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Centrally Mediated Disorders of Gastrointestinal Pain

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We identified 3 centrally mediated disorders of gastrointestinal pain in the context of epidemiology, pathophysiology, clinical evaluation, and treatment, including pharmacotherapy, brain–gut behavioral therapy and neuromodulation, with an emphasis on the importance of the physician-patient relationship. Centrally mediated abdominal pain syndrome is characterized by chronic abdominal pain. It has 2 main categories: category A, when the pain occurs without association with physiological events, and category B, when there is a variable association of pain with physiological events. Centrally mediated abdominal pain is thought to be predominantly a result of central sensitization with altered processing of visceral pain by spinal and brain networks rather than heightened peripheral afferent nerve excitability. Abdominal migraine is newly recognized in adults with paroxysmal, stereotypical episodes of intense abdominal pain. Narcotic bowel syndrome, or opioid-induced gastrointestinal hyperalgesia, is characterized by the paradoxical development of, or increases in, abdominal pain associated with continuous or increasing dosages of opioids.

Keywords: Centrally Mediated Abdominal Pain Syndrome; Abdominal Migraine; Narcotic Bowel Syndrome; Opioid-Induced Gastrointestinal Hyperalgesia; Central Sensitization.

In this article, we focused on the range of gastrointestinal (GI) disorders believed to have a predominantly central nervous system (CNS) determinant. There have been some advances in the understanding of the epidemiology, clinical presentation, long-term outcomes, treatment response, and overlap with many of the disorders of gut–brain interaction (DGBI). We describe each central disorder of GI pain individually, which includes centrally mediated abdominal pain syndrome (CAPS), abdominal migraine, and narcotic bowel syndrome or opioid-induced GI hyperalgesia.

D1. Centrally Mediated Abdominal Pain Syndrome

Definition

CAPS, previously termed "chronic idiopathic abdominal pain" and "functional abdominal pain syndrome,"[1,2] is characterized by continuous severe abdominal pain that is associated with loss of daily functioning.[3] Like other DGBI, CAPS cannot be explained by any structural or metabolic disorder using current diagnostic methods. It is believed that CAPS has a dominant central component that is not explained by peripheral sensitization only and may be consistent with alterations in endogenous central pain modulation systems, including dysfunction of descending and cortical pain modulation circuits.

The pain of CAPS is typically constant and may wax and wane in severity. It may be described as colicky, cramping, burning, dull, or aching and can be diffuse in nature. It is distinguished from other painful DGBI, such as irritable bowel syndrome (IBS), functional dyspepsia, and biliary pain, by the constant nature of the symptoms and chronic pelvic pain and its abdominal location. However, CAPS may overlap with these other conditions.

Epidemiology

The most important progress in our understanding of the epidemiology of CAPS has occurred through the global epidemiologic survey with Rome IV criteria. CAPS was rarely identified, as the overall prevalence was 0.02% in an internet survey.[4] Therefore, Rome IV criteria for CAPS[5] were highly restrictive in identifying individuals with CAPS in the general population. However, CAPS is not so rare in the DGBI specialty clinic. Patients with CAPS have high health care resource utilization,[6] imposing a substantial

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Abbreviations used in this paper: **CAPS, centrally mediated abdominal pain syndrome; CBT, cognitive behavioral therapy; CNS, central nervous system; CVS, cyclic vomiting syndrome; DGBI, disorders of gut–brain interaction; GI, gastrointestinal; 5-HT, 5-hydroxy tryptamine (serotonin); IBS, irritable bowel syndrome; NBS, narcotic bowel syndrome; SNRI, serotonin noradrenaline (norepinephrine) reuptake inhibitor; TCA, tricyclic antidepressant.**

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D1. Rome V Diagnostic Criteria[a] for Centrally Mediated Abdominal Pain Syndrome[b]

Must include *all* of the following:
1. Continuous abdominal pain
2. Relationship of pain with physiological events

Category A: No association with physiological events or
Category B: Variable association of pain with physiological events[c]

3. Pain limits some aspect of daily functioning[d]
4. Pain is not factitious
5. Another GI or non-GI disorder does not explain the continuous abdominal pain

[a]Criteria fulfilled for the last 3 months, with symptom onset at least 6 months before diagnosis.
[b]CAPS is typically associated with psychosocial comorbidities, but no specific psychosocial profile characterizes a diagnosis of CAPS.
[c]Physiological events may include eating, defecation, menstruation, positioning, or other visceral or somatic activities.
[d]Limitations of daily functioning include impairments in work, intimacy, social and leisure, family life, and caregiving for self or others.

economic burden.[7] In the US householder survey,[8] respondents with CAPS visited a physician a mean of 1.52 times in the previous year for abdominal pain and 5.66 times yearly for extra-GI symptoms.

Justification for Changes in Diagnostic Criteria

The committee believes that the Rome IV criteria to diagnose CAPS is too restrictive for clinical or investigative use. The previous Rome IV criteria specified "no or only occasional relationship of pain with physiological events." This phrase is interpreted as "no association with physiological events" to distinguish it from IBS or other bowel disorders for research purposes. Using this definition, the Rome Foundation's Global Epidemiology Study,[4] evaluated the prevalence of DGBI in 54,127 individuals in 26 countries and found a frequency of CAPS of only 0.02% (95% CI, 0.01–0.03) and the diagnosis was seen in women only.

However, within gastroenterology and neurogastroenterology, we see a much larger proportion of patients with chronic abdominal pain (up to approximately 20% in some series of those with DGBI) referred to specialty practices and emergency facilities. Most patients have severe, nearly constant abdominal pain associated with physiological events such as eating and defecation. However, they do not fulfill the criteria for IBS, dyspepsia, or other DGBI due to the constancy of the symptoms. This group of patients "falls through the cracks" and needs identification for further clinical characterization and treatment.

One study[9] evaluated the diagnostic features and treatments in a cohort of 103 patients referred to a neurogastroenterology clinic with chronic and continuous abdominal pain. They found that one-half of the patients did not meet the Rome IV criteria for CAPS because physiological pain events (eg, worse with eating, defecation, or menses) modified the pain. Yet there were no differences between the traditional restrictive Rome IV CAPS group and those with chronic abdominal pain related to physiological events. This highlights the need to create another CAPS group with similar phenotypical features for Rome IV that meets the constant pain criteria but also permits changes in pain symptoms related to physiological events.

To address this issue, the committee queried the Rome Foundation global database to compare the prevalence and clinical features of traditional CAPS not associated with physiological events (category A) with a modified CAPS of chronic abdominal pain with a variable association with physiological events (category B). Therefore, category B patients also have constant pain (eg, unlike IBS) but with modification of pain intensity associated with physiological events. The frequency of CAPS category B is 0.11%, which is 5 times greater than the Rome IV traditional diagnosis of CAPS (category A) (Figure 1).

Furthermore, there has been a change in wording of the criterion "continuous or nearly continuous" to "continuous abdominal pain" as the committee agreed that the distinguishing feature of CAPS from other DGBI like IBS was the continuous nature of the pain and removing "nearly" reduces ambiguity about the diagnosis and helps to maintain higher-level specificity. In addition, continuous pain refers to pain in the awake state.

The data showed that CAPS category A and category B are similar in virtually all variables but different from non-CAPS individuals. Thus, a large underrecognized group of individuals with chronic abdominal pain associated with physiological events do not meet Rome IV CAPS or IBS criteria and have psychosocial distress, poor quality of life, and high health care utilization. Results from the Rome V Global Epidemiology and Validation Study strongly support the Rome V criteria.

Pathophysiology

CAPS exists at the far end of the DGBI pain severity spectrum compared with other disorders, such as IBS (Figure 2). The abdominal pain reported by patients with IBS has both gut and brain components, in addition to peripheral factors (eg, diet, infection, and mucosal immune function), which tend to enhance visceral signaling, leading to visceral hypersensitivity. In contrast, in CAPS, central pain mechanisms are thought to predominate and be driven more by psychobiological processes and psychiatric comorbidity, although experimental confirmation for this is needed. Clinically, we often see that some patients with IBS early in life develop CAPS later in life, although the pathways underlying this association are not clear. Many research studies have used CAPS criteria that exclude IBS and other GI disorders.[4,5,10] In clinical practice, it is common to see patients with CAPS as well as IBS or other DGBI.

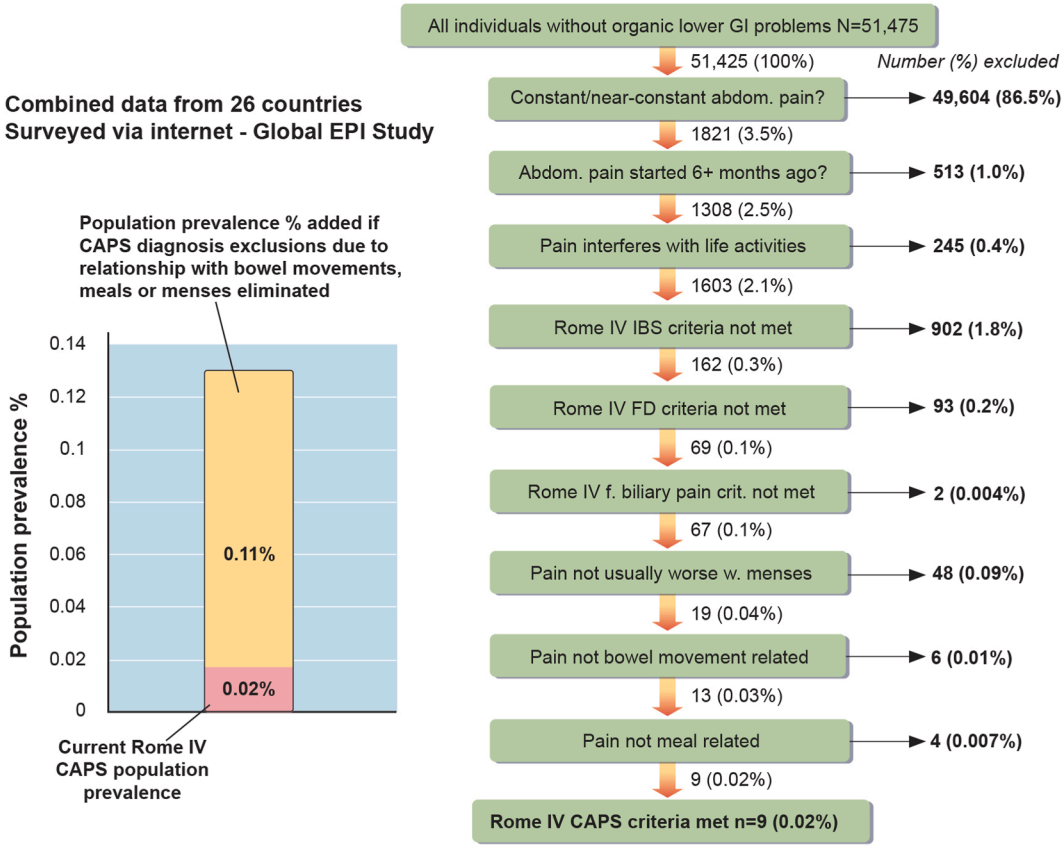

Figure 1. Prevalence of category A CAPS and category B CAPS. The *bar graph* represents the prevalence of Rome IV CAPS (category A) from the global epidemiology study (0.02%) compared with a modified CAPS (0.11%) in which chronic pain was also associated with physiological event–related bowel movements, menses, or meals (category B). abdom., abdominal; EPI, epidemiologic; f. biliary, functional biliary; crit., criteria; w., with.

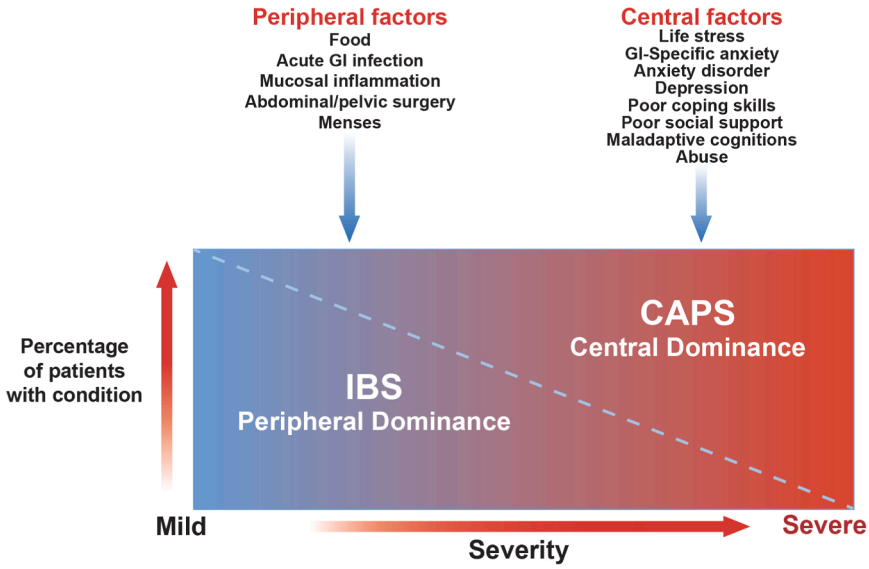

Figure 2. Continuum of severity and influencing factors between IBS and CAPS. CAPS reflects the end of a DGBI spectrum characterized by strong disinhibition and weak afferent excitation. Complex psychosocial factors often accompany CAPS. On a neurologic level, CAPS is likely the result of central sensitization with nociplastic pain characteristics, including disinhibited pain signals, reorganized central pathways and networks, and neuroinflammation.

The biology of abdominal pain. The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[11] This definition emphasizes that the presence of current or prior tissue damage is not a prerequisite for this very distressing sensation. CAPS does not easily fit into the traditional neuropathic or inflammatory pain categories. The International Association for the Study of Pain now classifies these disorders as "chronic primary pain."[12]

In chronic pain disorders, "central sensitization" is often a key pathophysiological mechanism. The International Association for the Study of Pain defines it as "increased responsiveness of nociceptive neurons in the central nervous system to normal or subthreshold afferent input."[13] However, this definition may be too broad, as many different underlying mechanisms may be involved and may differ among patients. Recently, the term "nociplastic pain" was introduced to cover pain arising from altered nociception, despite no clear evidence of actual or threatened tissue damage, lesion, or disease affecting the peripheral nociceptors.[14]

Nociceptive mechanisms at different levels of the sensory gut–brain pathway are involved in the pathophysiology of chronic pain and are relevant to CAPS. At the spinal cord level, increased sensory input from the peripheral nociceptors can cause neuronal sensitization of spinal dorsal horn neurons. This sensitization can also result from increased firing to repeated gut stimulations (wind-up) and various local reflexes are activated, which lead to central sensitization. At the level of the brainstem, defects in the normal descending inhibitory feedback systems exerting control on the afferent transmission at the level of the spinal cord dorsal horn are seen in many patients. Neuronal sensitization together with altered communication between pain modulatory areas and pathways, reorganization of structures and structural changes (such as atrophy), and a switch in neurotransmitter concentrations can contribute to the heightened perception of pain. Finally, recent studies suggested that neuroplasticity relevant to chronic pain[15] is modulated by microglia, which are resident immune cells of the CNS.[16] There is a plethora of evidence describing the altered structure, function, and neurochemistry in pain-processing and pain-modulatory brain circuits in various chronic pain conditions, typically measured using in vivo (functional) brain imaging techniques, including functional magnetic resonance imaging,[17] positron emission tomography,[18] and electroencephalography[19] or magnetoencephalography.[20] An overview of the most hypothesized pathophysiological

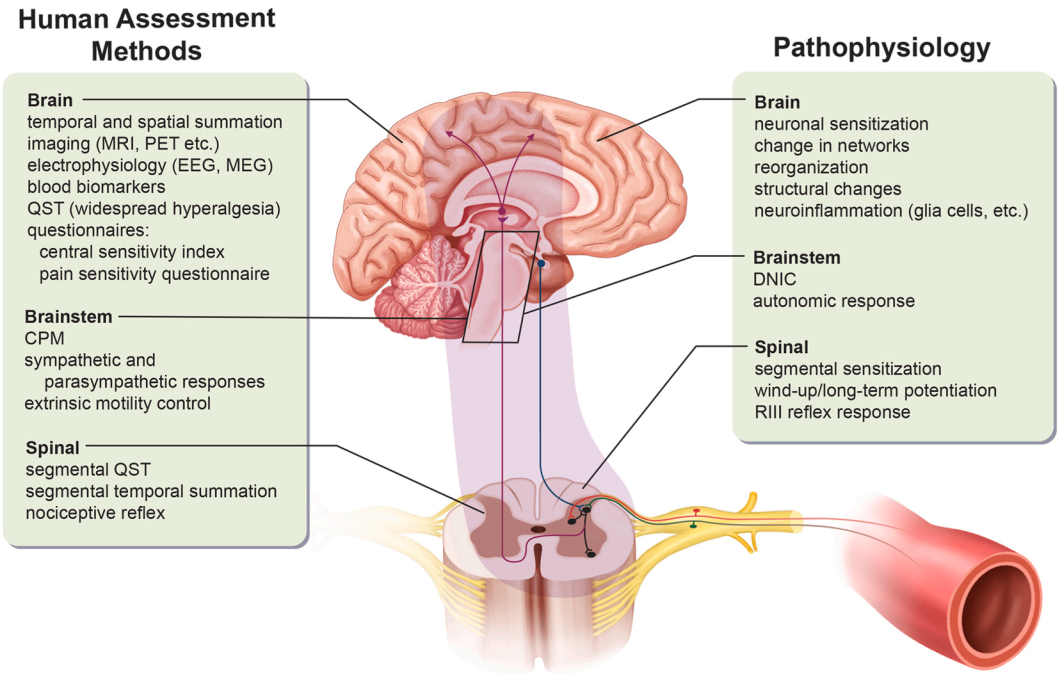

Figure 3. Schematic illustration of the most well-known pathophysiology of chronic pain and associated human assessment methods. At the spinal cord level, neuronal sensitization results in several physiological responses, such as increased firing to repeated gut stimulations (wind-up) and local reflexes. At the brainstem, defects in the normal inhibitory feedback systems controlling the afferent transmission are seen in many patients, as well as abnormal autonomic responses. The same mechanisms are brought into play in the brain, together with changes in communication between centers, reorganized structures and structural changes (such as atrophy), together with a switch in neurotransmitter concentrations. On the left are indicated some methods readily available for human studies. CPM, conditioned pain modulation; DNIC, diffuse noxious inhibitory control; EEG, electroencephalography; MEG, magnetoencephalography; MRI, magnetic resonance imaging; PET, positron emission tomography; QST, quantitative sensory testing; RIII reflex, a local reflex with loops primarily in the spinal cord, also called the nociceptive reflex.

mechanisms underlying them and their in vivo assessment methods is shown in Figure 3.

Psychiatric Comorbidities

Depression and anxiety. Both depression and anxiety[21] independently predict pain reporting, particularly among women.[22,23] Anxiety and depressive disorders have mainly been associated with increased pain severity and related disability.[24] In an epidemiologic study of more than 3000 community subjects, the estimated prevalence of major depressive disorder using cutoff symptom scores was 17%, and 54% of those with self-reported depressive symptoms of low mood and anhedonia frequently reported in patients with chronic abdominal pain.[25] Anxiety is present in up to 40% of patients with DGBI[26] and can occur both as ruminative worrying (generalized anxiety disorder) or panic symptoms. Anxiety may be health-related or symptoms-specific.

Suicide. Chronic abdominal pain may be an independent risk factor for suicidal ideation, particularly among women.[27] Factors increasing the risk of suicide include unemployment, poor sleep, a feeling of helplessness, and the use of illicit drugs for pain control.[28]

Post-traumatic stress disorder. Post-traumatic stress disorder in CAPS and related medical treatment is increasingly recognized as a mechanism by which pain can be exacerbated and is critical to probe during a patient interview.[29,30] Considering the role of implicit memory (eg, sensory emotional memories that often include GI symptoms) in the development and recovery from trauma-related disorders is particularly important in patients with trauma-related amplification of their CAPS.[31] A history of abuse predicts poorer health status, greater health care use, greater disability, and lower health-related quality of life.[32,33]

Somatic symptom disorder. *The Diagnostic and Statistical Manual of Mental Disorders,* 5th edition, text revision somatic symptom disorder[34] has replaced the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition somatization disorder and has redefined somatization in terms of positive symptoms[35–39] as somatic symptoms that are very distressing and disabling and that are associated with excessive and disproportionate thoughts, feelings, and behaviors for a period of at least 6 months.[40]

Psychological Factors Affecting Centrally Mediated Abdominal Pain Syndrome

There is a movement more generally across the classification of mental disorders to move away from categorical constructs (eg, diagnoses) and embrace more mechanistic constructs, taking etiology into account.[41] Overlapping constructs, including health anxiety, symptom-specific anxiety, attentional bias, symptom hypervigilance, cognitive inflexibility, alexithymia, catastrophizing,[42–44] and resilience,[45–47] have been linked to DGBI independent of psychiatric comorbidity. Psychological factors coupled with chronic pain can negatively impact the physician-patient relationship and directly influence treatment outcomes.[48]

Brain–gut behavioral therapies. Several recent reviews summarized findings regarding these modalities for DGBI[49] and further empirically supported approaches can be found in the psychosocial section.

Clinical Evaluation

Medical history.

Description of the pain. A detailed history focusing on the description of pain is essential.[50] CAPS pain is usually persistent and diffuse, resulting in daily functional loss, such as reduced productivity and missed work, school, and social events. Patients with CAPS commonly have other unpleasant extraintestinal symptoms (eg, musculoskeletal pain).

Symptom-related behaviors. Although symptom-related behaviors typify CAPS, they have limited diagnostic value, as they can occur in patients with structural disease.

Family interaction. Continuous chronic pain impairs the patient's capacity to contribute, straining social connections and altering the patient's self-perception and family's perception.[51]

Presence of other medical disorders. Both "organic" and other "functional" disorders are often comorbid in patients with CAPS, such as fibromyalgia; chronic fatigue syndrome; chronic back or knee pain; pseudoseizures or chronic regional pain syndrome[9]; hypermobile Ehlers-Danlos syndrome, with or without autonomic abnormalities; quiescent inflammatory bowel disease; diverticular disease; endometriosis; gallstones; hemorrhoids; abdominal hernia; chronic pancreatitis; peripheral neuropathy; IBS; cyclic vomiting syndrome (CVS) or gastroesophageal reflux disease; depression; anxiety disorders; post-traumatic stress disorder; chronic pelvic pain syndrome; bladder pain syndrome; pelvic congestion; and endometriosis.[52,53]

General principles.

Extensive and repeated testing to exclude alternative diagnoses should not be undertaken routinely for the diagnosis of CAPS.[54]

Behavioral features of CAPS.

Focusing attention on complete relief of symptoms. Many patients arrive at the consultation with unrealistic expectations, given the longevity of their symptoms and hopes to delineate a hitherto undiscovered "organic" diagnosis. The health care provider should help the patient set realistic treatment goals. Good communication can detect, address, and clarify these concerns, thereby enabling a more collaborative treatment approach.[55]

Seeking health care frequently. Close follow-up is central to reducing unnecessary health care utilization.[52]

Taking limited personal responsibility for self-management. The focus of management should be toward targeted medical therapy and adaptation to persistent symptoms. The primary responsibility for care must be shared between the patient and health care professional as joint stakeholders aiming to empower patients. Motivating

patients to take ownership of their pain management is helpful.[56]

Making requests for narcotics. Long-term opioid use in chronic visceral pain syndromes often does not improve pain control, functional ability, or health-related quality of life,[10] yet up to two-thirds of patients with CAPS will have been, or are currently being, treated with opioids.[9]

Requesting diagnostic studies. Patients with CAPS may seek additional diagnostic tests due to pain severity and perceived diagnostic uncertainty.

Expression of pain of variable intensity through verbal and nonverbal methods. Verbal and nonverbal pain descriptions, such as improper grimacing during examination, may vary with anticipatory anxiety and other psychological factors explaining this.

Urgent reporting of intense symptoms. Some patients may be prone to catastrophizing their symptoms and exaggerating their urgency and intensity, leading to more frequent than usual presentation to emergency departments.

Minimizing the potential role of psychological factors. Patients' fear that physicians will not take them seriously if they have psychological illnesses may lead to the minimization of psychological variables contributing to chronic pain.

Physical examination. There is no substitute for examining the patient to clarify pain location and radiation patterns.[57] In the previously uninvestigated patient, physical findings can guide the diagnostic workup and quickly identify an underlying cause (eg, abdominal wall pain[58]). The following general features can be observed in patients with CAPS: (1) no dominant autonomic arousal (ie, tachycardia, increased blood pressure, or diaphoresis) at pain, (2) presence of multiple surgical scars without clearly understood indications,[59] (3) the "closed eyes sign" (ie, when the abdomen is palpated, the patient with CAPS often winces with their eyes closed),[60] and (4) the "stethoscope sign" (ie, the use of a stethoscope to palpate the abdomen reduces the behavioral response to pain to manual palpation).

Inspection, auscultation, percussion, and palpation may provide information supportive of diagnoses other than CAPS but, of these techniques, palpation is the most useful. Rebound tenderness is used to detect peritoneal inflammation[61] and aneurysms can be detected by palpation.[62] Maneuvers are used to detect tenderness in retroperitoneal or pelvic regions that are difficult to approach via anterior abdominal examination, such as the obturator sign and the psoas sign. Carnett's test can help to differentiate visceral from somatic pain.[58] First, the site of maximal abdominal pain is identified and afterward, the patient is asked to tense his or her abdominal muscles by raising his or her head and trunk or lower extremities off the examining table. A positive test result (ie, identical or increased tenderness when performing this maneuver) is suggestive of abdominal wall pain.[63] Several studies have suggested that chronic abdominal wall pain caused by anterior cutaneous nerve entrapment syndrome is a more frequent cause of chronic abdominal pain than previously expected.[64,65] The focused physical examination of a patient presenting with chronic abdominal pain should also include a digital rectal examination and visual inspection of the perineum.[61]

Investigations. The concept of "alarm features" or "red flags" has helped to validate the positive predictive value of symptom-based criteria for IBS,[66] and this approach can be applied to the diagnosis of CAPS.[67] In general, a minimal diagnostic workup should include routine laboratory tests to exclude inflammation and signs of GI bleeding (eg, anemia and fecal blood loss).[68] If alarm features are identified based on patient history, physical examination, or laboratory screening investigations, the physician should investigate appropriately for potential causes of abdominal pain other than CAPS.

Differential diagnosis. Various other DGBI are important differential diagnoses from CAPS. If pain is intermittent and patients have major relief from symptoms with defecation, IBS is the most likely diagnosis, and if the pain is mainly intermittent and situated in the epigastrium or the right upper quadrant, alternative diagnoses to consider include functional dyspepsia or functional biliary pain.

Many systemic illnesses that originate in, or involve, GI organs[69] produce chronic abdominal pain, that is, acute porphyria, diabetes mellitus, malignancies, thoracic disc herniation,[70] or spinal cord injury.[71] An important differential diagnosis from CAPS is chronic mesenteric ischemia[72]; its characteristic features are postprandial abdominal pain, fear of eating, and weight loss. Moreover, intra-abdominal vascular entrapment syndromes, such as median arcuate ligament syndrome and superior mesenteric artery syndrome, nutcracker syndrome, May-Thurner syndrome, endometriosis or other gynecological causes,[73] and abdominal wall pain due to anterior cutaneous nerve entrapment syndrome,[74] should be considered. These conditions should be ruled out by testing only if there is corroborating evidence that a specific condition has a strong likelihood of being the cause of the symptoms.

CAPS must also be differentiated from feigned pain or malingering, which are defined as the intentional production of false or grossly exaggerated physical symptoms with the intention of attaining secondary gain (eg, avoiding work, seeking disability or malpractice compensation, or obtaining drugs).[67] It should also be stressed that feigned pain or malingering is different from factitious disorder, in which external incentives are not the motivation for symptom production.[34] Quantitative sensory testing can also provide an understanding of the pain mechanisms under normal and pathophysiological conditions.[56]

Treatment

Establishing an effective provider-patient relationship. A successful provider-patient relationship requires both parties to bring to the table a set of tools that can facilitate effective communication and collaboration.[48,75]

Patient-related issues. There are several key attitudes that patients with CAPS need to understand and accept.

Realistic expectations concerning treatment. The clinician must help the patient develop realistic expectations regarding the management of a chronic disorder.

Readiness to enter into a therapeutic relationship. Patients with chronic pain may feel helpless and dependent on the clinician and may thus take little responsibility for their pain management.

Readiness to take responsibility for care. For CAPS in particular, responsibility for care needs to be shared because this approach improves clinical outcomes.[76]

Physician-related issues. There are several key features for the physician to apply in the care of patients with CAPS[48]:

1. Listen actively
2. Accept CAPS as a true disorder
3. Offer empathy
4. Use a questioning style and nonverbal messages
5. Validate
6. Set realistic treatment goals
7. Educate
8. Reassure
9. Negotiate
10. Maintain boundaries
11. Be aware of time constraints

General principles of treatment. Below are a few general principles that must be considered before undertaking specific forms of treatment[77]:

1. Base treatment on symptom severity and the degree of disability
2. Know when to refer to a mental health care professional
3. Know when to refer to a multidisciplinary DGBI or pain treatment center
4. Be aware of sociocultural bias
5. Recommend face-to-face practice rather than virtual appointments

Pharmacological therapy. Medical treatment is more likely to be effective if the physician provides it within a well-developed patient-physician relationship using effective communication skills[48] and, particularly for CAPS, a comprehensive biopsychosocial illness theory and treatment plan.[48] The following guidelines will help medical providers use the more appropriate medications to care for their patients with CAPS.

Central and peripheral neuromodulator medications. We presume that patients with CAPS category A in whom association with physiological events does not exist and the pain is considered to occur due to central mechanisms will be more likely to respond to centrally acting neuromodulators[78] and those with category B may respond to both central and peripheral neuromodulators, such as antispasmodics and laxatives, because of the association with physiological events.

The rationale for the use of central neuromodulators for centrally mediated abdominal pain syndrome. Based on the Rome Foundation's definitional guidelines,[79] gut–brain neuromodulators describe medications that work in the brain and gut and/or along the gut–brain axis. Peripheral neuromodulators work mainly on the primary afferent nerves and the enteric nervous system. Central neuromodulators are the primary pharmacologic agents for treating chronic moderate to severe pain. Pharmacologic treatments directed toward the gut (eg, probiotics, antibiotics, secretagogues, bile acid sequestrants, and serotonin antagonists) will likely not be effective for CAPS category A and may have a partial effect for category B. In general, treatment for CAPS requires centrally targeted medications such as central neuromodulators or other "brain–gut axis therapies."[49] These treatments also apply to CAPS category B. The rationale and scientific basis for the information and recommendations are discussed below.[76,79,80]

Antidepressants. Tricyclic antidepressants (TCAs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) activate norepinephrine and serotonin (5-hydroxytryptamine [5-HT]) and effectively treat chronic pain in DGBI[81,82] directly through analgesic and indirectly through antidepressant and anxiolytic effects. They are also commonly used for unexplained somatic symptoms and syndromes. Adverse effects are usually immediate over the first several days and diminish over a week or so, and the benefit of an antidepressant in reducing pain may take several weeks.[83]

Tricyclic antidepressants. First-line treatment involves TCAs, as they have been the most extensively studied. Moderate dosages (10–25 mg building up to 75 or 100 mg, depending on the specific agent) are commonly used. Secondary amine TCAs (ie, desipramine and nortriptyline), compared with tertiary amine TCAs (ie, amitriptyline and imipramine), are favored because they have less anticholinergic and antihistaminic adverse effects.[80] They may also be used in higher dosages to manage the pain.

Serotonin-norepinephrine reuptake inhibitors. SNRIs may also be considered first-line treatment for pain management, as they have fewer adverse effects than TCAs and can be used in patients with constipation. Nausea occurs in approximately 15%–20%, but is minimized when taken with meals. Duloxetine is prescribed in 30–60 mg/d or 90 mg/d dosages, but venlafaxine requires higher dosages (>150 mg/d) to achieve noradrenergic activation.[79]

Selective serotonin reuptake inhibitors. Selective serotonin reuptake inhibitors are typically not helpful for CAPS. However, they can improve anxiety-related symptoms to augment low-dose TCA or SNRI use. Selective serotonin reuptake inhibitors can also help to improve constipation.

Atypical antipsychotics. The second-generation antipsychotics, such as quetiapine or olanzapine, may also be used as second-line augmenting agents for CAPS. In low dosages (eg, 25–100 mg once daily at bedtime compared with 400–800 mg for psychiatric disorders), quetiapine augments the pain benefit of TCAs or SNRIs.[84] In 1 study,

patients with painful IBS or CAPS who were unresponsive to 4 weeks of treatment with TCAs or SNRIs showed up to a 50% benefit.[84] The olanzapine[85] dose is approximately 10% of quetiapine, that is, 2.5–10 mg once daily at bedtime. As with all antipsychotics, however, there is a risk for metabolic and/or motor adverse effects.

Additional central neuromodulators. Gabapentin, pregabalin, and mirogabalin are anticonvulsant $\alpha 2\delta$ ligands used to treat several chronic pain syndromes, such as neuropathic pain (including visceral diseases such as chronic pancreatitis) and functional somatic syndromes, including fibromyalgia.[86,87] They may work by dampening dorsal horn signaling to the brain.[79] Buspirone (10–20 mg twice daily) or tandospirone (10–20 mg 3 times daily) is a nonbenzodiazepine anxiolytic (5-HT1A partial agonist) agent used in psychiatry to augment the effect of antidepressants and is used for functional dyspepsia.[88] Mirtazapine is a complex tetracyclic antidepressant (noradrenergic and specific serotonergic antidepressant) mainly used for treating depression and anxiety. At low doses it has antihistaminergic properties and at higher doses it has high noradrenergic activity together with high 5-HT1A receptor–mediated serotonergic activity. The dosage is usually 7.5–30 mg given at night because of its sedative properties. Weight gain frequently occurs.

Peripheral analgesics. Most nonopioid analgesics (eg, acetaminophen, aspirin, and nonsteroidal anti-inflammatory drugs) offer little benefit for chronic pain conditions, possibly because of local or anti-inflammatory effects rather than pain signaling. Narcotic analgesics must be avoided in CAPS because of the likelihood of addiction and the possibility of developing narcotic bowel syndrome (NBS)[5] (see below).[89]

Augmentation treatment. Usually, a second centrally acting agent[90,91] or one that acts peripherally or a brain–gut behavioral treatment is added to the antidepressant, which may then be lowered in dose. A low-dose atypical antipsychotic such as quetiapine may be added to a TCA or an SNRI to augment pain control, reduce anxiety, and enhance sleep.[84] When combining medications, it is important to have a familiarity with each agent's adverse effect profile and be aware of potential hazardous adverse effects to antidepressants, such as serotonin syndrome.

Symptom relapse prevention. Symptom relapse prevention relates to the concept that continued treatment with a neuromodulator beyond achieving clinical benefit will reduce the likelihood of relapse or recurrence.[92–94] Continuing or starting brain–gut therapies (eg, cognitive behavioral therapy [CBT] and hypnosis)[49] also reduces relapse risk.

For additional information for treating CAPS with central neuromodulators, see video at: https://romedross.video/neuromodulatorsgrandrounds.[79]

Brain–gut behavioral therapies. Several recent reviews summarized findings regarding these modalities for DGBI.[49,95]

Rationale for brain–gut behavioral therapies in the management of CAPS. Established psychological treatments[96] targeting the brain–gut pathway, including autonomic nervous system,[97,98] are likely to have a benefit. Psychological factors can amplify the experience of pain[99–102] and this attribute lends further rationale to the use of psychological interventions for the management of CAPS.[103]

Cognitive behavioral therapy. CBT is well-supported in the treatment of refractory DGBI, with the most robust data in IBS[96,104,105] and several chronic pain conditions.[106–108] CBT techniques focus on challenging negative or maladaptive thoughts. There are digital behavioral therapies that are showing promise to increase access and efficiency of care delivery.[109] Most CBT-mediated pain management programs have 2 components. First, psychoeducation is used to explain how individuals can gain control over their pain and how various cognitive-affective processes and behaviors serve to amplify pain experience.[110] Secondly, skills training is a strategy known to modify the pain experience. Skills might include relaxation techniques to modify arousal, reduce muscle tension, and alter attentional focus. Patients can be taught "distraction techniques."[111] CBT techniques focus on challenging negative or maladaptive thoughts, including pain catastrophizing (eg, belief that the pain is disabling) or unhelpful worry (eg, "What if it never gets better?").

Psychodynamic interpersonal therapy. Psychodynamic interpersonal therapy has been evaluated in some large randomized controlled trials of severe and refractory IBS.[112] Psychodynamic interpersonal therapy focuses on people's emotional state as opposed to their thought processes, the relevance of how prior experience (including early formative experiences)[113] can shape people's coping behaviors in response to pain[114] and illness and the influence on coexisting chronic stressors that impact recovery.[115] Psychodynamic interpersonal therapy appears to be particularly helpful for patients who report a history of sexual abuse.[116]

Hypnotherapy. Accumulating evidence suggests that gut-focused hypnotherapy is effective in relieving the symptoms of functional abdominal pain or IBS.[117–119] Postulated mechanisms of hypnosis effects include relaxation, inducing somatosensory experiences (eg, warmth), induction of sense of control over gut, and altered perceptual experience of symptoms.[120,121] Focusing on somatic awareness and down-regulation of pain sensations occur through techniques such as guided imagery and post-hypnotic suggestions.

Mindfulness and acceptance-based behavioral therapies. Mindfulness-based stress reduction[122] strives to improve one's ability to regulate attention to what is happening in the moment, without interpreting events, thoughts, or feelings. The practice of mindfulness helps patients separate the sensation of pain from their responses to the pain.[123,124] In IBS, mindfulness-based stress reduction can reduce visceral hypersensitivity, improve cognitive appraisal of symptoms, and improve quality of life. *Acceptance-based approaches* have also gained traction in the pain management literature as an effective treatment.[125] Research has shown that greater acceptance of

pain is associated with reports of lower pain intensity, less pain-related anxiety and avoidance, less depression, less physical and psychosocial disability, greater physical and social abilities, and greater work status.[126–128] In other pain syndromes, acceptance and commitment therapy is highly effective, but the research in painful DGBI is still ongoing.

Nonpharmacologic neuromodulation.

Acupuncture. Acupuncture[129,130] has been well documented in more well-defined diseases, such as acute[131] and chronic pancreatitis, where the latter is characterized with central reorganization and neuroplastic changes like in CAPS.[132]

Transcutaneous electrical nerve stimulation and neural blockade. Few reports have described the use of transcutaneous electrical nerve stimulation in patients with CAPS, and uncontrolled results are indeterminate.[133] Experimental studies have shown the effects of external transcutaneous vagal nerve stimulation (auricular or cervical) on motility and symptoms such as nausea and pain.[134,135] Percutaneous electrical nerve field stimulation showed effects on abdominal pain in a study.[136] Neurolytic celiac plexus blockade should be abandoned in benign diseases.[137]

Spinal cord stimulation. Spinal cord stimulation may have a role in patients after failed medical therapy,[138] but a specific clinical recommendation cannot be made.

Direct current stimulation. Transcranial direct current stimulation is a noninvasive method for brain stimulation based on low-intensity current that is delivered transcranially (1–2 mA) using relatively large electrodes generally placed on the scalp according to a bipolar montage (1 anode and 1 cathode).[139] With this rationale, neuromodulatory techniques,[140] including transcranial direct current stimulation, can also be tried in CAPS,[141] especially as transcranial direct current stimulation is inexpensive and has no major adverse effects.

Other interventions. Deep diaphragmatic breathing[142] and similar techniques can also be used partly as an activator of vagal pathways and, similar to electrostimulation, they can be beneficial in selected patients.[143,144]

D2. Abdominal Migraine

Definition

Abdominal migraines are stereotypical paroxysmal episodes of intense, recurrent abdominal pain associated with other symptoms, including pallor, headache, nausea, and vomiting. The symptoms may last for hours to days and resolve completely for weeks to months. Episodes may be associated with migraine headaches or CVS.

Epidemiology

No epidemiologic data existed for abdominal migraine in adults. However, results from the Rome V Global Epidemiology and Validation Study strongly support the considerable prevalence of abdominal migraine in adults. In children, abdominal migraine may range between 1.5% and 23% based on the diagnostic criteria used.[145,146] The study[146] that reported a prevalence of 23% used the *International Classification of Headache Disorders,* second edition.

D2. Rome V Diagnostic Criteria[a] for Abdominal Migraine[b]

Must include *all* of the following:

1. Paroxysmal, stereotypical episodes of intense abdominal pain lasting 1 hour or more, up to several days
2. The episodes are separated by weeks or months
3. The episodes occur at least 3 times per year and 2 times in the previous 6 months
4. The pain is incapacitating and interferes with everyday activities.
5. The pain is associated with 2 or more of the following
   - History of migraine headaches
   - Family history of migraine headaches
   - Anorexia, nausea, or vomiting with episodes
   - Photophobia
   - Pallor
   - Aura or prodrome preceding the full episode
6. After appropriate evaluation, no other medical condition can fully explain the symptoms.

[a]Criteria fulfilled for the last 3 months, with symptom onset at 6 months before diagnosis.
[b]Abdominal migraine is distinguished from CVS because the pain, not the vomiting, is dominant, and the vomiting is not repetitive.

Justification for Changes in Diagnostic Criteria

Abdominal migraine was first described in adults more than 100 years ago.[147] The author reported attacks of epigastric pain lasting for several days, associated with nausea and vomiting, and there was a personal or family history of migraines. Subsequently, attention to this disorder focused on children, beginning when Wyllie and Schlesinger[148] reported a recurrent abdominal pain syndrome associated with migraine headaches. In Rome II, abdominal migraine was recognized as a pediatric diagnostic entity[149] and it has continued as such through Rome V. The *International Classification of Headache Disorders,* third edition, also classifies abdominal migraine in children.

On approval of the Rome V Editorial Board, this committee members agreed to create a new category for adult abdominal migraine for several reasons. This diagnosis (1) is commonly accepted in children with abdominal pain, as dominant features including adolescents and like CVS may exist in adults; (2) is recognized in clinical practice by Rome Foundation members who see a large cohort of adults with episodic abdominal pain; (3) is likely underrecognized, as there is no diagnostic standard; and (4) was first reported in adults but was lost to further investigation. We also believe there is a gap need for this entity, as the clinical features are different from, for example IBS, because it is not associated with constipation or changes in bowel function, although diarrhea may be present.

Pathophysiology

As with all painful DGBI, the pathophysiology is multifactorial and overlapping. Like the pediatric entity, abdominal migraine has overlapping clinical and

pathophysiological features with CVS and migraine headaches. This overlap is clinically well recognized.[150] Although abdominal pain is not a criterion for CVS, many patients with CVS also have severe abdominal pain during vomiting episodes (vis-à-vis concurrent abdominal migraine). A history of migraine headache in a first-degree relative may occur in 34%–90% and a personal history of migraines occurs in 24%–57% of pediatric patients.[151] The co-association of these disorders has implications for treatment because the treatment strategies for migraine are effective in patients with abdominal migraine. In addition, the use of neuromodulators has been found to be effective for migraine, abdominal migraine, and CVS.[151]

Clinical Evaluation

The evaluation begins with a detailed history and physical examination. The medical history identifies the characteristic features of the disorder, for example, intense, stereotypical episodes of severe abdominal pain in combination with long (weeks to months) intervening symptom-free periods between episodes. However, there may be an overlap of abdominal migraine with pain due to other DGBI, like IBS or CAPS. Episodes may last anywhere from 2 to 72 hours and average approximately 17 hours. The abdominal pain is usually noncolicky and frequently described as dull, periumbilical, epigastric, midline, or difficult to localize and nonradiating.[152] Psychological stress may trigger episodes. The pain is not related to eating or defecation. A history or family history of migraine is common and episodes may be associated with nausea and vomiting. Other triggers may include lack of sleep, infection, and possibly histamine/tyramine-containing foods as seen in migraine headaches.

The clinical features often typify the triad of abdominal migraine, migraine headaches, and CVS (Figure 4). Like migraine headaches, there may be nonspecific prodromal symptoms, such as behavior or mood changes; auras including flashing lights; photophobia; and vasomotor symptoms with pallor and flushing. Seventy percent of patients have a history of migraine headaches. A history of symptom relief with antimigraine therapy further supports the diagnosis.[152]

Anorexia and nausea are commonly present, but vomiting is less severe than in patients with CVS. Diarrhea may also be present. Although pain is not a criterion for CVS, the presence of episodic pain with severe vomiting signifies overlap of abdominal migraine with CVS and the predominant symptom should direct the physician to the primary diagnosis and treatment approach. Pallor is commonly reported and may be related to autonomic instability during episodes.

Diagnosis involves fulfilling the Rome V criteria for abdominal migraine and an appropriate evaluation to exclude other diagnoses that may explain the symptoms. The paroxysmal nature of the episodes and their stereotypical features usually point to the correct diagnosis, precluding efforts to order expensive or invasive investigations. Chronic diseases, such as inflammatory bowel disease, rarely follow this episodic and distinct pattern and are often daily and ongoing. Furthermore, the absence of symptoms for weeks to months and a negative evaluation between episodes are uncommon in patients with chronic GI disorders.

Routine screening laboratory investigations, including complete blood count, complete metabolic profile, C-reactive protein, and fecal calprotectin, help evaluate for inflammatory conditions. Red flags require

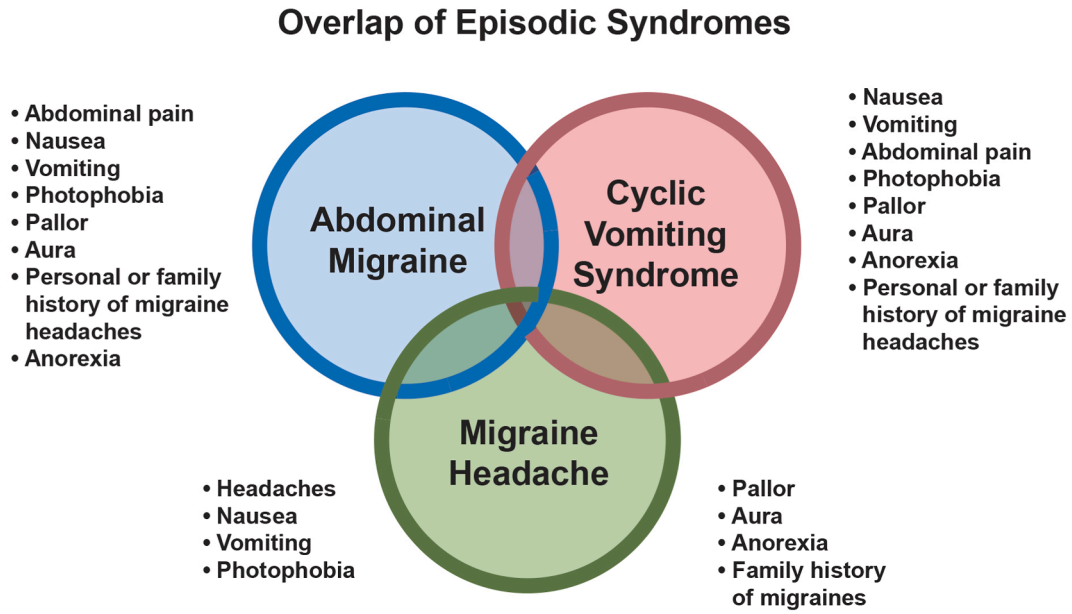

Figure 4. Overlaps among abdominal migraine, CVS, and migraine headaches. Patients with these 3 clinical conditions share common phenotypical features. They are all episodic and stereotypical in their clinical presentation and overlap in terms of associated symptoms, as noted above.

further evaluation, including weight loss, abnormal screening laboratory studies, abnormal physical examination, blood in the stool, or protracted vomiting. Given the severe nature of the symptoms, which frequently require emergency department visits, cross-sectional imaging modalities such as ultrasound, computed tomography, or magnetic resonance imaging are usually performed and are recommended if not done. However, repeat evaluation is not recommended unless the clinical features change.

Treatments

Like migraine headaches and CVS, treatment is aimed at aborting acute episodes and at prophylaxis to prevent future attacks. Treatment for acute attacks is like that for patients with other severe abdominal pain types, including intravenous hydration, antiemetic medication, and opioids when needed. Triptans empirically show benefits in aborting an acute attack.

For prophylactic therapy, β-blockers (eg, propranolol), calcium channel blockers (eg, flunarazine), serotonin antagonists (eg, cyproheptadine and pizotifen), and γ-amino butyric acid agonists (eg, valproate) are all used to treat cephalic migraine and are also used for abdominal migraine.[151,153] One double-blinded controlled study using pizotifen, an antimigraine medication, in children with abdominal migraine showed significant improvement in pain severity and days of abdominal pain over 4.[154] As a DGBI, we also recommend neuromodulators, either TCA (eg, desipramine or amitriptyline) or SNRI (eg, duloxetine)[79] and brain–gut therapies, including CBT.[49] Management of acute episodes may include triptans; pain relief, including intravenous paracetamol, nefopam, short-term opioids; antiemetics if there is nausea and vomiting, and histamine H1 receptor antagonists. Clinical trials with new antimigraine agents (eg, lasmiditan, galcanezumab, erenumab, and fremanezumab) for abdominal migraine are expected.[155–157]

D3. Narcotic Bowel Syndrome or Opioid-Induced Gastrointestinal Hyperalgesia

Definition

Opioid-induced hyperalgesia resulting from long-term opioid use is well recognized,[158–161] but in some patients abdominal pain is the primary manifestation and is referred to as NBS.[89] NBS was first described more than 30 years ago in the context of chronic opioid use. The defining feature of NBS is abdominal pain that escalates as the analgesic effect of opioids wanes between doses. NBS is characterized by the development of escalating abdominal pain in the context of continuous or escalating dosages of opioids.[5,89]

Epidemiology

The epidemiology of NBS is incompletely characterized, but the Rome V Global Epidemiology and Validation Study proved its presence. In a large community-based study, the prevalence of NBS was reported to be 0.17%, rising to 4%,[162] 3%,[163] or 6%[164] of those prescribed regular opioids. NBS has a female preponderance and its incidence peaks in the fifth decade. It is associated with comorbid chronic pain syndrome and higher educational attainment.[165,166]

D3. Rome V Diagnostic Criteria[a] for Narcotic Bowel Syndrome or Opioid-Induced Gastrointestinal Hyperalgesia

Must include *all* of the following:

1. Chronic or frequently recurring abdominal pain[b] that is treated with narcotics.
2. The nature and intensity of the pain are not explained by a current or previous GI diagnosis.[c]
3. Two or more of the following:
   a. The pain worsens or incompletely resolves with continued or escalating dosages of narcotics.
   b. There is a marked worsening of pain when the narcotic dose wanes and improvement when narcotics are reinstituted (soar and crash).
   c. There is a progression of the frequency, duration, and intensity of pain episodes

[a]Criteria fulfilled for the last 3 months, with symptom onset at least 6 months before diagnosis.
[b]Pain must occur most days.
[c]A patient may have a structural diagnosis (eg, inflammatory bowel disease or chronic pancreatitis), but the character or activity of the disease process is not sufficient to explain the pain.

Justification for Changes in Diagnostic Criteria

The NBS criteria were created from empiric observations of patients referred to a neurogastroenterology clinic.[89] Consistent with the Rome IV criteria, in a patient with abdominal pain and opioids and no other diagnosis to explain the symptoms, 2 or more of the 3 remaining items listed in the criteria above were permitted to make the diagnosis.

Opioid-induced gastrointestinal hyperalgesia. Distinctions exist between NBS and opioid-induced bowel disorder or opioid-induced constipation[167] because the former leads to hyperalgesia due to disturbances in CNS pain regulatory pathways.[5,89] Opioid-induced bowel dysfunction, in contrast, is often a dose-related motility problem and sphincter dysfunction caused by the peripheral effects of opioids on μ-receptors, manifesting as nausea, vomiting,[168] gastroparesis, ileus, pseudo-obstruction, and constipation. A subset of opioid-induced bowel dysfunction termed "opioid-induced constipation" is primarily defined by peripheral opioid effects specifically on the colon (see Rome V bowel disorders).[169]

Pathophysiology

Opioid receptors are present throughout the GI tract and the CNS. There is a seemingly paradoxical effect of opioids in NBS based on the evidence that opioids can both inhibit and facilitate pain signals.[170–172] The same central neurobiological systems that facilitate analgesia with short

courses of opioids may intensify the pain experience with chronic opioid use.[173,174] Although the specific mechanisms of NBS remain to be fully elucidated, the mechanisms of opioid-induced hyperalgesia, as frequently reported for somatic pain,[175] are likely to play a role.

Opioid-induced hyperalgesia likely has a physiological meaning.[176,177] Although there are several putative mechanisms to explain the central hyperalgesia caused by opioids, perhaps the most favored potential mechanism is that of glial cell activation in the dorsal horn of the spinal cord, which up-regulates peripheral afferent nociceptive signals traveling cephalad.[178] Activated dorsal horn glia (astrocytes and microglia) produce pro-inflammatory cytokines, nitric oxide, and excitatory amino acids (Figure 5). This event leads to central hyperalgesia with enhanced pain. Glial cell activation occurs in response to inflammation or infection; drugs such as morphine, an endogenous chemokine (fractalkine); peripheral injury; other activated glia; or even signals from the CNS, thus opening the possibility for central effects of stress on peripheral pain facilitation.[179]

Another factor contributing to pain intensity is the bimodal excitatory and inhibitory opioid modulation system in the dorsal horn. Activation of the Gi/Go protein-coupled inhibitory receptor leads to analgesia,[180] whereas activation of the Gs protein excitatory receptor produces hyperalgesia; these effects depend on the opioid concentration and treatment duration, as these factors impact how opioids modify action potentials.

A third potential contributing factor recognizes that descending pathways originating from the cingulate and prefrontal cortices, the rostral ventral medulla, and the periaqueductal gray can produce antinociception, although descending tracts passing through the dorsolateral funiculus can enhance pronociceptive input.[181]

Clinical Evaluation

Patients with NBS usually present with moderate to severe; colicky; or persistent, poorly localized abdominal pain.[182] They may have been prescribed opioids for intra-abdominal (eg, chronic pancreatitis, inflammatory bowel disease, and CAPS) or extra-abdominal (eg, orthopedic pain, fibromyalgia, or migraine headaches) diseases or after surgery for increasing discomfort. After using opioids for intermittent pain, patients may acquire tolerance and

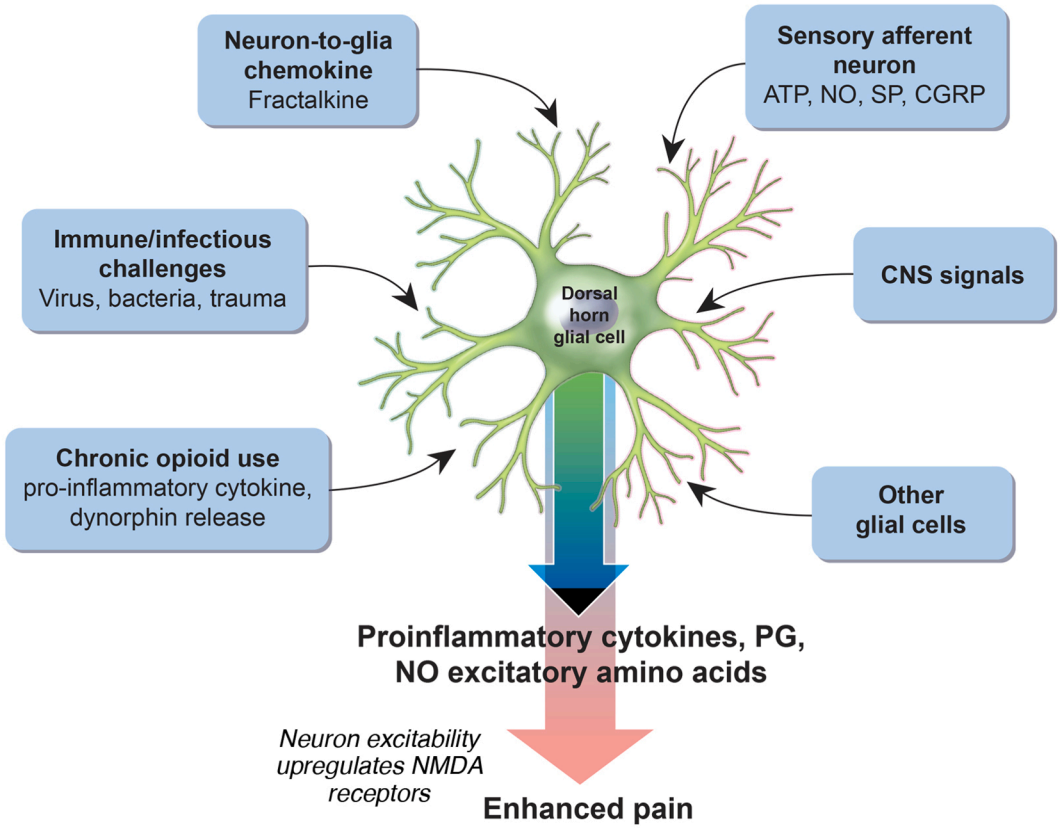

Figure 5. Activation of dorsal horn glia cell. The activation of dorsal horn glia cells, which leads to central hyperalgesia and enhanced pain, occurs in response to various noxious stimuli, including fractalkine release, infection, CNS signals, other activated glia, or chronic opioid use. This event leads to a vicious cycle of releasing proinflammatory cytokines, nitric oxide and excitatory amino acids, which increase neuronal excitability, promote N-methyl-D-aspartate receptors upregulation and ultimately enhance pain. ATP, adenosine triphosphate; CGRP, calcitonin gene-related peptide; NO, nitric oxide; PG, prostaglandins; SP, substance P. From Grunkemeier et al,[89] reproduced with permission.

tachyphylaxis, requiring higher dosages for clinical benefit.[183,184] Later, abdominal pain can become continuous and severe despite ongoing treatment.[89]

Although not confirmed for NBS, certain drugs have been found to induce opioid-induced hyperalgesia more frequently. These are fast-acting opioids such as fentanyl, remifentanil, and sufentanil.[185,186] However, fast-acting opioids are seldom used in longer-lasting treatments and hyperalgesia can also be a consequence of treatment with morphine and oxycodone.[176] However, methadone (with an agonistic effect on the N-methyl-D-aspartate receptor) might prevent opioid-induced hyperalgesia and, in fact, it has been used in treatment.[187] Buprenorphine may also have an antihyperalgesic effects, although mainly shown in experimental studies.[188] As such, it may be less prone to develop NBS and the patch formulations may give an advantage in patients with potential dysfunctions in the GI tract.[56] Therefore, information about medication use may also provide support for the diagnosis.

Patients with NBS also typically have significant psychosocial disturbances, including anxiety, depression, somatization, post-traumatic stress disorder, and personality disorders. The association of NBS with psychosocial disturbances often occurs with high health care use and increased health care expenditures due to procedures, surgeries, and medications.[189] These comorbidities are consistent with other GI and non-GI chronic pain syndromes. These features are helpful for diagnosis as related to treatment planning. However, they are not included in the diagnostic criteria for NBS.

Patients with NBS may have undergone extensive laboratory studies, typically producing normal results, and radiologic studies may show colonic fecal retention and/or signs of "ileus" or "incomplete bowel obstruction." Cross-sectional imaging is often performed to exclude obstruction, pancreatitis, inflammatory or ischemic bowel, or other intra-abdominal pathologies. These negative results, in addition to a focused history and physical examination and satisfaction of the diagnostic criteria for NBS, should be adequate to make the diagnosis of NBS.

NBS is a positive diagnosis that can occur solely (ie, in a patient developing abdominal pain after an operation or treatment for back pain) or it can be present alongside other structural GI disease, when the pain is out of proportion to the pain inferred to be from the structural disease.[190]

Identification of drug-seeking behavior. It is important to recognize that among those patients who report abdominal pain when on opioids, a subset may have a substance use disorder (ie, opioid use disorder).[191] Patients identified to exhibit these features should be referred to a substance abuse program and should not be treated for NBS, as recommended below.

Treatment

Understanding the patient. Patients with NBS are reluctant to stop using opioids, as they fear worsening pain. They also feel stigmatized by others (including health care providers) who view them as "drug-seeking" or having a psychiatric problem. By understanding these beliefs, the clinician can explore and address these, thereby delivering more effective treatment.

Clinician considerations in the treatment. A sound patient-physician relationship via good communication skills is a prerequisite to treating patients with NBS.[48,192] The clinician must feel committed to working with patients having this challenging diagnosis and be aware of possible unfavorable feelings toward patients perceived as "difficult."

Educating about the treatment. Once a commitment to treat is made, the physician must engage with the patient and discuss NBS and treatment options, including opioid detoxification. The Current Opioid Misuse Measure[193] might serve as a valuable tool to determine the severity of opioid misuse and the likelihood of successful detoxification.

Negotiating the treatment. Negotiating the treatment requires mutual trust and patient engagement in a shared plan of care.[48,79,89]

Treatment plan. Recommended protocols are published and reviewed elsewhere.[194]

To date, 1 study has evaluated the clinical outcome of NBS using an opioid detoxification protocol (Table 1).[165] The study involved 39 systematically detoxified patients in an inpatient medical facility. Detoxification lasted approximately 7 days and was successful in 89.7% of patients. A total of 60% of the participants were considered "responders" based on rigorous predefined criteria and only 11% of the patients reported worse pain after detoxification. The Current Opioid Misuse Measure[193] identified patients likely to be substance abusers. A low score (ie, few aberrant drug-related behaviors) was associated with successful responder status and an ability to remain off opioids at follow-up. When re-evaluated at 3 months post-detoxification, 43.2% of the patients had restarted opioid medications (and were more likely to have high Current Opioid Misuse Measure scores). At the end of the study follow-up period, more than two-thirds of the patients had restarted opioids. However, patients who remained off opioids at 3 months post-detoxification reported significantly lower abdominal pain scores than those who resumed opioids.

The results support the premise that opioid withdrawal can relieve NBS and that the pain reduces further when remaining off opioids. The clinician may refer the patient to a pain management program for further treatment, including detoxification.

Although not yet systematically studied in NBS, low-dose ketamine is proving to be an effective strategy as a substitute for opioids for chronic pain.[195] Ketamine is an N-methyl-D-aspartate receptor antagonist[196,197] that induces the release of nitric oxide and has anti-inflammatory effects. It has been found to have positive effects in patients with opioid induced hyperalgesia.[198,199]

Behavioral intervention strategies. NBS is a complex biobehavioral disorder with a high recidivism rate after detoxification. In part, this relates to enabling psychosocial

Table 1. Opioid Detoxification Protocol

Treatment approach: opioid detoxification
Effective communication with patient about pain management
Add TCA or SNRI before detoxification
Add augmenting agents as needed
Clonidine to prevent withdrawal symptoms
Mirtazapine for nausea
Quetiapine for sleep and pain management
Benzodiazepine for anxiolysis during detoxification
Psychological treatment for psychosocial support and pain management
Narcotic withdrawal
Convert total narcotic daily dosages of all opioids to a morphine equivalent
Give this daily dose as a continuous intravenous drip on day 1 and then reduce daily dosage by a fixed proportion (10%–33% predetermined) each day until off narcotics (usually 4–11 days)
Start clonidine at point 50% opioid withdrawal
Given 0.1 mg bid or tid and titrate up 0.6 mg/d as needed
Taper off at end of detoxification
By agreement once detoxification starts, the narcotic dosing does not change but augmenting agents may be used
Treatment of constipation
Use polyethylene glycol, a chloride channel activator, or a peripheral acting μ-opioid receptor antagonist as needed
Anxiety reduction
Use benzodiazepine IV or by mouth as needed on day 1 and adjust as needed to reduce anxiety
An atypical antipsychotic agent (ie, quetiapine or aripiprazole) may be substituted as needed
Psychological treatment
Consider having a mental health care provider available during detoxification
Augmentation treatments can be considered (eg, hypnosis, CBT, and medication)

From Drossman et al,[165] adapted with permission.
bid, twice daily; IV, intravenous; tid, 3 times daily.

factors and a health care system that can perpetuate NBS by maintaining the tendency for patients to remain on, or return to, opioids.

Medical treatment should continue using neuromodulators to raise the central pain threshold as well as concomitant treatment of psychiatric comorbidities such as anxiety and depression, see section on CAPS treatment for further details. An integrated model of care is needed with input from medicine and gastroenterology and psychology and psychiatry to provide CBT, hypnosis, or other brain–gut therapies leading to a long-term successful outcome. A recent study of patients with opioid-induced hyperalgesia showed superior pain tolerance in patients undergoing a combination of detoxification, psychotherapy, and medical management.[200] Please see the Supplementary Material for additional information.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2025.12.038.

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