

CLINICAL REVIEW

Chronic Constipation: An Evidence-Based Review

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Background: Chronic constipation is a common condition seen in family practice among the elderly and women. There is no consensus regarding its exact definition, and it may be interpreted differently by physicians and patients. Physicians prescribe various treatments, and patients often adopt different over-the-counter remedies. Chronic constipation is either caused by slow colonic transit or pelvic floor dysfunction, and treatment differs accordingly.

Methods: To update our knowledge of chronic constipation and its etiology and best-evidence treatment, information was synthesized from articles published in PubMed, EMBASE, and Cochrane Database of Systematic Reviews. Levels of evidence and recommendations were made according to the Strength of Recommendation taxonomy.

Results: The standard advice of increasing dietary fibers, fluids, and exercise for relieving chronic constipation will only benefit patients with true deficiency. Biofeedback works best for constipation caused by pelvic floor dysfunction. Pharmacological agents increase bulk or water content in the bowel lumen or aim to stimulate bowel movements. Novel classes of compounds have emerged for treating chronic constipation, with promising clinical trial data. Finally, the link between senna abuse and colon cancer remains unsupported.

Conclusions: Chronic constipation should be managed according to its etiology and guided by the best evidence-based treatment. (J Am Board Fam Med 2011;24:436–451.)

Keywords: Chronic Constipation, Clinical Review, Evidence-Based Medicine, Family Medicine, Gastrointestinal Problems, Systematic Review

The word “constipation” has varied meanings for different individuals. Although medical personnel define constipation as <3 bowel movements per week,^{1,2} patients often equate constipation with stool consistency, feelings of incomplete emptying, straining, and urge for defecation.^{3,4} Furthermore, the normalcy of bowel habit ranges widely from 3 bowel movements per day to 3 per week,⁵ with a tendency to underestimate while self-reporting⁶; hence, using defecation frequency alone may not be diagnostic of constipation. The Rome Foundation

was established in 1991 by Drossman et al, primarily to standardize consensus-derived criteria of functional gastrointestinal disorder, and released the Rome III criteria in 2006 for constipation as having at least 2 of the following: (1) straining during $\geq 25\%$ of defecation; (2) lumpy or hard stools in $\geq 25\%$ of defecation; (3) sensation of incomplete evacuation in $\geq 25\%$ of defecation; (4) sensation of anorectal obstruction/blockage in $\geq 25\%$ of defecation; (5) need for manual maneuvers to facilitate in $\geq 25\%$ of defecation; and (6) fewer than 3 defecations per week.^{7,8} Also, patients should rarely have loose stools without laxatives and be distinct from having irritable bowel syndrome.^{8,9} For constipation to be defined as chronic, a patient must be symptomatic for at least 6 months with applicable criteria for the previous 3 months.^{3,9} Although the validity of the Rome III criteria for constipation has been recently questioned,¹⁰ with a known disparity between self-reported and criteria-based definitions,¹¹ the use of colonic transit time^{12,13} and

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anorectal function tests¹⁴ as diagnostic tools is still controversial. In general, the prevalence of constipation among the general population in North America has been quoted as 1.9% to 27.2%,^{15,16} with 50% to 74% of the institutionalized elderly reporting daily use of laxatives.^{17,18} Women are 2 to 3 times more likely to have constipation than men in terms of prevalence^{3,15,19–21} and physical symptoms.^{15,20} Possible reasons include higher risk of injury to the pelvic floor from childbirth²² and the general willingness of women to report their symptoms and respond to surveys.²³ Advanced age is also a risk factor for chronic constipation, with the largest increase in prevalence after the age of 70 years.¹⁵ This can be due to effects of medication, immobility, and blunted urge to defecate. In the United States, constipation accounts for 7 million physician visits per year²⁴ and is among the top 5 outpatient gastrointestinal diagnoses.²⁵ Annually, diagnostic workup for constipation averages US\$3000 per patient,²⁶ and it takes another US\$4500 per person to provide treatment.²⁷ In general, constipation has a significant impact on quality-of-life indicators irrespective of culture and nationalities,²⁸ especially on the elderly.²⁹ A recent systematic review showed that impairment caused by constipation as measured by Health-Related Quality of Life scores predominates in the mental health domains and is comparable to that caused by serious chronic conditions such as osteoarthritis and diabetes.³⁰

Etiology of Chronic Constipation

Extrinsic Factors

Low fiber intake, inadequate hydration, reduced mobility as the result of general functional decline and institutionalization, reduced sensation of thirst, electrolyte disturbances (hypercalcemia, hypokalemia, hypermagnesemia), endocrine and metabolic disorders (eg, diabetes mellitus, hyperparathyroidism, hypothyroidism, chronic renal failure), neurological disorders (eg, dementia, Parkinson disease, neuropathies, multiple sclerosis, spinal cord injuries, cauda equine syndrome), psychological comorbidities (eg, depression, distress, personality disorders, or history of abuse), and concurrent medications (eg, anticholinergics, diuretics, β -blockers, opiates, iron supplements, calcium channel blockers, antidepressants, acetaminophen, aspirin and NSAIDs) all are said to contribute to chronic constipation, especially in the elde-

ly.^{17,31–36} Among them, the trio of insufficient dietary fiber, fluids, and exercise has been widely ascribed,³⁷ but in fact the evidence behind these 3 factors is inconsistent and of low to medium quality.³⁸ (See Notes section: Diagnostic Approach for Chronic Constipation.) The association between smoking, alcohol, and body mass index with chronic constipation L131(BMI) is inconclusive.^{36,39}

Intrinsic Factors

Normal defecation requires a series of orchestrated actions, starting with relaxation of the puborectalis muscles, descent of the pelvic floor with straightening of the anorectal angle, inhibition of segmental colonic peristalsis, contraction of the abdominal wall muscles, and finally, relaxation of the external anal sphincter with expulsion of feces. Intrinsic factors leading to chronic constipation can be broadly classified into 2 categories: pelvic floor dysfunction (PFD) and slow colon transit time (STC). A retrospective study reported the prevalence of PFD as 37% and STC as 23%,⁴⁰ based on physiologic tests. However, a clear distinction between the two is often impossible, with an overlap of up to 55%.^{40,41}

Anorectal/PFD involves laxity of the pelvic floor muscles, impaired rectal sensation, and decreased luminal pressure in the anal canal and have been documented as causes for chronic constipation in the elderly, especially in women.^{42–44} On the contrary, paradoxical contraction of the puborectalis and external anal sphincter during defecation can lead to incomplete emptying^{45,46} or even functional outlet obstruction. Finally, anatomic anomalies (such as rectal wall prolapse or rectocele) or perineal damage (from traumatic childbirth or sacral nerve injury) can also distort the normal functions of the anorectal/pelvic floor unit.

STC is a poorly understood condition thought to be a cause of intractable constipation in children⁴⁷ and young women.⁴⁸ It is characterized by reduced high-amplitude propagated contractions^{49,50} in the colon, leading to slow transit of feces, bloating, abdominal discomfort, and infrequent defecation.⁵¹ The protracted time in the colon also renders the feces hard and small and fails to mount sufficient rectal pressure to trigger the defecation reflex.⁵² Often, the pressure required is found to be higher than in subjects with normal colonic transit.⁵³ Various physiologic and histobio-

chemical findings have been postulated to explain the phenomenon of slow colonic transit: reduced cholinergic^{54,55} and enhanced adrenergic responses⁵⁵; mitigated gastrocolic reflex⁵⁶; dysynergy of rectosigmoid colonic activities^{57,58}; enteric neurodegeneration⁵⁹ of both the myenteric plexus ganglia^{60,61} and the interstitial cells of Cajal^{61,62}; and abnormalities of enteric neurotransmitters such as substance P,^{63–65} vasoactive intestinal peptides,^{63,64} and nitric oxide.^{63,66}

Complications of Chronic Constipation

(1) Fecal incontinence: Overflow incontinence caused by fresh fecal matter bypassing the inspissated obstructing bolus⁶⁷ may confuse the diagnosis of chronic constipation unless a rectal examination is performed. The odds ratio for developing fecal incontinence with chronic constipation is 1.7.⁶⁸

(2) Hemorrhoids: Prolonged straining and increase of intra-abdominal pressure raises the venous pressure in the plexus and arteriovenous anastomoses of the anorectal junction.⁶⁹ The relative risk for development of hemorrhoids with constipation is up to 4.1.⁷⁰

(3) Anal fissure: Trauma and sudden tear of the anal mucosa during evacuation of hard stool is usually an initiating event, but spasm of the internal anal sphincter leading to relative ischemia is thought to be the perpetuating factor.⁶⁹ It is estimated that anal fissure is 5 times more likely to develop with chronic constipation.^{70,71}

(4) Organ prolapse: Chronic constipation is a known risk for prolapse of pelvic organs such as the uterus, rectum, urinary bladder, and vagina⁷² and their recurrence.⁷³ The odds ratio for having rectal prolapse is quoted as 2.3.⁶⁸

(5) Fecal impaction and bowel obstruction: Prolonged stasis of fecal matter leads to impaction and giant fecolith obstructing the large bowel, necessitating surgery.^{74,75} Retrospective analysis revealed a 5- to 6-times increased risk of fecal impaction resulting from chronic constipation.^{68,70,71}

(6) Bowel perforation and stercoral peritonitis: Extremely impacted feces (fecaloma) can compress the colonic wall, causing an ischemic ulcer⁷⁶ and subsequent perforation,^{77,78} culminating in stercoral peritonitis^{78,79} and sometimes death.⁷⁹ It is not a common condition; fewer than 90 cases have been reported in the medical literature from 1894 to 2006.⁸⁰

Diagnostic Approach and Investigations

It is important to conduct a detailed history and physical examination before proceeding with investigations. It is imperative to understand the patient's views and definitions of chronic constipation, which may often differ from medical criteria. The clinician should also weigh the cost-benefits of investigations and only order those that help diagnose the etiology of chronic constipation and affect the treatment and prognosis in such patients. A brief outline of the diagnostic approach for chronic constipation is given in the Notes section: Diagnostic Approach for Chronic Constipation. It must be emphasized that these investigations are not indicated as routine studies except for differentiating between slow colon transit time and pelvic floor dysfunction, in which treatment would differ. Moreover, contrast studies and colonoscopy should be considered if the patient has a positive family history of colon cancer or inflammatory bowel disease and presents with alarming complaints of rectal bleeding, abrupt weight loss, anemia, or change in bowel habits.

Evidence-Based Management of Chronic Constipation

Methods

A literature search of published medical reports in all languages was performed from PUBMED, EMBASE, and the Cochrane Database of Systematic Reviews from inception to October 2010 using the OVID Portal of Queen's University, Kingston, Ontario. Abstracts were initially obtained using key words of "chronic constipation," "treatment," and "trials." Manual searches of references and review articles supplemented the computerized search, and only full-length articles were considered. Two reviewers (L.L. and T.R.) worked independently and went over the initial search for abstracts that satisfied the key words as mentioned. They then adopted a simple form to select studies that satisfied the following 2 inclusion criteria: (1) involving human subjects over the age of 18 years and (2) describing at least 1 form of treatment for chronic constipation. Evaluation of selected studies was performed by each reviewer (L.L. and T.R.) regarding their quality and evidence according to the Strength of Recommendations Taxonomy (SORT),⁸¹ with levels of evidence from I to III and recommendations from A to C. Any disagreement

was discussed and resolved among the reviewers to reach mutual consensus.

Results

One hundred forty-five abstracts were identified by using key words of “chronic constipation” AND “treatment” AND “trials.” Duplicates were removed, and, after imposing the selection criteria, only 62 relevant full-text articles were then retrieved for potential inclusion.^{9,34,46,82–141} They were deemed eligible on which mutual consensus was reached between the two reviewers (LL and TR). Additional consultation with the other two coauthors (WR and JK) was sought as required. The studies were then rated according to the SORT as below and summarized in the Notes section: Senna, *Melanosis Coli*, and Colon Cancer: Fact or Myth?

Lifestyle Modifications

Despite the fact that chronic constipation had been observed with deficiency in dietary fiber, fluids, or exercise, lifestyle modification to prevent or treat chronic constipation is still unsubstantiated.^{82,142} (See Notes section: Lack of Dietary Fiber, Fluid, and Exercises Will Cause Constipation: How True Is This?) However, such principles are widely disseminated to the public through pamphlets³⁷ and practice guidelines (http://www.worldgastroenterology.org/assets/downloads/en/pdf/guidelines/05_constipation.pdf). Studies only report benefits if there is a lack of any of the three. Physicians and allied medical professionals should be aware of the evidence when advising their patients.

Biofeedback

For the PFD type of chronic constipation, biofeedback provides a retraining of the sensation and control of the anorectum and pelvic floor, thereby eliminating paradoxical contractions during the process of defecation. Its value has been shown both in uncontrolled trials⁹³ and in recent randomized, controlled trials (RCTs)^{46,92,94} for improving both psychological and clinical outcome measures. There have been no reports of adverse effects for using biofeedback. As a result, the level of evidence and recommendation in using biofeedback for PFD type of chronic constipation is good except for the diversity of protocols and heterogeneity of trial designs.

Pharmacological Treatment

Medications for chronic constipation can be categorized into bulk-forming agents, stool softeners and emollients, osmotic agents, stimulants, chloride channel activators, 5-HT₄ receptor agonists, and guanylate cyclase-c receptor agonist.

Bulk-Forming Agents

Bulk-forming agents are fiber supplements that expand with water to increase bulk of the stool and enhance bowel movements. Commercially available preparations include psyllium (ispaghula husks), calcium polycarbophil, methylcellulose, and bran. Adequate fluid intake is a must for bulk-forming agents to work; lack of water enhances bloating and may paradoxically predispose to bowel obstruction. Among them, psyllium has superior efficacy in treating constipation, with at least 3 RCTs demonstrating benefits over placebo in improving colonic transit time and stool consistency.^{98–100} Two controlled trials reported the benefits of bran in reducing the use of laxatives in the elderly.^{102,103} In comparison, there is only 1 controlled trial for methylcellulose¹⁰⁴ and a case series for polycarbophil¹⁰⁵ supporting their clinical use. Bulk-forming agents are considered as first-line agents for chronic constipation, especially in patients with dietary fiber deficiency.

Stool Softeners and Emollients

Docusate sodium is a commonly prescribed stool softener that has a detergent effect. Although there is no known study comparing its stand-alone efficacy against placebo, one double-blind randomized trial found docusate to be inferior to psyllium in chronic constipation.⁹⁸ Another systematic review did show a small effect of docusate in increasing stool frequency in the chronically ill, but overall quality of evidence was poor. Hence, the recommendation for use of docusate sodium is only moderate. Mineral oil is an emollient used for its lubricating effect on stool, but no placebo-controlled, randomized trial has been reported. Aspiration and lipoid pneumonia is a known risk of using mineral oil in children¹⁴³ and the elderly.¹⁴⁴ The level of evidence for use of mineral oil is hence moderate. Stool softeners are often prescribed when bulk-forming agents do not work or are not preferred.

Osmotic Agents

Agents such as polyethylene glycol (PEG), lactulose, sorbitol, and magnesium hydroxide adsorb and retain water as the result of their hyperosmolar nature and enhance stool passage. PEG has the best evidence of use, with at least 3 well-designed RCTs demonstrating significant benefits of PEG over placebo^{106–108} in increasing stool frequency and softness. However, PEG can cause nausea, flatulence, and diarrhea, especially in the elderly, and the dosage should be titrated upward according to response.¹⁹ In fact, some studies also reported efficacy at a low dosage of PEG.^{145–147} For lactulose, at least 2 systematic reviews reported RCTs showing efficacy over placebo,^{109,110} and the evidence is considered superior. No randomized, placebo-controlled trials have been conducted with sorbitol, but at least 1 double-blind, randomized, crossover study showed no difference in efficacy when compared with lactulose.¹¹¹ Similarly, the use of magnesium hydroxide for chronic constipation is not supported by any placebo-controlled trials, with only 1 report of severe hypermagnesemia requiring hemodialysis after chronic use.¹¹² Osmotic agents are useful when first-line bulk-forming agents or stool softeners do not work.

Stimulants

Senna and bisacodyl are the most commonly used stimulants. They act on the myenteric plexus of the colon and stimulate peristaltic contractions,^{148,149} which decreases transit time.^{150,151} They also decrease water absorption from the lumen. For bisacodyl, there is a double-blind, randomized, placebo-controlled trial showing efficacy and safety over placebo¹¹⁴ and another open-labeled, randomized study showing comparable benefits with sodium picosulphate.¹¹³ The level and recommendation for using bisacodyl is superior. Surprisingly, despite the widespread use of senna for more than a century, there is no well-designed RCT comparing its efficacy with placebo. However, at least 3 controlled trials compared the effects of senna with another laxative in treating chronic constipation. It was found that senna was a better choice,¹¹⁵ or, senna enhanced the effects when given in combination.^{116,117} Even so, the recommendation for senna is only considered moderate. There has been intense debate as to the potential risk of colonic carcinoma as the result long-term use of senna,

based on the observation that senna use leads to *Melanosis coli*, an alleged risk for cancer of the colon. (See Notes section: Senna, *Melanosis Coli*, and Colon Cancer: Fact or Myth?)

Chloride Channel Activators

Chloride channel activators are bicyclic fatty acids that increase intestinal fluid secretion by selectively activating type 2 chloride channels (CIC-2) in the apical membrane of the gastrointestinal epithelium. Lubiprostone is a representative that was licensed in 2004¹⁵² and approved in 2006¹⁵³ by the Food and Drug Administration (FDA) for long-term treatment of chronic constipation. At least 3 double blind, randomized, placebo-controlled trials^{118–120} have shown efficacy of lubiprostone in increasing spontaneous bowel movements and improving self-reported symptoms of chronic constipation. Known adverse effects include headache, nausea, and diarrhea but are well tolerated. Long-term use of lubiprostone also appears to be safe.¹⁵⁴ Evidence and recommendation for use of lubiprostone is hence excellent.

5-Hydroxytryptamine Receptor Subtype 4 Agonists

5-Hydroxytryptamine receptor subtype 4 (5-HT₄) receptors are found in the primary afferent neurons, smooth muscle cells, enterochromaffin cells, and the myenteric plexus of the colon.¹⁵⁵ They mediate the release of other neurotransmitters that initiate peristaltic action in the bowel.^{155,156} Tegaserod, a 5-HT₄ partial agonist, was approved by the FDA for use in 2002 both for constipation the dominant type of irritable bowel syndrome and also for idiopathic constipation in patients under the age of 65 years. Despite its efficacy shown by multiple randomized, placebo-controlled, clinical trials from different countries,^{121–124} the FDA disapproved marketing of tegaserod in 2007 because of a small increased risk in cardiovascular events, which led to its final withdrawal in 2008. This led to public criticisms against the FDA for being paternalistic and counterproductive.^{125,126} Research interest in tegaserod still continues,¹²⁷ and 2 recent cohort studies have specifically shown a lack of association of cardiovascular events with tegaserod.^{128,129} Whether tegaserod will be relaunched in the future remains to be seen. Prucalopride is a highly selective 5-HT₄ agonist stimulating prokinetic activity of the colon in *in vitro* and *in vivo* studies of humans and animals.¹⁵⁷ Clinically, it sig-

nificantly improved bowel movements and other reported symptoms in patients with chronic constipation,¹³⁰ especially in severe cases,^{131–134} with no significant cardiovascular adverse events.¹³⁵ The level of evidence and recommendation for using prucalopride to treat chronic constipation is therefore superior, but it is only available in the European market.

Guanylate Cyclase-c Receptor Agonist

Linacotide is a 14–amino acid peptide that acts on guanylate cyclase-c receptors of the colonic epithelium and induces intestinal fluid secretion and reduces colonic transit time. Its clinical efficacy and safety have been tested in randomized, double-blind, placebo-controlled trials,^{158,159} with promising results thus far. Recommendation and level of evidence for prucalopride will not be forthcoming because of its experimental nature.

Other Treatments

Bacteriotherapy (Probiotics)

Lactobacillus and *Bifidobacterium* are recognized symbiotic flora in the large intestine that compete with harmful pathogens in binding to the surface of enterocytes and confer mucosal health. Both flora had been reported at low levels in patients with chronic constipation,¹⁶⁰ which supports the use of these probiotic bacteria for treating chronic constipation and other inflammatory bowel conditions.¹⁶¹ One prospective study showed that *Bifidobacterium* supplementation can relieve constipation in hypocaloric dieting,⁹⁵ whereas another prospective trial reported efficacy of *Lactobacillus* in improving chronic constipation in nursing home residents.⁹⁶ However, survival and viability of these probiotic bacteria as consumed in commercial form has yet to be standardized for such treatment to be officially endorsed.⁹⁷ Because of the lack of properly controlled trials, evidence and recommendation is poor.

Traditional Chinese Medicine

Chronic constipation was described in the ancient texts of Chinese medicine in 200 AD. It is treated by a combination of herbs and acupuncture, depending on the symptomatology. At least 2 RCTs have shown efficacy of a particular formula (Yun-Chang capsule; aka Hemp Seed Pill) in treating the functional type of chronic constipation.^{136,137} However, the overall quality of studies using tradi-

tional Chinese medicine for chronic constipation is heterogenous.¹³⁸

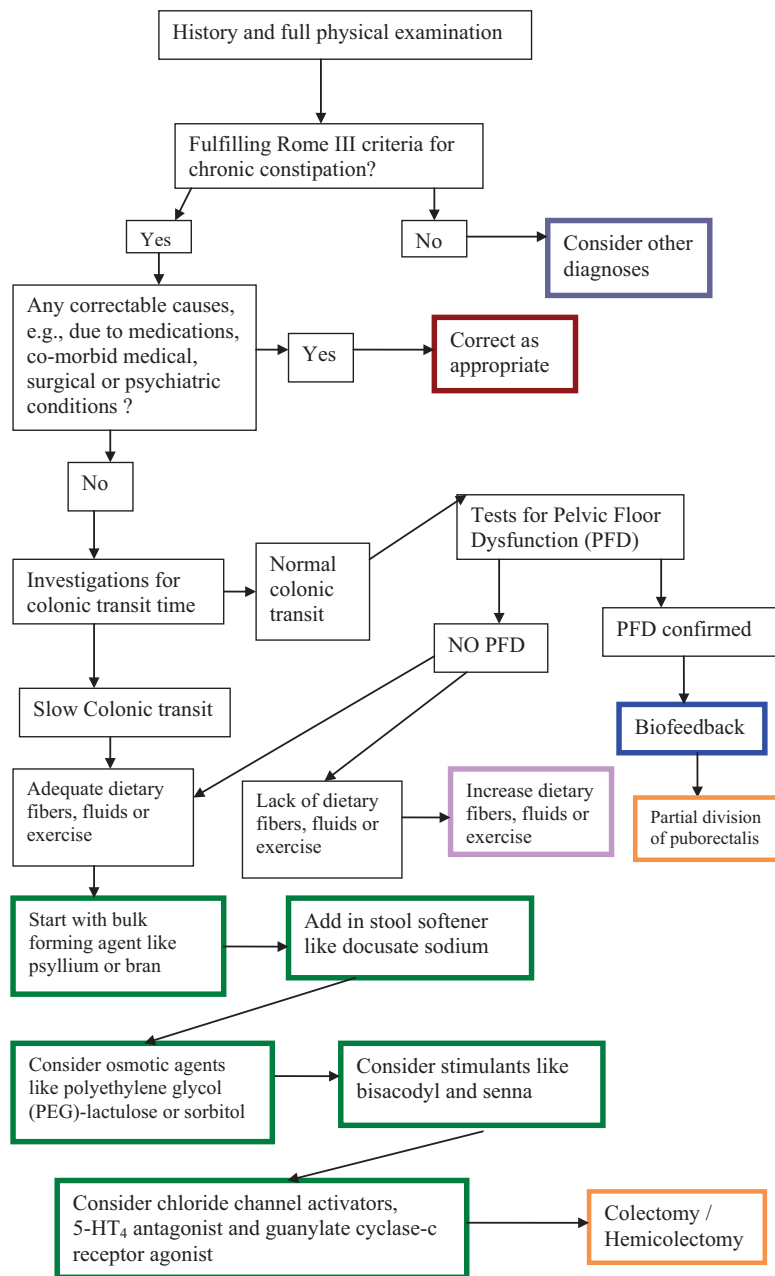
Surgery

Patients with intractable chronic constipation caused by slow colon transit who fail pharmacological treatments may be considered for surgery. Possible operations include total colectomy or partial colectomy. A recent systematic review based on case reports and case series concluded that such surgical operations can improve defecatory frequencies and decrease postoperative use of laxatives; however, there is heterogeneity in design among the studies, resulting in variable quality of evidence.¹³⁹ For the anismus type of PFD, at least 2 RCTs have shown benefits of partial division of puborectalis as compared with biofeedback¹⁴⁰ or *Botulinum* toxin injection.^{140,141}

Conclusions

It is indeed surprising that as a common condition found in at least one quarter of patients, chronic constipation is treated in a wide variety of ways, with relatively little evidence-based data, especially regarding dietary fiber, fluids and exercise. As with any other condition, a thorough history and physical examination is mandatory, with additional blood and special tests to confirm the diagnosis of chronic constipation and its subtypes. A practical triage approach is summarized in Figure 1), and the various evidence-based options for managing chronic constipation are listed in the order of their level of recommendation in Table 1. In summary, family physicians should look for pelvic floor dysfunction as a cause of chronic constipation, which is best treated by biofeedback. The classic triad of increasing dietary fiber, exercise, and fluids will benefit patients with actual deficiencies. The best pharmacological treatment for chronic constipation caused by slow colonic transit time is to start with a bulk-forming agent (psyllium or bran) and with a stool softener/osmotic agent (lactulose, PEG, or docusate), then add in stimulants (bisacodyl or senna) and finally the newer agents for severe or resistant cases (chloride channel activators or 5-HT₄ agonist). In recalcitrant cases, surgical treatment may be considered.

Figure 1. Flow diagram for management of chronic constipation.



Notes

Diagnostic Approach for Chronic Constipation

History includes (1) duration of complaint; (2) patient’s definition of constipation; (3) defecatory frequency; (4) stool consistency; (5) concurrent medication (eg, anticholinergics, diuretics, β -blockers, opiates, iron supplements, calcium channel blockers, antidepressants, acetaminophen, aspirin, and NSAIDs); (6) comorbidities (Parkinson, hypothyroidism); (7) use of supplements or laxatives; and (8)

lifestyle enquiry regarding the level of fluid intake, dietary fiber consumption, and daily exercise.

Physical examination includes (1) previous surgical scars; (2) abdominal distension and bowel sounds; (3) palpable mass (fecoliths); (4) inspection of anus for skin tags, hemorrhoids, fissures, hematomas, and prolapse; (5) rectal examination to assess anal reflex, sphincter tone, tenderness, out-pouching (rectocele), or mass in the rectum; (6) gynecological examination to exclude cystoceles or vagi-

Table 1. Summary of Various Management Options for Chronic Constipation According to the Strength of Recommendations Taxonomy (SORT)⁸¹

Treatment	Level of Recommendation	Comments	Reference
Nonpharmacological			
Increasing dietary fiber	C	No RCTs, data from multiple observational studies, results conflicting. More likely to be beneficial in people with fibers deficiency.	34,82–87
Increasing exercise	B	Two small RCTs with opposite results and 2 other cohorts showing benefits. More likely to be beneficial in people with lack of exercise.	9,83,88,89
Increasing fluids	C	One observational study and 1 controlled trial, the latter showing benefits of increased fluids only in presence of sufficient fiber intake.	90,91
Biofeedback	B	Useful in pelvic function disorder type of chronic constipation. Benefits reported with both uncontrolled trials and RCTs. However, protocols of biofeedback vary and are heterogeneous in nature; hence recommendation is not standardized.	46,92–94
Bacteriotherapy (probiotics)	C	One prospective study of bifidobacterium and one uncontrolled trial of <i>Lactobacillus</i> ; viability of preparation when consumed is questionable.	95–97
Surgery (colectomy/hemicolectomy)	B	One systematic review reported benefits based on case reports and no RCT; quality of studies was heterogeneous.	139
Surgery (partial division of puborectalis)	B	Two RCTs randomizing patients to surgical and nonsurgical treatments (biofeedback or <i>Botulinum</i> toxin injection).	140,141
Pharmacological			
Psyllium	A	At least 3 well-designed RCTs showing benefits over placebo.	98–101
Bran	B	Two controlled trials showed benefits in reducing use of laxatives.	102,103
Methylcellulose	B	Only 1 controlled trial of medium quality.	104
Polycarbophil	B	Only 1 case series of medium quality.	105
Polyethylene glycol	A	At least 3 RCTs showing benefits over placebo.	106–108
Lactulose	A	Two systematic reviews of RCTs with benefits over placebos.	109,110
Sorbitol	B	One double-blind RCT showing comparable efficacy of sorbitol with lactulose, not placebo.	111
Magnesium hydroxide (milk of magnesia)	C	No evidence of benefits from any studies, with 1 adverse report of overuse.	112
Senna	A	At least 3 controlled trials showing benefits over placebo.	115–117
Docusate sodium	B	One double-blind RCT comparing with psyllium.	98
Bisacodyl	A	One double-blind RCT with 1 open-labelled controlled trial.	113,114
Lubiprostone	A	At least 3 double-blind RCTs showing benefits over placebo.	118–120
Tegaserod	–	At least 3 RCTs from different centers showed benefits over placebo. Withdrawn from market by FDA because of concern; 2 recent cohorts claim no association with cardiovascular risks.	121–129
Prucalopride	A	At least 3 RCTs showing benefits over placebo, including severe chronic constipation. At present only marketed in Europe.	130–135
Traditional Chinese medicine	B	Two RCTs showing benefits of a particular formula, yet overall quality of studies are heterogeneous.	136–138

RCT indicates randomized, controlled trial; FDA, Food and Drug Administration.

nal/uterine prolapse; and (7) full neurological examination to exclude neurological causes.

Investigations include (1) blood tests such as complete blood count, serum glucose, and thyroid and renal functions maybe useful despite limited evidence.^{162,163} (2) Colon transit time: Radiograph study with the Sitz marker has been a standard test in distinguishing prolonged transit from normal transit but is unreliable in measuring segmental transit.¹⁶⁴ Scintigraphy with radioisotope is more accurate in measuring transit in different segments of the colon¹⁶⁵ but is more expensive and limited to centers with access to radioisotopes. (3) Anorectal manometry: Pressure exerted by the anal sphincter at rest (normal >80 mm Hg) and with defecatory attempt (normal >180 mm Hg) is measured with a balloon catheter in the anal canal.¹⁶⁶ (4) Balloon expulsion test: Patient is asked to expel a 50 mL rectal balloon (filled with air or water) within 60 seconds; failure to do so suggests pelvic floor dysfunction.¹⁴ (5) Defecography: Serial radiographs of the anorectum are taken when the patient is asked to expel thick barium paste from the rectum. Movement of the pelvic floor and anorectal angle is measured with reference to the sacro-coccygeal line.¹⁴ (6) Dynamic pelvic MRI gives better visualization of the pelvic floor dynamics than does conventional barium defecography and also reveals other anatomic defects contributing to impaired defecation.¹⁶⁷

Lack of Dietary Fiber, Fluid, and Exercises Will Cause Constipation: How True Is This?

Dietary Fiber

A prospective cohort of 3327 women found that higher daily fiber intake (20 g/d versus 7 g/d) significantly reduces the likelihood of self-reported constipation.⁸³ However, other studies have found no such association.^{34,84,85} Increasing daily dietary fiber intake may help constipation caused by fiber deficiency,^{34,84,86} but one should not assume that fiber deficiency is the main or sole cause.^{82,87} Evidence is Level 2C.

Exercise

One small, nonplacebo RCT reported that regular exercise decreases constipation as per Rome I criteria,⁸⁸ whereas another even smaller study did not show any benefit.⁸⁹ Two other cohort studies showed that physical activity significantly decreased

the self-reported symptoms in women.^{9,83} Evidence is Level 2C.

Fluids

A 3-month, prospective study of 21 012 nursing home residents age >65 years found a link between insufficient fluid intake and constipation.⁹⁰ One controlled trial showed that higher fluid intake improved chronic constipation in the presence of a high-fiber diet.⁹¹ Other than that there have been no known trials looking at the effects of increased fluids on chronic constipation. Evidence is hence 2C.

Senna, Melanosis Coli, and Colon Cancer: Fact or Myth?

Senna belongs to the genera of anthraquinone-containing herbal laxatives that also embrace aloe, cascara, frangula, and rhubarb. The active ingredients include sennoside A and B. *Melanosis coli* is a brownish-black discoloration of the colonic epithelium found with chronic use of anthraquinone laxatives,¹⁶⁸ with an association of 73% to 95%.^{147,169} Histologically, there is accumulation of lipofuscin-containing macrophages in the lamina propria of the colonic mucosa.¹⁷⁰ Lipofuscin is thought to derive from apoptotic bodies generated by anthraquinone-induced apoptosis of the colonic epithelial cells.^{168,171} *Melanosis coli* can resolve after discontinuation of anthraquinone laxatives.¹⁶⁹ In the last three decades, induction of aberrant crypt foci (ACF) in rat colon has been widely accepted as the pre-neoplastic lesions for modeling colorectal cancer.^{172–177} Although 2 studies showed that senna promoted formation of carcinogen-induced ACF in rat colon when given at high doses,^{178,179} other studies failed to show any effects of senna in initiating ACF per se or promoting existing ACF.^{180,181} In fact, one study even demonstrated a reduction of ACF in rat colon after long-term usage of senna.¹⁸² Similar data in humans are lacking, except for one study that showed increased ACF after a single high dose of senna colonic lavage.¹⁸³ A prospective study of 1095 patients reported an increased relative risk of 3.04 for colorectal cancer as a result of anthraquinone laxative abuse.¹⁸⁴ Similarly, a retrospective study of 3049 patients who underwent colonoscopy revealed a higher incidence of *Melanosis coli* in patients diagnosed with colonic adenomas¹⁸⁴ (which are not necessarily malignant). However, subsequent studies failed to demonstrate an association of anthraquinone laxatives

with colorectal carcinomas.^{180,185–188} Interestingly, one study even hypothesized that the higher rate of adenomas associated with *Melanosis coli* was due to enhanced ease to spot the white polyps against a dark-colored colon.¹⁸⁹ Taken together, the latest evidence does not support a role of senna in causing colon cancer in rats and humans.¹⁹⁰

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