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Chronic Constipation

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Abstract

Constipation is a common complaint that may be primary (idiopathic or functional) or associated with a number of disorders or medications. Although most constipation is self-managed by patients, 22% seek healthcare, mostly to primary care providers (>50%) and gastroenterologists (14%) which then result in large expenditures for diagnostic testing and treatments. There is strong evidence that stimulant and osmotic laxatives, intestinal secretagogues and peripherally restricted mμ-opiate antagonists are effective and safe; the latter drugs are a major advance for managing opioid-induced constipation. Constipation which is refractory to available laxatives should be evaluated for defecatory disorders and slow transit constipation using studies of anorectal function and colonic transit. Defecatory disorders are often responsive to biofeedback therapies, whereas slow transit constipation may require surgical intervention in selected patients. Both efficacy and cost should guide the choice of treatment for functional constipation and opiate-induced constipation. No studies have compared inexpensive laxatives with newer drugs that work by other mechanisms.

Keywords

Constipation; irritable bowel syndrome; laxatives; biofeedback therapy

Definition and Classification

Constipation is defined by bowel disturbances (ie, reduced frequency of bowel habits, hard stools, excessive straining to defecate, a sense of anorectal bloackge, anal digitation, and a sense of incomplete evacuation after defecation). By contrast to some physicians, who

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consider reduced stool frequency as the only symptom of constipation. patients are often troubled by the other symptoms of constipation.[1] Constipation may be primary alone or secondary to an underlying disorder.

There are 2 approaches for classifying chronic constipation. The American Gastroenterological Association criteria utilize colonic transit and anorectal tests to classify constipated patients into one of the three groups: normal transit constipation (NTC), slow transit constipation (STC), and pelvic floor dysfunction or defecatory disorders (DD).[2] Clinicians frequently assess colonic transit and anorectal functions in constipated patients who have not responded to pharmacotherapy.

By contrast, epidemiologic studies and pharmaceutical trials use the original, or suitably modified, so-called Rome criteria (the most recent iteration is the Rome IV criteria) which incorporate symptoms and anorectal assessments of rectal evacuation[3,4] (Figure 1, Table 1,[5,6]). DD are defined by bowel symptoms and anorectal tests indicative of impaired rectal evacuation. However, functional constipation (FC) and constipation-predominant IBS (IBS-C) are defined only by symptoms, bowel symptoms only (FC) or with abdominal pain that is temporally related with bowel disturbances (IBS-C, Table 1). Because the Rome criteria and the inclusion criteria for pharmacological studies in FC and IBS-C do not specify that anorectal tests should be normal, it is conceivable, perhaps likely that many patients with FC and IBS-C actually have an unrecognized DD.

We suspect that most practitioners use the generic term “chronic constipation” rather than differentiate between IBS-C and FC. That is not a significant limitation since dietary fiber supplementation and/or simple laxatives are beneficial for both in primary care. However, an assessment of the phenotype, guides and predicts the response to therapy. For example, pelvic floor biofeedback therapy, not laxatives, are the cornerstone of managing DD. The dose and response to treatment with secretagogues (e.g., lubiprostone) differs between FC and IBS-C. Medically-refractory isolated slow transit constipation is an indication for colectomy.

Some patients satisfy criteria for FC and IBS-C. Indeed, in one study, nearly 90% of IBS-C patients also had symptoms of FC. Conversely, approximately 44% of patients with FC also IBS-C criteria.[7] The Rome criteria specify that patients who have symptoms of IBS-C and FC should be diagnosed as IBS-C. An alternative, perhaps simpler, approach is to classify constipation based on the presence or absence of severe abdominal pain, regardless of the relationship between abdominal pain and bowel symptoms, into constipation with or without moderate or severe pain. Compared to constipated patients with no or mild pain, patients with severe pain report more somatic symptoms, worse overall health, and a greater impact of bowel symptoms on quality of life.[7]

Prevalence

In the community, the median prevalence is 16% in all adults. In older people, the prevalence is greater (ie, 33.5% in adults aged 60–101 years),[8,9] It is greater in non-Caucasians, in institutionalized people, and in women; the median prevalence ratio in

women to men is 1.5:1.[10] Women more frequently use laxatives and seek health care for their constipation.

Few studies have evaluated colonic transit and anorectal functions among constipated people in the community. In one study, 516 of 11,112 constipated patients in Olmsted County, Minnesota had anorectal tests; 245 had a defecatory disorder (DD), which approximates to an overall age- and sex-adjusted incidence rate of 19.3 (95% CI: 16.8–21.8) per 100 000 person-years. That figure is higher than the incidence rate of Crohn's disease (i.e., 5.8) in the same population.[11]

Risk Factors

Increasing age, female sex, Lower socioeconomic status, lower parental education rates, less self-reported physical activity, certain medications (Supplementary Table 1), stressful life events. physical and sexual abuse, and depression are associated with constipation.[2] Among nursing home residents, adverse drug effects may partly explain the high prevalence of constipation.[12] However, these associations do not imply causation.

Economic Impact and Impact on Quality of Life

In the United States, most constipated patients are self-treated. A minority (e.g., 22% in a U.S. household survey) seek healthcare for constipation.[13] However, the prevalence is high. Hence, for outpatient clinic visits, constipation ranks among the top five most common physician diagnoses for GI disorders,[14] accounting for almost 8 million ambulatory visits annually in 2001–2004 (i.e., 0.72% of all ambulatory visits)[15] to adult primary care providers (33%), pediatricians (21%), and gastroenterologists (14%). Every year, more than a million patients are referred to gastroenterologists for constipation. These 8 million physician visits far exceeded the number of persons who had colon or rectal cancer (142, 570) in the U.S. in 2010,[16] emphasizing the infrequency with which colon cancer occurs among chronically constipated patients. The direct medical costs for constipation were estimated in excess of $230 million annually.[17] The medical costs were twofold greater in women with than without constipation[18] In a more recent study of a commercially insured population, 33% of total annual all cause medical expenses were attributable to GI related symptoms in patients with constipation who incurred about $8700 more than non-constipated matched controls.[19] Approximately 75% of both groups were female and health care costs were higher in constipated patients with abdominal symptoms.

Among constipated people, general health, mental health and social functioning are worse than in healthy controls, and more so in hospitalized patients than in the community.[20] The mental and physical subcomponent scores in hospitalized constipated patients were comparable to patients with Crohn's disease. Among constipated people in the community, scores were comparable to patients with gastroesophageal reflux, hypertension, diabetes, and depression.[21]

Pathophysiology

Among patients who seek medical care, the most frequently implicated disturbances are colonic motor dysfunction (i.e., slow transit constipation) and impaired defecation (i.e., defecatory disorders), which may occur in isolation or coexist.[22–24] A substantial proportion of constipated patients have normal colon transit and anorectal functions. Abnormal colonic sensation and disturbances of the colonic microbiome may also contribute. Whereas some defecatory disorders are also associated with slow colonic transit,[24–26] it is useful to consider mechanisms of slow transit constipation and defecatory disorders separately.

Normal (NTC) and Slow Transit Constipation (STC)

Isolated STC is defined as slow colonic transit in the absence of a defecatory disorder or megacolon. Isolated STC, is regarded as a manifestation of colonic motor dysfunction, and may result from inadequate caloric intake.[27] However, only some patients with STC have colonic motor dysfunction as evaluated with manometry.[24, 28, 29] Perhaps this discrepancy between colonic transit and motor assessments with barostat-manometry reflect the intra-individual variability in colonic transit and manometry and the limited fidelity of non-high-resolution manometry catheters for detecting propagation of motor events. Also, factors other than colonic motor functions (e.g., the colonic microbiome) may affect colonic transit. NTC is not synonymous with IBS-C, since 23% of patients with IBS-C had delayed colonic transit in one study.[30].

Manometric abnormalities in STC include fewer high amplitude propagated contractions (HAPCs), retrogradely propagated or nonpropagated sigmoid or rectal phasic pressure activity. These disturbances may impede colonic flow.[31] Contractile responses to a meal and/or to pharmacological stimuli (e.g., bisacodyl or neostigmine) may also be impaired (Figure 1).[24, 32] Colonic inertia is defined by markedly reduced or absent responses to a meal and to a pharmacological stimulus (e.g., bisacodyl or neostigmine) rather than solely by slow transit constipation.[24, 33]A marked reduction in colonic intrinsic nerves and interstitial cells of Cajal may cause colonic motor dysfunction.[34] In medically-refractory patients with STC who do not have a defecatory disorder, this should prompt consideration of colectomy, as discussed later. The rationale for colonic manometry prior to colectomy is stronger in children than in adults.[35] Overexpression of progesterone receptors, which is associated with impaired smooth muscle contractile responses to acetylcholine and serotonin, is another explanation for slow transit constipation in women.[36]

Defecatory Disorders (DD)

DD are defined by symptoms of constipation and objective evidence of impaired rectal evacuation. Impaired evacuation may result from increased resistance to evacuation and/or inadequate rectal propulsive forces. High anal resting pressure, incomplete relaxation or paradoxical contraction of the puborectalis and external anal sphincters (“dyssynergia”) cause increased resistance to evacuation (Figure 2).[26, 37] However, these disturbances and other pseudonyms (e.g., obstructed defecation, outlet obstruction) refer to the same disorder. Other disturbances in DD include delayed colonic transit,[24, 38] rectal hyposensitivity,[39] and structural disturbances (e.g., rectoceles and excessive perineal descent).[40, 41]

To what extent these anorectal sensorimotor dysfunctions cause defecatory symptoms is unclear. Some asymptomatic people and patients with symptoms (e.g., rectal pain) other than DD have dysynergia, perhaps because it is challenging to simulate defecation during a test.[42–44] Some abnormalities (e.g., delayed colonic transit and rectal hyposensitivity) may be a consequence rather than a cause of DD.[38] The findings of different tests (e.g., anorectal manometry and defecography) may diverge. There is no gold standard for the diagnosis. Stool form influences the expression of symptoms in constipated patients; it is more challenging to expel hard than soft stools.[45]

The etiology of DD is unclear. Perhaps they result from neglecting the call to defecate and/or represent an inappropriate pattern, of sphincter contraction that is initiated by avoidance of pain or trauma.[46] Symptoms often begin in childhood. Indeed, one in three children with childhood constipation had persistent symptoms beyond puberty.[47]

Among patients with DD, slow colon transit may be secondary (e.g., related to physical obstruction to passage of contents by stool or rectocolonic inhibitory reflexes initiated by rectal distention from retained stool)[48] or the primary manifestation. For example, some patients with DD lack the colonic propagated sequences that normally precede defecation.[29] Perhaps the colonic motor dysfunction occurs first and predisposes to excessive straining, which leads to DD.

Other Disturbances

Some patients may have abnormal colonic and/or rectal sensation. Increased rectal sensation is associated with abdominal pain and bloating, suggestive of irritable bowel syndrome.[49, 50] Conversely, reduced rectal sensation may explain why some patients do not experience the desire to defecate.[23] Constipation is associated with alterations of the colonic mucosal microbiome independent of colonic transit; genera from Bacteroidetes were more abundant in constipated patients.[51] Disturbed synthesis of bile acids, which stimulated colonic secretion when they are not absorbed in the terminal ileum, has been observed.[52]

Clinical Evaluation

The clinical assessment should elicit the specific symptoms of constipation, clarify which are most distressing, and assess for medications that cause constipation (Supplementary Table 1). Alarm symptoms include blood admixed with stools, a sudden change in bowel habits, especially after the age of 50 years, anemia, weight loss, and a family history of colon cancer. The timing of symptom onset (e.g., onset during childhood), dietary calorie and fiber intake, a history of abuse, and obstetric events should be recorded. Patients should be asked about maneuvers (e.g., straining to begin and/or to end defecation) they use to defecate. Some symptoms (i.e., sense of anal blockage during defecation, need for anal digitation, or a sense of incomplete evacuation after defecation) are more suggestive of DD.[24] The utility of bowel diaries and pictures of stool form (e.g., by the Bristol Stool Form Scale) for efficiently and reliably characterizing bowel habits cannot be overemphasized. By contrast, self-reported stool frequency is unreliable and does not predict colonic transit.[53–55] Not infrequently, patients misperceive they have constipation because they do not have a bowel movement every day. In the United States, the normal range is 3–21 bowel

movements per week.[56] The ease of defecation is also influenced by stool form.[45] Among constipated women, straining to begin defecation is more frequent for hard stools than normal stools.[45] Patients with severe DD find it difficult to pass even soft stools and enema fluid. After a complete purge, it takes several days for residue to accumulate to form a normal fecal mass. This may explain why some patients skip a bowel movement for a few days after a bout of diarrhea. In constipated patients, laxatives can predispose to alternating constipation and diarrhea, which may lead to a misdiagnosis of irritable bowel syndrome.[57]

Many constipated patients also have symptoms such as abdominal bloating, distention or discomfort, which may be partly attributable to constipation per se.[58] For many patients, abdominal bloating, which may be associated with abdominal distention, is the most bothersome symptom.[59] Other symptoms include fatigue, malaise, fibromyalgia and psychosocial distress.

The clinical evaluation should identify diseases that cause constipation (Supplementary Table 2). A thorough perineal and rectal examination is necessary to identify DD. The resistance to insertion of the finger per anus reflects anal resting tone. Pelvic contraction is normally accompanied by elevation of the puborectalis and increased anal tone. When patients try to “expel the examining finger,” both muscles should relax with perineal descent by 2–4 cm.[60, 61] Features of DD include high anal resting tone, which manifests as increased resistance to insertion of the examining finger into the anal canal; during simulated evacuation there may be impaired relaxation or paradoxical contraction of the sphincter, and/or reduced perineal descent. Other findings include impacted stool in the rectum, fecal soiling, a rectocele, or puborectalis tenderness. A digital rectal examination is useful but not sufficient to identify DD. Among constipated patents, a rectal examination performed by a skilled examiner had a sensitivity of 80% and a specificity of 56% for predicting an abnormal rectal balloon expulsion test, which reflects a DD.[61] With less skilled examiners, the utility of a digital rectal examination is probably lower..

Diagnostic Tests

A complete blood count may be useful. The diagnostic utility and cost-effectiveness of fasting serum glucose, sensitive thyroid-stimulating hormone, and calcium is probably very low.[62] Among constipated patients, colonoscopy, to identify colon cancer is required only in patients with alarm clinical features, constipation refractory to medical management, and for patients who have not had an age-appropriate colon cancer screening procedure after the onset of constipation; this age specification is lower in some patients with a family history of colon cancer.[63]

A rectal balloon expulsion test and an anorectal manometry should be performed in constipated patients who do not respond to a high fiber diet and non-prescription laxatives. (Figure 3). When access to anorectal tests is not readily available, a trial of new secretory agents, which are expensive, may be considered before anorectal testing.

Rectal Balloon Expulsion Test

This test measures the time required to evacuate a water-filled balloon in the seated position; the normal value depends on the technique, and is generally less than 1 minute.[64, 65] While the test is highly sensitive and specific for identifying DD, the results may be falsely normal in patients with pelvic laxity, for example, as in over 90% of patients with a large rectocele, enterocele, peritoneocele, and/or sigmoidocele had a normal balloon expulsion test in 1 study.[66] Also, some patients with a DD may strain excessively to overcome increased resistance and expel the balloon. In these patients, the normal balloon expulsion test may not reflect normal anorectal functions.

Anorectal Manometry

A normal rectoanal inhibitory reflex excludes Hirschsprung's disease, which is very rare in adults. In addition to high anal resting pressure, manometry may reveal a reduced rectoanal gradient during evacuation. The latter may result from reduced rectal propulsive force and/or impaired anal relaxation (Figure 2). Even among healthy controls, the rectaoanal gradient (i.e., rectal – anal pressure) during evacuation is negative, for example up to −55 mmHg in asymptomatic women. This is counterintuitive because it would seem that a positive gradient is necessary for normal evacuation. This limits the utility of the rectoanal gradient during evacuation for diagnosing DD.[67, 68] We recommend that 2 or more of these 5 manometric abnormalities (i.e., anal resting pressure or anal pressure during evacuation greater than 90th percentile, rectal pressure, anal relaxation or rectoanal gradient less than the 10th percentile value in sex-matched controls) suggest a DD.

Defecography

In the United States, defecography is generally used when the results of anorectal manometry do not concur with the clinical impression and/or when anatomic abnormalities (e.g., a clinically significant rectocele) are suspected.[3] The most relevant findings in DD include inadequate or excessive perineal descent or widening of the anorectal angle during defecation.[41, 66, 69] Other features include internal rectal intussusception, solitary rectal ulcers, rectoceles and rectal prolapse. If the vagina and small intestine are opacified, enteroceles, bladder and uterovaginal prolapse are also visible. Methodological limitations to barium defecography can be minimized by using standardized techniques.[70, 71] Besides avoiding radiation exposure, MR defecography is preferable for visualizing the bony landmarks, which are necessary for measuring pelvic floor motion (Figure 2). However, with conventional, closed-configuration MR systems imaging is only possible in the supine position.[72]

Colonic Transit

Before the test, medications that slow or accelerate colonic transit should be discontinued. The most common and cost effective approach is to use radiopaque markers (Sitz-Mark, Konsyl Pharmaceuticals, Fort Worth, TX). The "Hinton technique", entails ingestion of a capsule containing 24 radiopaque markers. Normally, an abdominal x-ray taken 5 days later reveals less than 5 remaining markers in the colon.[73] Alternatively (i.e., "Metcalf technique"), a capsule containing 24 radiopaque markers is ingested on days 1, 2 and 3.

More than 68 markers combined on days 4 and 7 reflects slow colon transit.[74] The test is more reproducible in patients with simple constipation[53] than in defecatory disorders and colonic inertia.[75] Other equivalent options are scintigraphy[30] or a wireless pH-pressure capsule.[76] While a radiopaque marker study takes 5–7 days, scintigraphy requires 24 or 48 hours.[74] In constipated patients, measurements of colonic transit with radiopaque markers and scintigraphy and separately with the wireless motility-pH capsule are reasonably correlated.[53, 76] The capsule can also measure, small bowel transit, in a limited fashion, gastric emptying and colonic motor activity.[77] However, this study takes 5 days and requires patients to wear a data collection device.

Colonic Manometry and Barostat Testing

As detailed above, this test is used selectively in patients with medically-refractory slow transit constipation who are being considered for colectomy at specialized centers.[28] In adults, personal experience suggests the test is helpful in selected cases (e.g., among patients who have severe symptoms but only a borderline delay in colonic transit (Figure 1).

Putting it Together

After the clinical assessment, constipated patients may be tentatively classified into one (or possibly more) of the following categories:

1. NTC with normal colonic transit and defecation. Some patients with NTC also have symptoms of IBS-C (e.g., abdominal pain, bloating and incomplete defecation).
2. STC with slow colonic transit, normal defecation and absence of megacolon.
3. DD (anismus/dyssynergia; ineffective propulsive pressures; failure of relaxation; descending perineal syndrome)
4. STC and DD. Some patients also have features of IBS.
5. Opioid-induced constipation, which is defined by new, or worsening, symptoms of constipation when initiating, changing, or increasing opioid therapy[4]
6. Organic constipation (mechanical obstruction, or drug side effect; (Supplementary Table 1) or metabolic disorders; (Supplementary Table 2).

During the primary consultation, the clinical assessment is probably sufficient to exclude organic and secondary constipation in most patients, providing the basis for symptomatic treatment. Diagnostic studies for constipation will only be required in some cases.

Medical Management

Table 2 [78–82] summarizes common laxatives and newer pharmacological agents for chronic constipation. Drugs (e.g., bile-acid transporter inhibitors) that were effective in phase II trials but need further study will not be discussed.[83]

Adjunctive approaches

Except for patients with dehydration, increased fluid intake does not treat constipation.[62] There is an inverse relationship between physical activity and the severity of constipation.[62, 84] Moderate-to-vigorous intensive physical activity (20–60 minutes on 3 to 5 days per week) improved symptoms and quality of life in IBS.[85] The effects of probiotics on constipation are poorly understood.[86]

Dietary Fiber Supplementation and Osmotic Laxatives

Soluble dietary fiber (e.g., psyllium or ispaghula) supplements reduce bowel symptoms in chronic constipation[87] and IBS;[88] insoluble dietary fiber (e.g., wheat bran) do not. However, only one of 4 trials in constipated patients lasted more than 4 weeks; none were at low risk of bias. A meta-analysis of 17 trials concluded that soluble fiber improved global symptoms and constipation in IBS. However, the effects on abdominal pain were variable.[88] Hence, fiber supplementation, either through the diet or as a standardized fiber supplement (Table 2), should be considered as the first step in constipated patients, particularly in primary care. Beginning with a single daily dose taken with fluids and/or meals, the dose should be gradually adjusted after a 7–10 day period, recognizing that the response may manifest over several weeks'. Patients should be reminded that fiber supplements may increase gaseousness. This often improves over time and can be reduced by switching to another fiber supplement.

Another initial option is an osmotic agent, administered daily, and supplemented, when necessary, with stimulant laxatives. No studies have compared osmotic and stimulant laxatives. A meta-analysis of 7 controlled studies with 1141 patients who had chronic idiopathic constipation observed that the number needed to treat (NNT) for osmotic and stimulant laxatives was 3 (95% CI 2–4).[89] Osmotic agents (i.e., polyethylene glycol-based solutions (PEG), magnesium citrate-based products, sodium phosphate-based products, and nonabsorbable carbohydrates (ie lactulose)) draw fluid into the intestinal lumen to maintain gut isosmolality, thereby increasing stool water and colon propulsion. The dose should be titrated to produce soft but not liquid stools. For PEG, there is extensive evidence, including 1 controlled trial lasting 6 months, [89–92] and retrospective studies which confirm that treatment with PEG is safe and effective for up to 24 months.[91, 93] Patients prefer PEG preparations without electrolyte supplements.[94] For colonic cleansing, larger volumes of PEG with electrolytes are used.[95] Magnesium hydroxide and other salts improve stool frequency and consistency. [96] Among 244 constipated women, a natural mineral water rich in magnesium and sulfate was safe and improved symptoms of chronic constipation over 2 weeks compared to mineral water which was low in magnesium. While absorption of magnesium is limited, patients with renal disease may develop severe hypermagnesemia.[97] Side effects of sodium phosphate-based bowel cleansing preparations include hyperphosphatemia, hypocalcemia, and hypokalemia; less than one in 1000 individuals develop acute phosphate nephropathy.[97, 98] Hence, they should be avoided.

PEG was better than lactulose for improving stool frequency, stool consistency, and abdominal pain in a Cochrane Database review of 10 randomized trials.[99] In a randomized crossover study of 30 men, lactulose and sorbitol were equally effective but lactulose was

associated with more nausea.[100] Bacterial metabolism of these unabsorbed carbohydrates leads to gas production.

Stimulant laxatives such as senna, bisacodyl, and sodium picosulfate induce propagated colonic contractions. Even long-term use is very safe; bisacodyl and sodium picosulfate have anti-absorptive and secretory effects.[92, 101–105] These agents may be used as rescue agents, (e.g., if patients do not have a bowel movement for 2–3 days)[105] or more regularly if required. Stimulant suppositories (i.e., bisacodyl and glycerin) should be given about 30 minutes after breakfast in order to synchronize their effects with the gastrocolonic response. In a large study, sodium picosulfate improved stool consistency and frequency as well as ease of evacuation and quality of life compared to placebo.[92] Stimulant laxatives do not appear to damage the enteric nervous system.[106, 107] Unfortunately, it remains not uncommon for providers and pharmacists to warn of the “potential dangers” of using stimulant laxatives which may lead to underutilization of these effective and inexpensive agents.

In carefully selected patients with STC, the personal experience of one of the authors (AW) suggests that the prostaglandin E1 analog misoprostol, in varying doses, may be effectively used to avoid subtotal colectomy.

Intestinal Secretagogues

Secretagogues such as lubiprostone, linaclotide, and plecanatide are approved by the FDA for treating chronic constipation and IBS-C.[78, 108] These agents increase intestinal chloride secretion by activating channels on the apical (luminal) enterocyte surface. [78, 108] To maintain electroneutrality, sodium is also secreted into the intestinal lumen by other ion channels and transporters. To preserve isosmolality, water secretion follows. By increasing intestinal secretion, secretagogues accelerate transit and facilitate ease of defecation. Lubiprostone, a bicyclic fatty acid derivative of prostaglandin E1, primarily activates the apical CIC-2 chloride channels;[108] it accelerates small intestinal and colonic transit in healthy subjects,[109] In women of childbearing age, a negative pregnancy test should be documented before starting treatment and contraceptive measures are necessary.

Similar to the heat-stable enterotoxins that cause diarrhea, linaclotide is a 14-amino acid peptide.[78, 110] These ST, which are also homologs of the endogenous paracrine hormones uroguanylin in the small intestine and guanylin in the colon act on guanylyl cyclase C, which is expressed in brush border membranes of intestinal mucosal cells from the duodenum to the rectum. Linaclotide activates the intracellular catalytic domain of guanylyl cyclase C, which in turn converts guanosine triphosphate to cyclic guanosine monophosphate, inducing downstream effectors that open the cystic fibrosis transmembrane conductance regulator chloride channel and produce a net efflux of ions and water into the intestinal lumen.

Plecanatide is a newly approved guanylyl cyclase C agonist for the treatment of both chronic constipation and IBS-C. Plecanatide demonstrated efficacy and safety in a randomized placebo controlled trial of over 1300 patients with chronic constipation.[111] Both 3 mg and 6 mg doses demonstrated approximately 7% more efficacy than did placebo (20% for both

doses vs 12.8% placebo; p<0.004) over a 12 weeks trial. A recent systematic review and meta-analysis concluded that linaclotide and plecanatide were equally effective and safe, as might have been anticipated.[78]

Serotonin 5-HT$_4$ receptor agonists

By stimulating serotonin 5-HT$_4$ receptors, which are widely distributed on enteric neurons, 5-HT4 agonists release the excitatory neurotransmitter acetylcholine and induce mucosal secretion. The European Agency for Evaluation of Medicinal Products approved prucalopride, a 5-HT$_4$ agonist, for treating chronic constipation in women in whom laxatives fail to provide adequate relief.[112–115] It is currently not approved by the FDA but can be legally imported by patients, for example from Canada or Mexico. Prucalopride is safe and does not have cardiovascular side effects.

Comparison of pharmacological agents for chronic constipation

Based on meta-analyses,[89, 116] systematic reviews,[87] and the only head-to-head comparative study,[117] therapeutic trial(s) of fiber supplementation, osmotic laxatives, and/or stimulant laxatives, which are effective, safe, and generally less expensive, should be implemented before newer agents (secretagogues, serotonin 5-HT$_4$ receptor agonists in Europe) are considered (Table 2[78–82]). Several points in Table 2 deserve emphasis. First, these numbers may not be strictly comparable since different studies used different endpoints. Second, except for soluble fiber, there is more evidence for efficacy in chronic constipation than in IBS-C. While lubiprostone, linaclotide and plecanatide have been studied in IBS-C, there are no large high-quality trials of PEG, stimulant laxatives or prucalopride in IBS-C. Third, the evidence for efficacy in chronic constipation is strong for osmotic and stimulant laxatives which also have the most favorable cost-benefit ratios. Fourth, several well designed trials demonstrate that lubiprostone, linaclotide, and plecanatide are effective for treating chronic constipation and IBS-C. Lastly, since lack of response to traditional agents (e.g., laxatives) was not an entry criterion for the studies of the 3 secretogogues, the incremental utility of these newer agents over traditional approaches is unknown.

Treatments for Opioid-induced constipation (OIC)

Over the past two decades, the use of opiates and opioids for chronic pain has assumed epidemic proportions.[118] Between 40–90% of patients on opioids have constipation.[119] Opioids delay gastrointestinal transit, stimulate non-propulsive motor activity, increase intestinal segmentation and decrease electrolyte and water secretion into the gut. These effects work predominantly through opioid mμ receptors located in the gut as well as the central nervous system and may be difficult to overcome with most available laxatives. Lubiprostone is slightly better than placebo and is of similar efficacy to prucalopride, which is available in Europe.[120]

A more biologically plausible approach to OIC is to use an effective peripheral μ-opioid receptor antagonist. These drugs do not significantly counteract the benefits of pain reduction (Supplementary Table 3). For example, naloxegol is a pegylated derivative of naloxone that does not cross the blood-brain barrier. Two randomized, placebo-controlled

trials involving 1,352 subjects found that naloxegol in doses of 12.5 mg or 25 mg daily were superior to placebo over a 12-week trial.[121] Response rates to the 25 mg dose were significantly higher with drug vs. placebo (44.4% vs. 29.4%; 39.7% vs. 29.3%) with an NNT of 6.7 and 9.7 respectively. Similar results were seen among patients who previously had an inadequate response to laxatives. Similarly, in a meta-analysis, methylnaltrexone in doses of 0.15 mg/kg and 0.20 mg/kg body weight every other day when given subcutaneously, and 12 mg daily when given orally, were significantly superior to placebo.[122] These agents together with naloxone, naldemedine, and lubiprostone are approved for treating OIC in the United States. The peripheral μ-opioid receptor antagonist alvimopan shortens postoperative ileus but is not approved for treating OIC.[123]

Management of Defecatory Disorders

Non-structural DD are best managed by biofeedback-aided pelvic floor therapy, which is more effective than polyethylene glycol, sham feedback, or diazepam.[124] In one study, colonic transit normalized after biofeedback therapy in 65% of patients with disordered defecation, which suggests that pelvic floor dysfunction may delay colonic transit.[38] These trials employed 5–6 training sessions lasting 30–60 minutes at 2 week intervals. The therapist's skill and experience and the patient's motivation influence the response to biofeedback therapy. Aided by visual or auditory feedback of anorectal and pelvic floor muscle activity, which are recorded with surface electromyographic sensors or manometry, patients are taught to increase intra-abdominal pressure and relax the pelvic floor muscles during defecation. Thereafter, patients learn how to expel an air-filled balloon. When rectal sensation is reduced, sensory retrainingmay also be provided.

Regrettably, biofeedback therapy is not widely used to manage DD, perhaps because the therapy is not widely available and/or its benefits are not widely recognized. Many therapists inappropriately teach patients with DD to strengthen the external anal sphincter rather than improve coordination between abdominal and pelvic floor motion during evacuation. Third-party coverage for biofeedback therapy in DD has improved and may be more accepted when using the entirely appropriate term "muscle rehabilitation therapy". For example, in several states, the Centers for Medicare and Medicaid Servicesnow regard biofeedback therapy as medically necessary for treating adults with constipation due to DD unresponsive to laxatives. When insurance carriers deny approval for biofeedback therapy in patients with DD, the decision should be appealed because they may be unaware of the considerable evidence demonstrating the efficacy of pelvic floor retraining for DD.

Role of Surgery

Abdominal colectomy and ileorectal anastomosis is the next option in patients with medically-refractory slow transit constipation who do not have diffuse upper GI dysmotility or a DD.[125] Some studies suggest that quality of life improves and is sustained over time.[126] However, results are variable.[127] In general, studies in which colorectal physiologic assessments were incomplete observed poorer outcomes. Potential complications include ileus, small bowel obstruction, anastomotic leakage, and wound infections. Most episodes of small bowel obstruction are managed conservatively and do not require reoperation. Other

surgical or minimally-invasive approaches for slow transit constipation include antegrade colonic enemas that are administered by infusing water into the colon, either through an appendiceal conduit (Malone procedure) or indwelling cecostomy catheter (percutaneous endoscopic cecostomy, PEC).[127] Since a PEC can be performed under local anaesthesia and conscious sedation, it may be preferred to colectomy in patients who have a higher surgical risk due to co-morbidities. Also, a PEC is reversible. By comparison, 30% of patients have complications after the Malone procedure.[10] In patients with slow transit constipation, severe bloating and/or abdominal pain, a venting ileostomy may be useful to determine if symptoms are attributable to the small intestine or colon. An iliorectal anastomosis may be inadvisable if symptoms do not improve with a venting ileostomy.[128] In these situations, a colostmy is ill-advised because colonic transit is slow and persistent constipation may occur.

Other approaches

Sacral nerve stimulation, dividing the puborectalis muscle or performing a postanal repair [129,130] do not improve symptoms of constipation and are not FDA approved for use in the United States. Injection of botulinum toxin into the puborectalis muscle[131, 132] cannot be recommended for managing DD. The efficacy of the stapled transanal resection procedure, wherein staples are applied to the redundant rectal mucosa associated with rectocele and intussusception is uncertain and the link between symptoms and actual anatomic abnormalities is tenuous.[125] It is likely that anatomic abnormalities, such as intussusception and rectal prolapse are secondary to a DD and excessive straining, which is not remedied by the procedure. The adrenergic α_1 receptor antagonist reduced anal pressure at rest and during simulated evacuation but did not improve symptoms in patients with defecatory disorders.[133]

Conclusions

Constipation is a common symptom that can substantially affect quality of life. An algorithmic approach facilitates the management. A structural evaluation of the colon is only required in a minority of patients. Laxatives, biofeedback and surgery are all effective in treating selected patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

NTC	normal transit constipation
STC	slow transit constipation
DD	defecatory disorders

FC	functional constipation
IBS-C	constipation-predominant IBS
U.S.	United States
NNT	number needed to treat
PEG	polyethylene glycol
5-HT$_4$	5-Hydroxytryptamine receptor 4
FDA	United States Food and Drug Administration
OIC	Opioid-induced constipation
PEC	percutaneous endoscopic cecostomy

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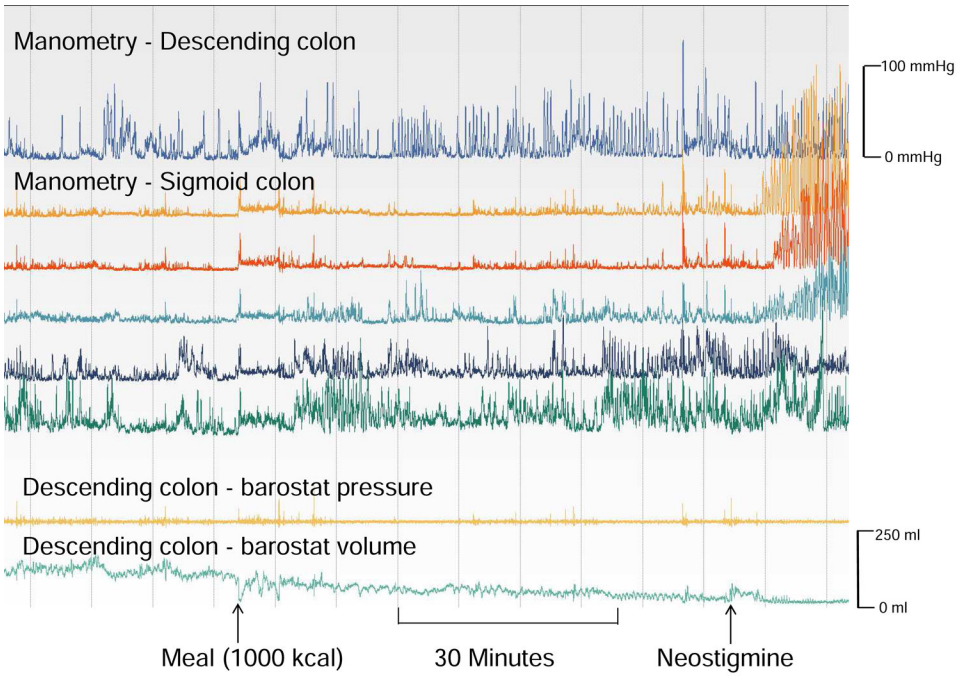

Figure 1. Normal colonic contractile responses to a meal in a patient with isolated slow transit constipation.

Motor activity was recorded with manometry and a barostat balloon under fasting conditions (30 minutes), for 1 hour after a meal, and for 15 minutes after the cholinesterase inhibitor neostigmine. Before the meal, phasic pressure activity was greater in the distal than the proximal sigmoid colon. Phasic activity increased after the meal and more so after neostigmine. The volume of a balloon, located between the uppermost and second manometry sensors and inflated to a constant pressure of 12 mmHg, declined after a meal, and more so after neostigmine, reflecting increased colonic tone.

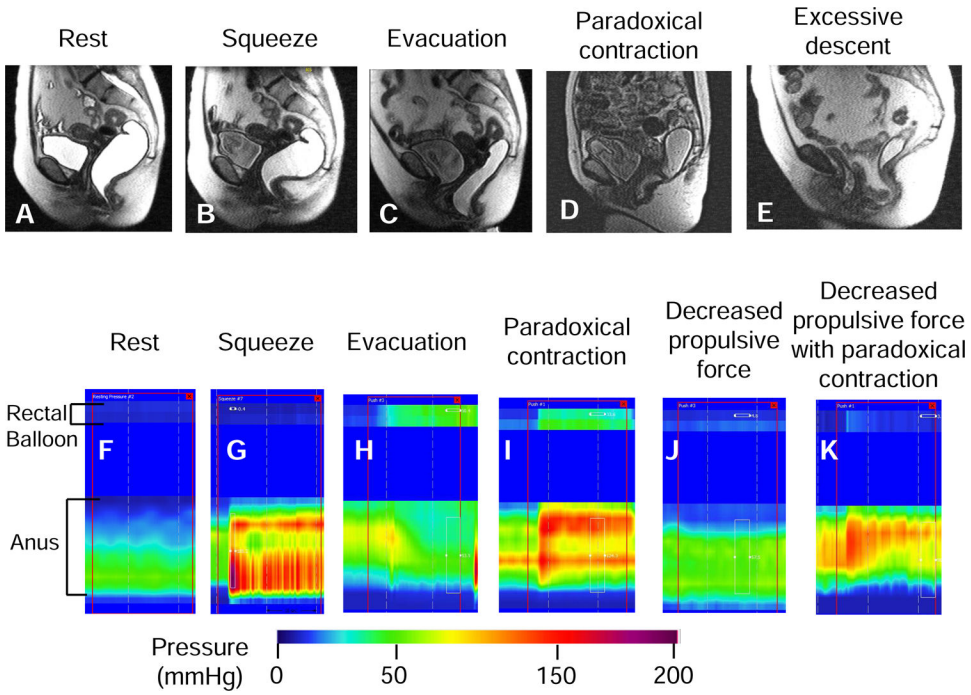

Figure 2. Representative examples of normal and abnormal anorectal evacuation recorded with MRI (upper panel) and high resolution manometry (lower panel).

With MRI, observe increased puborectalis indentation during squeeze (arrow, panel B) and normal relaxation of the puborectalis, perineal descent, opening of the anal canal and evacuation of ultrasound gel during evacuation (panel C). During evacuation in constipated patients, observe paradoxical contraction of the puborectalis (panel D) and exaggerated perineal descent with an enterocele (panel E). High resolution manometry shows increased anal pressure during squeeze (G) compared to rest (F). The white rectangle demarcates the duration of squeeze (G) and evacuation (H-K). Observe increased rectal pressure with anal relaxation during evacuation (H) in a healthy person. By contrast, during evacuation in constipated patients, observe increased rectal pressure with paradoxical anal contraction (I), no change in rectal pressure versus rest (J), and no change in rectal pressure with paradoxical anal contraction (K).

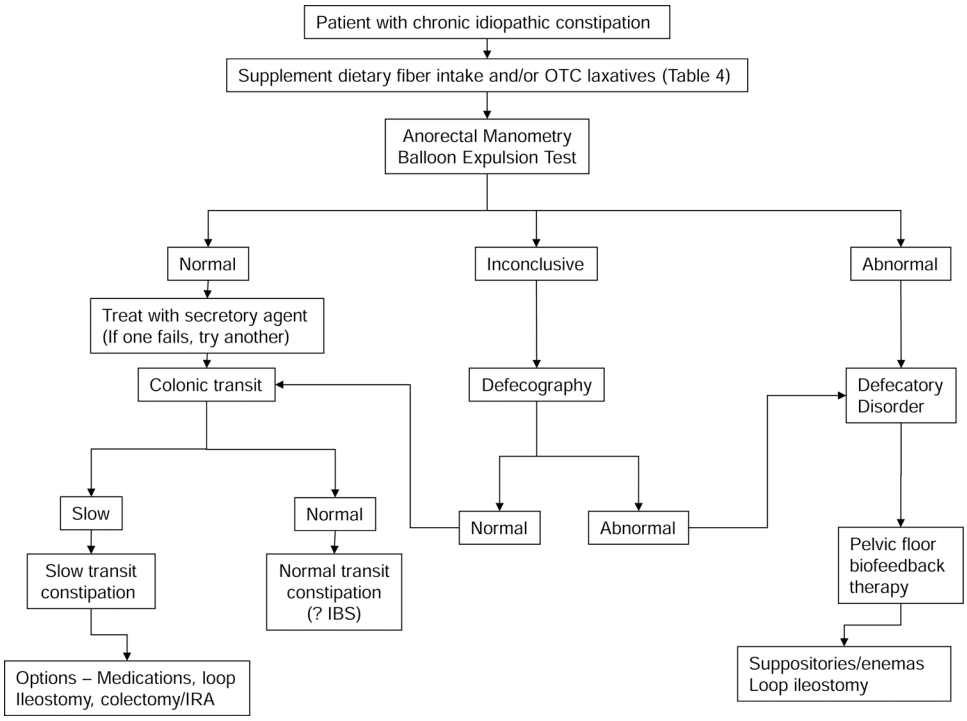

Figure 3.
Suggested algorithm for treating patients with chronic constipation

Table 1.

Differences between Functional Constipation and Constipation-Predominant IBS

Feature	Functional Constipation	Constipation predominant IBS
Symptom criteria [4]	Symptoms for ≥ 6-months and ≥ 2 following symptoms for >¼ defecations during past 3 months: • Straining • Lumpy or hard stools • Sensation of incomplete evacuation • Sensation of anorectal obstruction/blockade • Manual maneuvers to facilitate defecations; <3 defecations/week • Loose stools are not present, and there are insufficient criteria for IBS	Recurrent abdominal pain or discomfort at least 3 days per month in the past 3 months associated with 2 or more of the following: • Improvement with defecation • Onset associated with change in frequency of stool • Onset associated with change in form (appearance) of stool • <25% of bowel movements were loose stools
Upper gastrointestinal symptoms (eg, heartburn, dyspepsia), anxiety and depression, urinary symptoms [5]	Less common [a]	More common [a]
Prevalence of defecatory disorder [5]	Approximately 50% of patients	Approximately 50% of patients
Prevalence of increased rectal sensation [6]	Less common [a]	More common [a]

[a]The prevalence of these symptoms varies by symptom; hence specific figures are not provided ([a])

[b]The prevalence of increased rectal sensation varies among studies

Table 2.

OTC and Prescription Treatments for Chronic Constipation and Constipation-Predominant IBS

Courtesy of Dr Michael Hirsch, Department of Pharmacy, University of Wisconsin Hospitals, Madison, Wi

Treatment, frequency	Dose	NNT (95% CI) for CC and IBS-C [b]	Cost per month 2018$	Comments
Bulking agents: psyllium, daily	CC: Variable dose IBS-C: Variable dose	CC: 2 (1–3) [79] IBS-C: 10 (6–33) [79]	8.34	Start with low dose and increase gradually.
Polyethylene glycol, daily	CC: 17gm IBS-C	CC: 3 (2–4) [2] IBS-C: NA	8.73	More evidence in CC than IBS-C. Improved bowel symptoms but not abdominal pain in IBS-C[80]
Lactulose, daily	20g	NA	13.28	Can produce bloating and distension
Bisacodyl, daily	CC: 10mg IBS-C	CC: 4 (NA)[81] IBS-C: NA	5.17	Available as suppository, preferably administered 30 minutes after breakfast
Senna, daily	17.2 – 34.4mg		6.96	Widely used anthraquinone laxative
Prucalopride, daily	CC: 2mg IBS-C: NA	CC: 6 (5–9) [2] IBS-C: NA		Not approved in the United States. Available in Mexico, Canada, and Europe
Linaclotide, daily	CC: 72μg IBS-C: 290 μg	CC: 12 (6–29) (72 μg); 10 (6–19) (145 μg) [78] IBS-C: 6 (4–16) (290 μg)	466.47	Improves abdominal pain, bloating, and global IBS symptoms in IBS-C
Lubiprostone, twice daily	CC: 24μg IBS-C: 8 μg	CC: 4 (3–6) (24μg) [79] IBS-C: 12 (8–25) (8 μg)	445.32	Also improves abdominal bloating, discomfort, constipation severity in opioid-induced constipation[82]
Plecanatide, daily	CC: 3 mg or 6 mg IBS-C: or 6mg	CC: 11 (8–19) (3 mg); 12 (8–23) (6 mg) [78] IBS-C:9 (6–16) (3mg);9 (6–17) (6mg)	466.16	Same as linaclotide

[a] Abbreviations: CC = chronic constipation; IBS-C = irritable bowel syndrome of constipation.

[b] NNT indicates number needed to treat