Overview of chronic widespread (centralized) pain in the rheumatic diseases

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Literature review current through: Oct 2022. | **This topic last updated:** Mar 03, 2022.

INTRODUCTION

Patients with rheumatic diseases can not only experience localized pain directly resulting from those conditions but can also experience chronic widespread pain (CWP), as seen in patients with fibromyalgia. This pain, also termed centralized pain or nociplastic pain, results from a process termed central sensitization and is present in approximately 10 to 40 percent of patients with osteoarthritis (OA), rheumatoid arthritis (RA), spondyloarthritis (SpA), psoriatic arthritis, and systemic lupus erythematosus (SLE). Central sensitization is also prominent in many musculoskeletal pain disorders traditionally thought of as localized and focal musculoskeletal pain disorders, including chronic trauma-induced low back pain (LBP) and neck pain, such as following a motor vehicle accident (MVA); complex regional pain syndrome (CRPS); joint hypermobility syndrome (JHS); carpal tunnel syndrome; and lateral epicondylitis.

Recognition of central sensitization is important in clinical care; its symptoms can influence the assessment and adversely impact the outcome of patients with the associated rheumatologic and musculoskeletal disorders. Centralized pain is also an important mechanism underlying fibromyalgia and related chronic pain disorders, including irritable bowel syndrome, interstitial cystitis/bladder pain syndrome, and temporomandibular disorder. The management of chronic pain in patients with rheumatic disease requires a better understanding of centralized pain in chronic systemic and regional rheumatic and musculoskeletal pain disorders [1-3].

An overview of the mechanisms, clinical manifestations, diagnosis, and approach to treatment of central sensitization in patients with rheumatic and musculoskeletal diseases is

presented here. More detailed discussions of the pathogenesis, clinical manifestations, diagnosis, and treatment of the fibromyalgia syndrome in adults and children are described separately. (See "Pathogenesis of fibromyalgia" and "Clinical manifestations and diagnosis of fibromyalgia in adults" and "Differential diagnosis of fibromyalgia" and "Initial treatment of fibromyalgia in adults" and "Treatment of fibromyalgia in adults not responsive to initial therapies" and "Fibromyalgia in children and adolescents: Clinical manifestations and diagnosis" and "Fibromyalgia in children and adolescents: Treatment and prognosis overview".)

DEFINITIONS AND PAIN MECHANISMS

Definitions — Centralized pain, also referred to as central sensitization or central pain, can be defined as "an amplification of neural signaling within the central nervous system (CNS) that elicits pain hypersensitivity" [4]. In other words, the brain and the spinal cord "turn up the volume" in response to any potentially unpleasant stimulus. Central sensitization is characterized by hyperalgesia, an increased response to a painful stimulus, and allodynia, pain following a stimulus that is typically not irritating. Centralized pain begins and is perpetuated solely by CNS alterations, without a peripheral trigger or ongoing painful stimulus outside the CNS.

Conceptions of chronic and centralized pain have evolved, and some inconsistencies in how terms are used remain. Historically, chronic pain was categorized based upon the inciting peripheral pain mechanisms (figure 1) [4,5]. Chronic pain categories included inflammatory (ie, pain resulting from inflammatory pathology), focal structural (ie, pain resulting from focal anatomic pathology), and neuropathic (ie, pain resulting from nerve damage). As examples, the pain related to rheumatoid arthritis (RA) was seen as primarily inflammatory; that of osteoarthritis (OA) as primarily related to anatomic, structural pathology in the joint; and neuropathic as in that from diabetic neuropathy. Initially, the term central pain referred to pain localized to the CNS, such as that following a brain or spinal cord lesion [4].

Subsequently, centralized (or central) pain was used to refer to any pain condition that could not be explained by a peripheral source. Examples of central pain disorders include fibromyalgia, irritable bowel syndrome, and temporomandibular disorder [4] (see "Pathogenesis of fibromyalgia"). The pathophysiology of these central pain conditions does not follow traditional nociceptive pathways and was historically often considered psychogenic in origin or labeled as psychosomatic. According to this view, centralized pain was characterized as dysfunctional, in contrast to inflammatory, neurogenic, or structural pain, which were considered adaptive and potentially protective [4,5].

It is now recognized that each of these pain categories overlap, most notably neuropathic and centralized pain, depending upon their definition. For example, the International Association for the Study of Pain (IASP) restricts the term neuropathic pain to conditions with evidence of nerve damage, such as diabetic neuropathy [6]. By contrast, using the broader definition of central pain as that arising from the brain and/or spinal cord, centralized pain can be a component of any peripheral pain disorder [5]. Accordingly, central pain complicates the evaluation and treatment of every chronic pain condition. As an example, the painDETECT instrument, which was designed to measure neuropathic pain, cannot differentiate pain due to nerve damage from centralized pain [7].

Pain mechanisms in rheumatic disease — In most chronic painful disorders, the pain results from a combination of several interacting mechanisms, including inflammatory, structural, and centralized causes. Each pain category, particularly centralized pain, overlaps and intersects with the others to some degree (figure 1) (see 'Definitions' above). As an example, patients with RA may have an inflammatory synovitis causing structural knee damage and pain related to both processes, but the pain response is modified centrally, in the brain and spinal cord. As discussed below, chronic pain conditions often considered to have a peripheral structural etiology, such as chronic low back pain (LBP) or complex regional pain, are predominately central in nature [8-10].

Chronic widespread pain (CWP), without any known peripheral musculoskeletal pathology, is present in 5 to 15 percent of the population, and many of these individuals meet the classification criteria for fibromyalgia [4,5,11]. However, there is no formal definition of CWP, and it has been informally defined by applying the fibromyalgia diagnostic criteria of pain in the left side of the body, pain in the right side of the body, pain above the waist, pain below the waist, and axial skeletal pain [11,12]. A number of fibromyalgia diagnostic classification criteria have been proposed, all of which require the presence of widespread or multisite pain for at least three months, but also include symptoms such as fatigue and sleep disturbances [13]. These fibromyalgia criteria overlap with the informal criteria for CWP, and therefore, CWP and fibromyalgia are often used interchangeably.

There are genetic factors that predispose individuals to CWP/fibromyalgia. Candidate genes have included serotonin 5-HT2A receptor polymorphism T/T phenotype, serotonin transporter, dopamine 4 receptor, and catecholamine o-methyltransferase (*COMT*) polymorphisms, although no single strong genetic polymorphism has emerged [14]. Physical factors, including trauma, repetitive strain, infections, and obesity, and psychological factors, such as chronic stress and depression, are often considered to be inciting or perpetuating factors in fibromyalgia. (See "Pathogenesis of fibromyalgia".)

Neurophysiologic and neuroimaging changes in chronic widespread pain — Characteristic anatomic and functional markers of centralized pain can be detected

with neuroimaging, as can limited electrodiagnostic abnormalities. These observations have provided insights into the neurophysiologic changes in patients with CWP but remain research tools without direct applicability yet in clinical practice. (See "Pathogenesis of fibromyalgia".)

Allodynia and hyperalgesia were initially documented by a heightened pain response to mechanical pressure over a joint or muscle [15] (see 'Definitions' above). Centralized pain was also noted following exposure to other noxious stimuli, such as temperature or sound [15]. Fibromyalgia has been the prototype for centralized pain. In studies comparing patients with fibromyalgia with normal controls, the patients with fibromyalgia had lower mechanical and thermal pain thresholds and increased temporal summation of second pain, termed "windup" [15]. Maintenance of windup of secondary pain in fibromyalgia requires lower noxious stimulation than in controls, and this correlates with perceived pain intensity. This has often been demonstrated by quantitative sensory testing (QST), using heat and pressure-pain thresholds or tonic suprathreshold pain via the cold-pressor test [15].

Neuroimaging (magnetic resonance imaging [MRI]) and functional neuroimaging (fMRI) provide insight into the intricate mechanisms of central pain, demonstrating characteristic structural and functional brain MRI abnormalities in patients with fibromyalgia and other chronic pain disorders [16-18]. The abnormal findings on imaging tests have included decreased cortical thickness, diminished brain volumes, and increased levels of excitatory neurotransmitters, such as glutamate [16]. (See "Pathogenesis of fibromyalgia".)

The use of fMRI has allowed measurement of resting brain regional connectivity. Abnormal connectivity between two distinct brain regions, the default mode network (DMN) and the insula, was present in patients with fibromyalgia, and these alterations correlated with pain intensity [17]. Integrating fMRI with machine-based learning has revealed a particular pattern of pain response, a potential neural signature of pain [18]. This technique was used to demonstrate a fibromyalgia pain neural signature upon comparison of 37 fibromyalgia patients with 35 matched controls [19]. Analysis of the pattern of responses revealed a consistent imaging response to painful and nonpainful stimuli that distinguished fibromyalgia subjects from controls with 92 percent sensitivity and 94 percent specificity [19]. Although such studies need to be replicated and these techniques are too costly for routine clinical practice, they provide a framework for potential diagnostic utility.

An objective measure of regional brain changes associated with mood and personality traits, such as catastrophizing, has been provided by fMRI. As an example, the response to catastrophizing statements in 31 patients with fibromyalgia correlated with enhanced neural activity in the posterior cingulate cortex [20].

Another study, using functional and structural MRI together with questionnaire responses regarding pain severity, function, and body-mapping of pain, has shown that patients with

chronic widespread urologic pelvic pain syndrome (including patients with interstitial cystitis/bladder pain syndrome and patients with chronic prostatitis/chronic pelvic pain syndrome) had a similar pain neural signature to that of fibromyalgia patients [21].

Other modalities used to measure a heightened pain response have included resting state electroencephalography [22], magnetoencephalography [23], and positron emission tomography (PET) [24].

CLINICAL MANIFESTATIONS

Overview of clinical impact — The clinical, neurophysiologic, and imaging findings of chronic widespread pain (CWP)/fibromyalgia with centralized pain are common in patients with osteoarthritis (OA), inflammatory joint disorders, chronic back and neck pain, and other conditions. The presence of concomitant CWP/fibromyalgia, seen in at least one-quarter of patients with many of these rheumatologic and musculoskeletal disorders, adversely impacts the patient's level of pain and other symptoms and findings, potentially affecting composite disease activity measures and consequently impacting treatment decisions and outcomes of therapy. (See 'Osteoarthritis' below and 'Inflammatory arthritis and systemic autoimmune rheumatic diseases' below and 'Chronic low back and neck pain' below and 'Regional musculoskeletal and neuropathic pain conditions and other disorders' below.)

Osteoarthritis — CWP is seen in many patients with OA, where it is associated with increased severity of joint and soft tissue pain, including pain in multiple sites distant to the affected joint, reduced benefits from medications for pain, and worse pain outcomes following joint replacement surgery [25-35]. Pain severity generally correlates better with the degree of CWP and evidence of central sensitization than with the extent of radiographic OA. For example, in 39 patients with hip OA, there was no significant correlation of radiologic severity with pain, but there was a significant correlation with evidence of central sensitization, as measured by quantitative sensory testing (QST) ratings [36].

Prospective studies in patients with knee OA have found a 10 to 15 percent prevalence of CWP [25-27]. The prevalence of CWP/fibromyalgia in a general OA population is unknown. However, the incidence of developing new CWP in a cohort of patients with or at high risk of knee OA was noted in a group of studies [25-27]:

- OA patients with chronic knee pain followed for more than five years in two community-based cohorts, the Multicenter Osteoarthritis Study and the Osteoarthritis Initiative, were at an increased risk for subsequent pain in multiple other joints and soft tissue locations compared with patients initially lacking knee pain (80 and 64 percent with bilateral and unilateral knee pain, respectively, versus 50 percent) [25]. There was no specific pattern to the pain, and the findings did not vary when subjects with CWP at

baseline were excluded, consistent with central sensitization as the likeliest explanation for the findings.

- In knee OA patients, there was an association of underlying joint inflammation (based upon the presence of synovitis or effusions) with pain sensitization, as shown by decreased pressure pain thresholds (PPT), while bone marrow lesions were not associated with pain sensitization [26].

- PPT reduction and temporal summation were not associated with radiographic OA but correlated with pain severity, suggesting that pain sensitization in OA may often be a "trait" or patient characteristic of those individuals predisposed to central sensitivity, rather than a "state" determined by OA joint pathology [27].

A range of studies has documented a major role for CWP and central sensitization in OA-related pain and as a marker for diminished pain reduction with medication and more adverse pain outcomes after joint replacement surgery. The following studies are representative:

- The discordance between knee pain and OA radiographic severity was related to the degree of central sensitivity in a study of 113 knee OA patients using QST [28]. There was heightened pain sensitivity in the high pain/low radiographic knee OA group, compared with low pain sensitivity in the low pain/high radiographic group.

- Preoperative CWP was associated with poorer patient outcomes after joint replacement in OA patients undergoing knee or hip replacements, as shown by the association of the presence and severity of CWP/fibromyalgia with greater postoperative analgesic use and poorer pain outcomes [29,30]. For each one-point increase in the preoperative fibromyalgia severity scale, there were greater than 7 mg more morphine equivalents needed postoperatively, and the odds of failing to meet the threshold for improved outcome increased by 18 percent [30].

- Other studies also demonstrate an association of CWP with greater pain. In one study, one-third of knee OA patients had evidence of central sensitization based on QST measures of temporal summation and windup [31]. Additionally, the relationship between QST and fibromyalgia was evaluated in 128 OA patients scheduled to have knee replacements [32]. In females, but not in males, increased pressure pain sensitivity at multiple sites correlated with the presence of fibromyalgia and its symptom severity.

- The presence of CWP can be associated with reduced responses to nonsteroidal antiinflammatory drugs (NSAIDs). In a study in which knee OA patients demonstrated reduced pain thresholds at multiple anatomic sites and increased windup, the patients

with the greater evidence of centralized pain had the best response to NSAIDs, suggesting a central as well as a peripheral mechanism of action of NSAIDs [33].

- In a study of abnormal brain morphology associated with chronic pain, 16 patients with unilateral right-sided hip pain had neuroimaging before and nine months after hip arthroplasty [34]. There were significant differences in brain gray matter volume, especially in the thalamus, in those hip OA patients compared with healthy controls. Nine months after surgery, the areas of reduced thalamic gray matter volume were found to have "reversed" to levels in the controls. Another report also noted regional structural brain changes in patients with advanced knee OA that improved after knee replacement [35]. However, structural changes did not correlate with QST evidence of pain disinhibition.

Socioeconomic status, mood, and sleep disturbances, as well as catastrophizing, are also important factors in pain severity, disability, and outcome in OA [37-39].

There was a correlation of central sensitization with potential serologic biomarkers in OA patients [40]. An elevated matrix metalloproteinase-mediated breakdown of C-reactive protein (CRP) was associated with temporal summation. In subjects with knee OA, women exhibited greater sensitivity to a variety of painful stimuli in comparison to men [40,41].

Nonetheless, despite the impact of central sensitization, there is evidence that structural joint damage does play an important role in pain severity. As an example, in a study of more than 1000 OA patients in a within-person, case-control study of patients discordant for pain between their knees, severity of radiographic knee OA correlated strongly with knee pain severity [42].

Inflammatory arthritis and systemic autoimmune rheumatic diseases

Rheumatoid arthritis — CWP/fibromyalgia is present in a moderate proportion of patients with rheumatoid arthritis (RA), particularly those with seronegative RA. A number of features are evident in this group [43-56]. RA patients with comorbid fibromyalgia symptoms have greater pain despite less inflammatory synovitis. The patients with both fibromyalgia and RA have higher scores on standard measures of RA disease activity and greater medication use than patients with RA alone. The presence of CWP/fibromyalgia is associated with greater discordance between patient and physician global assessments.

The reported prevalence of fibromyalgia in RA has been estimated from 13 to 40 percent [43-45]. In one study, the incidence of fibromyalgia in early RA subjects was 3.6 to 6.8 cases per 100 person-years, was highest during the first year after the diagnosis, and correlated with pain severity and poor mental health [46]. Additionally, seropositivity inversely correlated with concurrent fibromyalgia. Similarly, an electronic health record (EHR)-based phenome-

wide association study, using EHR-derived clinical phenotypic data, also demonstrated a strong association of fibromyalgia with RA seronegativity [47].

A number of studies have identified similar characteristics among patients with RA and concurrent fibromyalgia. They have higher levels of pain, fatigue, sleep and mood disturbances, neuropathic symptoms, and worse physical and mental health, compared with patients without fibromyalgia, yet they exhibit lower levels of systemic and joint inflammation, as indicated by CRP levels or based upon joint ultrasound (table 1) [48]. In patients with RA, neuropathic symptoms, based upon elevated painDETECT scores, are strongly associated with concurrent fibromyalgia [49]. Although the painDETECT instrument was designed to measure neuropathic pain, it does not differentiate central from peripheral pain (see 'Definitions' above); thus, the elevated painDETECT scores likely measure central pain [7,49].

Patients with RA and fibromyalgia have higher disease activity scores, worse outcomes, and take more medications than those without fibromyalgia [44,45,50]. In one study, 20 percent of RA patients had concurrent fibromyalgia and, compared with those without fibromyalgia, had worse scores on sleep, tender joint count, and neuropathic pain, as well as RA disease activity [50]. None achieved a clinical remission by Simplified Disease Activity Index (SDAI) remission criteria. Additionally, concurrent fibromyalgia accounts for much of the patient-clinician discordance in global assessment ratings in RA patients [51]. Patients with RA and concurrent fibromyalgia more often used prednisone and analgesics and less often used methotrexate [52]. They were also more likely to be identified as receiving inappropriate therapy.

Generalized allodynia, including to light touch and cool temperatures, is present in patients with RA [53]. In RA patients, CRP levels were inversely associated with pain thresholds at joints but not at nonjoint sites [54]. Sleep disturbances were associated with pain thresholds at both joint and nonjoint sites, suggesting that central sensitization may link pain sensitivity and abnormal sleep. A 2011 systematic literature review found significant evidence for central sensitization in RA, including increased windup and generalized hyperalgesia at joints and nonarticular sites [55]. In 263 RA patients, the contribution of centralized pain to overall pain ratings was determined by QST, measuring PPTs, temporal summation, and conditioned pain modulation [57]. RA patients with evidence of low PPTs and high temporal summation had greater pain ratings.

Neuroimaging in RA demonstrated structural changes including increase in gray matter content in the basal ganglia and smaller intracranial volume [56]. This suggests that anatomic changes in certain brain regions, such as increase or decrease in structure, may reflect altered pain response. There was no evidence for cortical gray matter atrophy. Fifty-four patients with RA underwent functional neuroimaging (functional MRI [fMRI]) and were

also evaluated for fibromyalgia symptoms [58]. There was a positive correlation of regional brain connectivity from the default mode network (DMN) to the left mid/posterior insula with the severity of fibromyalgia, similar to that noted in patients with fibromyalgia.

The interaction of peripheral inflammation with central sensitization was investigated in comparing RA patients with concomitant fibromyalgia with those without fibromyalgia [59]. In those RA patients with fibromyalgia, increased functional connectivity of various brain regions correlated with a higher erythrocyte sedimentation rate (ESR), suggesting a "bottom-up" role of pain centralization. This implied that central pain in RA, including in those patients who don't meet the criteria for fibromyalgia, is bidirectional and may respond to traditional RA therapy.

Spondyloarthritis and psoriatic arthritis — Concurrent CWP/fibromyalgia is present in 10 to 30 percent of patients with spondyloarthritis (SpA) and associated with greater symptoms, higher disease activity measures, and in some studies, more use of biologic therapies, but without higher levels of inflammatory markers or extraspinal disease [60-66]. Fibromyalgia is also seen in patients with psoriatic arthritis, where it is also associated with increased levels of composite disease activity measures [67,68].

Estimates of the prevalence of fibromyalgia in SpA have varied from 5 to 25 percent [60]. In a multicenter study from the United Kingdom of more than 1500 subjects with axial SpA, 21 percent met criteria for fibromyalgia [61]. Patients who met fibromyalgia criteria had worse disease activity scores, global severity, and quality of life, as well as more mood disturbances and fatigue. Concurrent fibromyalgia did not correlate with an elevated CRP or evidence of extraspinal disease but did correlate with a greater likelihood of receiving biologic therapy. There was also a much greater adverse impact on work in those with concurrent fibromyalgia.

Because ankylosing spondylitis (AS; radiographic axial SpA) may not be associated with clinically apparent synovitis, there has been concern that it may be misdiagnosed as fibromyalgia. However, in 200 patients with axial SpA and 100 with fibromyalgia, this misdiagnosis was unusual [62]. Fibromyalgia patients rarely met the classification criteria for AS, although 13 to 20 percent of the AS in this study met the criteria for fibromyalgia.

Another group found no difference in the proportion of patients with AS and concurrent fibromyalgia who received anti-tumor necrosis factor (TNF) therapy compared with those without fibromyalgia, but twice as many with concurrent fibromyalgia, present in 21 percent of the patients, had stopped treatment after two years [63]. In 500 patients with axial SpA, 38 percent met the criteria for fibromyalgia [64]. Those with concurrent fibromyalgia had a poorer response to TNF inhibitors, which were related to lower scores on self-reported disease activity instruments rather than to a suboptimal physiologic response. The bidirectional effect of inflammation on central pain described above in RA has also been

noted in AS. In a study of 801 patients with AS, the presence of fibromyalgia correlated with both disease activity and widespread pain symptoms [69]. Starting a TNF inhibitor and improving disease activity decreased the presence of concurrent fibromyalgia.

As in patients with RA, neuropathic symptoms as determined by elevated painDETECT scores are found in most patients with AS, and they correlated with structural neuroimaging changes, including decreased gray matter in the primary somatosensory cortex [65]. This group also reported that fatigue in patients with AS negatively correlated with gray matter volume in the dorsal and ventral attention networks, the somatosensory cortices, and the caudate nucleus, and positively correlated with increased gray matter within the executive control network and putamen [66]. They also found decreased white matter connectivity in patients with high fatigue scores.

Concurrent CWP/fibromyalgia has also been identified in a substantial proportion of patients with psoriatic arthritis. In one report, fibromyalgia was present in 53 percent of patients with psoriatic arthritis compared with 5 percent of controls [67]. In another study, 18 percent of 73 patients with psoriatic arthritis had fibromyalgia, all but one of whom was female [68]. Disease activity measures were significantly higher in those with concurrent fibromyalgia, and none of those patients met criteria for minimal disease activity of their psoriatic arthritis. (See "Clinical manifestations and diagnosis of psoriatic arthritis".)

Systemic lupus erythematosus and Sjögren's syndrome — CWP/fibromyalgia is seen in 20 to 40 percent of patients with both systemic lupus erythematosus (SLE) and Sjögren's syndrome and is associated with somatic symptoms, fatigue, and cognitive difficulties [70,71].

As noted for each of the rheumatic diseases, patients with SLE and concurrent fibromyalgia do not have increased SLE immune or inflammatory activity measures but have greater self-reported mood disturbances, fatigue, sleep disturbances, and poorer quality of life and disability.

In patients with SLE, headache, abdominal pain, neurologic symptoms, fatigue, cognitive problems, and muscle pain or weakness were increased in association with concurrent fibromyalgia, but Raynaud phenomenon, rash, fever, easy bruisability, and alopecia were not [71]. The relationship between pain and cognitive dysfunction in SLE was largely explained by depression and sleep disturbances [72]. (See "Clinical manifestations and diagnosis of systemic lupus erythematosus in adults", section on 'Clinical manifestations'.)

Similarly, in patients with Sjögren's syndrome, the prevalence of fibromyalgia has varied from 14 to 50 percent [73-75]. The presence of fibromyalgia in Sjögren's syndrome correlated with fatigue, arthralgias, increased somatic symptoms, and high self-administered disease activity but not with inflammatory or serologic markers [76]. (See

"Clinical manifestations of Sjögren's syndrome: Extraglandular disease" and "Clinical manifestations of Sjögren's syndrome: Exocrine gland disease".)

Chronic low back and neck pain — Findings of CWP/fibromyalgia, including both generalized symptoms and characteristic neuroimaging changes, are often seen in patients with chronic low back or neck pain.

- **Chronic low back pain** – In a primary care setting, one-third of women with chronic low back pain (LBP) met the American College of Rheumatology (ACR) criteria for CWP [77]. Those subjects with concurrent CWP had more pain, mood disturbances, persistent pain, were more often on disability, and were more often female [77,78]. Generalized hyperalgesia, similar to that in fibromyalgia, was present in patients with chronic LBP [79]. fMRI in those chronic LBP subjects with hyperalgesia demonstrated similar regional brain abnormalities to those noted in subjects with fibromyalgia. A number of investigators have found gray matter loss and other structural brain changes in chronic LBP patients that correlated with the duration and severity of pain [80-82].

  As in fibromyalgia, alterations in regional brain connectivity have been identified in patients with chronic LBP. These have included connections involving the medial prefrontal cortex, the insula, and the DMN [8,83]. In subjects with chronic LBP, the clinical pain rating correlated positively with connectivity strength between the DMN and the right insula [8]. The neural functional connectivity was altered in subjects with subacute and chronic LBP compared with controls [9]. However, there was evidence for greater regional connectivity disorganization in the chronic LBP subjects, suggesting a neural correlate of transition from subacute to chronic LBP. Patients with chronic LBP had regional brain reductions in mu-opioid receptor availability compared with control subjects [84]. Depressed mood adversely impacts default mode connectivity in chronic LBP and should be accounted for in future studies if neuroimaging connectivity is to be considered as a biomarker for chronic pain [85,86]. (See "Evaluation of low back pain in adults".)

- **Chronic neck pain** – Central sensitization is prominent in subjects with chronic neck pain. Pressure and thermal pain thresholds were measured within one month of a whiplash injury and then at two, three, and six months [87]. Those patients with persistent moderate or severe pain at six months were the only subjects with generalized hyperalgesia. This occurred within one month and was unchanged over the six-month study.

  Chronic cervical pain following a neck injury has been associated with multiple somatic symptoms [88]. Twenty percent of subjects presenting to an emergency department after a motor vehicle accident (MVA) had widespread pain [89]. The presence of

widespread pain correlated with depressive and somatic symptoms and catastrophizing prior to the MVA, but not with direct MVA factors.

Diffusion-weighted MRI was compared in patients with chronic neck pain after trauma with those with idiopathic chronic neck pain [90]. Those with trauma-induced neck pain had structural regional brain changes suggestive of central sensitization. Gray matter cortical volume reduction correlated with cognitive disturbances as well as pain severity. (See "Evaluation of the adult patient with neck pain".)

Regional musculoskeletal and neuropathic pain conditions and other disorders — A number of chronic pain conditions that are considered localized or regional have clinical and experimental evidence for central sensitization, including complex regional pain syndrome (CRPS), carpal tunnel syndrome, and chronic shoulder pain, as does the hypermobility type of Ehlers-Danlos syndrome (hEDS):

- **Complex regional pain syndrome** – CWP has been noted in a significant number of patients diagnosed with CRPS [91]. The presence of CWP/fibromyalgia correlated with the duration of symptoms in patients with CRPS [92]. Each year from the inciting event that triggered CRPS was associated with a 0.3 increase in the fibromyalgia severity score. (See "Complex regional pain syndrome in adults: Pathogenesis, clinical manifestations, and diagnosis".)

  Neuroimaging has demonstrated structural and functional changes in gray and white matter in patients with CRPS [10,93-96]. Regional gray matter atrophy was related to duration and intensity of pain [94,95]. Greater reductions in functional DMN connectivity was noted in CRPS patients compared with controls [95]. Neuroimaging changes varied in subjects with early compared with late stages of CRPS [10].

- **Carpal tunnel syndrome** – Carpal tunnel syndrome was detected electrophysiologically using electromyography in 21 percent of patients with fibromyalgia compared with 3 percent of matched controls [97]. PPTs were lower in multiple locations in both hands, rather than just in the involved hand, in subjects with carpal tunnel syndrome compared with controls [98]. The decrease in PPTs correlated with pain duration and pain intensity. There was regional brain somatosensory cortex remapping that correlated with pain symptoms in patients with carpal tunnel syndrome [99]. Another group concluded that maladaptive primary somatosensory cortex neuroplasticity results in persistent functional deficits of carpal tunnel syndrome [100]. Central sensitization was evaluated as a risk factor for poor outcome in 120 patients treated with carpal tunnel release [101]. Central sensitization, measured by elevated scores on the central sensitization inventory (CSI) and PPT in the forearm, correlated with symptom severity, duration, and worse functional outcome after surgery. (See "Carpal tunnel syndrome: Clinical manifestations and diagnosis".)

- **Chronic shoulder and elbow pain** – A systematic review found strong evidence for central sensitization in patients with chronic shoulder pain, including those diagnosed with subacromial impingement syndrome [102]. Abnormal functional connectivity in pain-processing regions of the periaqueductal gray matter was present in subjects diagnosed with chronic neck and shoulder pain associated with cervical spondylotic radiculopathy [103]. (See "Evaluation of the adult with shoulder complaints".)

  Fifty percent of patients with chronic unilateral epicondylitis met criteria for fibromyalgia [104]. Those with concurrent fibromyalgia had lower PPT, increased pain and disability, and poorer response to treatment. Pain sensitization was measured by the PPT at the contralateral mid-dorsal forearm and the pain sensitization questionnaire (PSQ) in 131 patients with lateral epicondylitis of less than six months' duration [105]. Pain sensitization correlated with symptom severity and with persistently increasing disability after one year of nonsurgical treatment. (See "Elbow tendinopathy (tennis and golf elbow)".)

- **Ehlers-Danlos syndrome and joint hypermobility syndrome** – Most patients with hEDS report CWP [106]. Ehlers-Danlos syndromes (EDS) are a group of genetic disorders characterized by joint hypermobility as well as skin and vascular fragility [106]. (See "Clinical manifestations and diagnosis of Ehlers-Danlos syndromes" and "Overview of the management of Ehlers-Danlos syndromes".)

  Joint hypermobility syndrome (JHS) is considered by many experts in rheumatology and in clinical genetics to be indistinguishable from, if not identical to, the most common variant of EDS, hEDS, but the precise relationship between hEDS and JHS remains uncertain. Thus, as expected, most patents with JHS have CWP and many meet criteria for fibromyalgia [107]. The CWP symptoms have substantial clinical impact. (See "Clinical manifestations and diagnosis of hypermobile Ehlers-Danlos syndrome and hypermobility spectrum disorder", section on 'Clinical manifestations' and "Clinical manifestations and diagnosis of hypermobile Ehlers-Danlos syndrome and hypermobility spectrum disorder", section on 'Diagnosis'.)

  Hypersensitivity to heat and cold, as well as increased windup, correlated with pain intensity in subjects with JHS/hEDS [108,109].

DIAGNOSIS

Approach to diagnosis — The diagnosis of centralized pain is based on the chronicity and widespread nature of pain (table 2):

- The pain should be present for at least three months consecutively.

- It should be either widespread or multisite. Widespread pain is defined as pain in the left side of the body, pain in the right side of the body, pain above the waist, pain below the waist, and axial skeletal pain; multisite pain is defined as affecting at least six of nine potential sites (ie, head, neck, chest, upper back, lower back, right arm, left arm, right leg, and left leg) (figure 2) [11,13].

- In addition, sleep disturbances, fatigue, and/or mood disturbances should be present.

Central pain may be present in any localized or systemic disease, and it can then be especially difficult to determine whether the pain stems from the associated disease or is central in origin (see 'Differential diagnosis' below). For example, in a patient with widespread pain and a history of arthritis, excess pain when palpating multiple soft tissue sites, rather than joints, would suggest a diagnosis of chronic widespread pain (CWP)/fibromyalgia. Patients with CWP/fibromyalgia often describe their symptoms with comments like: "It hurts all over," "It feels as if I always have the flu," "I feel like a truck ran me over in the morning."

Diagnostic evaluation — The diagnostic evaluation of patients with CWP includes:

- Ascertaining and recording the duration, severity, and location of pain. A pain manikin can be helpful in documenting the sites of pain, and these are available in paper or electronic forms (figure 2) [13].

  Associated somatic symptoms, particularly fatigue and sleep disturbances, should be present in patients with CWP (table 2). Cognitive disturbances, such as memory loss, confusion, and problems with executive function, are present in the vast majority of patients with centralized pain conditions. Various neuropathic symptoms, especially dysesthesias in the absence of obvious nerve damage, are common, and scores on the painDETECT instrument are similar in fibromyalgia to scores in neuropathic disorders [7].

  Screening instruments for central pain, including the central sensitization inventory (CSI) [110] and the painDETECT measure [7], have been used in some studies but are not generally used in clinical practice.

- A thorough musculoskeletal examination, which is critical to identify synovitis or any structural abnormalities. Tenderness over joints, as well as soft tissues, should be documented. It is also useful to identify allodynia and hyperalgesia when palpating soft tissue sites throughout the body.

- A complete blood count and an acute phase response measure, either an erythrocyte sedimentation rate (ESR) or a C-reactive protein (CRP). Initially, only limited laboratory testing is required. We do not routinely obtain serologic testing, such as tests for

antinuclear antibody (ANA) or rheumatoid factor (RF). In selected patients, such as those with symptoms or findings suggesting a muscle disease or thyroid disorder, respectively, muscle enzymes and thyroid function tests may be obtained, although routine testing is not cost-effective [111].

A general overview of the evaluation of chronic pain in adults is presented separately. (See "Evaluation of chronic non-cancer pain in adults".)

For research purposes, quantitative sensory testing (QST), which utilizes various techniques to measure pain sensitivity, and brain imaging have been the most commonly employed tools to document and measure central pain.

In the future, a common neural signature may emerge that can provide a biomarker of central sensitization. However, until such a biomarker has been validated, CWP/fibromyalgia will be diagnosed based upon the presence and chronicity of generalized, multisite pain and associated somatic symptoms, such as fatigue and sleep disturbances, in the absence of a known peripheral inciting event.

Differential diagnosis — Common rheumatologic disorders comprise the bulk of the differential diagnosis. Some rheumatic diseases, such as systemic lupus erythematosus (SLE), polymyalgia rheumatica (PMR), spondyloarthritis (SpA), and myopathy or myositis, may be especially difficult to exclude in patients presenting primarily with widespread pain and fatigue (table 3). The differential diagnosis of fibromyalgia is discussed in more detail separately. (See "Clinical manifestations and diagnosis of fibromyalgia in adults" and "Differential diagnosis of fibromyalgia".)

- **Rheumatoid arthritis** – Swelling and inflammation in multiple joints is the cardinal feature of rheumatoid arthritis (RA) and is not a feature of fibromyalgia/CWP. However, some patients, especially in early RA, may present with just minimal joint swelling. RA is associated with fatigue, morning stiffness, and nonspecific neuropathic symptoms, also common in fibromyalgia/CWP. However, even in early RA, the acute phase reactants, the ESR and CRP, are usually elevated and some synovitis should be noted on examination. (See "Clinical manifestations of rheumatoid arthritis" and "Overview of the systemic and nonarticular manifestations of rheumatoid arthritis" and "Diagnosis and differential diagnosis of rheumatoid arthritis".)

  In patients with known RA and concurrent fibromyalgia/CWP, certain characteristics should alert the clinician to central pain mechanisms (table 1). These include pain out of proportion to joint abnormalities; major mood, sleep, and cognitive disturbances; and prominent, unexplained neuropathic symptoms. In this situation, the acute phase reactants are often normal, rheumatoid serologic tests are negative, and

joint ultrasound does not reveal significant inflammation or swelling. (See 'Rheumatoid arthritis' above.)

- **Systemic lupus erythematosus** – Patients with SLE may initially exhibit few abnormal findings on examination. SLE patients may present with a rash, fatigue, and arthralgias. A dermatologic consultation may clarify whether the rash is consistent with SLE. As mentioned, using serologic testing to "screen" such patients will lead to false-positive ANA testing. However, the presence of very elevated ANA titers, anti-deoxyribonucleic acid (DNA) antibodies, or hematologic abnormalities would be strong evidence for SLE. (See "Clinical manifestations and diagnosis of systemic lupus erythematosus in adults".)

- **Polymyalgia rheumatica** – PMR may also present with few abnormal physical findings. Peripheral joint synovitis is unusual in PMR. Patients tend to be over the age of 60, often present quite abruptly, and complain of proximal muscle stiffness rather than diffuse pain. Patients with PMR almost always have an elevated ESR or CRP. (See "Clinical manifestations and diagnosis of polymyalgia rheumatica".)

- **Spondyloarthritis** – Limited spine mobility is the cardinal symptom of SpA but may not be present early or in all patients. SpA may also begin with nonspecific symptoms, such as chronic low back pain (LBP) and stiffness with no peripheral joint abnormalities on examination. In such situations, early diagnosis may require radiographic or other imaging evidence of sacroiliitis or abnormalities involving various spinal joints. However, in patients meeting criteria for an axial SpA, a fibromyalgia misdiagnosis was uncommon [62]. (See "Clinical manifestations and diagnosis of peripheral spondyloarthritis in adults" and "Diagnosis and differential diagnosis of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis) in adults".)

- **Myopathy** – Myopathy, either inflammatory or drug-induced (most often from statins), may also begin with few physical findings. However, generalized muscle weakness, rather than pain, is characteristic of any myopathy. The key laboratory finding is elevated muscle enzymes, such as creatine kinase (CK). (See "Approach to the patient with muscle weakness" and "Statin muscle-related adverse events" and "Clinical manifestations of dermatomyositis and polymyositis in adults".)

- **Other disorders** – Rarely, endocrine disorders, particularly hypothyroidism and hyperparathyroidism, present with CWP. The association of vitamin D deficiency with CWP/fibromyalgia has been controversial. Selected testing for these conditions may be considered, but routine testing is not cost-effective [111]. Medications that cause CWP include aromatase inhibitors and bisphosphonates, although the pain is typically joint or bone, rather than diffuse soft tissue pain. (See "Clinical manifestations of hypothyroidism" and "Diagnosis of and screening for hypothyroidism in nonpregnant

adults" and "Primary hyperparathyroidism: Clinical manifestations" and "Primary hyperparathyroidism: Diagnosis, differential diagnosis, and evaluation" and "Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer", section on 'Side effects' and "Risks of bisphosphonate therapy in patients with osteoporosis", section on 'Musculoskeletal pain'.)

TREATMENT

Treatment approach — We take the same approach to the treatment of centralized chronic widespread pain (CWP) in patients with associated rheumatic and musculoskeletal disorders as in patients with fibromyalgia without such comorbid conditions, utilizing an integrated multimodal biopsychological management plan. The treatment approach to fibromyalgia is described in detail separately. (See "Initial treatment of fibromyalgia in adults" and "Treatment of fibromyalgia in adults not responsive to initial therapies".)

Management principles — An understanding of several treatment principles can improve management and outcomes in patients with CWP/fibromyalgia and a concurrent rheumatologic condition. These include:

- **Timely recognition of the centralized pain syndrome** – Understanding that central sensitization underlies the historically categorized functional somatic syndromes provides the framework for an integrated diagnostic and therapeutic biopsychological illness model. It then follows that seemingly distinct conditions like fibromyalgia, irritable bowel syndrome, chronic headaches, temporomandibular joint pain, and chronic pelvic/bladder pain syndromes share characteristics of chronic pain, fatigue, and cognitive, mood, and sleep disturbances. Rather than attempting to tease out individual features of these common illnesses, a diagnosis is based on symptoms common to all (table 2). This common symptom-based approach will foster an earlier affirmative diagnosis, rather than a diagnosis of exclusion.

  Timely recognition of primary central pain conditions is cost-effective, as demonstrated in decreased health care costs and utilization once a diagnosis of fibromyalgia was made in the primary care setting [112]. The accuracy of a fibromyalgia diagnosis in general practice is poor, and there is inadequate knowledge regarding the fibromyalgia diagnostic criteria [113,114]. (See "Initial treatment of fibromyalgia in adults".)

- **Recognition of symptomatic impact and prognostic implications of centralized pain** – CWP/fibromyalgia is associated with reduced benefit from joint replacement surgery, adverse events (complex regional pain syndrome [CRPS] following wrist fracture), and other interventions; CWP may also result in overestimation of inflammatory disease activity and may lead to inappropriate disease management by

assuming the disease is active or flaring based on symptom severity [50-52,63,64,67] (see 'Prognosis' below). Preoperative centralized pain predicted poor outcome in knee osteoarthritis (OA) joint replacement [115]. Since central sensitization adversely affects the outcome of spine surgery, joint arthroplasty, and carpal tunnel release, it is prudent to evaluate patients for generalized pain hypersensitivity prior to these procedures. Signs of central sensitization should also alert the clinician that a patient may be at risk for adverse events. For example, after a distal radius fracture, the presence of fibromyalgia correlated strongly with the patient developing CRPS [116].

- **Importance of acknowledgment and patient education regarding neurophysiologic underpinning of CWP/fibromyalgia** – Understanding that central sensitization is not simply a psychogenic illness allows health care providers to avoid the mind-body dualism and provide a foundation to educate the patient and avoid the common patient fear that, "He thinks it is all in my head." These patients will benefit from a more individualized biopsychological treatment program. (See "Initial treatment of fibromyalgia in adults" and "Treatment of fibromyalgia in adults not responsive to initial therapies".)

- **Recognition that treatment of the rheumatic disease might reduce centralized pain** – The interplay of centralized pain with inflammatory, immune, and structural input should be kept in mind in disease management (figure 1), as some evidence suggests that treatments considered to be antiinflammatory, such as nonsteroidal antiinflammatory drugs (NSAIDs) [33], or immune-mediated, such as tumor necrosis factor (TNF) inhibition [117], also have a beneficial impact on central sensitization in systemic rheumatic diseases such as RA [59] and AS [69]. Likewise, central pain is affected by structural disease, as noted with the improvement in quantitative sensory testing (QST) hyperalgesia and neuroimaging regional abnormalities following successful arthroplasty [33,35]. Immune and inflammatory factors are present in central sensitization [31,40]. Therefore, optimal treatment of the associated rheumatic condition will improve the concurrent central pain. However, there are no studies to indicate how treating CWP/fibromyalgia affects the concurrent rheumatic condition itself.

PROGNOSIS

There is strong evidence that central sensitization adversely affects pain severity and various outcome measures and can influence measures used to assess disease activity of systemic rheumatic diseases and regional musculoskeletal pain conditions (table 4). However, it is not established whether treatment of the rheumatologic disorder affects the chronic widespread pain (CWP)/fibromyalgia or whether the prognosis for the CWP/fibromyalgia in

these patients is different from that for fibromyalgia alone. (See "Initial treatment of fibromyalgia in adults", section on 'Prognosis'.)

As examples of the effects of CWP on symptoms, assessment, and outcomes:

- In osteoarthritis (OA) patients who had knee or hip replacements, the presence and severity of CWP/fibromyalgia correlated with greater analgesic use and poorer pain outcomes [29,30]. (See 'Osteoarthritis' above.)

- Autoimmune and inflammatory rheumatic disease patients with concurrent fibromyalgia/CWP report more pain and poorer outcome than patients without fibromyalgia [44,45,50,61,68,71]. This has been noted in patients with rheumatoid arthritis (RA), spondyloarthritis (SpA), and autoimmune systemic rheumatic disease (eg, systemic lupus erythematosus [SLE] and Sjögren's syndrome). However, these disease activity measures are often self-report instruments that do not correlate with worse inflammatory parameters or structural disease progression. Therefore, central sensitization may affect disease management because of overestimation of disease activity or misattribution of the source of symptoms or a perceived disease flare due the degree of overall symptom severity. (See 'Rheumatoid arthritis' above and 'Spondyloarthritis and psoriatic arthritis' above and 'Systemic lupus erythematosus and Sjögren's syndrome' above.)

- In a study of 647 patients with more than three months of low back pain (LBP) (chronic LBP) in primary practices in Germany, 25 percent also had findings of CWP [78]. Patients with concurrent CWP had greater pain and a longer duration of pain, were less often working, and more often on disability. They were also more likely to have constant, rather than intermittent, attacks of chronic LBP. Similarly, in an Australian study, CWP one month after a neck injury correlated strongly with poor outcome at six months [87]. Centralized pain has also been found to worsen the outcome in patients with carpal tunnel syndrome [101], shoulder pain [102], and lateral epicondylitis [105].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Fibromyalgia".)

SUMMARY

- Centralized pain, also referred to as central sensitization or as nociplastic pain, is defined as an amplification of neural signaling within the central nervous system (CNS) that elicits pain hypersensitivity; this results in hyperalgesia, an increased response to a

painful stimulus, and allodynia, pain following a stimulus that is typically not noxious. In most chronic painful disorders, the pain results from a combination of several interacting mechanisms, including inflammatory, structural, and centralized causes. Characteristic anatomic and functional markers of centralized pain can be detected with specialized neuroimaging, as can limited electrodiagnostic abnormalities. (See 'Definitions and pain mechanisms' above.)

- The clinical and neurophysiologic and imaging findings of chronic widespread pain (CWP)/fibromyalgia with centralized pain are common in patients with osteoarthritis (OA), inflammatory joint disorders, chronic back and neck pain, and other conditions. The presence of concomitant CWP/fibromyalgia, seen in at least one-quarter of patients with many of these disorders, adversely impacts the patient's level of pain and other symptoms and findings, potentially affecting composite disease activity measures and consequently treatment decisions, and outcomes of therapy. (See 'Clinical manifestations' above and 'Osteoarthritis' above and 'Inflammatory arthritis and systemic autoimmune rheumatic diseases' above and 'Chronic low back and neck pain' above and 'Regional musculoskeletal and neuropathic pain conditions and other disorders' above.)

- The diagnosis of centralized pain is based upon the chronicity and widespread nature of pain (table 2). The pain should be present for at least three months consecutively and either widespread or multisite (figure 2). In addition, sleep disturbances, fatigue, and/or mood disturbances should be present. By definition, the diagnosis of centralized pain is considered only after a peripheral cause of the pain, whether structural, inflammatory, or neuropathic, has been excluded based upon a thorough history and physical examination, and with selected laboratory testing. (See 'Approach to diagnosis' above.)

- The diagnostic evaluation of patients with CWP includes ascertaining and recording the duration, severity, and location of pain (table 1 and figure 2); a thorough musculoskeletal examination; and limited laboratory testing, including a complete blood count and an acute phase response measure, either an erythrocyte sedimentation rate (ESR) or a C-reactive protein (CRP). We do not routinely obtain other laboratory testing, such as an antinuclear antibody (ANA), rheumatoid factor (RF), muscle enzymes, or thyroid function tests unless indicated by specific clinical features suggesting an additional diagnosis. (See 'Diagnostic evaluation' above.)

- Common rheumatologic disorders comprise the bulk of the differential diagnosis. Some rheumatic diseases, such as systemic lupus erythematosus (SLE), polymyalgia rheumatica (PMR), spondyloarthritis (SpA), and myopathy or myositis, may be

especially difficult to exclude in patients presenting primarily with widespread pain and fatigue (table 3). (See 'Differential diagnosis' above.)

- We take the same approach to the treatment of centralized CWP in patients with associated rheumatic and musculoskeletal disorders as in patients with fibromyalgia without such comorbid conditions, utilizing an integrated multimodal biopsychological management plan. In addition, attention should be given to timely diagnosis and intervention, recognition of the symptomatic impact and prognostic implications of CWP, and patient education regarding the diagnoses and the neurophysiologic basis for the patient's condition. Optimal therapy of the concurrent rheumatic and musculoskeletal condition will help to reduce the impact of centralized pain in the rheumatic diseases. (See 'Treatment approach' above and 'Management principles' above.)

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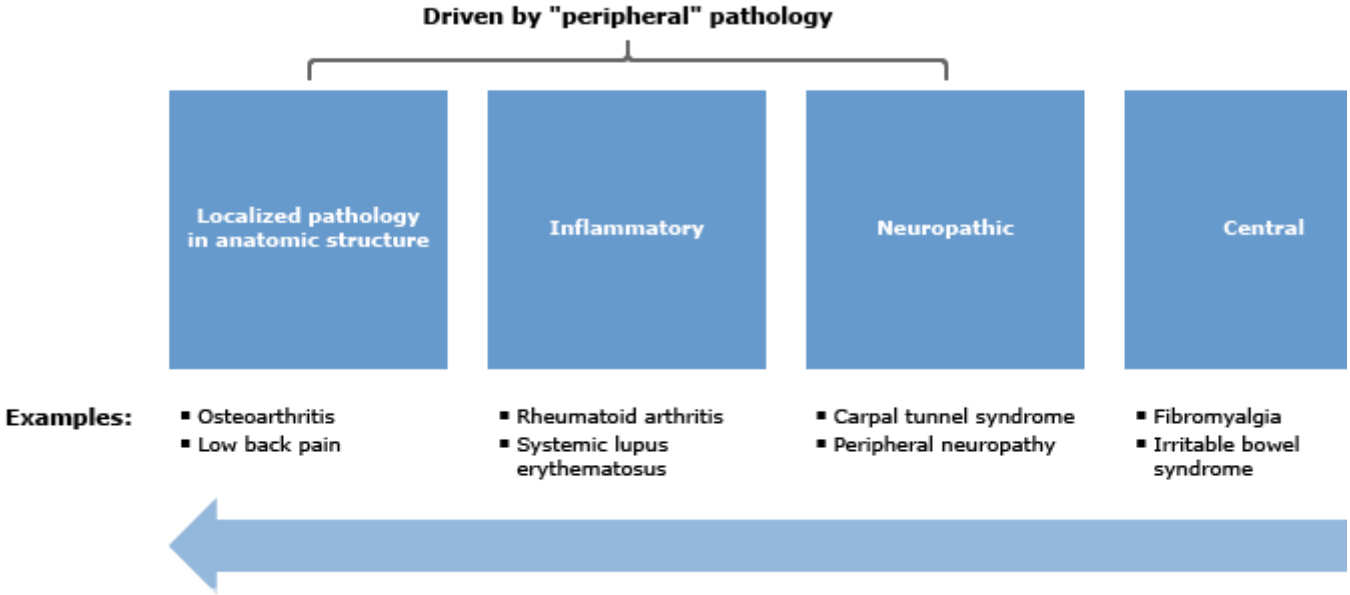
Topic 118590 Version 8.0

GRAPHICS

Pain categories traditionally thought to be distinct, now known to intersect/overlap



General pain categories overlap with central pain a component in each.

Graphic 119785 Version 1.0

Characteristics of patients with rheumatoid arthritis and concurrent fibromyalgia

Pain out of proportion to joint abnormalities
Greater mood disturbances
Greater sleep disturbances
Neuropathic symptoms
Often seronegative
Low inflammatory markers (CRP, ESR)
Less inflammation (joint examination, joint ultrasound)

RA: rheumatoid arthritis; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

Graphic 119787 Version 1.0

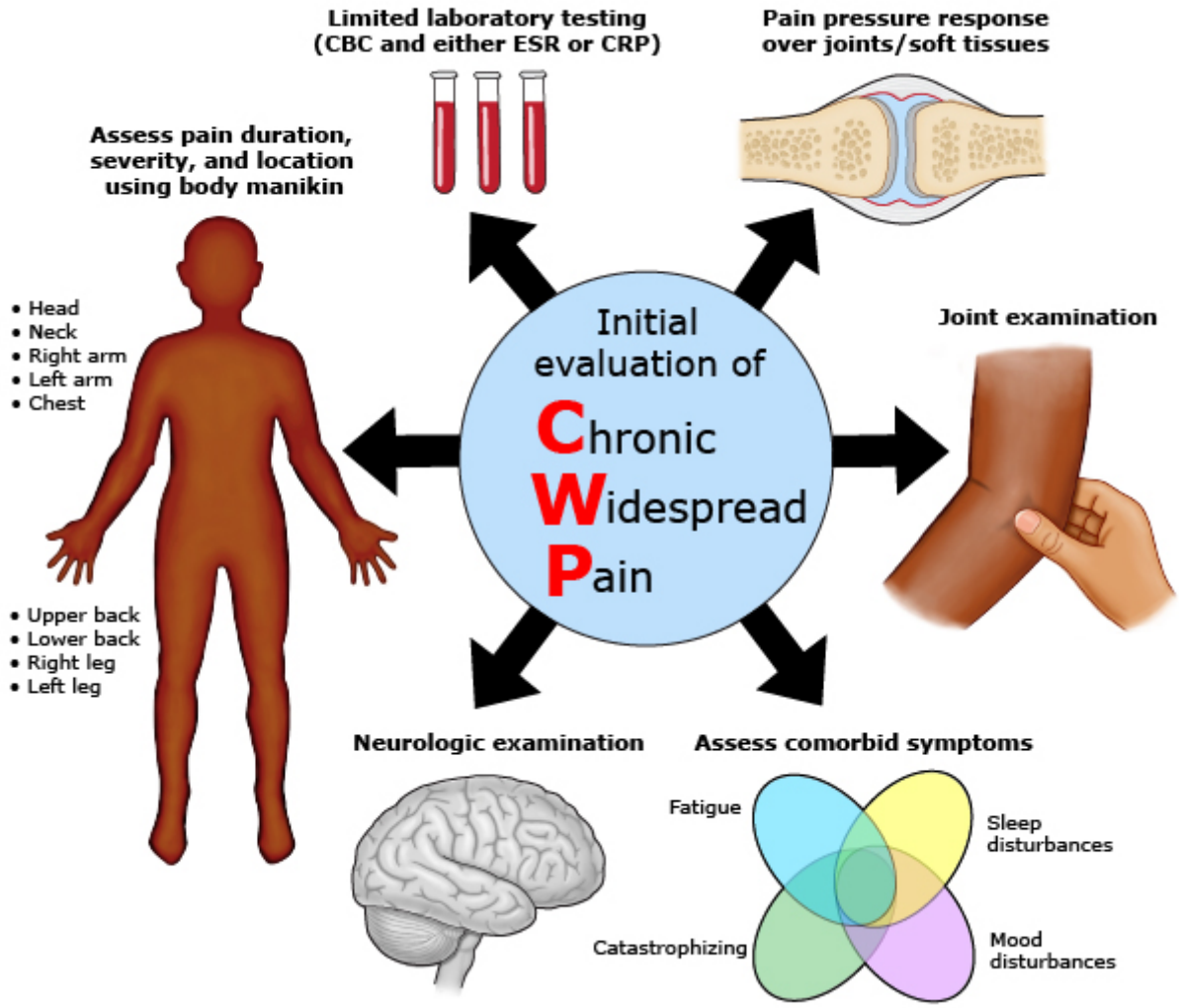
Diagnosis of centralized pain conditions

Chronic (at least 3 months) widespread (or multisite) pain
Allodynia, hyperalgesia ▪ On palpation of widespread soft tissue sites
No obvious structural, inflammatory, neuropathic cause ▪ No joint swelling, inflammation ▪ No abnormal neurologic findings
Coexisting symptoms ▪ Fatigue ▪ Sleep disturbances ▪ Mood disturbances ▪ Cognitive disturbances ▪ Catastrophizing ▪ Neuropathic symptoms
Normal acute phase reactants (ESR, CRP)
In selected cases, muscle enzymes, thyroid function tests

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Graphic 119790 Version 1.0

Initial evaluation of chronic widespread pain



CBC: complete blood count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Graphic 119789 Version 2.0

Systemic rheumatic diseases difficult to exclude in patients presenting primarily with widespread pain and fatigue

Rheumatic disease	Helpful differential diagnostic features
SLE	▪ Rash, systemic signs/symptoms, elevated ESR/CRP ▪ Significantly positive ANA, anti-DNA antibody ▪ Abnormal hematologic tests
PMR	▪ Proximal muscle stiffness rather than pain ▪ Age greater than 60 ▪ Elevated ESR/CRP
Spondyloarthritis	▪ Primarily back pain and stiffness ▪ Limited spine mobility ▪ Elevated ESR/CRP ▪ Abnormal radiographs/imaging
Myopathy/myositis	▪ Muscle weakness ▪ Elevated CK

SLE: systemic lupus erythematosus; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ANA: antinuclear antibodies; PMR: polymyalgia rheumatica; CK: creatine kinase.

Graphic 119794 Version 1.0

Impact of central sensitization

Condition	Observed impact of central sensitization
Osteoarthritis	▪ QST and neuroimaging abnormalities improved after joint replacement ▪ Correlated with pain severity, poor outcome ▪ Correlated with opioid use
RA	▪ Higher pain and disease activity scores but no correlation with inflammation/damage ▪ Correlated with neuropathic symptoms, QST ratings ▪ Correlated with adverse outcome, lack of remission, inappropriate therapy
Spondyloarthritis	▪ Worse disease activity scores and outcomes ▪ Poorer response/inappropriate use of biologics
SLE	▪ Greater mood and sleep disturbances ▪ Poorer outcome
Chronic LBP	▪ Greater pain, mood disturbances, adverse outcome
Joint hypermobility syndrome	▪ Correlated with pain severity, poor outcome
Chronic whiplash	▪ Correlated with pain severity, poor outcome, cognitive disturbances
Carpal tunnel syndrome	▪ Correlated with poor surgical outcome
Lateral epicondylitis	▪ Correlated with pain severity, duration, poor response to treatment

QST: quantitative sensory testing; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; LBP: low back pain.

Graphic 119795 Version 1.0

Contributor Disclosures

Don L Goldenberg, MD No relevant financial relationship(s) with ineligible companies to disclose. **Peter H Schur, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Philip Seo, MD, MHS** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

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