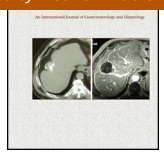
Digestive and Liver Disease 45 (2013) 886–893

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld



Review article

Chronic constipation: A critical review

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ARTICLE INFO

Article history:
Received 11 December 2012
Accepted 18 March 2013
Available online 30 April 2013

Keywords:
Clinical review
Constipation
Evidence-based medicine

ABSTRACT

Chronic constipation is a very common symptom that is rarely associated with life-threatening diseases, but has a substantial impact on patient quality of life and consumption of healthcare resources. Despite the large number of affected patients and the social relevance of the condition, no cost-effectiveness analysis has been made of any diagnostic or therapeutic algorithm, and there are few data comparing different diagnostic and therapeutic approaches in the long term. In this scenario, increasing emphasis has been placed on demonstrating that a number of older and new therapeutic options are effective in treating chronic constipation in well-performed randomised controlled trials, but there is still debate as to when these therapeutic options should be included in diagnostic and therapeutic algorithms. The aim of this review is to perform a critical evaluation of the current diagnostic and therapeutic options available for adult patients with chronic constipation in order to identify a rational patient approach; furthermore we attempt to clarify some of the more controversial points to aid clinicians in managing this symptom in a more efficacious and cost-effective manner.

1. Introduction

Chronic constipation is a very common and heterogeneous condition characterised by unsatisfying defecation associated with infrequent stools, difficult stool passage, or both [1]. It has a prevalence of 14% in the general population [2], and a significant impact on patient quality of life [3,4], working productivity [5], and consumption of healthcare resources [6]. Over the last ten years, both old and new treatments with different mechanisms of action have proved to be effective [7], but their role in the therapeutic approach still needs to be optimised. The aim of this review is to perform a critical evaluation of the diagnosis and treatment of chronic constipation in adults, concentrating on the most controversial issues raised by the current availability of effective treatments. Take-home messages are included at the end of each section.

1.1. Definitions

There are various definitions of chronic constipation, and the apparently small differences between them need to be acknowledged as they create groups of patients with potentially distinct responses to treatments. One of the most widely used is based on the Rome III criteria (Table 1) [8]. Whether the combination of two or more different symptoms identifies different subsets of patients remains unclear [9,10], as whether a bowel diary is needed to overcome the discrepancy between recalled and recorded bowel habits [11,12].

An alternative approach is to define constipation on the basis of a patient's dissatisfaction with the frequency of defecation and stool passage [1]. This approach is underpinned by the concept that it is the patients' perceived degree of dissatisfaction that makes a symptom more or less relevant. There are no details as to how this should be measured, but the symptoms should be considered clinically important and treated when they are severe enough to impair the patient's quality of life [1], a variable that is also influenced by psychological factors [13]. Moreover, the challenge of a definition based on dissatisfaction is that many people have their own, possibly erroneous conception of what constitutes a normal bowel habit: for example, elderly patients with normal bowel frequency (>3 times/week) often regard themselves as being constipated and take laxatives [14].

A third definition used in clinical trials is a modified version of the Rome criteria in which abnormal bowel frequency (<3 bowel movements/week) is the necessary condition for inclusion [15–19]. This restriction makes the patients more uniform and provides an objective parameter for assessing treatment efficacy, but excludes the important subgroup of patients who feel constipated despite normal bowel frequency [11,14]. It might also limit the possibility of extrapolating clinical trial results to the general population and

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1590-8658/$36.00
http://dx.doi.org/10.1016/j.dld.2013.03.016

Table 1
Rome III functional constipation criteria.[a]

1. Must include at least 2 of the following:
   a. Straining during at least 25% of defecations
   b. Lumpy or hard stools in at least 25% of defecations
   c. Sensation of incomplete evacuation for at lest 25% of defecations
   d. Sensation of anorectal obstruction/blockage for at least 25% of defecations
   e. Manual manoeuvres to facilitate at least 25% of defecations (*e.g.* digital evacuation, support of the pelvic floor)
   f. Fewer than three defecations per week
2. Loose stools are rarely present without the use of laxatives
3. Insufficient criteria for diagnosis of irritable bowel syndrome

[a] Criteria fulfilled for the previous three months with symptom onset at least six months prior to diagnosis.

Table 2
Classes of medications (examples) and diseases associated with secondary constipation [24,25].

Medications:	Opiates (morphine), anticholinergic agents, tricyclic antidepressants (amitriptyline), antispasmodics (dicyclomine, mebeverine, peppermint oil), calcium channel blockers (verapamil, nifedipine), antiparkinsonian drugs, anticonvulsants (carbamazepine), sympathomimetics (ephedrine), antipsychotics (chloropromazine, clozapine, haloperidol, risperidone), diuretics (furosemide), antihypertensives (clonidine), antiarrhythmics (amiodarone), beta-adrenoceptor antagonists (atenolol), antihistamines, calcium or aluminium containing antacids, calcium supplements, iron supplements, antidiarrheal (loperamide), 5-HT3-receptor antagonists (ondansetron), bile acid sequestrants (cholestyramine), non-steroidal anti-inflammatory drugs (ibuprofen)
Organic stenosis:	Colorectal cancer; other intra- or extra-intestinal masses; inflammatory, ischemic or surgical stenosis
Endocrine or metabolic disorders:	Hypothyroidism, hypercalcemia, hyperparathyroidism, diabetes, porphyria, chronic renal insufficiency, pan-hypopituitarism, pregnancy
Neurological disorders:	Spinal cord injury, Parkinson's disease, cerebrovascular disease, paraplegia, multiple sclerosis, autonomic neuropathy, spina bifida
Enteric neuropathies:	Hirschsprung's disease, chronic intestinal pseudo-obstruction
Myogenic disorders:	Myotonic dystrophy, dermatomyositis, scleroderma, amyloidosis, chronic intestinal pseudo-obstruction
Anorectal disorders:	Anal fissures, anal strictures

the elderly, in whom the major complaints defining constipation are straining and hard stools rather than reduced bowel frequency [14,20].

Another debated point is whether irritable bowel syndrome with constipation (IBS-C) is a different entity from chronic/functional constipation. Some researchers consider the two conditions indistinguishable [1] because the abdominal pain and discomfort characterising IBS can also be associated with constipation [21,22]. Furthermore, although the Rome III criteria exclude IBS-C from the definition of functional constipation [8], if this requirement is not enforced, there is a large overlap between the two [23]. These observations suggest a continuum based on the severity of pain or discomfort [23], but do not exclude the possibility that the patients at the two extremes of the spectrum may benefit more from treatment aimed specifically at relieving abdominal pain or correcting the defecation disorder/colonic transit. In particular, the presence of abdominal pain in patients with chronic constipation is associated with a poorer quality of life and more frequent extra-intestinal somatic symptoms than in constipated patients with no abdominal pain [21].

Take-home messages (1)

The different definitions of chronic constipation create groups of patients with potentially distinct treatment responses.

Physicians prefer using objective and physical factors when defining constipation, whereas patient dissatisfaction may be unrelated to these factors.

Chronic constipation and irritable bowel syndrome with constipation often overlap.

2. Causes and pathophysiology

Most cases of chronic constipation are primary or idiopathic, but it is also necessary to acknowledge that a few cases may be *secondary* to a number of medications or diseases (Table 2) [24,25], because reducing or stopping the medications or treating the primary diseases may help to relieve the symptom. The long and heterogeneous list of conditions that induce constipation indicates that many pathophysiological mechanisms finally cause the same symptoms, which are often indistinguishable from those of the primary form.

The pathophysiology of *primary* chronic constipation is multifactorial and includes diet, colonic motility and absorption, anorectal motor and sensory function, and behavioural and psychological factors. Most studies have investigated the impact of only one factor at a time, whereas their multiplicity, overlapping nature, and bidirectional interplay should be taken into account in order to avoid oversimplification. Although it is conceivable that a better understanding of the pathophysiology of the condition might help in the planning of more rational therapy, the complex interactions of various pathophysiological factors suggest that therapeutic strategies based on only one of them should be considered with caution.

2.1. Diet

A fibre-rich diet accelerates transit time, softens stool and increases stool weight, but a diet that is poor in fibre can induce constipation [26]. However, the consumption of dietary fibre is no different between constipated and non-constipated subjects [27]. Increasing dietary fibre improves symptoms in patients with normal colonic transit and anorectal function, but not in constipated patients with delayed colonic transit and defecation disorders [28,29]. The latter are characterised by low stool weight and prolonged transit times regardless of the amount of fibre in their diet [26], which suggests that increasing their fibre intake does not normalise colonic transit and can even worsen their symptoms as a result of the gas produced by fibre metabolism.

2.2. Colonic motility and absorption

Delayed colonic transit is associated with small and hard stools [30] that are difficult to evacuate [31,32]. It has been found that faecal consistency and water content significantly correlate with colonic transit time [33], which suggests that prolonged colonic transit favours the time-dependent process of water absorption. Moreover, changes in colonic transit affect bacterial mass [34], and this may also influence colonic absorption and secretion.

Delayed colonic transit may be due to impaired colonic motor activity [35], but may also be secondary to voluntary stool retention [36], defecation disorders [37,38], or an inadequate caloric intake [39–41]. Studies of colectomy samples taken from patients with delayed colonic transit suggest that impaired motility might

be caused by abnormalities in interstitial cells of Cajal [42] or the overexpression of progesterone receptors in colonic circular muscle cells [43,44]. However, the normalisation of delayed transit after behavioural treatment in such patients [45], and changes in the male/female incidence ratio of constipation in patients aged > 60 years [46], suggest that structural abnormalities should not be considered an irreversible cause of impaired colonic motility.

2.3. Anorectal motor and sensory functions

Constipated patients frequently complain of difficulties in satisfactorily evacuating rectal contents, and the absence of a normal call for evacuation. Normal defecation requires a very complex interaction between colorectal motor and sensory functions that needs to be coupled with appropriate behaviour: the rectosigmoid has to be loaded with normal stools, rectal distension has to be normally perceived, and the voluntary act of defecation (abdominal contraction, and puborectalis and anal relaxation) has to be performed at the right time. A number of alterations in these functions have been observed in patients with defecation disorders, including: (1) a failure of external anal sphincter-puborectalis relaxation when attempting defecation (anismus) [47,48]; (2) a hypertonic internal anal sphincter [38,49]; (3) inadequate rectal propulsion during defecation [48]; (4) rectal hyposensitivity and hypotonicity [50]; (5) anatomical anorectal alterations such as large rectoceles or rectal prolapse [51,52]; (6) excessive perineal descent [49]; and (7) the uncoupling of the sensory component (urge to defecate) and the normal pre-defecatory motor activity of the colon [53]. These dysfunctions may co-exist and, when they do, it is unclear whether they are primary or secondary to constipation. It is also necessary to remember that the alterations are often unspecific (*i.e.* they can be found in normally defecating healthy subjects), and their assessment is greatly influenced by the way in which the voluntary act of defecation is performed, which may vary depending on the subject's degree of participation.

2.4. Behavioural factors

Withholding behaviour after experiencing a difficult and painful bowel movement is known to induce functional constipation in children [54], and leads to stool retention, rectal distension, and overflow faecal incontinence. The problem may persist into young adulthood [55], and returns to being a major cause of constipation in elderly hospitalised patients whose persistent disregard of the call to stool may lead to faecal impaction [56].

2.5. Psychological factors

Patients with constipation frequently have psychological morbidities in various domains (including somatisation, anxiety, and depression) [57], but it is difficult to establish how these alterations affect the pathophysiological factors underlying constipation in individual cases. Adverse life events, such as the loss of a parent, sexual or physical abuse [58], discrepancies between reported bowel symptoms and objective alterations [11,59], a concomitant eating disorder [39,40], dissatisfaction with standard treatments, and demanding or angry behaviour [60] all suggest an underlying psychological alteration or psychiatric diagnosis.

Take-home messages (2)

The multiplicity of conditions associated with chronic constipation suggests that the pathophysiology of the condition is multi-factorial and involves alterations in behavioural, colorectal and psychological factors.

3. Diagnosis

3.1. Clinical evaluation

A detailed clinical evaluation and rectal examination are the two most important steps when diagnosing chronic constipation [24]. The features that each patient rates as the most distressing should be defined and represent the first target of treatment: is the patient unsatisfied with the frequency or consistency of defecation, or is it the act of defecation that is difficult? It has been found that a feeling of incomplete evacuation, a sense of obstruction, and digital evacuation are all associated with defecation disorders [61]. An overlap with IBS is suggested by complaints of bloating and abdominal pain between defecations. A dietary review should not only consider the reduced fibre intake that may cause constipation, but also the possibility that a normal or excessive fibre intake can cause bloating and abdominal pain, particularly in patients with delayed transit. The different treatments that have been tried should be recorded in order to verify and optimise the doses and schedules of treatments. Bowel habits should be monitored, preferably with the aid of diary cards and a Bristol stool form because patient recall may be misleading [11,12]. Furthermore, any adverse life events, psychological disturbances, eating disorders, or behavioural modifications that may influence the act of defecation should be investigated [24].

Clinical evaluation should also consider the possibility of a secondary cause of constipation (Table 2) which although rare in the case of chronic symptoms, is often treatable. In most cases, a detailed clinical history is sufficient to identify the diseases or medications that may cause constipation. It is debated whether laboratory tests (complete blood counts, calcium levels, thyroid stimulating hormone) and colonoscopy should be routinely used to exclude organic disorders in patients with chronic constipation. The ACG recommends diagnostic studies for patients with alarm symptoms (hematochezia, weight loss, a family history of colon cancer or inflammatory bowel disease, anemia, positive faecal occult blood tests, and the acute onset of constipation in elderly subjects), or symptoms suggesting an organic disorder. The routine use of colon cancer screening is also indicated in all patients aged > 50 years [1].

All patients with chronic constipation should undergo a rectal examination [62] in order to look for causes of anal pain (such as fissures or thrombosed haemorrhoids) that may precipitate or be secondary to constipation. An anal contraction in response to a gentle stroke on the perianal skin excludes damage to the sacral nerve pathways. Palpation with the index finger should include a search for faecal impaction, which is often associated with a history of soiling and needs specific treatment. Resting sphincter tone should be assessed because, if it is increased, it may contribute to evacuation difficulties; digital assessments of anal tone at rest and during squeezing correlate with the pressures measured by means of manometry [63,64]. The anterior wall should be checked for the presence of a rectocele. The patient should then be asked to strain and try to push out the finger: the anal sphincter and pubo-rectalis should relax, and the perineum should descend less than 3.5 cm [62].

At this stage, as the nature of the symptoms disturbing the patient will have been clarified, secondary causes will have been reasonably excluded, and any dietary or behavioural abnormalities will have been corrected, an interpretative framework of the mechanisms underlying the symptoms can be offered to the patient and followed by treatment [1] with laxatives such as polyethylene glycol, sodium picosulfate or bisacodyl.

Take-home messages (3)

Patients with chronic constipation should undergo careful clinical evaluation including a rectal examination to identify those who require additional tests to seek secondary causes. However, in the

absence of alarm symptoms, empiric treatment can be started without any previous diagnostic testing.

3.2. Physiological studies of refractory constipation

If constipation fails to improve (refractory constipation), most experts suggest referring the patient for physiological studies of anorectal function (balloon expulsion tests, anorectal manometry, defecography) and colonic transit in order to establish whether he or she has a functional defecation disorder or slow transit constipation.

3.2.1. Rectal balloon expulsion test

This test is carried out by measuring the time required to expel a rectal balloon filled with 50 mL of water [65] or the volume inducing a sustained desire to defecate [66]. Most centres consider > 60 s abnormal [66], but up to 5 min has been used [65]. The test is influenced by body position and (like all tests measuring defecatory function) the patient's understanding and willingness to perform the voluntary act of defecation. Up to 16% of healthy subjects have difficulties in expelling the balloon [48].

3.2.2. Anorectal manometry

Anorectal manometry is performed by inserting a pressure-sensitive catheter with a balloon at its tip in the anal canal. Methods vary widely between different centres, and high-resolution manometry has recently been introduced [67]. Anorectal manometry provides information concerning the neuromuscular and sensory function of the anorectum and, in the rare patients with megarectum/megacolon, is useful for assessing the presence of the recto-anal inhibitory reflex which, when absent, may indicate Hirschsprung's disease or visceral neuropathy [68,69]. In most chronically constipated patients without bowel dilatation, the test has been used to assess the patterns of rectal and anal pressure during attempted defecation: a normal pattern is characterised by a >45 mmHg increase in intrarectal pressure associated with a >20% reduction in anal pressure. Traditional manometry reveals a non-synergistic pattern in 20% of normal subjects [48,70], and the same is found upon high-resolution manometry in all women aged ≤50 years [67]. These findings limit the usefulness of the rectoanal gradient during simulated evacuation as a means of diagnosing defecatory disorders.

3.2.3. Defecography

Defecography is performed by placing barium paste in the rectum, and studying the function of the anorectal region at rest and during attempted defecation by means of fluoroscopy [71]. A magnetic resonance imaging-based variant of defecograpy can also be used in order to avoid radiation exposure and allow visualisation of the perirectal structures [49]. The defecographic features of disordered defecation include incomplete anal opening, impaired pubo-rectalis relaxation or paradoxical pubo-rectalis contraction, reduced or increased perineal descent, and an inability to expel or retain rectal contents. In addition, defecography may reveal structural abnormalities such as rectoceles, enteroceles, rectal prolapse and intussusception. However, there are few data concerning normal values in healthy subjects, a substantial proportion of whom have both functional and structural alterations [49,71,72].

3.2.4. Colonic transit

Colonic transit can be assessed using radio-opaque markers [73], radioscintigraphy [38], or a wireless motility capsule [31,74]. The technique of Metcalf et al. is one of the most standardised in healthy subjects and minimises radiation exposure [73]. It involves the administration of 20 radio-opaque markers on days 1, 2 and 3, and the remaining markers are counted by means of a high-kilovoltage, fast-film, plain abdominal X-ray on day 4. Colonic transit is calculated in hours: 1.2× the number of markers. The upper 95th percentile in healthy subjects is 68 h [73].

3.2.5. Constipation sub-types

Depending on the results of these tests, chronic constipation can be categorised into three main sub-types: slow transit constipation, defecation disorder (with normal or delayed transit), and constipation with normal test results. Anorectal tests are useful when diagnosing defecatory disorders for which biofeedback is superior to laxatives in managing constipation [75]. Diagnosing slow transit constipation requires an assessment of colonic transit, which may warrant colectomy in patients with medically refractory symptoms [76]. However, the usefulness of assessing colonic transit and anorectal function is limited by a number of factors, and is still a subject of debate [77]. First of all, the association between symptoms and the sub-types defined on the basis of physiological tests is limited [9,10]. Secondly there is no gold standard anorectal test for diagnosing defecatory disorders, and there is limited concordance between the physiological tests [78]. Lastly, there is limited evidence that the test results have an impact on therapy. Two studies have shown that impaired rectal balloon expulsion is associated with a more favourable biofeedback outcome [65,79], which suggests that an abnormal result might be used to select candidates for this treatment, and explains why some experts indicate that anorectal function tests should be performed early [24,80,81]. However, others say that they may be delayed until all of the available treatments have been tried [25], or that they may not be needed at all [82]. In relation to colonic transit, three uncontrolled studies have found that patients with delayed transit show a poor response to fibre intake [27–29], which suggests that other therapeutic approaches may be preferable. A further two studies have found more psychosocial disturbances in constipated patients with normal colonic transit [11,59], which is in line with the suggestion that colonic transit is an excellent point of communication with patients that helps to clarify the meaning of symptoms and provides a framework in which to explain them [82]. However, whether these findings justify the extensive use of physiological diagnostic testing in the large population of constipated patients who fail to respond to the first laxative treatment remains an open question [1,24,25,77,82]. In an ethic of avoiding waste [83], their more restricted use may be recommended and formal cost-effectiveness analyses should be made in order to validate the proposed diagnostic algorithms.

Take-home messages (4)

Physiological tests (balloon expulsion test, anorectal manometry, defecography and colonic transit) for chronic constipation are not standardised and are non-specific.

The classification of patients with refractory constipation into patho-physiological subtypes lacks cost-effectiveness validation.

4. Management

There are many evidence-based therapeutic approaches to the treatment of chronic constipation, including biofeedback, osmotic and stimulant laxatives, and new pharmacological therapies that have different mechanisms of action and side effects.

4.1. Fibre supplements

Fibre supplements are traditionally considered the first-line treatment, although deficient fibre intake in patients with chronic constipation has not been demonstrated at referral centres [27], and there is little evidence that insoluble fibres are beneficial [84]. Fibre supplements are less effective in patients with slow transit constipation or defecatory disorders than in those with normal

Table 3
Mechanisms of action and side effects of evidence-based pharmacological approaches for chronic constipation [7].

Treatments and doses	Mechanisms of action and main advantages	% Response *vs* placebo. Number needed to treat (95% CI)	Duration of controlled trials	Disadvantages
Osmotic laxatives: polyethylene glycol 17 g daily	More water is drawn into the colon. Not absorbed systemically	61% *vs* 31% NNT = 3 (2–4)	6 months	Abdominal distension, flatulence, nausea, diarrhoea
Stimulant laxatives: bisacodyl and sodium picosulfate 5–10 mg daily	Increased colonic contractions; anti-absorptive secretory effects. Not absorbed and activated in the colon	58% *vs* 22% NNT = 3 (2–4)	4 weeks	Abdominal pain, diarrhoea
Prokinetic: prucalopride 1–2 mg daily	Serotonin 5-HT_4 receptor agonist; accelerates gastrointestinal and colonic transit	28% *vs* 13% NNT = 6 (5–9)	12 weeks	Headache, nausea, diarrhoea
Secretagogue: lubiprostone 24 μg twice daily	Chloride channel activator; increased intestinal fluid secretion	55% *vs* 33% NNT = 4 (3–7)	4 weeks	Nausea, diarrhoea. Should be avoided in pregnancy
Secretagogue: linaclotide 145–290 μg daily	Guanylate cyclase C receptor agonist; increased intestinal fluid secretion. Analgesic effect [89]	21% *vs* 5% NNT = 6 (5–8)	12 weeks	Diarrhoea

transit constipation [29]; they are generally safe, but may increase bloating, flatulence and abdominal pain, and may interfere with the absorption of some drugs [84]. A soluble fibre (psyllium) may benefit some patients with chronic constipation but, unlike osmotic and stimulant laxatives and the newer pharmacological agents, this treatment is supported by poor quality data [84], and one study has found that treatment with polyethylene glycol (PEG) was faster and more effective [85]. Taken together, these observations suggest that, rather than fibre supplementation, osmotic and stimulant laxatives should be considered for the first-line treatment of patients with chronic constipation seen at referral centres.

4.2. Biofeedback

This represents a behavioural treatment in which patients learn the physiological mechanisms of defecation, and how to use their diaphragms and abdominal and pelvic floor muscles in order to evacuate. Sensory retraining may also be provided [86]. Patient motivation and the expertise of the therapist are critical but not standardised factors that affect therapeutic responses. Randomised clinical trials have shown that biofeedback is more effective than both sham feedback and laxatives [86,87,75], particularly in the sub-group of patients with defecation disorders as 76% responded to bio-feedback and only 46% to standard laxative therapy [75,86]. However, experienced therapists are not widely available, and some experts have suggested that biofeedback should only be proposed after all of the other available treatments have been tried [25], although others indicate it as the first-line treatment for patients with defecation disorders [80,81]. Interestingly, the instrumental feedback might be less important than the interaction with the therapist [87], which suggests that verbal instructions from dedicated physicians or other techniques of home training may prove to be effective in the future [88].

4.3. Evidence-based pharmacological approaches

A recent systematic review and meta-analysis [7] has found that polyethylene glycol (PEG), sodium picosulfate, bisacodyl, prucalopride, lubiprostone and linaclotite are more effective than placebo in treating chronic constipation. Table 3 summarises the main advantages and disadvantages of these treatments emerging from randomised controlled trials, together with their efficacy. These results do not allow any head-to head comparison between the different treatments: the striking differences in the placebo responses (5–33%) in the different studies suggest more differences between patient populations or efficacy endpoints than true differences between treatments. Whatever the efficacy endpoint, a substantial proportion of patients remained unsatisfied with the treatments [90]. The definition of, and clinical approach to patients with "difficult", "refractory" or "intractable" constipation is still unclear [91]. The degree of patient dissatisfaction may be due to inefficacy and/or the side effects of treatments [90], or psychological alterations [60,92], but it is not known what the relative role of these factors is.

Most studies have not defined patient sub-types, and so it is unknown whether a better response can be obtained in certain subgroups. Suppositories, enemas and other concomitant laxatives have been allowed as "rescue" therapies during pharmacological trials, but how to optimise combined therapies with different mechanisms of action, or how and when to use rectal therapies, has been poorly investigated [91]. How long the patients should be treated and the long-term safety profile of treatments remain relatively unknown, although PEG and prucalopride have been safely used for more than two years [93,94].

4.4. Other approaches

In highly selected patients treatment strategies may include sacral nerve stimulation or surgery. However, the substantial morbidity and variable outcomes associated with these treatments should limit their use, with special arrangements being made for consent, audits or research [95].

Sacral nerve stimulation is based on the continuous low-amplitude electrical stimulation of sacral nerve roots, and has been claimed to be effective in patients with intractable constipation [96]. However, other studies with a median follow-up of more than two years have reported successful outcomes in only 29% of patients [97], and at least one event leading to failure in 58% (surgery in 33%) [98].

Of the surgical procedures, colectomy with ileorectal anastomosis is performed in patients with refractory slow transit constipation in whom a concomitant defecation disorder has been excluded or treated [76]. Between 39% and 100% of patients have said they were satisfied with the procedure [99]. A number of side effects have been reported, including abdominal pain, small bowel obstruction and re-operation, with prevalence rates varying from 0% to 90% [99]. The outcome may be worse in patients with co-existing psychiatric disturbances [100] and disordered motility in the higher segments of the gastrointestinal tract [101].

Stapled transanal rectal resection (STARR) of the redundant rectal mucosa has been proposed for patients with defecation disorders associated with the presence of rectoceles or internal rectal prolapse at defecography [102]. However the causal relationship between these conditions and symptoms remains uncertain as

rectoceles and internal rectal prolapse can also be encountered in normally defecating subjects [71]. One randomised trial found that STARR was superior to bio-feedback, with success rates of respectively 81% and 33%; however, there was an unusual drop-out rate of 50% in the bio-feedback arm [103]. The results seem to be less encouraging after a longer follow-up [104,105]. An overall post-procedural morbidity rate of 36% has also been reported, including faecal urge incontinence, severe anorectal pain and anorectal sepsis [106]. Laparoscopic ventral rectopexy has been used as an alternative with promising short-term results in patients with a defecation disorder and internal rectal prolapse [52].

Take-home messages (5)

Evidence-based therapeutic approaches are available for the treatment of chronic constipation, and should be preferred over treatments that continue to be recommended despite the lack of convincing evidence of efficacy.

The efficacy and side effects of surgical procedures for chronic constipation vary widely among centres. The morbidity reported after surgery discourages the unrestricted use of these therapeutic approaches.

4.5. Secondary constipation

In most cases, the therapeutic approach is similar to that used for the primary form but, in some cases, the causes are so specific that they allow targeted treatment. Some examples are methylnaltrexone or alvimopan for opioid-induced constipation [107], and specific behavioural training and retrograde cleansing programmes for patients with spinal cord injuries, multiple sclerosis or spina bifida [108].

4.5.1. Pregnancy

Constipation is frequent during pregnancy: osmotic and stimulant laxatives are not absorbed systemically, and their use has not been (and is not expected to be) associated with an increased risk of malformations [109]; stimulant laxatives are more effective than bulk-forming agents but may cause more side effects [110].

4.5.2. Intestinal pseudo-obstruction

It has been shown that prucalopride improves bloating and abdominal pain in the few constipated patients in whom gut dilatation is the manifestation of severe and widespread enteric neuropathy or myopathy (intestinal pseudo-obstruction) [111].

4.5.3. Faecal impaction

Impacted stools in the rectum should be fragmented and removed with enemas before titrating an osmotic laxative [112]. Preliminary data suggest that a combination of high-dose osmotic and stimulant laxatives can be safely and efficiently given to elderly patients with faecal impaction [113].

4.6. Emerging pharmacological therapies

Table 4 summarises the new pharmacological therapies for chronic constipation and IBS-C that are still under evaluation. Naronapride (ATI-7505) and Velusetrag (TD-5108) are two serotonin 5-HT_4 receptor agonists similar to prucalopride that increase colonic motility and are less likely to have cardiovascular side effects because of their receptorial selectivity [114–116]. Pumosetrag (MKC-733, DDP-733) is a partial 5-HT_3 receptor agonist that accelerates gastrointestinal transit, increases stool frequency, and improves straining and the sensation of incomplete evacuation; it has been proposed for patients with IBS-C [117]. Alvimopam and methynaltrexone are peripherally acting mu-opioid antagonists that have been developed to restore the constipation induced by opioids [107]. Plecanatide (SP-304) is a guanylate-cyclase C receptor agonist that stimulates luminal chloride secretion and has an effect that is similar to that of linaclotide. It is thought to act locally within the acidic regions of the intestines (the proximal duodenum and cecum), thus reducing the likelihood of unwanted side effects related to systemic absorption. It has been proposed for IBS-C [118]. Elobixibat (A3309) is a minimally absorbed ileal bile acid transporter inhibitor that reduces the ileal reabsorption of bile acids and increases propulsive contractions and secretion in the colon and bowel frequency [119].

Table 4
Emerging drugs for chronic constipation and irritable bowel syndrome-C.

Name	Class and mechanism of action	Status of clinical studies
Naronapride	5-HT_4 receptor agonist: prokinetic	Phase III
Velusetrag	5-HT_4 receptor agonist: prokinetic	Phase III
Pumosetrag	5-HT_3 receptor agonist: prokinetic	Phase II
Alvimopan	Opioid receptor antagonist	Phase III
Methylnaltrexone	Opioid receptor antagonist	Phase III
Plecanatide	Colonic secretagogue: activation of guanylate cyclase C receptor	Phase IIa
Elobixibat	Inhibition of bile acid reabsorption: prokinetic and secretagogue	Phase IIb

5-HT: serotonin.

5. Conclusions and perspectives

Over the last ten years, many myths and misconceptions have been abandoned [27], but there is certainly more to learn about ways of optimising the diagnosis and treatment of chronic constipation. This is particularly important because constipation is common and has a substantial economic impact. There is an increasing emphasis on evidence-based studies that demonstrate the efficacy of different treatments, but a substantial proportion of patients are still dissatisfied. Such patients should be better defined taking into account both the subjective and objective components of their dissatisfaction. Whether those defined on the basis of precise and reproducible diagnostic tests might benefit from specific therapeutic approaches remains a challenging question for future studies.

Conflict of interest statement

None declared.

Acknowledgements

We would like to thank Adil E Bharucha and Maura Corsetti for their constructive comments and Kevin Smart for reviewing the English text.

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