Evaluation and Treatment of Constipation in the Geriatric Population

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KEYWORDS

- Constipation • Elderly • Bowel training • Laxatives • Linaclotide • Lubiprostone
- Plecanatide • Tegaserod

KEY POINTS

- Chronic constipation, a common gastrointestinal disorder, has increased prevalence in elderly individuals because of polypharmacy, immobility, and physiologic changes in the intestinal tract and pelvic floor function caused by aging.
- A thorough history and physical examination including pelvic floor evaluation is necessary for assessment of severity and causation of constipation to guide the diagnostic work-up.
- Initial treatment approaches should include diet and lifestyle changes as well as review of medications, but recognition and treatment of pelvic floor dysfunction may be an important aspect of early treatment.
- Pharmacologic treatments include over-the-counter medications as well as newer prescription medications targeting various physiologic receptors, but few data are available regarding their safety in the elderly.

INTRODUCTION

Constipation is estimated to affect 33 million individuals in the United States alone and it is nearly twice as common in women compared with men.[1] The prevalence of constipation in women more than 65 years of age is 26% and 16% in men.[2] This prevalence may be influenced by a variety of factors, such as whether the patient is in a community setting versus institutional setting, the patient's diet, comorbidities, socioeconomic status, polypharmacy, and pelvic floor sensorimotor defecation disorders. The prevalence continues to increase with increasing age, to 34% in

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women and 26% in men more than 85 years of age.[2] In long-term care facilities, the prevalence of constipation may increase to almost 80%.[1,3] It is important to recognize that management of constipation in older individuals has inherent challenges that must be recognized in order to properly diagnose and treat this condition more effectively. This article discusses the definition of constipation, outlines the epidemiology of this disorder, as well as providing an understanding of the physiology of constipation in older individuals. Diagnostic approach as well as the non-pharmacologic and pharmacologic aspects of treatment, including evolving treatments, are discussed.

DEFINITION OF CONSTIPATION

The Rome criteria for constipation have recently been modified and define constipation as having 2 or more of the following features: less than 3 bowel movements per week, or for at least 25% of bowel movements having hard or lumpy stools, straining at stool, use of digital maneuvers, sensation of incomplete evaluation, or sensation of anorectal obstruction.[4] Loose stools should rarely be present without the use of laxatives and the criteria listed earlier should be fulfilled for the last 3 months with symptom onset starting at least 6 months before diagnosis. Although this newest definition states that there should be insufficient criteria for a diagnosis of irritable bowel syndrome, it does acknowledge that patients with constipation may have pain or bloating but that these should not be the predominant symptoms. The new criteria do recognize that these disorders should be thought of as a continuum rather than a distinct entity.

Constipation can be further divided into primary and secondary causes. Primary causes include slow transit constipation, pelvic floor dysfunction, and normal transit constipation. Patients with slow transit constipation have delayed transit of stool through the colon and this may be caused by primary defects in innervation of the gut (neuropathic) and/or the colonic smooth muscle (myopathic). Patients with pelvic floor dysfunction have difficulty expelling bowel movements because of inability to relax pelvic floor muscle, or improper coordination of abdominal and pelvic floor muscles while defecating, or the inability to produce the necessary propulsive forces in the rectum. Patients with normal transit constipation may also include patients with irritable bowel syndrome with constipation (IBS-C), for whom pain or discomfort is predominant and is relieved with defecation.[2] Irritable bowel syndrome may be less common in the elderly but it is still part of the spectrum of constipation in this age group. Also, it is important to realize that pelvic floor disorders may overlap in both normal and slow transit defecation.

Secondary causes of constipation can include neurologic disorders, medications, endocrine and metabolic disorders, myopathic disorders, cancer, paraneoplastic conditions, and medications (**Table 1**). Diet, psychological factors, and lifestyle may be additional contributory factors.

SPECIAL CONSIDERATIONS IN THE ELDERLY

A variety of pathophysiologic changes occur in the colon, sphincter muscles, and rectum in elderly individuals. **Table 2** summarizes these pathophysiologic changes and their clinical significance. These changes involve receptors in the colon as well as anatomic changes in the rectum resulting in changes in sensation, motor function, and reservoir function.[5]

Table 1 Common causes of constipation in the elderly	
Lifestyle	Diet (low fiber, low intake, very high fiber, high protein), sedentary lifestyle, travel, dehydration, ignoring the urge to defecate, anorexia
Medications	Anabolic steroids, analgesics (NSAIDs and opioids), antacids containing aluminum or calcium, anticholinergics, anticonvulsants, antidepressants (TCAs, NSRIs), antihistamines, antihypertensives (eg, calcium channel blockers, clonidine), anti-Parkinson medications, bile-binding agents (eg, cholestyramine), calcium or iron supplements, diuretics
Metabolic	Hypokalemia, hypercalcemia, hyperglycemia, chronic renal insufficiency
Endocrine disorders	Diabetes mellitus, hypothyroidism, pregnancy, porphyria, panhypopituitarism
Neuropathic disorders	Autonomic neuropathy, chronic intestinal pseudo-obstruction, Hirschsprung disease, multiple sclerosis, Parkinson disease, spinal cord injury
Myopathic	Amyloidosis, chronic intestinal pseudo-obstruction, dermatomyositis, scleroderma, myotonic dystrophy
Idiopathic	Ischemia, stroke
Intestinal disorders	Adenoma, cancer (colon or metastatic), diverticulitis/diverticulosis, adhesions, obstruction, hernia, foreign bodies, fecal impaction, inflammatory bowel disease, stenosis
Anorectal abnormalities	Rectocele, anal fissures/fistula, anal stenosis, proctitis, inflamed or thrombosed hemorrhoids

Abbreviations: NSAIDs, nonsteroidal antiinflammatory drugs; TCAs, tricyclic antidepressants; NSRI, Serotonin and Norepinephrine Reuptake Inhibitor.

DIAGNOSTIC CONSIDERATIONS
History and Physical Examination

Although many individuals more than 65 years of age are intact mentally and physically, history taking can be challenging when problems with vision, hearing, and memory occur. Clinicians must be vigilant and thorough. For instance, ascertaining what the patient means by constipation is particularly important: questions about stool form; frequency; straining; use of manual maneuvers; and occurrence of fecal impaction, seepage, and incontinence all are important. Elderly patients may have seepage or incontinence that reflects possible watery stool around solid stool but also reflects the physiologic changes noted earlier. It is also essential to take a social history and inquire about diet, living conditions, social supports, stressors, psychiatric comorbidities, and the patient's ability to do activities of daily living. Clinicians must screen also for alarm symptoms such as loss of appetite, weight loss, and sudden change in bowel function or bleeding.

Table 2			
Physiologic changes in the elderly colon/rectum			
Anatomic Structure	**Defect**	**Pathophysiologic Change**	**Clinical Result**
Colon			
Number of HAPCs	Decreased	Colonic propulsion decreased	Constipation
Transit time	Slowed	Colon transit slowed	
Anus			
Anal sphincter length	Decreased	Sphincter is weakened	Seepage/urgency/incontinence
Internal anal sphincter	Thinned/atrophic	Sphincter is weakened	Seepage/incontinence
External anal sphincter	Thinned/atrophic	Sphincter is weakened	Urgency/incontinence
Rectum			
Sensation	Decreased	Colorectal sensorimotor function is impaired	Seepage/incontinence
Compliance	Decreased	Reservoir function is impaired	Urgency/incontinence
Capacity	Decreased	Reservoir function is impaired	Urgency/incontinence
Pudendal Nerve			
—	Decreased function	Colorectal sensorimotor function is impaired	Seepage/incontinence

Abbreviation: HAPCs, high-amplitude propagating contractions.

When doing the physical examination, the clinician should observe the patient for general condition and mobility. A careful abdominal examination should involve looking for distention, feeling for palpable masses or stool, and inquiring and examining for hernias. The importance of the digital rectal examination cannot be overemphasized. The examination should be performed in the left lateral decubitus position. The perianal region should be inspected for skin lesions, hemorrhoids, and fissures. On digital examination, clinicians should be attentive to resting anal tone and ask the patient to squeeze and bear down to assess for pelvic floor dyssynergia or evidence of excessive perineal descent. Sensation can be assessed by using a Q-tip to stroke the perineal skin around the anus in a 4-quadrant fashion looking for the so-called anal wink. Neuropathy should be suspected if this does not occur.

Diagnostics

Basic blood work, such as complete blood count, comprehensive metabolic profile (includes calcium), and thyroid function tests, can be performed to rule out anemia and a metabolic disorder. Structural testing, such as a flexible sigmoidoscopy or colonoscopy, should be performed to rule out malignancy, inflammatory bowel disease, or solitary rectal ulcer syndrome. Mucosal findings of melanosis coli might provide evidence of chronic laxative use. Recent guidelines suggest that colon cancer screening should be started at age 45 years; at advanced ages, routine colon cancer screening may not be warranted and should be tailored to the individual.[6] Other structural examinations include radiologic procedures such as computed tomography (CT) scan of the abdomen and pelvis and pelvic ultrasonography (abdominal and transvaginal), which may help exclude malignancies. Ovarian tumors may present as bloating and change

in bowel habits.[7] The abdominal flat plate radiograph may be helpful to assess stool burden, obstruction, and impaction.

Physiologic tests are particularly helpful in diagnosing disorders of pelvic floor dysfunction or slow transit constipation. The primary test used to evaluate the pelvic floor is anal rectal manometry. This test can provide information on strength, tone, and sensation in the anus and rectum.[8] In addition, the balloon expulsion test, which is a 4-cm balloon filled with 50 mL of warm water or a silicon-filled stool-like device (fecom), is used to test function.[9] Most individuals can expel the balloon within 1 minute, and inability to do so is highly correlated with dyssynergic defecation.

Barium defecography or dynamic pelvic MRI defecography study not only provides information on pelvic floor function but can reveal structural abnormalities such as rectoceles, enteroceles, or pelvic organ prolapse that are also contributing to constipation.

Transit through the colon can be assessed with a Sitzmark capsule study, which contains 24 radio-opaque markers. The patient swallows the capsule on day 1 and an abdominal radiograph is taken on day 6. In patients with normal transit, fewer than 5 markers should be present.[10] The presence of 6 or more markers spread throughout the colon is suggestive of slow transit constipation.[10] An additional modality to assess transit is the wireless motility capsule. This swallowed device can assess both regional and whole-gut transit, and a recent study has confirmed its safety in the elderly.[11] Nuclear scintigraphy can be used to measure gastric, colonic, or whole-gut transit, but only a few centers in the United States perform the study.

LIFESTYLE AND DIETARY MODIFICATION

First-line therapies for the treatment of constipation consist of discussing diet, exercise, and bowel management techniques. Physicians may find it challenging to cover all of these issues in a single visit, so use of a nurse practitioner or a physician's assistant to perform dedicated counseling may be helpful in educating patients about this condition. **Box 1** covers important features of the nurse/physician assistant education material. Patients can also bring a significant other/caretaker to assist with remembering important teaching points. Helping patients understand the anatomy of the colon and pelvic floor may be the first step in empowering the patients to understand their conditions. In addition, the physician extender can review medications and also help identify issues that are interfering with patient compliance, such as visual impairments, hearing deficits, dietary habits, and declining cognitive function. Patients are encouraged to set up a schedule for defecation and take advantage of the stronger physiologic contractions that occur early in the morning. These contractions can be further stimulated by physical activity, eating a meal that includes fiber, and a hot beverage with caffeine (if feasible), which can intensify the gastrocolic reflex. Patients are encouraged to keep a stool diary that documents bowel movements, stool form based on the Bristol stool form scale,[12] and need to strain or use manual maneuvers and medications taken to improve defecation. Such visits can also be used to properly teach breathing techniques and use of manual maneuvers to facilitate defecation, such as splinting.

Dietary fiber in the average Western diet is often inadequate and usually about half the recommended dose.[13] Current recommendations suggest that women get 20 to 28 g of fiber and men get 30 to 38 g of fiber in their diets.[14] Patients should be encouraged to increase dietary fiber in the forms of nuts, fruits, and vegetables. Soluble fiber can create less gas and bloating than insoluble fiber. The goal is to increase fiber slowly by no more than 5 g/wk and to increase it as tolerated. Patients with slow transit

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Box 1
Tips for teaching bowel management techniques

- Assess the patient's functional status: cognitive abilities, visual and hearing impairments.

- Review patient medications, both prescription and nonprescription (do not forget to ask about supplements), to identify medications that may exacerbate constipation.

- Discuss diet and encourage increasing fiber to appropriate levels (20–28 g/d for women, 30–38 g/d for men) and also increasing fluids (5–8 235-mL [8 oz] glasses of water/hydrating fluids per day) as allowed.

- Encourage patient to keep a diary of diet and bowel movements and form over 1 week, which may indicate dietary and fluid intake (a diary incorporating Bristol stool form may be helpful).

- Encourage patient to eat breakfast with a hot beverage to help with the gastrocolic reflex.

- Encourage daily physical activity if the patient is able.

- Encourage patients to listen to their bodies and go to the bathroom when the urge occurs.

- Use of anatomic drawings may aide in patients' understanding of their condition, especially pelvic floor maneuvers to assist with defecation.

- When sitting on the toilet, patients should sit tall and use a small stool under their feet. Ideal toileting time is 3 to 5 minutes, but definitely not more than 10 minutes.

- To assist with pelvic floor function and increasing intra-abdominal pressure, patients should use diaphragmatic breathing, which involves taking a deep breath and exhaling slowly over 10 seconds while pushing the stomach forward and relaxing the anus. Allow 20 seconds between breaths.

- Patients should be instructed not to strain because this creates pelvic floor congestion. Relaxation of strain reverses the congestion.

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constipation may not be able to reach the desired goals, and some patients with excessive bloating may respond better with alternative diets, such as the low-FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) diet. There is also evidence that prunes and kiwi fruit specifically can be efficacious in increasing gut motility.[15,16]

PHARMACOLOGIC TREATMENTS FOR CHRONIC CONSTIPATION

If dietary and lifestyle modifications do not successfully, or only partially, relieve symptoms, pharmacologic therapies should be considered as the next therapeutic option. In addition to appropriate classification into normal or slow transit constipation with or without pelvic floor dysfunction, treatment in the elderly should be individualized with special consideration of the patient's medical history (cardiac, neurologic, and renal comorbidities), mobility and functional status, level of independence of living, cost of therapy, medications, and potential adverse effects and interactions.[17] The treatment of chronic constipation in the elderly may also be challenging because older adults who have a cumulative incidence of chronic constipation for many years, or even decades, compared with younger patients, may have more treatment-refractory symptoms.[18] Elderly adults may also be more at risk of constipation because they may be on constipating medications such as calcium channel blockers, antidepressants, analgesics, antiparkinsonian drugs, antacids, and diuretics.[19] Moreover, with pharmacotherapy for constipation, elderly patients are at a higher risk of fecal incontinence in response to catharsis, an under-reported symptom, compared

with younger patients.[20,21] It is important to consider all these factors before proceeding to pharmacotherapy. Commonly used over-the-counter treatments for chronic constipation are listed in **Table 3**.

Soluble fiber supplements are bulk-forming agents that have been shown to improve constipation and should be used as the first-line treatment. Bowel function is facilitated by increasing water absorbency of the stool.[22] Synthetic bulking agents include psyllium, methylcellulose, calcium polycarbophil, and wheat dextrin (US trade name Benefiber). Despite widespread use of bulking agents, the evidence regarding their efficacy has been inconsistent.[23,24] The dose of these agents may be increased gradually on a weekly basis to maximize efficacy and minimize adverse side effects, such as bloating, flatulence, abdominal cramping, and (rarely) diarrhea. They may be used alone or in combination with laxatives or other cathartic medications. Patients with slow transit constipation or anatomic or functional issues with evacuation are likely not to benefit from fiber supplementation and may experience exacerbation of symptoms.[19]

In patients not responding to bulk laxatives alone, the addition of osmotic laxatives should be considered as a next step. High-molecular-weight polyethylene glycol (PEG) is a large polymer with substantial osmotic activity that holds on to intraluminal

Table 3
Over-the-counter treatments for constipation

Medication	Mechanism of Action	Recommended Dosing	Efficacy (NNT)	Possible Side Effects
Calcium polycarbophil Or Methylcellulose Or Wheat dextrin	Bulking agent	Variable: titrate to effect	NA	Bloating, abdominal cramps, flatulence, or rarely diarrhea
Psyllium	Bulking agent	Variable: titrate to effect	1–3	Bloating, abdominal cramps, diarrhea
PEG	Osmotic agent	17 g	2–4	Nausea, bloating, diarrhea, flatulence, abdominal cramps
Magnesium-based laxatives	Osmotic agent	Variable	NA	Nausea, vomiting, electrolyte disturbances in CKD
Bisacodyl (5 mg)	Stimulant	Two 5-mg tablets	4	Nausea, abdominal cramps, diarrhea
Senna (8.6 mg) Anthraquinone	Stimulant	2 tablets daily to 2 tablets twice a day	NA	Nausea, abdominal cramps, bloating, diarrhea, flatulence, melanosis coli
Cascara sagrada	Stimulant	2 tablets daily	NA	Nausea, abdominal cramps, bloating, diarrhea

Abbreviations: CKD, chronic kidney disease; NA, not available; NNT, number needed to treat; PEG, polyethylene glycol.

water by creating an osmotic gradient. By retaining or drawing water into the gut lumen, PEG use leads to increased bowel motility.[25] Several controlled trials, lasting up to 6 months, have revealed that this treatment is effective,[26] and studies up to 24 months have confirmed its safety.[27] The major side effects of PEG are bloating and flatulence.

Saline laxatives, including magnesium citrate, are also available over the counter and work by an osmotic effect with retention of fluid to increase stool frequency and consistency.[28] Magnesium-based laxatives should be used with caution in patients with kidney disease because they may develop hypermagnesemia, which may lead to prolongation of the QT interval, bradycardia, and hypotension.[29]

Stimulant laxatives such as bisacodyl and senna exert their primary effects through alteration of electrolyte transport in intestinal mucosa and enhancement of colonic motility.[30]

They can be used safely as rescue laxatives if patients have no bowel movements for 2 to 3 days[31]; however, long-term safety of stimulant laxatives has not been confirmed. Side effects include abdominal cramping, distention, nausea, and diarrhea. Although long-term use of stimulant laxatives that contain anthraquinone, such as senna, can cause melanosis coli, they do not seem to impair the enteric nervous system based on studies in animal models.[32,33] This knowledge should be used to dispel the notion that chronic use of these agents causes nerve damage and worsening constipation.

Although stool softeners, suppositories, enemas, and probiotics are commonly used, the evidence to support their use is lackluster. Bisacodyl or glycerin suppositories may be helpful in the elderly with a defecation disorder to aid in evacuation. The suppository should be given 30 minutes after breakfast in order to take advantage of the gastrocolic reflex.[34]

When over-the-counter treatments are ineffective in remedying chronic constipation, there are several prescription therapies available. Current prescription and US Food and Drug Administration (FDA)–approved pharmacologic treatments for chronic constipation are listed in **Table 4**. Studies investigating the efficacy and safety of pharmacologic agents used for treatment of chronic constipation in the elderly are limited. Trials of adult patients often include only a limited number of study subjects aged more than 65 years.

Lactulose is a prescription osmotic laxative that has been in use since the1950s. It is a nonabsorbable carbohydrate that exerts its effect by altering intestinal osmolality. It is safe at a dose of 20 g (30 mL) once daily. Lactulose can cause significant abdominal bloating, discomfort, and flatulence, which may decrease patient acceptance and, because it contains lactose and galactose, caution must be used in patients with diabetes.[35]

Linaclotide and plecanatide are intestinal secretagogues approved by the FDA for treatment of chronic constipation. They are minimally absorbed peptide agonists of guanylate cyclase C receptor that bind on the apical side of intestinal epithelial cells, resulting in generation of cyclic guanosine monophosphate (cGMP). The increase of cGMP levels within the intestinal cells triggers a signal transduction cascade that activates the cystic fibrosis transmembrane conductance regulator. This activation causes secretion of chloride and bicarbonate into the intestinal lumen, increasing luminal fluid secretion and accelerating intestinal transit.[36,37] Linaclotide works in a pH-independent manner and is active in both the small and large intestines at a broad pH of 5 to 8, whereas plecanatide works in a pH-dependent way at more acidic pH of 5.5 to 7, and causes fluid secretion mostly in the upper small intestine. Linaclotide is available in 3 doses: 72, 145, and 290 μg daily. In elderly patients, a lower starting dose

Table 4
Prescription agents for constipation

Treatment	Mechanism of Action	Recommended Dose	Efficacy (NNT)	Potential Side Effects
Lactulose	Osmotic	20 g daily	NA	Bloating, cramping, diarrhea, flatulence, nausea, vomiting High doses may cause electrolyte disturbances
Linaclotide	GC receptor agonist	72 or 145 μg (CIC) or 290 μg (IBS-C) daily	10	Diarrhea, cramping, flatulence, headache
Plecanatide	GC receptor agonist	3 mg daily	11–12	Diarrhea
Lubiprostone	Chloride channel activator	8 μg BID (IBS-C, women only) 24 μg BID (CIC)	3–6	Nausea,[a] diarrhea, SOB
Prucalopride	Serotonin (5-HT4) receptor agonist	2 mg daily, 1 mg for severe renal disease or ESRD	5–9	Diarrhea, headache, <1% suicidal ideation/depression
Tepanor	Inhibitor of sodium/hydrogen exchanger 3	50 mg BID (IBS-C only)	NA	Diarrhea, bloating, flatulence

Abbreviations: 5-HT4, 5-hydroxytryptamine 4; BID, twice daily; CIC, chronic idiopathic constipation; ESRD, end-stage renal disease; GC, guanylate cyclase; IBS-C, irritable bowel syndrome with constipation; SOB, Shortness of breath; NNT, number needed to treat.
[a] Nausea: higher incidence at 24-μg dose (31%); at 8-μg dose, nausea occurred in 8%. Recommended to take medication with food.

may be prudent. Plecanatide is available in the single dose of 3 mg daily. The main adverse reaction to both linaclotide and plecanatide is diarrhea, occurring at a rate of 16% to 19% and 5% respectively.[37–39] Reassuring data from a recent pooled analysis of 451 patients more than 65 years of age with both chronic idiopathic constipation and IBS-C confirmed that plecanatide is well tolerated in the elderly demographic and no serious events of diarrhea occurred.[40]

Lubiprostone, another intestinal secretagogue approved by the FDA for chronic constipation at a dose of 24 μg twice a day and IBS-C–predominant constipation at 8 μg twice a day, is a bicyclic fatty acid derivative of prostaglandin E1 that increases fluid secretion into the lumen of the intestine by activating apical chloride channel 2. By increasing intestinal fluid secretion, transit time in both small and large intestines is accelerated.[41] The dose for chronic constipation is 24 μg twice a day. The main side effect is nausea, which can be mitigated when the medication is taken with meals. Lubiprostone has been also approved by the FDA for treatment of opioid-induced constipation.

In 2018, the FDA approved prucalopride for the treatment of chronic constipation. It is a highly selective serotonin 5-hydroxytryptamine 4 (5-HT4) receptor agonist that increases the release of serotonin (5-HT) by the enterochromaffin cells in the intestinal mucosa of the small bowel. It acts on neurons along the enteric nervous system. By releasing acetylcholine, it stimulates intestinal motility directly. In addition, it secretes fluid into the intestines, which has an additional prokinetic effect. Prucalopride at a dosage of 1 and 4 mg once daily was found to be superior to placebo in 4-week and 12-week trials. It was safe and well tolerated in patients 65 years of age or

older.[42,43] In the United States, the recommended dose in adults is 2 mg once daily with a lower dose (1 mg daily) recommended for patients with kidney disease. Adverse events include abdominal pain, nausea, diarrhea, abdominal bloating, flatulence, headache, dizziness, and fatigue. Uncommon but potentially serious adverse events include exacerbation of depression and suicidality, warranting extreme caution in at-risk patients. Two 5-HT4 receptor agonists were approved for treatment of chronic constipation in the past (cisapride in 1993, tegaserod in 2002), but both were subsequently withdrawn from general use because of serious cardiovascular events, including cardiac ischemia, strokes, cardiac arrhythmias, and prolongation of the corrected QT interval. Tegaserod became available again in 2019 but is only recommended for patients between the ages of 18 and 65 years.[44] Prucalopride is a highly selective 5-HT4 receptor agonist that has not been associated with any cardiovascular adverse events.[45]

Tenapanor is a first-in-class agent, a selective sodium-hydrogen exchanger (NHE3) inhibitor that was approved in 2019 for the treatment of IBS-C.[46] It also is approved to treat hyperphosphatemia in patients with chronic kidney disease. It works by decreasing the absorption of sodium from the intestines, resulting in water secretion in the lumen, which in turn causes softer stool because of increased intestinal transit. In phase III double-blind, placebo controlled trials, tenapanor 50 mg twice daily met the combined primary end point of greater than or equal to 30% reduction in abdominal pain and an increase of greater than or equal to 1 completed spontaneous bowel movement in the same week for greater than or equal to 6 of 12 treatment weeks.[47,48] Chief side effects were diarrhea and abdominal distention.[46]

FECAL IMPACTION

If constipation continues to be an issue, awareness of the risk of fecal impaction must be present. Fecal impaction results from the person's inability to sense a stool in the rectum, and this impaired sensitivity fails to provide a signal for the bowel to evacuate. Risk factors include altered abnormal anatomy, such as an anal stricture or rectal mass, in addition to rectal sensorimotor dysfunction and decreased mobility, which are more common in institutionalized elderly.[49] Rectal examination is essential in the evaluation of constipation and may reveal a rectum full of hardened stool. The practitioner must also be aware that the impaction may occur above the rectum, in which case abdominal radiograph or cross-sectional imaging may be required for detection. Treatment of fecal impaction includes digital disimpaction with manual fragmentation followed by warm-water enemas. If this is ineffective, distal colonic cleansing using warm-water enemas with the aid of a sigmoidoscopic or use of water-soluble contrast media such as Gastrografin for both diagnostic and therapeutic purposes may be necessary.[50] In rare cases, if there is abdominal tenderness and a concern for ischemia or perforation, emergent imaging with CT and possible surgery may be required because a rare complication of fecal impaction is stercoral ulcer perforation.[51] Because recurrence of fecal impaction is common, it is important to treat constipation proactively with dietary measures, adequate fluids, and pharmacotherapies.

BIOFEEDBACK/VISCERAL MANIPULATION

Elderly patients who do not respond to medical therapy or who have had fecal impaction may also meet Rome IV criteria for a defecation disorder.[52] Defecation disorders result in impaired evacuation with inadequate or absent intrarectal propulsion and either paradoxic or inadequate anal sphincter relaxation during simulated defecation.

This important cause of chronic constipation is likely underdiagnosed because, in addition to clinical suspicion, physiologic testing such as anorectal manometry, balloon expulsion testing, colon transit study, or fluoroscopic or magnetic resonance defecography is required, but may not be readily available. If a defecation disorder without evidence of structural abnormality such as rectocele, enterocele, or prolapse is identified, biofeedback-aided pelvic floor therapy is the best management option. Even if those structural abnormalities are present, conservative biofeedback/pelvic floor rehabilitation by an experienced practitioner is still warranted if possible. Often, patients with a defecation disorder may also have an epiphenomenon or coexistent slow transit constipation, and treatments for these disorders may need to be combined.[53] With biofeedback, defecation disorders have been shown to be eliminated in 91% of patients, and 85% had confirmed improvement in the balloon expulsion test.[54] However, high-quality biofeedback may not be widely available. Furthermore, patients need to participate actively in this form of therapy and this may not be always possible if limitations in mobility or cognition are present. Medicare and Medicaid in most states in the United States now provide coverage of this effective treatment.

Another therapy for patients who fail biofeedback is visceral manipulation. Visceral manipulation is being taught by physical therapists, has commonly also been used by osteopaths, and can be used in patients who fail biofeedback.[55] There are no randomized controlled studies of this modality, but a small study in elderly patients with stroke showed that, compared with standard physical therapy, there were significant improvements in several intestinal symptoms, including abdominal pain/discomfort, frequency of bowel movements, and bloating.[56] An added advantage of this therapy is that it does not require the patient to be mobile, although studies suggest that physical activity does help with constipation.

SURGICAL INTERVENTIONS

Surgical interventions should be approached carefully in elderly patients, who may have comorbidities that increase risk. If a patient with severe slow transit constipation without global gut hypomotility and or defecation dysfunction is refractory to medical treatments, subtotal colectomy with ileorectal anastomosis could be considered.[57] Confidence that there is no element of defecation disorder and that the underlying cause is a motility delay is imperative to avoid poor postoperative outcomes. Alternatively, less invasive surgeries, such as percutaneous endoscopic cecostomy with insertion of an indwelling catheter or appendiceal conduit (Malone procedure), may be used to infuse water into proximal colon. These minimally invasive surgeries can be performed under local anesthesia with conscious sedation, making them less risky.[58] Potential postoperative intestinal complications include ileus, anastomotic leakage or bleeding, small bowel obstruction, and wound infection. Emergent endoscopy and subsequent surgery may be required for obstruction from a sigmoid or cecal volvulus (and bascule subtype), which may result from long-standing constipation and associated colonic redundancy.[59]

NOVEL TREATMENTS

Several small studies have evaluated sacral nerve stimulation (SNS) in chronic constipation but the results have been conflicting. A recent report showed that SNS has a 30% response in refractory constipation.[60] Bilateral transcutaneous tibial nerve stimulation was studied in a small number of geriatric patients (aged >65 years) with refractory chronic constipation and showed a reduction in both time spent on the toilet and

stool softener use.[61] Neither of these treatments has been approved by the FDA at the time of this writing.

In addition, a vibrating capsule is also under investigation for the treatment of constipation (Vibrant capsule). It is made of biocompatible materials that stimulate the walls of the large intestine to increase peristalsis and generate spontaneous bowel movements.[62] There have been 2 double-blind sham-controlled phase II studies in patients with chronic constipation. The studies differed in the way the pulses were delivered from the capsules. Post hoc analyses of the 2 studies showed that, during and within 3 hours of the onset of vibrations, there was a significantly greater percentage of complete spontaneous bowel movements in the active group compared with the sham group, but overall responder rates were not different between the 2 groups. The only serious adverse event was an anxiety attack in 1 patient.

OPIOID-INDUCED CONSTIPATION

Opioid analgesic therapy is commonly used to treat chronic noncancer pain in adults, including elderly patients. Opioid-induced constipation (OIC) is the most common adverse effect, occurring at a rate of 41%.[63] Evidence suggests the risk of OIC increases with age.[64] Opioids cause constipation by blocking opioid receptors, including the μ-opioid receptor, and cause slowing of colonic transit and decreasing intestinal and colonic secretion.[65] Nonpharmacologic and pharmacologic treatments that are available for the management of OIC have not been well studied in the elderly, and treatment guidelines specifically for the management of elderly patients with OIC are not available. However, a review of the evidence in the literature for treatment of adult patients with OIC recommends nonpharmacologic interventions (eg, dietary measures, increased fluid ingestion, increased physical activity, biofeedback training), and use of over-the-counter laxatives as first-line therapy.[66] However, these initial measures are ineffective in more than 50% of patients. More recently, a new generation of therapeutic agents known as peripherally acting μ-opioid receptor antagonists (PAMORAs) has been tested in OIC, and some of these agents directly target opioid receptors in the gut. A recent American Gastroenterological Association Institute Technical Review on the Medical Management of

Table 5
Peripherally acting μ-opioid receptor antagonists used in opioid-induced constipation

Medication	Dose	Side Effects
Methylnaltrexone	450 mg daily orally Or 8 mg/0.6 mL SC daily Or 12 mg/0.6 mL SC daily	Abdominal pain Opioid withdrawal (rare) Renal/liver failure requires dose adjustment Bowel tear
Naldemedine	0.2 mg orally daily	Abdominal pain Nausea and vomiting Diarrhea Bowel tear
Naloxegol	12.5–25 mg orally daily[a]	Abdominal pain Diarrhea Opioid withdrawal (rare) Bowel tear

Abbreviation: SC, subcutaneous.
[a] Do not take with grapefruit juice.

OIC that focused on the efficacy of laxatives, PAMORAs (naldemedine, naloxegol, alvimopan, and methylnaltrexone), selective 5-HT agonists (prucalopride), and intestinal secretagogues (lubiprostone) concluded that there was indirect evidence (moderate quality) that supported the use of over-the-counter laxatives but there were insufficient data comparing the efficacy of laxatives versus prescription medications targeted to treat OIC.[67] The investigators also found that there was evidence to support the use of naldemedine (high-quality evidence), naloxegol (moderate quality), and methylnaltrexone (low quality) for OIC but limited evidence to support the use of lubiprostone (low quality) and prucalopride (low quality). The findings in this review are consistent with other recent systematic reviews of therapies for the management of OIC.[68,69] Of note, analysis of 3 phase 3 clinical trials in patients aged greater than or equal to 65 years showed that naldemedine was effective in OIC, 51.8% versus 37.6% in placebo, which was statistically significant. **Table 5** provides a listing of PAMORAs and doses used in OIC.

SUMMARY

Chronic constipation in the elderly is a common digestive symptom that adversely affects quality of life and health care costs. Its reported prevalence is high, especially for patients living in residential care. A comprehensive evaluation of historical factors unique to this demographic includes mobility assessment, access to food and hydration, coexistent conditions, and the medications used to treat them. Careful physical examination and physiologic testing if first-line interventions fail is key to managing elderly patients, who may have an overly robust response to catharsis and incontinence if diminished rectal sensorimotor dysfunction or sphincteric weakness is present, exacerbation of abdominal distress if a defecation disorder or fecal impaction is present, and coexistent physical limitations worsening symptoms. Diet and lifestyle modifications are often ineffective to manage constipation in the elderly and a multifactorial approach is suggested. Fiber supplementation, regimented bowel routines and behavior techniques, and osmotic laxatives are an effective first line of therapy for many patients. A consistent clinical history of issues with evacuation or inadequate or paradoxic response to standard initial therapy should prompt an assessment for a defecation disorder. If identified, and the patient is able to participate, biofeedback is the treatment of choice. Although data to support safety in this demographic are sparse, there is evidence to support safety and efficacy of pharmacotherapy, including secretagogues and the prokinetics linaclotide and prucalopride in the elderly. The prokinetic agent tegaserod should be avoided in patients 65 years of age or older because of the risk of cardiac and intestinal ischemia. Use of lactulose may be limited because of increased diarrhea if lactose intolerance is present, and magnesium-based cathartic agents may put patients with renal disease at risk of toxicity. Surgery is rarely indicated in the management of constipation. Novel treatments need to be explored in larger clinical trials. Additional attention to addressing therapy for constipation in the elderly is needed to tailor treatment in this complex population and to improve the quality of life of these patients while minimizing side effects of urgency, diarrhea, incontinence, and electrolyte derangements.

CLINICS CARE POINTS

- Clinicians must distinguish primary from secondary constipation in elderly individuals.

- Pelvic floor dysfunction significantly contributes to constipation in elderly individuals and rectal exam and anorectal manometry are important diagnostic tools
- Fecal seepage or incontinence do not rule out constipation and may reflect water around solid stool
- In patients with normal transit constipation increasing fiber supplementation and fluids is first line therapy
- Patients with slow transit constipation are not likely to benefit from fiber supplementation and may experience exacerbation of symptoms
- Treatment of pelvic floor dysfunction can improve CIC 20-50%.
- Linaclotide, Plecanatide, Lubiprostone and Prucalopride have all shown proven efficacy in treating chronic constipation
- Surgical treatment for constipation should primarily be considered only in severe slow transit constipation without serious co-morbidities
- For opioid induced constipation no studies have compared OTC laxative to PA-MORAs but moderate to high quality evidence exist for the use of naloxegol and naldemedine.

DISCLOSURE

S. Lucak: consultant for Abbie Vie, Allergan, and Ironwood; speaker's bureau for Abbie Vie, Alfasigma, and Ironwood. T.N. Lunsford: Biomerica InFoods IBS technology. L.A. Harris has done consulting for Allergan, Ironwood, Salix Pharmaceuticals, Takeda (formerly Shire), Commonwealth Laboratories, and the Rome Foundation.

REFERENCES

1. Suares NC, Ford AC. Prevalence and risk factors of chronic idiopathic constipation in the community: systematic review and meta-analysis. Am J Gastroenterol 2011;106:1582–91.
2. Gallegos-Orozco JF, Foxx-Orenstein AE, Sterler S, et al. Chronic constipation in the elderly. Am J Gastroenterol 2012;107:18–25.
3. Fleming V, Wade WE. A review of laxative therapies for treatment of chronic constipation in older adults. Am J Geriatr Pharmacother 2010;8:514–50.
4. Mearin F, Lacy BE, Chang L, et al. Bowel disorders. Gastroenterology 2016;150:1393–407.
5. Yu SW, Rao SS. Anorectal physiology and pathophysiology in the elderly. Clin Geriatr Med 2014;30(1):95–106.
6. Wolf AMD, Fontham ETH, Church TR, et al. Colorectal cancer screening in average –risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin 2018;68(4):250–81.
7. Olson SH, Mignone L, Nakraseive C, et al. Symptoms of ovarian cancer. Obstet Gynecol 2001;98(2):212–7.
8. Rao SS, Singh S. Clinical utility of colonic and anorectal manometry in chronic constipation. J Clin Gastroenterol 2010;44(9):597–609.
9. Lee BE, Kim GH. How to perform and interpret balloon expulsion test. J Neurogastroenterol Motil 2014;20(3):407–9.
10. Bharucha AD, Phillips SF. Slow transit constipation. Gastroenterol Clin North Am 2001;30(1):77–95.
11. Rao SS, Paulson J, Saad R, et al. Assessment of colonic, whole gut and regional transit in elderly constipated and healthy subjects with novel wireless pH/pressure capsule (Smart Pill®). Gastroenterology 2009;136:A950.

12. O'Donnell L, Virjee J, Heaton KW. Detection of pseudodiarrhoea by simple clinical assessment of intestinal transit rate. BMJ 1990;300:439–40.
13. Storey M, Anderson P. Intake and race/ethnicity influence dietary fiber intake and vegetable consumption. Nutr Res 2014;34:844–50.
14. U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015 – 2020 dietary guidelines for Americans. 8th Edition. December 2015. Available at: http://health.gov/dietaryguidelines/2015/guidelines/. Accessed July 5, 2020.
15. Attaluri A, Donahoe R, Valestin J, et al. Randomised clinical trial: dried plums (prunes) vs. psyllium for constipation. Aliment Pharmacol Ther 2011;33(7):822–8.
16. Chang CC, Lin YT, Lu YT, et al. Kiwifruit improves bowel function in patients with irritable bowel syndrome with constipation. Asia Pac J Clin Nutr 2010;19(4):451–7.
17. Locke GR 3rd, Pemberton JH, Phillips SF. American Gastroenterological Association Medical Position Statement: guidelines on constipation. Gastroenterology 2000;119(6):1761–6.
18. Choung RS, Locke GR 3rd, Rey E, et al. Factors associated with persistent and nonpersistent chronic constipation, over 20 years. Clin Gastroenterol Hepatol 2012;10(5):494–500.
19. Vazquez Roque M, Bouras EP. Epidemiology and management of chronic constipation in elderly patients. Clin Interv Aging 2015;10:919–30.
20. Ditah I, Devaki P, Luma HN, et al. Prevalence, trends, and risk factors for fecal incontinence in United States adults, 2005-2010. Clin Gastroenterol Hepatol 2014;12(4):636–43.e2.
21. Leung FW, Rao SS. Approach to fecal incontinence and constipation in older hospitalized patients. Hosp Pract 2011;39(1):97–104.
22. Suares NC, Ford AC. Systematic review: the effects of fibre in the management of chronic idiopathic constipation. Aliment Pharmacol Ther 2011;33(8):895–901.
23. American College of Gastroenterology Chronic Constipation Task Force. An evidence-based approach to the management of chronic constipation in North America. Am J Gastroenterol 2005;100(Suppl 1):S1-S4.
24. Ramkumar D, Rao SS. Efficacy and safety of traditional medical therapies for chronic constipation: systematic review. Am J Gastroenterol 2005;100(4):936–71.
25. Schiller LR, Emmett M, Santa Ana CA, et al. Osmotic effects of polyethylene glycol. Gastroenterology 1988;94(4):933–41.
26. Di Palma JA, Cleveland MV, McGowan J, et al. A randomized, multicenter comparison of polyethylene glycol laxative and tegaserod in treatment of patients with chronic constipation. Am J Gastroenterol 2007;102(9):1964–71.
27. Corazziari E, Badiali D, Bazzocchi G, et al. Long term efficacy, safety, and tolerability of low daily doses of isosmotic polyethylene glycol electrolyte balanced solution (PMF-100) in the treatment of functional chronic constipation. Gut 2000;46(4):522–6.
28. Dupont C, Campagne A, Constant F. Efficacy and safety of a magnesium sulfate-rich natural mineral water for patients with functional constipation. Clin Gastroenterol Hepatol 2014;12(8):1280–7.
29. Nishikawa M, Shimada N, Kanzaki M, et al. The characteristics of patients with hypermagnesemia who underwent emergency hemodialysis. Acute Med Surg 2018;5(3):222–9.
30. Schiller LR. Review article: the therapy of constipation. Aliment Pharmacol Ther 2001;15(6):749–63.

31. Kienzle-Horn S, Vix JM, Schuijt C, et al. Efficacy and safety of bisacodyl in the acute treatment of constipation: a double-blind, randomized, placebo-controlled study. Aliment Pharmacol Ther 2006;23(10):1479–88.

32. Kiernan JA, Heinicke EA. Sennosides do not kill myenteric neurons in the colon of the rat or mouse. Neuroscience 1989;30(3):837–42.

33. Tack J, Müller-Lissner S, Stanghellini V, et al. Diagnosis and treatment of chronic constipation–a European perspective. Neurogastroenterol Motil 2011;23(8): 697–710.

34. Bharucha AE, Wald A. Chronic constipation. Mayo Clin Proc 2019;94(11): 2340–57.

35. Bass P, Dennis S. The laxative effects of lactulose in normal and constipated subjects. J Clin Gastroenterol 1981;3(Suppl 1):23–8.

36. Bryant AP, Busby RW, Bartolini WP, et al. Linaclotide is a potent and selective guanylate cyclase C agonist that elicits pharmacological effects locally in the gastrointestinal tract. Life Sci 2010;86(19–20):760–5.

37. Sharma A, Herekar AA, Bhagatwala J, et al. Profile of plecanatide in the treatment of chronic idiopathic constipation: design, development, and place in therapy. Clin Exp Gastroenterol 2019;12:31–6.

38. Lembo AJ, Kurtz CB, Macdougall JE, et al. Efficacy of linaclotide for patients with chronic constipation. Gastroenterology 2010;138(3):886–95.e1.

39. Miner PB Jr, Koltun WD, Wiener GJ, et al. A randomized phase III clinical trial of plecanatide, a uroguanylin analog, in patients with chronic idiopathic constipation. Am J Gastroenterol 2017;112(4):613-621.

40. Menees SB, Franklin H, Chey WD. Evaluation of plecanatide for the treatment of chronic idiopathic constipation and irritable bowel syndrome-constipation in patients aged 65 or older. Clin Ther 2020;42(7):1406–14.

41. Barish CF, Drossman D, Johanson JF, et al. Efficacy and safety of lubiprostone in patients with chronic constipation. Dig Dis Sci 2010;55(4):1090–7.

42. 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(3):315–28.

43. Müller-Lissner S, Rykx A, Kerstens R, et al. A double-blind, placebo-controlled study of prucalopride in elderly patients with chronic constipation. Neurogastroenterol Motil 2010;22(9):991.e5.

44. In brief: tegaserod (Zelnorm) returns. Med Lett Drugs Ther 2019;61(1571):72.

45. Vijayvargiya P, Camilleri M. Use of prucalopride in adults with chronic idiopathic constipation. Expert Rev Clin Pharmacol 2019;12(7):579–89.

46. Markham A. Tepanor: first approval. Drugs 2019;79:1897–903.

47. Chey WD, Lembo AJ, Korner P, et al. Efficacy and safety of tenapanor in patients with constipation predominant irritable bowel syndrome: a 12 week, double-blind, placebo-controlled, randomized phase 3 trial. Am J Gastroenterol 2017; 112(Suppl 1):S226 [Abstract: 421].

48. Chey WD, Lembo AJ, Yan A, et al. Efficacy and safety of tenapanor in patients with constipation predominant irritable bowel syndrome: a 6-month, double-blind, placebo-controlled phase 3 trial (T3mpo-2). Gastroenterology 2018;154(6 Suppl 1):S-1362 [Abstract: 885].

49. De Giorgio R, Ruggeri E, Stanghellini V, et al. Chronic constipation in the elderly: a primer for the gastroenterologist. BMC Gastroenterol 2015;15:130.

50. Hussain ZH, Whitehead DA, Lacy BE. Fecal impaction. Curr Gastroenterol Rep 2014;16(9):404.

51. Vijayakumar C, Balagurunathan K, Prabhu R, et al. Stercoral ulcer not always indolent: a rare complication of fecal impaction. Cureus 2018;10(5):e2613.

52. Simren M, Palsson OS, Whitehead WE. Update on Rome IV criteria for colorectal disorders: implications for clinical practice. Curr Gastroenterol Rep 2017; 19(4):15.

53. Aziz I, Whitehead WE, Palsson OS, et al. An approach to the diagnosis and management of Rome IV functional disorders of chronic constipation. Expert Rev Gastroenterol Hepatol 2020;14(1):39–46.

54. Chiarioni G, Salandini L, Whitehead WE. Biofeedback benefits only patients with outlet dysfunction, not patients with isolated slow transit constipation. Gastroenterology 2005;129(1):86–97.

55. Archambault-Ezenwa L, Brewer J, Markowski A. A comprehensive physical therapy approach including visceral manipulation after failed biofeedback therapy for constipation. Tech Coloproctol 2016;20(8):603–7.

56. Pasin Neto H, Borges RA. Visceral mobilization and functional constipation in stroke survivors: a randomized, controlled, double-blind, clinical trial. Cureus 2020;12(5):e8058.

57. Bharucha AE, Rao SSC, Shin AS. Surgical interventions and the Use of device-aided therapy for the treatment of fecal incontinence and defecatory disorders. Clin Gastroenterol Hepatol 2017;15(12):1844-1854.

58. Wilkinson-Smith V, Bharucha AE, Emmanuel A, et al. When all seems lost: management of refractory constipation-Surgery, rectal irrigation, percutaneous endoscopic colostomy, and more. Neurogastroenterol Motil 2018;30(5):e13352.

59. Perrot L, Fohlen A, Alves A, et al. Management of the colonic volvulus in 2016. J Visc Surg 2016;153(3):183–92.

60. Gortazar de Las Casas S, Rubio-Pérez I, Saavedra Ambrosy J, et al. Sacral nerve stimulation for constipation: long-term outcomes. Tech Coloproctol 2019;23(6): 559–64.

61. Gokce AH, Gokce FS. Effects of bilateral transcutaneous tibial nerve stimulation on constipation severity in geriatric patients: a prospective clinical study. Geriatr Gerontol Int 2020;20(2):101–5.

62. Rao SSC, Lembo A, Chey WD, et al. Effects of the vibrating capsule on colonic circadian rhythm and bowel symptoms in chronic idiopathic constipation [published online ahead of print, 2020 May 25]. Neurogastroenterol Motil 2020;e13890. https://doi.org/10.1111/nmo.13890.

63. Kalso E, Edwards JE, Moore RA, et al. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. Pain 2004;112(3):372–80.

64. Rosti G, Gatti A, Costantini A, et al. Opioid-related bowel dysfunction: prevalence and identification of predictive factors in a large sample of Italian patients on chronic treatment. Eur Rev Med Pharmacol Sci 2010;14(12):1045–50.

65. Kurz A, Sessler DI. Opioid-induced bowel dysfunction: pathophysiology and potential new therapies. Drugs 2003;63(7):649–71.

66. Dorn S, Lembo A, Cremonini F. Opioid-induced bowel dysfunction: epidemiology, pathophysiology, diagnosis, and initial therapeutic approach. Am J Gastroenterol Suppl 2014;2(1):31–7.

67. Hanson B, Siddique SM, Scarlett Y, et al. American Gastroenterological association Institute clinical guidelines Committee. American Gastroenterological association Institute Technical review on the medical management of opioid-induced constipation. Gastroenterology 2019;156(1):229–53.e5.

68. Luthra P, Burr NE, Brenner DM, et al. Efficacy of pharmacological therapies for the treatment of opioid-induced constipation: systematic review and network meta-analysis. Gut 2019;68(3):434–44.

69. Nee J, Zakari M, Sugarman MA, et al. Efficacy of treatments for opioid-induced constipation: systematic review and meta-analysis. Clin Gastroenterol Hepatol 2018;16(10):1569–84.e2.