Review

Chronic abdominal pain in inflammatory bowel disease: a practical guide

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ABSTRACT

Pain is common in inflammatory bowel disease (IBD), yet many patients feel their pain is not addressed by healthcare professionals. Listening to a patient's concerns about pain, assessing symptoms and acknowledging the impact these have on daily life remain crucial steps in addressing pain in IBD. While acute pain may be effectively controlled by pain medication, chronic pain is more complex and often pharmacological therapies, particularly opioids, are ineffective. Low-dose tricyclic antidepressants and psychological approaches, including cognitive–behavioural therapy, have shown some promise in offering effective pain management while lifestyle changes such as a trial of low-fermentable oligosaccharides, disaccharides, monosaccharides and polyols diet in those with overlapping irritable bowel syndrome may also reduce pain. Patients benefit from a long-term, trusting relationship with their healthcare professional to allow a holistic approach combining pharmacological, psychological, lifestyle and dietary approaches to chronic pain. We present a practical review to facilitate management of chronic abdominal pain in IBD.

> 'it's all about the bowel movements. It's all about how often you go to the loo. … I don't think they focus on the pain so much.' [1]

KEY POINTS

- ⇒ Aim to create a long-term, trusting relationship with patients to allow an individualised, patient-specific, holistic approach to chronic pain management.
- ⇒ Ensure that modifiable causes for pain have been assessed, investigated and treated.
- ⇒ Treating coexisting irritable bowel syndrome may help to manage chronic inflammatory bowel disease pain. This includes antispasmodics, fermentable oligosaccharides, disaccharides, monosaccharides and polyols diet and tricyclic antidepressant medication.
- ⇒ Avoid opioid medication as this has no proven benefit and is associated with poorer outcomes.
- ⇒ Psychological therapies including cognitive–behavioural therapy can improve pain as well as improving quality of life.

INTRODUCTION

The majority of individuals with inflammatory bowel disease (IBD) experience pain regularly[2 3] and this has a negative impact on daily activities[4] while being associated with a poorer quality of life.[3 5] Pain management approaches frequently focus on reducing inflammation yet, one-third of individuals continue to experience pain despite mucosal healing[6 7] and pain often persists despite 'clinical remission'.[8] Furthermore, many pain medications such as opioids are ineffective for pain arising from the gut and for chronic pain lasting more than 3 months. Qualitative studies indicate that individuals with IBD pain can feel discredited, misunderstood and/or frustrated that lack of knowledge among clinicians leads to pain being insufficiently managed[1 9] while long-term, trusting patient–clinician relationships with regular review of pain were valued by patients.[10] In this practical guide, we describe the pathophysiology of chronic abdominal pain in IBD, outline pharmacological, psychological, dietary and lifestyle approaches to management.

Pathophysiology of chronic pain in IBD

A recent international consensus defines pain as 'an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage'.[11] Acute pain may prevent harm by initiating withdrawal from danger; however, this definition acknowledges that

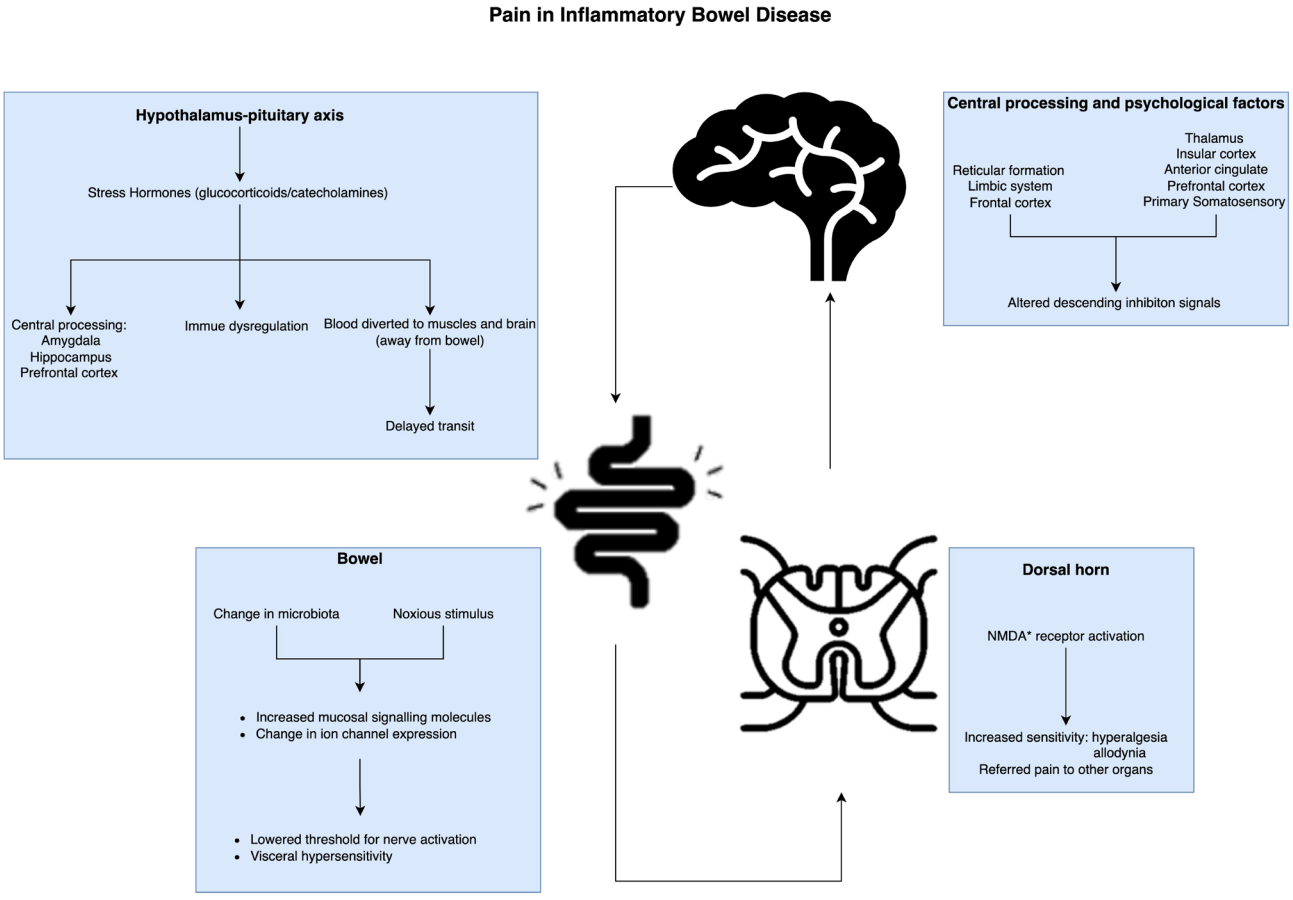

Figure 1 Pathophysiology of pain in inflammatory bowel disease. *N-methyl-D-aspartate.

pain often exists in the absence of tissue damage and in the presence of normal investigations. Chronic pain is a subjective experience unique to each individual and influenced by peripheral, central, environmental and psychosocial factors, all of which must be considered to understand and improve the individual's experience (figure 1).

Pathophysiology: viscera

Noxious stimuli in the intestine activate pain receptors; chemoreceptors are triggered by inflammatory mediators while mechanoreceptors are triggered by bowel distention. Bowel distention may occur because of strictures, adhesions or luminal gas. Chronic inflammation results in visceral hypersensitivity by increasing mucosal signalling molecules, changing ion channel expression and lowering the threshold for nerve activation.[12 13]

Pathophysiology: dorsal horn

Impulses are transmitted via nerves to the spinal cord where they synapse on second order nerves in the dorsal horn ganglia. Visceral inflammation has been shown to increase nerve excitability at this level via changes to the N-methyl-D-aspartate receptor and this is associated with hypersensitivity.[13 14]

Pathophysiology: hypothalamus–pituitary–axis

Pain can result in activation of the hypothalamus–pituitary–axis stress pathway, leading to glucocorticoid and catecholamine hormone production. These hormones act centrally to determine the emotional response to pain by integrating past experiences. Previous or current stress results in a heightened perception of pain, as shown on functional brain imaging.[15] Stress also activates the autonomic nervous system which increases blood pressure and diverts blood away from the gastrointestinal (GI) tract towards the brain and muscles. This can result in delayed gut transit and abdominal discomfort.[16] Finally, stress hormones modify immune function through cytokine production, which can lead to painful disease flares.[13]

Pathophysiology: central processing

Pain signals travel via nerves in the spinal cord to the thalamus and reticular formation before being processed in the cerebral cortex. This processing may be affected by IBD, even in remission, Crohn's disease (CD) patients had decreased grey matter volumes in areas of the brain involved with processing pain sensation when compared with controls, a finding also noted in other chronic pain syndromes.[17]

Pathophysiology: psychological factors

Emotional and cognitive processes can reduce pain inhibition signals travelling from the brain to the gut, resulting in gut hypersensitivity and persistent abdominal pain.[12 18] Additionally, psychological stress has been associated with altered gut microbiota[19] which leads to pain via altered intestinal cytokines and bowel distention. Inflammation and physical processes often initiate pain, but chronic pain may be maintained by psychological factors such as mood disorders, 'perceived stress' and 'pain-catastrophising', all of which were associated with increased IBD pain in a systematic review.[20]

Coexistent irritable bowel syndrome

A common source of pain in IBD is coexistent irritable bowel syndrome (IBS), a disorder of gut–brain interaction, which affects around one-third of individuals with IBD[21] and is 2–3 times more common in patients with IBD in remission than in the general population.[22] Chronic IBD pain and IBS share common pathophysiological features, and it is likely that there is an overlap between the two processes including low-grade mucosal inflammation, neuroimmune interactions[22 23] and alterations in the gut microbiota.[13 23] Additionally, there is a high prevalence of anxiety and depression in individuals with IBD[24] and those with anxiety and depression are more likely to experience IBS symptoms.[22]

Thus IBS-IBD overlap may explain why many past, current and proposed treatments for chronic IBD pain are those that may also improve IBS symptoms. It should, however, be noted that a qualitative study reported that many patients with IBD find the label of IBS unhelpful.[25]

Managing chronic abdominal pain in IBD

Cochrane reviews of randomised pain intervention studies for ulcerative colitis (UC) and CD had very low certainty of evidence due to small numbers as well as heterogeneity among studies and risk of bias[26 27] and further high-quality research is needed to improve both pharmacological and non-pharmacological approaches.[28] Here, we present a summary of the data available for managing chronic IBD-related abdominal pain interventions, as well as a checklist for assessing chronic pain in IBD (online supplemental information 1). In this review, we discuss CD and UC together under the umbrella of 'IBD', first because IBD chronic pain literature does not differentiate between the diseases (or has similar outcomes for both CD and UC) and second, because a similar prevalence of pain is reported in 4176 CD and 4255 UC individuals in the IBD BOOST study (17% UC vs 25% CD) and in quiescent CD and UC (60.2% vs 62.5%, respectively).[29 30] Holistic management of chronic pain is paramount, addressing pharmacological, psychological and lifestyle approaches (figure 2).

Managing chronic abdominal pain in IBD: modifiable causes for abdominal pain

To manage pain, modifiable causes should be identified and treated (see figure 3). If an individual reports feeling pain despite having no evidence of a disease flare, it is important to rule out the causes below.[31]

Managing chronic abdominal pain in IBD: pharmacological approaches

Non-steroidal anti-inflammatory drugs

Non-visceral inflammatory pain typically responds well to non-steroidal anti-inflammatory drugs (NSAIDs) and NSAID use can alleviate pain associated with axial and peripheral arthropathies that occur in IBD. However, many clinicians are wary of NSAIDs due to perceived risk of IBD flares,[32] although a recent systematic review including two randomised controlled trials (RCTs) demonstrated no statistically significant increase in the risk of disease flares[33] and, where increased risk has been demonstrated, it appears to be highest in ileal CD,[33] with frequent use (more than five times per month)[34] and with COX-1 inhibitors.[33]

> NSAIDs have a role in pain control in select patients with IBD, particularly in the context of extraintestinal musculoskeletal symptoms, however, caution should be exercised regarding the risk of disease flares; selective COX-2 inhibitors may be preferable to minimise this risk.

Antispasmodics

There are no studies directly reviewing the use of antispasmodics in IBD and most data relate to their use in IBS. As outlined above, IBS commonly coexists

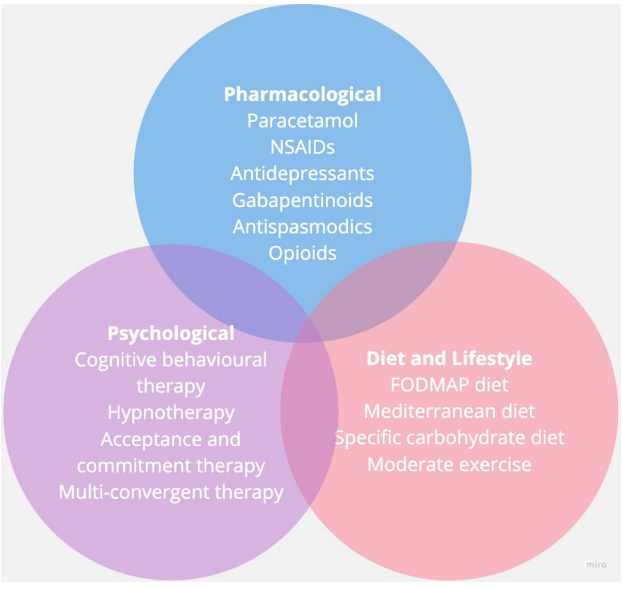

Figure 2 Approaches to pain management with most patients requiring an integrated, holistic and multimodal approach. FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides and polyols; NSAIDs, non-steroidal anti-inflammatory drugs.

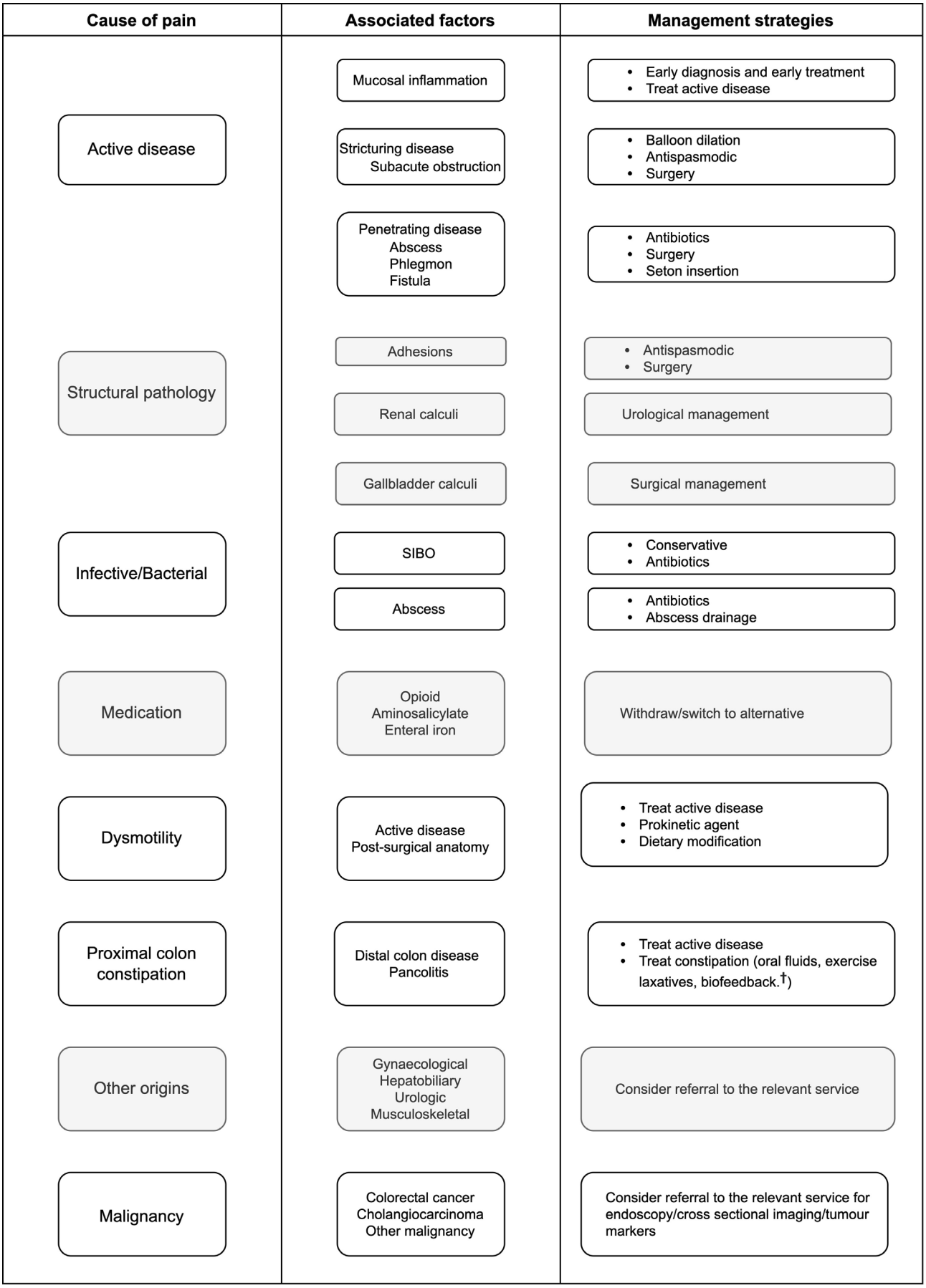

Figure 3 Modifiable causes for abdominal pain. †see Miller *et al*.[29] SIBO, small intestinal bacterial overgrowth.

alongside IBD and the American Gastroenterological Association advise antispasmodics for patients with IBD with IBS/functional symptoms.[35] Systematic reviews, including a network meta-analysis of IBS RCTs, have demonstrated that antispasmodic drugs and peppermint oil are significantly more efficacious than placebo at 4–12 weeks.[36] Caution must be exercised in patients with risk of obstruction as anticholinergic effects may mask or exacerbate symptoms.

Antispasmodics provide symptom control for IBS, however, consider the risk of side effects, including constipation, prior to use in IBD.

Opioids

Opioids are very effective in treating acute pain or pain caused by cancer. However, for chronic pain there is limited evidence of any benefit and for patients with IBD, opioids do not improve pain or quality-of-life scores and reduced hospital opioid prescribing does not worsen pain scores.[37–39]

Instead, long-term opioid use may be associated with increased pain and side effects including constipation, nausea, vomiting, immunosuppression, sexual dysfunction, addiction, sedation and respiratory depression.[40–44] Regular use of strong opioids in IBD has been associated with a twofold increase in premature mortality[45] and is a predictor for serious infection.[46]

Opioids are frequently prescribed to manage coexisting musculoskeletal and rheumatological complaints,[47] despite there being no proven benefit of chronic opioid use above simple analgesia in these conditions[48] and The National Institute for Health and Care Excellence (NICE) guidelines do not recommend the use of opioids in musculoskeletal symptom control.[49–51] Likewise, the British Society of Gastroenterology guidelines discourage opioid use in IBD[52] and the Faculty of Pain Medicine advises against the use of opioids for chronic pain beyond 2–4 weeks of modest doses.[41]

Atypical opioids

Partial opioid receptor agonists such as buprenorphine offer analgesic effects with reduced withdrawal effects, less dysphoria and an improved safety profile compared with regular opioids. However, there remain long-term side effect and dependence risks.[53] Naltrexone antagonises opioid receptors, yet at low doses it has paradoxical analgesic effects. Small studies have shown benefit in pain control in IBD with a favourable side effect profile compared with regular opioids, but this requires further evaluation.[54] Loperamide and diphenoxylate, which do not readily cross the blood–brain barrier, exploit the antidiarrhoeal and antisecretory effects of opioids and animal models have indicated that loperamide may also reduce pain via blockade of sodium channels.[55] Significant improvement in IBD abdominal pain was seen in individuals treated with loperamide for 1 week compared with placebo.[56]

Avoid opioid prescribing for chronic pain in IBD. Where opioid prescribing is unavoidable this should be a joint decision with the patient to trial a modest dose over 2–4 weeks with counselling that those who do not achieve useful pain relief within this period are unlikely to gain benefit in the long term.[26] See Opioid Aware https://www.fpm.ac.uk/opioids-aware for further guidance.

Antidepressant medications

Antidepressant medications (ADMs), such as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs), regulate the neurotransmitters serotonin, norepinephrine and corticotropin-releasing factor to alter gut motility and modulate signals between the gut and the brain resulting in an overall reduction in pain.[57] These medications may also improve pain by treating coexistent IBS and it has been suggested that ADMs could modify IBD activity, but a systematic review found the evidence inconclusive in this regard.[58]

Tricyclic antidepressants

Certain TCAs, including amitriptyline and nortriptyline, are licensed in the UK to treat neuropathic pain and are used off-licence for abdominal pain not responding to first-line treatment.[59] TCAs are also used to treat depression but the dosage for pain is much lower. In a retrospective cohort study of TCA use in patients with mild or inactive IBD, 85.2% of whom had abdominal pain, there was a moderate improvement in global well-being scores. The improvement was similar to that seen in IBS treated with TCAs and pain scores were not recorded.[60] A systematic review of IBS treatment showed that low dose TCA treatment had a lower relative risk of abdominal pain compared with placebo.[61] Side effects of TCAs include sedation, overdose toxicity, cardiotoxic effects and anticholinergic effects. Constipation may be beneficial in individuals for whom diarrhoea is an issue, while taking doses at night can use TCA's sedative effect.

SSRIs and SNRIs

Few studies have examined the effect of SSRIs/SNRIs on pain in IBD and those that have generally show little benefit.[62–64]

Two systematic reviews of ADMs in IBS showed no significant effect of SSRIs on abdominal pain.[36 61] The side effects of SSRIs and SNRIs include agitation, insomnia, sexual dysfunction, nausea and diarrhoea and these must be taken into account when considering their use, particularly in individuals troubled by increased stool frequency.[57]

Low-dose TCAs may help manage pain in IBD and coexistent IBS. There is little evidence for the benefit of SSRIs or SNRIs.

Gabapentinoids

The gabapentinoids gabapentin and pregabalin are analogues of gamma-aminobutyric acid (GABA) with anticonvulsant, central and possibly peripheral, analgesic actions. Anti-inflammatory properties of gabapentinoids have been demonstrated in animal models and may represent another mode of action by which pain in IBD can be altered.[65]

The impact of gabapentinoids on IBD pain has not been directly studied, instead benefit has been extrapolated from trials in chronic pancreatitis, oesophageal hyperalgesia and rectal sensitivity.

For patients with IBS with rectal hypersensitivity, pregabalin increased distension sensory thresholds to normal levels[66] and gabapentin significantly increased threshold pressures for bloating, discomfort and pain in IBS with diarrhoea.[66 67] For chronic pancreatitis, pregabalin treatment significantly improved pain relief when compared with placebo[68] and pregabalin prevented proximal oesophageal hyperalgesia following oesophageal acidification.[69]

The substantial side effect profile includes somnolence, GI upset and risk of dependency. Somewhat controversially, NICE does not recommend their use for the treatment of chronic pain.[70]

Gabapentinoids may improve chronic visceral pain; however, more evidence is required in IBD. Their side effects and the risk of dependency need to be considered carefully.

Cannabinoids

The human endocannabinoid system (ECS) is a neuromodulatory system which responds to both endogenous and exogenous cannabinoids, such as Δ^9-tetrahydrocannbinol (THC) and cannabidiol (CBD). Cannabinoid receptors are found in the GI tract as well as the central nervous system and the ECS has a role in modulating pain sensation. Observational cohort data indicate that 17.6% of patients with IBD regularly use cannabis and 83.9% of users felt cannabis improved their abdominal pain.[71] Two small studies have shown improved IBD clinical scores in individuals smoking or inhaling cannabis[72 73]; however, follow-up was short and abdominal pain was not specifically evaluated.

Regression analysis linked prolonged cannabis use with an increased risk of surgery after adjusting for tobacco smoking and demographic status.[71]

Medical cannabis is not approved for use in IBD and there is currently no evidence of its benefit in treating IBD-related abdominal pain.

Managing chronic abdominal pain in IBD: psychological approaches

A recent systematic review reported six studies using behavioural therapies to manage IBD-related pain and included individuals who were predominantly in remission.[74] The review concluded that relaxation techniques and changing cognitions show promise but in view of the scarcity of evidence, further research is warranted. The IBD-BOOST study explores a tailored, online, facilitated cognitive behavioural intervention for symptom control.[29] Of all 8486 patients included in the initial survey, 42% report wanting support for pain management and the results of the RCT of a facilitated online behavioural therapy intervention are keenly awaited; potentially offering a pragmatic approach to chronic pain management in IBD. A small cohort study demonstrated a significant reduction in abdominal pain in stress management groups compared with those without stress management although there was no adjustment for IBD activity.[75] A study of 20 patients allocated to relaxation training had significantly lower pain scores than a group of 20 allocated to attention control[76] and relaxation techniques improved pain in patients with IBD randomised to intervention compared with waiting list controls.[77] Studies of adolescent and paediatric participants have shown improved pain scores through cognitive behavioural therapy (CBT) and coping skills; however, the results are not widely representative with two studies including only adolescent females, another only those with anxiety disorder, and the effect of high attrition rates were noted.[78–81] IBD-specific CBT improved quality of life and decreased anxiety and depression in patients with IBD with poor quality of life.[82] Acceptance and commitment therapy (ACT) and multiconvergent therapy improve several outcomes in IBD including quality of life but the impact on pain has not been specifically assessed.[83 84]

With regard to the impact of behavioural therapies on IBS, a recent systematic review demonstrated that CBT and gut-directed hypnotherapy had the most evidence for efficacy however, there was a high risk of bias.[85] An RCT of 431 adults with functional bowel disorders showed that CBT was significantly more effective than education in improving quality of life despite having little effect on pain, and may enable an improved ability to live with pain.[86]

A systematic review of the use of mindfulness for pain control concluded that existing evidence was limited and inconclusive.[87] An IBD-specific review showed no effect on symptoms, although mindfulness did improve quality of life.[88] While overall IBS symptoms can be significantly improved long term with hypnotherapy, no studies in IBD-related pain have been conducted.[89] One study has shown that individuals with UC in remission randomised to gut directed hypnotherapy had clinical relapse 78 days later than

those randomised to attention control alone, however, pain was not directly assessed and there was no difference in quality of life.[90]

There is some limited evidence regarding psychological approaches in IBD-related pain with CBT improving overall quality of life, coping mechanisms and pain.

Diet and lifestyle approaches

The low-fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) diet contains low levels of FODMAP. These carbohydrates are poorly absorbed in the small intestine, are highly osmotic and are rapidly fermented by bacteria in the gut. This leads to fluid and gas distention of the bowel which may result in symptoms such as bloating, flatulence, cramping and diarrhoea. A diet reduced in FODMAPs, followed by FODMAP reintroduction, is well recognised as an effective approach to managing abdominal pain in IBS[91] and its role in reducing abdominal pain in IBD was supported in a recent systematic review.[92 93] An additional two studies indicate significantly more patients with IBS symptoms and quiescent IBD had resolved or improved abdominal pain, after 6–8 weeks of low-FODMAP diet.[94 95] Low-FODMAP diets are low in fibre and may lead to constipation; compliance may be challenging due to the diet's restrictive nature and it has been linked to a reduction in total bacteria and butyrate-producing bacteria, which are important for anti-inflammatory and immune regulatory functions.[92] It is, therefore, important that the food reintroduction phase of the diet is followed, under the supervision of a dietician.

A comparison of the specific carbohydrate diet (SCD) and Mediterranean diet (MD) in IBD found that both improved abdominal pain at week 6 but, while the SCD may lead to deficiencies in key vitamins, an MD is generally easy to follow.[96] Many individuals with IBD follow a gluten free diet (GFD) in the absence of coeliac disease. A recent systematic review and meta-analysis of dietary interventions for induction and maintenance of remission in IBD reported mixed findings; one study showed that symptoms, including pain, improved in two-thirds of individuals while a prospective study found no variation in hospitalisations or flares but a poorer quality of life in those with GFD.[97] Further research is needed in this area.[98]

Moderate exercise can improve quality of life in IBD and improve GI symptoms in IBS, however, the effect on pain in IBD has not been studied.[35]

The FODMAP diet offers short-term benefit to those with coexistent IBS and is best carried out for a time limited period, under the supervision of a dietician.

CONCLUSION

Managing chronic pain in IBD continues to be a challenge for clinicians and patients alike. By listening to patients, acknowledging their symptoms and assessing pain with pain severity scales we can begin to manage chronic pain effectively. Few research studies focus specifically on pain in IBD and assessment of specific interventions to improve pain outcomes are badly needed. A collaborative approach between clinician and patient, reviewing disease activity, psychosocial factors, current medications and comorbidities must be undertaken to achieve optimal symptom control.

Early diagnosis and suppression of inflammation may prevent irreversible central and peripheral changes that contribute to chronic pain. Considering the poor efficacy and side effect profile of many pharmacological agents, notably opioids, the management of chronic pain in IBD should largely comprise non-pharmacological approaches. Psychological approaches have shown promise and further research is needed. In the future, integrated psychological and pain services need to be part of a holistic approach to caring for individuals with IBD (figure 2).

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