REVIEW

CME

Chronic Constipation in the Elderly

Juan F. Gallegos-Orozco, MD[1], Amy E. Foxx-Orenstein, DO[1], Susan M. Sterler, RN[1] and Jean M. Stoa, RN[1]

Constipation is one of the most frequent gastrointestinal disorders encountered in clinical practice in Western societies. Its prevalence increases with age and is more frequently reported in female patients. Chronic constipation has been associated with considerable impairment in quality of life, can result in large individual healthcare costs, and represents a burden to healthcare delivery systems. This review will focus on the definition, epidemiology, diagnostic approach, and non-pharmacologic as well as pharmacologic management of chronic constipation in the elderly, including an overview of new medications currently under clinical investigation.

INTRODUCTION

Constipation is one of the most frequently diagnosed gastrointestinal disorders. Most studies estimate the prevalence of constipation in the general population to be 12–19% (1,2). The prevalence increases with age and is more frequent in females (1). In studies of self-reported constipation, 26% of women and 16% of men 65 years or older considered themselves to be constipated; in the subgroup of persons 84 years or older, the prevalence was 34 and 26%, respectively (3,4). Most persons consider it a nuisance, yet the reality is that constipation is associated with impaired quality of life (5), significant individual healthcare costs, and a large economic burden. Nearly 85% of physician visits for constipation result in a prescription for laxatives and >$820 million are spent per year on over-the-counter laxatives (6,7).

HOW DO WE DEFINE CHRONIC CONSTIPATION?

Chronic constipation is a symptom-based disorder characterized by unsatisfactory defecation due to infrequent stools, difficult stool passage, or both. Difficult stool passage includes symptoms of straining, difficulty expelling stool, a sense of incomplete evacuation, hard or lumpy stools, prolonged time to stool, or a need for manual maneuvers to pass stool, which has been present for at least 3 of the prior 12 months (8). This is the definition often applied by clinicians when diagnosing a patient with chronic constipation, while for research purposes, a more stringent definition is provided by the Rome III criteria (9) (**Table 1**).

WHAT IS THE IMPACT OF CHRONIC CONSTIPATION IN THE ELDERLY?

Constipation is one of the most common gastrointestinal disorders encountered in clinical practice. Up to one-fifth of the general population suffers from chronic constipation during their lifetime (1,2). The prevalence of constipation varies depending on the definition used, the age of the population studied, whether it is self-reported or diagnosed by a healthcare provider, as well as the setting in which the investigation is performed (community, outpatient, hospitalized, or long-term care facility). In studies of self-reported constipation, 26% of women and 16% of men 65 years or older considered themselves to be constipated; in the subgroup of persons 84 years or older, the prevalence was 34 and 26%, respectively (10–12). In a community-based study from Olmsted County, MN, the overall self-reported prevalence of constipation per 100 persons aged 65 years or older was 40 (95% confidence interval (CI): 38.9, 44.4); for functional constipation, it was 24.4 (95% CI: 22, 26.9), and for symptoms of outlet obstruction or delay, it was 20.5 (95% CI: 18.2–22.8) (13).

If defined solely on the basis of number of bowel movements weekly, the prevalence of constipation decreases to <10% when using a definition of two or fewer stools per week. Notably, of persons who consider themselves to be constipated, <10% have fewer than two bowel movements weekly and nearly half actually have a bowel movement on a daily basis (14,15). As might be assumed from this, difficulties with defecation that present often as hard stools and straining are quite prevalent in the elderly (16). In a community-based study in the United States of persons older than 65 years that reported being constipated, persistent straining was reported by 65% and almost 40% reported passage of hard stools on a regular basis (17). Similarly, up to a fifth of elderly people met diagnostic criteria of rectal outlet delay (**Table 2**) (3,18).

Constipation and defecation problems are even more frequent among elderly residents of long-term care facilities (16,19). A study from Finland revealed that 57% of women and 64% of men reported chronic constipation or rectal outlet delay; while the prevalence increased to 79 and 81%, respectively, in a nursing

[1]Division of Gastroenterology, Mayo Clinic in Arizona, Scottsdale, Arizona, USA. **Correspondence:** Amy E. Foxx-Orenstein, DO, Division of Gastroenterology, Mayo Clinic in Arizona, 13400 E Shea Boulevard, Scottsdale, Arizona 85259, USA. E-mail: foxx-orenstein.amy@mayo.edu

Table 1. Rome III diagnostic criteria for functional constipation

1. Must include two or more of the following:

    a. Straining during at least 25% of defecations

    b. Lumpy or hard stools in at least 25% of defecations

    c. Sensation of incomplete evacuation for at least 25% of defecations

    d. Sensation of anorectal obstruction/blockage for at least 25% of defecations

    e. Manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)

    f. Fewer than three defecations per week

2. Loose stools are rarely present without the use of laxatives

3. There are insufficient criteria for IBS

Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis

IBS, irritable bowel syndrome.
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Table 2. Rome III diagnostic criteria for functional defecation disorders

1. The patient must satisfy diagnostic criteria for functional constipation (Table 1)

2. During repeated attempts to defecate must have at least two of the following:

    a. Evidence of impaired evacuation, based on balloon expulsion test or imaging

    b. Inappropriate contraction of the pelvic floor muscles (i.e., anal sphincter or puborectalis) or <20% relaxation of basal resting sphincter pressure by manometry, imaging, or EMG

    c. Inadequate propulsive forces assessed by manometry or imaging

Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis

EMG, electromyography.
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home setting. Also telling is the fact that 50–74% of long-term care residents use laxatives on a daily basis (12).

The high rate of recurrence of constipation and/or rectal outlet problems in the elderly results not only in diminished health-related quality of life and high economic burden, but contributes to complications such as fecal impaction, stercoral ulcers, volvulus, and visits to the hospital to correct these problems (15). Healthcare workers caring for the elderly, especially the more debilitated, need to be cognizant of the frequency of constipation and defecatory problems in this population, and be prepared to diagnose and offer remedy in a timely fashion to reduce morbidity.

HOW DO WE CLINICALLY CLASSIFY CHRONIC CONSTIPATION?

For ease of approach to diagnosing the root source and contributing causes of constipation, as well as to guide treatment, constipation can be divided into primary and secondary types.

Primary types of chronic constipation can be classified as:

- Slow-transit constipation, characterized by prolonged stool transit through the colon and reduced rectal sensation, can be the result of primary dysfunction of the colonic smooth muscle, its innervation, or both. It can also occur in the setting of a generalized intestinal motility disorder.
- Defecation disorders, characterized by difficult or unsatisfactory expulsion of stool from the rectum, can result from dyssynergic defecation (impaired relaxation/coordination of abdominal and pelvic floor muscles during evacuation), impaired perineal descent, as well as anorectal or urogynecological structural abnormalities (**Table 3**).
- Constipation-predominant irritable bowel syndrome, in which abdominal discomfort or pain relieved by defecation is the predominant symptom.

In practice, there can be overlap of primary types of constipation in the individual patient (20). We have focused our review on the management of chronic constipation not associated with irritable bowel syndrome, as this truly is a topic of its own, and for which excellent reviews have been recently published (21–23).

There are numerous secondary causes and situations that increase the risk of constipation (**Table 4**).

WHAT ARE THE COMMON MECHANISMS INVOLVED IN CONSTIPATION IN THE ELDERLY POPULATION?

The current thinking is that changes in colonic motility and physiology that predispose patients to constipation are not primarily age-related, but rather a consequence of extrinsic factors closely associated with aging, as described below. Nonetheless, studies of colonic physiology in the elderly have documented intrinsic changes that can predispose this population to develop constipation (reviewed in Feldstein *et al.* (24) and Harari (25)):

- Reduced number of neurons in the myenteric plexus and impaired response to direct stimulation (26,27), which eventually result in myenteric dysfunction
- Increased collagen deposition of the left colon, leading to abnormalities in colonic and rectal compliance and dysmotility (26)
- Reduction in the amplitude of inhibitory nerve input to the circular muscle layer of the colon, resulting in lack of segmental motor coordination (28)
- Increased binding of plasma endorphins to intestinal receptors in persons 60 and older (29)

Changes in anorectal function have also been well documented in the elderly, and include

- Diminished resting and maximal anal sphincter pressure, possibly secondary to decreased muscle mass and contractility, together with pudendal nerve damage associated with perineal descent in elderly women (30,31)
- Decreased maximal squeeze pressure and loss of rectal wall elasticity (32)

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Table 3. Causes of pelvic floor dysfunction

Anal fissure
Anal stricture
Dyssynergic defecation
Pelvic floor descent (impaired or excessive)
Proctitis
Rectocele
Thrombosed hemorrhoids
Urogynecologic dysfunction

- Defecography of elderly females demonstrate a frequent failure of rectal evacuation due to insufficient opening of the rectoanal angle and an increased degree of perineal descent when compared with younger females (26,33)
- Fibro-fatty degeneration and increased thickness of the internal anal sphincter with aging (34,35).

WHAT ARE THE COMMON FACTORS THAT CONTRIBUTE TO CONSTIPATION IN THE ELDERLY?

Many factors particular to the elderly population have been identified as contributing to constipation, such as increased use of anticholinergic agents, opioid analgesics, calcium supplements, calcium-channel blockers, and NSAIDs (non-steroidal anti-inflammatory drugs). Anticholinergic drugs reduce intestinal smooth-muscle contractility and have been associated with daily laxative use in nursing home residents and community-dwelling elderly persons (36). Constipation is a frequent side-effect from oral calcium supplementation that contributes to non-compliance in the elderly (37). Calcium-channel antagonists are associated with rectosigmoid dysmotility and can result in severe constipation, especially in patients taking nifedipine and verapamil (38). NSAIDs, probably through their effect on prostaglandin metabolism, also increase the risk of constipation in the elderly and can lead to poor compliance, even more frequently than symptoms of dyspepsia (39). Of note, NSAIDs have also been associated with an increased risk of stercoral ulcer perforation in elderly patients with chronic constipation (25).

Other relevant factors that can lead to constipation include dietary changes that are commonly seen in the elderly, such as poor fluid intake, diets low in fiber, and proportionally high in protein and fat, or are of small quantity. Also, impaired mobility, neurological or cognitive disorders such as Parkinson's disease, stroke, spinal cord disease, dementia, depression, along with nursing home residence and metabolic factors increase the risk of constipation (25).

HOW SHOULD WE EVALUATE THE ELDERLY PATIENT WITH CONSTIPATION?

Evaluation of elderly patients with constipation or rectal outlet symptoms must be individualized to the patients' particular

Table 4. Common causes of secondary constipation and conditions associated with constipation

Drugs
Anabolic steroids
Analgesics
Opioids
Non-steroidal anti-inflammatory drugs
Anticholinergics
Anticonvulsants
Antidepressants
Antihistamines
Antihypertensives
Anti-Parkinsonian
Diuretics
Metal ions
Neuropathic and myopathic disorders
Amyloidosis
Autoimmune
Chagas disease
CNS lesions
Connective tissue disorders
Diabetes mellitus
Hirschprung's disease
Idiopathic
Paraneoplastic syndromes
Parkinson's disease
Post-viral colonoparesis
Pseudoobstruction
Spinal or ganglion tumor
Stroke
Conditions associated with constipation
Anorexia
Dehydration
Ignoring the urge to defecate
Diet
Low intake
Low fiber
High protein
Very high fiber
Hyperglycemia
Hypokalemia
Hypothyroidism
Pregnancy and childbirth
Psychological and psychiatric disorders
Sedentary lifestyle
Travel
CNS, central nervous system.

medical and psychosocial circumstance. Not all patients require the same diagnostic approach, especially when it comes to the more invasive procedures.

The first step in evaluating an elderly patient with constipation should always be a detailed history and physical examination, including an adequate visual and digital anal examination. In the elderly patient presenting with loose stools, the digital rectal examination is very useful to assess for fecal impaction as a cause of overflow incontinence, as if misdiagnosed, these patients can erroneously be treated with antidiarrheals, which will only worsen their condition. This initial clinical assessment will aid in determining primary and secondary causes of constipation, as well as the presence of "alarm" symptoms and signs. Use of the Bristol Stool Scale can offer patients a visual and numeric reference and caretakers a rough estimate of colonic transit time. Low scale numbers (#1, 2) mean slower, while high values (#5–7) support faster transit although impaired rectal sensation or barrier function can also influence stool appearance (40). Key alarm features include involuntary weight loss of >10 lb, hematochezia, family history of colorectal cancer or inflammatory bowel disease, positive fecal occult blood testing, iron deficiency anemia, acute onset of constipation or a notable change in bowel habit in the recent past (8). When alarm symptoms are present, a dedicated evaluation of the colon with colonoscopy, or in selected cases, computed tomographic colonography should be performed. Other testing will depend on the clinician's suspicion for other causes of constipation. In the absence of alarm features, the diagnostic approach can be guided based on a patient's symptomatic response to initial empiric treatment and to their presenting symptoms, which may point to a primary type of constipation (8). For prolonged delay in stool evacuation studies of colonic transit using radiopaque markers (normal ≥80% of markers pass by day 5) or nuclear medicine transit may identify slow transit. SmartPill (SmartPill Corporation, Buffalo, NY), a novel ambulatory and non-invasive method to evaluate intestinal motility has been recently described. By detecting intraluminal changes in pH, temperature, and pressure, the wireless motility capsule provides a measure of gastric emptying, and of small bowel and colonic transit time, which closely parallels the results obtained with radiopaque markers (41,42). Colon transit may be delayed in the presence of pelvic floor dysfunction and normalize with treatment. For patients with difficult evacuation or hard stools anorectal manometry with balloon expulsion and in selected cases, traditional proctography or a magnetic resonance imaging defecogram can be performed and help guide treatment (43). Diagnostic studies should be employed if the information gained is apt to alter treatment.

WHAT IS THE CURRENT NON-PHARMACOLOGIC MANAGEMENT OF CHRONIC CONSTIPATION?

Educating patients on the importance of diet, exercise, and toilet training can lead to improved symptoms so often that it is considered a first-line treatment for constipation. If available, consultation with a dedicated nurse educator with expertise in this area provides a great resource for patients (**Table 5**). Patients are

Table 5. Nurse educator recommendations in the treatment of the elderly patient with chronic constipation

Identify learning barriers for each patient (i.e., hearing or visual impairment, cognitive decline, etc.)

Keep a detailed bowel diary and provide education to improve toileting

Perform a thorough review of the prescription and non-prescription medications the patient is taking and identify those that can cause or exacerbate constipation

Specific dietary recommendations regarding well-balanced healthy diet, adequate fluid, and fiber intake

Recommend regular physical activity (i.e., walking, swimming, yoga, Thai Chi, etc.)

Frequent follow-up visits or phone calls with the nurse educator to improve compliance and assess clinical response and need for further intervention

recommended to keep a detailed diet log as well as a diary of stool frequency and consistency (Bristol Stool Scale), together with any associated symptoms such as straining or the need for manual or positional maneuvers to facilitate defecation. Emphasis should be put on recognizing and responding to the urge to move their bowels, especially in the morning. We often recommend a regimented daily routine that ends with an evening dose of fiber supplement (bulk and soften), and begins with mild physical activity, a hot (preferably caffeinated) beverage, and a fiber cereal (induce high amplitude peristaltic contractions) within an hour of arising, followed by a visit to the toilet when the first urge is perceived. This routine takes advantage of known factors that stimulate defecation, including physical activity, the gastro-colic reflex, hot fluid, caffeine, and fiber (44,45).

Most healthy Americans consume less than half of the recommended daily intake of fiber (20–35 g/day) (46). Increased dietary fiber intake can result in decreased colonic transit times and increased stool bulk (47), and should be used as a first-line treatment of patients with chronic constipation, especially of mild-to-moderate severity. The aim should be to increase dietary fiber to the daily recommended amount or as much as tolerated. This can be done through fiber-rich foods such as bran, fruits, vegetables, and nuts. When unable to achieve the goal by dietary means, adding fiber supplements can be useful. In elderly patients with constipation, adding bran 10 g twice daily resulted in significantly shorter colonic transit times (89 vs. 126 h) compared with patients who received psyllium 6 g twice daily (48). As increases in fiber intake can result in gas and bloating, the aim is to augment fiber intake slowly by about 5 g/day every week until the target is met (20,46,49).

Alternative ways to increase fiber intake include incorporating prune juice or prunes in the patient's diet. Two recent randomized trials demonstrated efficacy in promoting spontaneous bowel movements and relieving constipation-related symptoms in middle-aged women with mild-to-moderate constipation with the use of prunes or prune juice compared with psyllium. The first one randomized women to a 6-week course of daily psyllium (6 g fiber/day) vs. a modified bowel recipe (1 cup of unprocessed bran, 1 cup of applesauce, and ¼ cup of prune juice equivalent to 6 g fiber/day).

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Both groups demonstrated similar improvement in validated constipation questionnaires, although the bowel recipe group had a significant improvement in straining (50). The other study was an 8-week, randomized trial of 40 subjects (37 women) with constipation who received either 50 g of prunes twice daily (6 g fiber/day) or psyllium 11 g twice daily (6 g fiber/day) for 3 weeks each, in a crossover trial with a 1-week washout period. The primary outcome measure was the number of complete spontaneous bowel movements per week, and was significantly improved with prunes compared with psyllium; similarly, stool consistency scores improved with prunes vs. psyllium. Of note, straining and global constipation symptoms were similar between both treatments, and both were rated as equally palatable, and both were safe and well tolerated (51). The above results support the use of prunes or prune juice as a safe and less costly alternative to psyllium in the initial management of patients with mild-to-moderate constipation.

There is a subgroup of patients with constipation who respond consistently poorly to a high-fiber diet, such as those with refractory slow-transit constipation or with severe pelvic floor dyssynergy, in whom we recommend minimizing dietary fiber content, much like the low-residue diet commonly used in patients with gastroparesis. We encourage these patients to puree, cook, and chew well any fiber-rich foods and to avoid any fiber supplements. Treatment then focuses on osmotic agents to increase stool water content without bulking or on stimulant laxatives to enhance propulsion.

There has been a tremendous spike in interest and use of probiotics within the past few years. A recent meta-analysis of three randomized placebo-controlled trials in adults with functional constipation suggested that treatment with *Bifidobacterium lactis* DN-173 010 (52), *Lactobacillus casei* Shirota (53), and *Escherichia coli* Nissle 1917 (54) resulted in favorable effects on stool frequency and consistency (31). Nonetheless, until more robust clinical evidence on efficacy and safety has been published, these agents should still be considered investigational for the treatment of constipation (55).

Biofeedback training is an important treatment option that has proven especially useful in the patient with dyssynergic defecation, which is characterized by impaired coordination between pelvic floor muscle relaxation and abdominal wall motion or the effort necessary for defecation. The goal of anorectal biofeedback is to retrain patients to relax the pelvic floor muscles while at the same time produce a propulsive force using the abdominal muscles (**Table 6**). It generally results in improved defecation plus patient satisfaction as reported in several randomized clinical trials (56–60).

Another non-pharmacological therapeutic option in selected patients with treatment-resistant constipation is electrical stimulation. Limited clinical information supports the use of sacral neuromodulation for intractable chronic constipation in patients who have failed conservative management. The mechanism of action is unclear, but it is currently thought that neuromodulation of the extrinsic neural control of the colon or modulation of inhibitory reflexes may explain the benefits seen in the treatment of constipation with this modality. There is currently a paucity of data on this topic, and further research is warranted (61).

Table 6. Anorectal biofeedback for patients with dyssynergic defecation

The retraining process involves insertion of a rectal catheter with the sphincter muscles straddling four sensors
A balloon at the end of the catheter is inflated with air, which allows monitoring of abdominal effort
Verbal instruction is given to the patient on what relaxation feels like
• The patient takes a deep breath, exhaling a strong steady breath though the mouth while at the same time pushing the abdomen forward and relaxing the anal sphincter
• This exercise should last 10 seconds with a 20-second rest period and repeated until evacuation is complete
This push maneuver assists with increasing intra-abdominal pressure while at the same time relaxing the pelvic floor muscles, thus assisting with forward stool propulsion
The anorectal biofeedback program is generally done on a weekly basis for a total of six sessions (programs can vary)

WHAT ARE THE CURRENT PHARMACOLOGIC TREATMENT OPTIONS FOR THE ELDERLY WITH CHRONIC CONSTIPATION?

Numerous over-the-counter laxatives are available for treating the symptoms of chronic constipation and are generally regarded as second-line therapy to life style, non-pharmacologic interventions (62,63). These remedies include bulking agents, stool softeners, stimulant laxatives, and osmotic agents (64,65).

Fiber or bulking agents

Fiber or bulking agents refer to organic polymers that increase the water-absorbency properties of stool, thereby increasing stool bulk, consistency, and weight. Within this category are bran and psyllium (natural), and methylcellulose and calcium polycarbophil (synthetic). The main side-effects of fiber are flatulence, abdominal bloating (less with synthetic fiber) and distention, unpalatability, and rarely bowel obstruction (62,65). Although routinely used as first-line pharmacologic therapy in patients with constipation, bulking agents are not useful for all patients. This is especially true in patients with proven slow transit or in those with pelvic floor dysfunction, where only 20 and 37% improved after 6 weeks of psyllium supplementation, respectively (66).

Stool softeners

Stool softeners function primarily as detergents allowing a more effective interaction between water and solid stool, thereby softening stool consistency and facilitating evacuation of hard stool. This category includes docusate sodium and ducosate calcium. They are not very effective and there are insufficient data to support their use in patients with chronic constipation (65,67).

Stimulant laxatives

Stimulant laxatives work by direct stimulatory effects of the myenteric plexus on contact with the colonic mucosa and also by inhibiting water absorption. The net result is an increase in intestinal motility. Medications in this category include senna, cascara

sagrada, aloe, bisacodyl, and sodium picosulfate (which is not currently available in the United States). Except for sodium picosulfate (68) and bisacodyl (64), there is limited evidence to support the routine use of these agents. In a recent meta-analysis, both of these trials were included and both of these agents were better than placebo in increasing the number of complete spontaneous bowel movement, with a number needed to treat (NNT) of 3 (95% CI: 2–3.5) (64). The NNT represents the number of patients, similar to the study patients, who need to be treated to obtain one fewer bad outcome or one improved outcome compared with the control group treatment. It is calculated as the reciprocal of the absolute risk reduction (69). Stimulant laxatives are associated with significant side-effects including abdominal cramping and discomfort, occasional electrolyte abnormalities, and the frequent occurrence of melanosis coli, which of note, is of no clinical consequence other than being a marker of chronic laxative use at the time of colonoscopy. For this reason, we do not use them first line in treatment of the chronically constipated patient.

Osmotic laxatives

Osmotic laxatives refer to a group of agents that contain poorly absorbed ions or molecules, hence creating on osmotic gradient within the intestinal lumen and resulting in increased water retention within the lumen, and consequently an increase in stool water content. This leads to softer stool and ease of propulsion through the colon (20). Within this category are polyethylene glycol (PEG), lactulose, sorbitol, milk of magnesia, and magnesium citrate. PEG (available over-the-counter and by prescription) is a non-absorbable, non-metabolized osmotic agent, which has been used for chronic constipation as well as for colon preparation in patients undergoing colonoscopy. Good quality evidence supports the use of both PEG and lactulose in the treatment of chronic constipation (70–74). In a recent meta-analysis it was estimated that the NNT to improve constipation with osmotic laxatives was 3 (95% CI: 2–4) (64). Comparisons between PEG and lactulose favor the former (75–77), this is especially relevant now that PEG can be found over-the-counter in the United States. Patients on osmotic laxatives can have abdominal cramping, bloating, and flatulence, but rarely do they cause electrolyte imbalance. They are considered safe for long-term use, and we use them routinely in our practice (64).

Chloride-channel activator

Lubiprostone is a chloride-channel activator (available by prescription only) that selectively activates type 2 chloride channels in the enterocyte's apical membrane, resulting in chloride secretion into the intestinal lumen followed by passive diffusion of sodium and water (78). The net effect is an increase in stool water content, which in turn causes bowel distention, peristalsis, and laxation without a direct effect on gastrointestinal smooth muscle (79). In contrast to the dose of 8 μg twice daily used in patients with constipation-predominant irritable bowel syndrome, a higher dose is used in patients with chronic constipation. In this setting, 24 μg twice daily has been shown to be effective in both open-label and randomized controlled trials (80–82). The calculated NNT for lubiprostone in this patient population is 4 (95% CI: 3–7) (64).

No significant electrolyte changes have been reported with prolonged use of lubiprostone, but it frequently causes nausea (30%), diarrhea, and headache (83). Of note, this drug was better tolerated among persons >65 years of age, in whom adverse events were less frequent then in younger patients (80).

WHAT'S ON THE HORIZON FOR MEDICAL THERAPY OF CHRONIC CONSTIPATION?

Up to one-half of patients treated for constipation report less than ideal results, which has prompted a search for more and better medications (17). These include guanylate cyclase (GC) activators, serotonergic enterokinetic agents, motilin agonists, and opioid receptor antagonists (84–87). For a complete review on the current management of opioid-induced constipation, please refer to Dr Camilleri's recent article in the *American Journal of Gastroenterology* (88).

GC activators

Linaclotide is a novel GC-C receptor agonist. It activates the GC-C receptor on the apical surface of intestinal epithelial cells, resulting in an increase in intra- and extracellular cyclic guanosine monophosphate. The net effect is increased secretion of chloride and bicarbonate into the intestinal lumen and consequently increased fluid secretion and accelerated stool transit (89). Linaclotide (150–300 μg/day) increased the number of weekly spontaneous bowel movements, improved stool consistency, straining, and severity of constipation (90,91). In a recent meta-analysis, the calculated NNT for linaclotide vs. placebo was 6 (95% CI: 5–8) (64). The most common side-effect is dose-dependent diarrhea, but <5% of patients discontinued its use due to adverse events (64,90,91).

Serotonergic enterokinetic agents

Prucalopride is a highly selective and readily bioavailable 5-HT$_4$ receptor agonist with minimal activity at other serotonin receptors. Prucalopride does not undergo metabolism through CYP3A4 and thus has less drug–drug interaction potential than other 5-HT$_4$ receptor agonists (92). Recent randomized controlled trials have demonstrated prucalopride's efficacy for treating chronic constipation (93–97). One of these specifically addressed the use of prucalopride in patients older than 65 years of age and concluded that it had beneficial effects on bowel movements, constipation-related symptoms, and quality of life, and that it was safe and well tolerated by this patient population (95). There are no significant differences in clinical efficacy between the 2- and 4-mg daily dose of prucalopride and in a recent meta-analysis, the calculated NNT to improve constipation was 6 (95% CI: 5–9) (64). The most common side-effects reported with prucalopride are headache, nausea, and diarrhea (64).

Velusetrag (TD-5108) and norcisapride (ATI-7505) are novel selective 5-HT$_4$ receptor agonists currently under development for treating chronic constipation (98). A recent randomized, placebo-controlled, 4-week trial of velusetrag (15, 30, or 50 mg daily) concluded that it was efficacious and well tolerated in patients with chronic idiopathic constipation (99). In a pharmacodynamic study, norcisapride (ATI-7505) was shown to accelerate colonic transit in

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healthy volunteers (100), and more recent early phase 2 trials of 80 mg twice daily show clinical benefits (64).

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