

**Defining Constipation**

While doctors tend to equate constipation with reduced stool frequency, patients endorse a wide variety of clinical complaints. The Rome III criteria embrace the diversity of symptoms experienced by patients with chronic constipation (Longstreth et al., 2006):

**Rome III Criteria for the Diagnosis of Functional Constipation**

Two or more of the following six features must be present*:

- Straining during at least 25% of defecations
- Lumpy or hard stools in at least 25% of defecations
- Sensation of incomplete evacuation for at least 25% of defecations
- Sensation of anorectal obstruction/blockage for at least 25% of defecations
- Manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
- Fewer than three defecations/wk.

*Criteria fulfilled for the previous three months with symptom onset at least six months prior to diagnosis. In addition, loose stools should rarely be present without the use of laxatives, abdominal pain is not required, and there should be insufficient criteria for irritable bowel syndrome. These criteria may not apply when the patient is taking laxatives.

It is important to note that in a recently reported study there was a large overlap between functional/chronic constipation and IBS-C and patients frequently transitioned between these diagnoses over time (Wong et al., 2010). This study reinforces clinical experience which suggests that the lines between IBS-C and CC are often blurred – suggesting that IBS-C and CC represent a spectrum of disease rather than 2 separate and distinct clinical entities.

**Epidemiology and Burden of Illness**

Constipation is a common problem in the U.S. which for some, can be intermittent and requires little to no intervention, while for others, it can be life altering with tangible negative effects on a person’s personal and professional lives. The prevalence of constipation ranges from 2-28% in Western countries depending upon the population demographics and the definition of constipation. The prevalence of self-reported constipation is higher in women than men (Pooled odds ratio based upon 45 studies = 2.22, 95% CI: 1.87-2.62) and in older adults (Pooled OR based upon 3 studies for persons >60 years of age = 1.41 (1.17-1.70)) (Suáres et al., *Am J Gastroenterol* 2011; Gallegos-Orozco et al., 2012).

Constipation results in more than 2.5 million physician visits, 92,000 hospitalizations, and several hundred million dollars of laxative sales/year in the United States. In an analysis of physician visits for constipation in the United States between 1958 and 1986:

- 31% of patients were seen by general and family practitioners
- 20% were seen by an internist
- 9% visited a surgeon
- 9% consulted an obstetrician-gynecologist
- 4% of patients were seen by a gastroenterologist

**Pathophysiology of Chronic Functional Constipation**

Functional constipation can be divided into three broad categories with the following clinical features (Schiller et al., 2001; Mertz et al., 1999).

Normal-transit Constipation – 59-71% of patients with functional constipation – despite their reports of constipation, careful physiological testing with manometry and transit testing are normal. Slow-transit constipation: 11-13% of patients with functional constipation. Common in young women and with associated disordered colonic function which leads to hard, small stools. Though it is widely held that reduced stool frequency identifies patients with slow transit constipation, the literature does not fully support this dogma. On the other hand, there is literature to support a correlation between hard stool consistency and slow transit constipation (Saad R et al., 2010).

The Bristol Stool Form Scale is a validated means of describing stool form which can provide some insights into whether colon transit is fast or slow (Figure 1).

Dyssynergic Defecation – 13-28% of patients with functional constipation. Normal defecation requires a series of coordinated physiological actions which allow the passage of stool from the rectum: contraction of the abdominal wall muscles, relaxation of the puborectalis muscle, straightening of the anorectal angle, and relaxation of the external anal sphincter.
Failure of one or more of these actions can lead to defecatory dysfunction or dyssynergic defecation.

Structural Causes of Chronic Constipation – Rectocele, enterocele, inususception, and rectal prolapse can also cause difficult defecation and can be detected with a detailed digital rectal examination or imaging studies such as defecography or dynamic MRI.

Clinical Assessment
It is important to determine what the patient means when reporting constipation. It is valuable to assess the duration, frequency and severity of constipation symptoms as well as associated complaints such as abdominal pain, discomfort and distension. The history should include an assessment of stool consistency, stool size, and degree of straining during defecation and whether or not bleeding has been seen by the patient. A few clinical features can help distinguish between CC patients with slow colonic transit and dyssynergic defecation. Features of the history which should prompt consideration of dyssynergic defecation include a sensation of incomplete evacuation, excessive straining even when stools are loose, the need for digital manoeuvres to facilitate defecation and failure to respond to traditional laxative therapies.

Other areas to cover in the clinical assessment include:
- Dietary history – daily fiber and fluid intake
- Past medical history – particularly obstetric and surgical histories
- Social history – behavioural background, depression etc.
- Physical examination
- Rectal examination

The presence of warning symptoms or signs, such as unintentional weight loss, rectal bleeding, and family history of colon cancer or inflammatory bowel disease, should be elicited. A long duration of symptoms that have been refractory to conservative measures is suggestive of a functional colorectal disorder. By contrast, the new onset of constipation, particularly in patients aged 50 years and older, may indicate an “organic” disease process and thus, should prompt early evaluation with colonoscopy. The finding of unexplained iron deficiency anaemia should also prompt early evaluation with colonoscopy and in selected cases, upper endoscopy.

More detailed physiological testing to rule out dyssynergic defecation (anorectal manometry, balloon expulsion testing, defecography or dynamic MRI) or slow transit constipation (radio-opaque marker study or wireless motility/pH capsule testing) is typically reserved for patients with constipation that proves refractory to dietary and lifestyle recommendations and empiric laxative therapies.

Treatments for Chronic Constipation

Lifestyle Modifications
Commonly employed lifestyle modifications include increased intake of dietary fiber, fluid intake, and exercise. A review of studies assessing dietary fiber and fluid intake found no differences between those with constipation and controls (Müller-Lissner et al., 2005). However, epidemiologic studies suggest an inverse relationship between physical activity and constipation (Brown et al., 2000; Kinnunen, 1991; Donald et al., 1985). Further, several marginal quality clinical trials suggest that increased dietary fiber & fluid intake along with physical activity may offer benefits to those with constipation symptoms (Anti et al., 1998; Sturtzel et al., 2008; Graham et al., 1982; De Schryver et al., 2005; Karam et al., 1994).

Pharmacological Treatment
Medications for chronic constipation can be categorized into bulking agents, stool softeners and emollients, osmotic agents, stimulants, prosecretory agents, prokinetics, and bile acid modulators.

Bulking Agents
Bulking agents, which include a variety of natural and synthetic fiber supplements, treat constipation by increasing the water content of stool, increasing biomass and secondary effects on peristalsis. Fiber supplements also exert effects on the gut microbiome which may affect bowel function. Soluble fiber supplements include psyllium (ispaghula husks), calcium
polyacryarbphil, methylcellulose, inulin and wheat dextrin. Insoluble agents include bran, flax seed, rye and variety of other non-digestible seeds and vegetables matter. Psyllium is the best studied fiber supplement. In a number of randomized, controlled trials (RCTs), this agent has demonstrated superiority over placebo for global constipation symptoms (Fenn et al., 1986), increasing stool frequency (Ashraf et al., 1995), and normalizing defecation (Nunes et al., 2005). Soluble fiber supplements appear more effective and better tolerated than insoluble fiber products (Suares & Ford, *Aliment Pharmacol Ther* 2011; Brandt et al., 2005; Ramkumar et al., 2005). Adequate fluid intake is required for bulk forming agents to work properly. Bulking agents should be started a low doses and gradually titrated to desired effect. Common side effects include dose dependent bloating, flatulence and abdominal distension.

Stool Softeners

Dioctyl sulphosuccinate is the most commonly prescribed stool softener, commercially available as either ducosate sodium or ducosate calcium. Being an anionic detergent, ducosate is thought to work by lowering the surface tension of stool allowing water to penetrate. Four RCTs have been published, three comparing ducosate to placebo with inconsistent findings (Castle et al., 1991; Fain et al., 1978; Hyland et al., 1968) and one comparing ducosate to psyllium with psyllium proving superior to ducosate at increasing stool frequency (McRorie et al., 1998). Although considered safe with few side effects, stool softeners are of arguable effectiveness in treating the symptoms of chronic constipation. Hence, these agents are typically most useful for patients with mild or infrequent constipation.

Osmotic Agents

Agents such as polyethylene glycol (PEG), lactulose, sorbitol, and magnesium hydroxide create a luminal osmotic load which results in net intestinal water secretion with consequent effects on stool consistency, fecal biomass, and colonic transit. PEG 3350 has been studied in multiple high quality RCTs demonstrating significant benefits over placebo for stool frequency and consistency in patients with chronic constipation. PEG has also been found to be more effective and better tolerated than lactulose in patients with chronic constipation (Lee-Robichaud et al., 2010). The usual starting dose of PEG 3350 is 17 grams in juice or water per day. The dose can be titrated upward to the desired clinical effect. At standard doses, PEG is generally well tolerated. The most common side effects include nausea, flatulence, and diarrhea.

Lactulose is a nonabsorbed, synthetic carbohydrate which is fermented by colonic bacteria to gases and short chain fatty acids which create an osmotic load. Lactulose has proven more efficacious for the treatment of chronic constipation in several RCTs (Bass et al., 1981; Sanders et al., 1978; Wesselius-De Casparis et al., 1968). The usual dose of lactulose is 10-40 grams/day. Lactulose can cause dose dependent side effects including bloating, flatulence, cramping and diarrhea.

The use of magnesium hydroxide for chronic constipation is anecdotal as no placebo-controlled RCTs have been published. Although generally safe and likely effective in mild constipation symptoms, care must be exercised with its use in chronic renal disease given the risk of hypermagnesemia.

Stimulants

A variety of stimulant laxatives are in use including the anthraquinones (senna, cascara, aloe) and diphenylmethanes (bisacodyl, sodium picosulfate). Their primary effect on the colon is the stimulation of peristalsis either by direct irritation of the colonic wall or stimulation of sensory nerves on the colonic mucosa. Some stimulants are also believed to inhibit water absorption in the colon. Their onset is rapid, often times stimulating defecation within 6-12 hours of dosing. There are 2 recent large, high quality RCTs demonstrating superiority of sodium picosulfate (Mueller-Lissner et al., *Am J Gastroenterol* 2010) and bisacodyl (Kamm et al., 2011) over placebo in the treatment of CC. The use of anthraquinones like cascara and senna is largely based on anecdotal evidence as no placebo-controlled RCTs have been published in the treatment of CC. Overall, the safety of long term stimulant laxative use is unknown. Side effects including diarrhea, cramping, bloating and nausea can be limiting.

Some have argued that prostaglandin analogs like misoprostol exert stimulant and prosecretory effects in the GI tract. In a placebo controlled trial, misoprostol has demonstrated effects on transit time, bowel frequency and stool weight (Soffer et al., 1994). However, misoprostol often causes dose dependent side effects including nausea, bloating and abdominal cramping and carries an FDA pregnancy category X.

Newer Agents for Treating Chronic Constipation

Prosecretory Agents

Lubiprostone – Lubiprostone is an oral bicyclic fatty acid derivative of prostaglandin E1 that selectively activates the type-2 chloride channel located on the apical membrane of human intestinal epithelial cells. (Cuppoletti et al., 2004) thereby increasing chloride-rich fluid secretion into the GI tract. Active intestinal chloride secretion increases passive paracellular movement of sodium ions and water and a resultant net increase in intestinal electrolytes and water, (Cuppoletti et al., 2004) softening the feces and increasing stool biomass with attendant secondary effects on peristalsis and transit (Lang et al., 2008; Owen, 2008).
In two phase III randomized, placebo-controlled trials, lubiprostone, 24µg twice daily, increased the number of spontaneous bowel movements in patients with chronic constipation. Lubiprostone improved consistency, and reduced overall severity of symptoms (Saad et al., 2008). An open label extension trial found that lubiprostone provided similar efficacy and safety in patients with chronic constipation for up to 48 weeks (Lembo et al., Dig Dis Sci 2011). Lubiprostone, 24µg twice daily, was approved by the FDA in 2006 for the treatment of men and women with chronic constipation. Subsequently, a lower dose of 8 mcg twice daily has also been shown to be effective and has been approved for the treatment of women with IBS-C (Drossman et al., 2009). The most common side effects were nausea, headache, and diarrhea. Nausea is a dose dependent side effect of lubiprostone. Roughly 30% of patients starting the higher dose of 24 mcg bid will report some degree of nausea. In contrast, only 8% of patients taking the lower dose of 8 mcg bid reported nausea. Most nausea associated with lubiprostone is mild and transient. The incidence of nausea can be minimized by dosing this medication with food.

**Linaclotide** – Linaclotide is a 14-amino acid synthetic peptide that selectively binds to and activates the guanylate cyclase C receptor on the luminal surface of the intestinal enterocyte resulting in the production of cGMP (Bryant et al., 2010). Intracellular cGMP results in activation of the cystic fibrosis transmembrane regulator (CFTR) leading to increased active secretion of chloride and passive paracellular movement of sodium and water into the intestinal lumen leading to improvements in stool frequency, consistency and intestinal transit. Based upon studies in animals, it has been suggested that extracellular cGMP may reduce visceral hyperalgesia by inhibiting firing of visceral afferent nerve fibers (Bhuracha et al., 2010).

Two randomized, 12-week multi-center, double-blind, placebo-controlled trials which enrolled 1276 patients with chronic constipation have been reported (Lembo et al., N Engl J Med 2011). Patients received either linaclotide 145µg or 290µg or placebo once daily for 12 weeks. The primary endpoint was three or more complete spontaneous bowel movements (CSBMs) per week and an increase of one, or more, CSBMs from baseline during at least 9 of the 12 study weeks. Both doses of linaclotide proved superior to placebo for this rigorous endpoint (p<0.01). The improvements for all of the prespecified secondary endpoints were significantly greater with linaclotide vs. placebo. The incidence of adverse events was similar among all study groups, with the exception of diarrhea, which led to discontinuation in 4.2% of patients at both doses of linaclotide. Linaclotide is currently under review by the US FDA as a treatment for patients with CC and IBS-C.

**Prokinetics**

**Prucalopride** – Prucalopride, a full 5-HT4 agonist, is a benzofuran derivative that accelerates colonic transit in healthy humans and in patients with functional constipation (Tack, 2009). Three large, 12-week, randomized, placebo-controlled phase III trials of similar design that evaluated the efficacy and safety of prucalopride 2 mg or 4 mg once daily versus placebo in patients with chronic constipation have been published (Tack et al., 2011). When the results of the phase III studies (N = 1924) were combined, the percentage of patients with an average of at least three CSBMs/ week over the 12-week treatment period was 23.6%, 24.7%, and 11.3% for prucalopride 2 mg, prucalopride 4 mg, and placebo, respectively (P = 0.005). All other secondary efficacy endpoints, including patients’ satisfaction with their bowel function and treatment and their perception of the severity of their constipation symptoms, were improved significantly by prucalopride compared to placebo.

The most frequent adverse effects with prucalopride were headaches, nausea, and diarrhea which tended to occur soon after initiation and to be transient. No cardiovascular side effects were observed, nor were any electrocardiographic abnormalities reported. Unlike cisapride and tegaserod, prucalopride does not interact with hERG potassium or 5HT1b channels—both postulated to play a role in potential adverse cardiovascular outcomes (Tack J et al., 2012). This agent is available for the treatment of women with CC in Canada and many countries in Europe but not in the U.S.

**Bile Acid Modulators**

Increasing colonic bile acids might offer a novel strategy to improve chronic constipation. Bile acids can alter intestinal and colonic motility and secretion. Recent work has investigated specific bile acid analogs or drugs which alter bile acid reabsorption as novel therapies for IBS-C. The results from a trial which evaluated the effects of chenodeoxycholic acid (CDCA) on colonic transit and clinical parameters in female IBS-C patients were recently reported. CDCA significantly accelerated overall colonic transit and improved clinical outcomes including stool frequency, stool consistency and facilitated the passage of stool. The most common side effect with CDCA was abdominal cramping/pain which was reported by over 40% of patients compared with none in the placebo group (Rao et al., 2010). Further studies to clarify whether lower doses of CDCA might offer benefits to constipation without worsening abdominal pain in IBS-C patients are eagerly awaited.

A3309 is a novel small molecule which inhibits ileal bile acid transporters resulting in greater delivery of bile acids to the right colon with consequent effects on motility, transit and secretion. A3309 has been shown to accelerate colon transit...
in animals and humans (Maneerattanaporn et al., 2011). A recent phase IIb clinical trial in 190 CC patients demonstrated that A3309 at doses of 10 and 15 mg per day, but not 5 mg per day significantly increased the frequency of spontaneous bowel movements (SBM) after 1 week (primary endpoint) and over the entire 8 week randomization period. A3309 also reduced the time to first SBM and complete SBM, improved stool consistency and decreased straining compared to placebo (Chey et al., 2011). An interesting incremental clinical benefit of A3309 was that it decreased serum lipid levels. The most common side effects with A3309 were abdominal pain/cramping, bloating, diarrhea or gas were reported more commonly in the hemp seed than placebo group. Side effects including increasing weekly CSBM rates, straining, and need for rescue therapy (Cheng et al., 2011). Safety data were not reported in this trial. A third randomized, double-blind placebo-controlled phase IIb trial of a3309, a bile acid transporter inhibitor, for chronic idiopathic constipation. Am J Gastroenterol 2011;106:1803-12.

REFERENCES


CAM Therapies for Chronic Constipation

Several recent studies have evaluated CAM therapies in patients with CC. Attaluri and colleagues recently reported a single-blind randomized, cross-over trial in 40 constipated patients which evaluated the benefits of prunes (50 grams or ~ 6 prunes bid) or psyllium (11 grams bid) for 3 weeks. The primary outcome of mean complete spontaneous bowel movements per week as well as stool consistency improved to a greater degree with the prunes compared to psyllium (Attaluri et al., 2011). Palatability and tolerability were similar between groups. In another study of 20 constipated patients, artichokes laced with the probiotic Lactobacillus paracasei IMPC 2.1 (2x1010 CFU daily) for 15 days were more effective than ordinary artichokes at improving stool consistency and overall constipation symptoms (Riezzo et al., 2012). Safety data were not reported in this trial. A third randomized, double-blind trial from Hong Kong found that hemp seed pill at a dose of 7.5 grams bid for 8 weeks was more effective than placebo at increasing weekly CSBM rates, straining, and need for rescue therapy (Cheng et al., 2011). Side effects including abdominal pain/cramping, bloating, diarrhea or gas were reported more commonly in the hemp seed than placebo group (13.3% vs. 3.3%).

REFERENCES


