

Managing Pain in Inflammatory Bowel Disease

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Abstract: Pain is a common complaint in inflammatory bowel disease, and it has significant consequences for patients' quality of life. A thorough evaluation to determine the source of patients' pain should include clinical, laboratory, radiologic, and endoscopic assessments as indicated. Differentiating among active inflammation, secondary complications, and functional pain can be complicated. Even when all active disease is adequately treated, clinicians are often left with the difficulty of managing chronic pain. This paper will review the benefits and limitations of several commonly used treatments and promising future therapies. A suggested treatment algorithm will provide some guidance in this challenging area of inflammatory bowel disease management.

Pain is a common complaint among patients with inflammatory bowel disease (IBD).¹⁻³ Pain is a component of several disease activity indices, and it is one of the principal concerns for patients.^{4,5} Pain is a common reason for the poor quality of life (QOL) often seen in patients with IBD.^{2,6,7} Also, the uncontrollable aspects of pain are associated with profound anxiety. This anxiety can lead to maladaptive coping mechanisms that make pain even more difficult to manage.⁸ This paper will discuss how intervention using a multidisciplinary approach to pain management can break this cycle of pain.

Etiology of Pain in Inflammatory Bowel Disease

Sources of Pain

Pain is an evolutionary adaptation designed to warn of damage that could lead to long-term injury. In IBD, pain may be the only sign that the disease is progressing and that stronger therapy will be required. Ongoing intestinal inflammation or subsequent complications, such as abscesses or strictures, are common causes of pain in IBD. Intermittent, partial small-bowel obstruction in Crohn's disease can frequently cause pain and may necessitate a low-residue

Keywords

Inflammatory bowel disease, irritable bowel syndrome, pain, management

diet. Bile-acid malabsorption can induce diarrhea and cramping that will often respond to bile-acid sequestration. Extraintestinal manifestations involving the joints, skin, and eyes can also frequently cause pain. Several common sources of pain in IBD are listed in Table 1.

A complaint of pain should trigger further investigation regarding potential etiologies. This investigation may include an assessment for signs of inflammation, such as an elevated white blood cell count, sedimentation rate, or C-reactive protein level. The presence of fecal leukocytes or an elevated fecal calprotectin level may also be informative. Neuropathic pain should prompt an evaluation for vitamin B₁₂ deficiency, especially in a patient who has undergone a large ileal resection. Often, colonoscopy or upper endoscopy will be necessary to confirm evidence of disease. Radiologic imaging (small-bowel follow-through, computed tomography enterography, or magnetic resonance enterography) or wireless capsule endoscopy may be helpful in evaluating disease beyond the reach of the endoscope. Small-bowel imaging is often necessary to identify strictures or adhesions that can be insidious sources of pain.

Even after careful verification of clinical and endoscopic remission, 20% of patients will continue to have pain.⁹ In the SONIC trial, over one third of patients entering the study with a diagnosis of moderate-to-severe Crohn's disease did not have evidence of active disease on endoscopy.¹⁰ One reason for this finding may be the high rates of irritable bowel syndrome (IBS) in patients with IBD.^{11,12} In one study, patients with IBD that was in complete remission were still 2–3 times more likely to have IBS-like symptoms compared to the general population.¹ High rates of anxiety and depression in IBD patients may contribute to these functional symptoms.^{13,14} Indeed, IBD patients with greater anxiety and depression were more likely to complain of IBS symptoms.^{1,15} Despite the consequences of these psychological problems, one study found that

only 40% of IBD patients with depression were receiving medical therapy.¹⁴

Increasingly, evidence supports a more direct connection between IBD and IBS. Low-grade inflammation and neuroimmune interactions seem to play a direct role in the development of IBS.¹⁶ Similarly, occult inflammation in IBD patients who are in remission has been associated with IBS-like symptoms.¹⁷ This finding suggests a mechanism wherein residual inflammation in quiescent IBD triggers IBS-like symptoms in much the same way that a gastrointestinal infection can cause postinfectious IBS.¹⁸ This blurring of the line between IBD and IBS has caused some researchers and clinicians to question the model of a functional-organic dichotomy.¹⁹

Mechanisms of Pain

All pain in IBD begins when pain-producing, or nociceptive, stimuli are detected by specialized primary afferent neurons called nociceptors (Figure 1). Membrane-bound receptors on nociceptors are capable of responding to a wide array of stimulus modalities, including chemical, thermal, and/or mechanical stimuli.^{20,21} Activation of nociceptors then stimulates second-order neurons in the spinal cord via excitatory glutamatergic synapses. The neural signal is then transmitted up the spinal cord to the brainstem and the thalamus, which in turn communicate with multiple areas of the cerebral cortex, including the somatosensory cortex, insula, and anterior cingulate cortex.²² When this neural signal reaches the higher centers of the brainstem and the brain, it gives rise to the conscious sensation of pain.

Overlying these sensory pathways are powerful systems for modulating incoming information. Some nociceptors are capable of releasing substances that can alter both their own function and the function of neighboring neurons.²³ Modulation of synaptic communication between nociceptors and second-order neurons in the spinal cord can also lead to hyperalgesia.²⁴ In addition,

Table 1. Common Sources of Pain in Inflammatory Bowel Disease

Inflammatory sources of pain		Noninflammatory sources of pain	
<i>Intestinal</i>	<i>Extraintestinal</i>	<i>Intestinal</i>	<i>Extraintestinal</i>
Gastritis	Peripheral arthritis	Strictures	Nephrolithiasis
Enteritis	Sacroiliitis	Adhesions	Cholelithiasis
Colitis	Ankylosing spondylitis	Small-bowel obstruction	
Abscesses	Primary sclerosing cholangitis	Narcotic bowel syndrome	
Fistulae	Erythema nodosum		
Fissures	Pyoderma gangrenosum		
Irritable bowel syndrome	Iritis		
	Uveitis		

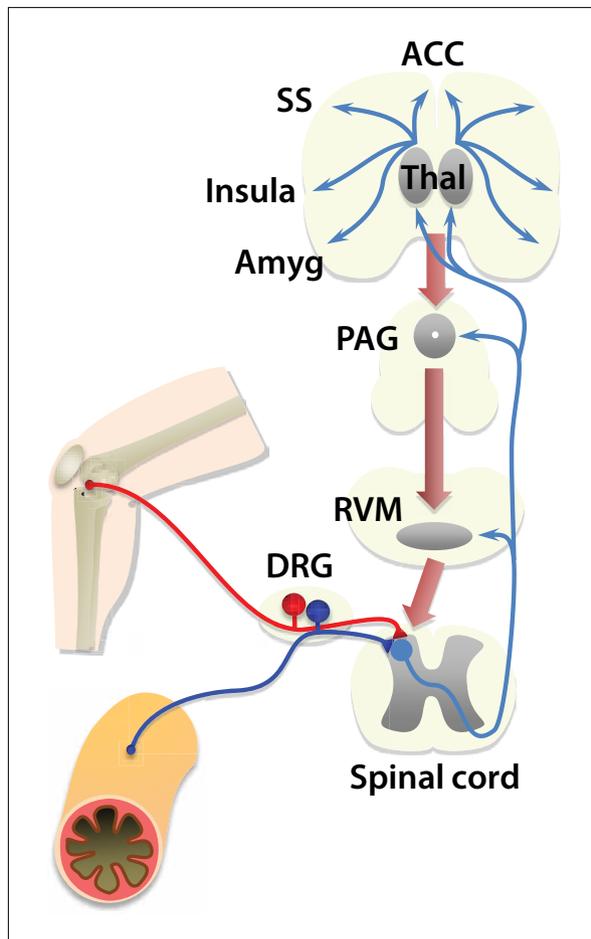


Figure 1. Mechanisms of pain in inflammatory bowel disease. Nociceptive stimuli can be detected by either somatic primary afferents (red) or visceral primary afferents (blue).

ACC=anterior cingulate cortex; Amyg=amygdala; DRG=dorsal root ganglia; PAG=periaqueductal gray matter; RVM=rostral ventromedial medulla; SS=somatosensory cortex; Thal=thalamus.

activation of structures within the brainstem, specifically the periaqueductal gray matter of the pons and the rostral ventromedial medulla, can either inhibit or facilitate the incoming transmission of sensory information.^{25,26} Lastly, multiple centers within the brain are able to modulate the perception and response to nociceptive stimuli that ultimately lead to the experience of pain.²⁷ All of these modulatory mechanisms have been implicated in chronic pain conditions.

There are several ways in which pain from visceral organs is unique compared to somatic pain. The majority of visceral primary afferents are polymodal—capable of sensing mechanical, thermal, and chemical stimuli—which permits them to transmit a diversity of signals from

the environment.²⁸ Most of these sensory afferents are also able to respond to graded stimuli well into the noxious range; in a sense, almost all visceral sensory afferents are capable of generating pain. All visceral organs receive a dual nerve supply, and both sets of nerves may possess distinct functional properties and contribute in distinct ways to visceral pain.^{29,30}

Once in the spinal cord, the visceral afferents arborize into an extensive network that extends throughout the spinal cord and overlaps with other primary afferent neurons.³¹ In sharp contrast, cutaneous sensory afferents make relatively circumscribed connections in the spinal cord to produce the characteristic dermatomal pattern. Consequently, visceral stimuli—including nociceptive stimuli—are capable of recruiting large sections of the central nervous system, resulting in the diffuse, poorly localized, and often referred nature of visceral pain.

Therapeutic Options

When pain is associated with active IBD, the primary treatment will often be escalation of IBD therapy. However, pain may persist despite adequate IBD therapy, or pain may arise from a non-IBD source. In these situations, the use of other analgesics may be required (Table 2).

Nonsteroidal Anti-Inflammatory Drugs

Use of nonsteroidal anti-inflammatory drugs (NSAIDs) in IBD is generally reserved for the management of arthritis. NSAID use is highly effective in other inflammatory arthropathies and is often recommended as a first-line therapy.^{32,33} Acetaminophen may be used instead of NSAIDs to limit side effects, but it is less effective.³⁴

NSAIDs act as anti-inflammatory analgesics primarily by inhibiting the production of prostaglandins by cyclooxygenase (COX) enzymes. Under conditions of inflammation, NSAIDs' analgesic effect is mediated through inhibition of the inducible form of the enzyme, COX-2. Nonselective NSAIDs also inhibit the constitutively produced COX-1 enzyme, which maintains the mucosal integrity of the intestine. The combination of reduced prostaglandin production and direct toxicity results in the familiar gastrointestinal side effects associated with NSAIDs.^{35,36}

Several early case reports raised questions about NSAIDs' potential to exacerbate IBD.³⁷⁻⁴⁰ Subsequent case-control studies of IBD patients noted high rates of NSAID use, although only in hospitalized patients who presumably had greater need for analgesics.^{41,42} No association between NSAID use and disease flares was seen in clinic patients.^{43,44} The largest study to evaluate this association examined over 500 IBD patients who were followed for 1 year.⁴⁵ This study found no associa-

Table 2. Common Medications for Visceral Pain

Class	Medication	Starting dose	Maximum dose	Common side effects
Antispasmodics	Hyoscyamine XR	0.125–0.25 mg every 4–6 hours or 0.375–0.75 mg BID	1.5 mg/day	Constipation, dizziness, dry mouth, sedation, urinary retention
	Dicyclomine	20 mg QID	160 mg/day	
Tricyclic antidepressants	Amitriptyline	25–50 mg at bedtime	150 mg/day	Dry mouth, dizziness, sedation, weight gain
	Desipramine	10–25 mg at bedtime	200 mg/day	Dry mouth, constipation, hypotension, sedation, weight gain
	Nortriptyline	10 mg at bedtime	150 mg/day	
SSRIs	Escitalopram***	10 mg QD	20 mg/day	Anorexia, diarrhea, headache, insomnia, nausea, sedation, weight loss
	Fluoxetine***	20 mg QD	80 mg/day	
	Paroxetine***	20 mg QD	50 mg/day	
	Sertraline*	25–50 mg QD	200 mg/day	
	Citalopram**	20 mg QD	60 mg/day	
SNRIs	Venlafaxine***	37.5 mg QD	150 mg/day	Headache, insomnia, nausea
	Duloxetine***	20–60 mg QD	120 mg/day	Dizziness, insomnia, sedation, nausea
Atypical antidepressants	Bupropion***	100 mg BID	450 mg/day	Headache, insomnia, seizure risk, weight loss
	Bupropion XR***	150 mg QD	400–450 mg/day	
Atypical opioids	Tramadol**†	50 mg QD	400 mg/day	Constipation, diaphoresis, nausea, seizure risk
Anticonvulsants	Gabapentin	300 mg at bedtime	3,600 mg/day	Difficulty concentrating, nausea, sedation, weight gain
	Pregabalin**	75 mg BID	450 mg/day	Confusion, dizziness, sedation, weight gain

*May require dose adjustment in patients with hepatic insufficiency. **May require dose adjustment in patients with renal insufficiency. †Avoid in patients on a monoamine oxidase inhibitor.

SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; XR=extended-release formulation.

tion between NSAID use and flares (odds ratio [OR], 0.99; 95% confidence interval [CI], 0.61–1.60), even with daily NSAID use.⁴⁵

Controlled trials of NSAIDs in IBD have been lacking. A small study showed a 20–30% increased risk of flares in patients who were started on NSAIDs compared to patients who were started on acetaminophen.⁴⁶ All NSAID-treated patients experienced a flare within 9 days of starting the medication, but most were able to re-attain remission simply by stopping the NSAID.⁴⁶

Given the potentially reduced risk of gastrointestinal toxicity associated with selective COX-2 inhibitors, these drugs would be a logical alternative in IBD.^{47,48} A retrospective chart review found that only 7% of IBD patients suffered a flare after being treated with a COX-2 inhibitor, and over 80% of patients had improvements in pain.⁴⁹ A subsequent randomized, placebo-controlled trial of over 200 patients with quiescent IBD found similar rates of disease exacerbation in patients treated with celecoxib or placebo (3% vs 4%).⁵⁰

Clinicians should keep in mind that NSAIDs are available in over-the-counter formulations, so many IBD patients are already using these drugs for pain management. Several studies have shown rates of NSAID use of 50–75% among IBD patients, compared to 10% among other gastroenterology outpatients.^{45,51} Since most IBD flares in patients taking NSAIDs occur quickly and resolve with cessation of the medication, quickly withdrawing these medications at the first sign of a flare would be advisable. Selective COX-2 inhibitors are likely safer, although concerns about potential cardiovascular risks may limit their use.^{52,53} Given the limited data, avoiding the use of NSAIDs in most cases would be prudent. In patients with debilitating arthritis that cannot be controlled by other means, cautious use of COX-2 inhibitors could be considered. However, safety data on regular, long-term use of these medications in patients with IBD is lacking. Further randomized controlled studies would help to clarify this controversial aspect of pain management.

Opiates

Opiates are frequently used to treat severe acute pain. However, the role of these drugs in chronic noncancer pain (CNCP) is complicated by several issues, including side effects, abuse, and diversion to other individuals. Despite these concerns, the use of long-term opioid therapy for CNCP has been increasing dramatically.^{54,55} While evidence demonstrates pain relief with short-term opioid use, this benefit often does not translate into improved functioning over the long term.⁵⁶ The few studies of opioid use for CNCP have shown little-to-no benefit, resulting in some disillusionment with long-term opioid therapy.^{57,58}

There is surprisingly little information about the prevalence of opioid use in IBD. An early study reported chronic opioid use in 30% of IBD patients, although this study only included patients referred for psychiatric evaluation.⁵⁹ In all patients presenting to an IBD clinic, the frequency of opioid use ranged from 3% to 13%.^{60,61} Opioid use may be a marker for more severe IBD, as studies have found that patients who were treated with opiates were more likely to have worse disease activity and pain and were almost twice as likely to require surgical intervention.^{60,62}

Interestingly, over half of IBD patients who returned for follow-up care were able to discontinue opiates.⁶² These patients were more likely to be adherent to medical therapy and to have disease activity and pain that were under control.⁶² This finding suggests that most patients with IBD can be successfully weaned from opiates if their disease is treated and their pain is managed with alternative strategies.

Complications of Opiate Use Opiate side effects—such as nausea, respiratory depression, sedation, and euphoria/dysphoria—are common but will usually subside with time.⁵⁸ Constipation is an exception to this statement, and routine initiation of a bowel regimen is recommended when starting opiates.⁶³ While constipation would be a welcome respite for most IBD patients, it could be dangerous if patients are at risk for developing toxic megacolon. Narcotic bowel syndrome is another particularly worrisome complication of chronic opioid use. This syndrome is characterized by chronic abdominal pain of an unexplained nature or intensity that worsens with increasing doses of opiates.⁶⁴ This syndrome can precipitate a vicious cycle wherein the physician continually increases the dose of opiates in a self-defeating attempt to control the patient's pain.

Recent concerns about the safety of opiate use in IBD patients were raised by an analysis of data from the TREAT registry, a prospective, long-term registry of patients with Crohn's disease. In this registry, the use of opiates was found to be associated with increased mortality (OR, 1.84; $P=.044$), although this association was not significant when the analysis adjusted for other risk factors.⁶⁵ However, opiate use was a risk factor for serious infections (OR, 2.38; $P<.001$), even after adjusting for severity of disease and use of immunosuppressive agents.⁶⁵ The authors suggested that this finding may be due to opiates masking early signs and symptoms of infection. However, another possibility is that opiates have a direct effect on infection due to decreased gut motility and bacterial translocation through the damaged mucosa of the inflamed intestine.⁶⁶ There is also evidence for opiates having direct immunosuppressive effects that could predispose patients to infections.⁶⁷

Other major concerns when prescribing opiates are addiction and diversion. While no perfect solution to these problems exists, there are various means that physicians can use to help identify individuals who are at risk for opiate abuse.⁶⁸ The method we employ at our institution is the opioid risk tool.⁶⁹ This screening tool is easy to use and serves primarily as an indicator of when to adopt a more cautious approach and seek further assessments. In addition, tools that can track prescriptions of abused medications—like the Controlled Substance Utilization Review and Evaluation System, an online registry of Schedule II–IV prescriptions written in California—are invaluable resources for documenting patient behavior.

Patients deemed to be at high risk for abuse of chronic opiate therapy may warrant careful psychological evaluation and close monitoring by physicians. Patients who have the most difficulties with opioid therapy are often clinically depressed.⁷⁰ Most multidisciplinary pain

Table 3. Typical Features of Noncompliance with Opioid Therapy

- Unexpected results on toxicologic screening
- Frequent requests for dose increases
- Concurrent use of nonprescribed psychoactive substances
- Failure to follow the dosage schedule
- Failure to adhere to concurrently recommended treatments
- Frequently reported loss of prescriptions or medications
- Frequent visits to the emergency room for opioid therapy
- Missed follow-up visits
- Frequent extra appointments at the office or clinic
- Prescriptions obtained from a second provider
- Tampering with prescriptions

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medicine programs have access to psychologists who are trained to evaluate chronic pain patients. In addition, all clinicians should watch for worrisome signs in patients who are taking opiate medications; these signs are listed in Table 3. At the same time, clinicians must differentiate signs of addiction from symptoms and behaviors indicative of inadequate analgesia (“pseudoaddiction”) or pain anxiety. Consultation with a pain psychologist can be invaluable in this situation.

Antidepressants

Antidepressants are often recommended as an “adjuvant analgesic” to reduce the need for chronic opioid therapy.⁷¹ Much of the evidence for the use of antidepressants in IBD comes from studies of IBS. Two meta-analyses of trials that used predominately tricyclic antidepressants (TCAs) to treat IBS showed an overall benefit.^{72,73} While other studies have not been as favorable, TCAs are still considered to be a mainstay of therapy in IBS.^{74,75} Studies of selective serotonin reuptake inhibitors (SSRIs) in IBS have been less promising. Several studies have shown that SSRIs have no effect on abdominal pain in IBS patients, although a meta-analysis did show a reduced risk of overall symptoms compared to placebo (OR, 0.62; 95% CI, 0.45–0.87).⁷⁶⁻⁷⁹

There have been few studies of antidepressants in IBD. The only clinical trial to date was a nonrandomized, open-label study of paroxetine (Paxil, GlaxoSmithKline) that showed significant improvement in several components of QOL, although this study only included patients who had already been diagnosed with depression.¹⁵ A

recent review of 12 studies, most of which were case reports, also found improvements in patients with anxiety and depression.⁸⁰

There are interesting preliminary reports on the use of bupropion in IBD. Case reports involving a total of 6 patients with Crohn’s disease who were treated for smoking cessation or depression showed improvements in disease activity even when patients did not stop smoking.^{81,82} One possible mechanism for this effect could be attenuation of tumor necrosis factor α levels by bupropion via dopaminergic receptors.⁸³ Further research into this interesting finding is warranted.

Anticonvulsants

Anticonvulsants, predominately gabapentin and pregabalin (Lyrica, Pfizer), are often used to treat neuropathic pain, and more recently they have been used to treat visceral pain. Several small studies of these 2 medications have shown beneficial effects on visceral hypersensitivity in patients with IBS.^{84,85} Further clinical trials for visceral pain are needed.

Psychotherapy

Behavioral and/or cognitive psychotherapy can be an effective complementary therapy to help patients cope with pain that cannot be completely eradicated. Some form of psychotherapeutic intervention is routinely recommended when using chronic opioid therapy.⁶³ Cognitive behavioral therapy is one of the more common psychotherapeutic techniques used in this setting, with studies showing improvement in QOL and functioning in patients with IBS.^{74,86} Two meta-analyses have shown modest but significant benefits with cognitive behavioral therapy, especially in patients who have not responded to medical therapy.^{79,87}

While the days of psychotherapy as a primary treatment for IBD are long past, there is increasing physiologic and clinical evidence that stress can trigger flares.^{45,88,89} Psychotherapeutic interventions in IBD have produced modest improvements in anxiety, depression, and coping mechanisms; although these improvements occurred without an effect on disease activity, they did lead to a reduction in healthcare utilization.^{90,91}

Future Therapies

Transient Receptor Potential Vanilloid Receptor Subtype 1 Antagonists Transient receptor potential vanilloid receptor subtype 1 (TRPV1) is a membrane-bound ion channel found throughout the nervous system that has been implicated in acute and chronic pain states. It has been shown to contribute to visceral hypersensitivity and mechanosensitivity produced by inflammatory

mediators.⁹²⁻⁹⁵ Importantly, intestinal levels of TRPV1 expression have been shown to correlate with chronic pain in IBD.^{96,97} Compared to quiescent controls, IBD patients with IBS-like symptoms had a 5-fold increase in the number of TRPV1 fibers in mucosal biopsies.⁹⁸ Several TRPV1 antagonists are being evaluated as treatments for chronic pain, and early clinical studies have been promising.⁹⁹

Nerve Growth Factor Antagonists The increased expression of TRPV1 and subsequent visceral hypersensitivity are thought to be partly driven by increased nerve growth factor (NGF) signaling. NGF is a ligand to the tyrosine kinase A (TrkA) receptor located on

sensory neurons. Inflammation results in increased levels of NGF, which stimulates the TrkA receptor; TrkA stimulation leads, in turn, to an increase in inflammatory mediators and increased sensitivity to pain.^{100,101} NGF is upregulated in biopsies of patients with chronic visceral pain.^{97,102,103} A monoclonal antibody directed against NGF was shown to be effective in osteoarthritis, and clinical trials of NGF antagonists in visceral pain are ongoing.¹⁰⁴

Kappa Opioid Receptor Agonists Kappa opioid receptor agonists (KORAs) also show promise, as they appear to modulate visceral afferent function in both naïve and hypersensitive states.^{105,106} Asimadoline, a

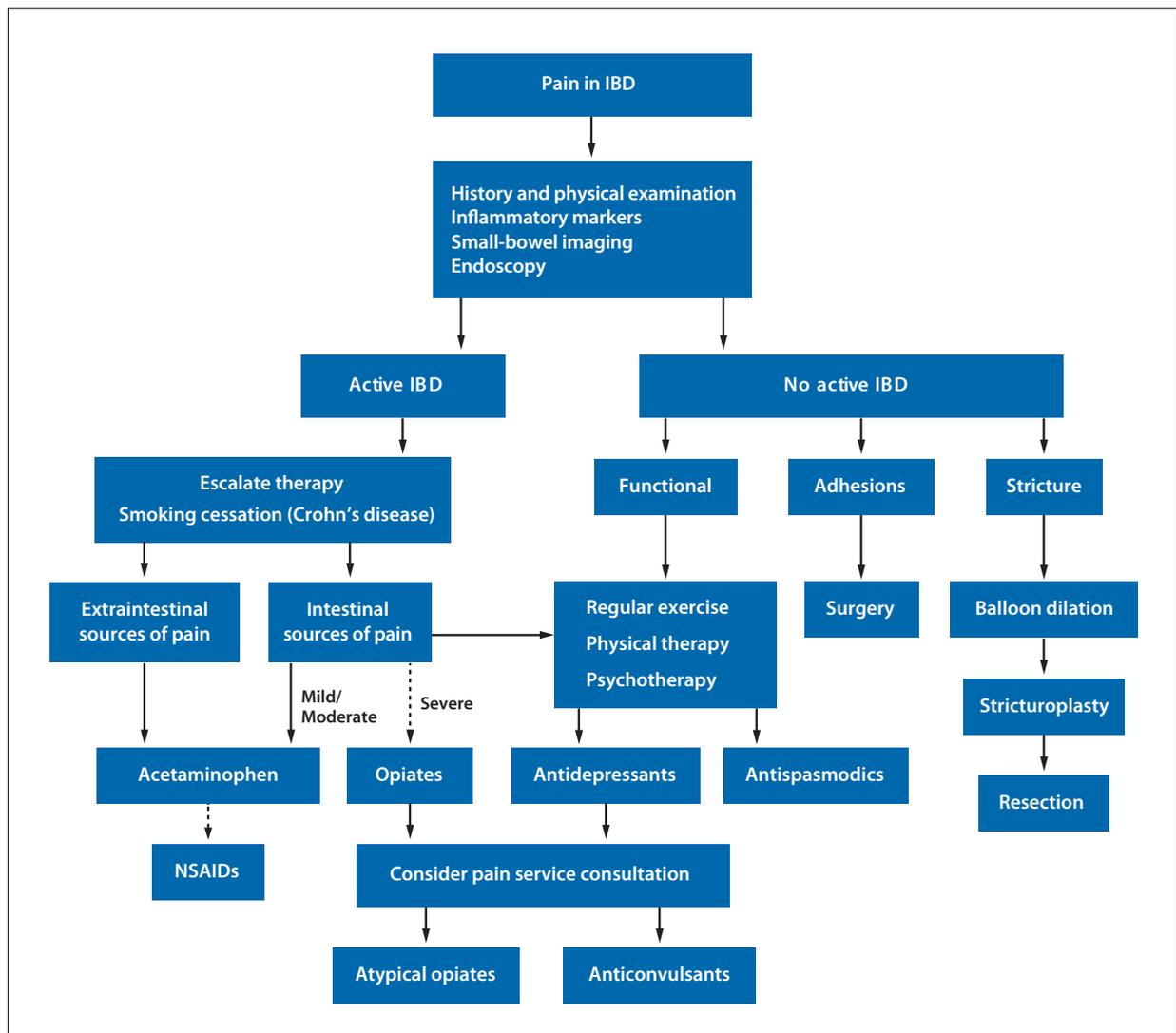


Figure 2. Treatment algorithm for pain in inflammatory bowel disease (IBD). The dashed arrows indicate that the drugs should be used with caution.

NSAIDs=nonsteroidal anti-inflammatory drugs.

peripherally restricted KORA, has been shown to reduce symptoms in IBS patients, but this agent is not yet commercially available.¹⁰⁷

Treatment Recommendations

Currently, there are no specific therapies for treating visceral pain. Consequently, we recommend a multidisciplinary approach similar to that used for patients with other chronic pain conditions. This approach involves a combination of noninvasive measures such as aerobic exercise, physical therapy, medications, and psychotherapy. This approach has been shown to be effective for chronic abdominal pain.¹⁰⁸ A suggested treatment algorithm is illustrated in Figure 2.

The first step in treating pain in IBD should always be to evaluate the patient for active disease. If escalation of IBD therapy does not relieve symptoms, then over-the-counter analgesics may be initiated. Care should be taken to rule out complications such as strictures or adhesions that will respond only to surgery. Given that anxiety and depression are frequent comorbidities of IBD, formal psychiatric evaluation and treatment can be helpful. The use of an antidepressant, especially a TCA, may help with pain even in the absence of a psychiatric diagnosis. Opiates should be used with caution in IBD patients, preferably for a well-defined interval such as during induction of remission or during the postoperative period. If opiates are used, patients should be given an opiate contract that clearly delineates all expectations and requirements, and a single physician should prescribe all pain medications.

Conclusion

Often, simply validating a patient's pain and offering support can go a long way toward relieving pain and anxiety. The relief of suffering is one of the most basic duties of a physician, and yet it is often one of the most challenging.¹⁰⁹ Understanding the causes of pain and knowing how to manage them are essential skills for all physicians who care for patients with IBD. This paper has explained the sources and mechanisms of pain in IBD and has provided a guide to treating pain safely and effectively. Hopefully, the paper will bring some relief of suffering to everyone involved in this often frustrating problem.

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