A Mechanism-Based Approach to Physical Therapist Management of Pain

Ruth L. Chimenti, Laura A. Frey-Law, Kathleen A. Sluka

R.L. Chimenti, PT, PhD, Department of Physical Therapy and Rehabilitation Science, University of Iowa, Iowa City, Iowa.

L.A. Frey-Law, PT, PhD, Department of Physical Therapy and Rehabilitation Science, University of Iowa.

K.A. Sluka, PT, PhD, Department of Physical Therapy and Rehabilitation Science, 1-242 MEB, University of Iowa, Iowa City, IA 52242 (USA). Address correspondence to Dr Sluka at: kathleen-sluka@uiowa.edu. Dr Sluka is a Catherine Worthingham Fellow of the American Physical Therapy Association.

[Chimenti RL, Frey-Law LA, Sluka KA. A mechanism-based approach to physical therapist management of pain. *Phys Ther.* 2018;98:302–314.]

Accepted: February 12, 2018
Submitted: June 13, 2017

Pain reduction is a primary goal of physical therapy for patients who present with acute or persistent pain conditions. The purpose of this review is to describe a mechanism-based approach to physical therapy pain management. It is increasingly clear that patients need to be evaluated for changes in peripheral tissues and nociceptors, neuropathic pain signs and symptoms, reduced central inhibition and enhanced central excitability, psychosocial factors, and alterations of the movement system. In this Perspective, 5 categories of pain mechanisms (nociceptive, central, neuropathic, psychosocial, and movement system) are defined, and principles on how to evaluate signs and symptoms for each mechanism are provided. In addition, the underlying mechanisms targeted by common physical therapist treatments and how they affect each of the 5 categories are described. Several different mechanisms can simultaneously contribute to a patient's pain; alternatively, 1 or 2 primary mechanisms may cause a patient's pain. Further, within a single pain mechanism, there are likely many possible subgroups. For example, reduced central inhibition does not necessarily correlate with enhanced central excitability. To individualize care, common physical therapist interventions, such as education, exercise, manual therapy, and transcutaneous electrical nerve stimulation, can be used to target specific pain mechanisms. Although the evidence elucidating these pain mechanisms will continue to evolve, the approach outlined here provides a conceptual framework for applying new knowledge as advances are made.

Whether acute or chronic, pain is a leading reason for patients to seek physical therapy. Approximately 100 million Americans suffer from persistent pain.[1] The cost of persistent pain in America, including decreased productivity at work and health care, is estimated between $560 and $635 billion, which is greater than cardiovascular disease, cancer, and diabetes combined.[2] The Department of Health and Human Services recently published a National Pain Strategy,[3] highlighting the insufficient training in pain assessment and treatment for many clinicians. The National Institutes of Health and the Interagency Pain Research Coordinating Committee also recently published the Federal Pain Research Strategy, which identified as a top priority the need to develop, evaluate, and improve models of pain care.[4] Accordingly, the purpose of this article is to provide an overview of a mechanism-based approach to physical therapy pain management that includes the evaluation and treatment of 5 pain mechanisms: nociceptive, central, neuropathic, psychosocial, and movement system. Recently, the International Association for the Study of Pain (www.iasp-pain.org) released a new term, *nociplastic*, designed to be a third descriptor to be used instead of "central" or "central sensitization." Nociplastic pain is defined as pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain.

A mechanism-based approach to pain management incorporates and builds on the biopsychosocial model by defining specific pathobiology in pain processing, pain-relevant psychological factors, and movement system dysfunction. The term "pain mechanisms" is used to delineate factors that can contribute to the development, maintenance, or enhancement of pain. Further, these pain mechanisms can also occur in a cyclical manner in reaction to the pain. A patient may have multiple pain mechanisms occurring simultaneously, and 2 individuals with the same diagnosis could have different underlying mechanisms contributing to their pain. Accordingly, a mechanism-based approach requires evaluating specific pain mechanisms as well as prescribing the appropriate treatments to target altered mechanism(s). Although each pain mechanism can be addressed individually, the efficiency of an intervention may be maximized when multiple pain mechanisms are targeted simultaneously.

This mechanism-based approach to care is common in pharmaceutical pain management. People with neuropathic pain are often prescribed gabapentinoids because of their ability to block calcium channel activity that is enhanced in this condition[5]; people with inflammatory nociceptive pain are often prescribed anti-inflammatory medications (eg, nonsteroidal anti-inflammatory drugs and tumor necrosis factor inhibitors)[6]; and those with nociplastic pain are often prescribed reuptake inhibitors to modulate central inhibition.[6] On the other hand, in physical therapy, many treatments evolved and were used clinically before we understood how they produced their effects. For example, initial clinical studies used transcutaneous electrical nerve stimulation (TENS) to reduce pain in the 1960s, but we did not fully understand the mechanisms for how TENS reduces pain until this century.[7–19] What has emerged in recent years is the knowledge that many physical therapist interventions have multiple mechanisms of action and are thus considered multimodal pain treatments. For example, research shows that exercise can alter all 5 pain mechanisms: nociceptive, neuropathic, nociplastic, psychosocial, and movement system.[20–38]

We have expanded the mechanism-based approach from the pathobiological processes only (ie, biomedical model) to include psychological and movement system dysfunction. Recognizing the importance of pain mechanisms for individualizing care is not novel,[39–42] but has not been widely implemented in physical therapist practice. This article will provide a brief overview of a mechanism-based approach to pain management, including several evaluation and treatment options, and facilitate an appreciation for how these mechanisms may overlap and interact. Throughout this article the reader is referred to other sources providing detailed information on how to identify, evaluate, and treat individual pain mechanisms. Benefits of a mechanism-based approach are that it expands physical therapist practice to include latest research from a number of fields and enables the use of targeted interventions with the goal of optimizing outcomes. However, methods of pain mechanism assessment continue to evolve for clinical use and it is often difficult to differentiate between pain mechanisms. With time, clinical tools will continue to develop to advance the mechanism-based approach. This approach is also open to the integration of additional pain mechanisms as they are identified with future research.

Overview of Pain Mechanisms

The initiation, maintenance, and perception of pain is influenced by biological, psychosocial, and movement system factors (Fig. 1). Biological pain mechanisms can be categorized into 3 classes, including nociceptive (peripheral), nociplastic (nonnociceptive), and neuropathic (Fig 1A).[39,43,44] Pain often originates in the peripheral nervous system when nociceptors are activated due to an injury, inflammation, or mechanical irritant. Nociceptive signals are relayed to the spinal cord and up to the cortex through ascending nociceptive pathways resulting in the perception of pain. Peripheral sensitization of nociceptive neurons can enhance or prolong the pain experience, even without sensitization of central neurons (Fig. 2). Accordingly, nociceptive pain is primarily due to nociceptor activation, albeit processed through the central nervous system (CNS), typically resulting in acute localized pain, such as an ankle sprain. Within the CNS, nociceptive signals are under constant modulation by cortical and brain-stem pathways, which can be facilitatory or inhibitory, and modulate both emotional and sensory components of pain.[45] Nociplastic pain conditions are due to alterations of nociceptive processing, most likely

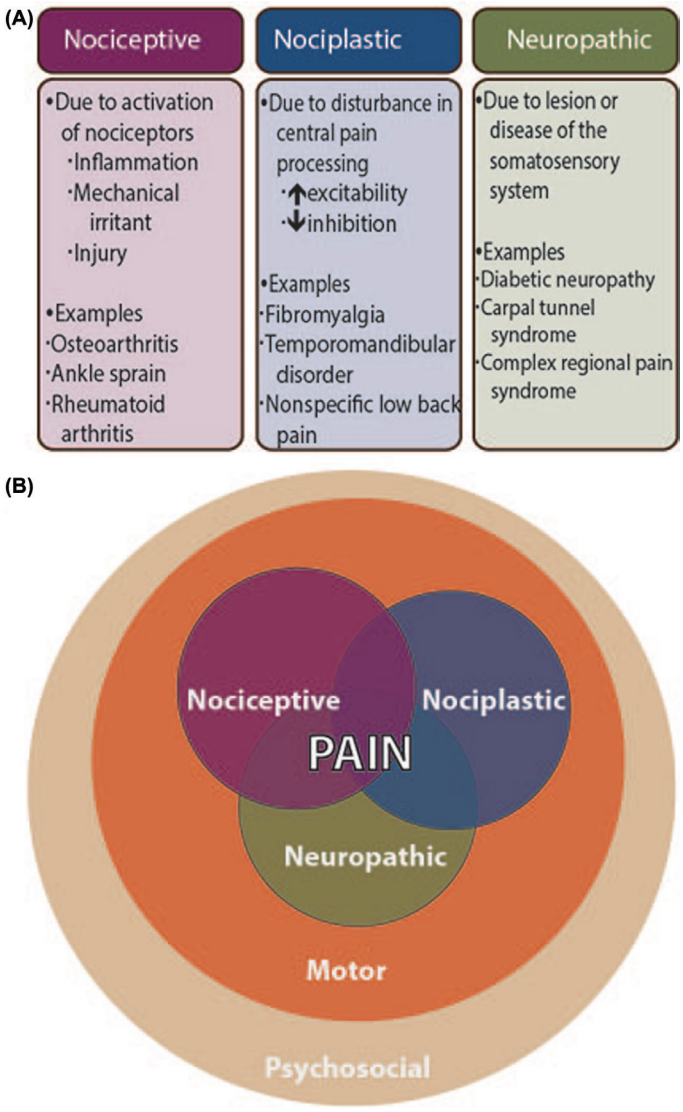

Figure 1.
Schematic diagrams representing a mechanism-based approach to pain management. (A) Description and examples of 3 pain mechanisms (nociceptive, nociplastic, and neuropathic) that contribute to pain, as previously outlined by Phillips and Clauw.[39] People with pain can have 1 or a combination of mechanisms contributing to their pain. (B) Schematic representation of 3 pain mechanisms occurring within the context of movement system and psychosocial factors.

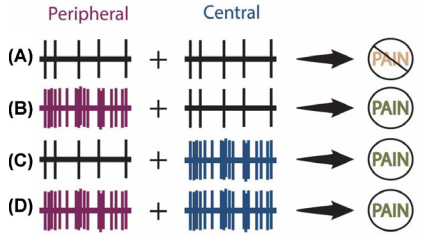

Figure 2.
Diagram illustrating how peripheral and central sensitization can lead to pain. (A) Condition with no pain. Normal nociceptor activity and central neuron activity usually do not produce pain. (B) Condition with peripheral sensitization. Enhanced nociceptor activity activates nonsensitized central nociceptive neurons to result in pain. (C) Condition with central sensitization but without peripheral sensitization. Normal activation of nociceptors activates sensitized central neurons to result in pain. (D) Condition with both peripheral sensitization and central sensitization contributing to pain. Treatments aimed at peripheral nociceptive input would be effective in people with peripheral sensitization but would have minimal effects in people with central sensitization and partial effects in people with both peripheral sensitization and central sensitization.

within the CNS, such as enhanced central excitability and/or diminished central inhibition, often referred to as central sensitization (Fig. 2). Nociplastic pain is typically chronic and more widespread than nociceptive pain, with fibromyalgia as the classic example.[12] Nociplastic pain can occur independently of peripheral nociceptor activity; however, some conditions involve both nociceptive and nociplastic pain mechanisms (eg, peripheral and central sensitization) to varying degrees along a continuum, such as low back pain or knee osteoarthritis (Fig. 3).[39] Pain conditions with enhanced peripheral and central sensitization may respond well to removal of only the peripheral input, which can eliminate central sensitization in some cases (eg, total knee replacement). However, removal of the peripheral input may only have a partial effect with residual central sensitization causing continued pain.[12,39] Neuropathic pain occurs when there is a lesion or disease within the somatosensory system.[39] This could occur due to direct injury to the nerve, such as carpal tunnel syndrome, or due to metabolic diseases, such as diabetes. Nociceptive, nociplastic, and neuropathic pain may not respond equally well to various treatments, thus, the understanding of underlying mechanisms will help to guide treatment choices aimed at these mechanisms.

These 3 biological pain processes can be influenced by, as well as directly influence, psychosocial factors (Fig. 1B).[39,46] Addressing maladaptive psychosocial factors can maximize therapy effectiveness for acute and chronic pain conditions.[46,47] Negative emotionality factors, such as depression or fear avoidance beliefs, may augment other pain mechanisms and contribute to the maintenance of a painful condition.[47,48] Psychological factors are hypothesized to be critical in the transition from acute to chronic pain and predictive of the development of chronic pain

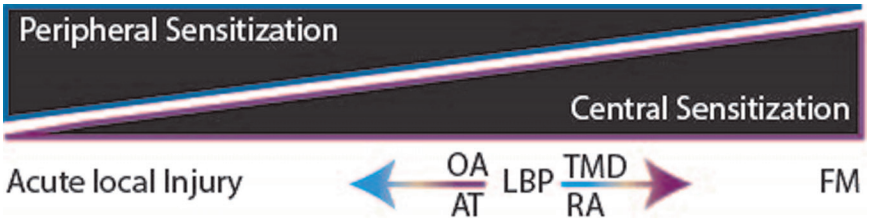

Figure 3.
In pain conditions, peripheral sensitization and central sensitization vary across a continuum. Sensitization of the peripheral nervous system contributes to a large proportion of pain with an acute localized injury, whereas sensitization of the central nervous system contributes to a large proportion of pain with chronic widespread pain conditions, such as fibromyalgia (FM). For other diagnoses, depicted in the midrange as low back pain (LBP), osteoarthritis (OA), rheumatoid arthritis (RA), Achilles tendinopathy (AT), and temporomandibular joint disorder (TMD), people can have high levels of peripheral sensitization, high levels of central sensitization, or both.

postoperatively.[46,49–51] Therefore, therapeutic interventions often benefit from considering these psychosocial factors.

As physical therapists, evaluation and treatment of the movement system is a key component of our care for patients with pain.[52] Clearly, we recognize "antalgic gait" patterns as movement influenced by pain; overuse syndromes as painful conditions induced by repetitive movement; and the nociceptive withdrawal reflex as a well-characterized link between afferent pain pathways and the efferent motor system. However, the relationships between pain and the movement system are complex and often highly variable between individuals.[53] Pain can produce increased muscle contraction, tone, or trigger points[54]; it can result in muscle inhibition or fear-avoidance behaviors resulting in disuse and disability,[55] or both facilitation and inhibition in opposing muscle groups.[56] Thus, targeted interventions may help reduce motor responses that exacerbate pain or improve function by minimizing the motor effects of pain. The integration of physical therapists' expertise in the movement system with the other pain mechanisms has the potential to elevate our level of care to more effectively evaluate and treat pain conditions.

Evaluation of Pain Mechanisms

Evaluation of pain mechanisms can help individualize care to a patient rather than a diagnosis, and is a step toward providing precision medicine to patients with pain. The use of anatomic or radiographic diagnoses alone (ie, medical model) without consideration of the underlying pain mechanism(s) (ie, enhanced biopsychosocial model) is insufficient to guide rehabilitative care. Although peripheral pathology is linked to musculoskeletal pain,[57] symptom severity can be modulated by central processing, psychosocial factors, and the movement system. The common mismatch between tissue pathology and pain is supported by findings among asymptomatic 80-year-olds, where 96% have signs of disk degeneration and 62% have rotator cuff tears on imaging.[58,59] In order to apply a mechanism-based approach, one must first evaluate for signs and symptoms suggestive of changes in peripheral tissues and nociceptors, reduced central inhibition and/or enhanced central excitability, neuropathic pain signs and symptoms, psychosocial factors, and altered movement patterns. Once the primary pain mechanism(s) are identified, then a clinician can be more specific with their overall assessment. For example, with patient referred for low back pain (anatomic region), the physical therapist may identify pain associated with fatigue and sleep dysfunction (central indicators), high kinesiophobia (psychosocial factor), and abdominal muscle weakness (movement system factor). By defining the mechanisms contributing to a patient's pain, a clinician can prioritize and target specific interventions to the primary pain mechanism(s).

Evaluation of biological pain mechanisms is informed through patient-reported history, questionnaires, and potentially quantitative sensory testing (QST). Unfortunately, identification of nociceptive, nociplastic, and neuropathic pain mechanisms are not directly measurable, but must be inferred from indirect assessments. Nociceptive pain is indicated by pain localized to the area of tissue injury within normal tissue healing time. Peripheral factors can also contribute to chronic musculoskeletal pain, but are more challenging to discern. Enhanced peripheral sensitivity, such as primary hyperalgesia, can be detected by lowered pressure pain thresholds at the site of injury compared to the contralateral side.[60,61] However, interpretation of this test may be confounded by the presence of secondary hyperalgesia on the contralateral side, indicating the need for established norms in a pain-free population. Nociplastic pain conditions include more diffuse symptoms such as widespread pain, fatigue, sleep dysfunction, and cognitive disturbances, but can also involve relatively isolated pain due to altered CNS processing, such as secondary hyperalgesia or referred pain.[62] Researchers use several QST measures to identify altered pain processing,[60,63] which may have clinical utility once further developed and characterized. Enhanced central excitability can be assessed by enhanced pain response to a repetitive noxious stimulus (eg, von Frey filament for 10–30 s), referred to as temporal summation of pain.[60,64] However, temporal summation is also a normal response to repetitive noxious stimulation,[64] and as yet we do not have normative values to indicate an enhanced response for clinical populations. Pain inhibition is evaluated using a conditioned pain modulation (CPM) test, which employs a "pain inhibits pain" modulation. CPM measures pain thresholds at a distant site during/after a conditioning noxious stimulus (eg, pressure pain threshold of leg during immersion of hand in ice-cold water).[65] Most pain-free individuals exhibit

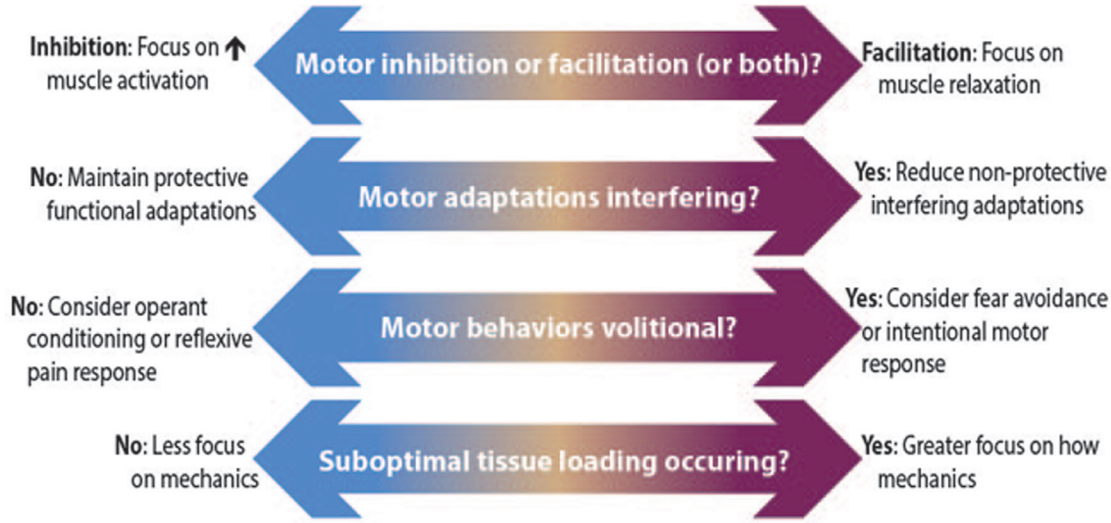

Figure 4.
Four continua of movement system adaptations to pain and how they can affect an exercise program.

increased pain thresholds (less sensitivity), whereas in chronic pain conditions there are often reduced or no change in pain thresholds.[63] Currently, limitations to using QST as a clinical indicator are the lack of both norms to aid in the interpretation of findings and established test metric standards. Finally, neuropathic pain is evidenced by positive neural symptoms such as tingling, burning, and dysesthesia, and/or negative neural symptoms, such as loss of sensation. These symptoms can be evaluated using sensory testing and/or the painDETECT questionnaire.[66]

Based on a patient's self-reported history, a clinician may choose to screen for ongoing psychological factors contributing to pain. Psychological factors can be assessed clinically using 1 or more instruments available to screen for depression,[67,68] anxiety,[68,69] pain catastrophizing,[70] fear of movement or reinjury,[71,72] or pain self-efficacy.[73] The use of abbreviated screening tools, such as a 2-item depression screening test, require little time and have greater accuracy than a physical therapist's personal assessment.[74] There are also screening tools available to help determine the appropriate level of care for patients with psychosocial concerns, such as pursuing an intervention implemented solely by physical therapists trained in the biopsychosocial approach versus a multidisciplinary team with a clinical psychologist.[75-77]

Physical therapists have unique skills to evaluate patient-specific movement dysfunction. In people with pain, movement system changes are unique to each individual, can be task dependent, and can range from subtle to severe.[12,78] Several considerations for evaluation of movement system function in relation to pain are outlined in Figure 4. For some patients, pain can cause motor inhibition (eg, weakness[79]), whereas others have motor facilitation (eg, increased muscle tension[80]). It is important to determine if the motor dysfunction is a direct result of pain, or a more long-term adaptation that is volitional or reflexive. If it is a direct result of pain, reducing the pain will likely restore the movement pattern.[79] The phase of healing is also relevant for determining how a motor adaptation should be addressed in physical therapy. For someone with a recent hip fracture, assistive devices are initially used to help reduce the load on the injured limb, but, with time, patients may need help restoring nonprotective motor adaptations to avoid prolonged loading imbalances.[81]

The value of identifying pain mechanisms for each individual, rather than assuming any particular pain mechanism(s) to be associated with certain diagnoses, is improved personalized treatment. Pain processing physiology, psychological states, and movement function can vary widely within a single diagnosis.[62] For example, people with fibromyalgia demonstrate dysfunctional central inhibition, based on lowered inhibitory CPM, compared to healthy controls. Yet, some individuals with fibromyalgia have normal CPM responses, while some healthy controls exhibit reduced CPM inhibition (Fig. 5A).[12] Further, not all individuals with pain exhibit elevated psychosocial factors. For example, in an ongoing clinical trial,[82] only 26% of women with fibromyalgia had high pain catastrophizing and 51% had high fear of movement (Fig. 5B). Although these percentages are higher than those of healthy controls (1.1% with high pain catastrophizing), many women with fibromyalgia did not report these psychological constructs. Finally, movement patterns in individuals with low back pain can vary substantially, with either increased or decreased extensor muscle activation.[53] Together these research findings illustrate that heterogeneity in pain mechanisms can be substantial between individuals within the same pain diagnosis (eg, high variability in central pain processing measures or psychological

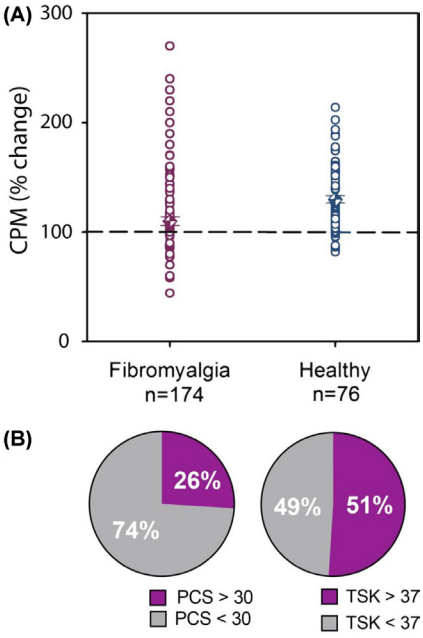

Figure 5.
(A) Scatterplot showing the variability in conditioned pain modulation (CPM) in people with fibromyalgia and healthy controls, represented as the percent change in pressure thresholds before and after the CPM test. In a comparison of people with fibromyalgia and healthy controls, although there was an overall decrease, on average there were clearly people with fibromyalgia who presented with normal CPM and healthy controls who presented with reduced CPM. (B) Analysis of data from an ongoing fibromyalgia activity study with transcutaneous electrical stimulation (n = 172) revealed the variability in psychological measures in people with fibromyalgia[82]; 26% had high scores on the Pain Catastrophizing Scale (> 30/52), and 51% had high scores on the Tampa Scale of Kinesiophobia (> 37/68).

assessments), that patients may present with only certain components of a pain mechanism (eg, high fear of movement but no pain catastrophizing or depression), and that patients can present with multiple pain mechanisms (eg, central sensitization and heightened psychosocial factors). Although physical therapists routinely assess a variety of outcomes for sensory, motor, function, and emotional/affective components of pain, we suggest adding assessments from a mechanistic standpoint as the next step in advancing optimal pain care.

Mechanisms Underlying Physical Therapist Interventions

Once pain mechanisms are identified, the second phase of the mechanism-based approach is to provide treatment(s) targeting these mechanisms. Outlined below are brief summaries of how several potential therapies (exercise, manual therapy, TENS, and patient education) can alter individual pain mechanisms, but is not an exhaustive list. Although the underlying mechanisms of several treatments have been well documented, our mechanistic understanding of many other treatment options remains incomplete. These 4 treatments were chosen for their common use and documented effectiveness for pain treatment. Each type of intervention can involve various forms, which we do not specifically address. For example, studies on exercise can include aerobic and/or strengthening. Manual therapy can include soft-tissue massage, stretching, or joint mobilization. Pain education and cognitive-behavioral therapy–informed techniques used by physical therapists encompass a wide range of topics, including education, coping strategies, problem solving, pacing, relaxation and imagery.[47,63,83–85] TENS can be used with a variety of settings, such as low or high frequency. Figure 6A summarizes potential mechanisms, also further described below, with more extensive reviews available elsewhere.[12]

Although a pain mechanism-based approach may be novel for physical therapy, pharmacology has long used treatments targeting a specific pain mechanism to maximize therapeutic benefit (Fig. 6B). For example, a randomized double-blind placebo-controlled trial in patients with peripheral neuropathic pain found treatment response differed based on nociceptor phenotype. Oxcarbazepine, a sodium channel blocker that reduces nociceptor activity, had a larger effect in the "irritable nociceptor" group than the "nonirritable nociceptor" group (number needed to treat = 4 vs 13).[86] Thus, the knowledge of nociceptor phenotype in this patient population helps inform which pharmacological treatment may be most effective. Although we provide only a partial list of all possible interventions for pain, our intention is to demonstrate how the mechanism-based approach may be applied when attempting to match treatments to underlying pain mechanisms.

Nociceptive Mechanisms

Exercise therapy. Basic science evidence shows that exercise reduces nociceptor activity by decreasing ion channel expression, increasing expression of endogenous analgesic substances in exercising muscle (neurotrophins), and altering local immune cell function (increased anti-inflammatory cytokines).[20–27] Further, exercise restores normal movement of joint and tissue,[87] which could hypothetically remove a mechanical irritant to a nociceptor. Thus, exercise decreases nociceptor excitability, increases peripheral inhibition, and promotes healing of injured tissues, which makes exercise particularly useful to those with nociceptive pain.

Manual therapy. Basic science evidence shows that joint manipulation activates analgesic systems peripherally (cannabinoid, adenosine) in several animal models of pain.[88] In animal models, stretching increases expression and release of mediators that reduce inflammation, such as resolvins to promote healing and reduce pain.[89,90] Additionally, massage therapy reduces expression of inflammatory genes and cytokines that activate nociceptors, and increases the tissue repair genes.[91] Further, manual therapy techniques restore normal movement of joint and connective tissue,[92] which could hypothetically remove a mechanical irritant to a nociceptor. Thus, manual therapy can target nociceptive pain because it increases peripheral inhibition, promotes healing of injured/inflamed tissues, and may reduce mechanical activation of a nociceptor.

TENS. Application of TENS can target distinct nociceptive pain mechanisms.[7–11] TENS can alter sympathetic activity to reduce pain through activation of local α2A-noradrenergic receptors,[7,8] activate peripheral inhibitory μ-opioid

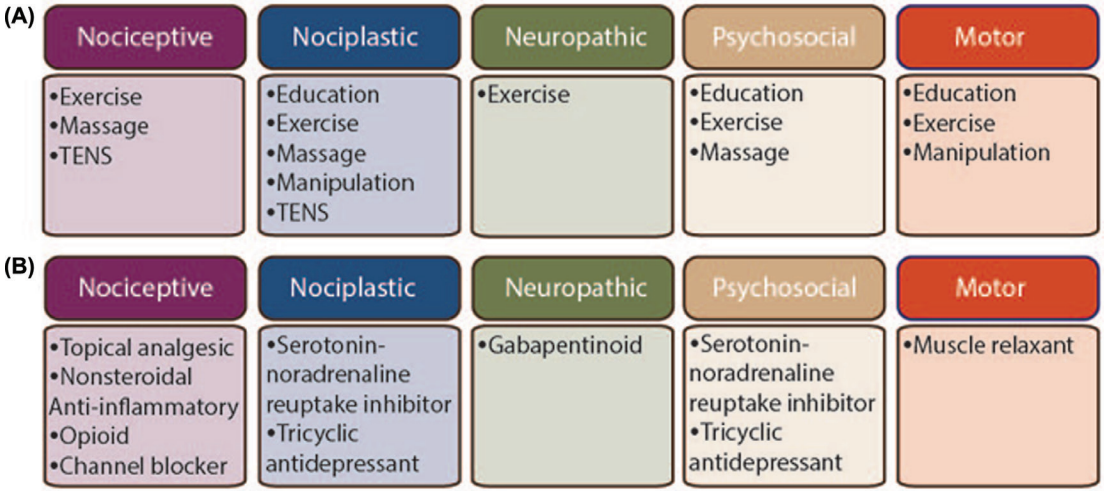

Figure 6.
(A) Diagram illustrating sites of action, based on currently available mechanistic data, of common physical therapist treatments on the 5 mechanistic categories for pain. Exercise works to modify all 5 mechanisms and can be considered a multimodal therapy. Currently known mechanisms of action of common physical therapist treatments on pain are outlined in detail in the text. TENS = transcutaneous electrical nerve stimulation. (B) Diagram illustrating sites of action, based on currently available mechanistic data, of common pharmacological treatments on the 5 mechanistic categories for pain. Many physical therapist treatments target multiple mechanisms, whereas most pharmaceutical agents target a single mechanism.

receptors,[9] and reduce the excitatory neurotransmitter, substance P, which normally increases in injured animals.[10,11] Thus, TENS would be useful for those with enhanced sympathetic activity and nociceptor sensitization.

Central Mechanisms

Education. Educating patients about pain mechanisms and challenging maladaptive pain cognitions/behaviors can alter central pain processing.[63,83] In people with chronic pain, an increased understanding of pain using the "explain pain"[93] paradigm corresponds to an increase in pain threshold[83] and increases in CPM (central inhibition).[63] Thus education may be useful for those with maladaptive cognitions and behaviors associated with altered CNS processing.

Exercise therapy. The most studied, and well-accepted, central mechanism to produce analgesia by exercise involves activation of descending inhibitory systems with increases in endogenous opioids and altered serotonin function.[28–31] Studies in animals and people have shown that regular exercise can prevent or reduce the risk of developing chronic pain.[28,94–97] Mechanistically, regular exercise reduces central excitability and expression of excitatory neurotransmitters in spinal cord, brain stem, and cortical nociceptive sites.[28] In animal models of pain, regular aerobic exercise increases release of endogenous opioids in the midbrain and brain stem, specifically the periaqueductal gray and rostral ventromedial medulla.[28,29,31] In the serotonergic system there is decreased expression of the serotonin transporter and increased release of the neurotransmitter serotonin in the rostral ventromedial medulla that leads to enhanced analgesia.[28–30,98] Additionally, regular exercise reduces glial cell activation, increases anti-inflammatory cytokines, and decreases inflammatory cytokines in the spinal cord.[24,94] In parallel, QST in healthy adults shows greater levels of exercise are associated with lower central excitability (ie, temporal summation), greater pain thresholds, and greater inhibition (CPM).[28,96,97] Thus, regular exercise can modulate pain sensitivity by altering central nociceptive processing and increasing central inhibition in both animals and people, making it an ideal choice for those with nociplastic pain.

Manual therapy. There is growing evidence that massage and joint manipulation modulate central pain mechanisms.[87,99–106] Massage activates descending inhibitory pathways, using oxytocin to produce analgesia,[99,100] whereas joint mobilization uses serotonin, noradrenaline, adenosine, and cannabinoid receptors in the spinal cord to produce analgesia.[87,101,102] Joint mobilizations can also reduce glial cell activation in the spinal cord.[103] In people, manipulation reduces central excitability as measured by reduced temporal summation, in the region of primary hyperalgesia,[107] and reduced secondary hyperalgesia in those with chronic pain.[106,108] Thus, manual therapy techniques activate central inhibitory mechanisms and reduce central excitability to produce analgesia in both people and animal models of pain.

TENS. TENS works primarily through central mechanisms by increasing central inhibition and reducing central excitability.[12–19] Studies in animal models of pain show that high and low-frequency TENS analgesia activates multiple central pathways, including the spinal cord, rostral ventromedial

medulla, periaqueductal gray, and multiple cortical sites.[13,14,19] The central inhibitory neurotransmitters involved in the analgesia include μ-opioid and serotonin receptors (low frequency) and delta-opioid receptors (high frequency),[14,15] which have been confirmed in people with chronic pain.[16,17] TENS also produces analgesia through activation of $GABA_A$ receptors and muscarinic receptors (M1, M3) in the spinal cord.[18,109] In parallel, TENS also reduces central sensitization measured directly in nociceptive dorsal horn neurons,[110] and reduces release and expression of excitatory neurotransmitters (glutamate and substance P), glial cell activation, and inflammatory cytokines and mediators in the dorsal horn.[10,11,111] In individuals with fibromyalgia, high-frequency TENS restores central inhibition (CPM), and increases pressure pain thresholds at the site and outside the site of stimulation, supporting a modulation of central nociceptive processing in humans.[112] Thus, TENS activates central inhibitory pathways and reduces central sensitization simultaneously to reduce pain and hyperalgesia.

Neuropathic Mechanisms

Exercise therapy. Regular aerobic exercise increases anti-inflammatory cytokines (eg, interleukin 4) and the expression of M2 macrophages, which secrete anti-inflammatory cytokines at the site of injury.[24,32] Regular aerobic exercise can also decrease expression of M1 macrophages and inflammatory cytokine production at the site of injury.[24,32] These effects on cytokines and macrophages promote nerve healing and analgesia in animal models of neuropathic pain.[24,32] In people with diabetic neuropathy, a decrease in pain is associated with increased growth of epidermal nerve fibers after a regular exercise program.[113] Thus, exercise can be considered a disease-modifying treatment in neuropathic pain conditions by promoting healing of injured tissues.

Manual therapy. In animal models of neuropathic pain, mobilization promotes healing by increasing myelin sheath thickness in peripherally injured nerves.[103] Theoretically, manual therapy techniques, like those used in neural mobilization, could ameliorate nerve compression as cadaver studies show dispersal of intraneural fluid with neural mobilization.[114,115] Thus, manual therapy has the potential to improve healing and reduce nerve compression in neuropathic pain; however, these effects need to be confirmed in future studies.

Psychosocial Mechanisms

Education. Education and cognitive-behavioral therapy–informed techniques are aimed at changing beliefs and behaviors that contribute to distress, fear, catastrophizing, and anxiety. For example, patients with acute low back pain educated using a fear-avoidance model and graded exercise (see home study course[116]) had lower fear-avoidance beliefs.[47] Pain education reduces pain catastrophizing and negative pain cognitions, but may not directly affect pain scores.[117–119]

Exercise therapy. Exercise is a well-accepted means to improve a number of negative psychological factors that are related to pain, including catastrophizing, depression, and cognitive dysfunction.[33,34] Exercise also improves learning, memory, and neurogenesis.[120,121] In mice, voluntary exercise reduces depressive behaviors with concomitant increases in brain-derived neurotrophic factor and opioid receptor expression in the hippocampus.[122,123] Although the neurobiological mechanisms in humans are less clear, Cochrane reviews indicate exercise reduces depressive symptoms[124] and improves cognitive function.[125] Pain catastrophizing can also decline with exercise,[126] and is negatively correlated with the magnitude of exercise-induced analgesia.[127] Thus, exercise reduces negative psychological factors associated pain, and can improve cognitive and social factors.

Manual therapy. There are a number of studies suggesting that massage reduces psychological distress. Massage decreases cortisol in the blood in people with a wide range of pain conditions, including juvenile rheumatoid arthritis, burn injury, migraines, and autoimmune disorders.[128,129] Massage also reduces stress and anxiety in people without pain.[130–132] However, the effects of manual therapy, particularly mobilizations, on other pain-related psychological constructs is not well characterized.

Movement System

Education. Educational techniques for altering the movement system are often given in combination with an exercise program, making it difficult to assess the effect of education alone. For example, there was a greater improvement in performance of a straight leg raise and forward bend after pain education with exercise compared with an anatomy education with exercise,[117] suggesting that pain education with exercise has the potential enhance changes in movement patterns. Additionally, relaxation techniques, biofeedback and cognitive-behavioral therapy–informed techniques can reduce motor facilitation or muscle spasm.[133] Thus, neuroscience education may be particularly useful to help improve general function, whereas biofeedback and relaxation techniques could be more useful for those with enhanced motor facilitation.

Exercise therapy. The type of exercise prescribed will depend on the movement system dysfunction found in the assessment (Fig. 4). For example, strengthening may be optimal if weakness and motor inhibition are present,[36] but may be less effective if muscle spasm or motor facilitation is present.[134] Stretching may be effective for tight or limited joint range of motion, thereby normalizing movement and subsequently reducing pain.[135,136] Graded exercise or graded exposure may be useful for patients with volitional, nonprotective movement system adaptations that interfere with activity participation.[37,38] Further, as mentioned above, neuromuscular reeducation can help normalize movement patterns, resulting in reduced pain with activity.[87] A systematic review showed that strengthening and strengthening combined with aerobic exercise demonstrated moderate or large effect sizes on pain and function in women with fibromyalgia, whereas aerobic alone resulted in no effect or small effect sizes.[35] Although more research

is needed to determine adequate dose, timing, and combinations of exercise types, exercise can alter the movement system in order to improve function and disability.

Manual therapy. Manual therapy can be used to relieve pain, increase joint range of motion, and improve function for a variety of musculoskeletal pain conditions.[91,108,137] Spinal manual therapy techniques ranging in force from manipulation with high velocity thrust to a nonthrust mobilization technique decrease motor neuron excitability.[138,139] On the other hand, manipulation increases activity of the oblique abdominal muscles in those with low back pain.[140] Thus, manipulation may be useful to help normalize motor function; however it is unclear at present which techniques work best for increasing versus decreasing motor activity.

TENS. The use of a pain-relieving modality, such as TENS, may normalize movement if pain is reflexively causing abnormal motor activation or if there is increased pain with activity since it works best to reduce movement-evoked pain.[112] Although TENS may not directly target the movement system, this, and any pain relieving technique, may be used to target pain-induced nonvolitional abnormal motor patterns, or increase patient tolerance for exercise.

Implementation of the Mechanism-Based Approach

Although each pain mechanism can be addressed individually by the treatments discussed above, the efficiency of an intervention can be maximized when considering multiple pain mechanisms might be addressed simultaneously. Physical therapists routinely prescribe exercise to address alterations in the movement system, and the choice of exercise type is informed by concurrent pain mechanisms when using a mechanism-based approach. For example, for patients with a nociceptive-driven pain condition, a region-specific exercise program may be most effective. In contrast, patients with nociplastic pain may benefit more from a generalized strengthening or an aerobic conditioning program aimed at altering central inhibition and excitation. In addition, as people with chronic pain often have movement-evoked pain, the addition of an adjunct treatment, such as TENS,[112] may be useful to improve exercise tolerance. For patients with fear of movement, graded-exposure to exercise, where exercises are progressed based on the patient's level of fear, may work to increase function while also decreasing pain-related fear.[37,38,47] Further, the intensity of exercise needed to reduce pain and improve function is likely much less than intensities typically recommended for health benefits of physical activity.[77] In fact, as shown by a wide range of clinical trials (see table of systematic reviews on exercise-induced analgesia),[12] just 2 or 3 times per week for 20 to 30 minutes is adequate to produce pain relief and improve function in a variety of painful conditions.

Although nearly all patients receive some education about their pain condition, the type of education may be distinctly different depending on the evaluation. Individualized patient education based on pain-mechanisms could range from focusing on modification of maladaptive beliefs for those with high pain catastrophizing to education of underlying central mechanisms for those with nociplastic pain. In patients with chronic low back pain, exercise combined with targeted pain education, was more effective at reducing pain and disability compared to exercise with a biomechanical pain education approach.[141,142] Sociocultural factors may be addressed by encouraging family members and physicians to emphasize active patient participation in exercise prescription, which also improves intervention adherence.[143,144]

Based on known underlying mechanisms, physical therapist interventions may produce additive or even synergistic interactions with pharmaceutical agents, or enhance effectiveness of multiple physical therapist interventions. For example, repeated application of a single frequency of TENS produces analgesic tolerance.[145,146] However, combining low- and high-frequency TENS (eg, simple modulated pulse mode) prevents tolerance.[147] Exercise, which uses serotonergic mechanisms, could produce longer-lasting effects in those taking reuptake inhibitors. Alternatively, negative interactions between treatments may also occur. For example, in mice and people with opioid tolerance, low-frequency TENS does not produce analgesia.[16,146] Thus, understanding the mechanisms will help to make better individualized treatment choices based the patient's current treatment program.

Although we have a fairly strong understanding of underlying mechanisms for physical therapist interventions, and understand conceptually how individual treatments might affect different types of pain mechanisms, there are limited studies using these nonpharmacological treatments in a mechanism-based manner. Most clinical studies compare 2 treatments, such as 2 different exercise programs, in a recruited population without considering the underlying mechanisms, with mixed results.[86,92] We suggest that future studies should be designed to identify treatments based on underlying mechanisms, and test if targeted treatments produce improved outcomes. Future studies should also investigate the multimodal effects of combining multiple physical therapist interventions, as well as combining physical therapy and pharmaceutical treatments targeting underlying mechanisms to provide clinicians with the most effective treatment programs for pain.

Conclusion

Although there is much we have yet to learn about underlying pain mechanisms and optimal interventions, significant advances have occurred in the science of pain that are clinically relevant to physical therapists. Pain is now recognized as more than a peripherally driven symptom; it is a multidimensional construct that can become a disease itself when chronic.[1] Whether patients present to therapy for acute or persistent pain conditions, the goals of therapy are often aimed at reducing pain and restoring function. The mechanism-based approach provides an additional conceptual framework for physical therapists to make educated

treatment decisions that incorporate known basic science and clinical evidence with individualized assessments to optimize patient care and clinical effectiveness. Although the evidence elucidating these pain mechanisms will continue to evolve, the approach outlined here provides a conceptual framework to apply new knowledge as advances are made.

Author Contributions

Concept/idea/research design: R.L. Chimenti, L. Frey-Law, K.A. Sluka
Writing: R.L. Chimenti, L. Frey-Law, K.A. Sluka

Funding

The writing of this article was supported by National Institutes of Health grants (ref nos. NIH R01 AR061371, NIH UM1 AR063381, NIH NIAMS R03 AR065197). R.L. Chimenti's time spent writing was supported by a postdoctoral fellowship in pain research (ref no. T32 NS045549-12) and K99 AR0715170. The funding sources played no role in the writing of this manuscript.

Disclosure

Dr Chimenti and Dr Frey Law completed the ICJME Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest. Dr Sluka serves as a consultant for Novartis Consumer Healthcare/GSK Consumer Healthcare, receives a research grant from Pfizer Inc, and receives roylaties from IASP Press.

DOI: 10.1093/ptj/pzy030

References

1 Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. Washington, DC: National Academies Press (US); 2011.

2 Gaskin DJ, Richard P. The economic costs of pain in the United States. *J Pain*. 2012;13:715–724.

3 Interagency Pain Research Coordinating Committee. National pain strategy: a comprehensive population health-level strategy for pain. https://iprcc.nih.gov/sites/default/files/HHSNational_Pain_Strategy_508C.pdf. Accessed January 31, 2018.

4 Interagency Pain Research Coordinating Committee. Federal pain research strategy. https://iprcc.nih.gov/sites/default/files/FPRS_Research_Recommendations_Final_508C.pdf. Accessed January 31, 2018.

5 Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain*. 2007;132:237–251.

6 Scholz J, Woolf CJ. Can we conquer pain? *Nat Neurosci*. 2002;5(suppl):1062–1067.

7 King EW, Audette K, Athman GA, Nguyen HO, Sluka KA, Fairbanks CA. Transcutaneous electrical nerve stimulation activates peripherally located alpha-2A adrenergic receptors. *Pain*. 2005;115:364–373.

8 Nam TS, Choi Y, Yeon DS, Leem JW, Paik KS. Differential antinociceptive effect of transcutaneous electrical stimulation on pain behavior sensitive or insensitive to phentolamine in neuropathic rats. *Neurosci Lett*. 2001;301:17–20.

9 Sabino GS, Santos CM, Francischi JN, de Resende MA. Release of endogenous opioids following transcutaneous electric nerve stimulation in an experimental model of acute inflammatory pain. *J Pain*. 2008;9:157–163.

10 Rokugo T, Takeuchi T, Ito H. A histochemical study of substance P in the rat spinal cord: effect of transcutaneous electrical nerve stimulation. *J Nippon Med Sch*. 2002;69:428–433.

11 Chen YW, Tzeng JI, Lin MF, Hung CH, Hsieh PL, Wang JJ. High-frequency transcutaneous electrical nerve stimulation attenuates postsurgical pain and inhibits excess substance P in rat dorsal root ganglion. *Reg Anesth Pain Med*. 2014;39:322–328.

12 Sluka KA. *Mechanisms and Management of Pain for the Physical Therapist*. 2nd ed. Seattle, WA: IASP Press; 2016.

13 DeSantana JM, Da Silva LF, De Resende MA, Sluka KA. Transcutaneous electrical nerve stimulation at both high and low frequencies activates ventrolateral periaqueductal grey to decrease mechanical hyperalgesia in arthritic rats. *Neuroscience*. 2009;163:1233–1241.

14 Kalra A, Urban MO, Sluka KA. Blockade of opioid receptors in rostral ventral medulla prevents antihyperalgesia produced by transcutaneous electrical nerve stimulation (TENS). *J Pharmacol Exp Ther*. 2001;298:257–263.

15 Sluka KA, Deacon M, Stibal A, Strissel S, Terpstra A. Spinal blockade of opioid receptors prevents the analgesia produced by TENS in arthritic rats. *J Pharmacol Exp Ther*. 1999;289:840–846.

16 Leonard G, Goffaux P, Marchand S. Deciphering the role of endogenous opioids in high-frequency TENS using low and high doses of naloxone. *Pain*. 2010;151:215–219.

17 Sjolund BH, Eriksson MB. The influence of naloxone on analgesia produced by peripheral conditioning stimulation. *Brain Res*. 1979;173:295–301.

18 Radhakrishnan R, Sluka KA. Spinal muscarinic receptors are activated during low or high frequency TENS-induced antihyperalgesia in rats. *Neuropharmacology*. 2003;45:1111–1119.

19 Xiang XH, Chen YM, Zhang JM, Tian JH, Han JS, Cui CL. Low- and high-frequency transcutaneous electrical acupoint stimulation induces different effects on cerebral mu-opioid receptor availability in rhesus monkeys. *J Neurosci Res*. 2014;92:555–563.

20 Shankarappa SA, Piedras-Renteria ES, Stubbs EB Jr. Forced-exercise delays neuropathic pain in experimental diabetes: effects on voltage-activated calcium channels. *J Neurochem*. 2011;118:224–236.

21 Gandhi R, Ryals JM, Wright DE. Neurotrophin-3 reverses chronic mechanical hyperalgesia induced by intramuscular acid injection. *J Neurosci*. 2004;24:9405–9413.

22 Sharma NK, Ryals JM, Gajewski BJ, Wright DE. Aerobic exercise alters analgesia and neurotrophin-3 synthesis in an animal model of chronic widespread pain. *Phys Ther*. 2010;90:714–725.

23 Leung A, Gregory NS, Allen LA, Sluka KA. Regular physical activity prevents chronic pain by altering resident muscle macrophage phenotype and increasing interleukin-10 in mice. *Pain*. 2016;157:70–79.

24 Bobinski F, Teixeira JM, Sluka KA, Santos ARS. Interleukin-4 mediates the analgesia produced by low-intensity exercise in mice with neuropathic pain. *Pain*. 2017 November 15 [E-pub ahead of print]. doi: 10.1097/j.pain.0000000000001109.

25 Jankord R, Jemiolo B. Influence of physical activity on serum IL-6 and IL-10 levels in healthy older men. *Med Sci Sports Exerc*. 2004;36:960–964.

26 Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. *J Appl Physiol*. 2005;98:1154–1162.

27 Ortega E, Bote ME, Giraldo E, Garcia JJ. Aquatic exercise improves the monocyte pro- and anti-inflammatory cytokine production balance in fibromyalgia patients. *Scand J Med Sci Sports*. 2012;22:104–112.

28 Lima LV, Abner TSS, Sluka KA. Does exercise increase or decrease pain? Central mechanisms underlying these two phenomena. *J Physiol*. 2017;595:4141–4150.

29 Brito RG, Rasmussen LA, Sluka KA. Regular physical activity prevents development of chronic muscle pain through modulation of supraspinal opioid and serotonergic mechanisms. *Pain Rep*. 2017;2:e618.

30 Mazzardo-Martins L, Martins DF, Marcon R, et al. High-intensity extended swimming exercise reduces pain-related behavior in mice: involvement of endogenous opioids and the serotonergic system. *J Pain*. 2010;11:1384–1393.

31 Stagg NJ, Mata HP, Ibrahim MM, et al. Regular exercise reverses sensory hypersensitivity in a rat neuropathic pain model: role of endogenous opioids. *Anesthesiology.* 2011;114:940–948.

32 Bobinski F, Martins D, Bratti T, et al. Neuroprotective and neuroregenerative effects of low-intensity aerobic exercise on sciatic nerve crush injury in mice. *Neuroscience.* 2011;194:337–348.

33 Glass JM. Review of cognitive dysfunction in fibromyalgia: a convergence on working memory and attentional control impairments. *Rheum Dis Clin North Am.* 2009;35:299–311.

34 Moseley GL. Evidence for a direct relationship between cognitive and physical change during an education intervention in people with chronic low back pain. *Eur J Pain.* 2004;8:39–45.

35 Busch AJ, Webber SC, Brachaniec M, et al. Exercise therapy for fibromyalgia. *Curr Pain Headache Rep.* 2011;15:358–367.

36 Jan MH, Lin CH, Lin YF, Lin JJ, Lin DH. Effects of weight-bearing versus nonweight-bearing exercise on function, walking speed, and position sense in participants with knee osteoarthritis: a randomized controlled trial. *Arch Phys Med Rehabil.* 2009;90:897–904.

37 Macedo LG, Smeets RJ, Maher CG, Latimer J, McAuley JH. Graded activity and graded exposure for persistent nonspecific low back pain: a systematic review. *Phys Ther.* 2010;90:860–879.

38 George SZ, Wittmer VT, Fillingim RB, Robinson ME. Comparison of graded exercise and graded exposure clinical outcomes for patients with chronic low back pain. *J Orthop Sports Phys Ther.* 2010;40:694–704.

39 Phillips K, Clauw DJ. Central pain mechanisms in chronic pain states: maybe it is all in their head. *Best Pract Res Clin Rheumatol.* 2011;25: 141–154.

40 Max MB. Is mechanism-based pain treatment attainable? Clinical trial issues. *J Pain.* 2000;1(3 suppl):2–9.

41 Woolf CJ, Max MB. Mechanism-based pain diagnosis: issues for analgesic drug development. *Anesthesiology.* 2001;95:241–249.

42 Kumar SP, Saha S. Mechanism-based classification of pain for physical therapy management in palliative care: a clinical commentary. *Indian J Palliat Care.* 2011;17:80–86.

43 IASP Task Force on Taxonomy . Part III: pain terms—a current list with definitions and notes on usage. In: Merskey H, Bogduk N, eds. *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms.* 2nd ed. Seattle, WA: IASP Press; 1994: 209–213.

44 Kosek E, Cohen M, Baron R, et al. Do we need a third mechanistic descriptor for chronic pain states? *Pain.* 2016;157:1382–1386.

45 McMahon SB, Koltzenburg M, Tracey I, Turk D. *Wall & Melzack's Textbook of Pain E-Book.* 6th ed. Philadelphia, PA: Elsevier; 2013.

46 Edwards RR, Dworkin RH, Sullivan MD, Turk DC, Wasan AD. The role of psychosocial processes in the development and maintenance of chronic pain. *J Pain.* 2016;17(9 suppl):T70–T92.

47 George SZ, Fritz JM, Bialosky JE, Donald DA. The effect of a fear-avoidance-based physical therapy intervention for patients with acute low back pain: results of a randomized clinical trial. *Spine (Phila Pa 1976).* 2003;28:2551–2560.

48 Rakel BA, Blodgett NP, Bridget Zimmerman M, et al. Predictors of postoperative movement and resting pain following total knee replacement. *Pain.* 2012;153:2192–2203.

49 Filardo G, Roffi A, Merli G, et al. Patient kinesiophobia affects both recovery time and final outcome after total knee arthroplasty. *Knee Surg Sports Traumatol Arthrosc.*2016;24: 3322–3328.

50 Granot M, Ferber SG. The roles of pain catastrophizing and anxiety in the prediction of postoperative pain intensity: a prospective study. *Clin J Pain.* 2005;21:439–445.

51 Magni G, Moreschi C, Rigatti-Luchini S, Merskey H. Prospective study on the relationship between depressive symptoms and chronic musculoskeletal pain. *Pain.* 1994;56: 289–297.

52 American Physical Therapy Association. *Physical Therapist Practice and The Movement System.* Alexandria, VA: American Physical Therapy Association; 2015.

53 Hodges P, Coppieters M, MacDonald D, Cholewicki J. New insight into motor adaptation to pain revealed by a combination of modelling and empirical approaches. *Eur J Pain.* 2013;17:1138–1146.

54 Simons DG, Travell JG, Simons LS. *Travell & Simons' Myofascial Pain and Dysfunction: Upper Half of Body.* Vol 1. Baltimore, MD: Lippincott Williams & Wilkins; 1999.

55 Vlaeyen JW, Kole-Snijders AM, Rotteveel AM, Ruesink R, Heuts PH. The role of fear of movement/(re)injury in pain disability. *J Occup Rehabil.* 1995;5:235–252.

56 Lund JP, Donga R, Widmer CG, Stohler CS. The pain-adaptation model: a discussion of the relationship between chronic musculoskeletal pain and motor activity. *Can J Physiol Pharmacol.* 1991;69:683–694.

57 Yusuf E, Kortekaas MC, Watt I, Huizinga TW, Kloppenburg M. Do knee abnormalities visualised on MRI explain knee pain in knee osteoarthritis? A systematic review. *Ann Rheum Dis.* 2011;70:60–67.

58 Brinjikji W, Luetmer PH, Comstock B, et al. Systematic literature review of imaging features of spinal degeneration in asymptomatic populations. *AJNR.* 2015;36:811–816.

59 Teunis T, Lubberts B, Reilly BT, Ring D. A systematic review and pooled analysis of the prevalence of rotator cuff disease with increasing age. *J Shoulder Elbow Surg.* 2014;23:1913–1921.

60 Demant DT, Lund K, Finnerup NB, et al. Pain relief with lidocaine 5% patch in localized peripheral neuropathic pain in relation to pain phenotype: a randomised, double-blind, and placebo-controlled, phenotype panel study. *Pain.* 2015;156:2234–2244.

61 Fischer AA. Pressure threshold meter: its use for quantification of tender spots. *Arch Phys Med Rehabil.* 1986;67:836–838.

62 Clauw DJ. Fibromyalgia: a clinical review. *JAMA.* 2014;311:1547–1555.

63 Van Oosterwijck J, Meeus M, Paul L, et al. Pain physiology education improves health status and endogenous pain inhibition in fibromyalgia: a double-blind randomized controlled trial. *Clin J Pain.* 2013;29:873–882.

64 Nie H, Arendt-Nielsen L, Andersen H, Graven-Nielsen T. Temporal summation of pain evoked by mechanical stimulation in deep and superficial tissue. *J Pain.* 2005;6:348–355.

65 Nir RR, Granovsky Y, Yarnitsky D, Sprecher E, Granot M. A psychophysical study of endogenous analgesia: the role of the conditioning pain in the induction and magnitude of conditioned pain modulation. *Eur J Pain.* 2011;15:491–497.

66 Freynhagen R, Baron R, Gockel U, Tölle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin.* 2006;22:1911–1920.

67 Whooley MA, Avins AL, Miranda J, Browner WS. Case-finding instruments for depression: two questions are as good as many. *J Gen Intern Med.* 1997;12:439–445.

68 Pilkonis PA, Choi SW, Reise SP, et al. Item banks for measuring emotional distress from the Patient-Reported Outcomes Measurement Information System (PROMIS®): depression, anxiety, and anger. *Assessment.* 2011;18:263–283.

69 Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med.* 2006;166:1092–1097.

70 Sullivan MJL, Bishop SR, Pivik J. The Pain Catastrophizing Scale: development and validation. *Psychological Assessment.* 1995;7: 524–532.

71 Waddell G, Newton M, Henderson I, Somerville D, Main CJ. A Fear-Avoidance Beliefs Questionnaire (FABQ) and the role of fear-avoidance beliefs in chronic low back pain and disability. *Pain.* 1993;52:157–168.

72 Roelofs J, Goubert L, Peters ML, Vlaeyen JW, Crombez G. The Tampa Scale for Kinesiophobia: further examination of psychometric properties in patients with chronic low back pain and fibromyalgia. *Eur J Pain.* 2004;8:495–502.

73 Anderson KO, Dowds BN, Pelletz RE, Edwards WT, Peeters-Asdourian C. Development and initial validation of a scale to measure self-efficacy beliefs in patients with chronic pain. *Pain.* 1995;63:77–84.

74 Haggman S, Maher CG, Refshauge KM. Screening for symptoms of depression by physical therapists managing low back pain. *Phys Ther.* 2004;84:1157–1166.

75 Hill JC, Dunn KM, Lewis M, et al. A primary care back pain screening tool: identifying patient subgroups for initial treatment. *Arthritis Rheum.* 2008;59:632–641.

76 Main CJ, Wood PL, Hollis S, Spanswick CC, Waddell G. The Distress and Risk Assessment Method: a simple patient classification to identify distress and evaluate the risk of poor outcome. *Spine (Phila Pa 1976).* 1992;17:42–52.

77 Booth J, Moseley GL, Schiltenwolf M, Cashin A, Davies M, Hübscher M. Exercise for chronic musculoskeletal pain: a biopsychosocial approach. *Musculoskeletal Care.* 2017;15:413–421.

78 Hodges PW, Smeets RJ. Interaction between pain, movement, and physical activity: short-term benefits, long-term consequences, and targets for treatment. *Clin J Pain.* 2015;31:97–107.

79 Henriksen M, Aaboe J, Graven-Nielsen T, Bliddal H, Langberg H. Motor responses to experimental Achilles tendon pain. *Br J Sports Med.* 2011;45:393–398.

80 Philips C. The modification of tension headache pain using EMG biofeedback. *Behav Res Ther.* 1977;15:119–129.

81 Briggs RA, Houck JR, Drummond MJ, Fritz JM, LaStayo PC, Marcus RL. Asymmetries identified in sit-to-stand task explain physical function after hip fracture. *J Geriatr Phys Ther.* 2017 March 1 [E-pub ahead of print]. doi: 10.1519/JPT.0000000000000122.

82 Noehren B, Dailey DL, Rakel BA, et al. Effect of transcutaneous electrical nerve stimulation on pain, function, and quality of life in fibromyalgia: a double-blind randomized clinical trial. *Phys Ther.* 2015;95:129–140.

83 Archer KR, Motzny N, Abraham CM, et al. Cognitive-behavioral-based physical therapy to improve surgical spine outcomes: a case series. *Phys Ther.* 2013;93:1130–1139.

84 Jensen MP, Turner JA, Romano JM, Karoly P. Coping with chronic pain: a critical review of the literature. *Pain.* 1991;47:249–283.

85 Sullivan MJ, Adams H, Rhodenizer T, Stanish WD. A psychosocial risk factor–targeted intervention for the prevention of chronic pain and disability following whiplash injury. *Phys Ther.* 2006;86:8–18.

86 Demant DT, Lund K, Vollert J, et al. The effect of oxcarbazepine in peripheral neuropathic pain depends on pain phenotype: a randomised, double-blind, placebo-controlled phenotype-stratified study. *Pain.* 2014;155:2263–2273.

87 Macedo LG, Maher CG, Latimer J, McAuley JH. Motor control exercise for persistent, nonspecific low back pain: a systematic review. *Phys Ther.* 2009;89:9–25.

88 Martins DF, Mazzardo-Martins L, Cidral-Filho FJ, Gadotti VM, Santos AR. Peripheral and spinal activation of cannabinoid receptors by joint mobilization alleviates postoperative pain in mice. *Neuroscience.* 2013;255:110–121.

89 Corey SM, Vizzard MA, Bouffard NA, Badger GJ, Langevin HM. Stretching of the back improves gait, mechanical sensitivity and connective tissue inflammation in a rodent model. *PLoS One.* 2012;7:e29831.

90 Berrueta L, Muskaj I, Olenich S, et al. Stretching impacts inflammation resolution in connective tissue. *J Cell Physiol.* 2016;231:1621–1627.

91 Crane JD, Ogborn DI, Cupido C, et al. Massage therapy attenuates inflammatory signaling after exercise-induced muscle damage. *Sci Transl Med.* 2012;4:119ra113.

92 van der Wees PJ, Lenssen AF, Hendriks EJ, Stomp DJ, Dekker J, de Bie RA. Effectiveness of exercise therapy and manual mobilisation in ankle sprain and functional instability: a systematic review. *Aust J Physiother.* 2006;52:27–37.

93 Moseley GL, Butler DS. *Explain Pain Supercharged.* Adelaide, South Australia, Australia: Noigroup Publications; 2017.

94 Sluka KA, O'Donnell JM, Danielson J, Rasmussen LA. Regular physical activity prevents development of chronic pain and activation of central neurons. *J Appl Physiol (1985).* 2013;114:725–733.

95 Grace P, Strand K, Galer E, et al. Prior voluntary wheel running is protective for neuropathic-like pain. *J Pain.* 2016;17(4 suppl):S90.

96 Geva N, Defrin R. Enhanced pain modulation among triathletes: a possible explanation for their exceptional capabilities. *Pain.* 2013;154:2317–2323.

97 Andrzejewski W, Kassolik K, Brzozowski M, Cymer K. The influence of age and physical activity on the pressure sensitivity of soft tissues of the musculoskeletal system. *J Bodyw Mov Ther.* 2010;14:382–390.

98 Bobinski F, Ferreira TAA, Córdova MM, et al. Role of brainstem serotonin in analgesia produced by low-intensity exercise on neuropathic pain after sciatic nerve injury in mice. *Pain.* 2015;156:2595–2606.

99 Lund I, Ge Y, Yu LC, et al. Repeated massage-like stimulation induces long-term effects on nociception: contribution of oxytocinergic mechanisms. *Eur J Neurosci.* 2002;16:330–338.

100 Agren G, Lundeberg T, Uvnäs-Moberg K, Sato A. The oxytocin antagonist 1-deamino-2-D-Tyr-(Oet)-4-Thr-8-Orn-oxytocin reverses the increase in the withdrawal response latency to thermal, but not mechanical nociceptive stimuli following oxytocin administration or massage-like stroking in rats. *Neurosci Lett.* 1995;187:49–52.

101 Skyba DA, Radhakrishnan R, Rohlwing JJ, Wright A, Sluka KA. Joint manipulation reduces hyperalgesia by activation of monoamine receptors but not opioid or GABA receptors in the spinal cord. *Pain.* 2003;106:159–168.

102 Martins DF, Mazzardo-Martins L, Cidral-Filho FJ, Stramosk J, Santos AR. Ankle joint mobilization affects postoperative pain through peripheral and central adenosine A1 receptors. *Phys Ther.* 2013;93:401–412.

103 Martins DF, Mazzardo-Martins L, Gadotti VM, et al. Ankle joint mobilization reduces axonotmesis-induced neuropathic pain and glial activation in the spinal cord and enhances nerve regeneration in rats. *Pain.* 2011;152:2653–2661.

104 George SZ, Bishop MD, Bialosky JE, Zeppieri G Jr, Robinson ME. Immediate effects of spinal manipulation on thermal pain sensitivity: an experimental study. *BMC Musculoskelet Disord.* 2006;7:68.

105 Bialosky JE, Bishop MD, Robinson ME, Barabas JA, George SZ. The influence of expectation on spinal manipulation induced hypoalgesia: an experimental study in normal subjects. *BMC Musculoskelet Disord.* 2008;9:19.

106 Moss P, Sluka K, Wright A. The initial effects of knee joint mobilization on osteoarthritic hyperalgesia. *Man Ther.* 2007;12:109–118.

107 Bialosky JE, Bishop MD, Robinson ME, Zeppieri G Jr, George SZ. Spinal manipulative therapy has an immediate effect on thermal pain sensitivity in people with low back pain: a randomized controlled trial. *Phys Ther.* 2009;89:1292–1303.

108 Paungmali A, O'Leary S, Souvlis T, Vicenzino B. Hypoalgesic and sympathoexcitatory effects of mobilization with movement for lateral epicondylalgia. *Phys Ther.* 2003;83:374–383.

109 Maeda Y, Lisi TL, Vance CG, Sluka KA. Release of GABA and activation of $GABA_A$ in the spinal cord mediates the effects of TENS in rats. *Brain Res.* 2007;1136:43–50.

110 Ma YT, Sluka KA. Reduction in inflammation-induced sensitization of dorsal horn neurons by transcutaneous electrical nerve stimulation in anesthetized rats. *Exp Brain Res.* 2001;137:94–102.

111 Sluka KA, Vance CG, Lisi TL. High-frequency, but not low-frequency, transcutaneous electrical nerve stimulation reduces aspartate and glutamate release in the spinal cord dorsal horn. *J Neurochem.* 2005;95:1794–1801.

112 Dailey DL, Rakel BA, Vance CG, et al. Transcutaneous electrical nerve stimulation reduces pain, fatigue and hyperalgesia while restoring central inhibition in primary fibromyalgia. *Pain.* 2013;154:2554–2562.

113 Kluding PM, Pasnoor M, Singh R, et al. The effect of exercise on neuropathic symptoms, nerve function, and cutaneous innervation in people with diabetic peripheral neuropathy. *J Diabetes Complications.* 2012;26:424–429.

114 Gilbert KK, Smith MP, Sobczak S, James CR, Sizer PS, Brismee JM. Effects of lower limb neurodynamic mobilization on intraneural fluid dispersion of the fourth lumbar nerve root: an unembalmed cadaveric investigation. *J Man Manip Ther.* 2015;23:239–245.

115 Brown CL, Gilbert KK, Brismee JM, Sizer PS, Roger James C, Smith MP. The effects of neurodynamic mobilization on fluid dispersion within the tibial nerve at the ankle: an unembalmed cadaveric study. *J Man Manip Ther.* 2011;19:26–34.

116 George SZ, Fritz JM. Physical therapy management of fear-avoidance in patients with low back pain. In: Wilmarth MA, Godges J, eds. *Including the Patient in Therapy: The Power of the Psyche.* Orthopaedic Section Home Study Course. Alexandria, VA: American Physical Therapy Association; 2003:1–20.

117 Moseley GL, Nicholas MK, Hodges PW. A randomized controlled trial of intensive neurophysiology education in chronic low back pain. *Clin J Pain.* 2004;20:324–330.

118 Gallagher L, McAuley J, Moseley GL. A randomized-controlled trial of using a book of metaphors to reconceptualize pain and decrease catastrophizing in people with chronic pain. *Clin J Pain.* 2013;29:20–25.

119 Meeus M, Nijs J, Van Oosterwijck J, Van Alsenoy V, Truijen S. Pain physiology education improves pain beliefs in patients with chronic fatigue syndrome compared with pacing and self-management education: a double-blind randomized controlled trial. *Arch Phys Med Rehabil.* 2010;91:1153–1159.

120 Boehme F, Gil-Mohapel J, Cox A, et al. Voluntary exercise induces adult hippocampal neurogenesis and BDNF expression in a rodent model of fetal alcohol spectrum disorders. *Eur J Neurosci.* 2011;33:1799–1811.

121 Shors TJ, Anderson ML, Curlik DM II, Nokia MS. Use it or lose it: how neurogenesis keeps the brain fit for learning. *Behav Brain Res.* 2012;227:450–458.

122 Duman CH, Schlesinger L, Russell DS, Duman RS. Voluntary exercise produces antidepressant and anxiolytic behavioral effects in mice. *Brain Res.* 2008;1199:148–158.

123 de Oliveira MS, da Silva Fernandes MJ, Scorza FA, et al. Acute and chronic exercise modulates the expression of MOR opioid receptors in the hippocampal formation of rats. *Brain Res Bull.* 2010;83:278–283.

124 Cooney GM, Dwan K, Greig CA, et al. Exercise for depression. *Cochrane Database Syst Rev.* 2013;(9):CD004366.

125 Angevaren M, Aufdemkampe G, Verhaar HJ, Aleman A, Vanhees L. Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. *Cochrane Database Syst Rev.* 2008;(3):CD005381.

126 Vincent HK, George SZ, Seay AN, Vincent KR, Hurley RW. Resistance exercise, disability, and pain catastrophizing in obese adults with back pain. *Med Sci Sports Exerc.* 2014;46:1693–1701.

127 Naugle KM, Naugle KE, Fillingim RB, Riley JL III. Isometric exercise as a test of pain modulation: effects of experimental pain test, psychological variables, and sex. *Pain Med.* 2014;15:692–701.

128 Field T, Hernandez-Reif M, Seligman S, et al. Juvenile rheumatoid arthritis: benefits from massage therapy. *J Pediatr Psychol.* 1997;22:607–617.

129 Field T, Hernandez-Reif M, Diego M, Schanberg S, Kuhn C. Cortisol decreases and serotonin and dopamine increase following massage therapy. *Int J Neurosci.* 2005;115:1397–1413.

130 Field T, Ironson G, Scafidi F, et al. Massage therapy reduces anxiety and enhances EEG pattern of alertness and math computations. *Int J Neurosci.* 1996;86:197–205.

131 Cady SH, Jones GE. Massage therapy as a workplace intervention for reduction of stress. *Percept Mot Skills.* 1997;84:157–158.

132 Brennan MK, DeBate RD. The effect of chair massage on stress perception of hospital bedside nurses. *J Bodyw Mov Ther.* 2006;10:335–342.

133 Seo JT, Choe JH, Lee WS, Kim KH. Efficacy of functional electrical stimulation-biofeedback with sexual cognitive-behavioral therapy as treatment of vaginismus. *Urology.* 2005;66:77–81.

134 Gam AN, Warming S, Larsen LH, et al. Treatment of myofascial trigger-points with ultrasound combined with massage and exercise: a randomised controlled trial. *Pain.* 1998;77:73–79.

135 Kelley MJ, Shaffer MA, Kuhn JE, et al. Shoulder pain and mobility deficits: adhesive capsulitis. *J Orthop Sports Phys Ther.* 2013;43:A1–A31.

136 Martin RL, Davenport TE, Reischl SF, et al. Heel pain-plantar fasciitis: revision 2014. *J Orthop Sports Phys Ther.* 2014;44:A1–A33.

137 Page MJ, Green S, McBain B, et al. Manual therapy and exercise for rotator cuff disease. *Cochrane Database Syst Rev.* 2016;(6):CD012224.

138 Bulbulian R, Burke J, Dishman JD. Spinal reflex excitability changes after lumbar spine passive flexion mobilization. *J Manipulative Physiol Ther.* 2002;25:526–532.

139 Dishman JD, Bulbulian R. Spinal reflex attenuation associated with spinal manipulation. *Spine (Phila Pa 1976).* 2000;25:2519–2524.

140 Ferreira ML, Ferreira PH, Hodges PW. Changes in postural activity of the trunk muscles following spinal manipulative therapy. *Man Ther.* 2007;12:240–248.

141 Moseley L. Combined physiotherapy and education is efficacious for chronic low back pain. *Aust J Physiother.* 2002;48:297–302.

142 Pires D, Cruz EB, Caeiro C. Aquatic exercise and pain neurophysiology education versus aquatic exercise alone for patients with chronic low back pain: a randomized controlled trial. *Clin Rehabil.* 2015;29:538–547.

143 Damush TM, Perkins SM, Mikesky AE, Roberts M, O'Dea J. Motivational factors influencing older adults diagnosed with knee osteoarthritis to join and maintain an exercise program. *J Aging Phys Act.* 2005;13:45–60.

144 Wilcox S, Der Ananian C, Abbott J, et al. Perceived exercise barriers, enablers, and benefits among exercising and nonexercising adults with arthritis: results from a qualitative study. *Arthritis Rheum.* 2006;55:616–627.

145 Liebano RE, Rakel B, Vance CG, Walsh DM, Sluka KA. An investigation of the development of analgesic tolerance to TENS in humans. *Pain.* 2011;152:335–342.

146 Chandran P, Sluka KA. Development of opioid tolerance with repeated transcutaneous electrical nerve stimulation administration. *Pain.* 2003;102:195–201.

147 Desantana JM, Santana-Filho VJ, Sluka KA. Modulation between high- and low-frequency transcutaneous electric nerve stimulation delays the development of analgesic tolerance in arthritic rats. *Arch Phys Med Rehabil.* 2008;89:754–760.