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Diagnosing and treating chronic musculoskeletal pain based on the underlying mechanism(s)

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A B S T R A C T

Until recently, most clinicians considered chronic pain to be typically due to ongoing peripheral nociceptive input (i.e., damage or inflammation) in the region of the body where the individual is experiencing pain. Clinicians are generally aware of a few types of pain (e.g., headache and phantom limb pain) where chronic pain is not due to such causes, but most do not realize *there is not a single chronic pain state where any radiographic, surgical, or pathological description of peripheral nociceptive damage has been reproducibly shown to be related to the presence or severity of pain*. The primary reason for this appears to be that both the peripheral and central nervous systems play a critical role in determining which nociceptive input being detected by sensory nerves in the peripheral tissues will lead to the perception of pain in humans. This manuscript reviews some of the latest findings regarding the neural processing of pain, with a special focus on how clinicians can use information gleaned from the history and physical examination to assess which mechanisms are most likely to be responsible for pain in a given individual, and tailors therapy appropriately. A critical construct is that, within any specific diagnostic category (e.g., fibromyalgia (FM), osteoarthritis (OA), and chronic low back pain (CLBP) are specifically reviewed), individual patients may have markedly different peripheral/nociceptive and neural contributions to their pain. Thus, just as low back pain has long been acknowledged to have multiple potential mechanisms, so also is this true of all chronic pain states, wherein some individuals will have pain primarily due to peripheral nociceptive input, whereas

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in others peripheral (e.g., peripheral sensitization) or central nervous system factors ("central sensitization" or "centralization" of pain via augmented pain processing in spinal and brain) may be playing an equally or even more prominent role in their pain and other symptoms.

Introduction

The notion that chronic pain should be treated based on the underlying mechanisms present in each individual rather than the disease causing the pain is not new. It was first raised nearly two decades ago by Mitchell Max, and later by Clifford Woolf and others [1,2]. However, these authors opined that we should do this in the future; this manuscript suggests that we might finally have made enough scientific progress in the pain field to begin to implement these techniques in clinical practice. Making this distinction is critical clinically as both the drug and nondrug therapies that will work for any given patient with chronic pain might be much better guided by a nuanced view of the mechanisms of their pain rather than knowing which of these "diagnoses" the patient is suffering from.

Fig. 1 briefly describes at least three different underlying mechanisms that can be operative in chronic pain states: peripheral/nociceptive, (peripheral) neuropathic, and central neuropathic, or "centralized" pain. Some authors prefer to use the term "neuropathic pain" for any pain of neural origin, whereas others prefer to reserve this term for conditions where there is identifiable damage to the nervous system. We acknowledge this and prefer to use the term "centralized" pain to refer to the fact that the central nervous system (CNS) (rather than the peripheral nervous system) is prominently involved in maintaining the pain. This distinction between peripheral neuropathic pain (where peripherally directed therapies such as topical treatments, injections, and/or surgery might be helpful, and should be considered) and centralized pain (where these are generally not options) is extremely important.

Of note, although specific diagnoses are noted in Fig. 1 as being considered peripheral/nociceptive, peripheral neuropathic, or centralized, this is meant to indicate the primary underlying mechanism for pain in each of these diagnoses. Again, the emphasis of this manuscript is that some individuals with

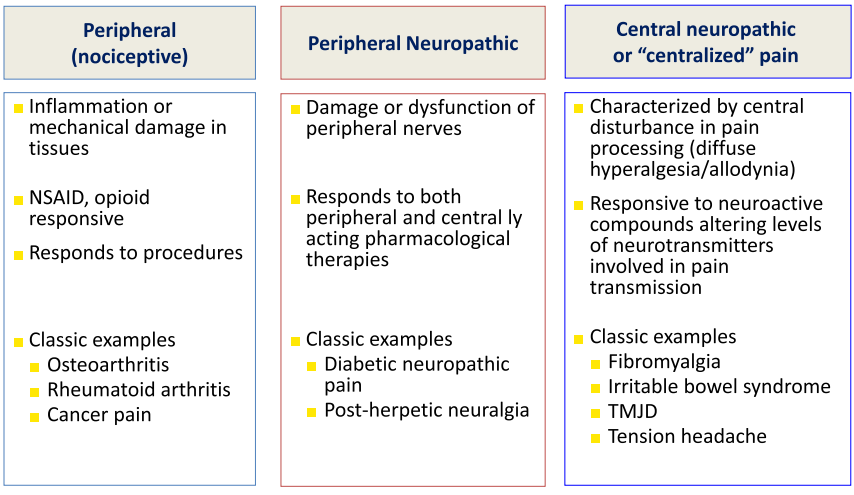

Fig. 1. Mechanistic characterization of pain.

osteoarthritis (OA) or rheumatoid arthritis (RA) (and even cancer pain) have evidence that they have centralized their pain and should likely be treated with centrally acting treatments, whereas some individuals with conditions such as FM or irritable bowel syndrome (IBS) may have peripheral contributions to their pain that may need to be identified and treated.

FM as the prototypical central or centralized pain state

The term "central pain" was originally used to describe individuals with pain following a stroke or spinal cord lesion that subsequently developed pain. In this case, "central" referred to the fact that the *lesion* leading to pain occurred within the CNS – either the spinal cord or the brain. Another term that has often been used to describe a similar phenomenon is "central sensitization." This term was originally coined to refer to a specific spinal cord mechanism that we now realize as being one of many potential causes of augmented CNS pain processing [3]. Because both central pain and central sensitization have these historical meanings, we have typically used terms such as central augmentation or amplification to refer more broadly to the many CNS mechanisms that enhance the perception or modulation of pain differentially between individuals, and we have used the term "centralized pain" to indicate that this phenomenon plays a role in any individual with chronic pain.

"Centralized pain" as newly defined was originally thought to be confined to individuals with idiopathic or functional pain syndromes, such as fibromyalgia (FM), headache, IBS, temporomandibular joint disorder (TMJD), and interstitial cystitis (IC) [4–6]. These pain syndromes have been shown to be very familial/genetic and to strongly co-aggregate in individuals and families [7,8]. The symptoms experienced by individuals with centralized pain syndromes have been well characterized, and these consist of multifocal pain (with a high current and lifetime history of pain in many bodily regions) and a cluster of co-occurring somatic symptoms (i.e., fatigue, sleep disturbances, and memory difficulties) [7,9]. Even when individuals are identified as having a new onset of a regional pain syndrome, questioning typically reveals very high rates of pain in other body regions, and somatic symptoms other than pain [9]. Overwhelming evidence reveals that what is often labeled as a single chronic regional pain syndrome is, upon closer evaluation, a chronic illness beginning much earlier in life, where the pain merely occurs at different points of the body at different points in time and is given different labels by subspecialists focusing on "their region" of the body.

Kato and colleagues, using a large Swedish twin registry, performed a series of studies first demonstrating the comorbidities with chronic widespread pain and examining a number of these central or "functional" pain syndromes and the relationship of these symptoms with those of depression and anxiety [10]. These studies clearly demonstrated that functional somatic syndromes such as FM, CFS, IBS, and headache have latent traits (e.g., multifocal pain, fatigue, and memory and sleep difficulties) that are different from (but overlap somewhat with) psychiatric conditions such as anxiety and depression. These findings are concordant with the results of functional neuroimaging studies. For example, individuals with FM alone primarily have increased activity in the regions of the brain that code for the sensory intensity of stimuli (e.g., the primary and secondary somatosensory cortices, posterior insula, and thalamus), whereas FM patients with comorbid depression also have increased activation in brain regions coding for the affective processing of pain, such as the amygdala and anterior insula [11]. The notion that there are two overlapping sets of traits, one being pain and sensory amplification, and the other being mood and affect, is also supported by genetic studies of idiopathic pain syndromes [8]. Twin studies have also been useful in teasing out potential underlying mechanisms versus "epiphenomena." Buchwald and colleagues compared identical twins with and without symptoms of FM or chronic fatigue syndrome, and they found that, in many cases, the two twins share abnormalities in sleep or immune function, yet have markedly different symptom profiles. These investigators likewise suggested that this is evidence of a problem with biological perceptual amplification in the affected twins [12].

Current evidence suggests that genetic factors are approximately 50% responsible for overall sensitivity to experimental pain, and that the same genes that have been identified to increase sensitivity to experimental pain also render individuals more likely to develop chronic pain over the course of their lifetime. There are at least five sets of genes that have shown to both change an individual's pain sensitivity and increase their likelihood of developing one or more chronic pain states,

including catechol-O-methyltransferase (COMT) (an estrogen-sensitive enzyme that may play a more prominent role in females), a number of sodium channel mutations, guanosine triphosphate (GTP) cyclohydroxylase, types 2 and 3 adrenergic receptors, and a potassium central nervous system channel gene (KCNS) [13–18]. These are the genes have been most consistently shown to confer a higher risk of pain sensitivity or the development of chronic pain, but not all studies have confirmed these findings [14,19,20].

As with most illnesses that may have a familial or genetic underpinning, environmental factors may play a prominent role in triggering the development of FM and other centralized pain states. Environmental "stressors" temporally associated with the development of either FM or chronic fatigue syndrome include early-life trauma; physical trauma (especially involving the trunk); certain infections such as hepatitis C, Epstein–Barr virus, parvovirus, and Lyme disease; and emotional stress. The disorder is also associated with other regional pain conditions or autoimmune disorders [21–23]. Of note, each of these "stressors" only triggers the development of FM and/or chronic fatigue syndrome in approximately 5–10% of individuals who are exposed; the overwhelming majority of individuals who experience the same infections or other stressful events regain their baseline state of health.

In fact, emerging evidence from a number of different areas in the pain field suggests that the same characteristics that are often attributable to FM patients, in fact, more broadly represent a "pain-prone phenotype." Fig. 2 portrays the fact that female sex, early-life trauma, a personal or family history of chronic pain, a personal history of other centrally mediated symptoms (insomnia, fatigue, memory problems, and mood disturbances), and cognitions such as catastrophizing have all been shown to be present in subsets of individuals with any chronic pain state, and these factors predict which individuals are more likely to transition from acute to chronic pain.

In addition to the study of centralized pain states, we have made significant advances in our broader understanding of chronic pain pathogenesis. Data from experimental sensory testing and functional neuroimaging studies suggest wide individual variation in sensory sensitivity that adheres to a bell-shape distribution across a wide variety of chronic pain states with a subset of individuals displaying hyperalgesia or augmented CNS activity across pain states [23–25]. The centralized pain states originally identified as having diffuse hyperalgesia/allodynia include FM, IBS, TMJD, idiopathic low back pain, tension headache, IC, and vulvodynia [26–37]. Functional neuroimaging studies, especially those using functional magnetic resonance imaging (fMRI), corroborate these experimental pain testing findings, and these studies show that individuals with centralized pain states have increased neuronal activity in the pain-processing regions of the brain when they are exposed to stimuli that healthy individuals find innocuous [34,38–40].

Several meta-analyses of fMRI studies have summarized the brain regions that show activation when experimental pain is applied to human subjects, and these generally agree with single-photon emission computed tomography (SPECT) and positron emission tomography (PET) studies noted earlier. Activation sites across studies vary to some degree, depending on experimental paradigm and

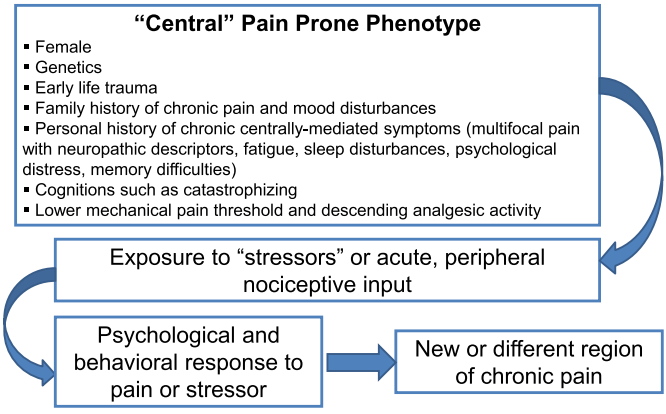

Fig. 2. Pain-prone phenotype.

pain stimulus (i.e., heat, cold pressure, electric shock, ischemia, etc.). However, the main components of this "pain matrix" are the primary and secondary somatosensory cortex (SI and SII), the insular cortex (IC), the anterior and midcingulate cortex (ACC), the posterior cingulate gyrus (PCC) and the thalamus; that is, the pain system involves somatosensory, limbic, and associative brain structures [41,42]. It is more or less true that the medial structures in this matrix respond to the affective dimension of pain (i.e., the emotional valence of pain), whereas the lateral structures (e.g., somatosensory cortices) are more involved in the sensory processing of pain (i.e., where it is and how intense it is). However, this is overly simplistic. Within a single brain region such as the insula, the posterior insula is more involved in sensory processing, and the anterior more involved in affective processing, and even the left-to-right balance of insular activity might be associated with the emotional valence of pain [43].

Many potential mechanisms can cause augmented central pain processing. The two receiving the most attention and study have been increased windup and the lack of descending analgesia. Although both of these mechanisms can be tested experimentally, the study of descending endogenous analgesic pathways holds the most promise for successfully "segmenting" patients with chronic pain into those with a central predominance to their pain. For example, attenuated descending analgesic activity (experimentally observed as reduced diffuse noxious inhibitory control (DNIC)) is seen in 10–20% of controls, but approximately 60–80% of individuals with conditions such as FM or IBS [44–49] demonstrate this deficit. Neither hyperalgesia nor deficiencies in descending analgesic activity are generally seen in individuals with psychiatric disorders such as depression [11,50]. The baseline presence of hyperalgesia and/or the absence of descending analgesia have been shown to predict the subsequent intensity of an acute painful experience, analgesic requirements following surgery, and the subsequent development of chronic pain [51,52]. Diatchenko, Maixner, and colleagues performed a longitudinal study of 202 young pain-free women, arguably the best single study of this nature performed to date, and followed them up for 2 years, with the outcome of interest being those women who developed new-onset TMJD [53]. An individual's pain threshold at baseline (i.e., while asymptomatic) was a strong predictor of the development of TMJD, as any individual on the "hyperalgesic side" of a bell-shaped curve of pain sensitivity at baseline was nearly 3× as likely to develop TMJD as an individual in the bottom half of pain sensitivity. These results have recently been replicated in a much larger cohort, and they showed that pressure pain threshold was the single experimental measure of pain threshold with respect to predicting the future onset of TMJD [54].

Regarding the clustering of co-occurring somatic symptoms, as well as higher than expected rates of mood disorders, the best supported pathogenic theory with centralized pain states is that centrally acting neurotransmitters that are known to play a role in causing the pain in these conditions (e.g., low norepinephrine, gamma-aminobutyric acid (GABA), serotonin, high glutamate, and substance P) also play prominent roles in controlling sleep, mood, alertness, etc [7]. Clinicians might best understand pain and sensory processing by considering this type of processing to be controlled in a manner very similar to immune function. Just as high levels of pro-inflammatory cytokines, or low levels of anti-inflammatory cytokines, can move an individual towards hyperimmune function, so also are there neurotransmitters that are similarly known to either increase or decrease pain transmission in the CNS. Overall, the analogy of an increased "volume control" or "gain" setting on pain and sensory processing is supported by studies from a variety of sources. Similar to essential hypertension, where a variety of root causes can lead to elevated systemic blood pressure, these disorders represent "primary hypertension of pain and sensory processing pathways." Elevated levels of neurotransmitters that tend to be pro-nociceptive (i.e., on the left side of Fig. 3) or reduced levels of neurotransmitters that inhibit pain transmission (i.e., on the right side of Fig. 3) have a tendency to increase the volume control, and drugs that block neurotransmitters on the left or augment activity of those on the right will typically be found to be effective treatments, at least for a subset of individuals with this spectrum of illness.

The arrows in Fig. 3 indicate the direction of the abnormalities in the neurotransmitter levels (in either the cerebrospinal fluid (CSF) or brain) that have been identified to date in FM. As noted, in FM, there is evidence for increases in the CSF levels of substance P, glutamate, nerve growth factor, and brain-derived neurotrophic factor, and low levels of the metabolites of serotonin, norepinephrine, dopamine, and GABA, any of which could lead to an "increase in the volume control" and augmented pain and sensory processing [55–59]. The only neurotransmitter system that has been studied to date and not found to be out of line in a direction that would cause augmented pain transmission is the

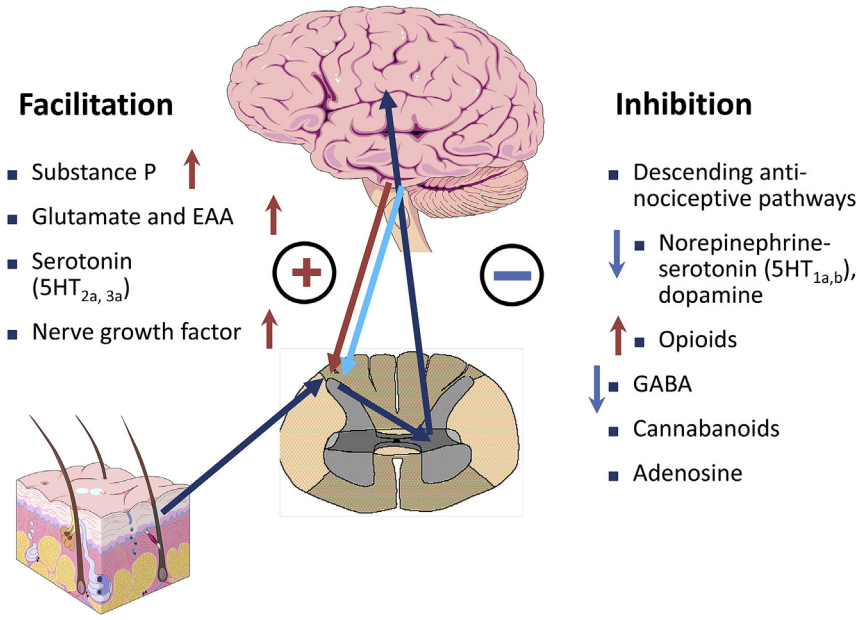

Fig. 3. CNS influences on pain and sensory processing.

endogenous opioid system. Both CSF levels and brain activity by functional neuroimaging appear to be augmented, not reduced (as would be necessary to *cause* augmented pain processing), in FM, which may be the reason why opioidergic drugs do not work well to treat FM and related pain syndromes [60,61].

Potential role of peripheral factors in centralized pain states

Although FM, IBS, and other centralized pain states were originally classified as autoimmune or inflammatory diseases (i.e., fibrositis and spastic colitis) and then later not, recent findings are leading to a reconsideration of whether subtle inflammatory changes may be responsible for some of the symptoms seen. Immunological cascades have a role in the maintenance of central sensitivity and chronic pain, which is enhanced through the release of pro-inflammatory cytokines by CNS glial cells; thus, the traditional paradigm regarding inflammatory versus noninflammatory pain may gradually become less dichotomous. As may be expected in any complex biological system, a delicate apparatus of checks and balances is at work in the spinal transmission of pain. Multiple inhibitory transmitters act at the spinal level to reduce the "volume" of pain transmission. Serotonin, norepinephrine, enkephalins, dopamine, and GABA are among the better known players in this balance.

Furthermore, studies suggest that maintenance of central augmentation requires persistent noxious peripheral input, even in syndromes such as IBS and FM, which are characterized by the absence of well-defined, localized, pain-causing lesions [62]. In fact, a recent study of 68 FM patients with myofascial pain syndromes and 56 FM patients with regional joint pain showed that peripheral trigger point injections and hydroelectrophoresis ameliorate FM pain and increase pain thresholds at sites distant from the therapeutic interventions, providing further evidence that painful peripheral stimuli contribute to the perpetuation of central augmentation interventions [63].

Finally, many studies have identified a small fiber neuropathy in many individuals with FM [64–66]. The meaning of this remains unclear. That the prominent and ubiquitous symptoms seen in FM such as fatigue, memory problems, and memory and mood disturbances are due to a small fiber neuropathy seems to be a remote possibility. Moreover, small fiber neuropathy has been found in many disparate conditions that are not accompanied by widespread pain (e.g., sarcoidosis and Fabry's disease) and in

many regional pain conditions, making it even more likely that this finding is an effect of the disorder (akin to finding atrophy of brain regions involved in pain processing) rather than the cause, but only time will tell.

The role of central factors in rheumatic disorders where pain was classically believed to be primarily due to peripheral nociceptive input

Osteoarthritis

Historically, the "disease" of OA has been viewed primarily as damage to the cartilage and bone. As such, the magnitude of damage or inflammation of these structures should predict symptoms. Population-based studies suggest otherwise; 30–50% of individuals with moderate to severe radiographic changes of OA are asymptomatic, and approximately 10% of individuals with moderate to severe knee pain have normal radiographs [67,68]. Psychological factors do account for some of this variance in pain and other symptoms, but only to a small degree [69,70]. This failure of peripheral damage, inflammation, or even psychological factors to explain the presence, absence, or severity of chronic pain should not be surprising. To date, no chronic pain state involves a strong relationship between peripheral factors and the level of pain reported.

The work done to date supports the hypothesis of OA as a mixed pain state, and that CNS factors are highly influential in some individuals. The fact that central factors may play a pivotal role in OA helps explain, in turn, the fact that comorbid somatic symptoms known to be associated with centralized pain conditions (e.g., fatigue and sleep problems) are very commonly present in OA, and these are not explained by a purely "peripheral" model of this disorder [71,72]. Moreover, for some time, there have been small studies suggesting that OA patients display diffuse hyperalgesia to mechanical or heat stimuli [73]. Kosek demonstrated that individuals with OA of the hip had reduced descending analgesic activity, which partially normalized following hip arthroplasty, suggesting that the central factors were being at least partly driven by peripheral nociceptive input [74]. Since then, increasingly more studies have been performed showing that groups of individuals with OA have lower overall pain thresholds than controls, and have less efficient descending analgesic activity [73,75]. Gwilym and colleagues used both experimental pain testing and more sophisticated functional neuroimaging procedures to show evidence of augmented CNS processing of pain in 20 OA patients, and then in a separate study they showed that atrophy of the thalamus was seen at baseline on OA, which improved following arthroplasty [76,77]. Finally, recent randomized controlled trials (RCTs) have demonstrated that compounds that alter pain neurotransmitters centrally such as serotonin and norepinephrine (e.g., duloxetine and tricyclics) are efficacious in OA [78,79]. However, this does not mean that peripheral factors are unimportant in OA. A recent study by Neogi and colleagues elegantly demonstrated that, in individuals with asymmetric knee osteoarthritis (KOA), the pain levels in each knee were strongly related to joint space narrowing in the affected knee [80]. Rather, the aggregate data suggest that in some individuals central factors are superimposed upon the more traditional peripheral factors leading to the need for a broader and more flexible approach to diagnosis and treatment.

A series of recent studies by Brummett et al. demonstrated the importance of comorbid centralized pain in OA with respect to treatment response. Both studies examined large cohorts of individuals undergoing knee or hip arthroplasty, and they examined how the degree of "fibromyalgianess," measured using the 2011 survey criteria for FM, contribute to the responsiveness of OA to (a) opioids administered in the perioperative period and (b) improvement in pain following arthroplasty [81,82]. Each study examined slightly different size cohorts of >500 individuals undergoing hip or knee total arthroplasty. Patients were preoperatively phenotyped using validated self-reported questionnaires, including the 2011 survey criteria for FM, which consists of a measure of widespread pain assessed from a body map and six questions about comorbid symptoms such as fatigue or trouble thinking (total score = 0–31). The continuous (0–31) measure has been termed "fibromyalgianess" (FMness). For the study examining opioid consumption, perioperative opioid usage was calculated as oral morphine equivalents. This score was the only self-reported measure to predict perioperative opioid consumption. For each one-point increase in this scale from 0 to 31, individuals needed 9 mg more oral morphine equivalents of opioids in the perioperative period. When individuals taking opioids prior to surgery were excluded from the analyses, this figure still remained statistically significant, with >7 mg

greater oral morphine equivalents of opioids needed in the perioperative period. These are amongst the first data to show what has long been anecdotally noted – that centralized pain is less responsive to opioids than nociceptive pain. This group has recently replicated these findings in a cohort of women undergoing hysterectomy [83,84].

In a similar dataset using the same baseline phenotypic variables, Brummett explored whether centralization of pain (measured via the same 2011 survey criteria for FM) was predictive of failure to respond to the arthroplasty with the intended reduction in pain [82]. Again, this measure was highly predictive of a poor outcome, and again this did not just occur in the "tip of the iceberg" in individuals who might meet the diagnostic criteria for FM. FMness was independently predictive of less improvement in pain (Est 0.18, SE 0.02, $p < 0.00001$). Lower baseline overall pain, higher doses of preoperative opioids, and total knee arthroplasty (TKA) (vs. total hip arthroplasty (THA)) were also predictive ($R^2 = 0.43$). Similar predictors were seen with the logistic regression of Brief Pain Inventory (BPI) change, with patients 18% less likely to meet the threshold of pain improvement for every one-point increase on the 31-point scale (adjusted odds ratio (aOR) 0.78, $p < 0.00001$). Again, these are amongst the first data to conclusively show that as pain becomes more centralized in individuals with OA, it becomes less responsive to surgical procedures (that are obviously aimed at reducing nociceptive input rather than centrally mediated pain responsiveness).

Chronic low back pain

In contrast to FM and OA, LBP has long been acknowledged to be a mixed pain state, with good evidence for subsets of patients with nociceptive pain, neuropathic pain, and centralized pain. The presence of nociceptive and neuropathic pain is obvious, whereas the evidence for centralized pain includes many studies showing diffuse hyperalgesia on quantitative sensory testing as well as features of augmented pain processing, changes in brain size and shape, and neurochemical abnormalities all consistent with a subset of chronic low back pain (CLBP) patients having prominent central nervous contributions to their pain [34,85–90]. This ultimately has been confirmed by the fact that the drug duloxetine, which primarily works centrally, has been shown to be effective in CLBP just as in OA [91].

Thus, any clinical evaluation of these patients requires that measures possibly helpful in identifying subsets of individuals with nociceptive versus neuropathic versus centralized pain must use a battery capable of detecting each subset. As previously noted, the 2011 FM survey criteria seem to perform well in identifying the centralized pain subset – a recent study showed that 42% of a tertiary referral population of CLBP met the criteria for FM [92]. To identify individuals with CLBP who have neuropathic pain, tools such as the PainDETECT should be used [93–95]. Using batteries such as these, studies have begun to validate that individuals with all three mechanisms can be identified in individuals with CLBP. For example, one group recently showed the discriminative validity of mechanism-based classifications of pain by identifying discriminatory clusters of clinical criteria predictive of "nociceptive," "peripheral neuropathic," and "central sensitization" pain in patients with low back (±leg) pain disorders [96]. This study was a cross-sectional, between-patient design using the extreme-group method. Four hundred and sixty-four patients with low back (±leg) pain were assessed using a standardized assessment protocol. After each assessment, patients' pain was assigned a mechanism-based classification. Clinicians then completed a clinical criteria checklist indicating the presence/absence of various clinical criteria. Multivariate analyses using binary logistic regression with Bayesian model averaging identified a discriminative cluster of seven, three, and four symptoms and signs predictive of a dominance of "nociceptive," "peripheral neuropathic," and "central sensitization" pain, respectively. Each cluster was found to have high levels of classification accuracy (sensitivity, specificity, positive/negative predictive values, and positive/negative likelihood ratios).

Discussion

Critical information that can be gleaned from the history and physical examination to help identify the underlying mechanism(s) of pain

It might seem a giant leap to move from experimental pain testing, brain imaging, and genetic studies in centralized pain states to a better understanding of the diagnosis and treatment of any

chronic pain, but in reality this is not such a leap. Much of the same information attained via these sophisticated research methods can also be obtained (albeit less precisely) by performing a history and physical examination, as noted in Fig. 4.

For example, individuals with centralized pain states very often demonstrate altered noxious thresholds (the point at which a sensory experience such as pressure, heat, or sounds become bothersome) for virtually every type of sensory stimulus [97]. This can be easily understood by patients and clinicians alike when the phenomenon is likened to "an increased volume control in the brain for any sensory stimuli." Because of this, individuals with FM or other centralized pain states will often note that they find noises, odors, and bright lights very bothersome, and this sensory sensitivity likely even explains many of the visceral symptoms these individuals experience (e.g., indigestion, heartburn, abdominal pain, and urinary urgency and frequency). Sometimes, merely highlighting this physiological understanding of pain augmentation can be extremely helpful to patients, because when they develop new symptoms that follow this same pattern they are less concerned that "there is something wrong," which would otherwise often trigger a frustrating "search for the cause of the pain."

Although there are a number of ways to determine how pain sensitive an individual is, current evidence suggests that assessing the pressure pain threshold (i.e., tenderness to palpation, in contrast to assessing heat or cold pain threshold) is the most reliable and reproducible method for identifying individuals with centralized pain [54]. Experimental pain testing is not yet available as a routine test in clinical practice, so methods of assessing tenderness in practice include performing a tender point count, or incorporating alternative methods of assessing pain threshold into routine practice. For example, one method of assessing the overall pain threshold while also obtaining other valuable diagnostic information is to assess pain thresholds in the hands and arms of all patients with chronic pain. A rapid examination by applying firm pressure over several interphalangeal (IP) joints of each hand, also over the adjacent phalanges, and then caudally to firmly palpate the muscles of the forearm including the lateral epicondyle region, is one method of assessing the overall pain threshold as well as obtain additional diagnostic information about the patient. If the individual is tender in many of these areas, or in just the muscles of the forearm, they are likely diffusely tender (i.e., have a low central pain threshold). However, if the individual is only tender over the IP joints and not the other regions, and especially if there is any swelling over these joints, one should be more concerned about a systemic autoimmune disorder (e.g., rheumatoid arthritis or lupus). Alternatively, sometimes individuals are only tender over the phalanges, and in these instances one might suspect a metabolic bone disease or condition causing periostitis (e.g., hypothyroidism and hyperparathyroidism).

Choosing pharmacological therapy based on the underlying mechanism(s) of pain

Fig. 5 shows the classes of drugs that seem most effective in different underlying mechanisms of pain. For peripheral/nociceptive, noninflammatory pain states such as OA, treatment guidelines typically recommend first using acetaminophen, and then nonsteroidal anti-inflammatory drugs (NSAIDs). Acetaminophen is now generally thought to be safer, but less effective, than NSAIDs.

- Pain in many body regions
- Higher current and lifetime history of chronic pain in several body regions
- Multiple somatic symptoms (e.g., fatigue, memory difficulties, sleep problems, mood disturbance)
- More sensitive to other sensory stimuli (e.g., bright light, loud noises, odors, other sensations in internal organs)
- 1.5 to 2x more common in women
- Strong family history of chronic pain
- Pain triggered or exacerbated by stressors
- Generally normal physical examination except for diffuse tenderness and nonspecific neurological signs

Fig. 4. Clinical characteristics of centralized pain.

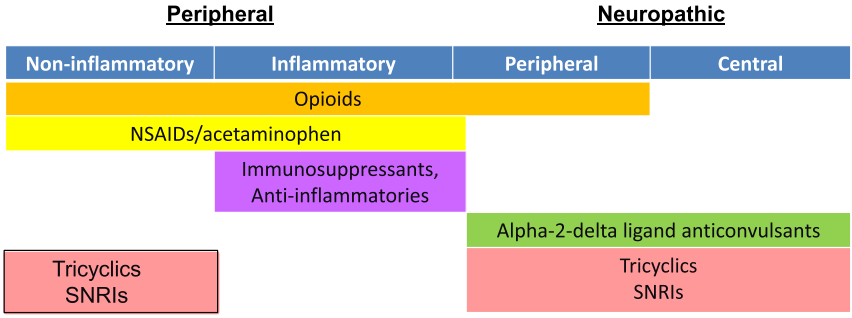

Fig. 5. Drugs for pain based on underlying mechanisms.

Although opioids were previously considered to be very useful for pain refractory to these treatments, the latest meta-analyses of opioids in OA challenge this notion and generally recommend against opioid use.

Although older studies supported the fact that tricyclic compounds may be effective in OA, these drugs have significant toxicity, especially in the elderly. Because of this, newer drugs that also likely work by increasing serotonergic and noradrenergic activity, such as tramadol and duloxetine, are more commonly used. Although most in the pain field strongly suspect that these latter "centrally acting" analgesics (this term is used cautiously as most analgesics have potential peripheral and central mechanisms) will be more effective in individuals with peripheral/nociceptive pain that has centralized, to date there have been no studies that have definitively proved this.

In inflammatory, peripheral pain states such as RA, in addition to the mentioned drugs, a whole host of anti-inflammatory or "disease-modifying" drugs are also used. It is likely that these drugs both directly reduce pain by reducing inflammation and reduce peripheral sensitization that may occur due to ongoing inflammation.

The classes of drugs that preferentially work for neuropathic or centralized pain states again include the serotonin–norepinephrine reuptake inhibitors (e.g., tricyclic antidepressants (TCAs), tramadol and duloxetine) as well as the alpha-2-delta calcium channel ligands (pregabalin and gabapentin).

Peripheral pain syndromes (including both inflammatory and noninflammatory peripheral pain, and peripheral neuropathic pain) can also be treated with topical agents or injections. Injections of corticosteroids, hyaluronic acid preparations (for OA in joints that can be injected), agents that ablate nerves, or capsaicin (effective in both OA and neuropathic pain) are all therapeutic options.

Research agenda

- To realize there is not a single chronic pain state where any radiographic, surgical, or pathological description of peripheral nociceptive damage has been reproducibly shown to be related to the presence or severity of pain
- To gain properly critical information from the history and physical examination of the patients to help identify the underlying mechanism(s) of pain
- To fully understand the potential role of peripheral factors in centralized pain states
- To determine the classes of drugs that seem most effective in different underlying mechanisms of pain

Practice points

- Advances in our understanding of pain over the past decade are finally bringing the dream of "personalized analgesia" closer to reality.
- Using clues from a history and physical examination, clinicians can now, at a minimum, identify the subsets of individuals with heretofore considered "peripheral" pain syndromes, and treat these individuals with more centrally than peripherally directed pharmacological and nonpharmacological approaches.
- However, considerably more study is necessary to determine if we can extrapolate our understanding of conditions such as FM, OA, and CLBP more broadly, and if these segmentation techniques really do identify subsets of patients who will preferentially respond to peripherally or centrally acting analgesics.

Conflicts of interest

Dr. Clauw has performed consulting and/or received research funding from Pfizer, Eli Lilly, Merck, Nuvo, Cerephex, Iroko, Tonix, Theravance, IMC, Zynerba, and Samumed.

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