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Mechanisms of chronic pain – key considerations for appropriate physical therapy management

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ABSTRACT

In last decades, knowledge of nociceptive pain mechanisms has expanded rapidly. The use of quantitative sensory testing has provided evidence that peripheral and central sensitization mechanisms play a relevant role in localized and widespread chronic pain syndromes. In fact, almost any patient suffering with a chronic pain condition will demonstrate impairments in the central nervous system. In addition, it is accepted that pain is associated with different types of trigger factors including social, physiological, and psychological. This rational has provoked a change in the understanding of potential mechanisms of manual therapies, changing from a biomechanical/medical viewpoint, to a neurophysiological/nociceptive viewpoint. Therefore, interventions for patients with chronic pain should be applied based on current knowledge of nociceptive mechanisms since determining potential drivers of the sensitization process is critical for effective management. The current paper reviews mechanisms of chronic pain from a clinical and neurophysiological point of view and summarizes key messages for clinicians for proper management of individuals with chronic pain.

KEYWORDS

Pain; sensitization; manual therapy; mechanisms

Introduction

Recent estimates indicate that chronic pain has reached epidemic levels in both the US and Europe. The prevalence of chronic pain in United States (US) adults over the age of 18 has been estimated at 30.7 and 43%, depending on the source [1,2] with similar statistics reported in the United Kingdom [3]. The social and financial ramifications of this epidemic are staggering, particularly in terms of disability and reduced quality of life [4], and the increased risk of hospitalization, institutionalization, and mortality [5].

Several factors may contribute to the high rate of chronic pain, including the fact that our population is getting older. Novak et al. [6] reported that the prevalence of chronic pain increased steadily with age from a low of 14.3% in 18–25 years old to as high as 62% in the over 75 age group. Similarly, the prevalence of disabling musculoskeletal chronic pain increased in the latter years of the twentieth century then stabilized in the early years of the twenty-first century [7]. Thus, the process of aging, including social, psychological, and physiological changes contribute in some manner to chronic pain. Sedentary lifestyle is another major contributor to chronic pain. In modern society, more and more occupations require a significant amount of time sitting in front of a computer. Physical inactivity is a known risk factor for development of chronic pain [8] and central changes in pain processing may occur more readily in persons with a sedentary way of life.

The response to increased levels of chronic pain has been a sharp rise in prescription of opioids. Over the past 15 years, there has been a marked increase in the prescription of almost all types of opioid medications while at the same time opioid misuse and the number of patients seeking rehabilitation for substance abuse has also increased [9]. It is clear that chronic pain is a global problem associated with aging and sedentary lifestyle, and that prescription of opioid medications as a sole solution is unlikely to resolve this current epidemic.

In simplest terms, chronic pain has been defined by its persistence, with the cut point typically defined as greater than three months [10]. However, it is clear that several factors differentiate this condition in terms of disability, contributing factors and underlying mechanisms of pain. One important dimension in the characterization of chronic pain is the concept of pain interference, which has been defined as the extent to which pain limits or interferes with functional activities and daily routines [11]. A second differentiating feature of chronic pain is whether it is widespread, defined as pain hypersensitivity experienced not only at the affected body part but

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throughout the body. Many chronic pain conditions, including fibromyalgia [12] have varying degrees of diffuse pain and symptoms. Disability is reported to be more severe [13] and quantitative sensory findings more abnormal [14] in patients with widespread rather than regional chronic pain conditions. Other factors have been utilized in the characterization of pain. The Initiative of Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) has developed a consensus of recommendations for improving the design, execution, and interpretation of clinical trials of treatments for pain [15] and factors such as disease, comorbidities, pain duration, and pain intensity, among others, have been suggested for characterization of the pain.

Both medical and rehabilitative management of chronic pain have begun to target various pain mechanisms as one strategy for combatting chronic pain. The purpose of this narrative is to describe the underlying neurophysiologic mechanisms of chronic pain and to propose rehabilitative methods that may address aberrant pain mechanisms.

Contributing factors and risk factors to chronic pain

Several factors have been identified as potentially contributing to the change from acute to chronic pain. These can be characterized into three different but related categories including social, physiological, and psychological factors. A selected number of factors have been listed below.

Social factors

Social factors are the personal characteristics that influence an individual's personality, attitudes, and lifestyle. In addition to advanced age, several other social influences may contribute to chronic pain. Tenuous housing and employment status have been independently associated with chronic pain [16], as well as low educational levels and low family income [17–19]. Stress over financial or housing insecurity may promote aberrant pain processing. Social isolation and recent divorce, separation, or death of a spouse have also been associated with progression to chronic pain [13,20]. A history of physical abuse and specifically, sexual abuse [21,22] has been identified in the medical history of many subjects with chronic pain. Finally, being a recent immigrant or non-Caucasian may predispose an individual to this disease [13,23].

Physiological factors

In addition to advancing age and low physical activity, another major physiological contributor to chronic pain is poor sleep quality. Studies have demonstrated in both animal models [24] and human studies [25,26] that inadequate or interrupted sleep results in impaired pain inhibitory mechanisms. In addition, a complex relationship exists between menopause and chronic pain due to the fact that menopause occurs with aging, and is associated with increased rates of insomnia and depression [27]. A major consideration with chronic pain is to determine the number of co-morbidities a patient may demonstrate, such as headache and obesity [28].

Psychological factors

Numerous studies have identified depression and anxiety as major contributing factors in chronic pain. A recent meta-analysis found that persons with chronic pain experienced a range of psychological impairments related to anxiety, depression, anger/hostility, self-esteem, and general emotional functioning [29]. Burke et al. [30] reported that depression and chronic pain may co-occur in up to 80% of individuals suffering from those disorders. Clearly, physical therapy management must acknowledge these contributing factors when considering rehabilitative strategies in subjects with chronic pain.

Mechanisms of chronic pain

Interaction between peripheral and central mechanisms for chronic pain

There is significant debate on the role of nociceptive sensitization mechanisms in the etiology and pathology of chronic pain, particularly the interaction of peripheral and central factors. Briefly, *peripheral sensitization* is defined as an increased responsiveness and reduced threshold of peripheral nociceptors to noxious stimulation of their receptive fields [10]. This occurs in response to a noxious event such as inflammation occurring with tissue injury. Inflammatory mediators cause neuroplastic changes of the nociceptors innervating the damaged tissue. Peripheral sensitization is a protective mechanism and by definition, is limited to nociceptors within the site of the inflammatory milieu and will resolve as tissues heal and inflammation recedes [31]. *Central sensitization* is defined as the increased response of nociceptive neurons in the central nervous system to noxious stimuli, mediated by amplification of signaling to the central nervous system, potentially at both spinal and supraspinal levels [10]. Two main mechanisms have been recognized as contributing to central sensitization: an increased excitation (i.e. sensitization) by long-lasting peripheral nociceptive stimuli or impaired descending pain inhibition (see review by Woolf [32]). While directly determining central sensitization is not possible in humans, laboratory studies have indirectly determined the former in various patient populations by demonstration of diminished threshold to elicit the nociceptive reflex [33–36] and the latter by examining conditioned

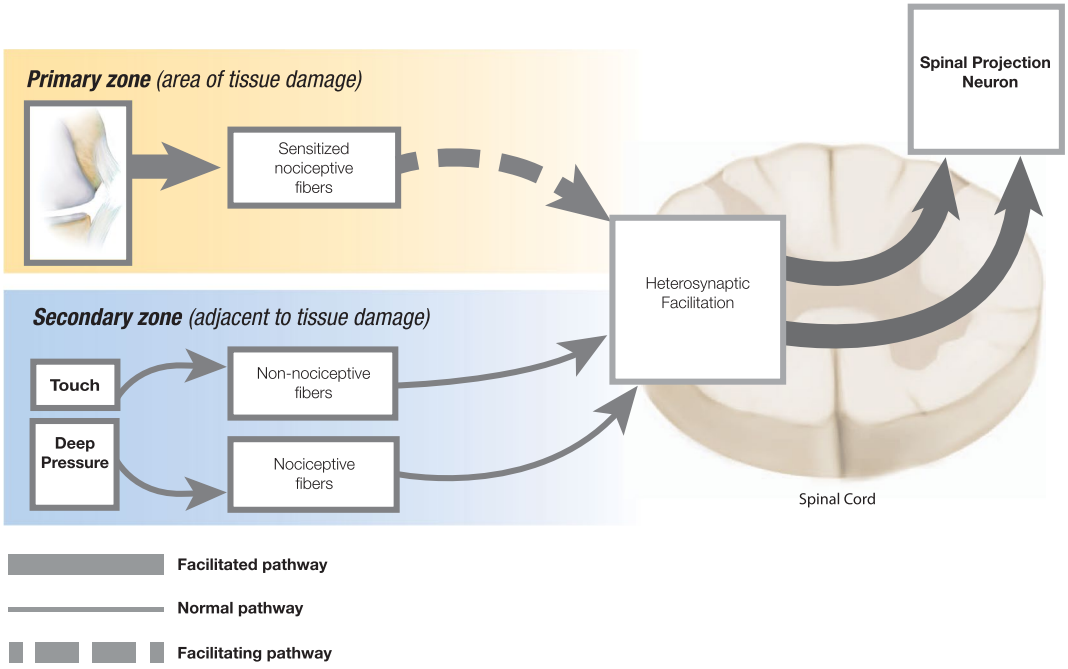

Figure 1. Heterosynatic facilitation.
Note: Purported mechanism underlying allodynia and secondary hyperalgesia.

pain modulation [37–40]. One mechanism associated with peripheral and central sensitization is neurogenic inflammation. When sensitized peptidergic (e.g. C fibers) are stimulated, neuropeptides, such as substance P and calcitonin gene-related peptide (CGRP) are secreted at the periphery which facilitates vascular changes, plasma extravasation and pain [41], and at the dorsal horn [42], which facilitates central sensitization. Moreover, it has been demonstrated in cutaneous tissues that Aβ fibers, which typically deliver sensory input, such as light touch and vibration, to the spinal cord may undergo a phenotypic change in the presence of inflammation and begin to express C-fiber associated neuropeptides (e.g. substance P) at the periphery and centrally at the dorsal horn [43]. This phenomenon likely occurs in other sensitized tissues as well and would indicate that even non-painful input, such as exercise or manual therapy in the patient with chronic pain, can cause a flare-up of symptoms.

Mechanical hyperalgesia

Distinct clinical findings have been associated with specific mechanisms of central sensitization. Expanded locus of pain is an example of this and may present in various ways such as enlarged distribution of hyperalgesia, increased number of areas of pain including mirror-image pain, regional pain, and even widespread pain. One mechanism that may explain the expansion of pain beyond the area of insult/injury, (i.e. secondary hyperalgesia) is heterosynaptic facilitation (Figure 1) [44]. While repetitive peripheral input may sensitize synaptic connections to dorsal horn neurons (homosynaptic facilitation), secondary hyperalgesia is thought to occur due to interneuronal facilitation of adjacent spinal projection pathways (heterosynaptic facilitation) [45]. Arendt-Nielsen and Graven-Nielsen [46] have described this as an opening of 'silent' (ineffective) synapses in the spinal cord by nociceptive input from musculoskeletal tissues, which may also be the genesis of referred pain. Mirror image pain may represent a segmental spread of secondary hyperalgesia, while regional (spreading) hyperalgesia may represent an extra-segmental expansion of secondary hyperalgesia throughout the lower or upper extremities. Heterosynaptic facilitation underlies most major changes in neuron receptive field properties and in pain sensitivity, and is likely responsible for secondary hyperalgesia and allodynia [44,47]. However, impairment of descending inhibitory mechanisms may also be responsible, at least in part, for widespread hyperalgesia [48]. Schliessbach et al. [49] found that generalized (widespread) central hypersensitivity affected 17.5–35.3% of patients with chronic pain, depending on the normative standard used. One measure commonly used to objectively quantify hyperalgesia is pressure pain threshold (PPT), defined as the pressure stimulus of least intensity at which an individual perceives pain [50]. This is typically measured through use of a pressure algometer, with an applicator tip (1 cm^2) designed to stimulate deep somatic tissues. Sites for measurement are chosen to identify the extent of pain expansion and comparison is made to the contra-lateral side or to normative values when available. Several studies have used this assessment tool and have clinically identified central sensitization in chronic conditions including tension-type headache [51], carpal tunnel syndrome [52], and low back pain [53]. Similarly, central sensitization has been also demonstrated in

non-musculoskeletal widespread pain conditions such as irritable bowel syndrome [54] and migraine [55]. All of these studies support the presence of central sensitization in chronic pain conditions but do not exclude the role of peripheral sensitization mechanisms.

Mechanical allodynia

Another clinical finding indicative of central sensitization is allodynia, which is defined as the experience of pain with a normally non-noxious stimulus. It is typically measured dynamically by lightly brushing the skin [56], and thereby only stimulates low threshold non-nociceptive receptors. The presence of allodynia following musculoskeletal injury or chronic condition is generally considered to be centrally mediated, occurring due to extra-synaptic facilitation of spinal projection neurons [44,45]. Specifically, the transient receptor potential cation channel (TRPV1) has been implicated in this mechanism [57]. Tactile allodynia is not uncommon in musculoskeletal conditions or non-musculoskeletal conditions [58] and is often found in the region of most pain [59]. Mapping allodynia can be of value clinically as it may serve as an important outcome measure for reassessment.

Thermal hyperalgesia

In addition, to mechanical hyperalgesia/allodynia, thermal sensitivity is also considered a manifestation of sensitization mechanisms. Thermal quantitative sensory measures, such as heat or cold detection thresholds, or heat pain/cold pain detection thresholds, are used to identify lesions in somatosensory pathways or neuroplastic changes due to chronic pain, and have been commonly used in assessment of neuropathic pain [60]. For example, following peripheral nerve lesions, increased expression of cold-sensing ion channels in dorsal root ganglion cells has been found in an animal model study, which may be the genesis of cold hypersensitivity [61]. It is important to note that pain thresholds are more appropriate than detection thresholds for assessing thermal nociceptive pathways in chronic pain [56]. This may be related to the fact that heat hyperalgesia is thought to be a sign of peripheral nociceptor sensitization [62] and cold hyperalgesia is considered a feature of neuropathic pain as a result of peripheral nerve injury [63]. Nevertheless, changes in thermal sensitivity in uninjured areas are also considered due to central sensitization mechanisms. For instance, bilateral thermal hyperalgesia has been found in individuals with strictly unilateral carpal tunnel syndrome [64]. In addition, thermal pain sensitivity was found to be an important factor in predicting success with management of carpal tunnel syndrome [65]. Cold pain hyperalgesia has been demonstrated in patients with strictly unilateral musculoskeletal pain conditions such as lateral epicondylalgia and associated with higher disability [66], however, other studies have failed to find thermal changes in musculoskeletal disorders without neuropathic involvement [67–69]. Clearly, further research on the relationship between thermal sensitivity and chronic pain is warranted.

Hypoesthesia

Deficits in innocuous sensory modalities such as cutaneous mechanical detection threshold or vibration sense may occur due to a peripheral nerve lesion resulting in sensory deficits. The resulting clinical finding would be hypoesthesia, defined as a decreased sensitivity to stimulation [10]. However, it is possible that pain may cause an inhibition of innocuous input particularly at the site of pain, resulting in hypoesthesia. In fact, a study employing experimentally induced pain demonstrated reduced vibrotactile sensitivity at the site of pain [70]. The authors referred to this phenomenon as a 'touch gate' suggesting that pain inhibited sensory afference at a supra-spinal level. Alternatively, other researchers have suggested the mechanism of pain induced hypoesthesia may be spinally mediated [71]. Deficits in mechanical detection (light touch), vibration perception, and proprioception are common in chronic pain conditions, but have mostly been reported in chronic musculoskeletal conditions. The functional significance of pain induced hypoesthesia is mostly unknown, however, diminished vibration detection acuity has been associated with perceived instability during a functional task [59].

Dynamic measures of central sensitization

It has been argued that many quantitative sensory measures are static in nature and provide only a snapshot of the neurophysiologic status of the central nervous system. Dynamic measures provoke the system through application of painful stimuli in a specific manner. Two methods commonly used in the laboratory and perhaps less so clinically are temporal summation and conditioned pain modulation. Temporal summation is the clinical correlate of neurophysiological phenomenon of windup, which is defined as the progressively increasing activity in dorsal horn cells following repetitive activation of primary afferent C-fibers (Figure 2) [42]. Temporal summation is produced by repetitive high threshold C- and/or Aδ-fiber stimulation applied at a frequency of less than 3 Hz [72,73] and subjective measures of pain are collected at specific intervals (Figure 2) [74]. A steeper slope of increasing pain is indicative of centrally mediated pain indicating facilitated synaptic efficacy at the dorsal horn [73].

Conditioned pain modulation examines the ability of descending pain mechanisms to inhibit pain. A test stimulus (baseline measure of pain threshold) is applied

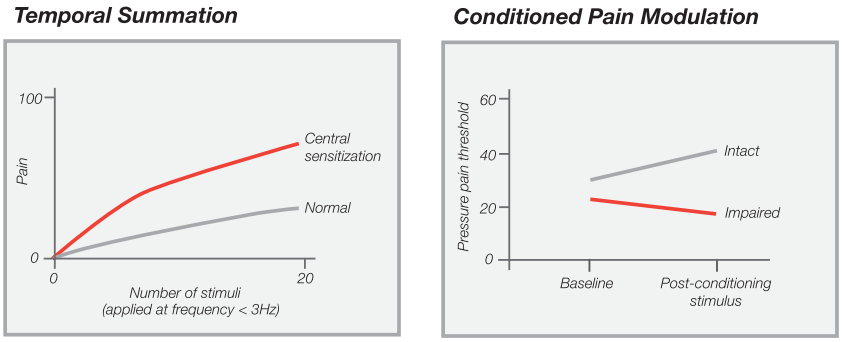

Figure 2. Dynamic measures of central sensitization. (A) Temporal summation, (B) Conditioned pain modulation.

before and after application of a conditioning stimulus, such as cold pain or ischemic pain, at a distant site. The conditioning stimulus should activate the diffuse noxious inhibitory control (DNIC) system which is one of the main descending pain inhibition pathways [75]. In a normal response, the test stimulus is perceived as less painful following application of the painful conditioning stimulus (Figure 2). This represents the body's adaptation of incoming nociceptive information to momentary as well as ongoing needs and requirements [37]. When these mechanisms are impaired, the perception of the test stimulus is unchanged or worsened.

Clinical considerations for pain mechanisms-based management

Clinical and basic science evidence has demonstrated that proper management of patients with chronic pain should be multimodal and approached from a personalized patient's perspective including proper passive and/or active strategies, active listening, empathy, and consideration of psycho-social issues based on clinical findings during the subjective and objective examination. This is particularly important in patients with chronic pain since it is helpful to encourage patients to choose among various treatment options after proper explanation of the benefits and risks of each therapeutic approach. Asking the patient to participate in decision processes allows them to take responsibility for the management of their condition [76]. Interventions for individuals with chronic pain should be applied based on current knowledge of nociceptive pain mechanisms. The challenge facing clinicians is how to select the proper therapeutic approach for each patient, who is likely to differ in individual presentation [77]. Key indicators of central sensitization may include the presence of regional or widespread hyperalgesia (often measured by PPT), allodynia (in the absence of cutaneous injury), absence of pain modulation with application of painful stimuli (conditioned pain modulation), and steeper elevation in pain response to temporal summation. Findings that may increase suspicion of central sensitization and trigger further testing include the presence of heightened pain either at rest or in response to an activity/intervention, spontaneous pain without trigger, increased number of areas of pain or expanded areas of pain that follow no typical distribution, and/or the presence of hypoesthesia or dysesthesia in the area of most pain that does not follow the distribution of a nerve.

Top-down sensitizers

Determining the drivers of the sensitization process is critical for effective management. For example, objective measures are available to identify psychological contributors, such as depression and anxiety to the pain presentation. These are sometimes referred to as 'top down' sensitizers [37]. When appropriate, clinicians may use strategies to address these contributors [78]. Proper referral and communication with other health care providers is critical in the holistic care of the patient with chronic pain.

Bottom-up sensitizers: inflammation

Determining the potential 'bottom up' drivers of central sensitization is also important. Inflammation is a potent driver of the sensitization process and thus, must be a target in the rehabilitation plan of care. In a study of over 1100 subjects with knee OA, Neogi et al. [79] found that inflammation, as evidenced by synovitis or effusion, was significantly associated with pain sensitization. In terms of medical interventions, Etoricoxib, (Merck, Kenilworth NJ) a non-steroidal anti-inflammatory (NSAIDS) Cox-II inhibitor medication, has been demonstrated to modulate central sensitization [80]. In comparison to placebo, this medication diminished PPTs, regional sensitization, and temporal summation but had no effect on conditioned pain modulation. More and more, medical practitioners are choosing to target specific pain mechanisms in their prescription of medications [81]. Also in subjects with knee OA, excitability of nociceptive pathways measured via the nociceptive reflex (an indirect indicator of central sensitization) was reduced after joint aspiration and further reduced following intra-articular corticosteroid injection, further demonstrating the importance

Table 1. Physical therapy interventions for chronic pain and targeted neurophysiologic mechanisms.

Physical therapy intervention	Neurophysiologic mechanism
Active interventions	
Promote quality sleep	Disturbed sleep can result in impaired pain inhibition
Aerobic exercise	Promotes descending inhibition of pain
Isometric exercise	Systemic and local inhibitory mechanisms
25% MVC* until task failure Brief MVC* (3 s duration/1 min apart)	
Educational – Cognitive interventions	
Pain science education	Diminishes psychological (top down) drivers of pain
Graded approach to increased functional activity	Promotes pain relief and well-being without triggering inflammatory flare thought to occur via neurogenic inflammation
Passive interventions	
Manual Therapy	Decreases central sensitization Promotes descending inhibition of pain
TENS	Promotes descending inhibition of pain
Noxious electrical stimulation	Promotes descending inhibition of pain

Note: *MVC: Maximum voluntary contraction.

of controlling inflammation [82]. Medical management has also targeted inflammation in non-musculoskeletal disorders such as inflammatory bowel syndrome [83].

Importance of proper dosage

Accordingly, while manual therapy and therapeutic exercise typically exert hypoalgesia by activating descending inhibitory pain mechanisms [40,84], in subjects with central sensitization the opposite may occur; exercise [85] and potentially manual therapy may induce hyperalgesia if not properly controlled. In fact, aggressive exercise or manual therapy in an early stage of rehabilitation may be detrimental if excessive or forceful movements trigger sensitized peripheral nociceptors and cause increased or prolonged pain. This flare response may occur through mechanisms of neurogenic inflammation where inflammatory mediators such as Substance P and CGRP are released into the periphery and promote pain and chronic inflammation [41]. Further, patients with chronic pain conditions such as fibromyalgia may experience greater exercise induced hypoalgesia with lower intensity exercise. Clinicians must be skilled at discerning and interpreting patient symptoms during rehabilitative programs through serial reassessment. The aim of any intervention is the restoration of the function by limiting the chance of sustained central nervous system facilitation. Directing treatment at aberrant pain processing may have the result of diminishing pain and increasing function (Table 1).

Sleep quality

An important objective in the rehabilitation of the chronic pain patient is to encourage proper sleep hygiene. Altered/interrupted sleep patterns causes impairment of descending pain mechanisms [25,26], which can promote widespread hyperalgesia and hinder rehabilitative aims. Evaluation of sleep quality may be inconsistent in typical rehabilitative practice settings. A recent systematic review and meta-analysis suggested that the Pittsburgh sleep quality index was a reliable and valid screening tool for sleep dysfunction in non-clinical and clinical samples [86]. Components of sleep quality include sleep efficiency, sleep latency, sleep duration, sleep quality, sleep disturbance, sleep medication use, and daytime dysfunction due to sleepiness [87]. Trouble with falling asleep, staying asleep, and feeling tired were reported as 3 of the main issues for individuals with persistent pain [88]. Clinicians may educate patients on sleep quality and advise them on positions of comfort in the case of pain interrupted sleep.

Aerobic exercise as a pain intervention

Often individuals with chronic pain become extremely deconditioned, due to sedentary lifestyles and activity related painful flare-ups. They become fearful of exercise because they believe that pain equates to tissue damage. The result is a negative cycle of pain and deconditioning. Developing an aerobic exercise routine is valuable as aerobic activity activates descending pain modulation [89]. The clinician may need to progress aerobic routine in a graded manner, gradually increasing time or distance to avoid flare-ups. In the case of regional pain due to central sensitization, the clinician may choose to aerobically exercise the unaffected limbs. For example, in the patient with chronic neck pain, a walking program may be effective while swimming may be beneficial in the chronic visceral pain population. In the lower extremity patient, reduced weight-bearing treadmill walking may be a means to initiate aerobic exercise with the goal of progressing to an independent walking program. Exercise of higher intensity (60–75% V O2max) most consistently produced exercise induced analgesia after aerobic exercise in a low back pain cohort [90] and may be a standard for aerobic exercise in other chronic pain populations.

Muscle contraction as a pain intervention

Proper strength is important for normal balance, gait, and overall function. Recent evidence has suggested that strengthening programs may be effective in the management of chronic pain. Specifically, clinical trials have demonstrated that workplace strength training was valuable in reducing pain and preventing job disruption [91,92]. While strength training has the value of protecting and stabilizing joints and other tissues, it is also known that exercise has analgesic effects, in particular isometric exercise. With isometric contraction, greatest decrease in sensitivity to noxious stimulus occurs after low-intensity contractions (25–50% MVC) held for longer duration [93]. Strength training should be progressed in a graded manner.

Noxious electrical stimulation as a pain intervention

Experimentally, noxious stimulation is employed to induce descending pain modulation when investigating conditioned pain modulation. In the clinical setting, noxious interventions may be used to produce pain relief in a similar manner. Although evidence is limited, it is likely that the treatment effects of interventions such as noxious electrical stimulation, cupping, and even dry needling may be mediated, at least in part, due to this mechanism. Studies in Achilles tendinopathy and knee OA have reported beneficial outcomes with noxious electrical stimulation [94,95].

Conclusion

One of the more significant challenges of chronic pain is the interpretation of the clinical manifestations of peripheral and central sensitization processes. This interpretation should determine treatment parameters, e.g. intensity, amplitude, and frequency of the techniques based on the dominance, peripheral, or central, of each patient. In addition, the potential neurophysiologic and tissue mechanisms underlying the effects (positive and negative) of any intervention should also be considered. Management of individuals with chronic pain should extend beyond local tissue-based pathology to incorporate therapeutic strategies directed at normalizing central nervous system sensitivity. The existence of a wide range of conservative treatments (i.e. medication, electro-physical agents, exercise, cognitive interventions, manual therapies) advocated for chronic pain, is an indication that not one treatment has proven superiority and also that a multi-modal, interdisciplinary approach is warranted.

Contributors

All listed authors had a role in formulation of this clinical commentary. All authors have reviewed and approved the submitted manuscript.

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