps in assessing the speed at which the stool moves through the colon. It is measured by three general methods:

1. Ingestion of radiopaque markers followed by abdominal radiograph.<sup>[52,53]</sup>
2. Radioisotopes and scintigraphy.<sup>[54]</sup>
3. Ingestion of pressure, PH capsule, tracking its movement.<sup>[39]</sup>

**Colonic Transit Scintigraphy:** It is non-invasive and quantitative method of evaluation of total and regional colonic transit.<sup>[40,55]</sup> Here, an isotope (<sup>111</sup>In or <sup>99</sup>Tc) is administered either in a coated capsule that dissolves in the colon or terminal ileum or encapsulated in a non-digestive capsule with a test meal. Subsequently, gamma-camera images are obtained at specific time points. Awareness about scintigraphic studies and their utility has been increasing. Although scintigraphy studies have been validated, reliable and reproducible, they are expensive, time consuming and limited.<sup>[56]</sup>

**Wireless Motility Capsule:** It provides a non-invasive method for measuring not only colonic transit but also the gastric emptying and small bowel transit line by utilizing PH changes throughout the gut, colonic transit and whole gut transit. WMC has good sensitivity and specificity for evaluating colonic transit Colonic and whole gut transit with WMC correlates well with

radiopaque markers and has higher specificity in diagnosing slow transit in constipation.<sup>[39]</sup> WMC lessened the need for further invasive motility tests. Thus, WMC can be useful for assessing colonic motility and transit.<sup>[57]</sup>

**Colonic Manometry:** It can be conducted under stationary and ambulatory condition i.e., it provides a complete assessment of overall motor activity at rest, during sleep, after waking, after meals, and after provocative stimulation such as drugs, meal, or balloon distensions.<sup>[39]</sup> It is performed by using solid-state probes and portable recorders or water-perfused stationary systems.<sup>[39,58]</sup> It provides reproducible and reliable information regarding the pathophysiology of constipation,<sup>[39]</sup> and can be used to explore the mechanisms and motor effects of pharmacological agents on the colon. Colonic manometry catheter is placed using one of 3 methods: nasal intubation with migration of probe into the colon, guide wire-assisted water perfused probe placement and retrograde direct probe placement.<sup>[59]</sup> Prolonged recordings over 24 h are favored to completely understand the comprehensive colonic motor profile. It helps to diagnose underlying myopathy or neuropathy and differentiate slower transit due to neuromuscular function.

**Anorectal Manometry:** It provides assessment of pressure activity in anorectum and provides info regarding rectal sensation recto anal reflexes and anal sphincter function at rest and drug defecatory maneuver.<sup>[45]</sup> Mainly used to detect defecatory disorders and hirschsprung disease.

Four Patterns of dyssynergic defecation has been described using anorectal manometry.

1. Type 1 is characterized by a paradoxical increase in the residual anal pressure in the presence of adequate propulsive pressure, that is, increase in intrarectal pressure ( $\geq 45$ mm Hg).
2. Type 2, characterized by an inability to generate adequate expulsive forces, i.e., no increase in intrarectal pressure, together with a paradoxical increase in residual intraanal pressure 3.
3. Type 3, characterized by generation of adequate expulsive forces, but absent or incomplete ( $< 20\%$ ) reduction in intraanal pressure and
4. Type 4, characterized by an inability to generate adequate expulsive forces, that is, no increase in intrarectal pressure and absence of incomplete reduction in residual intraanal pressure.

Rectal sensory testing may reveal rectal hyposensitivity. Anorectal manometry is useful for the diagnosis of dyssynergic defecation and altered rectal sensation and identifies subjects who could benefit from biofeedback therapy.<sup>[60]</sup>

**High Resolution Manometry:** High Resolution Manometry involves a solid-state manometric assembly

with 12 circumferential sensors spaced at 1-cm intervals (4.2 mm outer diameter). This device uses proprietary pressure transduction technology that allows each pressure sensing element to detect pressure over a length of 2.5mm in each of 12 radially dispersed sectors. The sector pressures are then averaged, making each sensor a circumferential pressure detector with the extended frequency response characteristic of solid-state manometric systems. The large numbers of closely spaced sensors provides greater detail of the pressure plots, and ensures more accuracy, especially when compared to 2-4 sensor water perfused manometry that can miss important findings.<sup>[61,62]</sup> Also, a high-definition manometry system with 256 circumferentially arrayed sensors that provides anal sphincter pressure profiles and topographic changes in three dimensions is available. This system is found to be feasible, well tolerated and provides comparable information to that obtained with ARM. It provides vector manometry profile and its 3D display provides both functional and anatomical information of anal sphincter.<sup>[63]</sup>

**Balloon Expulsion Test:** The balloon expulsion provides a simple, bedside assessment of a subject's ability to expel an artificial stool. There is no standard approach and several techniques have been used, including 25 ml or 50 ml balloons filled with warm water or air, 18mm spheres, silicone-filled artificial stool or weights attached to a pulley to assess the extra force required to expel a metal sphere in a lying position.<sup>[64]</sup> Most normal subjects can expel this balloon within 1 minute.<sup>[65]</sup> However many dyssynergics can expel the balloon; hence the test itself is insufficient to make a diagnosis.<sup>[38,60]</sup> Thus, although the failure to expel a balloon strongly suggests dyssynergia, a normal test does not exclude this possibility. Hence this test should be interpreted along with other physiologic tests.

**Rectal Barostat Test:** Barostat comprises of a highly compliant balloon that is placed in the rectum and connected to a computerized pressure-distending device (barostat). It can be used to assess rectal sensation, tone and compliance. The test can be useful for identifying patients with a normal, impaired or hyper compliant rectum and can help to detect megarectum.<sup>[67-68]</sup>

### General Treatment of constipation

#### Pharmacotherapy

The classification of laxatives is controversial. They have been categorized primarily by their mechanism of action, although the exact mechanisms are unclear. Most laxatives alter intestinal fluid and electrolyte transport mechanisms, thereby causing defecation.<sup>[68]</sup> the therapeutic options are many. Agents available for use are varied and include bulk-forming agents, hyper osmotic agents, stool softeners, lubricants, saline, and stimulant laxatives. Several dosage forms are available for laxatives.

#### **Bulk-forming Laxatives**

Bulk-forming agents include non absorbable polysaccharide and cellulose derivatives. These agents swell in water, forming an emollient gel that increases bulk in the intestines. Peristalsis is stimulated by the increased fecal mass that decreases the transit time. It is proposed that micro flora metabolize polysaccharides to osmotically active metabolites. The metabolites may alter intestinal motility and electrolyte transport.

Bulk-forming agents generally produce a laxative effect within 12 to 24 hours, but they may take 2 to 3 days to exert their full effect. They are generally safe with minimal side effects associated with their use. Flatulence may occur if doses are increased rapidly. Intestinal and esophageal obstruction may occur if insufficient liquid is administered with the dose. Therefore, the Food and Drug Administration (FDA) has tentatively ruled that psyllium in a granular dosage form poses an unacceptable risk for the development of esophageal obstruction, and has proposed to reclassify it as not generally recognized as safe and effective.<sup>[70]</sup> Granular dosage forms include, but is not limited to

- Any granules that are swallowed dry prior to drinking liquid;
- Any granules that are dispersed, suspended, or partially dissolved in liquid prior to swallowing;
- Any granules that are chewed, partially chewed, or unchewed, and then followed with liquid;
- Any granules that are sprinkled over food.

Patients using the non granular powder form should be cautioned to take each dose with at least one 240-mL glass of liquid.

Bulk-forming laxatives should not be recommended for patients with intestinal stenosis, ulceration, or adhesions. Rare reports of allergic reactions to karaya have been noted, characterized by urticaria, rhinitis, dermatitis, and bronchospasm.<sup>[68]</sup>

#### **Hyper osmotic Agents**

Glycerin, lactulose, and polyethylene glycol are hyperosmotic laxatives. They increase osmotic pressure within the intestinal lumen, which results in luminal retention of water, softening the stool. Lactulose is an unabsorbed disaccharide metabolized by colonic bacteria primarily to lactic, formic, and acetic acids. It has been proposed that these organic acids may contribute to the osmotic effect.<sup>[68]</sup> Polyethylene glycol (PEG) 3350 laxative is a synthetic polyglycol, which is absorbed in only trace amounts, and is not metabolized to hydrogen or methane by colonic bacteria.<sup>[71]</sup>

Glycerin is available only for rectal administration (suppository or enema) for treating acute constipation. Its laxative effect occurs within 15 to 30 minutes. Lactulose may take effect in 24 to 48 hours. It should be reserved for acute constipation because it is as effective as other less costly medications. Polyethylene glycol laxative is

available as a powder for solution that should be dissolved in 8 ounces of water, soda, coffee, or tea, then ingested. Its laxative effect occurs in 48 to 96 hours and should be used for 2 weeks or less.<sup>[72]</sup>

Side effects of glycerin include rectal irritation and burning and hyperemia of the rectal mucosa may occur. Lactulose is associated with flatulence, abdominal cramps, and diarrhea. Caution should be exercised when this agent is administered because it may also cause significant electrolyte imbalances and dehydration.<sup>[73]</sup> Whereas nausea, abdominal bloating, cramping, and flatulence may occur with PEG, there may be fewer symptoms than with lactulose because it does not cause fermentation in the gastrointestinal tract.<sup>[74]</sup> Studies directly comparing the side effect profile of lactulose versus PEG are needed. Its use is contraindicated in patients with known or suspected bowel obstruction.

#### **Stool Softeners**

Stool softeners are also called emollient laxatives. They include calcium, potassium, and sodium salts of dioctyl sulfosuccinate. Stool softeners are anionic surfactants that lower the fecal surface tension allowing water and lipid penetration. It has been proposed that these agents stimulate water and electrolyte secretion into the colon.<sup>[68]</sup>

Softening of the feces generally occurs after 1 to 3 days. Some products (e.g., docusate sodium with casanthrol) combine a stool softener with a laxative. Adverse effects are rare with docusate preparations. Mild gastrointestinal cramping may occasionally develop. Throat irritation has occurred following use of the docusate sodium solution.<sup>[75]</sup>

#### **Lubricants**

The primary lubricant laxative is mineral oil. Its mechanism of action involves lubrication of the feces and hindrance of water reabsorption in the colon. Mineral oil is indigestible and its absorption is limited considerably in the nonemulsified formulation. Greater absorption from the emulsion formulation has been reported, but the clinical significance is unsubstantiated.

The onset of action of orally administered mineral oil is 6 to 8 hours. Although adverse effects occur rarely with mineral oil, potentially significant effects may occur. Chronic use of mineral oil has been reported to cause impaired absorption of fat soluble vitamins (A, D, E, and K). Aspiration of the product may cause a lipoid pneumonia, so its oral use should be avoided in young children (<6 years), older adults, and debilitated patients. Administration at bedtime should be avoided to prevent aspiration. Foreign-body reactions in the lymphoid tissue of the intestinal tract have resulted from its limited amount of absorption. Seepage of the product from the rectum following high-dose oral or rectal administration may cause pruritus ani, increased infection, and decreased healing of anorectal lesions.<sup>[68,73]</sup>

#### **Saline Laxatives**

Magnesium, sulfate, phosphate, and citrate salts are used when rapid bowel evacuation is needed. The mechanism of action of these poorly absorbed ions is unclear, but it is believed that they produce an osmotic effect that increases intraluminal volume and stimulates peristalsis. Magnesium may cause cholecystokinin release from the duodenal mucosa, promoting increased fluid secretion and motility of the small intestine and colon.<sup>[76]</sup>

The laxative effect of the orally administered magnesium and sodium phosphate salts occurs within 0.5 to 6 hours. Phosphate-containing rectal enemas evacuate the bowel within 2 to 15 minutes.

Saline laxatives are safe for short-term management of constipation. They are useful in preparing for endoscopic examinations, eliminating parasites and toxic anthelmintics before or after therapy, removing poisons, and treating fecal impaction. They may cause significant fluid and electrolyte imbalances when used for prolonged periods or in certain patients. Dehydration may result from repeated administration without appropriate fluid replacement. The risk of hypermagnesemia in patients with renal dysfunction should be considered when magnesium salts are initiated because 10% to 20% of the dose may be absorbed systemically. Caution should be exercised when administering the sodium phosphate salts to patients with congestive heart failure when sodium restriction is necessary. These agents are not recommended for children under 2 years of age because of the potential for hypocalcemia in this population.

#### **Stimulant Laxatives**

Anthraquinone (sennosides) and diphenylmethane (bisacodyl) derivatives, castor oil, and dehydrocholic acid are stimulant laxatives. They are called stimulants because they stimulate peristalsis via mucosal irritation or intramural nerve plexus activity, which results in increased motility. Although this has been long regarded as the mechanism of action for these agents, their activity actually may be related to their effect on the colonic mucosal cells. It is proposed that stimulant laxatives modify the permeability of these cells, resulting in intraluminal fluid and electrolyte secretion.

Defecation occurs 6 to 12 hours after oral administration of these agents. Therefore, a single bedtime dose promotes a morning bowel movement. Unlike the other stimulant laxatives, dehydrocholic acid is administered at least three times daily. Rectal administration of bisacodyl and senna produces catharsis within 15 minutes to 2 hours.

Adverse effects of these medications include abdominal cramps, nausea, electrolyte disturbances (e.g., hypokalemia, hypocalcemia, metabolic acidosis, or alkalosis), and rectal burning and irritation with suppository use. Anthraquinone derivatives have been noted to cause melanosis coli (discoloring of colonic

mucosa), which is harmless and reversible. Hypersensitivity reactions may occur (rarely) with phenolphthalein and dehydrocholic acid, causing dermatologic manifestations (e.g., skin eruptions, rash, pigmentation, pruritus). These agents may also cause a pink or red discoloration of the urine.

Chronic use of stimulant laxatives should be discouraged and use beyond 1 week should be avoided. These agents may produce a “cathartic colon” if used for several years (15–40 years). The colon develops abnormal motor function, and the condition resembles ulcerative colitis on roentgenogram. Usually, discontinuation of laxative use restores normal bowel function. Several stimulant laxatives have been removed from the market by the FDA because they were classified as “not generally recognized as safe and effective” in animal carcinogenicity studies. Although only insignificant amounts distribute into the milk of nursing mothers, stimulant laxatives should be avoided during lactation.<sup>[77]</sup>

### Other Agents

Tegaserod maleate is a 5-hydroxytryptamine or serotonin subtype-4 (5-HT<sub>4</sub>), partial receptor agonist. It binds to 5-HT<sub>4</sub> receptors, present largely in the gastrointestinal tract, stimulating intestinal peristalsis and secretion. It is indicated for patients less than 65 years of age with chronic constipation and IBS with constipation (see “Irritable Bowel Syndrome”).

The recommended oral dose of tegaserod in patients with chronic idiopathic constipation is 6 mg twice daily (bid) before meals for up to 12 weeks of therapy. Common side effects of tegaserod include diarrhea, which may be severe in some patients, abdominal pain, and headaches.<sup>[78]</sup>

Inhibition of cytochrome P450 isoenzymes 1A2 and 2D6 may occur with tegaserod. However, there are no clinically significant drug interactions reported with its concomitant use. Although not clinically significant, tegaserod may reduce digoxin levels by 15%. Therefore, monitoring is important in patients who begin tegaserod and are dosed at the lower limit of normal with digoxin.<sup>[78]</sup>

Tegaserod is contraindicated in patients with severe renal impairment, moderate to severe hepatic impairment, a history of bowel obstruction, symptomatic gallbladder disease, suspected sphincter of Oddi dysfunction, or abdominal adhesions. It should be discontinued if severe diarrhea, hypotension, syncope, or sudden worsening of abdominal pain occurs. Tegaserod should also be discontinued immediately in persons who develop rectal bleeding, bloody diarrhea, or new or worsening abdominal pain, which may suggest ischemic colitis.<sup>[79,80]</sup>

The efficacy, safety, and tolerability of tegaserod has been demonstrated in a multicenter, double-blind, placebo-controlled study. Patients were randomized to

receive treatment with tegaserod 2 mg bid, 6 mg bid, or placebo. A total of 1,348 patients were enrolled in the study. Patients were considered to have responded to treatment if the number of bowel movements increased from baseline. The study demonstrated that the response rate was significantly higher in the tegaserod-treated patients than placebo. The response rates were 41.4% in the 2 mg bid group, 43.2% in the 6 mg bid group, and 25.1% in the placebo group.<sup>[78]</sup>

Data suggest a role for other agents in treating constipation. Naloxone and cisapride have been used to treat chronic idiopathic constipation. It has been postulated that endogenous opiates regulate colonic propulsive activity.<sup>[81]</sup> Consequently, the role of opiate receptor antagonists in treating constipation has been investigated. Naloxone (an opiate receptor antagonist) has reversed chronic idiopathic constipation at intravenous and oral doses of 20 to 30 mg per day.<sup>[82]</sup> In addition, naloxone causes acceleration of colonic transit, although it has not been shown to affect the number of bowel movements per 48 hours.<sup>[83]</sup> Further studies are needed to define the role of this agent in treating chronic constipation.

Cisapride is a piperidinyl benzamide that is chemically related to metoclopramide. It is a prokinetic agent that enhances gastrointestinal motility throughout the entire length of the gastrointestinal tract. The mechanisms by which cisapride facilitates gastrointestinal motility have not been elucidated. However, a proposed mechanism involves its enhancement of acetylcholine release in the myenteric plexus of the gut.<sup>[84]</sup> Cisapride has no antidopaminergic effects.

In 2000, the FDA required the manufacturer of cisapride to discontinue active marketing of the drug due to reports of cardiac arrhythmias, some resulting in death.<sup>[85]</sup> It is available through the manufacturer under a limited-access program for patients in the treatment of severe chronic constipation, gastroesophageal reflux disease, gastroparesis, and pseudoobstruction.<sup>[86]</sup>

Cisapride, in oral doses of 5 to 20 mg, is absorbed rapidly and almost completely from the gastrointestinal tract. The oral bioavailability is approximately 40% to 50% and is enhanced by food. Its tissue distribution in humans is not known, however, it is metabolized extensively to metabolites with minimal pharmacologic activity. Its elimination half-life after oral administration is approximately 7 to 10 hours. Some evidence suggests that the half-life of cisapride may increase in older adults and those with hepatic impairment.<sup>[84]</sup>

Cisapride at a dose of 20 mg bid daily was investigated in patients with chronic idiopathic constipation or chronic laxative use. Cisapride increased stool frequency by 50% and reduced mean laxative intake by half.<sup>[33]</sup> In another study, cisapride was used to treat constipation at doses of 5 and 10 mg three times daily for 12 weeks.

Stool frequency was increased by approximately 70% with both doses, compared to 43% with placebo.<sup>[88]</sup>

Common side effects include abdominal cramping, borborygmi (intestinal rumbling), and diarrhea. Central nervous system (CNS) side effects, such as somnolence and fatigue, have been reported less often.

Concomitant administration of cisapride with other drugs may result in significant drug interactions. Cimetidine coadministration may cause a 45% increase in the bioavailability of cisapride.<sup>[84]</sup> Cisapride may enhance acenocoumarol absorption; therefore, monitoring coagulation times is advisable with anticoagulants.<sup>[84]</sup> Cisapride can accelerate gastric emptying, therefore patients should be monitored during concomitant use of agents with narrow therapeutic index (e.g., digoxin and phenytoin).

### Non pharmacologic Therapy

Some of the primary causes of constipation may necessitate non pharmacologic intervention for symptom relief. Deficient fluid and fiber intake have been suggested as causative factors. However, two large-scale studies have not demonstrated an association between fiber consumption and self-reported constipation.<sup>[91,92]</sup>

Fiber may be useful in preventing constipation. Fiber increases stool bulk, based on the ability of the polysaccharides to absorb and retain water and the extent of bacterial fermentation of these polysaccharides in the gut. A dietary bulk-forming agent such as bran may be useful in preventing constipation because it is only partially fermented by bacteria, resulting in increased stool bulk, accelerated transit time, and promotion of normal defecation.

Fiber intake may also have other health benefits. The FDA has ruled that labels on certain foods (i.e., breakfast cereals) containing soluble fiber from psyllium seed husk (PSH) may claim that, as part of a diet low in saturated fat and cholesterol, they can reduce the risk of coronary heart disease.<sup>[89]</sup> The ruling is based on evidence that consumption of approximately 7 g per day soluble fiber from PSH showed significant lowering of total and low-density lipoprotein cholesterol.

Increased fiber intake should be recommended cautiously. Rapid increases in dietary roughage may cause abdominal bloating and flatulence. Adequate fluid intake is also necessary to prevent fecal impaction. Generally, 240 to 360 mL fluid with each tablespoon of bran is sufficient.

Immobility and inactivity, common among debilitated patients and older adults, are risk factors for the development of constipation.<sup>[90]</sup> Regular exercise such as walking or jogging may improve constipation associated with a sedentary lifestyle. Pharmacologic intervention (e.g., laxatives) may be necessary if lifestyle modifications are unsuccessful.

### Treatment from different articles

Treatment of constipation is symptomatic and should be customized for each individual considering the cause of constipation, patient's age, comorbid conditions, underlying pathophysiology, and the patient's concerns and expectations. Both non-pharmacological and pharmacological treatment helps in managing the constipation.<sup>[93]</sup>

### Non-Pharmacological Treatment

In patients with no known secondary causes of constipation, conservative non-pharmacologic treatment measures generally are recommended as first-line therapy. These strategies typically include Lifestyle changes such as an adequate fluid intake, increased dietary fiber intake, regular nonstrenuous exercise, and dedicated time for passing bowel movements can be useful, but there is limited evidence to support these measures. However, these measures are effective in only a subset of patients.<sup>[93,94]</sup> Other non-pharmacologic therapies include biofeedback therapy, behavior therapy, and electric stimulation; however, these therapies are generally reserved for patients with outlet obstruction and are typically performed at highly specialized centers.<sup>[95-99]</sup>

### Biofeedback Therapy

This represents a behavioural treatment in which patients learn the physiological mechanisms of defecation, how to use their diaphragms, abdominal and pelvic floor muscles in order to evacuate. Sensory training may also be provided.<sup>[100]</sup>

### Pharmacological Treatment

#### Fiber Supplements or Bulking Agents

Also known as fiber/bulk laxatives are traditionally considered first line treatment. They are less effective in patients with slow transit constipation or defecatory disorder than in those with normal transit constipation. Soluble, but not insoluble, fiber agents facilitate bowel function by increasing water absorbency capacity of stool resulting in improved stool frequency and consistency. Common reported side effects include bloating, gas, and distention, but these symptoms often decrease with time. Some of the commonly used ones, such as methylcellulose, Bran, Calcium polycarbophil and psyllium.<sup>[101]</sup>

#### Osmotic Laxatives

Osmotic laxatives contain poorly absorbed ions or molecules, which create an osmotic gradient within the intestinal lumen, thereby retaining water in the lumen, leading to softer stools and improved propulsion. Osmotic laxatives are reasonable choice for patients not responding to fiber supplementation. Laxative selection should be based on relevant medical history such as cardiac or renal status, possible drug interactions, cost, and side effects. Abdominal discomfort, electrolyte imbalances, allergic reactions, and hepatotoxicity have been reported. There needs to be caution with the use of

magnesium-based laxatives in patients with renal disease. Some of the commonly used ones, such as polyethylene glycol, sorbitol, lactulose and magnesium salts.<sup>[102]</sup>

### Stimulant Laxatives

There is a limited evidence base supporting the use of stimulant agents in chronic constipation. Pharmacologically, they are either naturally occurring agents (such as senna and cascara) or phenolphthalein analogues (such as bisacodyl). They are hydrolyzed in the gut (by either enterocyte enzymes or colonic flora) and act by stimulating peristalsis, sensory nerve endings and possibly interfering with electrolyte flux to inhibit water absorption.<sup>[103]</sup>

### Stool Softeners, Suppositories and Enemas

Stool softeners, which enhances softer stool consistency, are overall of limited efficacy.<sup>[104,105]</sup> Suppositories (ie, glycerin and bisacodyl) help initiate or facilitate rectal evacuation. They may be used alone, but preferentially in conjunction with meals to capture the gastrocolic reflex or in conjunction with other agents.<sup>[106]</sup> Suppositories, which usually work within minutes, may be tried as part of a behavioral program for those with obstructed defecation and in institutionalized patients. Enemas may be used judiciously on an as-needed basis, particularly for obstructed defecation and to avoid fecal impaction. Tap water enemas seem safe for more regular use. Electrolyte imbalances such as hyperphosphatemia are more common with phosphate enemas and regular use is discouraged.<sup>[107]</sup> Soapsuds enemas can cause rectal mucosal damage with colitis and are not routinely recommended.<sup>[108]</sup>

### Novel Targets

#### Serotonin Agents

The serotonin-4 (5-HT<sub>4</sub>) receptor plays a pivotal role in the regulation of gastrointestinal function.<sup>[109]</sup> Activation of these receptors augments peristalsis by stimulating secondary messengers (acetylcholine and calcitonin gene-related peptide), enhancing proximal smooth muscle contraction, and relaxing distal smooth muscles resulting in effective peristalsis. These receptors also modulate cyclic adenosine monophosphate-mediated chloride secretion and visceral sensitivity.<sup>[110]</sup> Three 5-HT<sub>4</sub> receptor agonists have been tested for constipation: tegaserod, substituted benzamides (eg, cisapride, mosapride) and prucalopride.

#### Cisapride

In the past, cisapride, a first-generation promotility agent, which increases intestinal motor activity, was used clinically for the treatment of chronic constipation but it has been removed from the market due to cardiovascular sideeffects, with fatal cardiac arrhythmias due to its effect in QT interval prolongation.<sup>[111]</sup>

**Tegaserod** is a partial 5-HT<sub>4</sub> agonist that accelerates colonic transit in healthy volunteers and in patients with

constipation. Common side effects included transient diarrhea, abdominal pain, headache, and nasopharyngitis. Tegaserod was withdrawn in March 2007 due to incidence of ischemic cardiovascular adverse events. At present, tegaserod is available only on a restricted basis for use in IBS-C and CC in women younger than 55 years who are not at risk for cardiovascular events.<sup>[112,113]</sup>

**Prucalopride**, is a highly selective, high-affinity 5-HT<sub>4</sub> receptor agonist. Prucalopride has a 90% bioavailability after oral ingestion, with a half-life of 24 to 30 hours. The drug is well tolerated; the most common side effects are headache, nausea, abdominal pain, and diarrhea. Of importance, no clinical cardiovascular side effects have been noted.<sup>[114,115]</sup>

**Other 5-HT<sub>4</sub> agonists: Renzapride** is a mixed 5-HT<sub>4</sub> agonist and 5-HT<sub>3</sub> antagonist that accelerates gut transit and relieves symptoms of constipation.<sup>[116]</sup> However, the magnitude of effect is modest both for bowel frequency and abdominal pain symptoms.<sup>[117]</sup> Other 5-HT<sub>4</sub> agonists, such as **mosapride**, are currently in development for chronic constipation.<sup>[118]</sup>

#### Secretagogues

It includes Chloride Channel activators and Guanylate Cyclase C activators.

**Chloride Channel Activators: Lubiprostone** is a bicyclic fatty acid that activates type 2 chloride channels on the apical membrane of the enterocytes, which results in the chloride secretion with water and sodium diffusion.<sup>[119-121]</sup> Its effectiveness is limited by the side effect of nausea but can be improved when taken with food.

**Guanylate Cyclase C Activators Linaclotide**, a guanylin and uroguanylin analog, increases intestinal secretion by activation of the guanylate cyclase receptor.<sup>[122]</sup> Clinical trials have demonstrated the efficacy of linaclotide in constipation in improving stool consistency, straining, abdominal discomfort, bloating, global assessments, and quality of life.<sup>[123]</sup> The most common reported side effect is diarrhea. Caution should be used with these medications in light of their side-effect profile, cost, and efficacy compared to simple, less expensive alternatives.

**Neurotrophin-3** is a neurotrophic factor that stimulates the development, growth, and function of the nervous system. NT-3, at a dose of 9 mg subcutaneously 3 times per week, significantly increased SBMs, softened stool and ease of passage, improved constipation-related symptoms, and decreased colonic transit time. The drug can be administered only by a subcutaneous injection. Minor injection site reactions (approximately 33%) were the most common adverse events. After 4 weeks of therapy, approximately 50% of patients developed anti-NT3 antibodies.<sup>[124]</sup>

### Investigational Drugs

Research is also focusing on newer investigational agents that take novel mechanistic approaches to the treatment of patients with chronic constipation.

### Motilin Agonists

Motilin is a 22-amino-acid peptide, secreted from EC cells, that stimulates gut motility through activation of a G-protein-coupled motilin receptor found in the enteric nervous system and intestinal smooth muscle.<sup>[125]</sup> Recently a nonantibiotic, orally active motilin agonist, **Mitemincinal**, has been developed and is in phase 2 trials for IBS and gastroparesis, and is also being considered for CC.<sup>[126]</sup>

### Botulinum Toxin

*Clostridium botulinum* toxin type A (Botox), a potent neurotoxin that inhibits presynaptic release of acetylcholine, has been injected intramuscularly into the puborectalis muscle to treat defecatory disorders. Preliminary data suggest that botulinum toxin may be effective for treating patients with defecatory disorders in which spastic pelvic floor dysfunction causes outlet delay, including those who also have Parkinson's disease. Controlled trials have not yet been performed, however, and this approach is not recommended in lieu of biofeedback, for which clinical experience is greater.

**Opioid Antagonists:** Antagonists at enteric m-receptors, such as Methylnaltrexone and Alvimopan, are emerging agents for opiate-induced bowel dysfunction and for postsurgical ileus.<sup>[127]</sup> **Alvimopan** increased the mean spontaneous bowel movement frequency compared with placebo, and improved symptoms such as straining, incomplete evacuation, abdominal bloating and discomfort. In idiopathic chronic constipation alvimopan had minimal effects on colonic transit time and bowel frequency and did not benefit other bowel symptoms.<sup>[128]</sup> **Methylnaltrexone** has undergone phase III study in patients with opiate-induced constipation.<sup>[129]</sup> Given as a subcutaneous injection, 52% of patients had a spontaneous (nonlaxative induced) bowel movement within 4h after two or more of the first four doses compared with 8% in the placebo group. There are no studies that have tested the efficacy of methylnaltrexone in patients with idiopathic constipation.

### REFERENCE

- Sandler RS, Drossman DA. Bowel habits in young adults not seeking health care. *Dig Dis Sci.*, 1987; 32: 841-5.
- Koch A, Voderholzer WA, Klauser AG, Muller-Lissner S. Symptoms in chronic constipation. *Dis Colon Rectum*, 1997; 40: 902-6.
- Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Muller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut*, 1999; 45: Suppl 2: II-43-II-47.
- Ashraf W, Park F, Lof J, Quigley EM. An examination of the reliability of reported stool frequency in the diagnosis of idiopathic constipation. *Am J Gastroenterol*, 1996; 91: 26-32.
- Mertz H, Naliboff B, Mayer E. Physiology of refractory chronic constipation. *Am J Gastroenterol*, 1999; 94: 609-15.
- Voderholzer WA, Schatke W, Muhldorfer BE, Klauser AG, Birkner B, Muller-Lissner SA. Clinical response to dietary fiber treatment of chronic constipation. *Am J Gastroenterol*, 1997; 92: 95-8.
- Doig CM. ABC of colorectal diseases: paediatric problems. *BMJ*, 1992; 305: 462-4.
- Sultan AH, Kamm MA, Hudson CN. Pudendal nerve damage during labour: prospective study before and after childbirth. *Br J Obstet Gynaecol*, 1994; 101: 22-28.
- Cheung O, Wald A. Review article: the management of pelvic floor disorders. *Aliment Pharmacol Ther*, 2004; 19: 481-495.
- Sagar PM, Pemberton JH. Anorectal and pelvic floor function. Relevance of continence, incontinence, and constipation. *Gastroenterol Clin North Am*, 1996; 25: 163-182.
- Wedel T, Spiegler J, Soellner S, Roblick UJ, Schiedeck TH, Bruch HP, Krammer HJ. Enteric nerves and interstitial cells of Cajal are altered in patients with slow-transit constipation and megacolon. *Gastroenterology*, 2002; 123: 1459-1467.
- Mertz H, Naliboff B, Mayer EA. Symptoms and physiology in severe chronic constipation. *Am J Gastroenterol*, 1999; 94: 131-138.
- Bassotti G, Villanacci V. Slow transit constipation: a functional disorder becomes an enteric neuropathy. *World J Gastroenterol*, 2006; 12: 4609-4613.
- El-Salhy M, Norrgard O, Spinnell S. Abnormal colonic endocrine cells in patients with chronic idiopathic slow-transit constipation. *Scand J Gastroenterol*, 1999; 34: 1007-1011.
- Sjolund K, Fasth S, Ekman R, Hulten L, Jiborn H, Nordgren S, Sundler F. Neuropeptides in idiopathic chronic constipation (slow transit constipation). *Neurogastroenterol Motil*, 1997; 9: 143-150.
- Knowles CH, Nickols CD, Scott SM, Bennett NI, de Oliveira RB, Chimelli L, Feakins R, Williams NS, Martin JE. Smooth muscle inclusion bodies in slow transit constipation. *J Pathol*, 2001; 193: 390-397.
- Knowles CH, Scott SM, Lunniss PJ. Slow transit constipation: a disorder of pelvic autonomic nerves? *Dig Dis Sci.*, 2001; 46: 389-401.
- Bassotti G, Chistolini F, Nzepa FS, Morelli A, Colonic McCrea GL et al. Constipation in the older adult 2637 [www.wjgnet.com](http://www.wjgnet.com) propulsive impairment in intractable slow-transit constipation. *Arch Surg*, 2003; 138: 1302-1304.
- Bassotti G, Germani U, Fiorella S, Roselli P, Brunori P, Whitehead WE. Intact colonic motor response to sudden awakening from sleep in patients with chronic idiopathic (slowtransit) constipation. *Dis Colon Rectum*, 1998; 41: 1550-1555; discussion 1555-1556.

20. Shafik A, Shafik AA, El-Sibai O, Mostafa RM. Electric activity of the colon in subjects with constipation due to total colonic inertia: an electrophysiologic study. *Arch Surg*, 2003; 138: 1007-1011; discussion 1011.
21. Tong WD, Liu BH, Zhang LY, Zhang SB, Lei Y. Decreased interstitial cells of Cajal in the sigmoid colon of patients with slow transit constipation. *Int J Colorectal Dis.*, 2004; 19: 467-473.
22. Meunier P, Rochas A, Lambert R. Motor activity of the sigmoid colon in chronic constipation: comparative study with normal subjects. *Gut*, 1979; 20: 1095-1101.
23. Schang JC, Devroede G. Fasting and postprandial myoelectric spiking activity in the human sigmoid colon. *Gastroenterology*, 1983; 85: 1048-1053.
24. Lembo A, Camilleri M. Chronic constipation. *N Engl J Med*, 2003; 349: 1360-1368.
25. Thompson WG, Irvine EJ, Pare P, Ferrazzi S, Rance L. Functional gastrointestinal disorders in Canada: first population-based survey using Rome II criteria with suggestions for improving the questionnaire. *Dig Dis Sci.*, 2002; 47: 225-235.
26. Pezim ME, Pemberton JH, Levin KE, Litchy WJ, Phillips SF. Parameters of anorectal and colonic motility in health and in severe constipation. *Dis Colon Rectum*, 1993; 36: 484-491.
27. Rao SS, Welcher KD, Leistikow JS. Obstructive defecation: a failure of rectoanal coordination. *Am J Gastroenterol*, 1998; 93: 1042-1050.
28. Dinning PG, Bampton PA, Andre J, Kennedy ML, Lubowski DZ, King DW, Cook IJ. Abnormal predefecatory colonic motor patterns define constipation in obstructed defecation. *Gastroenterology*, 2004; 127: 49-56.
29. Gosselink MJ, Schouten WR. Rectal sensory perception in females with obstructed defecation. *Dis Colon Rectum*, 2001; 44: 1337-1344.
30. Gosselink MJ, Hop WC, Schouten WR. Rectal compliance in females with obstructed defecation. *Dis Colon Rectum*, 2001; 44: 971-977.
31. Gosselink MJ, Schouten WR. The gastrorectal reflex in women with obstructed defecation. *Int J Colorectal Dis*, 2001; 16: 112-118.
32. Liu S, Zou K, Song J. A study of anorectal manometry in patients with chronic idiopathic constipation. *J Tongji Med Univ*, 2000; 20: 351-352.
33. World Gastroenterology Organisation Practise Guidelines.
34. Herz MJ, Kahan E, Zalevski S, et al. Constipation: a different entity for patients and doctors. *Fam Pract*, 1996; 13:156-9. [PubMed: 8732327].
35. Talley NJ. How to do and interpret a rectal examination in gastroenterology. *Am J Gastroenterol*, 2008; 103: 820-2. [PubMed: 18397419]
36. Rao SS. Dyssynergic defecation. *Gastroenterol Clin North Am*, 2001; 30: 97-114. [PubMed: 11394039].
37. Tantiphlachiva K, Rao P, Attaluri A, Rao SSC. Digital Rectal Examination Is a Useful Tool for Identifying Patients With Dyssynergia. *Am J Gastroenterol*, 2010; 8: 955-960.
38. Rao SSC, Ozturk R, Laine L. Clinical utility of diagnostic tests for constipation in adults: a systematic review. *Am J Gastroenterol*, 2005; 100(7): 1605-15. [PubMed: 15984989].
39. Van den Bosch M, Graafmans D, Nievelstein R, Beek E. Systematic assessment of constipation on plain abdominal radiographs in children. *Pediatr Radiol*, 2006; 36: 224-6. [PubMed: 16418835].
40. Cowlam S, Vinayagam R, Khan U, et al. Blinded comparison of faecal loading on plain radiography versus radio-opaque marker transit studies in the assessment of constipation. *Clin Radiol*, 2008; 63: 1326-1331. [PubMed: 18996262].
41. Brandt LJ, Prather CM, Quigley EMM, et al. Systematic review on the management of chronic constipation in North America. *Am J Gastroenterol*, 2005; 100(1): S5-S21. [PubMed: 16008641].
42. Patriquin H, Martelli H, Devroede G. Barium enema in chronic constipation: is it meaningful? *Gastroenterology*, 1978; 75: 619-22. [PubMed: 710831].
43. Gerson DE, Lewicki AM, McNeil BJ, et al. The barium enema; evidence for proper utilization. *Radiology*, 1979; 130: 297-301. [PubMed: 104358].
44. Diamant NE, Kamm MA, Wald A, Whitehead WE. AGA technical review on anorectal testing techniques. *Gastroenterology*, 1999; 116: 735-60. [PubMed: 10029632]
45. Savoye-Collet C, Koning E, Dacher J. Radiologic evaluation of pelvic floor disorders. *Gastroenterol Clin North Am*, 2008; 37: 553-67. viii. [PubMed: 18793996].
46. Fletcher JG, Busse RF, Riederer SJ, et al. Magnetic resonance imaging of anatomic and dynamic defects of the pelvic floor in defecatory disorders. *Am J Gastroenterol*, 2003; 98: 399-411. [PubMed: 12591061].
47. Bolog N, Weishaupt D. Dynamic MR imaging of outlet obstruction. *Rom J Gastroenterol*, 2005; 14: 293-302. [PubMed: 16200243].
48. Bertschinger KM, Hetzer FH, Roos JE, et al. Dynamic MR imaging of the pelvic floor performed with patient sitting in an open-magnet unit versus with patient supine in a closed-magnet unit. *Radiology*, 2002; 223: 501-8. [PubMed: 11997560].
49. Qureshi W, Adler DG, Davila RE, et al. ASGE guideline: guideline on the use of endoscopy in the management of constipation. *Gastrointest Endosc*, 2005; 62(2): 199-201.
50. Evans RC, Kamm MA, Hinton JM, Lennard-Jones JE. The normal range and a simple diagram for recording whole gut transit time. *Int J Colorectal Dis.*, 1992; 7: 15-7. [PubMed: 1588218]
51. Lin HC, Prather C, Fisher RS, et al. Measurement of gastrointestinal transit. *Dig Dis Sci.*, 2005; 50: 989-1004. [PubMed: 15986844]
52. Stivland T, Camilleri M, Vassallo M, et al. Scintigraphic measurement of regional gut transit in

- idiopathic constipation. *Am J Gastroenterol*, 1991; 101: 107–15.
53. Van der Sijp JR, Kamm MA, Nightingale JM, et al. Radioisotope determination of regional colonic transit in severe constipation: comparison with radio opaque markers. *Am J Gastroenterol*, 1993; 34: 402–8.
54. Pepin C, Ladabaum U. The yield of lower endoscopy in patients with constipation: survey of a university hospital, a public county hospital, and a Veterans Administration medical center. *Gastrointest Endosc*, 2002; 56: 325–32. [PubMed: 12196767].
55. Manabe N, Wong BS, Camilleri M, et al. Lower functional gastrointestinal disorders: evidence of abnormal colonic transit in a 287 patient cohort. *Neurogastroenterol Motil*, 2010; 22: 293–e82. [PubMed: 20025692].
56. Tobon F, Reid NC, Talbert JL, Schuster MM. Nonsurgical test for the diagnosis of Hirschsprung's disease. *Am J Gastroenterol*, 1968; 278: 188–93.
57. Bassotti G, Betti C, Imbimbo BP, et al. Colonic motor response to eating: a manometric investigation in proximal and distal portions of the viscus in man. *Am J Gastroenterol*, 1989; 84: 118–22. [PubMed: 2916518].
58. Rao SSC, Singh S. Clinical utility of colonic and anorectal manometry in chronic constipation. *J Clin Gastroenterol*, 2010; 44: 597–609. [PubMed: 20679903].
59. Rao SSC, Mudipalli RS, Stessman M, Zimmerman B. Investigation of the utility of colorectal function tests and Rome II criteria in dyssynergic defecation (Anismus). *Neurogastroenterol Motil*, 2004; 16: 589–96. [PubMed: 15500515].
60. Rao SSC. Advances in Diagnostic Assessment of Fecal Incontinence and Dyssynergic Defecation. *Clin Gastroenterol Hepatol.*, 2010; 8: 910–919. [PubMed: 20601142].
61. Jones MP, Post J, Crowell MD. High-resolution manometry in the evaluation of anorectal disorders: a simultaneous comparison with water-perfused manometry. *Am J Gastroenterol*, 2007; 102: 850–5. [PubMed: 17397410].
62. Tantiphlachiva K, Attaluri A, Rao SSC. Is high-definition manometry a comprehensive test of anal sphincter function? Comparative study with manometry and ultrasound. *Neurogastroenterol motil*, 2008; 20: 2.
63. Gladman MA, Aziz Q, Scott SM, et al. Rectal hyposensitivity: pathophysiological mechanisms. *Neurogastroenterol Motil*, 2009; 21: 508–16. [PubMed: 19077147].
64. Rao SS, Hatfield R, Soffer E, et al. Manometric tests of anorectal function in healthy adults. *Am J Gastroenterol*, 1999; 94: 773–83. [PubMed: 10086665].
65. Gladman MA, Scott SM, Chan CLH, et al. Rectal hyposensitivity: prevalence and clinical impact in patients with intractable constipation and fecal incontinence. *Dis Colon Rectum*, 2003; 46: 238–46. [PubMed: 12576898].
66. Gladman MA, Lunniss PJ, Scott SM, Swash M. Rectal hyposensitivity. *Am J Gastroenterol*, 2006; 101: 1140–51. [PubMed: 16696790].
67. Delvaux MM. Visceral sensitivity in explaining functional bowel disorders: from concepts to clinical practice. *Acta Gastroenterol Belg.*, 2001; 64: 272–5. [PubMed: 11680047].
68. Jafri S, Pasricha PJ. Agents used for diarrhea, constipation, and inflammatory bowel disease; agents used for biliary and pancreatic disease. In: Hardman JG, Limbird LE, Gilman AG. *Goodman & Gilman's the pharmacological basis of therapeutics*. 10th ed. New York: McGraw-Hill, 2002; 1037–1047.
69. McRorie JW, Daggy BP, Morel JG, et al. A clinical study comparing stool softening and laxative efficacy of psyllium vs. docusate sodium. *Gastroenterology*, 1997; 112(Suppl): A787.
70. Anonymous. Laxative drug products for over the counter human use: proposed amendment to the tentative final monograph federal register. Proposed Rule. August 5, 2003; 68(150).
71. Lembo A, Camilleri M. Chronic constipation. *N Engl J Med*, 2003; 349: 1360–1368.
72. Polyethylene glycol 3350, NF powder for solution; prescribing information. Available at [http://www.drugs.com/PDR/MiraLax\\_Powder\\_for\\_Oral\\_Solution.html](http://www.drugs.com/PDR/MiraLax_Powder_for_Oral_Solution.html).
73. Tedesco FJ, Dipiro JT. Laxative use in constipation. *Am J Gastroenterol*, 1985; 80: 303–309.
74. DiPalma JA, DeRidder PH, Orlando RC, et al. A randomized, placebo-controlled multicenter study of the safety and efficacy of a new polyethylene glycol laxative. *Am J Gastroenterol*, 2000; 95: 446–450.
75. Anonymous. Safety of stool softeners. *Med Lett*, 1977; 19: 45–46.
76. Donowitz M. Current concepts of laxative action: mechanisms by which laxatives increase stool water. *Clin Gastroenterol*, 1979; 1: 777–784.
77. Anonymous. Laxatives. Replacing danthron. *Drug Ther Bull*, 1988; 26: 53–56.
78. Johanson, JF, Wald A, Tougas G. Effect of tegaserod in chronic constipation: a randomized double-blind, controlled trial. *Clin Gastroenterol Hepatol*, 2004; 2: 796–805.
79. Rivkin A. Tegaserod maleate in the treatment of irritable syndrome: A clinical review. *Clin Ther*, 2003; 25: 1952–1971.
80. Brinker AD, Mackney CA, Prizont R. Tegaserod and ischemic colitis. *N Engl J Med*, 2004; 351: 1361–1364.
81. Hedner T, Cassieto J. Opioids and opioid receptors in peripheral tissues. *Scand J Gastroenterol*, 1987; 130(Suppl): 36–40.
82. Kreek MJ, Schaefer RA, Hahn EF, et al. Naloxone, a specific opioid antagonist, reverses chronic idiopathic constipation. *Lancet*, 1983; 1: 261–262.

83. Kaufman PN, Krevsky B, Malmud LS, et al. Role of opiate receptors in the regulation of colonic transit. *Gastroenterology*, 1988; 94: 1351–1356.
84. Baron JA, Jessen LM, Colaizzi JL, et al. Cisapride: a gastrointestinal prokinetic drug. *Ann Pharmacother*, 1994; 28: 488–500.
85. Anonymous. FDA updates warnings for cisapride. FDA Talk Paper T00-6; January 24, 2000.
86. Anonymous. Limited-access protocol for the use of cisapride in the treatment of gastroesophageal reflux disease and other gastrointestinal motility disorders. Protocol No. CIS-USA-154. Janssen Pharmaceutica.
87. Muller-Lissner SA. Treatment of chronic constipation with cisapride and placebo. *Gut*, 1987; 28: 1033–1038.
88. Verheyen K, Vervaeke M, Demyttenaere P, et al. Double-blind comparison of two cisapride dosage regimens with placebo in the treatment of functional constipation. *Curr Ther Res.*, 1987; 41: 978–985.
89. Anonymous. Psyllium health claims: final rule. Federal Register Feb 18, 1998; 63: 8103.
90. Kinnunen O. Study of constipation in a geriatric hospital, day hospital, old people's home and at home. *Aging*, 1991; 3: 161–170.
91. Everhart JE, Liang V, Johannes RS, et al. A longitudinal survey of self-reported bowel habits in the United States. *Dig Dis Sci.*, 1989; 34: 1153–1162.
92. Sandler RS, Jordan MC, Shelton BJ. Demographic and dietary determinants of constipation in the US population. *Am J Public Health*, 1990; 80: 185–189.
93. Remes-Troche JM, Rao SSC. Diagnostic testing in patients with chronic constipation. *Curr Gastroenterol Rep*, 2006; 8: 416–24. [PubMed: 16968610].
94. Rao SS. Constipation: evaluation and treatment of colonic and anorectal motility disorders. *Gastroenterol Clin North Am*, 2007; 36: 687–711.
95. Rao SS. Constipation: evaluation and treatment. *Gastroenterol Clin North Am*, 2003; 32: 659–683. [PubMed: 12858610].
96. Shafik A, Shafik AA, el-Sibai O, Ahmed I. Colonic pacing in patients with constipation due to colonic inertia. *Med Sci Monitor*, 2003; 9: CR243–CR248.
97. Kenefick NJ, Vaizey CJ, Cohen CRG, Nicholls RJ, Kamm MA. Double-blind placebo-controlled crossover study of sacral nerve stimulation for idiopathic constipation. *Br J Surg.*, 2002; 89: 1570–1571. [PubMed: 12445068]
98. Chang HS, Myung SJ, Yang SK, et al. Effect of electrical stimulation in constipated patients with impaired rectal sensation. *Int J Colorectal Dis.*, 2003; 18: 433–438. [PubMed: 12677456]
99. Drossman DA, Toner BB, Whitehead WE, et al. Cognitive-behavioral therapy versus education and desipramine versus placebo for moderate to severe functional bowel disorders. *Gastroenterology*, 2003; 125: 19–31. [PubMed: 12851867]
100. Heymen S, Wexner SD, Vickers D, Noguerras JJ, Weiss EG, Pikarsky AJ. Prospective, randomized trial comparing four biofeedback techniques for patients with constipation. *Dis Colon Rectum*, 1999; 42: 1388–1393. [PubMed: 10566525].
101. Rao SS, Seaton K, Miller M et al, Randomised Controlled trial of biofeedback, Sham feedback and standard therapy for dyssnergic defecation. *Clinical Gastroenterology and Hepatology*, 2007; 5: 331–8.
102. Soares NC, Ford AC. Systematic review: the effects of fibre in the management of chronic idiopathic constipation. *Aliment Pharmacol Ther*, 2011; 33(8): 895–901.
103. Nyberg C, Hendel J, Nielsen OH. The safety of osmotically acting cathartics in colonic cleansing. *Nat Rev Gastroenterol Hepatol*, 2010; 7(10): 557–564.
104. Xing, J.H. and Soffer, E.E. Effects of laxatives. *Dis Colon Rectum*, 2001; 44: 1201–1209.
105. Ramkumar D, Rao SS. Efficacy and safety of traditional medical therapies for chronic constipation: systematic review. *Am J Gastroenterol*, 2005; 100(4): 936–971.
106. Castle SC, Cantrell M, Israel DS, Samuelson MJ. Constipation prevention: empiric use of stool softeners questioned. *Geriatrics*, 1991; 46(11): 84–86.
107. Leung FW, Rao SS. Approach to fecal incontinence and constipation in older hospitalized patients. *Hosp Pract (1995)*, 2011; 39(1): 97–104.
108. Sédaba B, Azanza JR, Campanero MA, Garcia-Quetglas E, Muñoz MJ, Marco S. Effects of a 250-mL enema containing sodium phosphate on electrolyte concentrations in healthy volunteers: An open-label, randomized, controlled, two-period, crossover clinical trial. *Curr Ther Res Clin Exp*, 2006; 67(5): 334–349.
109. Schmelzer M, Schiller LR, Meyer R, Rugari SM, Case P. Safety and effectiveness of large-volume enema solutions. *Appl Nurs Res*. 2004; 17(4): 265–274.
110. Beattie, D.T. and Smith, J.A. Serotonin pharmacology in the gastrointestinal tract: A review. *Naunyn Schmiedebergs Arch Pharmacol*, 2008; 377: 181203.
111. Camilleri M, Deiteren A. Prucalopride for constipation. *Expert Opin Pharmacother* 2010; 11: 451–61.
112. Locke GR, III, Pemberton JH, Phillips SF. AGA technical review on constipation. *Gastroenterology*, 2000; 119: 1766–1778. [PubMed: 11113099].
113. Degen, L., Matzinger, D., Merz, M., AppelDingemanse, S., Osborne, S., Luchinger, S. et al. Tegaserod, a 5-HT<sub>4</sub> receptor partial agonist, accelerates gastric emptying and gastrointestinal transit in healthy male subjects. *Aliment Pharmacol Ther*, 2001; 15: 1745–1751.
114. Prather, C.M., Camilleri, M., Zinsmeister, A.R., McKinzie, S. and Thomforde, G. Tegaserod accelerates orocecal transit in patients with constipation-predominant irritable bowel syndrome. *Gastroenterology*, 2000; 118: 463468.

115. Quigley EM, Vandeplassche L, Kerstens R *et al.* Clinical trial: the efficacy, impact on quality of life, and safety and tolerability of prucalopride in severe chronic constipation a 12-week, randomized, double-blind, placebo-controlled study. *Aliment Pharmacol Ther*, 2009; 29: 315–28.
116. Parkman HP, Rao SS, Reynolds JC *et al.* Functional Constipation Study Investigators. Neurotrophin-3 improves functional constipation. *Am J Gastroenterol*, 2003; 98: 1338–47.
117. George, A.M., Meyers, N.L. and Hickling, R.I. Clinical trial: Renzapride therapy for constipation predominant irritable bowel syndrome multicentre, randomized, placebo-controlled, double-blind study in primary healthcare setting. *Aliment Pharmacol Ther*, 2008; 27: 830837.
118. Scarpellini, E. and Tack, J. Renzapride: A new drug for the treatment of constipation in the irritable bowel syndrome. *Expert Opin Investig Drugs*, 2008; 17: 16631670.
119. Kim, H.S., Choi, E.J. and Park, H. The effect of mosapride citrate on proximal and distal colonic motor function in the guinea-pig *in vitro*. *Neurogastroenterol Motil*, 2008; 20: 169176.
120. Drossman DA, Chey WD, Johanson JF, *et al.* Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome – results of two randomized, placebo-controlled studies. *Aliment Pharmacol Ther*, 2009; 29(3): 329–341.
121. Johanson JF, Drossman DA, Panas R, Wahle A, Ueno R. Clinical trial: phase 2 study of lubiprostone for irritable bowel syndrome with constipation. *Aliment Pharmacol Ther.*, 2008; 27(8): 685–696.
122. Johanson JF, Morton D, Geenen J, Ueno R. Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of lubiprostone, a locally-acting type-2 chloride channel activator, in patients with chronic constipation. *Am J Gastroenterol*, 2008; 103(1): 170–177.
123. Bharucha AE, Linden DR. Linaclotide – a secretagogue and antihyperalgesic agent – what next? *Neurogastroenterol Motil*, 2010; 22(3): 227–231.
124. Vazquez Roque M, Camilleri M. Linaclotide, a synthetic guanylate cyclase C agonist, for the treatment of functional gastrointestinal disorders associated with constipation. *Expert Rev Gastroenterol Hepatol*, 2011; 5(3): 301–310.
125. Feighner SD, Tan CP, McKee KK *et al.* Receptor for motilin identified in the human gastrointestinal system. *Science*, 1999; 284: 2184–8.
126. Peters TL. GM-611 (Chugai Pharmaceutical). *Curr Opin Investig Drugs* 2001; 2: 555.
127. Emmanuel AV, Tack J, Quigley EM *et al.* Pharmacological management of constipation. *Neurogastroenterol Motil*, 2009; 21: 41–54.
128. Webster, L., Jansen, J.P., Peppin, J., Lasko, B., Irving, G., Morlion, B. *et al.* (2008) Alvimopan, a peripherally acting mu-opioid receptor (PAM-OR) antagonist for the treatment of opioid-induced bowel dysfunction: results from a randomized, double-blind, placebo-controlled, dose-finding study in subjects taking opioids for chronic non-cancer pain. *Pain*, 137: 428440.
129. Kelleher, D., Johanson, J., Pobiner, B., Carter, E. and Dukes, G. Alvimopan, a peripherally acting mu-opioid receptor (PAM-OR) antagonist a study in patients with chronic idiopathic constipation (CIC) not taking opioid medication. *Am J Gastroenterol*, 2006; 101: S480.
130. Thomas, J., Karver, S., Cooney, G.A., Chamberlain, B.H., Watt, C.K., Slatkin, N.E. *et al.* Methylnaltrexone for opioid-induced constipation in advanced illness. *N Engl J Med*, 2008; 358: 23322343.