ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

Pain Management in Patients With Inflammatory Bowel Disease

Eva Szigethy, MD, PhD
Professor of Psychiatry, Pediatrics, and Medicine
Director, Visceral Inflammation and Pain Center
Division of Gastroenterology
University of Pittsburgh School of Medicine
Pittsburgh, Pennsylvania

G&H How prevalent are acute and chronic pain in patients with inflammatory bowel disease?

ES Acute pain, such as abdominal distress in the context of an inflammatory flare, is very common; up to 80% of inflammatory bowel disease (IBD) patients will have some type of acute pain that resolves with appropriate treatment of the underlying inflammatory condition. Acute pain may also result from obstruction, such as when the patient has anatomic strictures.

Chronic pain is defined as pain that occurs consistently for 3 months or intermittently for 6 months. In IBD patients, chronic pain can persist in the relative absence of inflammation from IBD. In most studies, a range of 30% to 50% of IBD patients experience chronic pain.

The relatively wide margin of chronic pain is partly due to lack of agreement on how pain should be measured. Currently, there are numerous validated pain scales that measure pain severity and quality or other pain-related attributes, such as suffering or related disability, that are not specific to abdominal pain. The pain score will vary depending upon which scale is used and over the period of time being probed.

G&H Which are the most commonly used pain scales for IBD patients?

ES Some of the most commonly used pain scales for IBD patients were actually developed for irritable bowel syndrome (IBS). These scales ask about abdominal pain in the context of changes in bowel motility and stool consistency in terms of how watery or constipated it is (eg, the IBS Symptom Severity Scale).

In addition, the Brief Pain Inventory, which measures 2 dimensions of pain (severity and frequency), is commonly used but has not been validated for abdominal pain. The Visceral Sensitivity Index has been validated for measuring the severity of pain in IBS. The McGill Pain Questionnaire is also not specific for abdominal pain but provides information about pain intensity and also a qualitative description of the pain (eg, burning vs stabbing).

General pain intensity scales, such as the Visual Analog Scale or Numeric Rating Scale, are also common. Such measures rate pain on a scale of 0 to 10 either by drawing a notch on a 10-mm line or circling a number. Scales for children use faces instead of numbers, with 0 being represented by a smiley face and 10 being a crying face.

Pain management may also require the use of disability scales, such as the Sickness Impact Profile questionnaire and the Pain Disability Index, and, increasingly, scales that measure catastrophizing, such as the Pain Catastrophizing Scale. The latter group of scales measures the cognitive flexibility of the patient, which relates to how much the patient interprets pain in an even more negative way. The National Institutes of Health's PROMIS (Patient-Reported Outcomes Measurement Information System) instruments include

multiple validated and short self-report questionnaires available online that probe pain across several of these domains.

G&H What risk factors are associated with worse pain in patients with IBD?

ES Risk factors include the presence of an anxiety disorder or depression at the time of the pain and extreme ongoing or past stress (often in the form of trauma or adversity). There is a growing understanding that being diagnosed with IBD and undergoing the associated procedures, such as invasive colonoscopies and intestinal resections, can be perceived as traumatizing in certain patients, and such traumatic cognitive perceptions can be linked to worse pain.

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In addition, research is starting to look at the microbiome and whether the bacterial makeup in the gut influences the degree or severity of the patient's pain.

Finally, each time a patient has an inflammatory episode of IBD, nerve endings in the gut (anywhere in the gastrointestinal tract for Crohn's disease and in the colon for ulcerative colitis) are exposed to potentially noxious agents. This can result in visceral hyperalgesia at the level of the nerve endings, which can become and stay sensitized even when the inflammation is gone.

G&H Are there any other sources of pain in IBD patients?

ES Another important source of pain in IBD patients is joint pain. Many patients may have a functional component to their pain. Patients may have ongoing joint pain even when the inflammation is gone.

Pain in IBD patients may also be associated with other pain syndromes. Patients who have ongoing pain related to their IBD, especially when it is not active, and have conditions such as fibromyalgia or chronic headaches are often more refractory to treatment. These patients are thought to have a central pain syndrome, which means that their brain is interpreting the pain signal and exaggerating it.

G&H How can acute pain be treated in IBD patients?

ES The source of the pain needs to be treated. For example, if the source is a stricture or fistula, the pain may be relieved by a surgical procedure. If the source is a motility issue such as severe constipation or obstruction, that problem would need to be taken care of. In addition, active inflammation would need to be treated in all cases.

G&H How effective are antidepressants for treating chronic pain in IBD patients?

ES Various antidepressants have been studied for the treatment of chronic pain, especially in the relative absence of active inflammation, although most of these studies have been conducted in patients with IBS, not IBD. Selective serotonin reuptake inhibitors (SSRIs) do not seem to affect the pain directly, but they are very helpful in treating comorbid anxiety and depression. When these disorders improve, the patient's pain often improves secondarily.

The antidepressants that have been studied the most are probably tricyclic antidepressants (secondary and tertiary amines), which differ mainly in the degree of their side effects and particularly in terms of sedation. In animal models, tricyclic antidepressants have been shown to have anti-inflammatory effects in the gut. Even at low doses, tricyclic antidepressants appear to help the severity of pain in patients with IBD.

Tetracyclic antidepressants such as mirtazapine can also be helpful in patients with IBD. These agents work similarly to tricyclic antidepressants for treating pain, but they can also be very effective at helping people who experience sleep disturbance in addition to pain. However, tetracyclic antidepressants have not been formally studied in patients with IBD.

Serotonin noradrenergic reuptake inhibitors (SNRIs) appear to help pain as well as anxiety and depression. These agents can be taken at higher doses than tricyclic antidepressants and do not cause as many side effects. Common side effects of SSRIs and SNRIs are nausea, weight gain, sexual dysfunction, dizziness, and headaches. With tricyclic antidepressants, dry mouth, blurred vision, constipation, sweating, urinary retention, dizziness, and cardiovascular symptoms have been reported, particularly at higher doses. These antidepressant side effects are thought to be secondary to initial receptor sensitivity, which usually subsides after a few weeks, at which time the first therapeutic effects are seen.

G&H What other drugs can be used to treat pain in patients with IBD?

ES At moderate to sometimes high doses, mood stabilizers such as gabapentin, pregabalin, carbamazepine, lamotrigine, topiramate, and quetiapine can be effective for treating abdominal pain in IBD patients. Most studies on these drugs have been conducted in patients with neuropathic pain, and we have applied those findings to IBD patients with pain. Gabapentin and quetiapine have also shown positive effects in patients with IBS.

In addition, opioids have been used for pain in IBD patients, but it is important to use the lowest dose possible because of the dangers of these drugs. Opioids carry the risk of inducing hyperalgesia because of changes at the opiate receptor level, as well as possibly inducing inflammation (narcotic bowel syndrome).

Finally, doctors are starting to use partial agonist agents such as buprenorphine and naloxone for the treatment of pain. There have also been some interesting study findings on the role of ketamine in this setting, although this drug is not without side effects.

G&H What research has been conducted on the use of these drugs specifically in IBD patients?

ES There have been very few randomized, controlled trials of any of these medications in patients with IBD. One or two small trials have shown benefits with the use of tricyclic antidepressants in this setting, as has one study on SNRIs (duloxetine). IBD patients are often excluded from large-scale randomized trials of psychotropic agents, so doctors have to use their clinical intuition and study findings from other patient populations.

The nonpharmacologic interventions that have the most effect are cognitive behavioral therapy, medical hypnosis, and mindfulness meditation.

G&H Is there a role for medical marijuana in IBD patients experiencing pain?

ES Patients with pain are starting to ask about trying medical marijuana. Most states that have legalized medical marijuana, or are in the process of doing so, include IBD, especially Crohn's disease, as one of the allowable conditions for obtaining this drug. Medical marijuana is grown in specific locations, and both its concentration and quality are very tightly regulated.

Interestingly, although studies worldwide have shown that patients taking medical marijuana report a benefit from pain, controlled studies that have looked at the effects of medical marijuana in IBD patients in a relatively rigorous way have not found pain to necessarily improve in this setting. Some studies have shown improvement in IBD symptoms such as diarrhea, and most studies have shown that medical marijuana can help with sleep, nausea, and weight gain (by increasing appetite). Patient reports, which are subjective, are the only evidence of cannabis being helpful for abdominal pain.

In addition, it is important to differentiate between the use of a synthetic tetrahydrocannabinol agent and medicinal cannabis or marijuana directly from the source. The agents that appear to have the most effect on the gastrointestinal tract also cause the most side effects in the brain. These side effects can be long term because of the way that cannabis binds to fat cells. Finally, patients should be aware that even if medical marijuana is allowed at the state level, cannabis is still illegal at the federal level.

G&H What are the most common nonpharmacologic treatment options for pain in IBD patients?

ES The nonpharmacologic interventions that have the most effect are cognitive behavioral therapy, medical hypnosis, and mindfulness meditation. Often when patients have pain, they start becoming fearful of the pain and develop avoidance behaviors that frequently lead to disability. One of the models of cognitive behavioral therapy that has been shown to work for pain management teaches patients how to think about their pain differently, behave differently, and distract themselves from their pain. Patients have to interrupt those cycles so that they are not seeing pain as serious or threatening, or that they are feeling powerless. This approach helps patients feel that they have control and can be more responsible for reducing their pain.

Medical hypnosis and mindfulness meditation can help patients become experts at managing their physiology. With these methods, patients learn to use emotional gates in their mind so that they can become distracted or relatively oblivious to their pain by going into a deep relaxation. If a patient does not like to relax, these methods can change the level of consciousness of the patient in a way that allows him or her to cope better with pain.

In addition, there are several efficacious behavioral interventions that can help the many IBD patients with

chronic pain who also experience sleep disturbance. These interventions include having consistent sleep/wake times, not staying in bed if the patient does not fall asleep, keeping naps to a minimum to consolidate the sleep load at night, and keeping active with physical activity during the day to make the patient tired. If patients sleep better, they are better able to tolerate whatever pain they have and be active in their daily life, which reduces pain-related disability and suffering.

Finally, several other therapies are also being examined. One is acceptance and commitment therapy (ACT), which helps patients develop a different relationship with their pain and teaches them the coping skills to accomplish that goal. Randomized, controlled trials have demonstrated the efficacy of hypnosis and mindfulness meditation in reducing gastrointestinal symptoms and related suffering in IBD patients, and ACT has shown positive effects for other chronic pain conditions.

G&H Has there been any research on pain management specifically in pediatric patients with IBD?

ES Dr Tonya Palermo, a researcher at Seattle Children's Hospital, has developed a web-based protocol for chronic pain in general for children and adolescents that has been tested specifically for IBS. The protocol includes a program with positive reinforcement for progress in children and adolescents as well as a program for parents. The protocol has had high engagement and good results in terms of teaching pediatric patients coping strategies and teaching parents not to inadvertently enable bad behavior in their children.

In addition, cognitive behavioral therapy and mindfulness meditation have shown promise in pediatric IBD patients.

G&H What are the next steps in research in terms of pain management for IBD patients?

ES Further research is needed to determine whether there are safer ways to deliver opioids and cannabis in terms of reducing the potential for addiction and serious side effects, including death (with opioids). In addition, studies are beginning to examine the long-term use of opioids because of the current epidemic and the realization that these drugs are not as benign as originally thought.

Researchers are also currently looking at different mechanisms of inflammation. There might be inflammatory chemicals involved that are not directly part of IBD inflammation but that secondarily activate it. It would be helpful to find ways to target those chemicals directly.

As for future therapies, there has been some promise for both stimulation in the periphery as well as brain stimulation techniques; however, these techniques are not quite ready yet. In addition, some of the newer psychiatric medications are quite complex and target many different receptors. It would be helpful to understand where emotional and physical pain meet and how some of these newer agents might target both. Further research is also needed on ketamine, which is currently administered intravenously. An oral formulation is currently being developed. Ketamine has been shown to be useful for treating refractory depression and posttraumatic stress disorder. Many IBD patients with chronic pain have some type of trauma and have the propensity for posttraumatic stress reactions, so ketamine may have a role in this setting.

Dr Szigethy has no relevant conflicts of interest to disclose.

Suggested Reading

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