Topical Review

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Chronic pain in patients with inflammatory bowel disease

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> "My pain is exhausting, and it's rarely just pain. If not accompanied by diarrhoea, fatigue, or other debilitating symptoms, it's joined by a spiral of anxious thoughts about what the pain means……. I was constantly at doctors' and hospital appointments, but I was rarely asked about my pain. Even now, unless I'm in flare up, no one asks me about my pain or fatigue…. truthfully, those doctors and nurses don't have time to ask me about symptoms if I'm not flaring up…….IBD clinics even when interested aren't funded to manage those symptoms…and healthcare professionals dismissed my symptoms as they don't know what to say, as they don't understand pain in IBD, and they feel as powerless as I do…… given that pain is one of the top presenting complaints in IBD, I find it astonishing how little I get asked about it".
> (*Lucy Y*, first diagnosed with Crohn's disease 23 years ago. Reproduced with permission).

1. Introduction

Crohn's disease and ulcerative colitis ("inflammatory bowel disease" [IBD]) are chronic relapsing intermittently acute conditions, characterised by pathological changes in gut tissue, symptoms of diarrhoea, blood loss, and abdominal pain, long-term complications (fistulae, abscesses, and strictures), extra-abdominal manifestations such as arthritis, and systemic illness. Symptoms dominate IBD disease activity indices,[39,42] but the primary target for treatment is inflammation of the gut mucosa. This treatment has significantly improved over the past decade, notably through the use of immunomodulator and biologic drugs. However, the pattern, severity, impact, and prognosis of symptoms still vary substantially from patient-to-patient.

Clinicians caring for people with IBD focus on controlling the active bowel disease. Objective measures of disease activity, using endoscopy and imaging or surrogates such as faecal calprotectin, provide targets for disease-modifying drugs in trials and the clinic. However, there is a discrepancy between measures of gut inflammation and the extent and severity of patients' symptoms,[30] and neither are straightforwardly related to measures of the overall impact on patients' lives.[30] Early mucosal healing defined by endoscopy is associated with long-term improvements in symptom severity, but one-third of patients with healed mucosa do not achieve clinical remission.[76,77]

In particular, abdominal pain that persists beyond flares, despite optimal treatment of the gut disease, presents a common, disabling, and unresolved problem,[64,101] affecting patients' quality of life (QoL) and psychological well-being[58,75] and posing challenges for management.[66,87] For clinicians, this means disease-targeted treatment alone may not resolve the patient's pain and pain-related distress. The result is that chronic abdominal pain may dominate patients' lives—underrecognised in both specialist and primary care settings, poorly assessed, and inadequately treated.

In this Topical Review, we consider evidence about chronic abdominal pain in people with IBD. Our aim was to identify the extent to which general principles of modern chronic pain management[92] should have equal place in the IBD clinic and consultation alongside the clinician's concern for diagnosing and treating underlying gut pathology, to ensure that pain in all patients with IBD is properly recognised, formally assessed, and treated safely and effectively.

2. Occurrence, impact, and assessment of abdominal pain in inflammatory bowel disease

Pain is a prominent IBD symptom.[27,61,79] In large cohorts of patients with IBD, 60% report abdominal pain,[60] substantially more than the 25% prevalence observed in general population samples[1,51]; half have experienced it for more than 5 years.[100] Pain contributes to the impact of IBD on QoL.[47,58,60,75,99,101]

Qualitative studies illustrate how pain and other symptoms affect all aspects of the lives of people with IBD, including those (such as proximity to a toilet) specific to gut problems.[21] People with IBD describe "vicious circles" between pain and their other symptoms that create barriers to understanding and treatment of pain.[86] Reactions to pain vary from defeat to tolerance to acceptance, but all have emotional impact.[86] Pain is often not included as a predictor of QoL outcomes in prospective epidemiological research,[94] but emerges as an independent prognostic factor when it is.[95]

The dissociation between abdominal pain and indices of gut inflammation highlights that pain should be a target for management

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in its own right.[13,14] Yet, routine clinical assessment of patients with IBD does not necessarily include pain. It is one of 5 items in a commonly used clinical severity scale for Crohn's disease,[39] but not part of the widely used Mayo Clinic four-item scale for ulcerative colitis,[42] and only one small part of a common measure of IBD QoL.[54] Each of these scales has its uses for disease assessment, but pain assessments and measures of gut inflammation should form distinct and separate components of consultations with patients who have IBD, so that the need for additional pain management, beyond the relief achieved by control of mucosal inflammation, can be established, monitored, and acted upon.

One problem in achieving this is that there is no widely accepted fully tested pain assessment for patients with IBD, and there are challenges to developing one. In particular, it is not easy to separate pain from other IBD experiences (eg, bowel disturbance and psychological distress[31]) that together impair QoL in areas as diverse as sleep, eating and food enjoyment, fatigue, work capacity, and social relationships.[47] Meanwhile, application of current recommendations for chronic pain classification in *ICD-11*, notably the regular use of numerical rating scales for pain intensity, pain-related distress, and interference with activity,[92] would help reverse the neglect of this symptom in the clinic.

3. Mechanisms of abdominal pain in inflammatory bowel disease

Reversible causes of abdominal pain in IBD include strictures, abscesses, fistulae, and small intestinal bacterial overgrowth. Renal or gall bladder calculi, common in patients with IBD, form part of the differential diagnosis. Patients with IBD have a higher risk of colorectal cancer, primary sclerosing cholangitis, and cholangiocarcinoma. Surgery as part of IBD management, in particular multiple operations, confers the additional risk of postsurgical pain.

Most abdominal pain in people with IBD, however, is assumed to be triggered through activation of nociceptors in the gut by chemical, thermal, or mechanical stimuli.[74] Disease remission, assessed by resolution of gut inflammation or restoration of normal bowel habit, might therefore be expected to improve or resolve abdominal pain. However, 30% to 50% of patients with IBD report significant pain despite disease remission,[27,61,79] and patients themselves distinguish pain concurrent with active bowel disease from pain that persists beyond it.[60]

Visceral nociceptors innervate the gut sparsely; hence, deep abdominal pain or discomfort is often diffuse and poorly localised.[15] These nociceptors, like other sensory afferents, have cell bodies in the dorsal root ganglia and possess molecular specificity.[44] Most visceral afferents are autonomic and their roles in nociception and pain are unknown.[35] Abnormally prolonged sensitisation of visceral afferents in the gastrointestinal tract after acute inflammation can contribute to chronic pain.[12] CNS sensitisation is also apparent at the cellular level during acute inflammation[29] and further amplifies signalling from ascending spinal pathways. This process is maintained by dysregulation of descending control that emanates from the brain,[26] where structural and functional abnormalities in prefrontal and limbic regions have been observed.[6,45,89] Those brain regions are also involved in emotional regulation and learning[98] and may determine the capacity for behavioural adjustments needed to manage pain adaptively (for a given physical or social environment). The prefrontal–limbic abnormalities may explain the increased risks of mood and anxiety disorders in patients with IBD,[33] disorders linked to persistence and severity of their pain.[85]

Such comprehensive models counter the long history of "psychogenic" theories of abdominal pain.[84,93] Although healthcare professionals understand clearly that psychosocial factors contribute to the overall burden of living with IBD, less attention has been paid to how affective and cognitive factors modulate pain. New models highlight not only the role of cognitive, behavioral, and environmental factors underlying pain perception but also their interaction with visceral inflammation.[50]

However, the extent to which neuroanatomical changes determine the chronicity of pain in IBD is unclear nor is it known why or how they outlive episodes of gut inflammation to explain pain despite disease remission in susceptible patients with IBD. One clinical field producing insights to this problem is irritable bowel syndrome (IBS). Irritable bowel syndrome is a functional pain disorder that has abdominal pain as its cardinal symptom and can coaggregate with IBD.[70] Research clarifying the complexity of visceral sensations of patients with IBS has benefited from biopsychosocial research that draws on rapidly advancing methods and tools for genetic, cellular (eg, visceral nociceptors), systems-based (eg, gut and nervous system), and behavioural (eg, avoidance, maladaptive coping, cognitive biases, and reactivity) studies.[24,71] The extent of overlap between IBD and IBS clinical phenotypes and their gut pathophysiological profiles remains controversial,[7] but integrated explanations and mechanisms for why abdominal pain persists in the absence of continuing gut mucosal inflammation are likely relevant for both conditions.[66,70] Harnessing these insights to develop new or better approaches to pain management for persons with IBD will need not only a clearer understanding of what aspects of IBD pain are particularly challenging to patients, but also where and why existing treatments have failed or are limited.

4. Comorbid pain

Extra-abdominal disease is an additional source of chronic pain in people with IBD; these pain comorbidities include back and joint pain linked to axial and peripheral spondyloarthritis,[38,95] and conditions with higher prevalence in people with IBD such as migraine[62] and fibromyalgia.[55] Such extra-abdominal pain is a prominent predictor of reduced QoL and work productivity after adjustment for IBD activity.[38,95] Shared underlying causes of visceral pain may complicate the picture,[3] further illustrating the multiple mechanisms involved in the pain of patients with IBD.[25] The co-occurrence of pain syndromes adds to the complexities and challenges of treating the individual patient, including different targets for treatment of specific conditions such as fibromyalgia and spondyloarthritis.

5. Pharmacological approaches to chronic pain in patients with inflammatory bowel disease

Evidence continues to emerge that long-term pain outcomes are improved by active therapeutic targeting of mucosal inflammation.[91] Tofacitinib therapy, for example, significantly improved QoL vs placebo in patients with moderate-to-severe active ulcerative colitis, including significant relief of abdominal pain.[68] However, many patients will require additional pain management.

The well-known problems of using analgesic medication for long-term pain are exacerbated for patients with IBD.[98] Many analgesics have low efficacy and cause gut-related adverse effects in patients with IBD, including, paradoxically, pain.[100] The challenge is how to adequately treat chronic abdominal pain while avoiding the harms associated with medication use.

5.1 Opioids

Opioids are problematic. Immediate pain relief with short-term opioid use does not translate into improved functioning with long-term use.[23,36]. Opioids can cause gastrointestinal-related adverse effects, collectively called opioid-induced bowel dysfunction and including constipation, incomplete evacuation, bloating, and gastric reflux. Patients with IBD are at high risk for this condition because they suffer from chronic relapsing-remitting pain. Chronic high-dose opioid use can also induce visceral hyperalgesia (narcotic bowel syndrome) in a small subset of patients with IBD. This is highly intractable to treatment and a cause of prolonged hospital admission.[22,36,52]

Despite these problems, prescription opioid use is higher among patients with IBD compared with non-IBD patients[57] and, in England, for example, increased significantly from 1990 through 2013.[16] An estimated 5% of patients with IBD become heavy users of opioids within 10 years of diagnosis. IBD is an independent risk factor for becoming a heavy opioid user,[88] and risk increases with psychiatric comorbidity such as depression or anxiety.[37]

Research continues into whether currently available opioids can be delivered, or new opioids developed, with radically less potential for addiction and serious side effects,[18] and into strategies for limiting, reducing, and tightly monitoring opioid use in patients with IBD.[19,20] The specificity of visceral pain-signalling neurons provides potential for developing peripherally restricted analgesics specific for visceral pain, devoid of CNS effects.[15,18,44]

Meanwhile, chronic use of currently licensed prescription opioids is associated with poorer control of pain,[11] increased healthcare use,[65] and higher mortality in patients with IBD.[16] Long-term use of opioids therefore should, as far as possible, be avoided for pain management in these patients, and alternatives offered. National guidelines on opioid use for long-term pain concur in recommending education for informed consent and monitoring, commensurate with risk assessments.[40] If continual or repeated opioid-based analgesics are necessary, for example in patients with major abdominal fistulae, they should preferably be prescribed in settings with access to nonpharmacological interventions and resources for managing acute and long-term consequences of dose reduction or discontinuation.[4,20]

5.2 Alternatives to opioids

Alternative drugs to opioids also carry problems for this patient group. Nonsteroidal anti-inflammatory drugs are limited by risk of disease exacerbation.[12,59,81] Results of phase 2 trials suggest a potential role for anticonvulsants used for neuropathic pain, such as gabapentin and pregabalin,[81] known to improve rectal hypersensitivity in patients with IBS.[46,56] But while this might justify clinical trials in patients with IBD, none have been reported, and furthermore the addictive potential of these drugs and the additional burden on patients posed by their side-effect profile raise questions about their application to long-term nonmalignant abdominal pain.

Tricyclic antidepressants and selective norepinephrine reuptake inhibitors improve abdominal pain without some of the GI risks associated with conventional analgesics.[28,32,52] A meta-analysis of randomised controlled trials in IBS found that low-dose tricyclic antidepressants alleviate abdominal pain,[72] possibly by reducing afferent signals from the gastrointestinal tract.[34,63] Again there are no trials in patients with IBD, and treating chronic pain with these drugs carries familiar concerns about long-term dependency, side effects, and withdrawal.

Both endocannabinoid receptors (CB1 and CB2) are found in the gut and are potential targets for pain relief in IBD.[2,78] A phase 2a clinical trial of a CB2 agonist (olorinab) is underway, including pain as an outcome, in people with Crohn's disease and functional symptoms.[17] However, psychotropic effects from agonist activity at CB1 receptors remain a concern for most prescribable preparations, and evidence of efficacy from clinical trials of cannabis-based medicine for management of chronic pain in noncancer conditions generally is lacking.[82] There is a need to understand the mechanism of abdominal pain relief afforded by cannabis-based medicines in patients who report benefit,[43,73,83,96,97] and for robust investigations of efficacy and effectiveness in persons with IBD both short- and long-term.

6. Psychological approaches

The focus of psychological interventions in IBD has mainly been concerned with adherence to treatment and modification of lifestyle factors, including stress-induced flares, but is now addressing pain and symptoms, and applying skills for working around IBD pain.[5,8] Direct pain reduction by psychological methods has been demonstrated,[10,66,67] but requires replication in larger studies.[66] Self-management skills have in principle been endorsed by international guidelines.[49] Of specific psychological modalities, hypnotherapy has shown promise in abdominal pain,[69] although only one trial involved patients with IBD, targeting gut activity, pain, or coping with pain: gut-directed hypnotherapy extended time between flares in ulcerative colitis compared to attention controls.[48] The therapeutic value of psychological approaches has been attributed to anti-inflammatory effects,[48,80,87] but empirical mechanistic studies are lacking.

One source of evidence comes from studies of psychological interventions that are concerned more generally with relieving stress and improving quality of life in persons with IBD, factors linked to their pain experience.[85] Meta-analysis of 21 randomised controlled trials, however, yielded no evidence that psychological interventions improved emotional states and QoL, or reduced disease activity in the short- or long-term, in adults with IBD.[90] A narrative review echoes this conclusion.[5]

Nevertheless, where unhelpful beliefs about IBD and negative biases in processing information underlie maladaptive behaviours, there is no a priori reason why cognitive methods (including cognitive and behavioural methods, problem solving, and emotional regulation[53]) should not be effective in relieving pain-related distress and disability. A recent wait-list controlled study paints a more positive efficacy profile for multicomponent cognitive behavioural therapy, at least in decreasing effects of IBD on QoL as well as reducing anxiety and depression in those with lower baseline levels.[9]

Given the complexity of visceral pain, its strong psychological underpinnings, and the increased impact it exerts across multiple life domains as pain persists, additional research targeting visceral pain in patients with IBD is called for. This will likely require a theoretically informed, empirically derived conceptual model that reflects the clinical realities of patients with IBD, the trajectory of their symptoms and triggers, and is not "borrowed" from other symptomatically similar but not necessarily mechanistically similar GI diseases. A well-defined, empirically rooted conceptual model built specifically for IBD should go a long way to reconcile discrepant findings regarding the role of stress and the efficacy of interventions that target stress-sensitive symptoms, such as pain, through psychological treatments.

7. Conclusion and future directions

Pain is a common symptom in IBD, and represents a major health burden, significantly impacting QoL and psychological well-being. While optimal pharmacological treatment of gut inflammation is important for long-term control of symptoms, including pain, many persons with IBD continue to experience long-term abdominal pain. Chronic abdominal pain in these persons has multiple aetiologies and is complex. Available treatment options are limited. Current pain management strategies are not specific for IBD and many, notably opioid use, are ineffective and associated with several detrimental off-target effects. There is a clear need to develop practical patient-focused policies for safe, rational, appropriate, and effective use of current analgesic medications, and better alternatives for long-term pain management.

Several priorities for future research and practice stand out. First, develop and apply pain assessment for patients with IBD and ensure that pain is routinely assessed as a potential influence on outcomes in longitudinal studies. Second, integrate investigation of central and visceral hypersensitivity and pain processing with clinical and psychological studies as the basis for identifying and testing novel interventions, from molecular-specific drugs to tailored behavioural change. Third, improve the content and delivery of existing treatments, notably psychological approaches to chronic pain, for individuals, and the access of persons with IBD to all the options for chronic pain management established for other long-term painful conditions.

Many of the clinical and research issues are shared by all chronic pain conditions. Whilst the unique challenges facing patients with IBD and their clinicians must be recognised, it is also vital that silos between different clinical disciplines allied to different body viscera,[41] and to relevant pain management expertise,[9,38,49] are broken down, so the many shared problems of managing and understanding visceral and associated extra-abdominal pain in the context of IBD can be tackled more efficiently and effectively.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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