Pain Management in IBD

Madhusudan Grover, MD¹, and Douglas A Drossman, MD²

¹Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN; and ²UNC Center for Functional GI and Motility Disorders, University of North Carolina, Chapel Hill, NC, USA

Abdominal pain occurs in up to 70% of IBD patients during initial onset or acute flares [2]. It may be the only presenting complaint and a new onset or changing nature or intensity of pain may warrant further diagnostic investigations. The clinician needs to discern the origins of the pain and, as noted above, not all relate to disease inflammation or its consequences. For example, about 12% of individuals with inactive IBD were found to meet the Rome II criteria for functional abdominal pain syndrome (FAPS) [5]. In IBD, pain can arise from observable manifestations such as inflammation or obstruction, and also from altered motility, visceral hypersensitivity, and dysregulation of central nervous system (CNS)–enteric nervous system (ENS) control systems – all of which are not readily seen. When features of the latter predominate, this syndrome has been called “IBD–IBS” [3].
To understand where IBD–IBS fits into our clinical understanding of IBD, the first factor to consider is the epidemiological association: 10–15% of the population has IBS, so the same prevalence of IBS may be seen in patients with IBD [6,7]. However, since up to 42–62% of Crohn’s disease and 33% of ulcerative colitis (UC) patients in remission still have IBS symptoms [8,9], there need to be other considerations. A second feature is that merely having IBD even in remission may predispose to having IBS symptoms, and this appears to be related to the concept of post-infectious or post-inflammatory IBS (PI-IBS) [10]. In fact, IBS-like symptoms are 2–3 times more prevalent in IBD patients who are in remission than in a healthy population [8]. This PI-IBS can occur in clinical remission since microscopic inflammation may still upregulate visceral neurons leading to pain [11]. With PI-IBS, the visceral upregulation leading to pain and diarrhea is enabled by psychological distress or trauma (central sensitization) via CNS–enteric neural pathways [11,12]. Finally, the severity of symptoms – even in active IBD – does not always correlate with disease activity; patients may report symptoms out of proportion to the evident disease. Only 43% of patients with symptoms of pouchitis after ileal pouch-anal anastomosis for UC are actually diagnosed to have evidence of active inflammation of the pouch and this has been called “irritable pouch syndrome” [13]. Thus, the discerning clinician must consider the degree to which the various factors discussed contribute to symptoms, and this will lead to more directed treatment.

**Pathogenesis of IBD–IBS**

As conceptualized in Figure 1, possible associations relating inflammation, psychosocial distress, and physiological dysfunction can be responsible for IBS and pain symptoms. Firstly, an acute enteric infection will lead to mucosal inflammation and dysmotility (either directly or via inflammatory effects). This mucosal inflammation or dysmotility, or both, may lead to visceral hypersensitivity. The IBS pain like symptoms may result from visceral hypersensitivity in the gut and dysmotility. Psychosocial factors have an overarching effect on symptom development. This may occur through putative effects on mucosal inflammation (and inflammation may have reciprocal effects on psychological state via activation of peripheral or central cytokines, or both) through central influences on peripheral visceral sensitization or dysmotility (via descending corticofugal systems), or by direct effects on these symptoms via CNS modulation of incoming afferent input. These mechanisms are further elaborated in the section below.

**Abnormal motility**

Colonic inflammation can affect motility. In UC, inflammation reduces the basal contractile activity in the distal colon [14] and alters the colonic motor response to meals and to stimulation [15]. With Crohn’s disease, there is increased small-intestinal motility that occurs beyond the period of active disease [16] and after stimulation with carbachol [17], which may explain the greater reports of diarrhea in Crohn’s disease.

**Pain and visceral hypersensitivity**

Unlike acute pain, chronic pain is multidimensional with sensory, emotional, and cognitive contributions to the experience, and this relates to abnormalities in neurophysiological functioning at peripheral, spinal, and supraspinal levels [18]. Furthermore, with chronic pain, increased afferent visceral stimuli do not contribute as much as CNS upregulation of incoming visceral afferent signals, which can bring even regulatory (normally subliminal) signals to a point of conscious awareness and distress. The pathophysiology of chronic pain can be best understood in terms of following mechanisms:

- Ascending visceral pain transmission.
- Peripheral amplification of visceral afferent signals.
- Descending modulation of pain.
- Central amplification and the role of psychological distress.

**Ascending visceral pain transmission**

Figure 2 depicts the principal visceral (colonic) afferent pathways projecting to the spinal cord and then ascending to the thalamus and midbrain. These are the spinothalamic, spinoreticular, and spinomesencephalic tracts. The spinothalamic tract terminates in the medial and posterior thalamus from where thalamocortical fibers project to the primary somatosensory cortex. This pathway regulates sensory input arising from the periphery to the primary somatosensory cortex, and is thus involved in the perception of visceral pain.
discrimination and localization of visceral and somatic stimuli. The spinoreticular tract conducts sensory information from the spinal cord to the reticular formation in the brainstem, the latter associated with the reflexive, affective, and motivational properties of noxious stimulation. The reticulothalamic tract projects from the dorsal and caudal medullary reticular formation (dorsal reticular nucleus [DRN]) to the medial thalamus. Thalamocortical projections from the medial thalamus transmit sensory input to different areas of the brain, such as the cingulate cortex and insula that are involved with the processing of noxious visceral and somatic information. The brain regions innervated by these pathways that are activated in response to painful colorectal stimuli include the thalamus, anterior insula, amygdala, and anterior cingulate cortex (ACC). The latter region is comprised of two components, perigenual ACC and midcingulate cortex, with the former involved in affect and the latter in behavioral response modification.

This multicomponent integration of nociceptive information explains the variability in the experience and reporting of pain [19]. This conceptual scheme of pain modulation through both sensory and motivational-affective components has been demonstrated through positron emission tomography (PET) imaging [20]. Healthy subjects immersed their hands in hot water, and half were hypnotized to experience pain while the other half a non-painful or pleasant sensation. There was no difference in activity in the somatosensory cortex. However, subjects hypnotized to experience immersion as painful had significantly greater activation of the ACC. Thus, the hypnotic suggestion differentiated the functioning of these two pain systems and the suggestion of unpleasantness specifically encoded the anterior midcingulate portion of the ACC, an area involved with negative perceptions of fear and unpleasantness.

Peripheral amplification of visceral afferent signals

In addition to the abnormalities in central upregulation of afferent signals as seen with chronic pain, amplified signals from visceral inflammation and injury also occur in IBD as well as in IBS [3,21]. This can be either from increased peripheral receptor sensitivity or increased excitability of spinal or from higher CNS pain regulatory systems [22]. Frequent or recurrent pain episodes or painful procedures can later become generalized to a chronic and persistent symptom presentation, and this has been shown with persistent abdominal (e.g. IBS) pain developing after gynecological operations [23,24]. Again, psychological predisposition, such as anxieties about the outcome of the procedure or a poor coping style, contributes to the development of the postoperative pain and neuroticism; indeed, one’s vulnerability to stress has been associated with perpetuation of pain after cholecystectomy [25]. However, pre-operative treatment with local or regional anesthesia or nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce the severity of postoperative pain [22]. This suggests that the CNS response to peripheral injury can be reduced by prior reduction of afferent input to the spinal cord and CNS prior to sensitization. Therefore, recurrent peripheral injury, such as repeated abdominal operations in the psychologically predisposed host, might sensitize intestinal receptors, making perception of even baseline (regulatory) afferent activity more painful.

Thus, with PI-IBS or IBD–IBS there can be an inflammation-induced altered mucosal immune system (involving increased cytokine- and serotonin-producing enterochromaffin cells) sensitizing the visceral afferent nerves [26]. With IBD, increased neuronal excitability and release of mucosal neurotransmitters such as serotonin contributes to the peripheral sensitization observed during visceral inflammation even when patients are in clinical remission with their IBD [27]. Furthermore, patients with Crohn’s disease in remission who experience IBS-like symptoms have persistently increased levels of colonic tryptophan hydroxylase (a serotonin precursor) when compared with Crohn’s disease patients in remission without these symptoms [28]. In addition, the pain amplification is enabled by some degree of central emotional distress that amplifies the afferent signal to a point of conscious awareness via CNS...
influences on peripheral inflammatory/cytokine activity [12], as well as centrally via cingulate activation, as discussed above.

**Descending modulation of pain**

To understand how emotional distress can downregulate incoming visceral signals, it is necessary to readdress the fundamental concept of brain–gut regulation of pain via the gate-control theory and the descending modulation of painful stimuli [29]. **Figure 3** shows this central descending inhibitory system, believed to originate in the opioid-rich ACC and possibly also from other cortical regions. It is postulated that activation of this region by peripheral/visceral afferent activity might, in part, serve to downregulate these signals. Descending connections from the ACC and the amygdala to pontomedullary networks, including the periaqueductal gray, rostral ventral medulla, and the raphe nuclei, activate inhibitory pathways via opioidergic, serotonergic, and noradrenergic systems to the dorsal horn of the spinal cord, which acts like a “gate” to increase or decrease the projection of afferent impulses arising from peripheral nociceptive sites to the CNS [19].

**Central amplification and the role of psychological distress**

As noted above, while peripheral sensitization might influence the onset and short-term continuation of pain, the CNS is preeminent in the predisposition and perpetuation of chronic pain. Comorbid psychiatric diagnosis, major life stress, a history of sexual or physical abuse, poor social support, and maladaptive coping are associated with more severe and chronic abdominal pain and poorer health outcome [30]. Early-life stress in genetically predisposed individuals may lead to a permanently enhanced stress responsiveness, which in turn can result in alterations in stress-induced pain modulation systems. The links between emotional distress and chronic pain might be mediated through impairment in the limbic system’s ability to modulate visceral signals. Recent studies suggest that the motivational-affective component of the limbic or medial pain system, specifically the ACC, is dysfunctional in IBS and other chronic painful conditions [31]. In response to a painful stimulus, there is differential activation of the perigenual ACC, an area rich in opioids associated with emotional encoding, and the posterior ACC, also called the rostral midcingulate cortex. The latter is an area associated with unpleasantness, fear (along with the amygdala), and motor pain behavior. When using PET and functional magnetic resonance imaging (fMRI) to evaluate the ACC response to rectal distention or the anticipation of distention, IBS patients preferentially activate the midcingulate cortex and have less activation of the perigenual ACC relative to control subjects [32,33]. It is possible that, in IBS, activation of the descending inhibitory pain pathway originating in the opioid-rich perigenual ACC is supplanted by activation of the midcingulate cortex, the area associated with fear and unpleasantness. In addition, there is a strong correlation between life stress and maladaptive coping with ACC activation. Notably, antidepressant and psychological treatments are associated with a return of the dysfunctional ACC reactivity to a more normal state [34,35]. This finding also occurs in patients with depression [36]. These data suggest that emotional disturbances might aggravate the dysfunctional central pain regulatory pathways seen in chronic pain. These findings, which have not yet been investigated in IBD, are compelling and provide a mechanistic basis for understanding the central amplification of pain and the value of psychological and antidepressant treatments.

**Psychological factors in IBD**

The role for psychological factors in IBD is complex. Traditionally, physicians believe that stress contributes to the exacerbation of IBD but not to the etiology [37] and psychosocial factors affect illness behaviors such as physician visits independent of disease activity [38]. However, this thinking may be changing, as discussed below [37,39].

There is good evidence that stress affects symptom exacerbation. Higher scores for longstanding stress were shown to triple the risk of UC exacerbation over a subsequent 8–month period [37,40]. There is a significant correlation between depression [41] and psychological stress [42] leading to relapses of colitis [43]. The presence of IBS-like symptoms in patients...
with IBD can be predicted by the degree of anxiety, depression, and general well-being [44]. Depression and anxiety can also precede the onset of IBD. Patients with Crohn’s disease have been shown to have greater psychological disturbances than those with UC [45]. As the biological mechanisms resulting from psychological stress are evolving, stress is becoming a more or less accepted risk factor in IBD.

“Peripheral sensitization may influence the onset and short-term continuation of pain, while the CNS is preeminently involved in the predisposition and perpetuation of chronic pain”

Psychological factors influence outcomes both in terms of disease flare and the experience of the illness. Patients with IBD have reported reduced health-related QoL (HRQoL) and the level of psychological distress in these individuals was found to be comparable to that of age-matched patients with IBS [46]. Notably, 74% of IBD patients believe that their psychological state contributes to the course of their disease [47]. Co-morbid psychiatric diagnoses occurring with IBD are associated with lower HRQoL and more frequent relapses and poorer health status than for IBD patients without such co-morbidity, given similar inflammatory activity [41,48]. In one survey of 1000 patients with IBD, psychosocial difficulties were associated with a higher frequency of physician visits, whereas disease activity and symptoms ratings were not [38]. The greatest concerns reported by these patients were related to uncertain nature of illness, effects of medication, energy level, surgery, and developing cancer. Female gender, younger age, less education, greater disease activity, poor daily function, and poor global well-being and health were all related to having more concerns [38].

### Narcotic use in IBD

In recent times there has been growing use of narcotics in IBD; in fact, up to one-sixth of IBD patients are chronically treated with opioids [49]. Inability to prescribe NSAIDs and lack of other evidence-based options for managing chronic pain in IBD is strongly influencing physician behavior towards prescribing narcotics. However, there is no evidence for their benefit in IBD or any other chronic, non-malignant disorder, and chronic use puts patients at risk for adverse effects. In a study of 6000 Crohn’s disease patients, the use of chronic narcotics was an independent predictor for developing serious complications of active disease (e.g. obstruction or abscess), and over time, opioids can paradoxically increase pain. Table 1 lists diagnostic criteria for NBS [51]. The increased pain leads to the cycle of prescribing escalating dosages in a maladaptive effort to achieve adequate relief. Its prevalence may be increasing due to changes in healthcare practices that lead to increased opioid prescriptions for chronic, non-malignant pain, and the development of maladaptive therapeutic interactions around the use of narcotics. Recently, several physiological mechanisms have emerged to help explain the paradoxical hyperalgesia [52]:

- Activation of excitatory anti-analgesic pathways within a bimodal opioid regulatory system.
- Descending facilitation of pain at the rostral ventral medulla, and pain facilitation via endogenous dynorphin and cholecystokinin activation.
- Narcotic-induced glial cell activation that leads to cytokine release and inflammatory effects that upregulate signaling in the dorsal horn.

In an analysis of an Australian database, about 5% of Crohn’s disease patients without demonstrable organic pathology were chronic narcotic users and there was a 67% prevalence of psychiatric disorders, which was significantly higher than that for matched IBD controls not on narcotics [53]. Chronic abdominal pain was the major reason for narcotic use in this population. Narcotic use in IBD patients has been associated with female gender, more than two previous surgeries; moderate-to-severe pain; clinical disease activity; depression; anxiety; sexual, emotional, and physical abuse; and substance abuse [54]. Early recognition and treatment programs for chronic opioid use and associated psychosocial illnesses are likely to improve clinical outcome.

### Pain management strategies

For patients with IBD having chronic pain, it is important to gauge treatment based on both central and peripheral contributions: when to treat to reduce inflammation or the complications of active disease (e.g. obstruction or abscess), and when to reduce the central amplification of pain.

---

**Table 1. Diagnostic criteria for narcotic bowel syndrome [51].**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic or frequently recurring abdominal pain</td>
<td>that is treated with acute high-dose or chronic narcotics and in which all of the following occur:</td>
</tr>
<tr>
<td>• The pain worsens or incompletely resolves with continued/OR escalating dosages of narcotics.</td>
<td></td>
</tr>
<tr>
<td>• There is marked worsening of pain when the narcotic dose wanes and improvement when narcotics are reinstated (“soar and crash”).</td>
<td></td>
</tr>
<tr>
<td>• There is a progression of the frequency, duration, and intensity of pain episodes.</td>
<td></td>
</tr>
<tr>
<td>• The nature and intensity of the pain is not explained by a current or previous gastrointestinal diagnosis.</td>
<td></td>
</tr>
</tbody>
</table>

---

**LEADING ARTICLE**

PAIN MANAGEMENT IN IBD
associated with psychosocial factors using antidepressants and behavioral treatments. While a new onset or changing nature of abdominal pain in IBD can be a sign of a worsening inflammatory process or a complication, chronic pain in the absence of other warning symptoms is unlikely to be related to worsening IBD. Ordering a computed tomography scan or an endoscopy in such a patient is unlikely to be of value and may reinforce the concept of “something being missed” when appropriate management would include reassurance and attention to symptom adaptation or amelioration via ancillary pain treatment strategies, as discussed below. A list of chronic pain management strategies in IBD is shown in Table 2.

**Physician–patient relationship**

The cornerstone of management relies on an effective physician–patient relationship. Clinicians may feel challenged, frustrated, or even angry when caring for patients with chronic and painful disorders. The explanation for the symptoms may seem uncertain, and some physicians feel less capable than when treating an objectively measurable disease process. Thus, it is important for the treating physician to: firstly, understand that chronic pain symptoms do not necessarily require further studies unless “red flags” (e.g. fever or high white cell count) are noted; secondly, recognize the chronicity of IBD and reduce expectations for cure or rapid recovery; and thirdly, understand that their role is to provide support, guidance, and hope while facilitating the patient’s acceptance of this as a chronic disorder that requires shared responsibility for the management. This approach improves patient satisfaction, adherence to treatment, and clinical outcome, and also reduces litigation [55].

Table 3 lists some features that lead to a more effective physician–patient relationship when caring for chronic painful symptoms in an IBD patient.

**Narcotic withdrawal**

If NBS is present (see criteria in Table 1), the narcotics must first be discontinued [51]. This can usually occur on an outpatient basis, although inpatient withdrawal may be considered if the narcotic usage is high and there are secondary effects such as ileus, pseudo-obstruction, or electrolyte imbalances, or if there is limited patient motivation or family support. A general guideline is to start a tricyclic antidepressant (TCA) or serotonin–norepinephrine reuptake inhibitor (SNRI) at least several days before withdrawal begins. In addition, clonidine, an α₂-adrenergic receptor agonist that blocks the physiological effects of narcotic withdrawal, can be used. Combination of partial opioid agonist/antagonist (buprenorphine) and antagonist (naloxone) can also be used for induction and maintenance of opioid withdrawal. A detailed protocol for detoxification from opioids for NBS is described elsewhere [51].

**Antidepressants**

Antidepressants can be used for the management of chronic pain in IBD. In one study, 78% of gastroenterologists had treated IBD patients with antidepressants for pain, depression and/or anxiety, and insomnia [56]. The rationale for using antidepressants in low doses relates to reducing afferent signals from the gut, or to modulating bowel symptoms. Higher dosages are used to treat psychiatric comorbidities that can aggravate the pain. Brain imaging studies indicate that antidepressants may play a role in downregulating afferent visceral signals [55].

“Chronic pain management relies on an effective physician–patient relationship”

The emerging concept of neuroplasticity with loss of cortical neurons in psychiatric trauma, and neurogenesis (i.e. regrowth of neurons) with clinical treatment, provides the rationalization for the use of central treatments [57]. With post-traumatic stress disorders (PTSD) there is neuronal death in key areas, for example in the dental ganglion of the hippocampus after severe emotional trauma such as sexual abuse or war trauma [58]. Furthermore, recent fMRI studies now show reduced neuron density in other areas of the brain including cortical regions involved in emotional and pain regulation [59]. Notably, recent data suggests that antidepressant (and possibly psychological) treatments may restore lost neurons. Levels of brain-derived neurotrophic factor (BDNF), a precursor of neurogenesis, increase with antidepressant treatment and correlate with longer periods of treatment and with the degree of recovery from depression [60]. Furthermore, the longer the patients are treated with antidepressants, the lower is the frequency of relapse or recurrence of the depression [61]. These findings provide insight into how the CNS functions in response to emotional trauma and its associations with chronic visceral and somatic pain, and their treatments. Similar to hippocampal cell loss in PTSD, there is reduced cortical density in the anterior cingulate and prefrontal cortex and thalamus – regions that interface between emotion and pain regulation – in patients with severe depression or chronic pain [59]. These recent data on the effect on neuronal growth regulation in key areas of the central pain matrix provide...
new and important opportunities for research and patient care using antidepressants for treatment of chronic pain for FGIDs and other medical diseases including IBD.

The TCAs (e.g. desipramine, nortriptyline, and amitriptyline) and the new SNRIs (duloxetine, venlafaxine, and desvenlafaxine) are of particular value in treating chronic pain syndromes owing to their combined noradrenergic and serotonergic effects [62]. These agents have generally been more successful than selective serotonin reuptake inhibitors (SSRIs), the latter being more useful for treating associated psychiatric comorbidities such as anxiety, depression, and obsessional symptoms, as well as targeting global symptoms and coping rather than pain. Low doses of SNRIs (desipramine 25–75 mg at night or duloxetine 30 mg in the daytime) can be initiated and increased to full dosages if needed, particularly when depression is also present, and continued for 6–12 months or longer if needed.

“The rationale for using antidepressants in low doses in IBD relates to reducing afferent signals from the gut, or to modulating bowel symptoms”

It usually helps to use diagrams or to otherwise explain to the patient the physiological basis for treatment, which is to facilitate descending inhibitory pathways that block afferent visceral conduction. The physician also needs to clarify that these are “central analgesics” and not simply drugs for psychiatric conditions: they have independent effects on pain and can be used in lower dosages than those used to treat major depression. In addition, these medications are not “mind altering”, nor are they addictive, and they can be stopped without major withdrawal effects if necessary. Adherence can be enhanced by actively engaging with patients, to be available and address any side effects when they occur [62]. The side effects are dose-related. For the TCAs, consider sedation, constipation, dry mouth/eyes, weight gain, and sexual dysfunction. For the SSRIs, the effects relate to higher serotonin levels and include insomnia, agitation, sexual dysfunction, diarrhea, and diaphoresis. The SNRIs are more likely to produce nausea and, in rare cases, liver dysfunction and may be taken with a meal in divided dosages. Our studies have shown no relationship of dosage level for TCAs with clinical benefit [63], and interestingly, the “side effects” commonly reported after beginning treatment relate more to concurrent anxiety than to true side effects of the medication itself [64]. We also select medications based on the associated symptoms: a TCA when there is diarrhea, an SSRI with constipation, or mirtazepine with nausea. It is also important to understand the value of mental health referral in optimizing treatment when high doses or multiple psychotropic agents are used. Table 4 lists the potential benefits of psychopharmacological treatments in targeting FGIDs, which may be extrapolated to targeting chronic painful FAPS and IBS in IBD patients. A detailed review on the use of antidepressants and behavioral treatments for functional symptoms can be found elsewhere [65].

**Augmentation strategies**

Augmentation strategies can be useful for patients with refractory pain symptoms that are not responsive to single antidepressants.

### Table 3. Guidelines to enhance the physician–patient relationship.

| **Listen actively:** | • Focus on the patient’s world, i.e. “sit where the patient sits”.
|                     | • Allow the patient to tell his/her story without interruption.
|                     | • Seek to understand the symptom experience within a biopsychosocial context.
| **Identify and respond to the patient’s concerns and expectations:** | • What do you think is going on?
|                     | • What are your worries and concerns?
|                     | • What are your expectations from me?
| **Validate the patient and illness:** | • Acknowledge the pain.
|                     | • Acknowledge the impact of the illness.
|                     | • Provide a physiological explanation for the symptoms.
| **Set realistic and consistent limits when ordering of tests:** | • “Don’t just do something, stand there”.
|                     | • Order tests based on objective data rather than pain severity.
| **Psychosocial assessment:** | • Why is the patient coming now?
|                     | • Is there a history of traumatic life events?
|                     | • What is the impact of the pain on quality of life?
|                     | • What is the role of family or culture?
|                     | • What are the patient’s psychosocial resources?
| **Help the patient take on responsibility for the care:** | • Involve patient in treatment options.
|                     | • “How are you managing with your pain?” rather than “how is your pain?”
| **Provide some continuity of care (along with primary care provider):** |  |

### Table 4. Potential benefits for the use of psychopharmacological agents in functional gastrointestinal disorders.

| **Central effects:** | 1. Alters central pain perception: analgesia or antihyperalgesia.
|                     | 2. Therapeutic effects on mood: to manage general anxiety, hypervigilance, symptom-related anxiety, agoraphobia, and increased stress responsiveness.
|                     | 3. Treatment of associated psychiatric disorders: depression, post-traumatic stress disorder, or somatization.
|                     | 4. Treatment of associated sleep disturbances.
| **Peripheral effects:** | 1. Peripheral analgesic effects: alters visceral afferent signaling.
|                     | 2. Gastrointestinal physiology (motility and secretion): effects on cholinergic, noradrenergic, and serotonergic pathways.
|                     | 3. Smooth muscle effects on viscera: e.g. gastric fundic relaxation.

---

**Table 4**
or other treatments. Most gastroenterologists are not familiar with this method of treatment but since such strategies are commonly used in psychiatry, a psychiatric consultation to plan treatment is recommended. Thus, patients who are refractory to usual dosages of antidepressants or are experiencing side effects should be offered additional psychotropic medication to augment the clinical effect, since they act on different neuroreceptors. Buspirone, a non-benzodiazepine azapirone that has anti-anxiety properties, may enhance the analgesic effect of antidepressants and its visceral inhibitory effect can relieve postprandial early satiety or fullness [66]. This combination has shown benefit in our clinic, but well-designed studies are needed to prove efficacy. Recently, we have used a low dose of an atypical antipsychotic agent (e.g. quetiapine 25–100 mg) that acts on dopamine receptors for augmenting the antidepressant treatment in our patients with chronic pain syndromes [67]. This class of agents has anti-anxiety and sleep benefits, and may also have independent analgesic effects. Preliminary data from our clinic shows that about 50% of patients with chronic and severe FAPS who previously failed on antidepressants and who are prescribed quetiapine with an antidepressant stay on the antidepressant, and most of those that do achieve some benefit.

Additional medications
Gabapentin and pregabalin are increasingly being prescribed for chronic neuropathic pain conditions including peripheral neuropathies, and more recently for fibromyalgia. Their benefit in visceral or central pain syndromes are not established, although a few case reports have suggested benefit for visceral pain. Long-term treatment with benzodiazepines is not recommended because of their abuse potential and their tendency to interact with other medications.

Psychological treatment
There has been increasing interest in the use of psychological treatment such as hypnosis [68–70] and cognitive behavioral therapy (CBT) [71] for IBD; however, the evidence has been mixed [72]. Such treatments have shown benefit in IBS and other FGIDs.

- CBT identifies maladaptive thoughts, perceptions, and behaviors, and is used to develop new ways to increase symptom control.
- Stress management attempts to counteract the physiological effects of stress or anxiety.
- Hypnosis and dynamic (interpersonal) psychotherapy have been used primarily for IBS but additionally may have theoretical benefit for IBD, since the effects relate to facilitating descending inhibition of afferent pain signals. There is some evidence that hypnosis may be of benefit via modulation of cellular immune dysregulation during acute stress [73].

Based on the literature in IBS, these treatments may not improve the pain as much as the patient’s adaptation to the pain and enhancement of coping strategies (“the pain is still there but it doesn’t bother me as much”). Furthermore, these treatments can show up to 70% overall satisfaction with treatment (on a treatment satisfaction questionnaire; compared with a 38% response to the educational control condition) and, importantly, their effects are additive to other medical treatments, the benefit continues after the treatment period ends, there are no medical side effects [74], and treatment may reduce healthcare costs [75]. Critical to implementing psychological treatment is that the referring physician must help the patient accept the value of these treatments as part of their ongoing plan of care.

Conclusion
Pain in IBD can be related to worsening inflammation and its complications. However, chronic pain is more likely secondary to abnormalities in the neurophysiological functioning at peripheral, spinal, and supraspinal levels. The IBD process should be understood in terms of a biopsychosocial construct, and patients seeking care for pain should expect to be offered a comprehensive evaluation. Critical decision-making regarding when to manage inflammation with anti-inflammatory/ immunomodulatory treatments and when to target central processes with psychotropics/behavioral treatments is required. Ultimately, the goal should be to understand and treat pain in a multicomponent strategy, which will likely improve both patient and physician satisfaction.

You can submit comments and questions on this article at:
www.ibdmonitor.com

Disclosures
The authors have no relevant financial interests to disclose.

References
39. Drossman DA. Presidential address: gastrointestinal illness and the biopsychosocial


35. Morgan V, Pickens D, Gautam S et al. Amitriptyline reduces rectal pain related activation of


33. Naliboff BD, Derbyshire SW, Munakata J et al. Cerebral activation in patients with irritable


24. Longstreth GF, Preskill DB, Youkeles L. Irritable bowel syndrome in women having

19. Snape WJ Jr, Williams R, Hyman PE. Defect in colonic smooth muscle contraction in

8. Simren M, Axelson J, Gillberg R et al. Quality of life in inflammatory bowel disease in

7. Minderaa BA, Oldenburg B, Wissemaer JA et al. IBS-like symptoms in patients with

6. Hakanson HA, Schlitt CD, Riddle MS. Postinfectious irritative bowel syndrome — a meta-


4. Snapsi W, Jr., Yama S, Hyman PE. Deficit in colonic smooth muscle contraction in patients with

3. Casey K. Match and mismatch: identifying the neuronal determinants of pain. Ann Intern


Langstruth GF, Peddi KB, Youkels L. Irritable bowel syndrome in women having
diagnostic laparoscopy or hysterectomy. Relation to gynecological features and outcome.

Jessa R, Jess T, Beck H et al. Neurocriticism in relation to recovery and persisting pain after


Minderhaa JD, Smout AJ, Oldenburg B et al. A pilot study on chemoceptive duodenal

Minderhaa JD, Oldenburg B, Schipper ME et al. Serotonin synthesis and uptake in symptomatic patients with

Sperber AD, Morris CB, Grenmelt G et al. Development of abdominal pain and IBS following

Langstruth GF, Peddi KB, Youkels L. Irritable bowel syndrome in women having
diagnostic laparoscopy or hysterectomy. Relation to gynecological features and outcome.

Jessa R, Jess T, Beck H et al. Neurocriticism in relation to recovery and persisting pain after


Minderhaa JD, Smout AJ, Oldenburg B et al. A pilot study on chemoceptive duodenal

Minderhaa JD, Oldenburg B, Schipper ME et al. Serotonin synthesis and uptake in symptomatic patients with

Sperber AD, Morris CB, Grenmelt G et al. Development of abdominal pain and IBS following

Langstruth GF, Peddi KB, Youkels L. Irritable bowel syndrome in women having
diagnostic laparoscopy or hysterectomy. Relation to gynecological features and outcome.

Jessa R, Jess T, Beck H et al. Neurocriticism in relation to recovery and persisting pain after


Minderhaa JD, Smout AJ, Oldenburg B et al. A pilot study on chemoceptive duodenal

Minderhaa JD, Oldenburg B, Schipper ME et al. Serotonin synthesis and uptake in symptomatic patients with

Sperber AD, Morris CB, Grenmelt G et al. Development of abdominal pain and IBS following

Langstruth GF, Peddi KB, Youkels L. Irritable bowel syndrome in women having

Jessa R, Jess T, Beck H et al. Neurocriticism in relation to recovery and persisting pain after


Minderhaa JD, Smout AJ, Oldenburg B et al. A pilot study on chemoceptive duodenal

Minderhaa JD, Oldenburg B, Schipper ME et al. Serotonin synthesis and uptake in symptomatic patients with

Sperber AD, Morris CB, Grenmelt G et al. Development of abdominal pain and IBS following

Langstruth GF, Peddi KB, Youkels L. Irritable bowel syndrome in women having

Jessa R, Jess T, Beck H et al. Neurocriticism in relation to recovery and persisting pain after


Minderhaa JD, Smout AJ, Oldenburg B et al. A pilot study on chemoceptive duodenal

Minderhaa JD, Oldenburg B, Schipper ME et al. Serotonin synthesis and uptake in symptomatic patients with

Sperber AD, Morris CB, Grenmelt G et al. Development of abdominal pain and IBS following

Langstruth GF, Peddi KB, Youkels L. Irritable bowel syndrome in women having

Jessa R, Jess T, Beck H et al. Neurocriticism in relation to recovery and persisting pain after


Minderhaa JD, Smout AJ, Oldenburg B et al. A pilot study on chemoceptive duodenal

Minderhaa JD, Oldenburg B, Schipper ME et al. Serotonin synthesis and uptake in symptomatic patients with

Sperber AD, Morris CB, Grenmelt G et al. Development of abdominal pain and IBS following


