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REVIEW

Chronic constipation and abdominal pain: Independent or closely interrelated symptoms?

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Abstract

Constipation is both a symptom and a disorder, seen in both functional constipation and irritable bowel syndrome with constipation predominance (IBS-C). Despite the Rome IV criteria distinguishing between these conditions, they share many therapeutic approaches. This review aims to explore the relationship between constipation and abdominal pain and assess the evidence surrounding whether laxation improves abdominal pain and whether such a response to laxation differs between IBS-C and functional constipation. In patients with functional constipation, increasing frequency of bowel motions by laxatives regardless of mechanism of action is associated with reductions in the severity of abdominal pain, supporting the role of constipation as a contributor to abdominal discomfort. In patients with IBS-C, evidence from systematic reviews indicates that abdominal pain is driven by factors additional to constipation alone and that visceral analgesic modulation is also needed to optimize pain. Changing definitions of IBS-C and heterogeneity in clinical trial design including endpoints have raised uncertainty about the comparative ability of older laxatives without known neuromodulatory effects to improve chronic abdominal pain compared with new secretagogues and prokinetics for the management of IBS-C. While it is known that abdominal pain is associated with constipation and laxation contributes to relief of that pain, it remains unproven whether proposed visceral analgesic properties of new laxatives provide greater pain relief than laxation alone. However, it is likely that the response to laxation in IBS-C is only part of the puzzle.

Introduction

Cross-sectional analysis has estimated the overall prevalence of constipation to be 14% in the adult population.[1] Constipation has a substantial public health burden because of its considerable impact on patient health-related quality of life and subsequent financial consequences. Confusingly, constipation is both a symptom and a disorder. It is not uncommon for patients and carers to have different perceptions of what constitutes constipation, and having a shared lexicon concerning symptoms and management is of importance.[2] Constipation is characterized by unsatisfactory defecation with hard or infrequent stools, difficult stool passage, and/or a sensation of incomplete evacuation.[3] Constipation can be acute (typically less than 1 week in duration) or chronic (greater than 3 months). It may be secondary to other medical disorders and/or medications (e.g. hypothyroidism or opiates) or be a primary disorder due to alteration of bowel or anorectal function in the absence of structural disease. Chronic constipation is a heterogeneous condition, being variably associated with disordered defecation, bloating, and/or abdominal pain.[4] In an attempt to standardize definitions, clinical criteria were developed by the Rome Foundation. The most recent iteration is the Rome IV criteria and was published in 2016[5] (Table 1). Standardized definitions have been pivotal for clinical trial purposes but have less direct utility in clinical care. Generally, patients experiencing symptoms of chronic constipation fall into three diagnostic categories, namely, functional constipation (FC), irritable bowel syndrome with constipation predominance (IBS-C), and dyssynergic defecation.

The Rome IV criteria focus on symptoms associated with constipation as well as difficulty of defecation and do not categorize FC solely on the frequency of bowel movements. In particular, the definition necessitates the exclusion of IBS before a diagnosis of FC is made. The diagnostic criteria recognize that mild pain and/or bloating may be a feature but are not dominant symptoms in FC. In contrast, in IBS-C, abdominal pain is a dominant symptom that is temporally associated with at least two of the following: related to defecation, hard or lumpy stools, and/or infrequent stools.[6] The Rome IV IBS criteria place greater focus on pain with patients required to experience abdominal pain at least 1 day a week, compared with 3 days a month in previous iterations of the Rome criteria. This change was based largely on a qualitative questionnaire-based study of patients with IBS rather than mechanistic studies.[7] Essentially, the difference between IBS and FC is that, while patients diagnosed with FC may describe pain as part of their symptom complex, it is not the dominant symptom, whereas the diagnosis of IBS requires the presence of pain as a dominant symptom.

Despite efforts to separate these pathologies, the difference between FC and IBS-C can be challenging in the real-world setting.[8] Clinicians frequently note that patients with a diagnosis of FC may also complain of abdominal discomfort or pain, making the distinction between the two disorders somewhat arbitrary and dependent on the severity/significance of each symptom to the patient. These observations demonstrate a continuum based on the degree of pain or discomfort, and in reality, patients may oscillate from one disturbance to the other.[9] Therapeutic agents have demonstrated efficacy in both disorders; most agents that have shown efficacy for IBS-C (except neuromodulators) have demonstrated efficacy in FC (although they might not have an accepted regulatory indication for both), and a drug may be efficacious for FC but not beneficial for the pain of IBS-C.

In this review, we will explore the pathophysiology of pain in chronic constipation: whether there is an association between bowel movement frequency and abdominal discomfort/pain and whether laxation correlates with reduction in abdominal pain. We will also look at treatment options including the main classes of laxatives including bulking agents, stimulants, osmotics, and softeners as well as newer medications including serotonin receptor agonists and secretagogues. Finally, we explore how other factors apart from laxation can contribute to the mediation of abdominal pain.

Pathophysiology of pain in chronic constipation

A key differentiator between FC and IBS-C is the presence of pain as a dominant symptom. Patients with IBS-C have more extraintestinal symptoms and other pains than FC patients, suggesting a more complex phenotype. In addition, patients with IBS-C are significantly more psychologically distressed than FC, suggesting a centrally mediated component to symptom generation.[10] The underlying pathophysiological mechanisms of chronic pain are complex. In its simplest form, pain requires at least one of the following: (i) an abnormal, painful stimulus or (ii) an abnormal peripheral or central pain response to the perception of an ongoing or previous stimulus.[11] Teasing out the relative contributions of these factors in a patient with pain related to a functional bowel disorder is complex as abnormalities may exist on both fronts. For example, a patient with constipation may have an abnormal stimulus—increased distension of the bowel due to excessive fecal or gaseous contents leading to nociception—and/or an abnormal response—heightened pain response (allodynia) to a physiological gastrointestinal distension, or increased pain response to noxious stimuli (visceral hypersensitivity).

In patients with IBS-C, visceral hypersensitivity may be more prevalent than in those with FC.[12] The brain's response to visceral distension is heightened in patients with IBS with elements of anticipatory pain, an emerging concept termed interoceptive awareness.[12,13] Visceral sensation is transported via afferents to the dorsal horn of the spinal cord before reaching the cerebral cortex. There is separate nociception from physiological stimuli, which are peripheral projections of spinal afferents and generally have low distension and low activation thresholds, termed "muscular" and "mucosal" afferents, respectively.[14] Heightened sensitivity may occur because of sensitization at the level of peripheral afferent receptors or spinal dorsal horn neurons, alterations in descending modulation or in the cerebral cortex[15] (Fig. 1). Changes in the

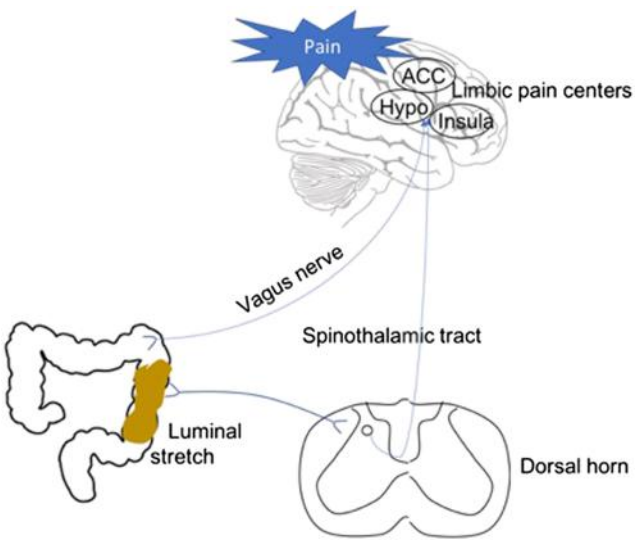

Figure 1 Bidirectional gut–brain axis. Diagrammatic representation for involvement of gut–brain axis in generation of pain. ACC, anterior cingulate cortex; Hypo, hypothalamus.

cortex are known as central amplification, a hallmark of fibromyalgia that can result in the perception of pain when noxious stimuli or peripheral input is not present.[16] This frequently occurs in conjunction with other centralized pain syndromes including chronic pelvic pain syndrome, migraine, and chronic fatigue syndrome.[17] Depending on the predominant pathophysiology, treatment focused solely on increasing bowel motion frequency and improving stool consistency may not be sufficient but should also be targeted towards the pain pathways both in the gut peripherally and centrally through neuromodulation. These different pathophysiological mechanisms mean that treatment needs to be tailored to the individual. If pain is a predominant feature, then use of neuromodulators such as tricyclic antidepressants may be used.[18]

Abdominal pain is the dominant symptom in patients with IBS-C and has the greatest association with reduced self-rated health. More than 75% of patients with all forms of constipation experience abdominal pain, independent of gender and colonic transit time.[19] In IBS-C, constipated patients with pain have a reduced quality of life and more extraintestinal somatic symptoms when compared with constipated patients who are free from abdominal pain.[20] Intense, recurrent, visceral pain is common in IBS and is related to defecation.[21,22] In one study, 11% experienced significant pain associated with constipation, usually epigastric and left sided in location, although it could be mesogastric if there was delayed rectal transit.[23] However, this multicenter study was conducted prior to the implementation of Rome criteria; thus, the recruitment may have had patients with IBS predominance. There was no evidence to suggest a direct relationship between severity of constipation and severity of pain.

Does laxation correlate with reduction in abdominal pain?

It has been demonstrated that pharmacologically reducing bowel frequency in healthy controls with loperamide can result in symptoms consistent with IBS-C, particularly an increase in "colonic pain."[24] Hence, inducing constipation causes pain even in normal individuals. When patients with spontaneous constipation and loperamide-induced constipation were compared, there was no difference in abdominal pain,[25] suggesting that in the absence of visceral hypersensitivity and allodynia, abdominal pain can be induced secondary to the luminal changes associate with constipation.

Treating simple constipation with laxation improves pain in both normal individuals with induced constipation and patients with FC. This appears to be independent of the mechanism of the laxation. There is a body of evidence supporting the notion that increasing bowel movement frequency is associated with reduction of abdominal pain. A systematic review[26] demonstrated that laxation attenuated pain in both chronic constipation and IBS-C, irrespective of the type of laxative. Meta-regression analysis found that more frequently weekly bowel motion significantly correlated with attenuations in pain scores in patients with chronic constipation and with IBS-C ($P < 0.001$).[26] It is interesting to note that while there was no correlation between degree of constipation and pain, treating the constipation improved the pain. There is no significant clustering of effect around classes of drugs, suggesting that improvement in pain is independent of mechanism of laxation. Pain scores varied between studies, with some using numeric rating scale 0–4 or 0–10 and others using visual analog scale, making comparisons difficult. While linaclotide has been proposed to have independent anti-nociceptive effects, it was also noted that polyethylene glycol (PEG), which works purely via its luminal osmotic effects, also resulted in improvements in pain scores, suggesting that normalization of the stool pattern should be a primary objective of management with secondary benefits in terms of abdominal pain in patients with chronic constipation.[27] Nevertheless, this meta-analysis did not include stimulant laxatives or prokinetic agents (other than a single trial using cisapride), all of which may be associated with the induction of colicky pain via their mechanism of action.

Certainly, early studies of stimulant laxatives in IBS found that, while stool frequency and form improved, colonic pain did not improved.[25] A similar situation is seen with some bulking agents, although this is likely related to the increased fermentation and bloating that may accompany their use. In general, these older studies have looked at whether abdominal pain was an adverse effect to the medication, rather than the relief in abdominal pain as a secondary outcome. More recent studies of bulking agents and of stimulant and osmotic laxatives have challenged this paradigm. There needs to be new research into the use of laxatives and their role in abdominal pain. In particular, direct head-to-head trials comparing the outcomes of laxatives with the newer secretagogues and prokinetics are required.

Broadly speaking, laxatives can be divided into four groups: dietary fiber and bulk-forming laxatives, stimulant laxatives, osmotic laxatives, and fecal softeners (Table 1). The relative risk of experiencing any adverse event with laxatives was 1.94. No significant differences have been detected in rates of abdominal pain as an adverse effect.[28–31]

1. *Bulking agents*. Bulking agents, which include dietary fiber and bulk-forming laxatives, are well-established treatments for constipation. The commonly reported adverse effects are flatulence and abdominal distension, which vary between agents. Studies of psyllium husk demonstrated that patients noted fewer hard stools as well as reduced incidence of abdominal pain.[32] However, this is in contrast to a report from Ashraf *et al*.[33] who found that 18% of patients who received psyllium experienced abdominal pain compared with 0% of controls. A systematic comparison of bulk-forming laxatives with dietary fiber (consisting of psyllium husk, ispaghula, and bran) found that the former increased stool frequency by a mean of 1.4 (95% confidence interval 1.1 to 1.8) bowel movements per week, improved stool consistency, and decreased abdominal pain.[34] However, it is difficult to distinguish whether dietary fiber may have increased pain resulting in a relative reduction in pain for bulk laxatives.
2. *Stimulant laxatives*. Stimulant laxatives are thought to increase intestinal motility, reducing the time available for salt and water absorption, and increasing secretion. Abdominal cramping is believed to occur secondary to increased intestinal contractile activity.[35] In a 4-week, double-blind, randomized, placebo-controlled study, bisacodyl[36] was effective in the treatment of chronic constipation with improvement in degree of straining, obstructive

Table 1 Summary of current pharmacological treatments for constipation, evidence for efficacy and endpoints achieved, and side effects

	Evidence (endpoints)	Side effects	Impact on pain
Osmotic laxatives			
Lactulose (fermentable osmotic laxative)	RCTs, improves stool frequency and symptoms, reduction in fecal impactions[60]	Abdominal gas, bloating, cramping, flatulence, nausea, sweet tasting	Increases pain[39,40]
Polyethylene glycol (non-fermentable osmotic laxative)	RCTs, improves stool consistency and frequency and straining[27–29,61,62]	Minimal; cramping and abdominal distention	Improves pain in CIC[28,29] No difference in IBS
Magnesium salts (non-fermentable)	No RCTs	Diarrhea, hypermagnesemia	No evidence
Bulking agents			
Dietary fiber, e.g. psyllium	Meta-analysis, improves stool frequency[63]	Bloating, abdominal distension	Equivocal depending on fiber formulation[32–34]
Stimulant laxatives			
Bisacodyl (diphenylmethane)	RCT, improves stool frequency and symptoms[36]	Diarrhea and abdominal pain	Increases pain[36]
Sodium picosulfate (diphenylmethane)	RCT, improves stool frequency and symptoms[64]	Diarrhea and abdominal pain	Increases pain[64]
Senna (anthraquinone)	No RCTs	Diarrhea and abdominal pain, melanosis coli	Equivocal[38,65]
Softener/lubricants			
Coloxyl (docusate)	RCT, no improvement in stool frequency or symptoms[66]	None reported	No evidence
Prosecretory agents			
Lubiprostone	RCTs, improves stool frequency and consistency,[45,67–70] reduced straining and bloating[45]	Nausea	No change[45,67–70]
Linaclotide	RCTs, improves stool frequency and consistency[71,72]	Diarrhea	Improves pain[53]
Plecanatide	RCTs, improves stool frequency and consistency[55,56,73]	Diarrhea, nausea	Improves pain[56]
Serotenergic agents			
Prucalopride	RCTs, improves stool frequency and consistency[49,74–78]	Headache, nausea diarrhea, abdominal pain	No change[49,74–78]

CIC, chronic idiopathic constipation; RCTs, randomized controlled trials.

symptoms, and need for rescue medication. However, there was increase in pain as an adverse event in patients receiving bisacodyl compared with placebo (2.5% *vs* 24.7% in the placebo group). A recent network meta-analysis found that diphenylmethane laxatives such as bisacodyl were most likely to cause pain compared with any other laxative treatment.[37] Often, a biphasic element of pain is observed where pain may be increased initially as stool starts to move and then reduced when laxation is effective. Despite the high prevalence of its use, there are no randomized placebo-controlled studies of senna in the management of constipation. A randomized double-blind crossover study for senna with fiber showed that combined senna and fiber use was more effective than lactulose for mean daily bowel frequency and ease of evacuation. There was no significant difference with cramps, although total numbers of patients studied were small.[38]

3 *Osmotic laxatives*. The common adverse effects of the osmotic laxatives are flatulence (restricted mainly to the fermentable preparations containing lactulose and mannitol), abdominal pain, and colic. Lactulose is a synthetic, non-digestible disaccharide (galactose/fructose). Up to 20% of patients receiving lactulose experience troublesome flatulence, abdominal cramps, and pain; these probably relate to colonic fermentation with gas release (hydrogen and methane) and subsequent colonic distension.[39,40] PEG is the principal ingredient in several bowel preparation solutions and is not absorbed from the gastrointestinal tract. PEG improves abdominal pain in patients with constipation.[28,29] In patients with IBS, PEG formulations have not found to alleviate pain more than placebo.[41] Here, they defined pain responders as having $\geq 30\%$ reduction in abdominal discomfort/pain compared with run-in mean for patients receiving PEG *versus* placebo in week 4 (47% *vs* 40%, respectively). Another double-blind randomized controlled trial used rectal pain thresholds from rectal distension (> 32 mmHg) and found no difference between PEG and placebo.[42] A Cochrane meta-analysis has reported PEG to be superior to lactulose in terms of efficacy (stool frequency per week, stool consistency, and requirement for additional laxatives) and side effects.[43] Two out of three trials favored PEG, while one trial found lactulose and PEG to be comparable when specifically considering relief of pain.

4 *Stool softeners*. Stool softeners include docusate sodium, a surfactant whose mechanism of action is through permitting water and lipids to penetrate the stool. This results in hydration and softening of the fecal material. There are no randomized controlled trials of stool softeners in the management of constipation. Lubricants (e.g. paraffin oil)

are used to lubricate the surface of the stool and make it softer. Some (e.g. castor oil) may also have an irritant action.

New drugs, new outcomes

In 2012, the Food and Drug Administration (FDA) put forward the recommendation of using standard endpoints in IBS trials, abdominal pain, and disordered defecation. Specifically, the IBS-C responder includes a greater than or equal to 30% decrease in the weekly mean daily scores for worst abdominal pain in the same week for greater than or equal to 50% of the treatment duration.[44]The FDA-recommended efficacy endpoint for FC does not include pain measurements. Furthermore, there are no standardized ways in reporting pain as an adverse event in these trials, which can make it challenging to compare between treatments and also to pick up safety signals concerning pain.

Greater attention is placed on patient-reported outcomes as well as the perceived adequacy of therapy, including subjective scores such as satisfaction with bowel movements. However, there is as yet no information about how older conventional laxatives alone perform on these criteria. Many of the trials allow the use of "rescue" laxatives. Most of the trials utilizing these criteria have involved chronic constipation rather than IBS-C. In these studies, reduced pain ratings during and following therapy were reported, triggering hypotheses about analgesic properties of these agents. As noted earlier, improving constipation in patients with simple constipation using simple laxatives also improves pain. The antinociceptive action is a potential differentiating factor from conventional laxatives and has been emphasized in reviews and marketing materials.

1 *Lubiprostone*. This is a selective activator of type 2 chloride channel (ClC-2 channel) and induces the secretion of intestinal fluids. Randomized control trials have demonstrated that lubiprostone can improve constipation symptoms[45] measuring abdominal bloating and discomfort (on a 0–4 scale, where 0 = absent and 4 = very severe) as well as patient-assessed global treatment effectiveness without significant side effects. In addition, the same group has demonstrated benefit on pain alleviation in IBS-C study where there was a trend for attenuation of daily abdominal pain (0–4 scale, where 0 = absent and 4 = very severe) at 1 month. The effect was sustained for the following 2 months, but the benefit was no longer statistically significant at the third month.[46]
2 *Prucalopride*. This is a selective 5-hydoxytrpamine $(HT)_4$ agonist. 5-HT impacts gut function and has multiple receptor sites present throughout the gastrointestinal system. 5-HT_4 receptors are involved in the neuronal release of acetylcholine, substance P, and calcitonin gene-related peptide, resulting in coordinated contraction and relaxation of gastrointestinal smooth muscle.[47] Prucalopride is a highly selective 5-HT_4 receptor agonist that has negligible affinity for human ether-a-go-go-related gene channel, which was responsible for cardiac toxicities seen with cisapride.[48] Over 12 weeks, prucalopride significantly improved bowel function and improved the severity of symptoms in patients with severe functional chronic constipation,[49] but it has not yet been studied in IBS-C. Rates of abdominal pain as an adverse event were no different to placebo. Tegaserod, a partial agonist for $5HT_4$ receptor as well as affinity for $5HT_1$ and $5HT_2$ receptors, has now been reapproved by the FDA for women under the age of 65 with IBS-C without a history of ischemic heart disease. A Cochrane review showed it improved overall symptomatology of IBS[50] and also when reanalyzed with current FDA endpoints.[51]
3 *Linaclotide*. This is a selective guanylate cyclase C (GC-C) agonist that has a unique property of secretory and visceral anti-nociceptive functions. Linaclotide binds to GC-C receptors on the luminal surface of enterocytes to induce intracellular cyclic GMP (cGMP). This causes the activation of the cystic fibrosis transmembrane conductance regulator resulting in water, bicarbonate, and electrolyte secretion into the intestinal lumen.[52] A randomized double-blind placebo-controlled trial found a dose-dependent increase in weekly complete spontaneous bowel movement frequency as well as clinical improvements demonstrated in daily abdominal discomfort ratings using a 7-point ordinal scale (0 = none and 6 = very severe).[52] In two parallel phase III clinical trials, linaclotide successfully improved bowel movement frequency and abdominal pain in IBS-C.[53] Patients were deemed responders if they had $\geq 30\%$ reduction in mean abdominal pain and/or discomfort score (11-point scales). This is consistent with current FDA study endpoints for IBS-C. The mechanism of the improvement in abdominal pain (in addition to the laxation) is believed to be related to cGMP released from colonic epithelial cells, which increases extracellular cGMP acting on and inhibiting nociception[54]; however, the exact mechanism is unknown. Another GC-C agonist, plecanatide, has demonstrated a similar efficacy and safety as linaclotide in both FC[55] and IBS-C[56] and is FDA approved for both indications.

Newer agents have been shown to reduce pain. However, it is unclear whether this is greater than the degree of relief from laxation or not. A meta-analysis of traditional laxatives (osmotic and stimulant) in addition to new agents (prucalopride, linaclotide and lubiprostone) was conducted with the primary outcome measure of efficacy assessed via change in mean number of stools or failure to respond to therapy. Secondary outcome measures explored side effects and found no significant difference in rates of abdominal pain looking at laxatives, prucalopride, lubiprostone, and linaclotide. However, the criteria used to define response varied between studies. All laxatives were superior to placebo for the treatment of chronic constipation.[31] Likewise, in another meta-analysis, all treatments reduced pain ratings in patients with chronic constipation and IBS-C by 0.58, except for colchicine and tegaserod.[26]

Laxation is not the whole picture

In IBS-C, the effect of laxation alone on pain is less than what would be expected in FC and often necessitates the addition of neuromodulators, indicating that additional mechanisms are likely to be contributing to the experience of pain. IBS-C is characterized by overlying disordered bowel motility, the added complexity of

visceral hypersensitivity, and altered cerebral processing of gut events and environmental stressors. This is defined by heightened sensation in response to physiological (allodynia) and painful (hypersensitivity) stimuli, with both peripheral and central abnormalities. This sensitivity to visceral pain is attributed to dysregulation of the brain–gut axis.[57] Hence, managing laxation with pharmacological methods alone is not sufficient to completely resolve abdominal pain in patients with IBS. Selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors are preferred over tricyclic antidepressants in IBS-C as they reduce intestinal transit time.[58] However, selective serotonin reuptake inhibitors have the adverse effect of upper gastrointestinal symptoms and have minimal effect on pain management.[18,59] Their mechanism is felt to be related to central effects, the reduction of activation of pain centers, and peripheral effects on colonic compliance. A systematic review of seven randomized controlled trials of neuromodulators on abdominal pain *versus* placebo was favorable for neuromodulators improving symptoms. It found a relative risk of abdominal pain not improving of 0.62 (95% confidence interval 0.43 to 0.88), However, there was considerable heterogeneity between studies (I^2 = 72%, P = 0.001) as well as inconsistencies with endpoints.[18] Hence, addition of central modulatory agents may be warranted in patients with IBS.

Conclusion

A key differentiator between FC and IBS-C is the presence of pain as a dominant symptom in IBS-C. Associated with pain is the presence of greater extraintestinal symptomology and psychological comorbidity in IBS-C compared with FC. The correlation between the increase in the weekly frequency of bowel motions and reductions in abdominal pain severity together with the apparent independence of these observations of the mechanisms of action of the laxative medications confirms the role of constipation as a contributor to abdominal discomfort and pain. It also suggests that laxation is a reasonable therapeutic goal in managing patients with simple constipation associated with abdominal pain. However, evidence indicates that abdominal pain has more pathogenic mechanisms than those associated with constipation, in particular in patients with IBS, and medications with specific neuromodulatory analgesic properties are partly needed to improve discomfort and pain associated with constipation, particularly those with IBS-C phenotype. There has been a considerable expansion in the number of new drugs that are available for treating FC, with a focus on analgesic properties. However, it is unclear whether this is more than the degree of relief from laxation or not. The conclusions from this review are limited by the difficulties in differentiating IBS-C from FC secondary to definitional changes and variable outcome measures in studies.

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