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Review

Clinical pain management: Current practice and recent innovations in research

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SUMMARY

Chronic pain affects one in five adults. It is not only a major cause of disability for individual patients but also a driver of costs for entire healthcare systems. Treatment of pain remains a challenge, and the use of opioids has further led to a concurrent opioid epidemic. In this review, we discuss current standard treatment options for chronic pain, including pharmacological, behavioral, and interventional treatments. In addition, we review ongoing research in different areas that will potentially unlock new therapies.

INTRODUCTION

In the United States, chronic pain, defined as pain lasting more than 3 months, is a devastating public health issue, affecting approximately 20% of adults and costing approximately $600 billion annually, more than any other medical condition.[1,2] Of the more than 50 million adults with chronic pain, 8% to 10% are estimated to have high-impact chronic pain, defined as pain that limits work or life activities.[1,3] In this review, we provide an overview of current treatment approaches for chronic pain and discuss select recent innovations in clinical pain research.

CURRENT TREATMENT APPROACHES

The International Association for the Study of Pain (IASP) defines pain as an "unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."[4] Chronic pain has traditionally been broadly categorized by pathophysiology as nociceptive and neuropathic pain (Table 1).[5] Nociceptive pain results from the activation of nociceptive receptors and ion channels in the peripheral nerves and is thought to be the consequence of traumatic insults to the peripheral tissue. In contrast, neuropathic pain is defined by IASP as pain "caused by a lesion or disease of the somatosensory nervous system."[6] While this broad categorization is helpful for guiding specific therapies as discussed further, it should be noted that quite a few pain syndromes have overlapping neuropathic and nociceptive components, such as low back pain that contains both myofascial and radicular symptoms, and many forms of cancer pain.[7,8] Recently, it has been recognized that certain pain conditions may also occur due to alterations in pain processing in the absence of clear evidence for actual or potential tissue or nerve damage, and this type of pain has recently been termed nociplastic pain.[9] A prominent example of nociplastic pain is fibromyalgia. Nociplastic pain can also occur in the context of nociceptive and/or neuropathic pain, as is seen in many widespread pain syndromes. The International Classification of Diseases 11th version includes a systematic classification of chronic pain into seven categories: chronic primary pain, chronic cancer-related pain, chronic postsurgical or posttraumatic pain, chronic neuropathic pain, chronic secondary or orofacial pain, chronic secondary visceral pain, and chronic secondary musculoskeletal pain.[10] Chronic primary pain is pain as a disease or health condition on its own, and nociplastic pain may underlie some of the similar pathophysiology. The other categories of pain are considered secondary pain syndromes, with pain as the result of an underlying disease. Chronic cancer-related pain is due to pain from the cancer itself or treatment for cancer. This pain can include neuropathic and nociceptive components. Chronic postsurgical pain or posttraumatic pain often includes neuropathic components. Chronic neuropathic pain can be subdivided into peripheral or central neuropathic pain. Chronic secondary or orofacial pain is due to an underlying illness, such as trauma or injury, dental disease, or temporomandibular disorders. Chronic secondary visceral pain arises from internal organs, including from the abdomen and pelvis. Chronic secondary musculoskeletal pain arises from the bones, joints, muscles, or soft tissues, and is often nociceptive in nature.

Regardless of the categories of pain, the current clinical paradigm has been to take a multimodal treatment approach for the management of chronic pain. This multimodal approach includes medications, restorative therapies, interventional therapies, behavioral therapies, and complementary and integrative health approaches (Table 2).[11] It should be noted that current approaches and guidelines typically focus on pain condition or symptoms,[12–15] and personalized or precision medicine for chronic pain remains a challenge.

Table 1. Three categories of pain pathophysiology

Categories	Examples	Location	Additional symptoms
Nociceptive	osteoarthritis, gout	typically localized	not typical
Neuropathic	pain diabetic peripheral neuropathy, posttherapeutic neuralgia	neuroanatomic distribution	paresthesias, numbness
Nociplastic	fibromyalgia	non-neuroanatomic distribution	fatigue, mood symptoms, cognitive symptoms, sleep disturbance

Note that pain may have more than one component.

Pharmacotherapies

Established agents for the management of nociceptive pain

Treatments for chronic, non-cancer, nociceptive pain are more well studied and supported by better available evidence than for other chronic pain conditions. Pharmacological options include non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, antidepressants, and opioids. In 2016, a systematic review and meta-analysis of randomized controlled trials (RCTs) evaluated NSAIDs for the treatment of non-specific chronic low back pain.[16] Six studies with 1,354 participants compared NSAIDs to placebo with a median follow-up of 56 days (IQR 13 to 91 days). The pooled mean difference in pain score on a 100 mm visual analog scale from baseline was −6.97 (95% confidence interval [CI] −10.74 to −3.19), favoring NSAIDs. Six additional studies with 1,161 participants compared NSAIDs to placebo with disability as the primary outcome, measured with the Roland Morris Disability Questionnaire, with a median follow-up of 84 days (IQR 42 to 105 days). The pooled mean difference in disability from baseline was −0.85 (95% CI −1.30 to −0.40), indicating efficacy for NSAIDs. Meanwhile, two smaller RCTs compared two types of non-selective NSAIDs against each other and found no significant differences. While most NSAIDs are taken in oral preparations, topical formulations are also available to avoid systemic side effects, particularly in patients with allergies to specific medications, gastroesophageal reflux disease, and cardiac disease. In 2016, a systematic review and meta-analysis of RCTs evaluated topical NSAIDs for chronic musculoskeletal pain.[17] This analysis identified six studies with 2,353 participants that compared topical diclofenac with placebo for osteoarthritis pain. The risk ratio for at least 50% pain relief after 6 to 12 weeks of treatment was 1.2 (95% CI 1.1–1.3) for treatment compared to placebo; the number needed to treat (NNT) was 9.8 (95% CI 7.1–16). Four studies with 2,573 participants examined the analgesic efficacy of topical ketoprofen. The risk ratio for at least 50% pain relief after 6 to 12 weeks of treatment was 1.1 (95% CI 1.01–1.2) for treatment compared to placebo, with an NNT of 6.9 (95% CI 5.4–9.3). These studies thus indicate that both systemic and topical NSAIDs are efficacious for nociceptive pain, whether pain is acute or chronic.

Acetaminophen is another agent that is often recommended for nociceptive pain, mostly due to its wide availability and favorable side effect profile at most low to moderate (<3 g daily) doses. However, a systematic review and meta-analysis from 2015 of RCTs of acetaminophen vs. placebo for non-specific spinal pain of any duration found no benefit of acetaminophen over placebo for spinal pain.[18] In contrast, in seven studies of hip or knee osteoarthritis with 3,153 participants, the pooled mean difference for pain intensity on a 0 to 100 scale was −3.7 (95% CI −5.5 to −1.9) in favor of acetaminophen at up to 3 months of treatment. The evidence for hip or knee osteoarthritis was considered high quality using the GRADE (grading of recommendations assessment, development) system but with small effect.

Antidepressants such as serotonin-norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs) are first-line agents for neuropathic pain (see further), but they have also been studied for pain conditions typically thought of as nociceptive in nature. In 2022, a systematic review and meta-analysis examined RCTs of antidepressants for hip and knee osteoarthritis pain.[19] In 9 RCTs with 2,038 participants, the pooled mean difference for pain intensity on a 10-point scale was −0.59 (95% CI −0.88 to −0.31) over 8 to 16 weeks in favor of antidepressants, though the results were not necessarily clinically meaningful due to the overall small therapeutic improvement in pain scores. However, in a separate analysis that examined six clinical trials with 1,904 participants that used a responder analysis, defined as at least 50% pain relief, 45.2% (95% CI 37.5%–54.9%) who received antidepressants and 28.6% who received placebo achieved pain relief, the NNT with antidepressants was found to be 6 (95% CI 4–11). Thus, antidepressants are likely helpful in at least a subset of patients with hip and knee osteoarthritis.

Opioids have been a mainstay for chronic pain management over the past several decades. The opioid epidemic arose in part from concerns that pain was being undertreated, and opioid prescribing increased as those medications were once marketed as analgesics with the false claim of low addictive potential.[27] Recent studies have begun to carefully examine the role of opioids in chronic pain management. In 2018, a systematic review and meta-analysis examined RCTs of opioids vs. any non-opioid for chronic non-cancer pain with at least one month of follow-up.[20] In 42 studies of 16,617 participants with follow-up for 3 months or longer, the pooled mean difference for pain reduction on a 10-point scale was −0.69 (95% CI −0.82 to −0.56) in favor of opioids over placebo, with a modeled risk difference for achieving a clinically important difference of 11.9% (95% CI 9.7%–14.1%). Fifty-one RCTs with 15,754 participants, meanwhile, showed a small benefit of opioids over placebo for physical function, but the change did not meet the criteria for the minimally clinically important difference. Further, nine RCTs of 1,431 participants showed no significant difference between opioids vs. NSAIDs for pain relief. Three RCTs of 246 participants showed no significant difference between opioids and

Table 2. Recent systematic reviews of pharmacologic, restorative, and behavioral approaches

Reference	Clinical population	Intervention	Number of studies	Sample size	Findings for pain intensity
Pharmacologic					
Enthoven et al., 2016[16]	chronic low back pain	non-steroidal anti-inflammatory (NSAIDs)	6 placebo-controlled RCTs	1,354	NSAIDs favored over placebo with median follow-up of 56 days
Derry et al., 2016[17]	chronic musculoskeletal pain due to osteoarthritis	topical NSAIDs	10 placebo-controlled RCTs	4,926	topical NSAIDs favored over carrier in studies of 6–12 weeks
Machado et al., 2015[18]	spinal pain	acetaminophen	3 placebo-controlled RCTs	3,344	no difference
Machado et al., 2015[18]	hip and knee osteoarthritis	acetaminophen	12 placebo-controlled RCTs	4,894	small benefit of acetaminophen over placebo
Leaney et al., 2022[19]	hip and knee osteoarthritis	antidepressants	9 placebo-controlled RCTs	2,122	non-clinically meaningful improvement for antidepressants vs. placebo. A small proportion of patients experience >50% pain relief with antidepressants.
Busse et al., 2018[20]	chronic non-cancer pain	opioids	9 RCTs of opioids vs. NSAIDs	1,431	no difference
Busse et al., 2018[20]	chronic non-cancer pain	opioids	3 RCTs of opioids vs. nortriptyline	246	no difference
Finnerup et al., 2015[21]	neuropathic pain	neuropathic medications	229 placebo-controlled RCTs	–	first-line treatments are gabapentin, pregabalin, serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs)
Farag et al., 2022[11]	fibromyalgia	amitriptyline, pregabalin, SNRIs	36 RCTs	11,930	duloxetine had greatest benefit over placebo
Restorative					
Geneen et al., 2017[22]	chronic non-cancer pain	physical activity/exercise	21 reviews (from which 264 studies exercise vs. no exercise)	19,642	inconsistent results for pain intensity but physical function improved with exercise
Gibson et al., 2019[23]	chronic pain, excluding headache	transcutaneous electrical nerve stimulation (TENS)	8 systematic reviews (51 RCTs)	2,895	due to very low quality of evidence, no conclusion could be drawn for short-term benefit
Johnson et al., 2022[24]	acute and chronic pain	TENS	381 RCTs of TENS vs. placebo or other treatments	24,532	benefit of TENS over placebo and other treatments during or immediately after TENS
Behavioral					
Williams et al., 2020[25]	chronic non-cancer pain, excluding headache	cognitive behavioral therapy (CBT)	23 RCTs of CBT vs. active control	3,235	small benefit of CBT over active control
Williams et al., 2020[25]	chronic non-cancer pain, excluding headache	behavioral therapy (BT)	8 RCTs of BT vs. active control	647	no difference
Williams et al., 2020[25]	chronic non-cancer pain, excluding headache	acceptance and commitment therapy (ACT)	5 RCTs of ACT vs. active control	443	no difference
Complementary					
Vickers et al., 2018[26]	musculoskeletal pain, chronic headache	acupuncture	39 RCTs of acupuncture vs. sham or no treatment	20,827	benefit of acupuncture over sham or no treatment

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nortriptyline for pain relief. Notably, these trials excluded patients with substance use disorders or other mental health disorders. Overall, the results from these studies raise the question of superior analgesic efficacy of opioid medications for chronic nociceptive pain. Despite this, approximately 22% of adults with chronic pain in the United States used prescription opioids in the past 3 months, based on data from the 2019 National Health Interview Survey.[28] Guidelines for prescribing opioids have been published, notably from the United States Centers for Disease Control and Prevention in 2016 and updated in 2022.[29,30] After the release of the 2016 guidelines, there were concerns for misapplication of the guidelines and unintended consequences, such as the use of hard dose limits or abrupt tapering of opioids.[31,32] For example, dose tapering after long-term opioid therapy was associated with the risk of overdose, mental health crisis, and fewer primary care visits.[33,34] The updated 2022 guidelines recommend an individualized, patient-centered approach.

Pharmacological management of neuropathic pain

In contrast to our knowledge of the molecular mechanisms and neural circuits for nociceptive pain, our understanding of the basic pathophysiology of chronic neuropathic pain remains inadequate, leading to fewer treatment options. In 2015, the Neuropathic Pain Special Interest Group of the IASP conducted a systematic review and meta-analysis of randomized, double-blind studies of oral and topical pharmacologic therapies for neuropathic pain, including postherpetic neuralgia, polyneuropathy, postamputation pain, posttraumatic and postsurgical neuropathic pain, and complex regional pain syndrome type II.[21] Based on the review, SNRIs, TCAs, and gabapentinoids (e.g., gabapentin and pregabalin) were recommended as first-line treatments for neuropathic pain. Capsaicin 8% patches, lidocaine patches, and tramadol were recommended as second-line treatments, and third-line treatments were botulinum toxin A and stronger opioids. Overall, treatment effects for even first-line agents were considered modest, with an NNT of 3.6 (95% CI 3–4.4) for TCAs, 6.4 (95% CI 5.2–8.4) for SNRIs, 6.3 (95% CI 5–8.3) for gabapentin, and 7.7 (95% CI 6.5–9.4) for pregabalin. Side effects of TCAs include anticholinergic and sedative effects. Common side effects of SNRIs include gastrointestinal discomfort and insomnia. Side effects of gabapentinoids include sedative effects, gastrointestinal discomfort, and peripheral edema. In line with these research findings, current practice has largely incorporated SNRIs, TCAs, and particularly gabapentinoids as key elements of a multimodal regimen for neuropathic pain.

Pharmacological management of nociplastic pain

Nociplastic pain is the least understood of all chronic pain conditions, even as it is thought to involve maladaptive circuit mechanisms in the central nervous system.[6] Nociplastic pain is typically treated with neuropathic pain medications. Fibromyalgia is the prototypic nociplastic pain condition. Fibromyalgia is characterized by diffuse musculoskeletal pain without obvious anatomic or neurological distributions, depression, fatigue, and sleep disturbance.[35] Unmanaged depressive symptoms predict poor outcomes during treatment for fibromyalgia, so depression is an important comorbidity to address in the treatment of chronic nociplastic pain.[36] Likewise, poorer sleep quality is associated with greater number of symptoms, including pain, memory complaints, anxiety, and concentration difficulties, underlying the importance of also addressing sleep for nociplastic conditions such as fibromyalgia.[37] In 2022, a systematic review and network meta-analysis examined RCTs for pharmacotherapies for fibromyalgia, specifically amitriptyline, duloxetine, pregabalin, and milnacipran.[11] Presenting effect sizes as standardized mean differences (SMDs), in 35 studies of 11,423 participants, duloxetine was associated with the highest pain reduction over placebo (SMD −0.33, 95% CI −0.36 to −0.30). Sixteen studies with 4,452 patients assessed sleep, and amitriptyline was associated with the greatest improvements in sleep compared to placebo (SMD −0.97, 95% CI −1.10 to −0.83). Duloxetine and pregabalin were associated with the greatest improvements in symptoms of depression, whereas amitriptyline and pregabalin were associated with the greatest improvements in fatigue. Consistent with these results, SNRIs, TCAs, and gabapentinoids are considered core elements in the therapeutic regimen for nociplastic pain, further supplemented by acetaminophen. Due to its tolerability, gabapentinoids have often been the first-line treatment. Unfortunately, nociplastic pain continues to show a relatively high degree of treatment resistance, despite limited success with available anti-neuropathic agents.

Ketamine, an emerging therapeutic option for refractory chronic pain

Ketamine is well known as an anesthetic and analgesic agent for over half a century. It is Food and Drug Administration (FDA)-approved for treating acute pain and for depression and is usually used as an infusion at low doses (0.3–0.6 mg/kg).[38–42] While its analgesic effects are typically short lived, its antidepressant and anxiolytic effects can last for several weeks. A number of studies have examined the efficacy of ketamine for postsurgical pain, and at least in the immediate postoperative period, it has shown efficacy in providing pain relief, reducing opioid use, and improving rehabilitation.[41,43–46] In addition to its use in perioperative setting, there is also positive data for ketamine in treating traumatic pain in emergency rooms.[47,48]

Ketamine has a multitude of analgesic mechanisms, through inhibition of a number of receptors including sodium channels. Its most pronounced action, however, is antagonism of N-methyl-D-aspartate receptors that are known to play a key role in chronic pain physiology; ketamine has been studied for a variety of chronic pain conditions. For example, perioperative infusion of ketamine has been shown to reduce the incidence and severity of chronic postoperative pain.[43,49,50] Ketamine has also been studied in complex regional pain syndrome (CRPS) and fibromyalgia. In RCTs, low-dose infusions in several consecutive days lowered pain scores for up to 12 weeks and in some cases even 6 months[51–53] Ketamine at low doses (0.3–0.5 mg/kg) has demonstrated acute analgesic effect in fibromyalgia; however, its effects may not be enduring.[54,55] Other chronic pain conditions that have been treated by ketamine include refractory headaches and cancer pain, with sometimes conflicting data and need for further higher quality studies.[56–59]

Non-pharmacologic approaches

Restorative therapies include physiotherapy, exercise, and transcutaneous electric nerve stimulation (TENS). An overview of Cochrane systematic reviews of RCTs of physical activity

and exercise for chronic pain was published in 2017.[22] Overall, it was noted that although physical exercise did not consistently change pain scores per se, it did significantly improve physical function. The overall quality of currently available evidence was considered low using the GRADE system, however, due to small sample sizes and limited follow-up periods in these studies. An overview of Cochrane systematic reviews of RCTs of TENS for chronic pain was published in 2019.[23] Due to the low quality of evidence based on the GRADE system, the authors were unable to conclude whether TENS was beneficial for pain. A more recent systematic review included RCTs of TENS for any pain with a primary outcome of pain reduction during or immediately after TENS.[24] In 91 RCTs of 4,841 participants, pain was lower with TENS compared to placebo (SMD −0.96, 95% CI −1.14 to −0.78); the evidence was considered of moderate quality based on the GRADE system. In 61 studies of 3,155 participants, pain was lower in TENS compared with other standard-of-care treatments (SMD −0.72, 95% CI −0.95 to −0.50); however, this evidence was considered of low quality.

Patients with chronic pain frequently experience mental health problems. The comorbidities of chronic pain and mood disorders in particular are highly prevalent.[60,61] Psychological and behavioral approaches are especially relevant in the biopsychosocial model of pain. A systematic review of RCTs for in-person delivered psychological treatments for chronic pain, excluding headache and cancer pain, was published in 2020.[25] Types of interventions included cognitive behavioral therapy (CBT), behavioral therapy (BT), and acceptance and commitment therapy (ACT). CBT focuses on reducing maladaptive thought patterns and improving coping skills. In contrast, BT focuses on methods to reduce maladaptive pain behaviors and increase adaptive behaviors. ACT is a type of CBT that focuses on accepting thoughts and feelings. CBT was the most commonly practiced intervention. In 23 studies of 3,235 participants, CBT had a small but consistent benefit for pain (SMD −0.09, 95% CI −0.17 to −0.01). CBT also had small benefits for disability and distress. The evidence was considered moderate in quality using the GRADE system. An analysis of eight studies of 647 participants of BT compared to active control, meanwhile, showed no difference for pain, disability, or distress. Five studies of 443 participants of ACT compared to active control also showed no difference for pain, disability, or distress. The evidence for BT and ACT was considered low-to-moderate quality using the GRADE system.

Complementary and integrative health approaches include mind-body interventions, acupuncture, and yoga. A systematic review and meta-analysis of RCTs was conducted of acupuncture vs. sham or no acupuncture for non-specific spinal pain, shoulder pain, chronic headache, or osteoarthritis. In 39 trials of 20,827 participants, effect sizes for acupuncture were close to 0.5 compared to no acupuncture and 0.2 compared to sham.[26] Therefore, there is likely a role for these low-risk, integrative health approaches to complement current pharmacological and behavioral treatments.

Interventional therapies

Interventional pain procedures may be an important part of multimodal treatment for pain, depending on the pain condition and patient comorbidities. Interventional procedures vary in complexity. Options for spine pain include epidural steroid injections, radiofrequency medial branch neurotomy, basivertebral nerve ablation, vertebral augmentation, and neuromodulation (including peripheral nerve stimulation and spinal cord stimulation [SCS]). For instance, for low back pain, studies have shown that lumbar epidural steroid injections are effective in the short and intermediate terms for relieving radicular pain due to disc herniation and possibly spinal stenosis.[62,63] Meanwhile, lumbar medial branch radiofrequency neurotomy can be effective in patients who present with relatively specific facet-mediated pain.[64] Options for joint pain include joint injections, regenerative therapies, and radiofrequency neurotomy. Certain neuropathic pain conditions may also be treated with sympathetic nerve blocks, peripheral nerve blocks, and neuromodulation, although the evidence for long-term benefits for some of these treatments remains somewhat mixed.

For patients who fail back surgery and/or fail other conservative pharmacological treatments and injections, SCS is an FDA-approved treatment.[65,66] This treatment modality is based on the concept of gate control theory, by which interneurons in the dorsal horn of the spinal cord can be activated by inputs from peripheral sensory neurons to inhibit excitatory neurons of the spinal cord.[67] External electric stimulation in the epidural space has been hypothesized to simulate the firing of interneurons in the spinal cord. SCS leads are placed to provide coverage of the body area where patient's pain occurs.[68] SCS typically operates in the frequency range of 40–60 Hz.[68]

Studies have generally confirmed the analgesic efficacy for SCS, where >50% of the patients have experienced pain relief within an average follow-up of 2 years, especially in patients who experience cervical or lumbosacral radiculitis, failed back surgery syndrome, diabetic peripheral neuropathy, and ischemic chest pain.[68–70] Despite its efficacy, however, SCS also has a number of side effects. A common side effect is paresthesia, which may become bothersome to patients over time, limiting long-term compliance of the device. Recent advances in ultra-high frequency stimulation (10,000 Hz) and burst stimulation have shown limited evidence for limiting paresthesia effects while still providing superior pain relief.[71–74] As an invasive therapy, SCS is associated with risks of infection. In addition, due to the high mobility of spine, lead displacement can occur, with incidence as high as 30% in some reports.[75] Overall, SCS is reserved for pain syndromes that are refractory and severe.

RECENT TRENDS AND INNOVATIONS IN CLINICAL PAIN RESEARCH

Despite the current available treatment options, many patients continue to suffer from pain. While there have been advances in understanding pain pathophysiology, unfortunately there have been fewer advances in novel therapeutics in the past three decades. For studies of investigational pain drugs, the probability of advancing from phase 2 to phase 3 studies was approximately 28%, and the likelihood of approval for drugs that underwent phase 3 studies in the United States was approximately 57%.[76] Possible reasons include difficulty in translating mechanistic findings from lower order animals (rodents) to humans,

inadequate sample size, lack of assay sensitivity, high placebo effect, and heterogeneous participant population. Pain is subjective, and in the biopsychosocial model of pain, pain is a complex experience encompassing biological, social, and psychological components. Thus, there is also difficulty in assessing pain clinically, and the heterogeneity of symptoms further complicates trial design. In the following paragraph, we highlight select recent innovations in clinical pain research.

Novel pharmacologic agents for pain

One notable success has been the approval of drugs for migraine targeting the calcitonin gene-related peptide (CGRP) peptide or receptor after the discovery of CGRP's role in migraine.[77,78] Recently, however, there has been a renewed focus on analgesic discovery in both academia, driven by the NIH Helping to End Addiction Long-term Initiative, as well as in the biotechnology industry, as newer targets have emerged that are going through vigorous clinical trials.

Voltage-gated sodium channels are important for the generation and propagation of action potentials. The α subunit is primarily responsible for the function of voltage-gated sodium channels. In humans, there are 9 isoforms, 7 of which are in neural tissues. Non-selective sodium channel blockers such as local anesthetics are helpful for pain but their use is limited by side effects due to blockade of sodium channels in central nervous system and cardiac tissues when given systemically. Among sodium channels, $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$ are primarily located in peripheral sensory neurons and are involved in nociception as evidenced by studies of gain-of-function and loss-of-function mutations in humans.[79–81] These channels thus have been investigated as potential therapeutic targets. A 2020 review provided a summary of clinical trials at the time of publication of compounds targeting $Na_v1.7$ and $Na_v1.8$.[82]

Since 2020, VX-548, an oral, highly selective $Na_v1.8$ inhibitor, was studied in two double-blind, placebo-controlled, phase 2 RCTs for postoperative pain.[83] In one trial, 303 adults who underwent abdominoplasty and reported a pain score of at least 4 on the Numeric Rating Scale (NRS) within 4 h after completion of surgery were randomized in a 1:1:1 ratio to one of the following regimens for 48 h: 100 mg VX-548 followed by 50 mg every 12 h, 60 mg VX-548 followed by 30 mg every 12 h, 5 mg hydrocodone and 325 mg acetaminophen every 6 h, or placebo every 6 h. Ibuprofen at 400 mg was allowed as a rescue analgesic. In the other trial, 274 adults who underwent a primary unilateral bunionectomy with a distal first metatarsal osteotomy and fixation under regional anesthesia and reported a pain score of at least 4 on the NRS within 9 h after the removal of a popliteal sciatic nerve catheter were randomized in a 2:2:1:2:2 ratio to one of the following regimens for 48 h: 100 mg VX-548 followed by 50 mg every 12 h, 60 mg VX-548 followed by 30 mg every 12 h, 20 mg VX-548 followed by 10 mg every 12 h, 5 mg hydrocodone and 325 mg acetaminophen every 6 h, or placebo every 6 h. Ibuprofen was again allowed as a rescue analgesic.

The primary endpoint for both VX-548 trials was the time-weighted sum of the pain intensity difference (SPID) over 48 h of VX-548 vs. placebo. Using last observation carried forward for imputation analysis for those who discontinued study medications, the least-square mean difference in the SPID48 for the high-dose VX-548 and placebo was 37.8 (95% CI 9.2, 66.4) in the abdominoplasty trial and 36.8 (95% CI 4.6, 69) in the bunionectomy trial, with higher values representing greater reductions in pain. As a secondary endpoint, using a reduction in pain of at least 30% in the NRS after 48 h as a threshold for success, 61% (95% CI 50%, 72%) in the high-dose VX-548 group, 59% (95% CI 48%, 71%) in the middle-dose VX-548 group, 54% (95% CI 43%, 65%) in the hydrocodone-acetaminophen group, and 48% (95% CI 37%, 59%) in the placebo group met this threshold in the abdominoplasty trial. For the bunionectomy trial, 83% (95% CI 74%, 93%) in the high-dose VX-548 group, 63% (95% CI 51%, 75%) in the middle-dose VX-548 group, 76% (95% CI 61%, 90%) in the low-dose VX-548 group, 68% (95% CI 57%, 80%) in the hydrocodone-acetaminophen group, and 58% (95% CI 46%, 70%) in the placebo group met this threshold. Most side effects were mild or moderate, with the incidence of headache and constipation higher in the VX-548 groups than placebo. Limitations of the study include a lack of reporting on the use of rescue medication and the enrollment of a majority of women and a majority of White participants. Though the studies' primary outcomes were assessed in comparison to placebo, the results were promising as an alternative to opioids. Additional results are awaiting publication from two phase 3 RCTs in postoperative pain that were recently completed (NCT05553366 and NCT05558410). Although these studies focused on acute pain, a phase 2 RCT in painful diabetic peripheral neuropathy was recently completed (NCT05660538), and a phase 2 RCT in lumbar radiculopathy is ongoing (NCT06176196). Results from these trials may support the use of this novel agent for treating chronic neuropathic pain.

Tetrodotoxin (TTX), a neurotoxin found in pufferfish and other animals, blocks certain voltage-gated sodium channels. TTX-sensitive voltage-gated sodium channels such as $Na_v1.7$ have been implicated in chronic pain.[79] A double-blind, placebo-controlled phase 2 RCT evaluated the safety and tolerability of multiple doses of TTX in chemotherapy-induced chronic neuropathic pain (CINP).[84] Participants with taxane- or platinum-based CINP were randomized in a 1:1:1:1:1 ratio to receive placebo twice a day, TTX 7.5 μg twice a day, TTX 15 μg twice a day, TTX 30 μg once a day, or TTX 30 μg twice a day, for four days via subcutaneous injection. The primary efficacy endpoint was a change in NRS score at 3 to 4 weeks post treatment from baseline. One hundred twenty-one participants completed the study. The mean change from baseline was greatest in the 30 μg once a day group (-1.7 ± 2.3), followed by the TTX 30 μg twice a day group (-1.5 ± 1.8), with a mean time to reach peak pain relief of about 3 weeks. The most frequent adverse events in the TTX groups were oral paresthesia and oral hypoesthesia. Two participants in the TTX group withdrew due to vertigo. A phase 2 RCT of TTX at 30 μg injected subcutaneously twice daily for 4 days vs. placebo is ongoing for CINP (NCT05359133).

Thus, recent and ongoing studies on modulators for $Na_v1.7$ and $Na_v1.8$ will likely generate data that may potentially result in newer analgesics without addiction or abuse potential.

Innovations in behavioral therapies

In addition to innovations in the pharmacological space, refinements in behavioral therapies continue to be studied. Pain

reprocessing therapy (PRT) was developed based on the understanding of pain itself as a primary disease process. In a randomized trial, 151 participants with chronic, primarily axial low back pain were randomized to PRT vs. placebo with an open-label subcutaneous saline injection to the back vs. usual care.[85] Participants underwent a baseline session with functional magnetic resonance imaging (fMRI) and were then randomized into treatment or control group. PRT consisted of a 1-h telehealth session with a physician, assessing nociplastic components of pain and providing education on pain processes, including centralization of pain in those thought to have this component. Participants then completed 1-h therapy sessions twice weekly for 4 weeks. The primary outcome was average pain over the last week based on the Brief Pain Inventory Short Form assessed at 1 month after the baseline session. At 1 month, participants in the PRT group reported a mean pain reduction of 1.79 (95% CI −1.65 to −0.71; $p < 0.001$) compared to placebo and a reduction of 2.4 (95% CI −2.28 to −1.32; $p < 0.001$) compared to usual care. Using an intention-to-treat analysis, 66% (95% CI 53%, 79%) in the PRT vs. 20% (95% CI 30%, 87%) in the placebo group vs. 10% (95% CI 2%, 18%) in the usual care group reported no-to-minimal pain at 1 month. At 1-year follow-up, 52% in the PRT group, 27% in the placebo group, and 16% in the usual care group reported no-to-minimal pain. In the PRT group, fMRI showed reduced evoked pain-related activity in the anterior prefrontal cortex and anterior midcingulate cortex compared to placebo, compatible with mechanisms of decreased central pain-aversive processing. The main limitation of this study is that its study population skewed to a relatively younger (mean [SD] age of 41.1 [15.6] years), well-educated, and White population. Studies of remotely delivered PRT are currently underway for veterans with chronic spinal pain (NCT06406699) and for racially/ethnically diverse adults with chronic back pain (NCT05820204).

Access and cost can be a barrier to behavioral therapies, and thus remotely delivered interventions are an area of active research. In a pilot, randomized study of adults with knee or hip osteoarthritis, 113 participants were assigned to an automated, internet-based version of pain coping skills training called PainCOACH vs. usual care.[86] The PainCOACH program consisted of eight self-direct modules, to be completed at a rate of one per week. Adherence was high, with 91% of participants randomized to PainCOACH completing all modules. Though not powered to assess efficacy, there were improvements in pain from the prior month. Pain was assessed at 8 weeks after the onset of treatment and with the pain subscale of the Arthritis Impact Measurement Scale 2 in the PainCOACH group vs. usual care, showing an effect size of 0.33. PainCOACH has also been studied in combination with 7 videoconferencing sessions with a physical therapist for home exercise in an RCT of 148 adults with chronic knee pain vs. internet-based educational material.[87] The primary outcomes were pain during walking and physical function measured with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) at 3 months. Pain during walking decreased from 6.1 (SD 1.4) to 3.3 (2.2) in the intervention group and from 6.2 (1.3) to 5.1 (2.0) in the control group at 3 months. Physical function on the WOMAC decreased from 33.1 (8.0) to 18.3 (10.7) in the intervention group and from 32.5 (8.3) to 27.6 (11.7) in the control group at 3 months. These results were similar at 9 months. PainCOACH has recently been updated, and the new version is known as PainTRAINER. PainTRAINER continues to be studied in other outpatient and home settings. An RCT of PainTRAINER vs. one-on-one delivered remote CBT vs. usual care is being conducted in participants with high-impact chronic pain and will provide valuable information about the clinical and cost-effectiveness of these online, remote interventions (NCT04523714).[88]

Virtual reality (VR)-delivered therapy is an attractive low-risk, behavioral intervention for chronic pain. In a recent RCT, 1,093 adults with chronic low back pain were assigned to skills-based VR or sham VR.[89] The skills-based VR program consisted of 56 immersive experiences integrating skills such as biofeedback, mindfulness, cognition and emotion regulation, and pain education. Overall, the total number of completed VR experiences was low. At 1 year, the skills-based VR group reported a decrease in Brief Pain Inventory pain intensity score of 1.7 (SD 2.1) from baseline compared to a 1.2 (SD 2.0) decrease in the sham group ($p < 0.001$). In a responder analysis with success defined as a 2-point reduction in pain intensity from baseline, 52% of the VR group and 42% of the sham group were responders.

Innovations in interventional therapies

Deep brain stimulation (DBS) delivers electric current to the brain through implanted leads. Two open-label trials in the United States were unsuccessful.[90] Recently, data from an ongoing clinical trial (NCT03029884) on DBS for chronic neuropathic pain showed that invasive neural recordings provided reliable prediction of chronic pain states, which can potentially drive closed-loop stimulation.[91]

Noninvasive brain stimulation techniques include repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). rTMS uses magnetic fields to induce electric currents to modulate cortical activity. A systematic review published in 2018 did not find clinically meaningful effects of single-dose or multiple-dose rTMS on chronic pain.[92] Recent studies have been conducted to optimize targets and dose. In a multicenter, double-blind, placebo-controlled randomized trial, 149 participants with chronic peripheral neuropathic pain were assigned to rTMS delivered to the primary motor cortex (M1) contralateral to site of pain, a main target for chronic pain; rTMS delivered to the left dorsolateral prefrontal cortex (DLPFC), the conventional target for depression; or sham rTMS.[93] The rTMS protocol consisted of 15 rTMS sessions over 22 weeks. Each session consisted of 30 trains of TMS pulses delivered at 10 Hz for 10 s with a 20 s intertrain interval for a total duration of 15 min. The primary outcome was change in average pain intensity from the Brief Pain Inventory over the 22 weeks of treatment and at week 25 (Group × Time interaction). For the primary outcome, M1-rTMS was more effective than sham, with a significant effect of time. DLPFC-rTMS had the same efficacy as sham rTMS. At 25 weeks, the decrease in average pain intensity was 1.5 (0.8) for the M1-rTMS group vs. 0.9 (2.2) and 0.8 (1.5) for the DLPFC-rTMS and sham groups, respectively. The most common side effects were headache and pain at the stimulation site. tDCS uses low-intensity electric current to modulate cortical activity. A systematic review in 2018

did not find an effect compared to sham; the evidence by GRADE was considered very low to low quality.[92] Thus, more studies on noninvasive brain stimulation techniques are needed.

Use of digital endpoints in pain clinical trials

Pain is a multidimensional experience, and traditionally, pain clinical trials have used patient-reported outcomes (PROs) to assess domains of pain, including pain intensity, physical function, mood, and participant global impression of change.[94] Such reporting system relies on participants' recall over a given period, which may be subject to various biases. Thus, new digital endpoints have emerged as an area of research for pain clinical trials. Ecological momentary assessment is a self-report methodology that assesses how participants are doing in their daily lives at multiple time points, which can reduce recall bias and increase ecological validity. This method has been used in chronic pain research since the 1980s, first using paper diaries and more recently using smartphones and smartwatches to input data.[95] To further decrease the burden for participants, recently there has been interest in using passively collected data from wearables to objectively track pain outcomes.

In a sub-study of the multicenter, single-arm, open-label REALITY (Long-Term Real-World Outcomes Study on Patients Implanted with a Neurostimulator) study, 15 participants with back pain or CRPS answered PROs during in-person visits at baseline and 3 and 6 months after SCS implant and monthly via a smartphone application.[96] Pain intensity was assessed daily using the smartphone application, and physical activity and cardiac measures were collected with a smartwatch, including data such as step counts, walking distance, heart rate, and heart rate variability. Median compliance for using the smartphone application, defined as completing PROs at least 3 times during the baseline and monthly for 6 months, was 88.8%. Median compliance for using the smartwatch was 84.7%, defined as wearing the watch for at least 7 days during the baseline period and 180 days after SCS implant. Using data collected passively through the smartwatch as well as data from the SCS controller and weather data, a random forest machine learning model was able to predict mild, moderate, and severe levels of pain with accuracy of 0.768 ± 0.012. Machine learning models were also able to predict other PRO categories, including Pain Catastrophizing Scale, several domains of PROMIS-29, and Oswestry Disability Index with high accuracy. While this study is limited by the relatively small sample size, it shows the feasibility of using digital devices to measure chronic pain in the home settings that can be tried in future studies of larger sample sizes. Other studies have examined the use of wearable measurements of daily activity on knee arthritis, non-specific spinal pain, and postoperative pain across different age ranges, and when combined with machine learning, some of these measures have been quite successful in predicting pain and track treatment outcomes in smaller cohorts.[97–101]

In addition to daily recorded activity, speech analysis has already been used to identify mood disorders, including post-traumatic stress disorder and depression, and its use is being explored for the detection of pain.[102,103] In a prospective, observational study of 60 patients with spinal disease who consulted with a neurosurgery department, patients used a smartphone application to report on pain intensity daily. Weekly, speech recording was done of patients reading from a standardized passage from Charles Dickens. A K-nearest neighbors machine learning model predicted pain intensity with an accuracy of 0.71.[104] Limitations of the study include small sample size. In the future, such digital endpoints may advance clinical trials, providing objective methods to capture treatment effects in real time.

Use of neuroimaging biomarkers in pain clinical trials

Subjective self-reports can further be complemented with objective neuroimaging and neurophysiological measurements. There is active research over the last three decades on the use of positron emission tomography scan, MRI including fMRI, and more recently electroencephalography to assess brain functions in the context of acute and chronic pain. These studies already point out specific regions in the brain (e.g., rostral and dorsal anterior cingulate cortex, insular cortex, etc.) that play critical roles in processing and regulating sensory and affective components of pain, but more recently, they are showing the roles of functional connectivity between different regions for the maintenance of chronic pain (e.g., corticostriatal circuit, etc.).[91,105–108] Such research can provide objective biomarkers for assessing the therapeutic effects of treatment and identify potential brain circuit targets for neuromodulation. Meanwhile, large genetic and genomic studies in patients with chronic pain, in addition to studies in animal models of chronic pain, can reveal novel molecular targets (e.g., α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptors, hyperpolarization-activated cyclic nucleotide-gated channels, etc.) for non-addictive pharmacological therapies.[109,110] Combining neuroimaging with genomic studies will enable us to develop a range of molecular, cellular, and systems neuroscience biomarkers with well-defined mechanistic roles.[111,112] These biomarkers will allow clinicians to take a precision-medicine approach to chronic pain, by making more accurate symptom- and disease-specific diagnosis and pairing with personalized treatment plan, predicting disease progression, and monitoring treatment responses.[113–115] For example, neuroimaging biomarkers may be used for enrichment of clinical trials, identifying those thought to have the most potential benefit from a therapeutic. Biomarkers can also be used as a measure of response.

CONCLUSIONS

Chronic pain remains a challenge to treat. Despite the armamentarium of available therapies, patients often experience inadequate pain relief. Currently, a "trial and error" approach remains typical in clinical settings, potentially leading to side effects and delays in adequate pain treatment, and more personalized, precision-medicine approaches are urgently needed. There are promising new therapeutics for pain encompassing pharmacologic agents as well as behavioral and interventional therapies. Incorporation of real-time digital endpoints may improve efficiency in assessing outcomes in clinical trials. Use of biomarkers and pharmacogenomics may also guide targeted treatments in the future.

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AUTHOR CONTRIBUTIONS

Conceptualization and writing, J.W. and L.V.D.

DECLARATION OF INTERESTS

J.W. is a cofounder and scientific advisor for Pallas Technologies, Inc., and is an inventor of a pending US patent application of pain treatment technology.

REFERENCES

1. Yong, R.J., Mullins, P.M., and Bhattacharyya, N. (2022). Prevalence of chronic pain among adults in the United States. Pain *163*, e328–e332. https://doi.org/10.1097/j.pain.0000000000002291.
2. Gaskin, D.J., and Richard, P. (2012). The economic costs of pain in the United States. J. Pain *13*, 715–724. https://doi.org/10.1016/j.jpain.2012.03.009.
3. Dahlhamer, J., Lucas, J., Zelaya, C., Nahin, R., Mackey, S., DeBar, L., Kerns, R., Von Korff, M., Porter, L., and Helmick, C. (2018). Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults - United States, 2016. MMWR Morb. Mortal. Wkly. Rep. *67*, 1001–1006. https://doi.org/10.15585/mmwr.mm6736a2.
4. Raja, S.N., Carr, D.B., Cohen, M., Finnerup, N.B., Flor, H., Gibson, S., Keefe, F.J., Mogil, J.S., Ringkamp, M., Sluka, K.A., et al. (2020). The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain *161*, 1976–1982. https://doi.org/10.1097/j.pain.0000000000001939.
5. Cohen, S.P., Vase, L., and Hooten, W.M. (2021). Chronic pain: an update on burden, best practices, and new advances. Lancet *397*, 2082–2097. https://doi.org/10.1016/S0140-6736(21)00393-7.
6. Fitzcharles, M.A., Cohen, S.P., Clauw, D.J., Littlejohn, G., Usui, C., and Häuser, W. (2021). Nociplastic pain: towards an understanding of prevalent pain conditions. Lancet *397*, 2098–2110. https://doi.org/10.1016/S0140-6736(21)00392-5.
7. Foster, N.E., Anema, J.R., Cherkin, D., Chou, R., Cohen, S.P., Gross, D.P., Ferreira, P.H., Fritz, J.M., Koes, B.W., Peul, W., et al. (2018). Prevention and treatment of low back pain: evidence, challenges, and promising directions. Lancet *391*, 2368–2383. https://doi.org/10.1016/S0140-6736(18)30489-6.
8. Doan, L.V., Yoon, J., Chun, J., Perez, R., and Wang, J. (2023). Pain associated with breast cancer: etiologies and therapies. Front. Pain Res. *4*, 1182488. https://doi.org/10.3389/fpain.2023.1182488.
9. Kosek, E., Cohen, M., Baron, R., Gebhart, G.F., Mico, J.A., Rice, A.S.C., Rief, W., and Sluka, A.K. (2016). Do we need a third mechanistic descriptor for chronic pain states? Pain *157*, 1382–1386. https://doi.org/10.1097/j.pain.0000000000000507.
10. Treede, R.D., Rief, W., Barke, A., Aziz, Q., Bennett, M.I., Benoliel, R., Cohen, M., Evers, S., Finnerup, N.B., First, M.B., et al. (2019). Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). Pain *160*, 19–27. https://doi.org/10.1097/j.pain.0000000000001384.
11. Farag, H.M., Yunusa, I., Goswami, H., Sultan, I., Doucette, J.A., and Eguale, T. (2022). Comparison of Amitriptyline and US Food and Drug Administration-Approved Treatments for Fibromyalgia: A Systematic Review and Network Meta-analysis. JAMA Netw. Open *5*, e2212939. https://doi.org/10.1001/jamanetworkopen.2022.12939.
12. Brophy, R.H., and Fillingham, Y.A. (2022). AAOS Clinical Practice Guideline Summary: Management of Osteoarthritis of the Knee (Nonarthroplasty), Third Edition. J. Am. Acad. Orthop. Surg. *30*, e721–e729. https://doi.org/10.5435/JAAOS-D-21-01233.
13. Macedo, F., Annaswamy, T., Coller, R., Buelt, A., Glotfelter, M.A., Heideman, P.W., Kang, D., Konitzer, L., Okamoto, C., Olson, J., et al. (2024). Diagnosis and Treatment of Low Back Pain: Synopsis of the 2021 US Department of Veterans Affairs and US Department of Defense Clinical Practice Guideline. Am. J. Phys. Med. Rehabil. *103*, 350–355. https://doi.org/10.1097/PHM.0000000000002356.
14. Harden, R.N., McCabe, C.S., Goebel, A., Massey, M., Suvar, T., Grieve, S., and Bruehl, S. (2022). Complex Regional Pain Syndrome: Practical Diagnostic and Treatment Guidelines. Pain Med. *23*, S1–S53. https://doi.org/10.1093/pm/pnac046.
15. Bril, V., England, J., Franklin, G.M., Backonja, M., Cohen, J., Del Toro, D., Feldman, E., Iverson, D.J., Perkins, B., Russell, J.W., et al. (2011). Evidence-based guideline: Treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology *76*, 1758–1765. https://doi.org/10.1212/WNL.0b013e3182166ebe.
16. Enthoven, W.T.M., Roelofs, P.D.D.M., Deyo, R.A., van Tulder, M.W., and Koes, B.W. (2016). Non-steroidal anti-inflammatory drugs for chronic low back pain. Cochrane Database Syst. Rev. *2*, CD012087. https://doi.org/10.1002/14651858.CD012087.
17. Derry, S., Conaghan, P., Da Silva, J.A.P., Wiffen, P.J., and Moore, R.A. (2016). Topical NSAIDs for chronic musculoskeletal pain in adults. Cochrane Database Syst. Rev. *4*, CD007400. https://doi.org/10.1002/14651858.CD007400.pub3.
18. Machado, G.C., Maher, C.G., Ferreira, P.H., Pinheiro, M.B., Lin, C.W.C., Day, R.O., McLachlan, A.J., and Ferreira, M.L. (2015). Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. BMJ *350*, h1225. https://doi.org/10.1136/bmj.h1225.
19. Leaney, A.A., Lyttle, J.R., Segan, J., Urquhart, D.M., Cicuttini, F.M., Chou, L., and Wluka, A.E. (2022). Antidepressants for hip and knee osteoarthritis. Cochrane Database Syst. Rev. *10*, CD012157. https://doi.org/10.1002/14651858.CD012157.pub2.
20. Busse, J.W., Wang, L., Kamaleldin, M., Craigie, S., Riva, J.J., Montoya, L., Mulla, S.M., Lopes, L.C., Vogel, N., Chen, E., et al. (2018). Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis. JAMA *320*, 2448–2460. https://doi.org/10.1001/jama.2018.18472.
21. Finnerup, N.B., Attal, N., Haroutounian, S., McNicol, E., Baron, R., Dworkin, R.H., Gilron, I., Haanpää, M., Hansson, P., Jensen, T.S., et al. (2015). Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol. *14*, 162–173. https://doi.org/10.1016/S1474-4422(14)70251-0.
22. Geneen, L.J., Moore, R.A., Clarke, C., Martin, D., Colvin, L.A., and Smith, B.H. (2017). Physical activity and exercise for chronic pain in adults: an overview of Cochrane Reviews. Cochrane Database Syst. Rev. *4*, CD011279. https://doi.org/10.1002/14651858.CD011279.pub3.
23. Gibson, W., Wand, B.M., Meads, C., Catley, M.J., and O'Connell, N.E. (2019). Transcutaneous electrical nerve stimulation (TENS) for chronic pain - an overview of Cochrane Reviews. Cochrane Database Syst. Rev. *4*, CD011890. https://doi.org/10.1002/14651858.CD011890.pub3.
24. Johnson, M.I., Paley, C.A., Jones, G., Mulvey, M.R., and Wittkopf, P.G. (2022). Efficacy and safety of transcutaneous electrical nerve stimulation (TENS) for acute and chronic pain in adults: a systematic review and meta-analysis of 381 studies (the meta-TENS study). BMJ Open *12*, e051073. https://doi.org/10.1136/bmjopen-2021-051073.
25. Williams, A.C.d.C., Fisher, E., Hearn, L., and Eccleston, C. (2020). Psychological therapies for the management of chronic pain (excluding headache) in adults. Cochrane Database Syst. Rev. *8*, CD007407. https://doi.org/10.1002/14651858.CD007407.pub4.

26. Vickers, A.J., Vertosick, E.A., Lewith, G., MacPherson, H., Foster, N.E., Sherman, K.J., Irnich, D., Witt, C.M., and Linde, K.; Acupuncture Trialists' Collaboration (2018). Acupuncture for Chronic Pain: Update of an Individual Patient Data Meta-Analysis. J. Pain *19*, 455–474. https://doi.org/10.1016/j.jpain.2017.11.005.

27. Rudd, R.A., Aleshire, N., Zibbell, J.E., and Gladden, R.M. (2016). Increases in Drug and Opioid Overdose Deaths–United States, 2000-2014. MMWR Morb. Mortal. Wkly. Rep. *64*, 1378–1382. https://doi.org/10.15585/mmwr.mm6450a3.

28. Dahlhamer, J.M., Connor, E.M., Bose, J., Lucas, J.L., and Zelaya, C.E. (2021). Prescription Opioid Use Among Adults With Chronic Pain: United States, 2019. Natl. Health Stat. Report, 1–9.

29. Dowell, D., Haegerich, T.M., and Chou, R. (2016). CDC Guideline for Prescribing Opioids for Chronic Pain - United States, 2016. MMWR Recomm. Rep. (Morb. Mortal. Wkly. Rep.) *65*, 1–49. https://doi.org/10.15585/mmwr.rr6501e1.

30. Dowell, D., Ragan, K.R., Jones, C.M., Baldwin, G.T., and Chou, R. (2022). CDC Clinical Practice Guideline for Prescribing Opioids for Pain - United States, 2022. MMWR Recomm. Rep. (Morb. Mortal. Wkly. Rep.) *71*, 1–95. https://doi.org/10.15585/mmwr.rr7103a1.

31. Dowell, D., Haegerich, T., and Chou, R. (2019). No Shortcuts to Safer Opioid Prescribing. N. Engl. J. Med. *380*, 2285–2287. https://doi.org/10.1056/NEJMp1904190.

32. Bohnert, A.S.B., Guy, G.P., Jr., and Losby, J.L. (2018). Opioid Prescribing in the United States Before and After the Centers for Disease Control and Prevention's 2016 Opioid Guideline. Ann. Intern. Med. *169*, 367–375. https://doi.org/10.7326/M18-1243.

33. Agnoli, A., Xing, G., Tancredi, D.J., Magnan, E., Jerant, A., and Fenton, J.J. (2021). Association of Dose Tapering With Overdose or Mental Health Crisis Among Patients Prescribed Long-term Opioids. JAMA *326*, 411–419. https://doi.org/10.1001/jama.2021.11013.

34. Magnan, E.M., Tancredi, D.J., Xing, G., Agnoli, A., Jerant, A., and Fenton, J.J. (2023). Association Between Opioid Tapering and Subsequent Health Care Use, Medication Adherence, and Chronic Condition Control. JAMA Netw. Open *6*, e2255101. https://doi.org/10.1001/jamanetworkopen.2022.55101.

35. Arnold, L.M., Bennett, R.M., Crofford, L.J., Dean, L.E., Clauw, D.J., Goldenberg, D.L., Fitzcharles, M.A., Paiva, E.S., Staud, R., Sarzi-Puttini, P., et al. (2019). AAPT Diagnostic Criteria for Fibromyalgia. J. Pain *20*, 611–628. https://doi.org/10.1016/j.jpain.2018.10.008.

36. Munipalli, B., Allman, M.E., Chauhan, M., Niazi, S.K., Rivera, F., Abril, A., Wang, B., Wieczorek, M.A., Hodge, D.O., Knight, D., et al. (2022). Depression: A Modifiable Risk Factor for Poor Outcomes in Fibromyalgia. J. Prim. Care Community Health *13*, 21501319221120738. https://doi.org/10.1177/21501319221120738.

37. Andrade, A., Vilarino, G.T., Sieczkowska, S.M., Coimbra, D.R., Bevilacqua, G.G., and Steffens, R.d.A.K. (2020). The relationship between sleep quality and fibromyalgia symptoms. J. Health Psychol. *25*, 1176–1186. https://doi.org/10.1177/1359105317751615.

38. Domino, E.F. (2010). Taming the ketamine tiger. 1965. Anesthesiology *113*, 678–684. https://doi.org/10.1097/ALN.0b013e3181ed09a2.

39. Sadove, M.S., Shulman, M., Hatano, S., and Fevold, N. (1971). Analgesic effects of ketamine administered in subdissociative doses. Anesth. Analg. *50*, 452–457.

40. Zarate, C.A., Jr., Singh, J.B., Carlson, P.J., Brutsche, N.E., Ameli, R., Luckenbaugh, D.A., Charney, D.S., and Manji, H.K. (2006). A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch. Gen. Psychiatry *63*, 856–864. https://doi.org/10.1001/archpsyc.63.8.856.

41. Doan, L.V., and Wang, J. (2018). An Update on the Basic and Clinical Science of Ketamine Analgesia. Clin. J. Pain *34*, 1077–1088. https://doi.org/10.1097/AJP.0000000000000635.

42. Ibrahim, L., Diazgranados, N., Franco-Chaves, J., Brutsche, N., Henter, I.D., Kronstein, P., Moaddel, R., Wainer, I., Luckenbaugh, D.A., Manji, H.K., and Zarate, C.A., Jr. (2012). Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vs add-on riluzole: results from a 4-week, double-blind, placebo-controlled study. Neuropsychopharmacology *37*, 1526–1533. https://doi.org/10.1038/npp.2011.338.

43. Remerand, F., Le Tendre, C., Baud, A., Couvret, C., Pourrat, X., Favard, L., Laffon, M., and Fusciardi, J. (2009). The early and delayed analgesic effects of ketamine after total hip arthroplasty: a prospective, randomized, controlled, double-blind study. Anesth. Analg. *109*, 1963–1971. https://doi.org/10.1213/ANE.0b013e3181bdc8a0.

44. Aveline, C., Gautier, J.F., Vautier, P., Cognet, F., Hetet, H.L., Attali, J.Y., Leconte, V., Leborgne, P., and Bonnet, F. (2009). Postoperative analgesia and early rehabilitation after total knee replacement: a comparison of continuous low-dose intravenous ketamine versus nefopam. Eur. J. Pain *13*, 613–619. https://doi.org/10.1016/j.ejpain.2008.08.003.

45. Doan, L.V., Li, A., Brake, L., Ok, D., Jee, H.J., Park, H., Cuevas, R., Calvino, S., Guth, A., Schnabel, F., et al. (2023). Single-Dose of Postoperative Ketamine for Postoperative Pain After Mastectomy: A Pilot Randomized Controlled Trial. J. Pain Res. *16*, 881–892. https://doi.org/10.2147/JPR.S389564.

46. Wang, J., Echevarria, G.C., Doan, L., Ekasumara, N., Calvino, S., Chae, F., Martinez, E., Robinson, E., Cuff, G., Franco, L., et al. (2019). Effects of a single subanaesthetic dose of ketamine on pain and mood after laparoscopic bariatric surgery: A randomised double-blind placebo controlled study. Eur. J. Anaesthesiol. *36*, 16–24. https://doi.org/10.1097/EJA.0000000000000860.

47. Sheikh, S., and Hendry, P. (2018). The Expanding Role of Ketamine in the Emergency Department. Drugs *78*, 727–735. https://doi.org/10.1007/s40265-018-0904-8.

48. Karlow, N., Schlaepfer, C.H., Stoll, C.R.T., Doering, M., Carpenter, C.R., Colditz, G.A., Motov, S., Miller, J., and Schwarz, E.S. (2018). A Systematic Review and Meta-analysis of Ketamine as an Alternative to Opioids for Acute Pain in the Emergency Department. Acad. Emerg. Med. *25*, 1086–1097. https://doi.org/10.1111/acem.13502.

49. Loftus, R.W., Yeager, M.P., Clark, J.A., Brown, J.R., Abdu, W.A., Sengupta, D.K., and Beach, M.L. (2010). Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. Anesthesiology *113*, 639–646. https://doi.org/10.1097/ALN.0b013e3181e90914.

50. Nielsen, R.V., Fomsgaard, J.S., Siegel, H., Martusevicius, R., Nikolajsen, L., Dahl, J.B., and Mathiesen, O. (2017). Intraoperative ketamine reduces immediate postoperative opioid consumption after spinal fusion surgery in chronic pain patients with opioid dependency: a randomized, blinded trial. Pain *158*, 463–470. https://doi.org/10.1097/j.pain.0000000000000782.

51. Sigtermans, M.J., van Hilten, J.J., Bauer, M.C.R., Arbous, S.M., Marinus, J., Sarton, E.Y., and Dahan, A. (2009). Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. Pain *145*, 304–311. https://doi.org/10.1016/j.pain.2009.06.023.

52. Schwartzman, R.J., Alexander, G.M., Grothusen, J.R., Paylor, T., Reichenberger, E., and Perreault, M. (2009). Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study. Pain *147*, 107–115. https://doi.org/10.1016/j.pain.2009.08.015.

53. Kiefer, R.T., Rohr, P., Ploppa, A., Dieterich, H.J., Grothusen, J., Koffler, S., Altemeyer, K.H., Unertl, K., and Schwartzman, R.J. (2008). Efficacy of ketamine in anesthetic dosage for the treatment of refractory complex regional pain syndrome: an open-label phase II study. Pain Med. *9*, 1173–1201. https://doi.org/10.1111/j.1526-4637.2007.00402.x.

54. Graven-Nielsen, T., Kendall, S.A., Henriksson, K.G., Bengtsson, M., Sörensen, J., Johnson, A., Gerdle, B., and Arendt-Nielsen, L. (2000). Ketamine reduces muscle pain, temporal summation, and referred pain in

fibromyalgia patients. Pain *85*, 483–491. https://doi.org/10.1016/S0304-3959(99)00308-5.

55. Noppers, I., Niesters, M., Swartjes, M., Bauer, M., Aarts, L., Geleijnse, N., Mooren, R., Dahan, A., and Sarton, E. (2011). Absence of long-term analgesic effect from a short-term S-ketamine infusion on fibromyalgia pain: a randomized, prospective, double blind, active placebo-controlled trial. Eur. J. Pain *15*, 942–949. https://doi.org/10.1016/j.ejpain.2011.03.008.
56. Mercadante, S., Arcuri, E., Tirelli, W., and Casuccio, A. (2000). Analgesic effect of intravenous ketamine in cancer patients on morphine therapy: a randomized, controlled, double-blind, crossover, double-dose study. J. Pain Symptom Manage. *20*, 246–252. https://doi.org/10.1016/s0885-3924(00)00194-9.
57. Lauritsen, C., Mazuera, S., Lipton, R.B., and Ashina, S. (2016). Intravenous ketamine for subacute treatment of refractory chronic migraine: a case series. J. Headache Pain *17*, 106. https://doi.org/10.1186/s10194-016-0700-3.
58. Pomeroy, J.L., Marmura, M.J., Nahas, S.J., and Viscusi, E.R. (2017). Ketamine Infusions for Treatment Refractory Headache. Headache *57*, 276–282. https://doi.org/10.1111/head.13013.
59. Amin, P., Roeland, E., and Atayee, R. (2014). Case report: efficacy and tolerability of ketamine in opioid-refractory cancer pain. J. Pain Palliat. Care Pharmacother. *28*, 233–242. https://doi.org/10.3109/15360288.2014.938881.
60. Hooten, W.M. (2016). Chronic Pain and Mental Health Disorders: Shared Neural Mechanisms, Epidemiology, and Treatment. Mayo Clin. Proc. *91*, 955–970. https://doi.org/10.1016/j.mayocp.2016.04.029.
61. Doan, L., Manders, T., and Wang, J. (2015). Neuroplasticity underlying the comorbidity of pain and depression. Neural Plast. *2015*, 504691. https://doi.org/10.1155/2015/504691.
62. Sharma, A.K., Vorobeychik, Y., Wasserman, R., Jameson, J., Moradian, M., Duszynski, B., and Kennedy, D.J.; Standards Division of the Spine Intervention Society (2017). The Effectiveness and Risks of Fluoroscopically Guided Lumbar Interlaminar Epidural Steroid Injections: A Systematic Review with Comprehensive Analysis of the Published Data. Pain Med. *18*, 239–251. https://doi.org/10.1093/pm/pnw131.
63. Smith, C.C., McCormick, Z.L., Mattie, R., MacVicar, J., Duszynski, B., and Stojanovic, M.P. (2020). The Effectiveness of Lumbar Transforaminal Injection of Steroid for the Treatment of Radicular Pain: A Comprehensive Review of the Published Data. Pain Med. *21*, 472–487. https://doi.org/10.1093/pm/pnz160.
64. Schneider, B.J., Doan, L., Maes, M.K., Martinez, K.R., Gonzalez Cota, A., and Bogduk, N.; Standards Division of the Spine Intervention Society (2020). Systematic Review of the Effectiveness of Lumbar Medial Branch Thermal Radiofrequency Neurotomy, Stratified for Diagnostic Methods and Procedural Technique. Pain Med. *21*, 1122–1141. https://doi.org/10.1093/pm/pnz349.
65. Knotkova, H., Hamani, C., Sivanesan, E., Le Beuffe, M.F.E., Moon, J.Y., Cohen, S.P., and Huntoon, M.A. (2021). Neuromodulation for chronic pain. Lancet *397*, 2111–2124. https://doi.org/10.1016/S0140-6736(21)00794-7.
66. Wang, J., and Chen, Z. (2019). Neuromodulation for Pain Management. Adv. Exp. Med. Biol. *1101*, 207–223. https://doi.org/10.1007/978-981-13-2050-7_8.
67. Melzack, R., and Wall, P.D. (1965). Pain mechanisms: a new theory. Science *150*, 971–979.
68. Deer, T.R., Mekhail, N., Provenzano, D., Pope, J., Krames, E., Leong, M., Levy, R.M., Abejon, D., Buchser, E., Burton, A., et al. (2014). The appropriate use of neurostimulation of the spinal cord and peripheral nervous system for the treatment of chronic pain and ischemic diseases: the Neuromodulation Appropriateness Consensus Committee. Neuromodulation *17*, 515–550, discussion 550. https://doi.org/10.1111/ner.12208.
69. Taylor, R.S., Desai, M.J., Rigoard, P., and Taylor, R.J. (2014). Predictors of pain relief following spinal cord stimulation in chronic back and leg pain and failed back surgery syndrome: a systematic review and meta-regression analysis. Pain Pract. *14*, 489–505. https://doi.org/10.1111/papr.12095.
70. Grider, J.S., Manchikanti, L., Carayannopoulos, A., Sharma, M.L., Balog, C.C., Harned, M.E., Grami, V., Justiz, R., Nouri, K.H., Hayek, S.M., et al. (2016). Effectiveness of Spinal Cord Stimulation in Chronic Spinal Pain: A Systematic Review. Pain Physician *19*, E33–E54.
71. De Ridder, D., Vanneste, S., Plazier, M., van der Loo, E., and Menovsky, T. (2010). Burst spinal cord stimulation: toward paresthesia-free pain suppression. Neurosurgery *66*, 986–990. https://doi.org/10.1227/01.NEU.0000368153.44883.B3.
72. Van Buyten, J.P., Al-Kaisy, A., Smet, I., Palmisani, S., and Smith, T. (2013). High-frequency spinal cord stimulation for the treatment of chronic back pain patients: results of a prospective multicenter European clinical study. Neuromodulation *16*, 59–65, discussion 65-56. https://doi.org/10.1111/ner.12006.
73. De Ridder, D., Plazier, M., Kamerling, N., Menovsky, T., and Vanneste, S. (2013). Burst spinal cord stimulation for limb and back pain. World Neurosurg. *80*, 642–649.e1. https://doi.org/10.1016/j.wneu.2013.01.040.
74. Tiede, J., Brown, L., Gekht, G., Vallejo, R., Yearwood, T., and Morgan, D. (2013). Novel spinal cord stimulation parameters in patients with predominant back pain. Neuromodulation *16*, 370–375. https://doi.org/10.1111/ner.12032.
75. Deer, T.R., Mekhail, N., Provenzano, D., Pope, J., Krames, E., Thomson, S., Raso, L., Burton, A., DeAndres, J., Buchser, E., et al. (2014). The appropriate use of neurostimulation: avoidance and treatment of complications of neurostimulation therapies for the treatment of chronic pain. Neuromodulation Appropriateness Consensus Committee. Neuromodulation *17*, 571–598, discussion 597-578. https://doi.org/10.1111/ner.12206.
76. Hay, M., Thomas, D.W., Craighead, J.L., Economides, C., and Rosenthal, J. (2014). Clinical development success rates for investigational drugs. Nat. Biotechnol. *32*, 40–51. https://doi.org/10.1038/nbt.2786.
77. Goadsby, P.J., Edvinsson, L., and Ekman, R. (1990). Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. Ann. Neurol. *28*, 183–187. https://doi.org/10.1002/ana.410280213.
78. Lampl, C., MaassenVanDenBrink, A., Deligianni, C.I., Gil-Gouveia, R., Jassal, T., Sanchez-Del-Rio, M., Reuter, U., Uluduz, D., Versijpt, J., Zeraatkar, D., and Sacco, S. (2023). The comparative effectiveness of migraine preventive drugs: a systematic review and network meta-analysis. J. Headache Pain *24*, 56. https://doi.org/10.1186/s10194-023-01594-1.
79. Fertleman, C.R., Baker, M.D., Parker, K.A., Moffatt, S., Elmslie, F.V., Abrahamsen, B., Ostman, J., Klugbauer, N., Wood, J.N., Gardiner, R.M., and Rees, M. (2006). SCN9A mutations in paroxysmal extreme pain disorder: allelic variants underlie distinct channel defects and phenotypes. Neuron *52*, 767–774. https://doi.org/10.1016/j.neuron.2006.10.006.
80. Faber, C.G., Lauria, G., Merkies, I.S.J., Cheng, X., Han, C., Ahn, H.S., Persson, A.K., Hoeijmakers, J.G.J., Gerrits, M.M., Pierro, T., et al. (2012). Gain-of-function Nav1.8 mutations in painful neuropathy. Proc. Natl. Acad. Sci. USA *109*, 19444–19449. https://doi.org/10.1073/pnas.1216080109.
81. Huang, J., Han, C., Estacion, M., Vasylyev, D., Hoeijmakers, J.G.J., Gerrits, M.M., Tyrrell, L., Lauria, G., Faber, C.G., Dib-Hajj, S.D., et al. (2014). Gain-of-function mutations in sodium channel Na(v)1.9 in painful neuropathy. Brain *137*, 1627–1642. https://doi.org/10.1093/brain/awu079.
82. Alsaloum, M., Higerd, G.P., Effraim, P.R., and Waxman, S.G. (2020). Status of peripheral sodium channel blockers for non-addictive pain treatment. Nat. Rev. Neurol. *16*, 689–705. https://doi.org/10.1038/s41582-020-00415-2.
83. Jones, J., Correll, D.J., Lechner, S.M., Jazic, I., Miao, X., Shaw, D., Simard, C., Osteen, J.D., Hare, B., Beaton, A., et al. (2023). Selective

Inhibition of Na(V)1.8 with VX-548 for Acute Pain. N. Engl. J. Med. *389*, 393–405. https://doi.org/10.1056/NEJMoa2209870.

84. Goldlust, S.A., Kavoosi, M., Nezzer, J., Kavoosi, M., Korz, W., and Deck, K. (2021). Tetrodotoxin for Chemotherapy-Induced Neuropathic Pain: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Dose Finding Trial. Toxins *13*, 235. https://doi.org/10.3390/toxins13040235.

85. Ashar, Y.K., Gordon, A., Schubiner, H., Uipi, C., Knight, K., Anderson, Z., Carlisle, J., Polisky, L., Geuter, S., Flood, T.F., et al. (2022). Effect of Pain Reprocessing Therapy vs Placebo and Usual Care for Patients With Chronic Back Pain: A Randomized Clinical Trial. JAMA Psychiatr. *79*, 13–23. https://doi.org/10.1001/jamapsychiatry.2021.2669.

86. Rini, C., Porter, L.S., Somers, T.J., McKee, D.C., DeVellis, R.F., Smith, M., Winkel, G., Ahern, D.K., Goldman, R., Stiller, J.L., et al. (2015). Automated Internet-based pain coping skills training to manage osteoarthritis pain: a randomized controlled trial. Pain *156*, 837–848. https://doi.org/10.1097/j.pain.0000000000000121.

87. Bennell, K.L., Nelligan, R., Dobson, F., Rini, C., Keefe, F., Kasza, J., French, S., Bryant, C., Dalwood, A., Abbott, J.H., and Hinman, R.S. (2017). Effectiveness of an Internet-Delivered Exercise and Pain-Coping Skills Training Intervention for Persons With Chronic Knee Pain: A Randomized Trial. Ann. Intern. Med. *166*, 453–462. https://doi.org/10.7326/M16-1714.

88. Mayhew, M., Balderson, B.H., Cook, A.J., Dickerson, J.F., Elder, C.R., Firemark, A.J., Haller, I.V., Justice, M., Keefe, F.J., McMullen, C.K., et al. (2023). Comparing the clinical and cost-effectiveness of remote (telehealth and online) cognitive behavioral therapy-based treatments for high-impact chronic pain relative to usual care: study protocol for the RESOLVE multisite randomized control trial. Trials *24*, 196. https://doi.org/10.1186/s13063-023-07165-8.

89. Maddox, T., Oldstone, L., Sackman, J., Maddox, R., Adair, T., Ffrench, K., Sparks, C., and Darnall, B.D. (2024). Twelve-month results for a randomized sham-controlled effectiveness trial of an in-home skills-based virtual reality program for chronic low back pain. Pain Rep. *9*, e1182. https://doi.org/10.1097/PR9.0000000000001182.

90. Coffey, R.J. (2001). Deep brain stimulation for chronic pain: results of two multicenter trials and a structured review. Pain Med. *2*, 183–192. https://doi.org/10.1046/j.1526-4637.2001.01029.x.

91. Shirvalkar, P., Prosky, J., Chin, G., Ahmadipour, P., Sani, O.G., Desai, M., Schmitgen, A., Dawes, H., Shanechi, M.M., Starr, P.A., and Chang, E.F. (2023). First-in-human prediction of chronic pain state using intracranial neural biomarkers. Nat. Neurosci. *26*, 1090–1099. https://doi.org/10.1038/s41593-023-01338-z.

92. O'Connell, N.E., Marston, L., Spencer, S., DeSouza, L.H., and Wand, B.M. (2018). Non-invasive brain stimulation techniques for chronic pain. Cochrane Database Syst. Rev. *4*, CD008208. https://doi.org/10.1002/14651858.CD008208.pub5.

93. Attal, N., Poindessous-Jazat, F., De Chauvigny, E., Quesada, C., Mhalla, A., Ayache, S.S., Fermanian, C., Nizard, J., Peyron, R., Lefaucheur, J.P., and Bouhassira, D. (2021). Repetitive transcranial magnetic stimulation for neuropathic pain: a randomized multicentre sham-controlled trial. Brain *144*, 3328–3339. https://doi.org/10.1093/brain/awab208.

94. Turk, D.C., Dworkin, R.H., Allen, R.R., Bellamy, N., Brandenburg, N., Carr, D.B., Cleeland, C., Dionne, R., Farrar, J.T., Galer, B.S., et al. (2003). Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. Pain *106*, 337–345. https://doi.org/10.1016/j.pain.2003.08.001.

95. May, M., Junghaenel, D.U., Ono, M., Stone, A.A., and Schneider, S. (2018). Ecological Momentary Assessment Methodology in Chronic Pain Research: A Systematic Review. J. Pain *19*, 699–716. https://doi.org/10.1016/j.jpain.2018.01.006.

96. Patterson, D.G., Wilson, D., Fishman, M.A., Moore, G., Skaribas, I., Heros, R., Dehghan, S., Ross, E., and Kyani, A. (2023). Objective wearable measures correlate with self-reported chronic pain levels in people with spinal cord stimulation systems. NPJ Digit. Med. *6*, 146. https://doi.org/10.1038/s41746-023-00892-x.

97. Bacon, K.L., Felson, D.T., Jafarzadeh, S.R., Kolachalama, V.B., Hausdorff, J.M., Gazit, E., Stefanik, J.J., Corrigan, P., Segal, N.A., Lewis, C.E., et al. (2024). Gait Alterations and Association With Worsening Knee Pain and Physical Function: A Machine Learning Approach With Wearable Sensors in the Multicenter Osteoarthritis Study. Arthritis Care Res. *76*, 984–992. https://doi.org/10.1002/acr.25327.

98. Deane, J., Arvanitidis, M., Briggs, M., Falla, D., and Johnson, M. (2024). Evaluating the efficacy of wearable biofeedback on the outcomes of exercise interventions in people with chronic non-specific spinal pain: protocol for a systematic review and meta-analysis. BMJ Open *14*, e085206. https://doi.org/10.1136/bmjopen-2024-085206.

99. Junghans-Rutelonis, A., Sim, L., Harbeck-Weber, C., Dresher, E., Timm, W., and Weiss, K.E. (2023). Feasibility of wearable activity tracking devices to measure physical activity and sleep change among adolescents with chronic pain-a pilot nonrandomized treatment study. Front. Pain Res. *4*, 1325270. https://doi.org/10.3389/fpain.2023.1325270.

100. Gungormus, D.B., Garcia-Moreno, F.M., Bermudez-Edo, M., Sánchez-Bermejo, L., Garrido, J.L., Rodríguez-Fórtiz, M.J., and Pérez-Mármol, J.M. (2024). A semi-automatic mHealth system using wearable devices for identifying pain-related parameters in elderly individuals. Int. J. Med. Inform. *184*, 105371. https://doi.org/10.1016/j.ijmedinf.2024.105371.

101. Wibowo, S., Chaw, W.L., Antuvan, C.W., and Hao, C. (2023). Use of Wearable Sensor Device and Mobile Application for Objective Assessment of Pain in Post-surgical Patients: A Preliminary Study. Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. *2023*, 1–4. https://doi.org/10.1109/EMBC40787.2023.10340199.

102. Marmar, C.R., Brown, A.D., Qian, M., Laska, E., Siegel, C., Li, M., Abu-Amara, D., Tsiartas, A., Richey, C., Smith, J., et al. (2019). Speech-based markers for posttraumatic stress disorder in US veterans. Depress. Anxiety *36*, 607–616. https://doi.org/10.1002/da.22890.

103. Wasserzug, Y., Degani, Y., Bar-Shaked, M., Binyamin, M., Klein, A., Hershko, S., and Levkovitch, Y. (2023). Development and validation of a machine learning-based vocal predictive model for major depressive disorder. J. Affect. Disord. *325*, 627–632. https://doi.org/10.1016/j.jad.2022.12.117.

104. Duey, A.H., Rana, A., Siddi, F., Hussein, H., Onnela, J.P., and Smith, T.R. (2023). Daily Pain Prediction Using Smartphone Speech Recordings of Patients With Spine Disease. Neurosurgery *93*, 670–677. https://doi.org/10.1227/neu.0000000000002474.

105. Segerdahl, A.R., Mezue, M., Okell, T.W., Farrar, J.T., and Tracey, I. (2015). The dorsal posterior insula subserves a fundamental role in human pain. Nat. Neurosci. *18*, 499–500. https://doi.org/10.1038/nn.3969.

106. Wager, T.D., Atlas, L.Y., Lindquist, M.A., Roy, M., Woo, C.W., and Kross, E. (2013). An fMRI-based neurologic signature of physical pain. N. Engl. J. Med. *368*, 1388–1397. https://doi.org/10.1056/NEJMoa1204471.

107. Baliki, M.N., Petre, B., Torbey, S., Herrmann, K.M., Huang, L., Schnitzer, T.J., Fields, H.L., and Apkarian, A.V. (2012). Corticostriatal functional connectivity predicts transition to chronic back pain. Nat. Neurosci. *15*, 1117–1119. https://doi.org/10.1038/nn.3153.

108. Ploner, M., Sorg, C., and Gross, J. (2017). Brain Rhythms of Pain. Trends Cogn. Sci. *21*, 100–110. https://doi.org/10.1016/j.tics.2016.12.001.

109. Tracey, I., Woolf, C.J., and Andrews, N.A. (2019). Composite Pain Biomarker Signatures for Objective Assessment and Effective Treatment. Neuron *101*, 783–800. https://doi.org/10.1016/j.neuron.2019.02.019.

110. Davis, K.D., Flor, H., Greely, H.T., Iannetti, G.D., Mackey, S., Ploner, M., Pustilnik, A., Tracey, I., Treede, R.D., and Wager, T.D. (2017). Brain imaging tests for chronic pain: medical, legal and ethical issues and recommendations. Nat. Rev. Neurol. *13*, 624–638. https://doi.org/10.1038/nrneurol.2017.122.

111. Sundaram, L., Gao, H., Padigepati, S.R., McRae, J.F., Li, Y., Kosmicki, J.A., Fritzilas, N., Hakenberg, J., Dutta, A., Shon, J., et al. (2018). Predicting the clinical impact of human mutation with deep neural networks. Nat. Genet. *50*, 1161–1170. https://doi.org/10.1038/s41588-018-0167-z.

112. Rockholt, M.M., Kenefati, G., Doan, L.V., Chen, Z.S., and Wang, J. (2023). In search of a composite biomarker for chronic pain by way of EEG and machine learning: where do we currently stand? Front. Neurosci. *17*, 1186418. https://doi.org/10.3389/fnins.2023.1186418.

113. Tetreault, P., Baliki, M.N., Baria, A.T., Bauer, W.R., Schnitzer, T.J., and Apkarian, A.V. (2018). Inferring distinct mechanisms in the absence of subjective differences: Placebo and centrally acting analgesic underlie unique brain adaptations. Hum. Brain Mapp. *39*, 2210–2223. https://doi.org/10.1002/hbm.23999.

114. Zorina-Lichtenwalter, K., Meloto, C.B., Khoury, S., and Diatchenko, L. (2016). Genetic predictors of human chronic pain conditions. Neuroscience *338*, 36–62. https://doi.org/10.1016/j.neuroscience.2016.04.041.

115. Davis, K.D., Aghaeepour, N., Ahn, A.H., Angst, M.S., Borsook, D., Brenton, A., Burczynski, M.E., Crean, C., Edwards, R., Gaudilliere, B., et al. (2020). Discovery and validation of biomarkers to aid the development of safe and effective pain therapeutics: challenges and opportunities. Nat. Rev. Neurol. *16*, 381–400. https://doi.org/10.1038/s41582-020-0362-2.