A Review of Select Centralized Pain Syndromes: Relationship With Childhood Sexual Abuse, Opiate Prescribing, and Treatment Implications for the Primary Care Physician

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Abstract
Pain can be broadly divided into 3 classes, including nociceptive or inflammatory pain (protective), neuropathic (pathological, occurring after damage to the nervous system), or centralized (pathological, due to abnormal function but with no damage or inflammation to the nervous system). The latter has been posited to occur when descending analgesic pathways are attenuated and/or glutamatergic transmission is facilitated. Additionally, this “pain prone phenotype” can be associated with early life trauma and a suboptimal response to opiates. This article will review the relationships between centralized pain syndromes (ie, fibromyalgia, chronic low back pain), childhood sexual abuse, and opiate misuse. Finally, treatment implications, potentially effecting primary care physicians, will be discussed.

Keywords
centralized pain syndromes, childhood sexual trauma, opiate misuse, serotonin–norepinephrine reuptake inhibitors, anticonvulsants

Patients with unexplained chronic pain have been described for centuries in the medical literature, although the terms used to describe these symptom complexes have changed frequently. The currently preferred terms for these syndromes are names that describe the prominent clinical features of the illness without an inability to identify the cause.1 One such nomenclature includes the rubric “functional somatic syndromes (FSSs),” or symptoms for which no organic cause can be found, which are a set of conditions defined by expert consensus or research diagnostic criteria that lack currently understood physical or biological etiology or demonstrate inconsistent laboratory abnormalities. Although these conditions are often characterized by symptoms such as pain, they are typically complex conditions with a multiplicity of symptoms. Compared with other medical conditions, these “unexplained conditions” are also commonly associated with psychological trauma in childhood or adulthood. Owing to the absence of distinct biomarkers that help define a syndrome, there is an ongoing debate as to whether FSSs should be defined as separate entities or as one syndrome.2

Lifetime history of sexual abuse is estimated to range between 15% and 25% in the general female population; however, estimates of the prevalence of sexual abuse in the population differ widely due in part to the use of varying definitions and methodology to measure abuse. There is no gold standard for measuring sexual abuse history because many experiences may be difficult to categorize and although some researchers use “unwanted” sexual experiences in their definitions of abuse, most use the more stringent requirement of sexual acts that result from use of force or threatening harm. Nonetheless, people who are sexually abused are at greater risk of a whole

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host of physical health disorders that may occur many years after the abusive incidents.³

Pain may be mechanistically characterized as peripheral/ non-nociceptive, neuropathic, or non-nociceptive/“central pain syndromes (CPSs),” each with its own underlying pathophysiology. Many investigators now believe that non-nociceptive/ CPS (aka, “chronic pain”) is itself a disease, and the location of the body where it arises may not be as relevant as an individual’s genetically determined pain sensitivity, combined with neuroplastic changes that can occur in the central nervous system (CNS) that lead to augmented pain transmission. These non-nociceptive pain states can be triggered by an initial peripheral injury or inflammatory process and may be regional or widespread. The concomitant influence of a separate outside stressors (ie, infection or trauma) may also play a role in the chronicity of the disease.⁴

Central sensitization (CS) is a proposed physiological phenomenon in which dysregulation in the CNS causes neuronal dysregulation and hyperexcitability, resulting in hypersensitivity to both noxious and non-noxious stimuli. Central sensitization has been proposed as the root etiology to a group of medically indistinct disorders for which no organic cause can be found, that is, CPS. These include fibromyalgia, irritable bowel syndrome (IBS), and tension headache/migraine, among others. These disorders are highly intercorrelated, share many common symptoms, including pain, and all demonstrate evidence of CS. Furthermore, several studies link childhood psychosocial trauma to the development of a CSS, although this association is complex.⁵

The purpose of this review is to examine non-nociceptive CPS in a way that focuses both on the similarities and on the differences between the syndromes, which may provide a better understanding of their etiology and inform future treatment. Additionally, we will review the relationship between adults with a history of childhood sexual abuse (CSA) and the CPS. Because not all physical symptoms are more highly represented in those with abuse history, we will summarize the physical symptom clusters most commonly associated with abuse history, including the CPS (“regional”) of abdominal pain/gastrointestinal disorders, pelvic pain/gynecologic disorders, and headache and low back pain (LBP), and the chronic widespread pain disorder of fibromyalgia. ³⁴ ⁶ ⁸ Finally, we will discuss the role of CS in the possible pathogenesis of CPS, and treatment implications, including the use of opiates in patients with CPS.

### Chronic Pelvic Pain

Chronic pelvic pain (CPP) is defined as “nonmenstrual pain of 6 or more months duration that is severe enough to cause functional disability or require medical or surgical treatment, p. 1557.” ³⁹ For these patients, this condition results in an overall decrease in their general state of health and quality of life. Chronic pelvic pain is estimated to account for up to 10% of all visits to gynecologists.¹⁰ It is the indication for 12% of hysterectomies and over 40% of gynecologic diagnostic laparoscopies, making it a major source of health care utilization.¹¹

Chronic pelvic pain has many etiologies covering several organ systems, including endometriosis, pelvic inflammatory disease, adhesions, IBS, and interstitial cystitis. However, in more than 50% of cases of CPP, the cause remains unknown. The diagnostic process usually includes a thorough history and physical, including a pelvic examination which may cause additional pain and suffering to the patient. Guided by appropriate clues from the initial evaluation, gynecologists may order further diagnostic tests including a pelvic ultrasound, a diagnostic laparoscopy, and a complete blood count.¹⁰

Chronic pelvic pain has long been known to be associated with a history of sexual abuse, with reports of 25% of newly diagnosed patients reporting a history of sexual abuse. These women have been reported to have worse daily functioning due to poor health, more dysfunction from pain, more medical symptoms and lifetime surgeries, and more days spent in bed compared to those with CPP without an abuse history.¹²

See Table 1 for evidence-based treatment of CPP.

Both medical and surgical approaches have been shown to yield similar rates of remission of the chronic pain. Despite aggressive treatments, up to 54% of women still experience chronic pelvic pain 12 months after medical or surgical therapies. These results suggest that in a significant number of patients having CPP, the cause may be CPS.³⁴

### Chronic Abdominal Pain/Irritable Bowel Syndrome

Functional gastrointestinal disorders (FGIDs) are a group of more than 20 conditions that result in impaired functioning of the gastrointestinal tract without a clear source of structural or biochemical abnormality. The most common of these conditions is IBS. As defined by the Rome III criteria, IBS is recurrent abdominal pain or discomfort occurring at least 3 days a month in the last 3 months associated with 2 or more of improvement with defecation, onset associated with a change in frequency of stool, and onset associated with a change in the form (appearance) of stool.³⁵ The definition of discomfort is further defined to be an uncomfortable sensation not described as pain. Symptoms of IBS can show considerable fluctuation over time. Onset of symptoms is noted to occur with an average of 4 distinct episodes of symptoms per month, each episode lasting up to 5 days.¹³ By 1 year of diagnosis, nearly 30% to 45% of patients will have a prolonged period of time symptom free.³⁶ Ultimately, however, 50% to 75% of patients with IBS will report persistent symptoms.³⁷

The pathophysiology of functional abdominal pain is incompletely understood although it has been postulated that peripheral sensitization of visceral afferents, CS of the spinal dorsal horn, and aberrancies within descending modulatory systems may have an important role.³⁸

Psychiatric conditions are also frequently comorbid in IBS evidenced by rates of depression at 31.4% in patients with IBS compared to 17.5% for controls and rates of generalized anxiety disorder at 16.5% for patients with IBS compared to 3.3% for controls.³⁹ ⁴⁰ Interestingly, among patients presenting with
| Centralized Pain Syndrome | Epidemiology | Evidence-Based Treatment | Comorbidity With Sexual Abuse |
|---------------------------|-------------|--------------------------|-------------------------------|
| Fibromyalgia              | 2% of US population<br>10 times more common in women | Both pharmacological and nonpharmacological interventions. Pharmacological therapies generally work in part by reducing the activity of facilitatory neurotransmitters (e.g., gabapentinoids reduce glutamate) or by increasing the activity of inhibitory neurotransmitters such as norepinephrine and serotonin (e.g., tricyclics, serotonin/norepinephrine reuptake inhibitors). A hyperactive endogenous opioid system may explain why opioids appear to be ineffective and low-dose naltrexone is a promising new treatment. The 3 best-studied nonpharmacological therapies are education, cognitive behavioral therapy, and exercise. Although in some trials the magnitude of the treatment response for these therapies often exceeds that for pharmaceuticals, comparatively, there is no clear evidence that a single intervention works best. | OR 1.94, CI 1.36-2.75 with a history of sexual abuse in childhood (10 studies; n = 13 095) | Three times as likely to be sexually based and develop a GI disorder -Study showed 36% of patients with severe and 21% of patients with moderate IBS vs 10% of healthy controls have a history of sexual abuse (N = 1264) |
| Irritable bowel syndrome (IBS) | 3.0-20.4% (lowest and highest estimated prevalences, respectively) of the US population<br>Rates of IBS higher in women, with an OR of 1.67 | Lubiprostone and linaclotide are novel agents, FDA approved for the treatment of IBS-constipation (C). Fiber supplements are not regulated by the FDA, but found to be efficacious. Antispasmodics used include peppermint oil, dicyclomine, and hyoscyamine. Loperamide has been found to be efficacious for multiple symptoms. Selective serotonin reuptake inhibitors: citalopram, fluoxetine, and paroxetine-efficacy data have been conflicting, but generally favorable. The tricyclic antidepressants, including amitriptyline, desipramine, imipramine, and doxepin have been studied extensively in the setting of IBS. Imipramine was found to have no benefit; but the others demonstrated efficacy at doses much lower than when used for treatment of major depression. Small studies have shown that both pregabalin and gabapentin improve IBS symptoms in persons with all types of IBS and IBS-C, respectively. Cognitive behavioral therapy (CBT) is also significantly associated with an improvement in symptoms. | OR 2.24, CI 1.07-4.70 with a history of sexual abuse in adulthood (4 studies; n = 13 095) | |
| Chronic pelvic pain (CPP) | 15% of women | Nonnarcotic analgesics, including acetaminophen, acetylsalicylic acid, and nonsteroidal anti-inflammatory drugs, are considered first line. Hormonal methods, considered second-line medications, especially if the pain has a cyclical pattern. Can include oral contraceptive pills, continuous prostegins, or gonadotropin-releasing hormone agonists. Conditions that have been shown to respond include endometriosis, interstitial cystitis, and irritable bowel syndrome. For refractory pain, options include tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and, as a last resort, opioids. Surgical management: nerve ablations have limited therapeutic value and only help midline pain. Hysterectomy with oophorectomy relieves pain for 60% to 95% of women but is less effective for women younger than 30 with no identified pelvic disease or with comorbid psychological problems. | 3.5 times more likely to have been sexually abused as an adult (N = 64 286) | 1.5 times more likely to have been sexually abused as a child (N = 64 286) |
first-time complaints of IBS, the severity of the anxiety and depressive features does not appear to differ greatly by the age of the patient; rather, only the severity of abdominal pain is more pronounced in younger ages. The extent of sites of FGID has been strongly related to trait anxiety in males and depression in females.

Importantly, there also tends to be a high prevalence of childhood and adult sexual abuse in patients with FGID as outlined in Table 1. Also, see Table 1 for a review of evidence-based treatments for IBS.

The expected treatment response for IBS varies considerably depending on the etiology of the disease process. In particular, IBS has been shown to have a significant relationship with a number of psychosocial factors including anxiety, depression, and abuse. More specifically, among patients who have been abused, a number of studies have shown these individuals are more likely to report functional gastrointestinal complaints, psychiatric symptoms, poorer adjustment to illness, and also a poorer health status in IBS. An extensive systematic review and meta-analysis analyzing a history of sexual abuse and lifetime diagnosis of somatic disorders found that patients with a history of sexual abuse had an increased risk of lifetime development of a FGID (OR 2.43; 95% CI, 1.36-4.31). Additionally, an association exists between a history of childhood abuse and the later development of a FGID later in life. Finally, patients with a history of sexual abuse may have different pain thresholds that can change their expected response to treatment. Evidence for this comes from a study comparing the rectal pain and urge thresholds in patients with IBS with and without a history of sexual abuse.

### Table 1. (continued)

| Centralized Pain Syndrome | Epidemiology | Evidence-Based Treatment | Comorbidity With Sexual Abuse |
|---------------------------|--------------|--------------------------|-------------------------------|
| Chronic daily headache (CDH) | 4.1% of US population | Treatment can be divided into nonpharmacological and pharmacological management (Silberstein et al., 2002). Nonpharmacological management includes exercise, smoking cessation, and proper sleep hygiene. Behavioral treatments, including relaxation therapy, cognitive behavioral therapy, and biofeedback. Pharmacologic therapy can be separated into 2 groups: abortive vs preventative. Abortive medications include dihydroergotamines, triptans, neuroleptics, corticosteroids, valproate sodium, magnesium, or ketorolac. Preventative medications include antidepressants, β-blockers, antiepileptics, and calcium channel blockers. | 25%-40% have a sexual abuse history (3 studies; N = 161, N = 949, N = 593) |
| Chronic back pain | 10% prevalence 80% of population experience low back pain at some level | Acetaminophen is first-line therapy because of its high safety profile. Nonsteroidal anti-inflammatory drugs (NSAIDs) provide similar analgesia but have significant gastrointestinal and renovascular adverse effects. Skeletal muscle relaxants, including benzodiazepines (eg, diazepam and alprazolam), antispasmodic medications (eg, cyclobenzaprine, carisoprolol, and tizanidine), and antispasticity medications (eg, dantrolene and baclofen) are recommended adjunctively, and for a short course to acetamenophen or NSAIDs. Antidepressants (SNRI, TCA) are recommended by ACP/APS guidelines recommend, however a Cochrane review concluded that they are no more effective than placebo. Opioid analgesics or tramadol are listed as options, but not first line, in the ACP/APS guidelines, stating potential benefits and harms should be carefully weighed. Anticonvulsants have also been used for chronic pain. Carbamazepine and gabapentin result in short term benefit in patients with radiculopathy but have not been shown to be of benefit for chronic low back pain. | RR of 4.2 with history of sexual abuse (N = 142) RR of 1.61 with history of intimate partner violence (N = 3568) |

Abbreviations: ACP/APS, American College of Physicians/American Pain Society; CI, confidence interval; FDA, Food and Drug Administration; IBS, irritable bowel syndrome; OR, odds ratio; SNRI, serotonin–norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant.
Results of this study showed that patients with a history of sexual abuse had both a significantly greater rectal pain threshold \( (P = .015) \) and also higher threshold of urge to defecate \( (P = .001) \). Thus, the multifactorial etiology of IBS has a considerable effect on disease outcomes. In particular, there is evidence to suggest a relationship between a history of sexual abuse and the prevalence of IBS.\(^4\) This is an essential aspect of the patient history to assess, as it further carries implications about the impact of disease and response rate to treatment. Clinician awareness about this relationship can help to increase identification of a history of abuse and provide improved outcomes by focusing on patient-specific treatment measures.

**Chronic Daily Headaches**

The term chronic daily headache (CDH) encompasses a variety of headache diagnoses including chronic migraine (CM), chronic tension-type headache (CTTH), and new daily persistent headache.\(^4\) Of the CDH subtypes, CM and CTTH are considered the most prevalent with CMs encompassing 78% of CDH and CTTH encompassing 15.3%,\(^49,50\)

Chronic headaches are typically differentiated from episodic headaches based on frequency, as chronic headaches are usually defined as occurring >15 days/month, whereas episodic headaches are defined as occurring <15 days/month. Chronic daily headache are typically classified as having “long duration” of >4 hours/episode. Before the diagnosis of CDH can be made, other, secondary headache causes, such as medication overuse headache (MOH), cerebrovascular disease, neoplasms, trauma, infection, and musculoskeletal disorders, must be ruled out. The different subtypes of CDH with their varying presentations are listed subsequently. Although each subtype of CDH has its own unique signs and symptoms, all of the subtypes share the commonality of occurring greater than 15 days/month and lasting greater than 4 hours/occurrence.\(^4\)

Chronic Migraine is typically described as unilateral, pulsating headache that is aggravated by normal daily physical activity. It may be accompanied by nausea, vomiting, photophobia, or phonophobia. An “aura” may precede or accompany the migraine attack. The patient may report the presence of a trigger for the migraine attacks. Chronic Migraine is 3 times more common in females than males, and onset is typically between the ages of 20 and 30.\(^51\)

In CTTH, pain is typically bilateral with a “pressure-like” quality. Patients may describe the sensation as “wearing a tight hat or wearing a tight band” around their head. Pain is not worsened with physical activity, and the symptoms of nausea, vomiting, photophobia, and phonophobia are rare.\(^52\) Chronic tension-type headache is more common in women and caucasians with peak onset within ages 30 to 40.\(^53\)

New daily persistent headache is a relatively rare CDH subtype that has features similar to CTTH but is notorious for its resistance to common headache treatments. Headaches are daily and unrelenting and often do not respond to conventional treatments. Pain is bilateral with a “pressing quality” that is not exacerbated by physical activity. Onset is typically within third to fifth decade of life for women and in fifth decade of life for men.\(^52\)

Various risk factors leading to the development of CDH have been identified. Nonmodifiable risk factors for the development of CDH include but are not limited to female gender, caucasian race, recent major life-changing events, and lower socioeconomic class.\(^5,15,54\) Modifiable risk factors include obesity, snoring, comorbid pain, head/neck injury, high caffeine intake, and medication overuse.\(^55\) It is important to consider MOH, when working-up CDH, as it is a frequent comorbid condition. Substance abuse is relatively common with MOH, as 68% of patients with MOH and CDH met 3 of the 5 Diagnostic and Statistical Manual of Mental Disorders, (Fourth Edition), criteria of substance dependence versus 20% of those with CDH and without MOH.\(^56\) As such, medications that contain addictive substances, such as opioids, barbiturates, or other narcotics, should be avoided when treating CDH.

Multiple psychiatric comorbidities have been found to be associated with CDH. One study found that 90% of patients with CDH had at least 1 psychiatric disorder. The most common psychiatric disorders identified are depressive mood disorders and anxiety disorders.\(^16,17,57\)

Several studies have examined the link between CDH and sexual abuse. These studies suggest that the coincidence of sexual abuse and CDH ranges somewhere between 25% and 40%.\(^58-62\) A comparative study found that 40% of patients with CDH and 27.3% of patients with episodic migraines had sexual and/or physical abuse, thus suggesting that abuse may play a role in the development of headache chronicity.\(^63\) In support of this idea, abuse has been suggested to have a role in “transforming” migraines from an episodic type to chronic type.\(^17\)

For evidence-based treatment of CDH see Table 1. There is scarce literature regarding treatment of CDH with patients having a sexual abuse history. It has been found that behavioral interventions have been found to be the most beneficial in treating CDH with patients with significant psychiatry comorbidities.\(^63\)

**Chronic Low Back Pain**

Chronic low back pain (CLBP) has greater than 10% prevalence in the population;\(^18\) however, the symptom of LBP is experienced by greater than 80% of all adults at some point in their lives,\(^19\) and in 85% of the cases there is never a definite physiological cause determined.\(^64\) Acute episodes of back pain are usually self-limited. Patients with persistent or fluctuating pain that lasts longer than 3 months are defined as having CLBP. Back pain is the leading cause of disability in Americans below the age of 45. Studies have found that the incidence of low back pain is highest in the third decade, and overall prevalence increases with age until the 60 to 65 year age-group and then gradually declines.\(^65\)

The 2007 Joint Clinical Practice Guideline issued by the American College of Physicians and the American Pain Society encourages clinicians to perform a focused history and physical examination to classify patients into 1 of the 3 broad
categories: nonspecific LBP, LBP potentially associated with radiculopathy or spinal stenosis, or LBP potentially associated with another specific spinal cause. The medical history should include questions about osteoporosis, osteoarthritis, and cancer, and a review of any prior imaging studies. Review of systems should focus on unexplained fevers, weight loss, morning stiffness, gynecologic symptoms, and urinary and gastrointestinal problems. Imaging has limited utility because most patients with CLBP have nonspecific findings on imaging studies and asymptomatic patients often have abnormal findings. In a study, a random sample of 148 patients aged 36 to 71 years—nearly half of whom had never experienced back pain—found magnetic resonance imaging (MRI) evidence of annular tears, disk bulges, disk protrusions, facet joint degeneration, end plate changes, and mild spondylolisthesis. The authors concluded that such MRI findings are therefore of limited diagnostic value. The differential diagnosis of chronic low back pain includes nonspecific or idiopathic (70%), such as lumbar sprain or strain, mechanical (27%), such as degenerative processes of disks and facets or spondylitis, referred pain (2%), such as diseases of the pelvic organs, gastrointestinal disease, and renal disease, and nonmechanical (1%), such as neoplasia.

Practice guidelines for nonspecific LBP recommend providing patients with evidence-based education that emphasizes the favorable course of this condition and that encourages them to remain active. See Table 1 for evidence-based treatment recommendations.

Although there are several medical and psychosocial risk factors for the development of CLBP, women with a history of intimate partner violence have an increased likelihood of developing CLBP with a relative risk of 1.61 and those with self-reported sexual abuse have a relative risk of 4.2 when compared to women without a reported history of abuse. In these same experimental cohorts, mental disorders, substance abuse, and/or some type of chronic pain symptom were experienced with a 5-fold risk increase in women victims of intimate partner violence. Women with current back pain were found to develop worsening back pain or disability with an odds ratio of 2.65 if they had been sexually abused, compared to similar patients without history of abuse. Furthermore, histories of psychosocial risk factors are more likely to predict nonremittance of back pain symptoms and disability, than MRI or discography. Women currently on disability had a 19.2% reporting of intimate partner violence, with CLBP being the second highest reason for disability at 3.5%. This finding suggests that while CLBP may not be the most common manifestation following abuse, it has a high likelihood of manifesting with disabling symptoms. Male victims of sexual abuse were also considered in some of these studies; however, men did not have the same degree of increase in chronic back pain as females in these studies, and their increased risk was not statistically significant.

The previous studies considered abuse at all age-groups, but there is evidence that CSA alone without recurrent abuse in later life may be enough to predict CLBP in later life. This is a significant risk since 1 in 12 children are potentially exposed to sexual violence. The Ontario Child Health Study determined that one of the greatest predictors of chronic pain conditions, most notably CLBP and headaches, was associated with childhood abuse that included sexual abuse. Depression was the most common comorbid condition in these patients. The male gender was again considered protective in the development of chronic pain following sexual abuse.

The course of chronic LBP with history of CSA often does not respond to treatment, even after back surgery has been done to correct the underlying problem. When considering patients who underwent back surgery with no obvious physiologic identifiable underlying cause, 60% of this group that did not improve after surgery had 3 or more childhood predisposing traumas which included sexual abuse. Types of abuse considered in this study were physical abuse, sexual abuse, emotional neglect or abuse, abandonment, and chemically dependent caregiver.

Chronic Widespread Pain: Fibromyalgia

Fibromyalgia syndrome (FMS) is classified as a rheumatologic disease with an estimated prevalence of 2% of the US population. Patients with fibromyalgia commonly have lifelong histories of diffuse, chronic pain that is likely associated with other symptoms like headaches, dysmenorrhea, chronic fatigue, IBS and other FGID, painful bladder syndrome, endometriosis, and other regional pain syndromes. In clinical practice, fibromyalgia should be suspected in patients having multifocal pain not fully explained by injury or inflammation and in most cases, musculoskeletal pain is the most prominent feature.

Early diagnostic criteria for FMS was defined by the American College of Rheumatology (ACR) to include a history of widespread pain present greater than 3 months and excessive tenderness to digital palpation in at least 11 of the 18 muscle-tendon points. The 2010 ACR modifications on diagnostic criteria proposed that severity of FMS can be assessed using symptom severity (SS), a composite score that integrated physician-rated cognitive problems: unrefreshed sleep, fatigue, and a somatic symptoms count. Using SS and widespread pain index or tender point count, investigators recommended a new case definition of fibromyalgia, which still accounts for 88.7% of those who met the previous ACR definition. Apart from sorting through the differential diagnosis, laboratory testing is not useful for establishing a diagnosis of fibromyalgia. Basic laboratory evaluation may include complete blood count, routine serum chemistries, thyrotropin, vitamin D, erythrocyte sedimentation rate, and C-reactive protein. Serologic studies such as antinuclear antibody and rheumatoid factor assays are generally avoided unless symptoms or signs (eg, swollen joints) suggest an autoimmune disorder.
The etiology of fibromyalgia is unknown. Patients with FMS commonly perceive this illness to be disabling and are more likely to incur chronic health problems such as metabolic syndrome. It has been theorized that pain perceived in patients with FMS involves a state of “centralized” pain. Centralized refers to CNS origins of or amplification of pain, which does not imply that peripheral nociceptive input (ie, damage or inflammation of body regions) is not contributing to these individuals’ pain but rather they report hyperalgesia and allodynia. In a similar regard, it can be thought that patients with fibromyalgia have impaired endogenous analgesic systems, in particular suboptimal functioning descending inhibitory pathways, which normally function to ameliorate pain. These pathways are both serotonergic (eg, dorsolateral pontine tegmentum) and noradrenergic (eg, rostral ventral medulla), which synapse in the spinal cord dorsal horn. Although the link between central pain and abuse history is yet to be fully elucidated, this pain-prone phenotype predicts failure to respond to opioids or operations performed to reduce pain.

There appears to be an association between sexual abuse history and fibromyalgia as demonstrated by several systematic reviews and meta-analyses with statistically significant odds ratios. The link between abuse history and fibromyalgia has proposed by some to involve dysregulation of the hypothalamic pituitary axis. However such a theory does not further explain the cause of pain nor associated symptoms among patients with fibromyalgia.

Perceived symptoms severity is worse in patients who are sexually abused when compared to those without such history among patients with fibromyalgia. In 1 study, when using cluster analysis to organize subsets of patients with FMS into more homogeneous groups, the childhood maltreatment (ie, history of CSA and/or neglect) group was more likely to have higher perceived stress, the most subjective pain and the poorest measurement in global functioning. Given their reduced global function, this subset of patients with FMS are more likely to incur frequent office visits and prolonged hospitalizations. Hence, eliciting a sexual abuse history should be an early step in evaluation of patients with fibromyalgia to foster better treatment outcomes. See Table 1 for a list of evidence-based treatment in FMS.

There are very few studies that compare treatment outcomes in patients with FMS having sexual abuse history. Collectively, patients with FMS having underlying CSA have shown poor response to exclusive pharmacological interventions. One study showed CSA history to be a predictor of treatment response to brief interdisciplinary treatments consisting of education, self-management session, and cognitive behavioral therapy.

Although comorbid mood disorders could possibly mitigate the above-mentioned finding, a study that compared patients with CSA in adult patients with FMS to population controls, after adjusting for depressed mood, found that the differences was not accounted for by depression. In this same study, adjusting for depression, however, fully accounted for group difference in physical abuse and emotional neglect.

Central Sensitization

Central sensitization is characterized by alterations in CNS processing. More specifically, the responsiveness of central neurons to input from unimodal and polymodal receptors is augmented, resulting in a pathophysiological state corresponding to CS, characterized by generalized or widespread hyper-sensitivity. Central sensitization encompasses impaired functioning of brain-orchestrated descending antinociceptive (inhibitory) mechanisms (especially, noradrenergic) and over-activation of ascending pain facilitatory pathways (especially, glutamatergic). The net result is augmentation rather than inhibition of nociceptive transmission. In addition to the switch in balance between inhibitory and facilitatory pathways, CS entails altered sensory processing in the brain. Indeed, a modulated “pain signature” arises in the brain of patients with CS. The altered pain neuromatrix comprises of (1) increased activity in brain areas known to be involved in acute pain sensations, for example, the insula, anterior cingulate cortex, and the prefrontal cortex but not in the primary or secondary somatosensory cortex and (b) brain activity in regions generally not involved in acute pain sensations, for example, various brain stem nuclei, dorsolateral frontal cortex, and parietal associated cortex. Although speculative, CS is believed to contribute to the pathogenesis of chronic pain in many FSS, including the ones previously discussed.

Childhood Sexual Abuse, Centralized Pain Syndromes, and Opiate Misuse

Chronic pain syndromes are often managed with opioid therapy, despite multiple studies and meta-analyses indicating that opioid therapy has limited efficacy in addressing chronic pain. It has been estimated that 20% to 24% of chronic pain patients abuse opioids. As such multiple screening tools such as the Opioid Risk Tool (and others) have been developed to assess a patient’s risk of developing an adverse drug-related behavior or an addiction to opioids. There are multiple risk factors that have been found to increase one’s chance of becoming an opioid abuser, including a history of sexual abuse; as such, questions about sexual abuse can be found in the above-mentioned listed screening tools for potential opioid abuse.

Studies have demonstrated that those patients with a history of CSA report more FSS/chronic pain and greater utilization of some aspects of health care particularly related to pain issues, compared to controls of similar age and sex. Furthermore, women who experienced CSA have a greater intensity of FSS symptoms and higher total number of symptoms. Finally, in addition to more frequent visits/year to their primary care physician, women with a history of CSA reported more surgical procedures than nonabused women.

There is a paucity of data about trauma history among individuals dependent on prescription opioids. A 2013 study showed that more than one-third of individuals dependent on prescription opioids had sexual trauma. That same study reported CSA
occurring at the (mean) age of 9.5 years. See Figure 1 for a summary of the relationship between these variables.

**Implications for Treatment**

Given the high prevalence of sexual abuse and the association of abuse with poor health status, it is important to ask the question Do physicians and other health professionals know about their patients’ abuse history? A national survey of women found that although about 30% experienced child sexual, physical, or emotional abuse, only 21% of the abused said they had discussed these issues with a physician. In another study of a primary care clinic, although the prevalence of childhood (37%) and adult (29%) sexual abuse was high and most women felt it was appropriate for their physician to inquire about previous abuse (61%), only 4% indicated that their health care provider asked about such incidents.

Why and when should health practitioners ask about abuse? Inquiring about abuse makes sense when the clinical data are suggestive of abuse. For example, it makes sense when (1) the patient has numerous painful chronic health symptoms (e.g., gastrointestinal, gynecologic, headache, widespread pain, and LBP) and (2) the patient is significantly affected by these symptoms, that is, frequent office visits/surgical intervention, poor quality of life, and severe disability. If the primary care provider is contemplating opiate maintenance therapy for any of these painful chronic conditions, past history of CSA significantly increases the probability of opiate misuse and as the rates of fatal overdose have increased concomitantly with an increase in the number of patients on long-term opioid therapy.

Although the following describes classes of medications and their level of evidence in treating FMS, in general, medications with the highest level of evidence in fibromyalgia are also being shown to work in subsets of individuals with CPS. Strong evidence has been demonstrated for dual reuptake inhibitors, such as the tricyclic compounds amitriptyline and cyclobenzaprine, and the serotonin norepinephrine reuptake inhibitors (norepinephrine serotonin reuptake inhibitors), milnacipran and duloxetine, and for the anticonvulsants pregabalin and gabapentin. Modest evidence exists for tramadol and selective serotonin reuptake inhibitors, with weak evidence for S-adenosyl-l-methionine.

Classes of drugs that are quite effective for “peripheral” pain due to damage or inflammation in peripheral tissues such as nonsteroidal anti-inflammatory drugs and opioids are either less or not effective analgesics in CPS. There are even some data suggesting that giving opioids to individuals with CPS may worsen their pain, by leading to opioid-induced hyperalgesia that could augment and worsen the baseline hyperalgesia.
Finally, although the aforementioned pharmacological therapies may work across all or most of these conditions, nonpharmacological therapies such as education, exercise, and cognitive behavioral therapy have been demonstrated to be effective across nearly all of the CPS conditions, as well.

Limitations of this Review

Despite the above-mentioned review supporting a relationship between CSA resulting in adverse health consequences, the available data are far from decisive. In review of the existing research literature on CPS and CSA, some pervasive shortcomings emerged. First, in general, most research is limited to small, convenience samples, with insufficient attention to the design of control groups and to sample size. Second, both childhood and adult sexual abuse tend to be based on self-report, rather than by objective, externally corroborated evidence. It cannot be assumed that a retrospective account of interpersonal abuse accurately describes what transpired. Memory is an active and complex, highly individualistic process, intimately entwined with a person’s self-image (which are themselves determined not only by adverse life experiences but also by constitutional characteristics such as cognitive style and coping strategies). One study demonstrated discrepant results in regard to the relationship between history of sexual abuse and chronic pain, depending on whether sexual abuse was assessed by retrospective recall or from official records.93

Conclusion

Building greater awareness of the association between sexual abuse and somatic disorders may lead to improved health care delivery and outcomes for sexual abuse survivors. As a group, survivors of abuse have higher medical care use and incur greater costs compared with the general patient population. Analysis of expenditures demonstrates that costs are primarily the result of increased use of primary care, specialty medicine, and pharmacy and laboratory services. Higher medical use may also expose these patients to greater risk without clearly defined benefits, including increased abdominal and pelvic surgeries, adverse effects of medications, and chronic opioid use and dependence.14

Despite evidence of high health care use among sexual abuse survivors, physicians remain largely unaware of this aspect of their patients’ medical history. Only 5% of sexual abuse survivors report a history of abuse to their physician. However, heightened awareness of these specific health associations may prompt earlier recognition and improve care for sexual abuse survivors.14

Given evidence of sexual abuse prevalence and related physical and mental health sequelae, we urge physicians to more routinely conduct inquiries about sexual abuse in patients with the identified somatic syndromes. Disclosure of abuse in the clinic setting may allow for earlier consultation with mental health professionals. Prompt recognition of the physical and psychological sequelae of sexual abuse may halt unnecessary medical escalation and provide care better suited to promote recovery.14

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