

REVIEW ARTICLE

Chronic constipation: advances in management

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Abstract Only a relatively small percentage of clinically constipated patients seek medical attention and most can be managed satisfactorily with conservative measures. This review mainly addresses those patients who have refractory or difficult-to-manage functional constipation who are referred to gastrointestinal specialists. Areas of review include insights into pathophysiology, the utility of diagnostic testing and the author's opinions concerning available pharmacologic agents, the role of behavioural therapies and the indications for surgical interventions in this heterogeneous group of patients.

Keywords biofeedback, constipation, dyssynergic defecation, laxatives.

INTRODUCTION

Chronic constipation is a complaint frequently seen in clinical practice. It is often mild and intermittent and the availability of non-prescription agents allows for much self-treatment.¹ Conversely, constipation can be unresponsive to simple interventions, prompting medical consultations, diagnostic evaluations and even hospitalizations. The majority of office visits for constipation are to primary care physicians with the most worrisome or difficult-to-manage patients referred to specialists or tertiary care centres.^{2,3} The most problematic patients are those who do poorly or fail to respond to medical therapy. What advances in our management of chronic constipation are of value to specialists in practice and in tertiary care centers

and what are the rational approaches to chronically dissatisfied patients? This article reviews our current understanding of the diagnosis and pathophysiology of chronic constipation, the benefits and limitations of functional tests of colon and anorectum, and the evidence for and limitations of new therapeutic approaches to this heterogeneous group of patients.⁴

DEFINITION AND PATHOPHYSIOLOGY OF CHRONIC CONSTIPATION

The expansion of the definition of constipation from the previously overly narrow one of 'infrequent defecation' has aligned our current medical definition of this disorder to encompass that of patients and the general population. In fact, infrequent defecation is an uncommon complaint among those who are constipated and there is little evidence that symptoms predict the presence or absence of colorectal dysfunction as defined by diagnostic testing. This expanded consensus definition (Table 1) appears to be generally accepted in the scientific community.⁴

It is intuitive that constipation in many patients is associated with disordered movement of stool through the colon or anorectum.^{1,5} This may be associated with a wide variety of disorders or with certain drugs (Tables 2 and 3). The increasing use of colonic transit studies using radioopaque markers or scintigraphy has identified subgroups of constipated patients who have slow transit through the colon and or the rectosigmoid colon. Slow colonic transit is a heterogeneous disorder which in some patients is associated with neuroenteric changes in the colon,⁶ whereas in others, it is related to disorders such as anorexia nervosa and to medications associated with proximal slowing of transit.⁵ However, many patients are found to have normal colonic transit when tested. This suggests other diagnostic possibilities such as the presence of a defecation disorder alone,

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Received: 27 February 2006

Accepted for publication: 7 July 2006

Table 1 American College of Gastroenterology Task Force: definitions of chronic constipation

Unsatisfactory defecation characterized by infrequent stool, difficult stool passage, or both

Difficult stool passage includes:

- Straining
- Hard/lumpy stool
- Difficulty passing stool
- Incomplete evacuation
- Prolonged time to stool
- Need for manual manoeuvres to pass stool

Symptoms must be reported for at least 3 months

American College of Gastroenterology Chronic Constipation Task Force. *Am J Gastroenterol* 2005; **100**(Suppl. 1): S1–S4.

Table 2 Secondary causes of functional constipation (partial list)

Metabolic and endocrine disorders

- Diabetes mellitus
- Hypothyroidism
- Hypercalcemia, hypokalaemia
- Pregnancy
- Porphyria
- Panhypopituitarism

Neurogenic disorders

- Hirschsprung disease
- Chagas disease
- Neurofibromatosis
- Ganglioneuromatosis
- Autonomic neuropathy
- Intestinal pseudo-obstruction (myopathy, neuropathy)
- Multiple sclerosis
- Spinal cord lesions
- Parkinson disease

Collagen vascular and muscle disorders

- Systemic sclerosis
- Amyloidosis
- Dermatomyositis
- Myotonic dystrophy

Table 3 Some drugs associated with constipation

Anticholinergics

- Antispasmodics
- Antidepressants
- Antipsychotics

Cation-containing agents

- Iron supplements
- Aluminum (antacids, sucralfate)

Neurally active agents

- Opiates
- Antihypertensives
- Ganglionic blockers
- Vinca alkaloids
- Calcium channel blockers
- 5HT₃ antagonists

an intermittent colonic dysfunction not present during the test, a misperception of normal bowel functions or simply an insensitivity of a single test to detect colonic dysmotility.

A major advance with important therapeutic ramifications has been the characterization of a number of defecation disorders, such as dyssynergic defecation and its functional equivalent, inadequate expulsion.^{7,8} As symptoms do not always predict whether such a disorder is present, the diagnosis currently depends upon physiologic testing which is best done in laboratories experienced with specific diagnostic testing.

Another conceptual advance has been to distinguish functional chronic constipation from irritable bowel syndrome (IBS) with a predominance of constipation. There has been a tendency to label those constipated patients with normal colonic transit as having IBS but with little evidence to justify it. Abdominal pain is an important hallmark of IBS patients which often requires treatment in conjunction with regulation of bowel habits.⁴ Moreover, there are no published studies to show that IBS with constipation is uniformly characterized by normal colonic transit. It is not always possible to distinguish patients with functional constipation from those with IBS, as many constipated patients have some abdominal discomfort. However, clinicians should try to make the distinction in clinical practice in accordance with consensus recommendations as codified in the Rome III guidelines.⁴

ADVANCES IN DIAGNOSTIC TESTING

There is widespread agreement that diagnostic testing in patients with chronic constipation should be employed only in those patients who fail to respond to initial therapy and that it is more important to perform studies which characterize colonic and anorectal functions rather than structure except in the presence of 'alarm symptoms'.^{9,10} In general, the use of colonoscopy and imaging studies has been excessive in this population and should be minimized.

Colon transit studies

It is often argued that colon transit studies are unnecessary in patients with refractory constipation because treatment will be similar regardless of the findings. This approach is debatable for several reasons. The demonstration of slow colonic transit while consuming a 20–25 g fibre diet suggests that fibre supplements and osmotic laxatives are likely to be both ineffective and counterproductive, causing increased bloating and discomfort. Such patients often do better

on less fibre and little if any osmotic laxatives together with prokinetics or stimulant laxatives. Moreover, it is only these patients with severe slow transit in whom subtotal colectomy can be considered. Conversely, the demonstration of normal colonic transit suggests the need to focus on a possible defecation disorder and should reassure physician and patient that colonic motor function is intact. Such patients may respond better to osmotic agents or fibre and are not candidates for surgery.

Although it is true that patterns of slow colon transit do not predict pathophysiology, some general conclusions can be made which are of practical value. The finding of slow transit in the rectum and sigmoid colon with normal transit proximally strongly suggests an anorectal dysfunction such as a defecation disorder or a psychosocial problem such as withholding behaviour. Slow transit in the right colon with normal anorectal testing suggests a neuroenteric disorder in the absence of conditions which may slow transit such as medications, an eating disorder, etc. This kind of analysis helps to distinguish subsets of patients and to identify rational treatment options when trying to manage the refractory patient.¹¹

Anorectal studies for defecation disorders

Anorectal manometry provides information on rectal sensation and compliance, relaxation of the internal anal sphincter and manometric patterns produced on attempted expulsion of the apparatus.¹⁰ During the latter manoeuvre, the rectal balloon provides some indication of the intra-abdominal pressures generated during expulsion efforts, whereas pressure recordings of the anal sphincters indicate relaxation or inappropriate contraction of the external anal sphincter. In patients with dyssynergic defecation, there is an increase in

external sphincter pressures during attempted expulsion of the balloon (Fig. 1). Typically, these patients are unable to expel a 50-mL water-filled balloon within 60 s while seated on a commode,¹² a test which can easily be used as an office-based screening method.

Barium defecography provides a two-dimensional quantification of rectal parameters and functional information regarding the completeness of rectal emptying. It has limited clinical usefulness: normal parameters for emptying of barium are broad, there is poor inter-observer agreement¹³ and there is limited information of importance for clinical decision making.¹⁴ Neither balloon expulsion nor defecography duplicates defecation with its associated colonic propulsive activity, and the latter is performed in a public setting which may lead to behavioural inhibition.

Anterior rectoceles are outpouchings of the recto-vaginal wall into the lumen of the vagina which can be palpated with the patient bearing down as if to defecate or identified on barium defecography. The relationship between rectoceles and preexisting defecatory dysfunction is unknown, that is whether prolonged straining results in the formation of a rectocele which, when it reaches a critical size, results in stool trapping and prolonged straining. What is clear is that most rectoceles are asymptomatic, but that defecation difficulties may occasionally arise when expulsive forces are misdirected into a large pouch. The key to management is to identify the latter prior to surgery.

Choosing a diagnostic strategy

Most chronically constipated patients do not require diagnostic studies beyond taking a careful history and performing a physical examination, especially of the rectum and pelvic floor. Colonoscopy or flexible sigmoidoscopy are indicated specifically in the

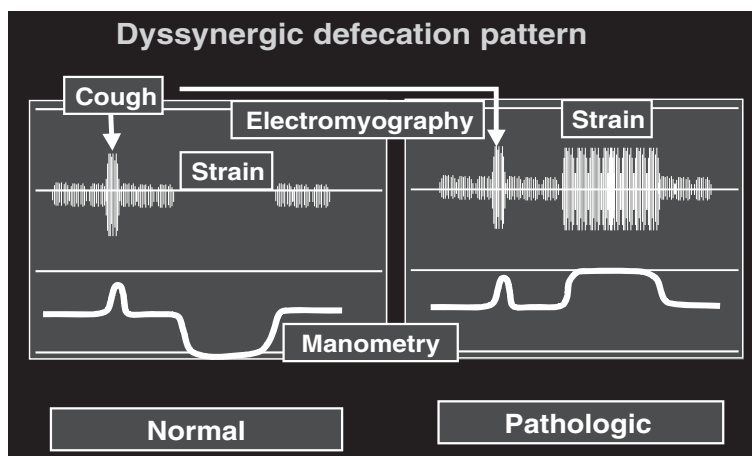


Figure 1 Anal sphincter electromyographic (EMG) and pressure responses to straining as if to defecate. Straining is normally associated with inhibition of sphincter EMG and pressure (left). In dyssynergia, sphincter EMG and pressure activity are increased inappropriately (right). [reproduced from Preston and Lennard-Jones. *Dig Dis Sci* 1985; **30**: 413–8. With kind permission of Springer Science and Business Media.]

presence of alarm symptoms (recent worsening of constipation, blood in the stools, weight loss, anorexia, nausea or vomiting) or as a screening procedure in patients over the age of 50 years.^{3,9}

As symptoms do not discriminate between physiological subgroups of patients with severe idiopathic constipation, the workup is similar regardless of presenting symptoms. A 2-week, prospectively obtained bowel diary and measurement of colonic transit time are the most useful diagnostic studies to obtain. Screening for a defecation disorder can be done in any physician's office using a simple handmade device to measure the expulsion of a water-filled balloon. Normal studies can reassure both the physician and patient that colorectal function is not seriously impaired. If the balloon expulsion test is abnormal, the patient should be referred to anorectal manometry. Upon completion of these studies, four patterns of colonic and anorectal function are possible (Fig. 2).

ADVANCES IN TREATMENT

The major developments in the treatment of chronic constipation in the past 10 years have encompassed five broad areas: the re-evaluation and availability of stimulant laxatives, the expanded role for newer osmotic agents, the recent introduction of enterokinetic drugs such as tegaserod and lubiprostone, the efficacy of biofeedback for defecation disorders and the evolution of the highly restricted but important role of surgery in selected patients with severe slow-transit constipation.

Stimulant laxatives

There has been a tendency by many physicians to avoid chronic use of stimulant laxatives because of unsubstantiated claims that they harm the colon, promote dependency and habituation and have the potential for

inappropriate use and abuse. These concerns have been over emphasized and are supported by few or no data.^{15,16} When used appropriately, stimulant laxatives are not harmful and are often both efficacious and cost-effective in many patients with occasional or chronic constipation.

The currently available stimulant laxatives include senna and bisacodyl (Table 4). Anthraquinone laxatives such as senna increase fluid and electrolyte accumulation in the distal ileum and colon after they have been metabolized to a pharmacologically active state by intestinal micro-organisms. They are also believed to stimulate sensory nerve endings when they contact colonic mucosa. Changes in the colon produced by chronic anthraquinone use include melanosis coli, a benign and reversible condition. There is no evidence that anthraquinone laxatives given in clinically appropriate doses cause enteric damage in either animals or humans.^{15,16}

Bisacodyl is a diphenylmethane laxative that when activated stimulates intestinal fluid accumulation and colonic motor activity in a way similar to anthraquinones. In 1997, the Food and Drug Administration reclassified phenolphthalein, another diphenylmethane, as '...not generally recognized as safe and effective...' after a study in rodents found an increased incidence of nongastrointestinal neoplasms.¹⁷ As a result, all phenolphthalein-containing laxatives were withdrawn in the US; however, subsequent studies have not demonstrated an increased risk of cancer in humans taking phenolphthalein laxatives.¹⁸ A confirmed relationship between any of the stimulant laxatives and the development of colonic neoplasms has not been substantiated.^{16,19}

Osmotic laxatives

Osmotic agents include magnesium-containing laxatives, polyethylene glycol (PEG) and nonabsorbable

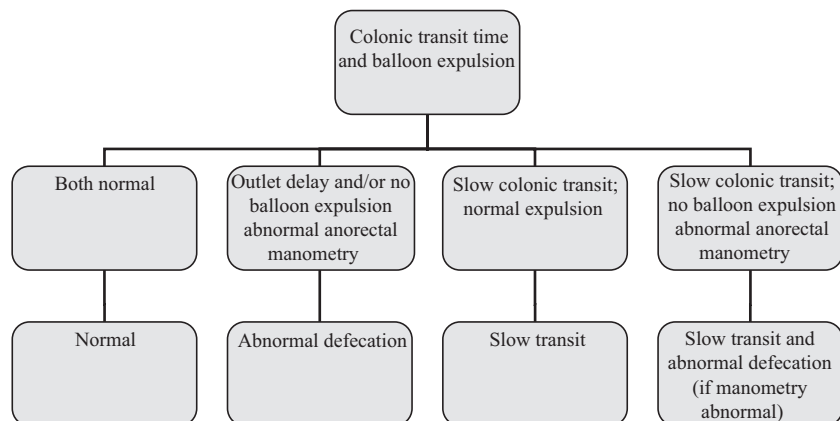


Figure 2 Evaluation and classification of idiopathic chronic constipation. In patients with severe and intractable constipation, colonic transit times and balloon expulsion are simple office-based studies that can evaluate colonic and anorectal function. The latter can be further evaluated with anorectal manometry which is best done at experienced centres. [From Ref. (1) with permission]

Laxative	Usual adult dose	Onset of action
Bulk-forming laxatives		
Psyllium	Up to 1 tsp TID	12–72 h
Methylcellulose	Up to 1 tsp TID	12–72 h
Calcium polycarbophil	2–4 tabs/day	24–48 h
Osmolar agents		
Polyethylene glycol (PEG)	8.5–34 g in 240 mL liquids	2–4 days
Lactulose	15–30 mL QD or BID	24–48 h
Sorbitol	120 mL of 25% solution QD	24–48 h
Glycerine	3 g suppository QD	15–60 min
Magnesium citrate	200 mL QD	0.5–3 h
Stimulant laxatives		
Bisacodyl	10–20 mg p.o. QHS	6–10 h
	10 mg suppository QD	15–60 min
Senna	2 to 4 tabs QHS	6–12 h
Other Agents		
Tegaserod	6 mg p.o. BID	24 h
Lubiprostone	24 µg p.o. BID	24 h

BID = twice daily; QD = every day; QHS = every night; tabs = tablets; TID = thrice daily; tsp = teaspoon.

Table 4 Representative agents for treatment of constipation

sugars such as lactulose and sorbitol (Table 4). Sorbitol and lactulose are degraded by colonic bacteria to low-molecular-weight acids that increase stool acidity and osmolarity and lead to the accumulation of fluid in the colon. PEG solutions have proven effective when given daily for periods of up to 6 months^{20,21} and are less likely than the nonabsorbable sugars to produce bloating and flatulence, as it is inert and not degraded by colonic bacteria. These agents are given once daily and should be adjusted to reduce abdominal bloating and flatulence and to modulate defecation. Evidence for the efficacy of PEG, lactulose and sorbitol is sufficiently strong, based upon the quality and number of published trials.⁹

Like fibre supplements (Table 4), osmotic laxatives may be counterproductive in certain subgroups of constipated patients. These include those with moderate to severe slow colonic transit, defecation disorders, megacolon, constipation associated with IBS, and patients with severe bloating and fullness. Often, less is more in such patients. For example, the presence of chronic megacolon indicates that the patient has a failed colon with little or no propulsive activity. Just as a physician would not recommend salt and water supplements to a person with end-stage congestive heart failure, one should not recommend bulk or osmotic laxatives, nor fibre supplements to a patient with chronic megacolon. Rather a fibre-restricted diet, accompanied by cleansing enemas once or twice weekly, should be used to minimize the build-up of faecal matter and gas.

Enterokinetic and secretory agents

The development of drugs to enhance colonic transit by increasing propulsive motor activity has been hampered by our limited knowledge of colonic motility and the pathophysiology of severe idiopathic constipation (Table 4). Cholinergic agents, cholinesterase inhibitors and metoclopramide have had little success. Although initial studies suggested cisapride to be efficacious, others reported disappointing results in patients with severe idiopathic constipation. The use of cisapride has been severely restricted in the US by the FDA because of the risk of cardiac toxicity.

There has been an intense interest in 5-hydroxytryptamine (serotonin) agonists, which stimulate intestinal motility, in part by facilitating enteric cholinergic transmission. Tegaserod, a partial 5-hydroxytryptamine-4 receptor agonist, is approved by the FDA for women with constipation-predominant IBS and in men and women with chronic constipation who are less than 65 years of age.^{22,23} There have been no studies of tegaserod in patients whose constipation is characterized by slow colonic transit or anorectal dysfunction. As the drug is significantly more expensive than laxatives, it is best restricted to patients who do not respond satisfactorily to less expensive agents.

The FDA recently approved lubiprostone for treatment of chronic functional constipation. The first drug of its chemical type, lubiprostone works by increasing intestinal fluid secretion by stimulating a specific intestinal chloride channel (ClC-2). The decision to approve the drug was based on the results of two

pivotal short-term trials which demonstrated significant improvement of constipation, abdominal bloating and discomfort, and three long-term studies of 6–12 months.²⁴

Some patients with severe constipation have been treated successfully with misoprostol, with and without PEG.²⁵ Further studies are needed to assess the safety and possible efficacy of this agent as well as lubiprostone in severely constipated individuals.

Biofeedback

One behavioural approach is the use of biofeedback to correct inappropriate contraction of the pelvic floor muscles and external anal sphincter during defecation (dyssynergic defecation). Studies have used anal EMG or sphincter pressure recordings during attempted expulsion of the apparatus. The patient watches the recordings and is asked to modify inappropriate responses through trial-and-error efforts. Uncontrolled studies in adults suggest that biofeedback is effective in over 70% of patients.²⁶ These findings have been confirmed in three randomized controlled studies^{27–29} which suggest that biofeedback is beneficial in that group of constipated patients who exhibit dyssynergic defecation and that benefits are sustained for at least 2 years without additional training. In contrast to an earlier study, biofeedback was not effective in patients with slow-transit constipation who exhibit no evidence of dyssynergia.²⁷ These studies and the experience of other centres suggest that biofeedback training should be the primary treatment option for patients with dyssynergic defecation.

What is the role of surgery for chronic constipation?

In select patients with severely incapacitating slow-transit constipation, colectomy with ileorectal anastomosis can ameliorate incapacitating symptoms.^{11,30} Limited resection of the colon to shorten or remove 'kinks' generally produces unsatisfactory results.¹⁶ Prior to surgery, studies should establish normal oesophageal, gastric, small intestine and anorectal function because evidence of a more extensive dysmotility disorder is associated with unsatisfactory results. Anorectal dysfunction is a contraindication to ileorectal anastomosis, unless dyssynergia can be corrected. There is a substantial complication rate with surgery and bloating and abdominal pain are unlikely to improve with surgery.³¹ Thus, subtotal colectomy should be offered with great reluctance in a

patient with abdominal pain and with the firm understanding that such surgery is highly unlikely to improve pain.

Surgery may be considered in patients with megarectum or megacolon if medical treatment fails.^{1,30} It is crucial that patients be categorized accurately because colonic abnormalities determine surgical options. In patients with a moderately dilated colon and a normal rectum, subtotal colectomy with ileorectal anastomosis offers the best results. If the entire colon and rectum are dilated, proctocolectomy with ileoanal anastomosis is an alternative if anal sphincter function is normal; if not, ileostomy should be performed.

The indications for surgical repair of a rectocele are not well defined, as surgery does not always improve symptoms.³⁰ Furthermore, the size of the rectocele does not seem to influence the surgical outcome. Optimally, one should demonstrate improved defecation when pressure is placed on the posterior wall of the vagina during defecation before a repair is entertained. Outcomes of surgical repairs for rectoceles are difficult to evaluate because reported symptoms are heterogenous and preoperative investigations and surgical techniques are variable.³⁰ All patients should be investigated for dyssynergic defecation before a rectocele repair is undertaken as the condition may recur if unrecognized dyssynergia is not corrected.

CONCLUSION

Constipation is a heterogenous and prevalent disorder, which can for the most part be treated by readily available laxatives and the identification and removal of aggravating factors such as constipating medications. Standard treatments are chosen on a basis of cost-benefit ratios and misconceptions concerning stimulant laxatives have led to unnecessary avoidance of these relatively inexpensive agents. An overemphasis on evidence-based analysis has tilted recommendations towards more expensive but not necessarily more effective agents which are best used when response to less costly agents is unsatisfactory.

Diagnostic testing should be reserved for patients with severe or difficult-to-manage constipation, with less emphasis on tests of colorectal structure and more on colorectal function. Defecation disorders are now increasingly appreciated as a cause of constipation poorly responsive to conventional therapy but highly responsive to behavioural approaches such as biofeedback. Use of surgery should be highly circumscribed and based in large part on diagnostic testing.

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