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Constipation Treatment
A Review

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Constipation seems like a ubiquitous condition, something people of all ages experience and many complain about. It is often associated with infrequent bowel movements; however, in reality, constipation has a wide array of symptoms including hard stools, feeling of incomplete evacuation, abdominal discomfort, bloating, distension, excessive straining, sensation of anorectal blockage, or need for manual maneuvers during defecation. Determining the cause of the constipation is essential to ensure the appropriate treatment approach. The patient evaluation consists of collecting subjective and objective information. Constipation has many different treatment options, with many treatments available as over-the-counter products as well as prescription medications. For most types of constipation, nonpharmacological and dietary changes are typically recommended as first-line treatment. Prescription medications are available with indications for specific types of constipation. Both nonpharmacological and pharmacological interventions have a key role, and follow-up is important to ensure treatment is appropriate and adequate.

Constipation seems like a ubiquitous condition, something people of all ages experience and many complain about. It is often associated with infrequent bowel movements; however, in reality, constipation has a wide array of symptoms including hard stools, feeling of incomplete evacuation, abdominal discomfort, bloating, distension, excessive straining, sensation of anorectal blockage, or need for manual maneuvers during defecation. Constipation is categorized into 3 subgroups based on the assessment of colonic transit and anorectal function. Determining the type of constipation is very important as it ensures how it should be further evaluated and treated.

Determining the cause of the constipation is essential to ensure the appropriate treatment approach. The patient evaluation consists of collecting subjective and objective information. This includes learning what symptoms the patient is experiencing, medications patient may be taking, and exploring red flag symptoms such as rectal bleeding or sudden weight loss. Learning what the patient has done so far to address the constipation is key as well. In addition, to further explore symptoms, patients may use the Bristol Stool Chart to document their stool history or bowel movement diaries, which are available on paper as well as apps. Depending on the findings, patients may be referred for a digital rectal examination and diagnostic tests such as a colonoscopy. In addition, guidelines recommend addressing the biopsychosocial components of constipation.

General Treatment Approach

Constipation has many different treatment options, with many treatments available as over-the-counter (OTC) products as well as prescription medications. In some kinds such as medication induced, a risk versus benefit analysis will be considered to determine whether the medication causing constipation can be changed to avoid further constipation or whether the constipation is an unfortunate side effect of the continued medication. Common medication classes that may cause constipation include anticholinergics, antidepressants, antihistamines, calcium channel blockers, diuretics, iron supplements, nonsteroidal anti-inflammatory drugs, and opioids. For most types of constipation, nonpharmacological and dietary changes are typically recommended as first-line treatment. This includes increasing fiber with food if possible and with bulk-forming agents as necessary, physical activity, hydration, creating routines for bowel movements, and considering way to use a toilet closer to the floor or elevating the feet.

First-Line Agents to Treat Constipation—Generally

Bulk Forming

Common bulk-forming agents include psyllium, methylcellulose, and wheat dextrin. These agents work

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by absorbing water and increasing fecal mass, which will increase the frequency and soften the stool. By doing this, it will make it easier for a patient to have a bowel movement. It is imperative to start adding fiber slowly and working up to the recommended 25–30 g/day because, at first, fiber can cause bloating, distension, flatulence, and cramping. By incorporating fiber into the diet slowly, these side effects can be avoided or mitigated.

Surfactants

Surfactants are another option for treatment commonly used by patients, but evidence is lacking for the use of surfactants in patients with chronic constipation. An example of a surfactant is docusate sodium. If used, this medication class works to lower the surface tension of stool, making it easier for water to enter the stool. Surfactant medications present minimal side effects but may not be as efficacious as other treatment options.

Stimulant

Stimulant laxatives work via alteration of electrolyte transport by the intestinal mucosa and increase intestinal motor activity. Stimulant laxatives include bisacodyl and senna products. Studies have shown that stimulant laxatives are more efficacious than placebo in the treatment of constipation by having more complete spontaneous bowel movements and an increase in quality-of-life scores. Long-term use of stimulant laxatives may cause electrolyte imbalances, so long-term use must be discussed with a healthcare provider (Brenner, 2012).

Osmotic

Osmotic agents produce an osmotic effect in the colon with resultant distension that promotes peristalsis. This class of medications causes water retention in the stool and increases stool frequency. This class of medications includes polyethylene glycol (PEG), lactulose, milk of magnesia (MOM), and magnesium citrate. Polyethylene glycol is considered superior to other medications in this class, and the OTC dose is 17 g dissolved in 4–8 oz of any type of liquid one-time daily (Wald, 2019a).

Laxatives

Laxatives come in many different forms such as powder, tablet, liquid, and suppositories. Suppositories are mainly used for defecatory dysfunction and work to liquefy stools by altering the water and electrolyte secretion, producing intestinal fluid accumulation and laxation to aid in bowel movements. Suppositories work locally and can be used daily to aid in bowel movements. Laxatives may be indicated in people 6 years and older; however, it is recommended that, especially when used in pediatric cases, people with certain chronic conditions and people inappropriately using laxatives chronically be further evaluated. Any person 6 years and older can use suppositories if needed.

Opioid-Induced Constipation

Opioid-induced constipation (OIC) is a common side effect of patients using opioid pain medications for their moderate to severe pain. The prevalence of constipation is estimated to be around 25% but can be as high as 64% in some patients (Veiga et al., 2018). To diagnose a patient with OIC is difficult as there is not a clear diagnosis for the condition. When making the diagnosis, providers must consider many factors such as history of constipation, physical examinations including a rectal examination, diagnostic tests, and patient medication therapy. Other things to consider are a change in opioid therapy, increase in dose of therapy, or initiation of new opioid therapy that could cause new or worsening symptoms of constipation. To make a diagnosis of OIC, two or more of the following symptoms must be present:

1. Straining during more than one fourth of defecations;
2. Lumpy or hard stools in more than one fourth of defecations;
3. Sensation of incomplete evacuation in more than one fourth of defecations;
4. Sensation of anorectal obstruction/blockage in more than one fourth of defecations;
5. Manual maneuvers to facilitate more than one fourth of defecations (e.g., digital evacuation, support of the pelvic floor); and
6. Fewer than three spontaneous bowel movements per week.

For patients who may be starting on long-term opioid therapy or believe they are at risk for developing constipation, there are ways to try to prevent constipation from occurring. Risk factors for developing OIC include increased age, immobility, poor diet, hypercalcemia, and others (Portenoy et al., 2019). If a patient has risk factors and/or is on long-term opioid therapy, an option is to use prophylactic laxative therapy. Other options include increased fluid intake, increased mobility, and/or a high-fiber diet to decrease the chances of constipation. All options are viable and should be chosen on the basis of patient-specific risk factors and patient preference.

Many different treatment options exist for OIC depending on the severity. For most patients, first-line therapy will be laxative therapy. Options for laxative therapy have been discussed earlier and are listed in Table 1. For refractory OIC, which is when a patient does not respond to first-line laxative therapy, prescription treatment should be considered. A simple and validated tool used when evaluating constipation is the Bowel Function Index, and prescription therapy is generally considered when a score of 30 or more points is recorded. Prescription therapy for OIC provides different options including peripherally acting mu-opioid receptor antagonists (PAMORAs) and Type 2 chloride channel activators.

Treatment of OIC: PAMORA

The PAMORAs include methylnaltrexone, naloxegol, naldemedine, and alvimopan. The class of medications includes opioid receptor antagonists blocking the opioid receptor binding at the mu receptors. Methylnaltrexone is a quaternary derivative of naltrexone with limited

Table 1. Medication Therapy for Constipation

Medication	Brand Name	Mechanism of Action	Onset of Action	Adverse Effects (>5%)	FDA Approval
Methylnaltrexone	Relistor	Peripherally acting opioid receptor antagonist that blocks opioid binding at the mu receptors in the GI tract to improve GI motility and GI transit time; does not affect opioid analgesic effects	Time to peak: SubQ: 30 minutes Oral: ~1.5 hours (delayed with high fat meal)	Abdominal pain, flatulence, nausea, dizziness, diarrhea, hyperhidrosis	Tablets and injection: OIC with chronic noncancer pain Injection: OIC with advanced illness
Naloxegol	Movantik	Mu-opioid receptor antagonist functioning peripherally in tissues of the GI tract	Time to peak: <2 hours	Abdominal pain, diarrhea, nausea, flatulence, vomiting	OIC in noncancer pain
Naldemedine	Symproic	Opioid antagonist that blocks binding at mu, delta, and kappa receptors	Time to peak: 0.75 hours; 2.5 hours with food	Abdominal pain, diarrhea	OIC in noncancer pain
Alvimopan	Entereg	Opioid receptor antagonist that blocks binding at the mu receptor; selectively and competitively binds to the GI tract mu-opioid receptors; does not affect opioid analgesic effects or induce withdrawal symptoms	Time to peak: ~2 hours	Hypokalemia, dyspepsia, anemia	Postoperative ileus, used only in the hospital setting
Lubiprostone	Amitiza	Locally acting chloride channel activator on the GI tract to increase intestinal fluid secretion and improve fecal transit	24–48 hours	Headache, nausea, diarrhea, abdominal pain, flatulence, abdominal distension	Chronic idiopathic constipation, irritable bowel syndrome with constipation, OIC
Linaclotide	Linzess (Linzess, 2017)	Agonist of guanylate cyclase-C on the luminal surface of intestinal epithelium, resulting in increases in intestinal fluid and GI transit acceleration	12–24 hours	Diarrhea, abdominal pain, flatulence, upper respiratory tract infection	Chronic idiopathic constipation, irritable bowel syndrome with constipation
Plecanatide	Trulance (Trulance, 2018)	Agonist of guanylate cyclase-C on the luminal surface of intestinal epithelium, resulting in increases in intestinal fluid and GI transit acceleration	12–24 hours	Diarrhea	Chronic idiopathic constipation, irritable bowel syndrome with constipation
Psyllium	Metamucil	Soluble fiber that absorbs water in the intestine to promote peristalsis and reduce transit time	12–72 hours	Gas, bloating, fluid overload	Constipation, dietary fiber supplement
Methylcellulose	Citrucel	Soluble fiber that absorbs water in the intestine to promote peristalsis and reduce transit time	12–72 hours	Gas, bloating, fluid overload	Constipation
Wheat dextrin	Benefiber	Soluble fiber that absorbs water in the intestine to promote peristalsis and reduce transit time	24–48 hours	Gas, bloating	Dietary fiber supplement
Docusate sodium	Colace	Lowers the surface tension of stool, making it easier for water to enter the stool	24–72 hours	Throat irritation	Constipation
Polyethylene glycol	MiraLAX	Osmotic agent that causes water retention in the stool and increased stool frequency	1–4 days	Diarrhea, flatulence, nausea, abdominal pain	Constipation
Lactulose	Enulose, Constulose	Osmotic effect in the colon resulting in distension promoting peristalsis	24–48 hours	Dehydration, hypernatremia, hypokalemia, cramps, flatulence, nausea, vomiting	Constipation, portal systemic encephalopathy
Milk of magnesia	Phillips Milk of Magnesia	Osmotic retention of fluid distending the colon with increased peristaltic activity; reacts with hydrochloric acid in the stomach to form magnesium chloride	0.5–3 hours	Watery stools and urgency, caution in renal insufficiency	Antacid, constipation
Bisacodyl	Dulcolax	Stimulates peristalsis by irritating the smooth muscle of the intestine; alters water and electrolyte secretion, producing net intestinal fluid accumulation and laxation	6–10 hours	Abdominal cramps	Constipation
Senna	Senokot, Ex-Lax, Geri-kot, Senna Lax, Senexon	Stimulate peristaltic activity on the intestine by direct action on the intestinal mucosa or nerve plexus, therefore increasing motility	6–12 hours	Diarrhea, nausea, vomiting	Constipation

Note. FDA = Food and Drug Administration; GI = gastrointestinal; OIC = opioid-induced constipation; SubQ = subcutaneously.

ability to cross the blood–brain barrier. Therefore, it functions as a peripheral acting opioid antagonist with actions in the gastrointestinal (GI) tract to inhibit opioid-induced decreased GI motility and delay in GI transit time. This is how it works to decrease OIC but does not affect opioid analgesic effects. Methylnaltrexone requires dosage adjustments for both renal and hepatic impairments ("Methylnaltrexone bromide oral," n.d.). Naloxegol works similarly to methylnaltrexone as it has limited ability to cross the blood–brain barrier and works peripherally in the GI tract to reduce the symptoms of OIC. A decreased dose of this medication is required with a creatinine clearance of less than 60 ml per minute and has not been studied in hepatic impairment, so avoid its use. Naloxegol is contraindicated for concomitant use with strong CYP3A4 inhibitors such as clarithromycin or ketoconazole ("Naloxegol oxalate oral," n.d.). Naldemedine works by blocking opioid binding at the mu, delta, and kappa receptors. It functions as a PAMORA, including actions in the GI tract to inhibit delay in GI transit time to decreasing constipating effects of opioids. There is no required dosage adjustment for renal impairment or moderate hepatic impairment. Naldemedine has not been studied in severe hepatic impairment, so its use should be avoided ("Naldemedine oral," n.d.). Alvimopan works by selectively and competitively binding the mu-opioid receptors in the GI tract and antagonizes the effects of opioid on GI motility and secretion without affecting the analgesic effects of opioids. This medication is specifically used for short-term hospitals use and a maximum of 15 doses (180 mg) can be given to a patient. There are no dosage adjustments needed for moderate renal or hepatic impairment. Its use should be avoided in severe renal and hepatic impairments ("Alvimopan oral," n.d.).

Treatment of OIC: Type 2 chloride channel activator

The type 2 chloride channel activator that is commonly used for OIC is lubiprostone. This medication works by inducing secretion of fluid into the intestines and bowel, allowing stool to pass more freely. It does this by acting locally on the apical membrane of the GI tract to increase intestinal fluid secretion and improve fecal transit. Lupiprostone bypasses the antisecretory effects of opiates, which suppress secretomotor neuron excitability. The dose when used for OIC is 24 μg twice daily. Dosing of this medication changes on the basis of indication. No dosage adjustments are needed for renal impairment or mild hepatic impairment. For moderate hepatic impairment, dosing should be decreased to 16 μg twice daily and for severe impairment dosing should be 8 μg twice daily initially ("Amitiza," 2018).

Chronic Idiopathic Constipation

Chronic idiopathic constipation (CIC) is diagnosed on the basis of the absence of physical abnormalities or other causes of constipation and the presence of the following in 25% of defecations—at least two of the following with straining: lumpy/hard stools, sensation of incomplete evacuation or obstruction, need for manual maneuvers, and less than three spontaneous bowel movements per week in addition to the rare presence of loose stools without laxative and insufficient criteria for irritable bowel syndrome (IBS).

Chronic Idiopathic Constipation: Treatment options

First-line therapy for CIC typically begins with nonpharmacological options: increasing fiber, fluid intake, physical activity, and behavioral changes such as having a routine for bowel movements. The American Gastroenterological Association next recommends osmotic agents such as MOM or PEG and then adding a stimulant laxative such as bisacodyl or senna. If the nonpharmacological and/or nonprescription therapies are not adequate, there are four prescription drugs currently on the market: lubiprostone, linaclotide, plecanatide, and prucalopride. Lubiprostone was the first medication on the market, and it works by selectively activating the ClC-2 chloride channel in the intestinal lumen, which leads to an efflux of chloride ions, followed by sodium ions into the small intestine. This, in turn, enhances intestinal fluid secretion and motility in intestine, facilitating the passage of stool. Lubiprostone is indicated in CIC, OIC, and IBS with predominant constipation (IBS-C), but the dose varies depending on the condition it is treating. The most common side effects are nausea and headache, and the medication should be taken with food and water. Both linaclotide and plecanatide are guanylate cyclase-C (GC-C) agonists—They bind to CG-C and act on the luminal surface of the intestinal epithelium. This causes an increase in the intra/extracellular cGMP, stimulates secretion of chloride and bicarbonate into the intestinal lumen, and ultimately increases intestinal fluid, accelerating transit. Linaclotide capsules are supposed to be swallowed whole on an empty stomach at least 30 minutes prior to the first meals. These capsules can be opened and gently swirled in bottled water or room temperature applesauce. The most common adverse effects include diarrhea, abdominal pain, flatulence, abdominal distension, upper respiratory tract infections, and sinusitis. Plecanatide tablets are also supposed to be swallowed whole or can be crushed and mixed with applesauce or water. Both are indicated in CIC and IBS-C as well. The last medication indicated for CIC is prucalopride, a selective serotonin Type 4 agonist, which stimulates colonic peristalsis and increases bowel motility. This is only indicated for CIC and can be taken with or without food, and adverse effects include headache, abdominal pain, diarrhea, and abdominal distension.

Irritable Bowel Syndrome

Irritable bowel syndrome is a chronic disorder of the GI tract that may present as altered bowel habits and/or abdominal pain without cause. There are approximately 10%–15% of adults and adolescents who have signs and symptoms consistent with IBS. Irritable bowel syndrome is broken down into different subtypes including IBS-C, IBS with predominant diarrhea (IBS-D), IBS with mixed bowel habits (IBS-M), and IBS unclassified (Wald,

2019b). This article focuses on IBS-C. There are many nonpharmacological treatment options for IBS-C including changes in diet, lactose avoidance, gluten avoidance, food allergy testing, physical activity, and fiber.

Irritable bowel syndrome: Treatment Options

Psyllium

In a study conducted by Ford et al. (2014), psyllium has been associated with improvements in symptoms of IBS-C over placebo. Psyllium is a soluble fiber that works by absorbing water in the intestine to form a viscous liquid that promotes peristalsis and reduces transit time (Ford & Talley, 2012). If patients fail a trial of psyllium, the next option is PEG for alleviation of constipation. Studies have shown that PEG does not show much benefit in improving abdominal pain in patients with IBS-C, but patients did have significantly more spontaneous bowel movements, improvement in bowel consistency, and reduction in severity of straining ("Psyllium oral," n.d.). If the patient fails a trial of PEG, other options for treatment of IBS-C include lubiprostone, linaclotide, or plecanatide. Lupiprostone is dosed at 8 μg/day when used for IBS-C, which is different from OIC dosing. Linaclotide and plecanatide work by binding and agonizing GC-C on the luminal surface of intestinal epithelium, increasing concentrations of intracellular and extracellular cGMP concentrations resulting in chloride and bicarbonate secretions into the intestinal lumen. This increases GI transit time and thus may reduce constipation (Brown et al., 2016). Medication therapy for IBS-C is discussed in Table 1.

Conclusion

Constipation is a common condition where symptoms present in a decreased frequency of bowel movements alongside other symptoms. Evaluating the patient is key to determining the cause of the constipation to ensure the appropriate treatment is recommended. Both nonpharmacological and pharmacological interventions have a key role, and follow-up is important to ensure treatment is appropriate and adequate.

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