Centrally Mediated Disorders of Gastrointestinal Pain

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Centrally mediated abdominal pain syndrome, formerly known as functional abdominal pain syndrome, can be distinguished from other functional gastrointestinal disorders by its strong central component and relative independence from motility disturbances. Centrally mediated abdominal pain syndrome is a result of central sensitization with disinhibition of pain signals rather than increased peripheral afferent excitability. A newly described condition, narcotic bowel syndrome/opioid-induced gastrointestinal hyperalgesia, is characterized by the paradoxical development of, or increases in, abdominal pain associated with continuous or increasing dosages of opioids. Patients only have relief when opioids are withdrawn. We define both conditions in the context of epidemiology, pathophysiology, clinical evaluation, and treatment, emphasizing the importance of a physician—patient relationship in all aspects of care.

Keywords: Chronic Abdominal Pain; Narcotic Bowel; Functional Abdominal Pain; Centrally Mediated Pain; Rome IV.

This paper describes our approach and recommendations related to 2 gastrointestinal (GI) disorders whose primary symptoms are believed to have a central determinant—centrally mediated abdominal pain syndrome (CAPS), formerly known as functional abdominal pain syndrome (CAPS), and a new condition, narcotic bowel syndrome (NBS)/opioid-induced GI hyperalgesia.

D1. Centrally Mediated Abdominal Pain Syndrome

Definition

CAPS is characterized by continuous, nearly continuous, or frequently recurrent abdominal pain that is often severe and only rarely related to gut function. CAPS is associated with loss of function across several life domains, including work, intimacy, social/leisure, family life, and caregiving for self or others, and must be present for at least 6 months before diagnosis.

Like other functional gastrointestinal disorders (FGID), CAPS cannot be explained by a structural or metabolic disorder using currently available diagnostic methods. Abdominal pain can be produced by or attributed to nondigestive organs, such as those in the urinary or gynecologic systems, and disorders in these locations that explain such pain should be excluded before the diagnosis of CAPS can be established. A substantial proportion of CAPS patients suffer significant negative contributions from multiple, probably unnecessary, surgical interventions performed in an attempt to address their pain complaints,1 and attribute their pain to “adhesions.” Adhesions can cause symptoms of acute or subacute obstruction, which in turn cause pain, but there is no good evidence that adhesions themselves are a cause for chronic unrelenting pain, such as that seen in CAPS.5

The predominance of pain as the central complaint, almost to the exclusion of other symptoms, distinguishes CAPS from other painful FGID, such as irritable bowel syndrome (IBS) and functional dyspepsia (FD), primarily by the poor relationship of pain with food intake or defecation. CAPS may represent the far end of the spectrum of IBS severity, where psychosocial factors and more generalized central hypersensitivity predominate. It is distinguished from chronic pelvic pain by its abdominal location and from “abdominal migraine” in that the pain from CAPS is constant rather than cyclical.

Pain associated with CAPS may be colicky in nature, as in IBS, although it tends to be more prolonged and widespread. Another description that is quite common, especially after a previous surgery, is that pain is burning in character; this form is particularly challenging to treat.3 CAPS can be associated with other unpleasant somatic symptoms and syndromes, such as fibromyalgia and chronic fatigue syndrome. While not part of the diagnostic criteria, psychological comorbidities are common when pain is persistent.

Abbreviations used in this paper: CAPS, centrally mediated abdominal pain syndrome; FD, functional dyspepsia; FGID, functional gastrointestinal disorder; GI, gastrointestinal; IBS, irritable bowel syndrome; NBS, narcotic bowel syndrome; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TLR, Toll-like receptor.
Epidemiology

CAPS is considered less common than other FGIDs, such as functional heartburn, FD, or IBS, with prevalence data ranging from 0.5% to 2.1%.⁴ CAPS seems to be between 1.5 and 2 times more common in women,⁴,⁵ and its prevalence reaches a peak in the fourth decade of life (35–44 years in the US household survey) and then decreases with age.⁶

Approximately 80% of CAPS patients have consulted a physician, and half had seen a physician between 1 and 3 times per year specifically for abdominal pain,⁴,⁷ 4 times more frequently than people without abdominal complaints. CAPS patients in the United Kingdom required 4.2 consult visits, completed 6.4 endoscopic or imaging investigations, and underwent 2.7 surgical interventions (primarily hysterectomy and exploratory laparotomy) during a follow-up period of 7 years.⁸ In the United States, CAPS patients missed work a mean of 11.8 days in the previous year, 3 times more than subjects without abdominal symptoms, and “felt too sick to go to work” at the moment of the survey in 11.2% of cases, compared with 3 times more frequently than respondents without FGIDs.⁴

Pathophysiology

The biology of CAPS is likely similar to other chronic visceral pain disorders, such as IBS, FD, and interstitial cystitis. While these disorders are all defined by discrete symptom criteria, they have in common comorbidity with other pain syndromes, predisposing life events, and treatment responses. As with many chronic somatic pain disorders, CAPS does not fit easily into the traditional categories of neuropathic or inflammatory pain. Rather, alterations in modulatory and motivational pain dimensions play a major role in both the generation and perpetuation of CAPS.

Altered central sensory processing in gastrointestinal pain syndromes: lessons learned from irritable bowel syndrome and functional dyspepsia. The brain receives interoceptive input from the abdominal viscera, which is then combined with cognitive, emotional, and other sensory information for conscious interpretation in the anterior insula. Neuroimaging studies in IBS are consistent with an abnormality in central processing of pain signals, with functional and structural abnormalities noted in sensory (mid-cingulate, insular, and somatosensory cortices, and thalamus), emotional arousal (anterior cingulate cortex, amygdala), and prefrontal cortical modulatory regions. Modulation of descending pain regulatory pathways in the brainstem by these cortical regions can lead to exaggerated sensitivity to both noxious and innocuous stimuli. Evidence that patterns of brain activation during anticipation of experimental pain are abnormal in IBS further supports this pathophysiologic model. Patients with FD show similar abnormalities compared with healthy control subjects.⁹

One way in which CAPS differs from IBS and FD is that the pain symptoms are, by definition, reported as more constant and unrelated to peripheral events, such as food intake or defecation. This suggests that, unlike IBS and FD, the phasic, physiologic visceral afferent input from the gut plays a lesser role in symptom generation. These observations, along with the common responsiveness of CAPS symptoms to low-dose tricyclic antidepressants (TCA), raises the question of whether some CAPS patients have a peripheral or gut-based neuropathic pathophysiologic process. Unfortunately, neither the characteristically enlarged pain referral areas nor the response to TCAs (which work on both peripheral and central neuropathic pain conditions) make it possible to differentiate between these possibilities. However, even in the setting of a peripheral insult, once central sensitization is established, symptoms can persist in the absence of ongoing abnormal peripheral stimulation or worsen with minimal stimulation. Because no consistent initiating triggers are noted in CAPS, and the risk factors seem to be primarily psychosocial, it is presumed that central processes, such as altered descending pain modulation, are responsible for the chronicity of CAPS.¹⁰

Altered brain structure in chronic pain. Altered brain structure has also been described in multiple visceral and somatic pain disorders. In women with IBS, increased cortical thickness in the somatosensory cortex and decreased cortical thickness in regions of pain processing, including the insula and anterior cingulate cortex, is observed.¹² IBS symptom severity was negatively correlated with the cingulate thickness, suggesting a role for loss of neural density in symptom generation. Using another metric

| D1. Diagnostic Criteria for Centrally Mediated Abdominal Pain Syndrome⁶
<table>
<thead>
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<tbody>
<tr>
<td>Must include all of the following:</td>
</tr>
<tr>
<td>• Continuous or nearly continuous abdominal pain</td>
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<tr>
<td>• No or only occasional relationship of pain with physiological events (eg, eating, defecation, or menses)⁷</td>
</tr>
<tr>
<td>• Pain limits some aspect of daily functioning⁶</td>
</tr>
<tr>
<td>• The pain is not feigned</td>
</tr>
<tr>
<td>• Pain is not explained by another structural or functional gastrointestinal disorder or other medical condition</td>
</tr>
</tbody>
</table>

⁶Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

⁷CAPS is typically associated with psychiatric comorbidity, but there is no specific profile that can be used for diagnosis.

⁸Some degree of gastrointestinal dysfunction may be present.

⁹Daily function could include impairments in work, intimacy, social/leisure, family life, and caregiving for self or others.
of brain structure, gray matter volume, IBS patients had
decreased volumes in widespread regions, including the
insula, amygdala, cingulate, and brainstem, with early life
trauma playing a role in these differences.13 Patients with
FD also exhibit altered brain structure, with decreased gray
matter density in multiple brain regions, including the
insula and prefrontal cortex.14 Both IBS and FD have been
shown to have abnormal structure of the brain’s white
matter tracts, with similar areas involved in the processing
of pain and emotion. The role of structural change in func-
tional pain disorders is not clear, with some debate as to
whether these changes are pre-existing vulnerability factors
for chronic pain, or side effects of the pain itself. Given the
severity and chronicity of pain symptoms in patients with
CAPS, the likelihood that structural brain changes exist is
high.

Genetic and environmental vulnerability to cen-
trally mediated abdominal pain syndrome. Animal
models and human studies suggest that complex genetic
influences play an important role in the predisposition to
chronic pain. It is considered likely that this predisposition
is a combination of genetic, environmental, and behavioral
factors. Early evidence suggests genes related to serotonin
reuptake, mucosal barrier function, pro- and anti-
flammatory cytokines, among others, may be involved.
Clinical and preclinical evidence suggests that there is a
strong association of aversive early life events and certain
types of psychosocial stressors with increased pain reports
and changes in brain function among patients with
FGID.15,16 The combination of genetic factors, learned
behavioral factors, adverse early life events, and adult stress
might determine, in part, the effectiveness of endogenous
pain modulation systems and thereby influence develop-
ment of CAPS.

Psychological factors can amplify the experience of
pain, lending further rationale for the use of psychological
interventions for the management of CAPS. For example,
depression and anxiety mediate the effect of pain on
function in chronic low back pain17 and a trauma history
can negatively influence pain experience, coping, and the
doctor—patient relationship.18 Finally, there is strong
empirical support for the importance of pain catastrophiz-
ing,19 fear avoidance behavior,20 self-efficacy,21 lack of
perceived control,22 and passive pain coping23 on pain
experience.

Clinical Evaluation

A wide range of disorders produce abdominal pain, and
the clinician should be aware of the large number of dif-
ferential diagnoses.24 Of great importance is the duration
of symptoms—the diagnostic approach to patients with
acute abdominal pain is completely different from patients
with long-standing abdominal pain. Evaluation should
consist of a clinical and psychosocial assessment, obser-
vation of symptom-reporting behaviors, a physical exami-
nation, and, in the absence of alarm features, conservative
efforts to exclude other medical conditions in a cost-
effective manner. Notably, for patients meeting diagnostic
criteria for CAPS who exhibit a longstanding history of pain
behaviors, certain psychosocial correlates and no alarm
features, the clinical evaluation usually fails to disclose any
other specific medical etiology to explain the illness and, in
line with this, clinical investigations could be limited.25
However, occasionally the evaluation might incidentally
identify other medical conditions of uncertain relation to
the presentation (eg, hepatic and/or renal cysts or gall-
stones). Efforts then must be directed toward under-
standing the relative contributions of CAPS and the elicited
findings or diagnoses, to the pain reported. A number of
clinical and behavioral features typify, but are not specific
for, CAPS. Their presence may aid in the planning of
diagnostic testing and are essential to designing the
treatment approach.

Medical History

Description of the pain. A carefully taken history
focused on the description of pain is crucial in these
patients, as pain is the central feature. Typically, the pain in
CAPS is constant, nearly constant, or frequently recurring,
with pain occurring more or less every day. The pain is
associated with loss of daily functioning, which is often quite
severe (eg, work and school absenteeism, limitations in
social activities). The pain is not, or only occasionally,
associated with physiological events, such as bowel move-
ments, eating, or menses. In addition, the patient often
describes the pain in emotional terms; the pain involves a
large anatomic area, rather than a precise location. Patients
with CAPS also frequently complain of several other painful
extraintestinal symptoms (eg, musculoskeletal pain) and
often there is a continuum of painful experiences beginning
in childhood or recurring over time.25

Symptom behaviors. Although there are symptom-
related behaviors that typify CAPS, they are neither sensi-
tive nor specific and have limited diagnostic value, as they
might also occur in patients with a structural disease. These
behaviors are usually considered maladaptive but poten-
tially modifiable (Figure 1).

Presence of other medical diagnoses. Symptoms
compatible with CAPS may coexist with other structural or
functional diagnoses, or at least these diagnoses have been
obvious or even dominating the picture initially. This
coexistence reflects a transition from more peripherally
based afferent neural activity due to bowel dysfunction, to a
pattern of central disinhibition usually associated with more
constant pain. A proportion of patients with CAPS may also
affirm abnormal bowel habit, but without any association
with their constant and severe pain. Patients with a struc-
tural painful disease might, over time, develop a condition
more compatible with CAPS, when the pain pattern evolves
as more continuous, severe, and nonresponsive to existing
treatment alternatives.

Concurrent psychosocial features and clinical/
psychosocial assessment. Patients with CAPS show no
consistent psychological profile, but psychosocial diffi-
culties/problems often contribute to poor health outcomes
in this group of patients. Many patients with CAPS fulfill
diagnostic criteria for comorbid psychiatric diagnoses,
including anxiety, depression, and somatization,26 but,
unlike patients with these primary diagnoses, patients with CAPS are often reluctant to accept that these could contribute to their symptom profile. A history of unresolved losses (eg, death of a parent, surgery),27 as well as a history of sexual and physical abuse, are common features in patients with CAPS,28 but it should be noted that their presence is by no means diagnostic of CAPS, but rather can explain the severity of the condition. Independent of diagnosis, a history of abuse predicts poor health outcomes.29 By answering a few questions, the physician can appraise effectively the clinical features of CAPS, identify the key psychosocial contributions to the disorder, and increase confidence in the diagnosis30 (Figure 2).

**Physical Examination**

The physical examination does not establish a diagnosis of CAPS, and only rarely does it identify other etiologies in chronic pain patients. Nevertheless, there is no substitute for examining the patient to clarify pain location and radiation patterns, and to legitimize the patient’s symptoms. Additionally, in the previously uninvestigated patient, important physical findings can direct the diagnostic workup and might expeditiously lead to an underlying cause (eg, abdominal wall pain).24,31

**Investigations.** Tests to exclude other diagnoses should not be done on a routine basis, but based only on the presence of “alarm signs” or “red flags” indicating a clinical suspicion of organic disease.32 A minimal diagnostic workup should include routine laboratory tests to exclude inflammation and signs of GI bleeding (anemia, fecal blood loss). If alarm features are identified by history, physical examination or laboratory screening investigations, the physician should examine the patient for causes of abdominal pain other than CAPS. However, in the absence of alarm features or screening abnormalities, no further tests are indicated, and in the presence of longstanding stable symptoms, the
diagnosis of CAPS is highly probable if all criteria for this diagnosis have been met. The appropriateness of this approach is supported by several recent studies demonstrating that diagnostic failures are very rare, and that the health-related quality of life for patients with an FGID does not increase after the patients have undergone investigations. Figure 3 displays an algorithm for the evaluation of CAPS.

Treatment

The management of CAPS relies on establishing an effective patient–physician relationship, following a general treatment plan (eg, setting treatment goals and basing treatment on symptom severity), and offering management that encompasses a combination of treatment options, including pharmacologic and/or psychologic treatments (Figure 4).

Establishing an Effective Patient–Physician Relationship

Patients and physicians must share responsibility for the treatment. For example, patients must hold realistic expectations about treatment and the provider can help adjust expectations through questions such as “How do you believe I can be helpful to you?” Patients must be ready to enter into a therapeutic relationship with a provider—in CAPS, the focus needs to move away from evaluation and cure toward facilitating adaptation to constant symptoms. Finally, patients must be ready to take responsibility in their care—this is associated with improvement in clinical outcomes.

Physicians and patients both benefit when physicians listen actively, accept CAPS as a true disorder, offer empathy, use an open-ended question style with matching body language, validate the patients’ feelings, set realistic treatment goals, educate the patient about the nature of their condition, reassure, negotiate and provide choices around treatment rather than directives, maintain boundaries, and are aware of time constraints.

Some additional principles to consider:

1. Base treatment on symptom severity and degree of disability. If pain is continuous and severe, or if the patient is reluctant to participate in a psychological intervention, antidepressants (eg, TCAs or serotonin-norepinephrine reuptake inhibitors [SNRIs]) are used for their analgesic effects.

2. Know when to refer to a mental health professional. Present the psychological referral as a means to help the patient manage the pain and reduce the emotional distress encumbered by the symptoms. Medical care should continue concurrent with psychological treatment.

3. Referral to a multidisciplinary functional GI or pain treatment center. Multidisciplinary functional GI or pain treatment centers provide comprehensive assessment and treatment. Care must be taken to avoid pain centers that focus on opioid treatment, which is contraindicated and raises the risk for NBS.

General Principles of Treatment

Pharmacologic therapy. Pharmacologic therapy for CAPS can be employed along with the general treatment approaches outlined here. Medical treatment is most effective within the context of a well-developed patient–physician relationship, and a comprehensive biopsychosocial treatment plan (Table 1).

Tricyclic antidepressants. TCAs are the most widely used psychotropic agents for treating medical (eg, postherpetic neuralgia, diabetic neuropathy) and functional pain syndromes (eg, fibromyalgia). Their analgesic effect is probably unrelated to the antidepressant effect because these drugs are helpful in many pain syndromes where psychopathology is less prominent or absent, and...
also because they are usually given in low ("subpsychiatric" dosages). Improvement in pain as with desipramine in IBS was not related to blood levels or medication dosage.45

TCAs (eg, amitriptyline, imipramine, desipramine, doxepine, and trimipramine) are helpful in relieving pain and reducing IBS symptoms in moderate to severe cases,40,46 with a pooled relative risk for clinical improvement with TCA therapy of 1.93. The most common side effects of TCAs include sedation or sometimes agitation, hypotension, constipation, urinary retention, xerostomia, and effects on sleep such as insomnia or nightmares.

**Selective serotonin reuptake inhibitors.** Selective serotonin reuptake inhibitors (SSRIs) have lesser analgesic effect compared with TCAs, likely due to a lack of effect on noradrenalin synaptic levels, as evidenced by experimental models.47 One multicenter study compared amitriptyline (a TCA) to citalopram (an SSRI) and placebo among patients with FD48 and showed significant reduction in symptoms relative to placebo with the TCA, but not the SSRI. SSRIs are probably less potent visceral analgesics than TCAs or SNRIs, but they will have significant effects on global well-being and anxiety-specific GI symptoms. Side effects may include nausea and diarrhea; sexual dysfunction with decreased libido and delayed orgasm; and neurologic/psychiatric symptoms, such as anxiety, nervousness, tremor, insomnia, and nightmares.

**Serotonin-norepinephrine reuptake inhibitors.** The available SNRIs (eg, duloxetine, venlafaxine, desvenlafaxine, and milnacipran), while used for depression, are being used increasingly for treating chronic pain. Their dual effects (analgesic and antidepressant) make them an attractive choice in depressed patients with pain syndromes,49 but their benefit for CAPS is theoretical (Table 1).

Decisions relating to which antidepressant to use (or whether to combine them) will depend on several factors, including the agent’s potential to address pain and side effects of diarrhea or constipation. These factors depend largely on the main receptor sites of action (Table 2).

**Atypical antipsychotics.** Quetiapine has been used in lower doses for treating medical patients with anxiety, sleep disturbance, and associated psychological comorbid symptoms, and for augmentation treatment with painful disorders like fibromyalgia.50 It can benefit patients with chronic abdominal pain by reducing anxiety, restoring normal sleep patterns, and possibly through a direct analgesic effect.51,52 Overall, it appears to augment the

<table>
<thead>
<tr>
<th>Table 1. Antidepressant treatment for CAPS</th>
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<tbody>
<tr>
<td><strong>Tricyclic antidepressants</strong></td>
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<tr>
<td>Treatment targets</td>
</tr>
<tr>
<td>Adverse events</td>
</tr>
<tr>
<td>Risk from overdose</td>
</tr>
<tr>
<td>Dose adjustment</td>
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<tr>
<td><strong>Selective serotonin reuptake inhibitors</strong></td>
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<tr>
<td>Treatment targets</td>
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<tr>
<td>Adverse events</td>
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<td>Risk from overdose</td>
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<tr>
<td>Dose adjustment</td>
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<tr>
<td><strong>Serotonin-norepinephrine reuptake inhibitors</strong></td>
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<td>Treatment targets</td>
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<tr>
<td>Risk from overdose</td>
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<tr>
<td>Dose adjustment</td>
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benefits of TCAs or SNRIs in patients not having an adequate clinical response.

Miscellaneous psychotropic medications. Mirtazapine, a tetracyclic antidepressant has increased noradrenergic activity and 5-HT1A serotonergic activity, which makes it helpful as an antiemetic and appetite stimulant, leading to weight gain, as in patients with FD. Bupropion is a nonbenzodiazepine, anti-anxiety agent that can augment the effect of antidepressants, and with 5HT1 agonist effects, it can improve symptoms of FD.

Anticonvulsants. Anticonvulsants, such as carbamazepine, lamotrigine, and, more recently, the a2Δ ligand agents, gabapentin and pregabalin, have been evaluated in some chronic pain syndromes, but have not been studied for chronic abdominal pain or CAPS. Brain imaging studies showed that pregabalin reduced chronic pain reports and this was associated with a reduction of the usually increased functional connectivity seen between brain regions in chronic pain states.

Analgesics. Most analgesics (eg, aspirin and nonsteroidal anti-inflammatory drugs) offer little benefit because their actions are somatic in location. Narcotic analgesics should be avoided because of the likelihood of addiction and the possibility of narcotic bowel syndrome and other GI side effects.

Augmentation treatment. With CAPS, sequencing high dosages of one medication after another may fail due to incomplete response or side effects. Augmentation involves the use, usually at lower dosages, of 2 or more treatments that act on different receptor sites or areas of the brain to enhance the therapeutic effect. Augmentation treatment using multiple psychotropic agents should be prescribed in consultation with or by a psychiatrist, psychopharmacologist, or medical physician with advanced training in the use of these medications.

Psychological treatment and antidepressants. An effective augmentation approach is to combine antidepressants with psychological treatment. Antidepressants can improve pain and vegetative signs of depression, while psychological treatments improve higher levels of brain functioning, such as coping, reappraising of maladaptive cognitions, and cognitive adaptation to previous losses and trauma. Psychological treatment can improve adherence to taking a medication, and conversely taking an antidepressant can increase psychic energy to improve the efficiency of the work of therapy. Studies have shown that antidepressants work in subcortical areas, such as the anterior cingulate cortex and insula, to improve connectivity to prefrontal and other cortical areas ("bottom up" effects), and psychological treatments work on prefrontal or cognitive ("executive") areas, "top-down" effects.

The effect size difference for combined treatment can be 50% or more than either monotherapy treatment. Four classes of psychotherapy hold the most promise in CAPS: cognitive—behavioral therapy, psychodynamic—interpersonal therapy, mindfulness/acceptance-based therapies and hypnotherapy. These are typically administered individually by a health psychologist or other mental health provider familiar with GI physiology, always in conjunction with medical treatment.

Other Interventions

Patients seldom gain substantial relief from their symptoms and seek out alternative treatment approaches. However, peripherally based treatments are unlikely to be more effective than centrally targeted modalities.

There is no evidence to support spinal manipulation, and minimal evidence to support transcutaneous electrical nerve stimulation or acupuncture, although the latter may have some putative effect on the opioid system and could be recommended. Neurolytic celiac plexus blockade in benign disease has been restricted to chronic abdominal pain from suspected structural sources, such as chronic pancreatitis, and with only modest success. Many patients with CAPS exhibit erythema ab igne, indicating the excessive use of hot water bottles, electric heating pads, etc, suggesting that heat seems to provide some degree of pain relief despite any direct evidence. Although uncontrolled studies suggest a significant diagnostic and therapeutic benefit of

Table 2. Antidepressant Receptor Site Effects

<table>
<thead>
<tr>
<th>Antidepressants</th>
<th>Norepinephrine</th>
<th>5-hydroxytryptamine</th>
<th>Histamine</th>
<th>Acetylcholine</th>
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<tbody>
<tr>
<td>TCAs (25-150 mg)</td>
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<td></td>
<td></td>
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<tr>
<td>Amitriptyline</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>Desipramine</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>SNRs (1-2 pills)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>nil</td>
<td>+</td>
<td>nil</td>
<td>nil</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>nil</td>
<td>+</td>
<td>nil</td>
<td>nil</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>nil</td>
<td>+</td>
<td>nil</td>
<td>nil</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>nil</td>
<td>+</td>
<td>nil</td>
<td>nil</td>
</tr>
<tr>
<td>Sertraline</td>
<td>nil</td>
<td>+</td>
<td>nil</td>
<td>nil</td>
</tr>
<tr>
<td>SNRs (variable)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>++</td>
<td>+</td>
<td>nil</td>
<td>nil</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>+++</td>
<td>+</td>
<td>nil</td>
<td>nil</td>
</tr>
<tr>
<td>Milnacipran</td>
<td>+++</td>
<td>+</td>
<td>nil</td>
<td>nil</td>
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Gastroenterology Vol. 150, No. 6
laparoscopic adhesiolysis in patients with chronic abdominal pain, the outcome may be placebo-related, and the detection of unsuspected diagnoses is rare. Repeated adhesiolysis should be minimized to those situations where it is likely that the adhesions are having a clinical effect such as intermittent small bowel obstruction.

**D2. Narcotic Bowel Syndrome/Opiate-Induced Gastrointestinal Hyperalgesia**

**Definition**

NBS is characterized by the paradoxical development of, or increases in, abdominal pain associated with continuous or increasing dosages of opioids. NBS can occur in patients with functional GI disorders or chronic GI diseases (eg, IBD, chronic pancreatitis), with painful malignant or nonmalignant diseases, or even in patients receiving high dosages of narcotics when recovering from surgery. Patients with NBS will have relief or meaningful improvement of their pain when the opioids are withdrawn.

**Epidemiology**

Opioids are the most commonly prescribed drug category in the United States. Most pain clinicians will not see NBS; its recognition is more familiar in GI practices where patients on opioids are referred for severe abdominal pain and presumed to have an FGID.

<table>
<thead>
<tr>
<th>D2. Diagnostic Criteria for Narcotic Bowel Syndrome/Opioid-Induced Gastrointestinal Hyperalgesia</th>
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</thead>
<tbody>
<tr>
<td>Must include all of the following:</td>
</tr>
<tr>
<td>1. Chronic or frequently recurring abdominal pain that is treated with acute high-dose or chronic narcotics</td>
</tr>
<tr>
<td>2. The nature and intensity of the pain is not explained by a current or previous GI diagnosis</td>
</tr>
<tr>
<td>3. Two or more of the following:</td>
</tr>
<tr>
<td>a. The pain worsens or incompletely resolves with continued or escalating dosages of narcotics</td>
</tr>
<tr>
<td>b. There is marked worsening of pain when the narcotic dose wanes and improvement when narcotics are re-instituted (soar and crash)</td>
</tr>
<tr>
<td>c. There is a progression of the frequency, duration, and intensity of pain episodes</td>
</tr>
</tbody>
</table>

Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

**Pathophysiology**

**Physiological features.** While there are several putative mechanisms to explain the central hyperalgesia of opioids, perhaps the most favored is that of glial cell activation in the dorsal horn of the spinal cord, which up-regulates peripheral nociceptive signals going cephalad. Dorsal horn glia (astrocytes and microglia), when activated, produce proinflammatory cytokines, nitrous oxide, and excitatory amino acids. This leads to central hyperalgesia with enhanced pain. Gli cell activation occurs in response to inflammation or infection, drugs such as morphine, an endogenous chemokines (fractalkine), from peripheral injury, other activated glial cells, or even in response to signals from the central nervous system, which opens the possibility for central effects of stress on peripheral pain facilitation. The glia cell, the immunocompetent cell of the central nervous system, are activated via Toll-like receptors (TLR4), which modify the pharmacodynamics of opioids by eliciting a proinflammatory reaction with disruption of glutamate homeostasis. Certain pharmacologic agents could potentially interrupt this pain-inducing pathway via disruption of TLR4 and TLR2 signaling, including TCAs.

Another potential contributing factor is the bimodal excitatory and inhibitory opioid modulation system in the dorsal horn. The Gi/o protein inhibitory receptor is activated, leading to analgesia with short-term opioid use, but also Gi protein excitatory receptor can be activated to produce hyperalgesia in some individuals when chronic high dosages of opioids are used. The Gi-coupled excitatory opioid receptors become progressively sensitized during chronic exposure of dorsal root ganglia to opioid agonists over time leading to tolerance of inhibitory pain effects and ultimately hyperalgesia via Gi-coupled activation. Clinically, the use of prolonged high-dose narcotic agonists may produce opioid hyperalgesia and NBS.

Descending pathways originating from the cingulate and prefrontal cortex, the rostral ventral medulla and periaqueductal gray can produce antinociception, although descending tracts through the dorsolateral funiculus can enhance pro-nociceptive input. These responses have been demonstrated to occur via activation or inactivation of “on” and “off” cells in the rostral ventral medulla. Activation of the off cells produces an inhibition of nociceptive input, while activation of the on cells is believed to facilitate nociceptive processing within the rostral ventral medulla and descending projections to the spinal cord. An animal model for NBS has been described in which morphine has led to the development of central and visceral hyperalgesia. Minocycline, a known inhibitor of microglia activation, resulted in normalization of the hyperalgesia during the morphine treatment.

**Clinical Evaluation**

Patients with NBS most often report moderate to severe colicky or constant abdominal pain, which is poorly localized. They may have been prescribed opioids initially for
intra-abdominal (eg, chronic pancreatitis, inflammatory bowel disease, CAPS) or extra-abdominal (eg, orthopedic pain, fibromyalgia, migraine headaches) conditions, or even develop increasing pain after surgery. Although initially receiving opioids for intermittent pain, patients soon develop tolerance and tachyphylaxis, which require escalating doses for continued clinical benefit. Eventually, reduced or no pain periods diminish and the abdominal pain becomes constant and severe despite ongoing treatment.59

The pain may be associated with other GI symptoms consistent with opioid bowel dysfunction, including nausea, vomiting, heartburn, constipation, and either overflow diarrhea or diarrhea from opioid withdrawal. Associated diagnoses may include gastroparesis, pseudo-obstruction, and opioid-induced constipation.

Patients may show psychosocial disturbances, including anxiety, depression, somatization, post-traumatic stress disorder, and personality disorders often associated with high health care use and increased health care expenditures due to procedures, surgery, and medications.65 Although these features are not a part of the diagnostic criteria of NBS per se, awareness of them is helpful in treatment planning.

Patients may have had extensive laboratory studies done, which are usually normal, and radiologic studies might show colonic fecal retention. Cross-sectional imaging has usually been done to exclude obstruction, pancreatitis, inflammatory or ischemic bowel, or other intra-abdominal pathology. These negative studies, in addition to a focused history and physical examination and meeting the diagnostic criteria, should be adequate to make a diagnosis of NBS.

NBS is a positive diagnosis that can occur solely (eg, in a patient developing abdominal pain after an operation or treatment for back pain), or it can be present alongside other structural GI diseases, when the pain is out of proportion to the pain inferred to be from the structural disease. For example, patients may have had pancreatitis with resolution of the lipase but worsening pain from the NBS, or may have inflammatory bowel disease without complications of bowel obstruction, deep ulcers, or serologic evidence for inflammation. The diagnosis is particularly challenging when the patient has active bowel disease and is also on opioids in the clinical setting of worsening abdominal pain. As such, there is no specific diagnostic evaluation recommended other than the good clinical judgment required to evaluate the activity of other comorbid medical diseases. In these cases, it might be reasonable to detoxify patients as a therapeutic trial to see if NBS is present.

There is no particular time frame or dosage of opioids required for diagnosis because NBS can occur within a few weeks and with varying dosages. Therefore, the diagnosis is based on the development of the clinical features in a setting of opioid use, and it is observed that patients most often are taking, on average, 75 mg or more daily of oral morphine equivalent.65

A subset of patients with abdominal pain on opioids may have opioid use disorder.75 These patients take opioids in larger amounts than intended, with a persistent desire to continue and crave for them, and fail to fulfill normal work, school, or home obligations.77 Patients with these features should be referred to a substance abuse program, as the likelihood of successful management of these patients in a medical setting is extremely low.

Treatment

**Understanding the patient.** It helps to understand that most patients with NBS want to be treated, but might not see reduction of opioids as a logical option. These patients believe that opioids have been “all that has helped” and fear being abandoned with worsening pain. They also feel stigmatized by others who they perceive see them as “drug seeking” or having a psychiatric problem.

**Clinician considerations in the treatment.** A sound patient–physician relationship through good communication skills is a prerequisite to the treatment of patients with NBS.76 The clinician must feel committed to work with these patients and be aware of possible negative feelings toward patients that s/he perceives as “difficult.”

**Educating about the treatment.** Once a commitment is made to treat, the physician must engage with the patient and discuss NBS and options for treatment, including opiate detoxification. The Current Opioid Misuse Measure79 is a useful tool to determine the severity of misuse and likelihood of detoxification. The treatment protocol discussed here involves complete detoxification because there is only evidence of clinical improvement with this approach65 and no evidence that NBS can be treated with continuation of opioids.

Negotiating the treatment requires mutual trust and patient engagement toward a shared plan of care,59 which can be facilitated through empathy, acceptance, and validation of the reality of the pain and its impact on the patient’s life, an open dialogue about the mechanism of NBS and the rationale for the recommended treatment, including the specifics of opioid detoxification and eliciting/addressing the patient’s concerns directly. If the patient says opioids have been the only effective treatment, the clinician can note that, despite using high-dose opioids, the patient is still not achieving benefit or it is incomplete; describe the value of more effective treatments for the pain (eg, tricyclic or SNRI antidepressants and central anxiety-reducing agents) to use during and after detoxification; note that once beginning the program, the protocol for opiate reduction will not change, but alternative agents can be used for pain and anxiety; provide realistic goals from the detoxification, which are to improve the pain (not necessarily achieve complete pain resolution) over the course of months; enlist friends and family members in discussions of the goals and treatment to ensure their support during the process and also to help prevent relapse; indicate the role of ancillary providers (eg, psychologists or psychiatrist, primary care physician, and physician assistant) to help in the process; and reaffirm their willingness to continue with the patient in the care regardless of the outcome.

Treatment plan is provided in Table 2.

**Clinical outcome.** The single outcome study in NBS detoxification included 39 patients who were systematically detoxified in an inpatient facility during a 7-day period with

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**Table 2.**

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<th>Details</th>
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**References:**

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a success rate of 89.7%. Sixty percent were considered “responders”; 11% percent had worse pain after detoxification. This committee believes that inpatient programs provide much more control over detoxification, and can usually be done in 1 week rather than outpatient programs, which take several weeks.

Conclusions

We described a set of GI pain disorders with a central determinant. These disorders are increasingly common and complex and must be approached from a comprehensive biopsychosocial model. The doctor–patient relationship is at the core of all evaluation and management decisions. CAPS is distinguished by chronic, unrelenting pain that interferes with several life domains and has no clear triggers, such as bowel movements, food, or menses. It may be at the far end of the spectrum of other FGIDs, such as IBS. Our newest disorder, NBS/opioid-induced GI hyperalgesia is characterized by the paradoxical development of worsening abdominal pain associated with increased use of opioids. The only treatment for NBS is to withdraw opioids, which requires a thoughtful and collaborative approach. Both CAPS and NBS require a substantial research effort over the next several years to more fully characterize their prevalence and features, understand their unique pathophysiology and identify more effective therapeutic targets.

References


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Conflicts of interest
The authors disclose no conflicts.