Cell Reports Medicine

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Review

An update on non-pharmacological interventions for pain relief

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https://doi.org/10.1016/j.xcrm.2025.101940

SUMMARY

Chronic pain affects a substantial portion of the population, yet current treatments often fail to provide adequate relief. Non-pharmacological interventions, which target behaviors and brain processes underlying the experience of pain, hold promises in offering relief for people with chronic pain. This review consolidates the current knowledge concerning the efficacy of non-pharmacological interventions for chronic pain. We focus on psychological interventions (e.g., cognitive behavioral therapy-based interventions and emotion-based therapies) that use mental techniques and physical practices (e.g., exercise, massage, acupuncture, and yoga) that use body techniques to reduce pain. The efficacy of neuromodulation is also discussed. Given that placebo and expectation effects may enhance benefits for non-pharmacological interventions, we also discuss placebo interventions and expectation management practices. Finally, we describe digital therapeutics as an emerging approach for managing chronic pain. We argue that non-pharmacological interventions are critical adjunctive or stand-alone interventions for chronic pain conditions.

INTRODUCTION

Chronic pain presents a pervasive challenge worldwide, incurring significant individual and societal burdens. Estimates of its prevalence in the population range from approximately 20% to 40%.[1,2] Chronic pain, irrespective of its etiology, detrimentally affects quality of life and imposes substantial economic costs, with estimates in the United States alone ranging from $560 to $635 billion annually in 2010 constant dollars. About one in fourteen adults are experiencing high-impact chronic pain,[3] which is defined as having pain most days during the past 3 months together with limitations in daily life or work activities because of pain.[4]

While medications represent the most common treatment approach for chronic pain, with various pharmaceutical classes recommended as first-, second-, or third-line options for chronic neuropathic pain management,[5] non-pharmacological interventions are often relegated to the status of last resort or are mentioned as considerations. However, many chronic pain patients do not achieve clinically significant pain relief through medication alone. A recent meta-analysis evaluating the efficacy of opioids for chronic pain found only marginal improvements in pain intensity compared to placebo.[6] Similarly, a systematic review on drug efficacy for neuropathic pain management suggested that the efficacy estimates of antidepressants and antiepileptics seem to have decreased with more recent large sample size randomized controlled trials (RCTs).[7]

Our narrative review will discuss an array of non-pharmacological approaches for managing chronic pain in adults, highlighting interventions with evidence for efficacy or effectiveness, patient acceptability, and potential mechanisms (Figure 1). These approaches will be considered independently of the pain type—whether neuropathic, nociplastic, or nociceptive (for definitions, see Box 1). Recognizing that diverse mechanisms underlie these interventions, we will address the challenge of unifying them under a single conceptual framework by adapting and expanding the embodied view of pain framework.[8]

An expanded embodied view of pain framework

Originally proposed by Eccleston,[8] we have expanded this framework to conceptualize pain as a set of biological and psychological changes that lead to behavioral and psychological consequences, ultimately altering the endogenous systems for nociception.

Using this adapted framework, we organize the non-pharmacological interventions selected for this review into a hierarchical structure, aligning each intervention within the framework to support recovery and enhance overall well-being.

Non-pharmacological interventions and treatments, in general, exert effects across both physiological and psychological dimensions. Yet each type of intervention typically has a "primary" target. For instance, interventions such as mindfulness meditation may primarily influence psychological processes by enhancing awareness and reducing stress,

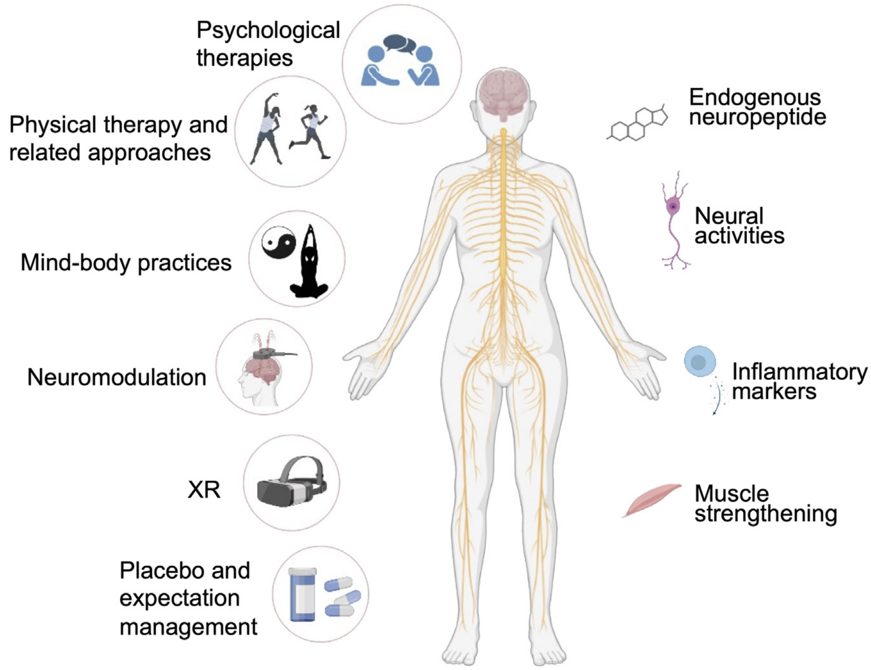

Figure 1. Non-pharmacological interventions may trigger a series of changes in the peripheral and central nervous systems
These changes include, but are not limited to, the release of endogenous neuropeptides (e.g., endorphins), changes in neural activities, reductions in inflammatory markers (e.g., cytokines interleukin-10 and tumor necrosis factor alpha), and muscle strengthening.

whereas physical therapies may initially target physiological mechanisms like muscle relaxation or improved circulation. Distinct intervention types may primarily operate at different levels along a continuum (Figure 2). Understanding these primary intervention targets along this continuum is crucial for defining their main mechanisms of action and integrating the interventions presented in the following, into a comprehensive treatment strategy.

At the most basic level, level 1 responses focus on physiological changes that occur without the involvement of cognitive or emotional processes. We will first consider interventions at this level, such as exercise, massage, neuromodulation, acupuncture, and dose-extending placebos, which primarily target the body's physical responses to pain. Additionally, while open-label placebos (OLPs) likely provide relief by modulating underlying physiological mechanisms, they may also involve cognitive mechanisms.

Level 2 responses address the psychological dimension of pain, involving cognitive and emotional processes that influence how pain is experienced. Interventions that primarily target psychological responses to pain—including cognitive behavioral therapy (CBT), acceptance and commitment therapy (ACT), emotional awareness and expression therapy (EAET), pain reprocessing therapy (PRT), and mindfulness-based practices—likely provide relief by directly altering one's cognitive and affective state, including improving pain coping or reinterpreting pain experiences.

Level 3 responses focus on dissociating from physical experience, manifesting as detachment forms like "marionette" (loss of control) and "immersion" (singular focus) experiences in response to intense, inescapable sensations such as pain. Interventions that focus on shifting focus away from the bodily experience—such as the use of augmented and virtual reality (VR) therapies—likely provide relief by creating an engaging environment designed to alter pain perception.

Lastly, we will consider the role of expectations (level 2), as these factors can enhance the benefits of all aforementioned non-pharmacological treatments. Expectations, in particular, act as a psychological mechanism that can amplify treatment outcomes by influencing how the body and brain respond to an intervention.[9] By integrating the impact of placebo effects and expectations into our framework, we acknowledge its potential to modulate both physiological and psychological processes, thus reinforcing the effectiveness of various treatment strategies.

INTERVENTIONS PRIMARILY TARGETING LEVEL 1 RESPONSES

Physical therapy and related approaches

Physical therapy is widely used for managing chronic pain. The practice of physical therapy is multifaceted, encompassing diverse approaches including manual therapy,[10] specific practices like the McKenzie method,[11] broader categories such as rehabilitation[10] andexercise,[12] as well as treatments based on physical stimuli—such as electrical currents, heat, or cold stimuli—to reduce inflammation and promote healing. With respect to the embodied framework, physical therapies primarily target physiological processes within level 1. However, these treatments can also result in psychological improvements. In some cases, physical therapies may explicitly incorporate level 2 processes into intervention, such as cognitive behavioral physical therapy, which integrates cognitive behavioral strategies to address beliefs, thoughts, and behaviors related to pain, thus bridging both levels within the framework. This multidimensional approach highlights the potential for physical therapies to operate across the continuum, promoting holistic benefits.

Here, we summarized findings about exercises actively performed by individuals to enhance strength and flexibility. We also discuss massage, which involves guided passive movements to alleviate tension. We included practices that are delivered by licensed physical therapists, as well as other practices, such as Pilates and aerobic exercises, which are physical in nature but not necessarily delivered by a licensed professional.

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Box 1. Key definitions

(1) **Chronic pain**: pain lasting more than three months. Chronic pain generally affects quality of life and functionality.
(2) **Neuropathic pain**: pain caused by a lesion of disease of the somatosensory system. Neuropathic pain is often severe and disabling.
(3) **Nociceptive pain**: this type of pain is caused by tissue damage or inflammation. It is usually well localized and can be either somatic (affecting the skin, muscles, bones, or joints) or visceral (affecting internal organs). Examples include arthritis pain, osteoarthritis, post-surgical pain, and injury-related pain.
(4) **Nociplastic pain**: this relatively new category refers to pain arising from altered nociception despite no clear evidence of actual or threatened tissue damage or evidence of disease or lesion of the somatosensory system. Fibromyalgia and irritable bowel syndrome are common examples.
(5) **Inflammatory pain**: this pain is associated with inflammation and is often a result of the body's immune response to injury or infection. Conditions like rheumatoid arthritis and inflammatory bowel disease are examples.
(6) **Mixed pain**: the term "mixed pain" is generally applied for pain including elements of both nociceptive and neuropathic pain, often seen in complex conditions like chronic back pain and cancer pain.
(7) **Complementary health approaches (CHAs)**: treatments outside conventional medicine, including mind-body practices, natural products, and traditional medicine.
(8) **Cognitive behavioral therapy (CBT)**: a psychological intervention that aims to modify behavior and thought patterns to alleviate pain and improve quality of life.
(9) **Emotional awareness and expression therapy (EAET):** a therapeutic approach that emphasizes the identification and communication of emotions to enhance emotional processing and regulation.
(10) **Acceptance and commitment therapy (ACT):** a type of CBT that encourages mindfulness, acceptance of difficult thoughts and feelings, and commitment to take action aligned with personal values.
(11) **Mindfulness:** a practice of being present and aware of one's thoughts, emotions, and sensations without judgment, often cultivated through meditation and other techniques.
(12) **Pain reprocessing therapy (PRT):** an approach focusing on reprocessing pain experiences, aiming to reduce the negative impact of pain through cognitive, emotional, and behavioral techniques.
(13) **Massage:** therapeutic manipulation of body tissues to promote relaxation, reduce muscle tension, and alleviate discomfort.
(14) **Pilates:** a system of exercises designed to improve physical strength, flexibility, and posture, focusing on controlled movements and breathing patterns.
(15) **Tai chi:** an ancient Chinese martial art characterized by slow, deliberate movements and deep breathing, promoting relaxation, balance, and overall health.
(16) **Yoga:** a holistic practice combining physical postures (asanas), breathing exercises (pranayama), and meditation to promote physical, mental, and spiritual well-being.
(17) **Qigong (chi kung):** a Chinese system of postures, movements, and breathing exercises designed to promote the flow of qi (life energy) in the body, enhancing health and vitality.
(18) **Exercise**: structured physical activity designed to improve fitness and reduce pain symptoms.
(19) **Neuromodulation**: techniques like repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) that modulate nervous system activity to reduce pain.
(20) **Placebo effects**: improvements in health outcomes resulting from the belief in the efficacy of a treatment, rather than the treatment itself.
(21) **Extended reality (XR)**: encompasses virtual reality (VR), augmented reality (AR), and mixed reality (MR) used for immersive therapeutic applications.

Exercise

Exercise is a form of physical activity aimed at improving or maintaining physical fitness. It is typically structured, planned, and repetitive.[13] Studies have shown that exercise reduces chronic pain severity and improves pain-related outcomes,[14] including physical function, mood, fatigue, and sleep quality, compared to no treatments.[15,16] According to the 2020 Comparative Effectiveness Review from the Agency for Healthcare Research and Quality (AHRQ),[17] exercise interventions improve pain and physical function.[17] However, the effects vary among different chronic pain conditions. For example, small reductions in chronic pain (around 1 point on a 0 to 10 scale) and small improvements in physical function (standard mean difference [SMD] = 0.3) were observed in the short term (1–6 months following intervention completion) compared with usual care and/or placebo interventions in chronic low back pain, osteoarthritis, and fibromyalgia. In contrast, evidence remains weak for improvements in short-term pain or physical function for chronic neck pain with exercise intervention.[18,19] Evidence for long-term effects of exercise has been reported, and further longitudinal studies are needed to confirm the long-term efficacy of exercise.[17]

While exercise is effective in improving chronic pain-related symptoms[20] and effect sizes are generally small to medium for all types of exercises, the "how" and "when" to implement exercise intervention for optimal effects are unclear. There is no

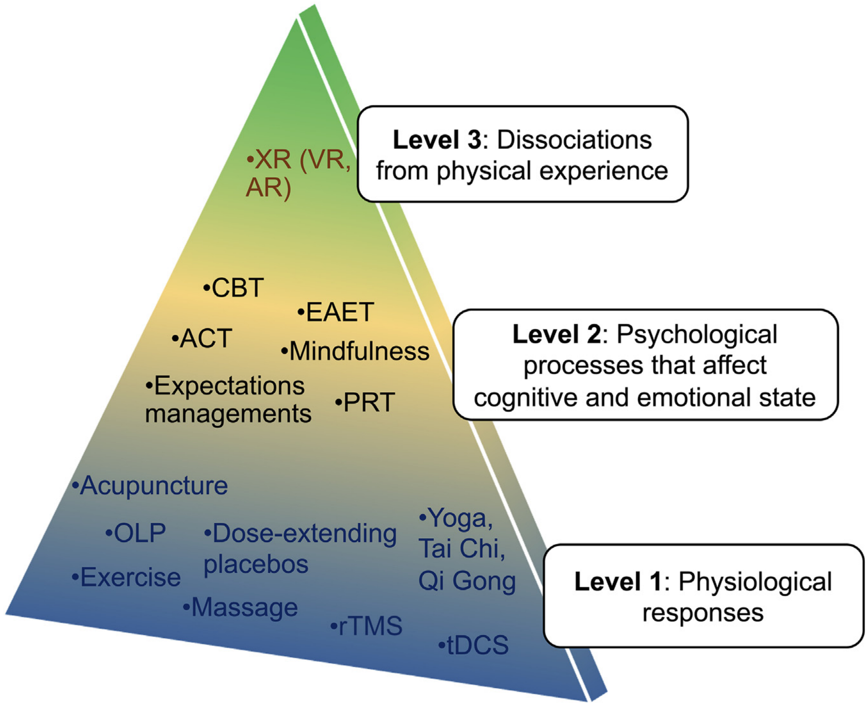

Figure 2. Adapted embodied view of pain framework

This framework categorizes pain responses into three levels along a continuum, illustrating how non-pharmacological interventions can address various aspects of the pain experience.

Level 1 responses: These involve physiological changes that occur independently of cognitive or emotional engagement. Interventions primarily targeting this level include physical therapy modalities such as exercise, massage, neuromodulation (e.g., repetitive transcranial magnetic stimulation [rTMS], transcranial direct current stimulation [tDCS]), acupuncture, open-label placebo (OLP) and dose-extending placebos, and mind-body practices. Some interventions may also incorporate psychological elements, reflecting their dual impact on pain management.

Level 2 responses: This level encompasses psychological processes that influence cognitive and emotional states. Interventions at this level include cognitive behavioral therapy (CBT), acceptance and commitment therapy (ACT), emotional awareness and expression therapy (EAET), pain reprocessing therapy (PRT), and mindfulness-based approaches. Certain interventions in this category may also address physiological responses, illustrating the interconnectedness of the pain experience.

Level 3 responses: This level responses involve dissociations from bodily experience. Interventions targeting this level include augmented reality (AR) and virtual reality (VR) therapies, which create immersive experiences designed to reduce pain perception. This framework assists clinicians in understanding pain as a multifaceted and disruptive force, guiding them in selecting appropriate intervention strategies tailored to different pain response levels. It is important to note that, while interventions are categorized by their primary focus, many operate across multiple levels of response, reflecting the complexity of pain mechanisms and the synergistic effects of non-pharmacological approaches.

consensus on guidelines for the best exercise practices for treating chronic pain.[21] The "how" question refers to the types and intensities of exercise that maximize analgesic effects, and the "when" question refers to the duration and timing of exercise to achieve optimal benefits.[22]

Moderate-intensity exercise, such as muscle performance exercise and muscle strength training, is effective in reducing chronic low back pain compared to active controls. Several RCTs examined the effects of 4–8 weeks[23–25] supervised muscle strength training with coaches (often 1 to 2 h per week) and found that the supervised strength training significantly reduced back pain intensity compared to the attention control groups.[23–25] Particularly, one RCT examined the effects of 6-week supervised muscle strength training (1-h session per week) compared with low-intensity exercise yoga (twice a week) and an education attention control in 157 individuals with chronic low back pain.[23] They found that only the supervised strength training, not yoga, significantly reduced back pain intensity compared to the non-exercise attention control group. However, findings from an RCT in 154 individuals with chronic low back pain indicated that the effects of muscle performance/stretching on pain intensity were small and not clinically relevant when compared with placebo treatments (i.e., detuned ultrasound therapy).[26]

Pilates, a form of controlled movement that focuses on strength, flexibility, and core stability, reduced chronic low back pain when compared with both passive and active controls.[27] It is typically self-guided or delivered by a trained instructor. In a pilot RCT (n = 47), 6-week Pilates (three times per week) significantly improved chronic pain intensity and physical function compared to the non-exercise control.[28] The benefits in favor of Pilates were further confirmed in a larger RCT in which 6-week Pilates with once, twice, and three times per week were compared to an attention control group in chronic low back pain.[29]

Aerobic exercise involves sustained, rhythmic movements that increase the heart rate and breathing for an extended period. Like Pilates, aerobic exercise is typically self-guided or delivered by a trained instructor. Typical aerobic exercises include jogging, running, and swimming. An early meta-analysis of 301 participants with chronic low back pain summarized the results of aerobic exercises.[30] It was found that aerobic exercises improved chronic pain (medium effect size SMD = 0.75), physical function (small effect size SMD = 0.44), and depression (large effect size SMD = 1.35) in chronic low back pain compared to baseline measures but did not show any improvements in objective measures such as heart rate, sit-and-reach test, or maximum oxygen consumption.[30] Note that the meta-analysis results are based on pre- and post-intervention sessions and therefore could not rule out the possibility of regression to the mean and placebo responses.

The optimal dosage of exercise varies based on chronic disorders and the underlying severity. Insufficient exercise might not trigger changes in physiological and biochemical levels, while overtraining may worsen symptoms.[31] There is no consensus on the optimal "dosage" of exercise, but most sessions last around 1 h, with intervention durations ranging from 5 to 12 weeks[23–25,27] Additionally, many studies lack accurate assessments of absolute intensity indices such as oxygen uptake, kcal or kJ per minute, resting metabolic rate, metabolic equivalents, and relative intensity.[13] The most common comparison is with standard or usual care, and the small effects could be due to adherence issues. In one study, the 6-month adherence rates of strength training (34%) and yoga (54%) were low. Not surprisingly, those who were able to maintain their activities benefited more than non-adherers.[23] Studies have shown that exercise has the greatest impact when implemented as a lifetime behavioral change rather than a short-term, disease-related practice.[31]

Massage

Massage therapy is another form of pain intervention that is physical in nature, defined as soft-tissue manipulation for therapeutic purposes by a trained massage therapist or occasionally physical therapist. The efficacy of massage for pain relief has been well-documented through multiple systematic reviews[32,33] and meta-analyses.[34,35] The most recent meta-analysis summarized findings from 34 RCTs and revealed a small to medium effect size for reducing chronic pain intensity compared to the active controls such as physical therapy and acupuncture (SMD = 0.26) and small effect size for improving quality of life (SMD = 0.14). However, while massage has been beneficial for pain intensity, it does not seem to improve physical function in people with chronic pain.[34] Massage is generally safe. In rare conditions, massages may lead to minor adverse events such as increased muscle soreness and stiffness.[35] It should be noted that the effects of massages tend to be short term (1–6 months following the completion of the treatment), with insufficient evidence supporting the long-term efficacy and effectiveness.[17]

Taken together, across multiple studies and diverse training methods, physical therapies including exercise and massages can decrease chronic pain across different pain conditions with varied effect sizes. In particular, exercise is more effective in reducing chronic pain in participants with chronic low back pain, osteoarthritis, and fibromyalgia, but less effective in those with neck pain.

Acupuncture

Acupuncture is a traditional Chinese medical practice, which involves inserting needles into specific points on the body. Acupuncture is typically delivered by a licensed acupuncturist, though some physicians or physical therapists may also be certified to deliver acupuncture or related techniques. The practice is based on the concept of "qi," which is believed to be the vital life energy. By stimulating specific points, acupuncture aims to balance the flow of qi and relieve pain.[36] While acupuncture fundamentally relies on somatosensory stimulation to activate neural and physiological pathways,[37,38] its therapeutic effects are further enhanced by the psychological elements inherent in the treatment experience such as patient expectations and the ritual of care.[39,40]

This combination of physiological stimulation and psychological influence contributes to its multifaceted efficacy, aligning with the embodied framework where treatments engage both level 1 (physiological) and level 2 (psychological) processes.

According to the 2020 Comparative Effectiveness Review from the AHRQ,[17] acupuncture could improve short-term chronic pain intensity with very small effect (mean difference 0.54 out of 10) and improve physical function (SMD = 0.23) in chronic low back pain with moderate strength of evidence.[17] Based on this meta-analysis, while acupuncture did not significantly influence pain intensity in neck pain and fibromyalgia, it demonstrated small improvements in physical functions for individuals with these conditions.[17] It should be noted that this meta-analysis compared acupuncture with a pool of several control comparators, including sham acupuncture, usual care, and attentional controls. To quantify the efficacy with specific comparators, a recent Cochrane meta-analysis synthesized 33 studies with a total of 8,270 participants with chronic low back pain. This meta-analysis showed that, compared to no treatment, acupuncture could alleviate chronic pain intensity (−20.32 out of 100 visual analog scale [VAS]) and improve physical functions (SMD = 0.53) immediately after the intervention and at the short-term follow-up. No improvements in quality of life were found in favor of acupuncture compared with usual care. However, when compared to the sham acupuncture, the pain alleviations did not reach clinical relevance at immediate term (−9.22 out of 100 VAS), short term (−10.04 out of 100 VAS), or intermediate term (−3.83 out of 100 VAS).[41]

The quality of the studies was generally moderate, but none of the studies blinded the person delivering acupuncture.[41] Therefore, the findings cannot rule out performance bias and the therapists' expectation effects.

Taken together, acupuncture holds the promise for improving chronic pain severity and physical functions when compared to no treatment with moderate strength evidence. However, the effect size was small, and acupuncture did not outperform the sham intervention in alleviating pain or physical functions in a clinically relevant manner.

Noninvasive brain neuromodulation

Neuromodulation techniques have been developed to stimulate the spinal cord[42] or the motor cortex to treat chronic pain.[43] Following the embodied view of pain, neuromodulation aligns with level 1 responses where physiological changes are triggered without directly engaging the cognitive and emotional components. In particular, transcranial noninvasive techniques (e.g., repetitive transcranial magnetic stimulation [rTMS] and transcranial direct current stimulation [tDCS]) have been proposed as an effective intervention for drug-resistant chronic refractory pain.[44–46] Primary motor cortex (M1) rTMS is derived from extradural motor cortex stimulation (EMCS). Repetitive sessions (5–10 over 1–2 weeks) of high-frequency rTMS (5–20 Hz) targeting the contralateral M1 have shown benefits in various pain conditions, including central, peripheral neuropathic pain, including facial pain, with effects lasting more than two weeks post-stimulation.

Anodal tDCS over M1 has been reported to alleviate pain in several peripheral neuropathic conditions. The Neuromodulation Appropriateness Consensus Guidelines offer a weak recommendation for the use of EMCS and M1 rTMS for chronic refractory neuropathic pain, as well as tDCS for peripheral neuropathic pain.[47] The primary advantage of noninvasive neurostimulation techniques is their excellent safety profile.

Targeting the M1[48] with figures of 8 coils (F8-coils) using a real double-blind procedure (i.e., double face coil, one active, one placebo) at high frequencies ($\geq$5 Hz) and high number of pulses ($\geq$1,000 per session) has shown to maintain analgesic effects for up to six months in a French multicenter study (*n* = 149).[49] Mechanisms are not related to an effect on motor pathway, as rTMS in experimental mice models may indeed directly modulate pain perception.[48] However, not all patients respond to rTMS. Recently proposed algorithms based on clinical or psychological variables may reduce the risk of therapeutic failure with M1 rTMS.[50]

One potential limitation of conventional rTMS is that F8-coils are limited to stimulating superficial cortical regions about 1 cm beneath the skull, and higher intensities required for deeper stimulation pose a risk of adverse events. To address this, deep rTMS was developed using Hesed (H)-coils, which have a multiplane winding design allowing for brain stimulation.[51] In a recent double-blind cross-over comparative study of the analgesic effects of "superficial" and "deep" rTMS of the primary motor cortex in 59 patients with central neuropathic pain,[52] both coils provided significantly similar analgesic effects, which was greater than sham, but the H-coil effects lasted longer, up to three weeks for some outcomes. Both rTMS methods produced similar analgesic effects, potentially through different mechanisms.[52] Meta-analyses show a small effect size of 0.79 out of 10 pain ratings for rTMS compared to sham[53] and a medium effect size of 0.50 for tDCS compared to sham.[54]

Initial rTMS studies were biased by the use of two coils (one active, one sham), thus creating a risk of unblinding, but newer studies now use double face coils, which can even been programmed using an USB key, thus increasing the quality of the blinding in rTMS trials.[55]

. In conclusion, there is weak evidence for the efficacy of noninvasive neuromodulatory techniques in decreasing chronic pain. The relatively similar efficacy of the different stimulation methods suggests that multiple brain mechanisms, yet to be discovered, are involved in their effects on chronic pain.

Placebo-based interventions for endogenous pain modulation

Placebos—inert substances—have been used to trigger placebo analgesic effects, which refer to the reduction of pain in response to placebos and constitute a form of endogenous pain modulation.[56–58] In the following, we discuss open-label and dose-extending placebos, for pain management. Given that placebo effects can be induced with and without explicit awareness of cognitive changes, placebo-based interventions can align with both level 1 and level 2 strategies.

OLPs

Clinical studies have shown promising results with OLPs, particularly in managing pain-related conditions. For instance, in a study by Kaptchuk et al., 80 patients with irritable bowel syndrome (IBS) were given either OLPs or no treatment. The group receiving OLPs reported significantly higher improvement in IBS symptoms compared to the control group at both 11-day midpoint and at 21-day endpoint.[59] Similarly, research by Carvalho et al. demonstrated that OLPs provided significant relief for chronic lower back pain compared to standard treatment.[60] In this study, 97 patients with at least three months of chronic lower back pain were randomized to receive two OLP tablets, taken twice daily, or treatment as usual, for three weeks.[60] The OLP induced statistically significant clinical benefit over treatment as usual. At the 5-year follow-up, differences were found in pain intensity. Additionally, reductions in the use of pain medication were noted, including analgesics, antidepressants, and benzodiazepines. Conversely, there was an increase in the utilization of alternative approaches to pain management.[61] Although this long-term follow-up lacks controls for spontaneous improvement and new interventions, the data suggest that reductions in pain and disability following OLP can be long lasting.

More recent trials, such as the one conducted by Kleine-Borgmann et al., further support the efficacy of OLPs in reducing pain, pain disability, and depressive symptoms in individuals with back pain (*n* = 122). These studies emphasize the safety and tolerability of OLPs, indicating their potential as a complementary approach to conventional treatments.[62] In contrast, Kleine-Borgmann et al. conducted a 3-year follow-up of the previously published RCT, which included records from 89 previously enrolled patients and investigated changes in pain intensity (primary outcome), disability, mood (secondary outcomes), and biopsychosocial factors and lifestyle (exploratory outcomes) from the baseline measures to follow-up. This trial showed no differences in any outcome measures between the groups with and without previous OLP treatment.[63]

In a recent randomized clinical trial, participants with chronic back pain who received a single nondeceptive placebo injection alongside information about placebo's potential benefits experienced reduced pain intensity at one month post-treatment compared to usual care.[64] While pain relief did not persist at the 1-year follow-up, significant improvements were observed in depression, anger, anxiety, and sleep quality. Brain imaging showed increased activity in pain-modulatory regions, suggesting that the placebo effect involves similar brain mechanisms as deceptive placebos, particularly in prefrontal-brainstem pathways.[64]

Dose-extending placebos

A cue associated with a specific pharmacological treatment can trigger a response similar to the treatment itself, maintaining its therapeutic effect without the active drug.[65–67] Research has shown that this approach can reduce the total dosage of medications needed for a clinical response in conditions such as spinal cord injury requiring opioids,[66] insomnia (e.g., zolpidem),[68] and organ-related immunosuppression after renal transplantation.[69]

Studies indicate that, after repeated administration of active treatments, like morphine, placebos can develop morphine-like effects, such as pain relief, in both humans[70,71] and laboratory animals.[72] Furthermore, these effects are generally more substantial than those from placebos given without prior active treatment. If placebos used in this learning-based manner can mimic the actions of active drugs, they could be employed to manage chronic pain symptoms, potentially reducing the side effects and risks associated with prolonged use of active medications. When evidence shows therapeutic benefits comparable to standard treatments, it becomes justifiable to consider integrating pre-approved, dose-extending placebos into clinical practice.

Both physiological aspects (level 1) and cognitive/behavioral mechanisms are involved in the placebo effects (level 2). Taken together, there is evidence for the short-term efficacy of both dose-extending placebo and OLP for the treatment of chronic pain. However, the long-term efficacy of these methods has not been established.

Mind-body practices

Mind-body practices including tai chi, yoga, and qigong offer a holistic approach to pain management and overall well-being, emphasizing the integration of physical movement, mental focus, and controlled breathing. These practices can improve flexibility, balance, and strength while reducing stress and promoting relaxation. These practices are typically delivered by certified instructors and do not require an advanced degree. Following the framework of embodied view of pain, mind-body practices align with both level 1, which involves physiological responses, and level 2 response that requires interruptions with awareness, given that those practices aim at enhancing awareness and introspection.

Tai chi is a traditional Chinese mind-body exercise practice characterized by slow, flowing movements and an emphasis on balance, flexibility, and mental focus.[73] A meta-analysis of 1,260 individuals with chronic pain showed medium effect sizes (SMD = 0.54 to 0.81) for the effect of tai chi practice on reducing pain intensity in osteoarthritis and chronic low back pain[74] compared to a mixed control condition including both active and passive controls. Another meta-analysis pooled results from 657 people with fibromyalgia and found that, compared with standard care, 12-week tai chi induced a net gain in reducing chronic pain intensity, improving sleep quality, and relieving fatigue with a medium effect size (SMD ranging from 0.57 to 0.92).[75]

Yoga is another form of mind-body intervention that focuses on physical postures, breathing training, and meditation. Findings from a meta-analysis with 16 RCTs with both active and passive controls suggested a medium effect size of 12-week yoga in improving chronic pain intensity (SMD = 0.69) and interference with moderate strength of evidence.[76] Studies from laboratory settings indicated that yoga increases experimental pain tolerance and produces neuroanatomical changes, such as neuroprotective effects and alterations in gray matter volume.[77–79] Those physiological changes could explain the attenuations in chronic pain beyond any placebo effects.[80]

Qigong is an ancient Chinese practice that utilizes coordinated movements, breathing techniques, and meditation to balance the body's vital energy, known as "qi" or "chi." An early RCT compared the efficacy of 6-month qigong and exercise therapy with a "wait-list" controls in individuals with chronic neck pain. Both qigong and exercise showed superiority in improving chronic pain severity, physical function, and quality of life, with no significant differences between the two.[81] Results of a meta-analysis showed medium effect sizes for qigong in reducing chronic pain when compared with placebo controls that performed sham qi gong with the same body movement without meditation or breathing exercises, although the quality of evidence remains low.[82] Many trials assessing the efficacy of mind-body practices, such as tai chi, yoga, and qigong, often include passive control conditions like wait-list controls or usual care.

Mind-body practices such as tai chi, yoga, and qigong align with both level 1 and level 2 of the embodied view of pain framework. These practices target level 1 by eliciting physiological responses such as improved flexibility, balance, strength, and neuroanatomical changes, which contribute to pain modulation. Additionally, they engage level 2, which involves processes requiring conscious awareness and introspection. The dual impact on both physiological and psychological levels underscores their holistic approach to pain management offering a moderate effect size in reducing chronic pain intensity.

INTERVENTIONS PRIMARILY TARGETING LEVEL 2 RESPONSES

Psychological therapies include a range of approaches aimed at intervening on chronic pain by addressing its cognitive, behavioral, and affective aspects. Traditionally, psychological therapies are delivered by a mental health provider over the course of 8–12 weekly sessions that are 60–90 min in duration. Psychological treatments can be delivered to the patient individually or in a group setting. Increasingly, clinical trials are testing the efficacy of different forms of delivery, including single session[83] and self-paced[84] interventions. In this review, we outline psychological therapies that are CBT based in theory, including CBT, ACT, and mindfulness-based therapies. These therapies focus on teaching strategies to cope with pain or live a valued life despite pain. Although CBT-based therapies have been tailored to specific chronic pain conditions, they are typically delivered similarly regardless of pain mechanism (e.g., nociplastic, nociceptive, and neuropathic). We also review newer psychological therapies including EAET and PRT. The goal of these therapies is typically pain reduction, and adverse events are rare, in response to psychological therapies.[85] Because these treatments operate on explicit psychological processes, they fall into level 2 of the embodied view of pain, which involves cognitive and emotional modulation of pain.

CBT

CBT is a well-researched approach that uses cognitive and behavioral techniques to improve physical function and to reinterpret unhelpful negative thoughts into more neutral or realistic ones. Goals of CBT for pain include reducing pain-related distress and optimizing physical function. CBT addresses pain management and also targets broader domains such as emotional well-being, functional capacity, sleep, and interpersonal skills. In addition to primary treatment outcomes related to pain, CBT has been shown to improve secondary outcomes including self-efficacy, psychological distress, and return to work.[86]

CBT is the most extensively studied and practiced psychological therapy for chronic pain (Table 1). A Cochrane systematic review examining psychological interventions for chronic pain identified and meta-analyzed data from 59 RCTS testing CBT among adults with mixed chronic pain conditions excluding headache and migraine.[85] The analysis indicated that CBT versus active control resulted in small effects on pain intensity,

Table 1. Effect sizes for each intervention based on selected meta-analyses

Intervention	Comparator(s)	MD/SMD[a]	Chronic pain population	No. of studies reviewed in the reported meta-analysis	Reference
Exercise	active control	MD = 1.00	chronic low back pain	k = 10	Skelly et al.[17]
Massage	active control (e.g., physical therapy and acupuncture)	SMD = 0.26	mixed chronic pain population	k = 34	Crawford et al.[35]
Acupuncture	sham acupuncture	MD = 0.92	mixed chronic pain population	k = 7	Mu et al.[41]
Transcranial magnetic stimulation (TMS)	sham TMS	MD = 0.79	mixed chronic pain population	k = 9	Goudra et al.[53]
Transcranial direct current stimulation (tDCS)	sham tDCS	SMD = 0.50	fibromyalgia	k = 8	Lloyd et al.[54]
Tai chi	active control (active therapy such as physical therapy and hydrotherapy)	SMD = 0.54	osteoarthritis	k = 8	Kong et al.[74]
Yoga	treatment as usual	SMD = 0.69	mixed chronic pain population	k = 16	Büssing et al.[76]
Qigong	wait-list	SMD = 1.12	mixed chronic pain population	k = 5	Bai et al.[82]
Cognitive behavioral therapy	active control (physical therapy, education, or medical regime)	SMD = 0.09	mixed chronic pain population (excluding headache)	k = 59	de C William et al.[85]
Acceptance and commitment therapy	active control (physical therapy, education, or medical regime)	SMD = 0.25	mixed chronic pain population (excluding headache)	k = 5	de C William et al.[85]
Mindfulness-based intervention	active control (education) + TAU	SMD = 0.19	mixed chronic pain population	k = 19	Hilton et al.[87]

Note: The effect sizes summarized here are based solely on the meta-analysis chosen for this narrative review. Since a systematic literature search was not conducted, the effect sizes shown here should be applied with caution in broader contexts.
[a]MD, mean difference on a 0 to 10 pain rating scale; SMD, standard mean difference.

disability, and psychological distress immediately after treatment, with stronger effects found when CBT was compared to treatment as usual.[85]

There is evidence for small efficacy of CBT with moderate strength evidence[85] for the treatment of different forms of chronic pain. This is a high-quality estimate that reflects a large number of trials, with active control conditions, with select quality indicators in place, and is composed of both efficacy and effectiveness trials, delivered to diverse chronic pain conditions.

The integration of communication technology, particularly mobile health innovations, is expected to play a pivotal role in future treatment strategies. In a complementary review of 15 trials that administered CBT via online platforms, a comparable generally favorable outcome was observed.[88] However, the level of confidence in the effect estimates for CBT delivered via online platforms was relatively low due to relatively small scale trials, with wait-list controls, and lack of reports of adverse events.[88] While the technological infrastructure for delivering behavior change interventions remotely already exists, there remains a need to develop a foundational understanding of how to cultivate effective therapeutic relationships over a distance and enhance traditional face-to-face CBT sessions.[89]

While CBT can indirectly influence physiological responses (level 1), its primary mechanisms and therapeutic strategies engage level 2, and there is a moderate strength of evidence highlighting the efficacy of CBT for improving pain-related outcomes, spanning numerous chronic pain conditions and including effectiveness trials.[85]

ACT

ACT entails cognitive, behavioral, and mindfulness-based approaches to increase psychological flexibility to live a value-driven life.[90–94] Applied to people with chronic pain, ACT helps people engage in value-directed behavior despite ongoing pain and discomfort, especially when previous attempts to control or reduce pain have been unsuccessful or counterproductive.

In a meta-analysis (k = 21), Ma et al. included both face-to-face and online/telephone-based ACT therapies from 1,962 individuals with mixed chronic pain conditions.[90] ACT led to significant improvements in chronic pain severity, pain-related function, anxiety, depression, and quality of life, with small to medium effect sizes. This meta-analysis suggests that longer session length and treatment duration were associated with larger treatment effects. However, most of the studies in this meta-analysis lacked blinding of personnel, and thus performance bias cannot be ruled out. Most studies lacked active control, comparing ACT to wait-list and treatment-as-usual groups. According to an updated Cochrane systematic review that compared ACT to active control (k = 5), there were no significant differences in the improvement of pain intensity, physical function, or emotional distress immediately post-treatment.[85]

ACT aligns with level 2 of the embodied pain framework, as it emphasizes psychological flexibility and conscious engagement with one's values despite the presence of pain. Moreover, the evidence suggests that ACT is generally effective for mixed chronic pain conditions, particularly when compared to passive control conditions. However, the results of meta-analysis suggest that, overall, ACT has not shown superiority over other active treatments (e.g., education and exercise) and that the current quality of evidence is low. Additional high-quality evidence from RCTs is needed to understand the effects of ACT on chronic pain outcomes.

Mindfulness-based interventions

Mindfulness-based interventions teach patients strategies to focus on the present moment and develop a non-judgmental awareness of their experiences. Applied to people with chronic pain, people learn to reduce judgment and suffering associated with pain. Several mindfulness-based approaches are available for chronic pain, including mindfulness-based stress reduction (MBSR[95]) and mindfulness-oriented recovery enhancement.[96] Mindfulness-based approaches can reduce stress and improve pain management by teaching patients a series of skills to manage pain independently.

Research includes both RCTs and nonrandomized trials investigating the efficacy of mindfulness for improving pain-related outcomes in people with diverse chronic pain conditions. A meta-analysis of 30 RCTs reported that mindfulness-based interventions resulted in a reduction in pain intensity with a small effect size.[87] Additional well-designed and large-scale RCTs are needed to fully understand the effects of mindfulness meditation on pain-related outcomes in people with chronic pain.[87]

The benefit of mindfulness as a stand-alone treatment was compared to pharmaceutical approaches, and some studies have compared group meditation training with standard care. These studies have found statistically significant and clinically meaningful improvements in pain intensity with mindfulness meditation. For example, an RCT compared the effectiveness of MBSR (n = 116) vs. CBT (n = 113) vs. usual care (n = 113) for adults with chronic low back pain.[97] People in both MBSR and CBT groups demonstrated moderate improvements in functional limitations that persisted at 6-month follow-up. There was no difference between MBSR and CBT.[97]

Mindfulness-based interventions correspond to level 2 of the embodied pain framework, as they cultivate present-moment awareness and a non-judgmental attitude toward pain experiences. Fostering a deeper awareness of their sensations and emotional responses, the evidence for the efficacy of mindfulness in chronic pain management is growing with relevant brain-based results demonstrating distinct mechanisms as compared with placebo effects.[98–100]

EAET

EAET is a recently developed therapy that focuses on addressing unresolved emotional issues and interpersonal conflict through structured emotional awareness and expression exercises, as a method of reducing pain and stress. To date, EAET has primarily been tested in chronic pain conditions thought to be driven primarily by neuroplastic processes, including fibromyalgia and unexplained chronic musculoskeletal pain (see review[101]). Three RCTs to date have demonstrated the superiority of EAET versus CBT for improving pain-related outcomes in people with fibromyalgia (n = 230)[102] and in two samples of older veterans with chronic musculoskeletal pain (n = 126,[103] n = 53[104]). For example, Yarns et al. found that EAET versus CBT led to greater reductions in pain severity at post-treatment. In addition, 35% of participants in the EAET group experienced at least a 50% reduction in pain compared to 7% of those in the CBT group,[103] at post-treatment.

EAET aligns with level 2 of the embodied view of pain, as it emphasizes the recognition and expression of emotions related to pain experiences. The evidence for the efficacy of EAET in treating chronic pain is strong, and the evidence base is growing. EAET is an emerging intervention, and additional RCTs are needed to understand its treatment effects. Future studies should aim to evaluate the effects of EAET when delivered to people with diverse chronic pain conditions, including those driven by nociceptive and neuropathic mechanisms.

PRT

PRT was recently developed with the goal of retraining the brain to reinterpret pain signals as non-threatening. Building on other pain neuroscience education approaches,[105] it focuses on changing beliefs about the nature and threat of pain. It introduces chronic nociplastic pain as a reversible brain-generated signal, rather than a sign of physical injury. There has been one RCT of PRT to date. Ashar et al.[106] conducted a 3-arm RCT comparing the effects of PRT, OLP, and treatment as usual on chronic back pain in a cohort of adults with nociplastic chronic back pain (n = 151). The results showed superior outcomes for PRT compared to OLP and usual care on back pain ratings as well as facilitated resting-state brain connectivity between the anterior prefrontal cortex and the anterior insula to the primary somatosensory cortex. A greater percentage of participants who received PRT were pain free or nearly pain free after treatment (66%), compared to only 20% of those who received a placebo and 10% of those who received usual care. Treatment effects were maintained at 1-year follow-up.

PRT not only involves changing the brain's physiological response to pain but also emphasizes cognitive restructuring—specifically, the belief systems around pain. By helping individuals understand and reinterpret pain as non-threatening, PRT engages in a more complex interplay between cognitive awareness and emotional processing, which aligns with the characteristics of level 2. This approach has been very recently developed with only 2 studies being published; thus, replication in future studies is essential.

Expectation management interventions

Expectations of treatment benefit facilitate the pain management and individual outcomes.[107–109] Expectations are anticipation of future events (e.g., pain reductions resulting from a behavioral intervention or pharmacological treatment).[110–114] Psychological interventions have been suggested as essential for addressing the dual crises of chronic pain and opioid use disorders.[115] Expectations about the efficacy of psychological treatment directly influence treatment outcomes. For example, results from RCTs show that CBT for chronic pain is less effective in improving pain-related outcomes when patients have lower expectations for treatment effects and perceive CBT to be less credible.[116,117] Increasingly, psychologists are encouraged to use positive expectation setting as a tool to increase the efficacy of intervention.[118,119] For example, low expectation of pain in the morning shapes daily orofacial chronic pain-related outcomes.[120]

Studies have found that treatment expectations are associated with improvements in chronic pain.[121–123] Evidence supporting the relationship between expectations and chronic pain treatment outcomes comes from a large study involving 2,722 participants with chronic pain.[121] In this study, participants were recruited from three multidisciplinary pain treatment centers. At baseline, expectations of pain relief over the next six months were measured using a VAS ranging from 0 (“no relief”) to 100 (“complete relief”). The results indicated that higher baseline expectations of pain relief predicted greater reductions in both chronic pain intensity and depressive symptoms. Expectations accounted for approximately 23% of the variance in chronic pain intensities.[121]

Although expectations and actual experiences are generally congruent, that is, one experiences what one expects, the relationship between positive expectations and pain-related outcomes may not always be linear.[124] In a study of how expectations are updated in laboratory settings, Kube et al.[125] demonstrated that overly positive expectations may be perceived as less credible after experiencing a discrepancy in feedback, leading to a decrease in expectation updating.

Several studies have used placebo manipulations to examine the role of expectations in pain-related outcomes.[126] Notably, expectations of pain relief can be modified through prior therapeutic experiences (e.g., conditioning), verbal suggestions, and social observations.[5,56,127]

Contemporary pain psychology interventions, including EAET and PRT (discussed earlier), use advancements in pain neuroscience and expectations, particularly predictive coding models of pain perception, to emphasize the reversibility of pain.[128] These interventions set expectations for pain relief at the beginning of the treatment, which might contribute to their strong treatment effects on pain outcomes. In fact, studies have shown that EAET outperformed CBT—an intervention that has historically centered on coping despite pain, rather than analgesia—on pain-related outcomes across several trials.[102,129]

Expectations regarding treatment outcomes play a crucial role in pain management, aligning with level 2 strategies that leverage cognitive behavioral principles to enhance the efficacy of psychological interventions. Moreover, the studies reviewed suggest that leveraging positive expectations about treatment success at various stages can enhance the effectiveness of psychological and pharmacological interventions in managing pain.

INTERVENTION PRIMARILY TARGETING LEVEL 3 RESPONSES

Extended reality (XR), encompassing VR, augmented reality (AR), and mixed reality (MR), has emerged as a new tool in therapeutic digital applications, particularly for pain management. By creating immersive and interactive environments, XR technologies foster immersive sensory experiences designed to shift attention away from bodily experience via dissociative techniques (level 3), which can result in better pain management.

VR’s efficacy in reducing clinical pain has been studied across various chronic pain conditions. For example, Jones et al. found pain reduction during a 5-min VR session for chronic pain patients ($n = 30$).[130] A home-based VR program also showed significant pain-related outcome improvements starting after two weeks ($n = 179$).[131] A follow-up trial with a 56-day VR intervention demonstrated reduced pain intensity and interference post-treatment compared to the sham treatment, with benefits lasting up to three,[132] 18,[133] and 24 months.[134] The Food and Drug Administration cleared EaseVRx, a prescription-use immersive VR system for chronic pain management, on November 16, 2021. This system employs multisensory contexts, which are embedded in a VR headset, controller, and breathing amplifier. It offers 56 sessions over eight weeks, focusing on skills like relaxation and pain rehabilitation. Eccleston et al. investigated the effect of VR on chronic low back pain in a cohort of 42 participants, comparing digital therapeutics VR (DTxP) with sham and standard care, a critical comparator to fully appreciate the efficacy of VR. DTxP participants showed greater reductions in fear of movement and disability, with improvements sustained over five months.[135]

VR has also shown promise in enhancing rehabilitation of adults with chronic pain by promoting engagement in aerobic and strengthening exercises. Key outcomes include pain reduction, increased enjoyment and engagement, improved mood, reduced exercise effort perception, and optimized functional movements.[22] Sustained exercise engagement, facilitated by VR, is crucial for long-term pain reduction and functional improvement in chronic pain patients. While extensive research has focused on VR’s role in motivating exercise, few studies have explored its impact on the exercise experience itself.[136,137] Immersive VR and the use of virtual agents and avatars could increase motivation and engagement in exercise, which could be particularly relevant for pain management.

Evidence suggests that XR treatment modalities can decrease pain-related symptoms with small to medium effect size (SMD = 0.45[138]). The premise of these technologies is that they are hypothesized to provide immediate pain relief through distraction and relaxation techniques but also contribute to long-term pain management by incorporating behavioral therapy principles and rehabilitation exercises.

XR technologies primarily target level 3 responses in pain management by creating immersive sensory experiences that utilize dissociative techniques to shift attention away from pain, while also incorporating behavioral therapy principles and rehabilitation exercises for long-term pain management.

CONCLUSIONS

While various non-pharmacological interventions can be effective in the short term, their long-term benefits often depend on consistent practice.[17,23] Additionally, it remains unclear whether these interventions are effective across different chronic pain conditions and pain mechanisms. For instance, effectiveness may vary among patients with chronic overlapping pain conditions and co-existing psychiatric disorders. To enhance pain management strategies, further research is essential to explore the combined effects of these non-pharmacological interventions, understand their long-term impacts, and assess their effectiveness across diverse pain conditions and mental health contexts.This review prioritized interventions that are well established in clinical practice today. As a result, we did not include certain approaches, such as hypnosis, biofeedback, vagal nerve stimulation, and electrical acupuncture, among others.

A multifaceted approach that integrates cognitive, emotional, and sensory strategies has the potential to significantly enhance treatment efficacy. Central to this approach is the role of expectations, which can influence pain perception and the effectiveness of non-pharmacological interventions. Emerging technologies that leverage dissociative techniques, such as XR therapies, can help shift patients' focus from pain, fostering engagement in therapeutic activities, and highlight the value of immersive experiences in pain management. Furthermore, placebo effects underscore the impact of psychological factors, demonstrating that conditioning can produce substantial pain relief, especially when combined with pharmacological treatments. The CDC Clinical Practice Guideline for Prescribing Opioids for Pain emphasizes that multimodal approaches integrating psychological therapies with exercise can reduce long-term pain and disability more effectively than isolated interventions.[139]

In conclusion, a combination of interventions across the three levels of the embodied model is likely to be more effective for chronic pain reduction than focusing on a single intervention alone. Therefore, we recommend incorporating these non-pharmacological treatments into clinical practice, ideally as early as the onset of pharmacological treatment or even beforehand. This recommendation is grounded in the fact that these interventions generally have minimal or no side effects and hold significant potential to optimize pain management and promote well-being.

ACKNOWLEDGMENTS

Part of this research is supported by the National Institutes of Health (L.C.: R01AT01033, R01AT011347, 1R01DE025946, and R21DE032532; R.A.: K23HD104934).

DECLARATION OF INTERESTS

The authors declare no competing interests.

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