Am J Transl Res 2026;18(7):5874-5890
www.ajtr.org /ISSN:1943-8141/AJTR0172738

Review Article

Potential mechanisms of acupuncture in regulating neuroinflammation and central sensitization in chronic pain: a narrative review of preclinical, clinical, and translational evidence

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Received March 18, 2026; Accepted May 22, 2026; Epub July 15, 2026; Published July 30, 2026

Abstract: Chronic pain (CP) is not a single disease. Its mechanisms vary across patients and pain phenotypes. In many cases, persistent pain is related to neuroinflammation and central sensitization. Acupuncture, especially electroacupuncture, is widely used in clinical practice. Recent evidence suggests that acupuncture may provide more than a short-time pain relief, potentially by modulating neuroinflammation and central sensitization. However, the relationships among acupuncture, neuroinflammatory regulation, central sensitization, and phenotype-specific clinical responses remain unclear. This narrative review summarizes studies in this field. We searched PubMed for articles published between January 2016 and February 2026 and screened references of relevant publications. Some earlier landmark studies were also included to explain key concepts. Experimental studies suggest that acupuncture potentially regulates central sensitization by influencing spinal glial activation, synaptic plasticity, descending pain inhibitory pathways, and autonomic-immune interactions. Clinical studies show more heterogeneous results. Patients with more central sensitization-related symptoms may experience improvements not only in pain intensity but also in sleep quality, fatigue, mood, and overall quality of life. In CP with mixed mechanisms, acupuncture may facilitate symptom relief and functional recovery. In neuropathic pain, measures such as allodynia, hyperalgesia, and other sensory symptoms may better reflect treatment response than pain intensity alone. Tools including the Central Sensitization Inventory, quantitative sensory testing, conditioned pain modulation, functional magnetic resonance imaging, and related biomarkers potentially help explain inter-individual differences in treatment responses. Current evidence is limited by heterogeneity in patient selection, acupuncture parameters, outcome measures, and the weak mechanistic links between preclinical findings and clinical endpoints.

Keywords: Acupuncture, electroacupuncture, chronic pain, neuroinflammation, central sensitization, nociplastic pain, quantitative sensory testing

Introduction

Chronic pain (CP) affects a substantial number of patients globally and is highly prevalent across musculoskeletal disorders, neurological illnesses, and functional pain syndromes. CP significantly impairs daily activities, sleep quality, mood, and overall quality of life [1]. In recent years, the International Association for the Study of Pain (IASP) has classified CP into three main mechanistic categories: nociceptive pain, neuropathic pain, and nociplastic pain [1, 2]. Unlike the traditional focus on peripheral tissue injury, the concept of nociplastic pain emphasizes "abnormal central processing of sensory signals" rather than mere peripheral damage [2, 3]. Central sensitization (CS) refers to heightened responsiveness of the central nervous system to both noxious and non-noxious stimuli. It manifests as amplified pain perception, reduced pain thresholds, and abnormal sensory processing, and is now considered a crucial pathophysiological mechanism underlying nociplastic pain and various refractory CP con-

https://doi.org/10.62347/OZVB4929

ditions, including fibromyalgia, chronic pelvic pain, and non-specific low back pain. Neuroinflammation has emerged as a pivotal contributor to the development and maintenance of CS. Persistent neuro-immune interactions potentially facilitate CP persistence through glial activation, release of inflammatory mediators, and abnormal synaptic plasticity, making this process a major mechanistic foundation of CP [4, 5].

Glial cells, especially microglia and astrocytes, are major mediators of neuroinflammation and can release diverse inflammatory mediators, modulating immune responses within the nervous system [6, 7]. Nevertheless, glial cells in the spinal dorsal horn and pain-relevant brain regions may remain activated under conditions of persistent peripheral inflammation, nerve injury, or chronic stress. These activated cells secrete inflammatory cytokines such as IL-1β, TNF-α, and IL-6, and promote abnormal synaptic plasticity via receptor phosphorylation, enhance excitatory transmission, and weaken inhibitory neural circuits, thereby sustaining central sensitization and potentially amplifying pain perception [8, 9]. Neuroinflammation may further disrupt the balance between excitatory and inhibitory synaptic transmission and alter neural network activity in the spinal cord and brain, reshaping pain processing [10, 11]. Thus, it is crucial to elucidate the precise contributions of neuroinflammation to central sensitization, as it may explain why some CP patients respond poorly to current treatments [9, 12].

Clinicians commonly use nonsteroidal anti-inflammatory drugs, opioids, and some anticonvulsants to manage CP, but these medications are not suitable for all patients. Nonsteroidal anti-inflammatory drugs may cause gastrointestinal injury, whereas opioids and anticonvulsants can induce central nervous system adverse effects; repeated opioid use also carries the risk of tolerance and dependence [13-15]. Acupuncture has increasingly been employed in CP management, representing a part of multimodal analgesia and integrative medicine [16, 17]. Current evidence indicates that acupuncture does not act through a single mechanism. It may modulate peripheral inflammatory responses, spinal nociceptive transmission, descending brainstem pathways, and autonomic-immune communication. Through these combined actions, acupuncture can influence neuroinflammation and central sensitization, which may partly explain its analgesic effects in some CP phenotypes [18-20]. Clinical and experimental studies suggest that acupuncture not only reduces pain intensity but also improves sleep, fatigue, mood, and functional status, all of which are closely associated with the burden of central sensitization [21, 22]. For instance, acupuncture stimulation can be converted into neurobiological signals that suppress local peripheral inflammation and attenuate central inflammatory activity via modulation of autonomic and neuroimmune pathways. These processes may in turn influence abnormal synaptic plasticity and intervene in upstream events related to central sensitization [18, 19, 23].

Nevertheless, the specific mechanisms of acupuncture, the most responsive patient populations, and the optimal treatment parameters remain highly heterogeneous, and clear translational gaps exist between preclinical findings and clinical practice [16, 17]. Previous reviews have discussed acupuncture analgesia, neuroinflammation, or central sensitization separately, with few have integrated these aspects while integrating preclinical mechanisms, clinical phenotypes, and translational assessment tolls.

Accordingly, this narrative review aims to provide a thematic synthesis of recent studies, with a particular focus on the potential effects of acupuncture, especially electroacupuncture, on neuroinflammation- and central sensitization-related processes in CP. Rather than producing pooled quantitative conclusions, the review summarizes major research lines, the current scope of supporting evidence, key controversies, and possible translational directions. Specifically, this review addresses: (1) whether acupuncture modulates the spinal microenvironment, brainstem descending pain modulatory system, and autonomic-immune axis; (2) whether patients with CP and diverse central sensitization-associated phenotypes exhibit differential responses to acupuncture; and (3) the potential utility of translational markers such as the Central Sensitization Inventory (CSI), quantitative sensory testing (QST), functional magnetic resonance imaging (fMRI), and electroacupuncture parameters in improving interpretability of acupuncture analgesia research. By synthesizing diverse types of evidence, this review seeks to inform more phenotype-oriented applications of acupunc-

ture within multimodal analgesic strategies. Concurrently, the current literature remains limited because of considerable heterogeneity among studies, insufficient causal evidence, and challenges in translating mechanistic findings into clinical decision-making.

Methods

Information sources

A rigorous search for preclinical, clinical, and translational studies related to neuroinflammation, central sensitization, CP, and acupuncture-relevant interventions, published from January 2016 to February 2026, was performed on PubMed. Additional relevant articles were identified through manual screening of references. Classic studies were also included to clarify core concepts and underlying mechanisms.

Search strategy

Both MeSH terms and free-text keywords were employed in the literature search. Search terms included "Acupuncture", "Electroacupuncture", "Chronic pain", "Central sensitization", "Nociplastic pain", "Neuroinflammation", "Microglia", "Astrocyte", "Descending pain modulation", "Quantitative sensory testing", and "Functional magnetic resonance imaging". Terms were combined according to the relevance of each topic.

Study selection was guided by topic relevance, conceptual significance, and clinical applicability. We focused on studies linking mechanistic findings with clinical acupuncture research. Preclinical studies, clinical trials, and systematic reviews were all considered. Methodological papers, consensus statements, and narrative reviews were also deliberately included if they provided relevant mechanistic or clinical insights. Evidence was synthesized narratively, with the main themes organized around mechanisms, clinical findings, and translational implications.

Evidence synthesis

Preclinical mechanistic evidence for the regulation of neuroinflammation and central sensitization by acupuncture

Current preclinical studies indicate that acupuncture, especially electroacupuncture, may modulate central sensitization in CP through multiple mechanisms. Most mechanistic studies have centered around three areas: regulation of the neuroinflammatory milieu and maladaptive synaptic plasticity in the spinal dorsal horn; modulation of the brainstem descending pain inhibitory system; and systemic inflammatory regulation via the autonomic-immune axis.

Collectively, these findings provide a preclinical framework for explaining how acupuncture potentially affects neuroinflammation, central sensitization, and pain-relevant symptoms in CP. Nevertheless, most evidence is derived from animal experiments or electroacupuncture studies in which the stimulation parameters were tightly controlled. It remains uncertain whether these mechanisms are applicable to human patients or reproducible in routine clinical practice. Therefore, preclinical findings should be interpreted primarily as a biological foundation for subsequent clinical phenotype analyses and translational study design, rather than as direct proof of the mechanisms underlying clinical efficacy. As revealed in **Figure 1**, an overall schematic framework has been established to depict how acupuncture may influence neuroinflammation and central sensitization in CP through multilevel pathways.

Regulation of glial cells and synaptic plasticity in the spinal dorsal horn by acupuncture: Current evidence indicates that electroacupuncture modulates not only pain perception in patients and animal models but also the neuroinflammatory environment in the spinal dorsal horn. By regulating peripheral inflammation and spinal neuroinflammation, electroacupuncture may reduce persistent sensitization and excessive amplification of pain-related signals at the spinal level, potentially attenuating central sensitization [24]. Animal studies have shown that electroacupuncture decreases microglial activation in the dorsal horn and upregulates M2 polarization markers, which are closely associated with tissue repair and anti-inflammatory processes. These effects have been observed in neuropathic pain models, including lumbar disc herniation and sciatic nerve ligation, and are consistent with increased mechanical pain thresholds [25, 26]. Collectively, a shift of glial cells from a pro-inflammatory state to an anti-inflammatory and reparative phenotype appears to be a key part of electroacupuncture-induced analgesia.

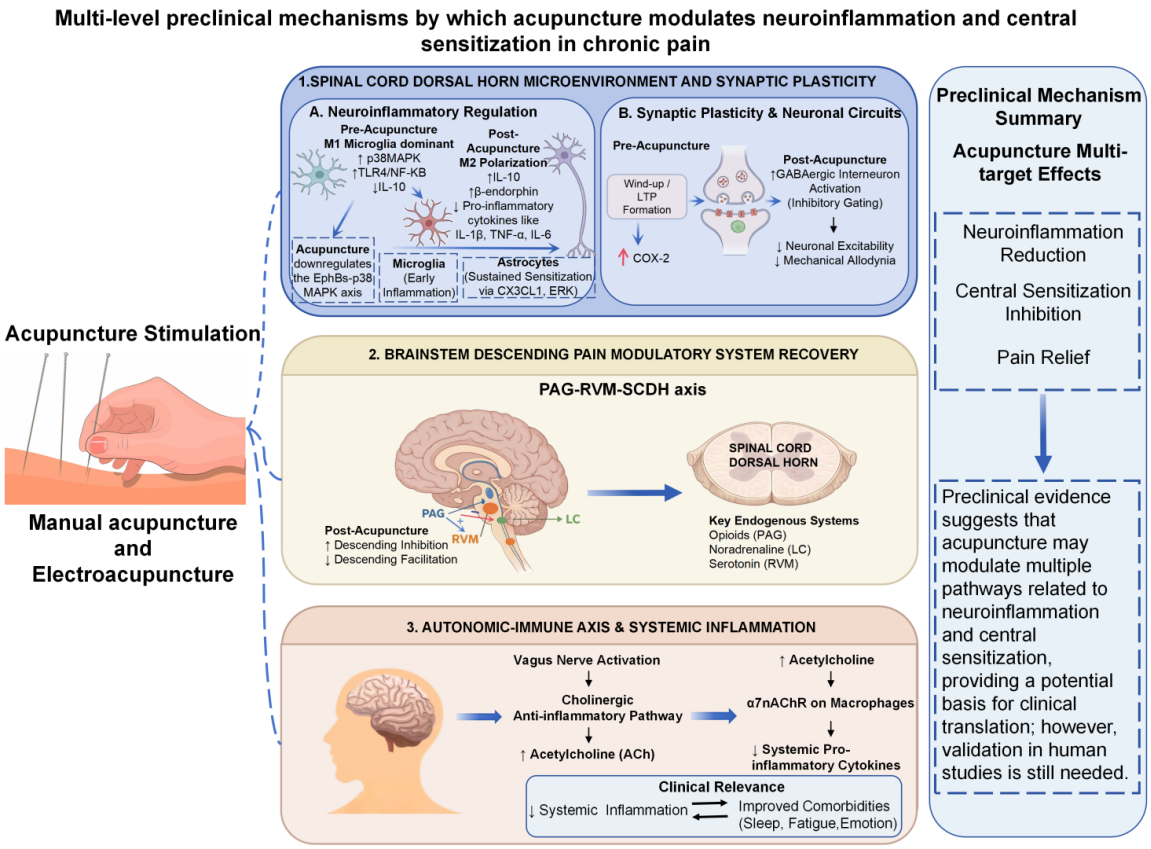

Figure 1. Multi-level framework of the potential effects of acupuncture on neuroinflammation and central sensitization in chronic pain.

In addition to glial phenotype modulation, anti-inflammatory cytokines and endogenous analgesic mediators may contribute to this process. Low-frequency electroacupuncture enhances IL-10 signaling in spinal microglia and increase the expression of endogenous analgesic mediators such as β-endorphin. Blockade of IL-10 or its signaling pathways markedly reduces the analgesic effect of electroacupuncture, suggesting that this pathway is partially necessary for its analgesia effect [27]. A related review integrating studies on IL-10 and endogenous analgesic systems enhances endogenous analgesic systems by promoting the release of anti-inflammatory mediators, thereby producing analgesia [28].

Notably, spinal glial cell regulation by acupuncture is not limited to microglia. As suggested by existing studies, microglia predominantly mediate early suppression of inflammation during electroacupuncture, whereas astrocytes contribute to the maintenance of prolonged central sensitization and the longer-term analgesia. Electroacupuncture may act along a "microglia-astrocyte-neuron" axis by downregulating C-X3-C motif chemokine ligand 1 (CX3CL1), inhibiting inflammatory signaling pathways such as p38 mitogen-activated protein kinase (p38 MAPK) and extracellular signal-regulated kinase (ERK), and further modulating astrocyte activation. These findings indicate that acupuncture potentially regulates the spinal neuroinflammatory microenvironment in a time-dependent and cell-specific manner, rather than targeting a single glial population [24].

At the signaling level, p38 MAPK is a major pathway involved in the pro-inflammatory response of microglia. Earlier studies indicated that electroacupuncture can inhibit microglial p38 MAPK activation under neuropathic pain conditions, decrease the release of pro-inflammatory mediators, and thereby attenuate pain hypersensitivity [29]. More recent work has linked this effect to the EphB receptors

(EphBs)-p38 MAPK-microglia axis, suggesting that electroacupuncture suppresses the pro-inflammatory glial cascade by modulating the coupling between upstream receptor signaling and p38 pathway [30].

Growing evidence further implicates upstream innate immune and inflammasome-related pathways in electroacupuncture-mediated anti-inflammatory and analgesic effects. For example, in migraine-like and chemotherapy-related neuropathic pain models, electroacupuncture inhibits Toll-like receptor 4 (TLR4)/nuclear factor kappa B (NF-κB) signaling, reduces pro-inflammatory cytokines including IL-1β, TNF-α, and IL-6, and attenuates glial activation in the spinal cord and trigeminal-related regions [31, 32]. As evidenced by these findings, acupuncture may act not only on downstream inflammatory pathways such as p38 MAPK, but also on upstream pattern-recognition receptor signaling such as TLR4, thereby interrupting the sustained neuroinflammation-to-central sensitization cascade.

Electroacupuncture effects in the spinal dorsal horn extend beyond immune modulation to local neural circuits. Under inflammatory pain conditions, A-fiber intensity electroacupuncture can recruit gamma-aminobutyric acid (GABA)-ergic neurons in the dorsal horn, enhancing inhibitory gating and reducing ascending nociceptive signal transmission [33]. Different electroacupuncture intensities also reduce dorsal horn neuronal sensitization and mechanical hypersensitivity, indicating direct modulation of the spinal excitatory-inhibitory balance [34].

Abnormal synaptic plasticity is considered a hallmark of central sensitization. In inflammation-related referred pain models, electroacupuncture inhibits spinal long-term potentiation (LTP), thereby reducing excessive responses of dorsal horn neurons to repeated stimuli, alleviating hyperalgesia and allodynia, and weakening central sensitization maintenance [35]. Additional studies have shown that electroacupuncture reduces spinal pro-inflammatory mediators such as cyclooxygenase-2 (COX-2) and decreases ionized calcium-binding adapter molecule 1 (Iba1)-positive microglial activation, further its role in alleviating pain hypersensitivity via combined modulation of pro-inflammatory signaling and glial activity [36, 37].

Overall, preclinical evidence indicates that electroacupuncture may attenuate spinal amplification related to central sensitization through combined effects on glial activation, pro-/anti-inflammatory signaling balance, inhibitory neural circuits, and abnormal synaptic plasticity.

Remodeling of the brainstem descending pain modulatory system by acupuncture: The persistence of CP is not only associated with ongoing peripheral input, but also correlates with dysfunction of the brainstem descending pain modulatory system (DPMS). Among these pathways, the periaqueductal gray-rostral ventromedial medulla (PAG-RVM) axis is a key regulatory circuit linking higher brain centers to the spinal dorsal horn, capable of either inhibiting or facilitating pain transmission. Animal studies have shown that electroacupuncture can induce coordinated signaling changes in the PAG-RVM pathway and the spinal dorsal horn, which correlate with reduced mechanical hypersensitivity, suggesting that electroacupuncture attenuates spinal sensitization by strengthening descending inhibition [38].

Within this process, neurotransmitter systems and receptor pathways within the PAG appear to play critical roles. Evidence indicates that the balance between excitatory and inhibitory neuronal populations within the PAG potentially determine whether the DPMS output is pain-facilitating or pain-inhibiting [39, 40]. This partially explains the variability of analgesic effects observed with diverse pathological states or electroacupuncture parameters. Furthermore, multi-omics studies have suggested that electroacupuncture can alter the molecular expression profile of the PAG, providing potential targets for modulating descending pain pathways [41].

Acupuncture-related descending analgesia is not restricted to the classical PAG-RVM axis. Previous studies suggest a broader brainstem and brain network involvement, including the locus coeruleus, raphe nuclei, amygdala, and nucleus accumbens, which jointly regulate neurotransmitters such as norepinephrine, serotonin, and endogenous opioid peptides, thereby influencing the processing of nociceptive information in the spinal dorsal horn. Descend-

ing noradrenergic pathways originating from the locus coeruleus may also contribute to acupuncture's effects in neuropathic pain [42].

Mechanistically, acupuncture appears to modulate multiple brainstem nuclei simultaneously. It potentially influences spinal nociceptive processing and alleviates central sensitization by altering the output state of several brainstem nodes within a broader pain-regulating network. Although the causal chain of this mechanism has not yet been fully established in humans, current animal studies provide strong preclinical support for the role of acupuncture in remodeling descending inhibitory systems.

Systemic regulation of the autonomic-immune axis by acupuncture: CP is often accompanied by persistent low-grade inflammation. Elevated peripheral inflammatory mediators may not only induce peripheral sensitization but also contribute to the maintenance of central sensitization via neuroimmune pathways. By modulating systemic inflammation, acupuncture may attenuate pain by acting on upstream factors that drive sensitization. Experimental models have shown that electroacupuncture produces anti-inflammatory effects, which are often linked to the vagus nerve-mediated cholinergic anti-inflammatory pathway. In this pathway, acupuncture stimulation activates vagal signaling, increasing acetylcholine release, which subsequently binds to receptors on immune cells, including macrophages, thereby suppressing the production and release of pro-inflammatory cytokines [43].

The autonomic-immune axis may also influence CP beyond peripheral inflammation. In conditions such as chronic widespread pain and fibromyalgia, lower vagal tone has been linked to pain persistence and increased symptom burden. Vagal regulation can modulate inflammatory activity, stress responses, and mood-associated symptoms. Consequently, acupuncture-mediated autonomic modulation may improve not only pro-inflammatory cytokine profiles but also sleep disturbance, fatigue, and emotional symptoms that are common in CP. The autonomic-immune axis may thus serve as a link connecting systemic inflammation, brain function, and symptom cluster, rather than acting solely as a peripheral anti-inflammatory pathway [44, 45].

However, current evidence regarding autonomic-immune modulation should be interpreted carefully. Studies investigating interventions such as acupuncture, electroacupuncture, auricular vagus nerve stimulation, and some other neuromodulatory approaches differ substantially in their mechanisms and cannot be considered inter-replaceable.

Gaps in the clinical translation of preclinical mechanistic evidence on acupuncture: Overall, some gaps still exist between how acupuncture works and what happens in real clinical practice. And these gaps are about translation. Most available evidence is gained from animal experiments. It remains unknown if such mechanisms fit human CP completely. No one can tell if those biological changes ease symptoms directly. In numerous studies, parameters of electroacupuncture are being very strictly controlled. Frequency, intensity, and treatment duration are three pivotal data. Practical clinical situations always show obvious differences. They are potentially linked to doctors' habits and patients' own conditions. Hence, it's really hard to compare results from different studies. Anesthesia is universally employed in most animal tests. Besides, only one disease model is adopted, and observation time is kept quite short. Real patients suffer from CP live with this condition over a long period. Emotional troubles and sleep issues can easily appear in them. They may also develop many other extra illnesses as well. This complex pain phenotype differs from animal model conditions. For this reason, future studies necessitate more standardized translational designs. These designs should better link preclinical mechanisms with clinical phenotypes and objective measures.

Clinical evidence of acupuncture across central sensitization-associated phenotypes of CP

Clinical cohort studies show that CP is highly heterogeneous. Even among patients sharing the same diagnosis, symptom profiles may differ substantially. Some patients exhibit a greater burden of central sensitization-associated features, including widespread pain sensitivity, sleep disturbance, emotional comorbidities, and functional impairment. Therefore, assessing acupuncture efficacy only by disease labels may be insufficient and partially explain inconsistent findings across studies. In this

context, patient stratification is used here to discuss treatment heterogeneity and does not represent a formal clinical diagnostic classification. The following sections focus on patterns of differential acupuncture efficacy across diverse central sensitization-associated phenotypes.

Clinical efficacy of acupuncture in CP with a high burden of central sensitization-associated features: In fibromyalgia, some forms of chronic pelvic pain, and other CP populations characterized by widespread pain, fatigue, sleep disturbance, and emotional burden, central sensitization-associated mechanisms are thought to play a major role. Available evidence suggests that acupuncture may produce multidimensional benefits in these patients, including reductions in pain intensity, improvements in fatigue, sleep disturbance, and overall quality of life [46, 47].

Similar findings have been reported in pelvic pain conditions, including chronic prostatitis/chronic pelvic pain syndrome and myofascial pelvic pain. In these patients, widespread pain, sleep disruption, mood disturbances, and overall functional impairment commonly co-occur; therefore, local pain reduction alone may not fully capture the therapeutic response, whereas broader changes across symptom clusters more accurately reflect clinical benefit [48-52].

Recent clinical trials in fibromyalgia populations further support this multidimensional framework. Acupuncture has been associated improvements in pain intensity, sleep quality, fatigue, autonomic-related indicators (e.g., heart rate variability), and overall quality of life [53]. Notably, patients suffering from high central sensitization-associated burden may be more sensitive to contextual and expectation effects, which can produce substantial responses in sham acupuncture groups, potentially diminishing observed differences between true and control interventions. Additionally, suboptimal treatment duration, frequency, or narrowly defined endpoints may further obscure specific effects.

Overall, current evidence suggests that acupuncture potentially provide clinical benefit in CP, particularly in patients with prominent central sensitization-associated features. Future clinical studies should prioritize the following aspects: (1) identifying patient subgroups most likely to benefit; (2) determining optimal treatment parameters; and (3) selecting multidimensional outcomes that accurately reflect treatment response.

Dual therapeutic effects of acupuncture in mixed-mechanism chronic pain (MMCP): Osteoarthritis and chronic non-specific low back pains often involve multiple pain mechanisms, including local tissue changes, structural abnormalities, peripheral inflammation, and central pain amplification. These conditions are better conceptualized as MMCP rather than purely peripheral or central pain. In this context, acupuncture may act through several pathways. Specific physiological effects, treatment context, patient expectations, patient-practitioner interactions, and sensory input from real or sham needling can all contribute to the overall response [54, 55]. Consequently, short-term pain intensity alone is insufficient to capture the full clinical value of acupuncture. Functional recovery, physical mobility, and long-term symptom control are also critical outcomes.

Osteoarthritis provides a typical example of MMCP. Evidence indicates that acupuncture can mitigate pain and improve joint function, although effect sizes vary across studies. Key factors influencing outcomes include needle insertion, electroacupuncture parameters, treatment duration, and the nature of control conditions [54, 56]. Improvements in walking ability and joint function are often observed, highlighting the importance of evaluating both pain- and function-related endpoints [57]. High-quality randomized trials in knee osteoarthritis have shown mixed results; some benefits may be attributable to non-specific factors rather than needling-specific mechanisms [58-60]. In chronic low back pain, the effects of acupuncture also extend beyond pain reduction. Studies demonstrate greater improvements in physical function and overall symptom burden than in short-term pain relieve [61]. The modest separation between verum and sham acupuncture in many trials suggests that non-specific components, including treatment context and expectation, contribute substantially to clinical outcomes [59, 62].

Patient heterogeneity further complicates interpretation. Local tissue pathology may domi-

nate pain in some cases, whereas central sensitization may be the primary driver in others. Consequently, responses to acupuncture vary depending on the dominant pain mechanism. Short-term pain scales such as VAS or NRS may fail to capture meaningful clinical changes in MMCP, especially for chronic non-specific low back pain, where functional improvement and quality of life may be more relevant indicators of benefit [61].

Overall, current evidence supports a dual therapeutic effect of acupuncture in MMCP, encompassing both pain relief and functional enhancement. However, the relative contributions of specific acupuncture mechanisms versus non-specific contextual factors remain unclear, emphasizing the need for multidimensional outcome assessment and individualized treatment approaches.

Effects of acupuncture on abnormal pain processing in neuropathic pain: Neuropathic pain is characterized by several clinical features such as allodynia and hyperalgesia, which reflect underlying pathophysiological mechanisms, including post-injury central amplification, spinal sensitization, and persistent neuroimmune dysregulation. Consequently, the therapeutic value of acupuncture in neuropathic pain cannot be assessed exclusively by pain intensity scores. Evaluation of abnormal pain processing, sensory symptom burden, and related functional limitations is essential. Moreover, neuropathic pain is heterogeneous. Its subtypes differ in etiology, disease course, and treatment response, and should not be treated uniformly [63, 64].

Current clinical evidence indicates that acupuncture or electroacupuncture can reduce pain intensity in some neuropathic pain conditions and may improve allodynia and pain-related physical limitation. Nonetheless, results remain inconsistent, likely attributable to heterogeneity in neuropathic pain etiology, disease courses, and study designs. Comorbid symptoms, including sleep disturbances, anxiety, and depression are common in neuropathic pain and should be assessed in future studies to better capture the broader effects of acupuncture [65].

Evidence also varies across neuropathic pain subtypes. In painful diabetic peripheral neuropathy, many trials and cohort studies report symptom relief. In chemotherapy-induced neuropathy, controlled studies show obvious improvements in physical symptoms and certain nerve-related signs. Systematic reviews suggest potential benefits in postherpetic neuralgia, although overall study quality and methodological consistency remain limited [47, 66-69].

These findings emphasize that, in neuropathic pain, both symptom outcomes and mechanistically relevant readouts are critical. Reliance on VAS or NRS scores alone is insufficient to evaluate true improvement in abnormal sensory processing. Overall, clinical evidence across diverse central sensitization-associated CP phenotypes demonstrates that acupuncture effects cannot be summarizes by changes in pain intensity. In patients with high central sensitization burden, multidimensional outcomes, incorporating pain sensitivity, sleep, fatigue, mood, functional recovery, walking ability, and longer-term physical quality of life, provide a more accurate assessment of therapeutic benefit. In MMCP, evaluation should include both pain- and function-related endpoints. In neuropathic pain, allodynia, abnormal sensory symptoms, and the overall neuropathic symptom burden better reflect underlying mechanism than VAS or NRS scores alone. Accordingly, future clinical studies should select endpoint systems that align with specific central sensitization-associated phenotypes, rather than relying on a single pain score. Phenotype-specific patterns of potential benefit and corresponding priority outcomes for acupuncture are summarized in **Table 1**.

Translational research and precision-oriented pathways for acupuncture analgesia

Research on acupuncture for CP has principally relied on subjective outcomes such as the VAS and NRS. These measures, however, can be influenced by treatment expectations, contextual effects, natural symptom fluctuations, and emotional comorbidities. Therefore, they may not fully distinguish whether observed clinical effects reflect acupuncture-specific modulation of CS-related processes, non-specific contextual factors, or a combination of both.

To address this issue, recent studies have increasingly incorporated multidimensional measures, including phenotype screening tools,

Table 1. Potential benefits and priority outcomes of acupuncture across different central sensitization-related chronic pain phenotypes

Phenotype category	Representative conditions	Main clinical characteristics	Potential major benefits of acupuncture	Priority outcomes to assess	Research implications
High central sensitization-related burden phenotype	Fibromyalgia, some forms of chronic pelvic pain, and certain widespread chronic pain conditions	Marked widespread pain, often accompanied by fatigue, sleep disturbance, emotional burden, and overall functional impairment	Benefits may extend beyond local pain reduction and may involve simultaneous improvement in pain, fatigue, sleep, and quality of life	Pain intensity, widespread pain sensitivity, fatigue, sleep quality, emotional status, quality of life, and autonomic-related indices	This phenotype may be more susceptible to nonspecific effects, expectancy effects, and treatment context; relying only on local pain scores may underestimate the overall benefit
Mixed-mechanism chronic pain	Osteoarthritis and chronic nonspecific low back pain	Coexistence of local structural abnormalities, peripheral inflammation, and varying degrees of central pain amplification	Acupuncture potentially provides both symptom relief and functional recovery, but the observed benefit potentially reflects a combination of specific physiological effects and nonspecific contextual effects	Pain intensity, functional scales, walking ability, physical quality of life, and long-term follow-up outcomes	If short-term VAS/NRS is used as the sole endpoint, the potential value of acupuncture for functional recovery and long-term management may be underestimated
Neuropathic pain	Painful diabetic peripheral neuropathy, chemotherapy-induced peripheral neuropathy, postherpetic neuralgia, etc.	Allodynia, hyperalgesia, sensory abnormalities, and high symptom burden, often accompanied by sleep and emotional comorbidities	Acupuncture may improve pain intensity, abnormal pain processing, and neuropathic symptom burden	Allodynia, hyperalgesia, neuropathic symptom scores, functional limitation, and sleep- and emotion-related outcomes	The maturity of evidence varies substantially across etiological subtypes; therefore, studies should preferably be interpreted by etiology-specific subgroups rather than pooled as a single entity

psychophysical measures, brain imaging, autonomic indicators, and selected biomarkers. Nonetheless, these measures capture distinct aspects of CP, such as clinical phenotype, sensory processing, central network-level changes, and mechanistic evidence. No single measure provides comprehensive information; therefore, a translational strategy integrating multiple modalities is required. Establishing a multidimensional evaluation framework across symptoms, function, and mechanisms can enhance the interpretability and translational value of acupuncture research.

Assessment tools for central sensitization and objective translational indicators: Currently, several tools are utilized in translational acupuncture research to characterize central sensitization and explain heterogeneous treatment responses, including CSI, QST, CPM, fMRI, and selected biomarkers [60]. Each tool provides information at a different level and should be interpreted according to its intended purpose **Table 2**.

The CSI is primarily a self-reported questionnaire utilized to screen clinical phenotypes. It helps identify patients with a higher burden of CS-associated features and can support subgroup analysis in clinical studies. Nevertheless, the CSI score should not be regarded as a direct mechanistic marker or an objective measure of central sensitization. Current evidence does not consistently show that patients with higher CSI scores respond more favorably to acupuncture. Therefore, the CSI is best employed as a phenotype-screening tool rather than a validated predictor of acupuncture efficacy. While symptom burden assessed by the CSI is correlated with central sensitization features, its direct association with acupuncture-specific mechanisms remains uncertain in clinical trials [60].

QST and CPM are tightly correlated with sensory processing and pain modulation. QST can quantify pain threshold, pain sensitivity, temporal summation, and other features relevant to central amplification, whereas CPM primarily reflects descending inhibitory function. These two assessments provide mechanistic information beyond symptom scales, particularly when exploring whether acupuncture modulates abnormal pain processing. For example, in patients suffering from knee osteoarthritis, randomized studies have demonstrated that electroacupuncture of different intensities may produce distinct effects on CPM, despite similar clinical outcomes, suggesting that psychophysical testing can reveal underlying mechanistic variation [58]. In fibromyalgia, baseline temporal summation has been reported to predict subsequent response to acupuncture, whereas expectation of pain relief did not [56]. In contrast, in chronic non-specific low back pain, temporal summation failed to predict clinically meaningful acupuncture effect across a 10-session treatment course [70]. Collectively, these findings suggest that QST-derived predictors are condition-specific and should not be interpreted as generalizable response markers for acupuncture [56, 70]. Furthermore, direct comparisons of clinical outcomes between patients with and without QST changes remain limited; current literature more frequently shows partial correspondence rather than a stable responder/non-responder classification [58, 60].

fMRI provides system-level evidence by enabling observation of changes in pain-relevant brain regions and functional connectivity. This makes fMRI more suitable for central network exploration than for routine patient stratification [71]. Nonetheless, fMRI findings should be interpreted cautiously due to methodological heterogeneity, including differences between resting-state and task-based designs, variability in pain conditions, diversity in acupuncture protocols, and inconsistent reporting of brain regions or network-level outcomes [71]. For instance, neuroimaging studies in low back pain used both resting-state and task-state fMRI, capturing different brain activity patterns and connectivity profiles, which complicates cross-study comparisons and limits firm conclusions [71]. Quite the contrary, supportive biological readouts, including inflammatory cytokines, neuropeptides, and autonomic indices, provide additional mechanistic context. These markers can reveal biological changes associated with symptom improvement and may help link psychophysical and clinical outcomes. Nevertheless, these markers alone cannot establish the causal mechanisms of acupuncture [60].

Collectively, these tools differ in nature and should not be regarded as interchangeable evi-

Table 2. Key translational assessment tools and their application levels in acupuncture research on central sensitization in chronic pain

Tool/measure	Primary dimension reflected	Main application	Strengths	Limitations	Potential value in acupuncture research
CSI (Central Sensitization Inventory)	Screening of central sensitization-related phenotype and symptom burden	Participant stratification, subgroup analysis, and clinical phenotype identification	Easy to administer, clinically feasible, suitable for large-sample studies	It is a patient-reported tool and potentially be influenced by subjective perception, comorbid symptoms, and overall symptom burden; it cannot be considered a direct mechanistic measure and is not yet a validated predictor of acupuncture responsiveness	Useful for identifying individuals with a potentially high central sensitization-related burden and for supporting phenotype-based interpretation of treatment heterogeneity, but it should not be used alone to infer mechanism or predict treatment response
QST (Quantitative Sensory Testing)	Pain processing characteristics, such as pain threshold, pain sensitivity, and temporal summation	Quantification of central amplification and sensory abnormalities	Relatively close to pain-processing mechanisms and provides mechanistically relevant information beyond symptom scales alone	Operationally demanding, highly dependent on standardization, and limited in cross-study comparability; predictive findings are not consistent across pain conditions, and direct responder/non-responder classification based on QST change remains limited	Useful for assessing whether acupuncture potentially influences pain amplification, sensory sensitivity, or temporal summation, and for exploring whether psychophysical changes parallel, dissociate from, or only partially correspond to symptom improvement
CPM (Conditioned Pain Modulation)	Endogenous descending inhibitory function	Assessment of descending pain modulation and mechanistic variation beneath symptom-level outcomes	Strong mechanistic relevance and potential to reflect descending inhibitory status	Sensitive to protocol design and testing conditions; evidence remains limited and not yet sufficient for routine clinical stratification	Useful for examining whether acupuncture potentially influences descending inhibitory function and for identifying mechanistic heterogeneity that potentially not be captured by pain scores alone
fMRI	Brain network activity and functional connectivity changes	Central mechanism exploration, network-level analysis, and translational neuroimaging studies	Enables observation of acupuncture-related brain network changes at the systems level	Methodologically heterogeneous, including resting-state vs task-based designs, differences in pain conditions, acupuncture protocols, control conditions, and reported brain regions/network outcomes; findings are informative but not yet sufficiently standardized for routine stratification	Useful for identifying recurring network-level themes and exploring central mechanisms of acupuncture analgesia, but current evidence does not support a single uniform neuroimaging signature across CP conditions
Autonomic function indices (e.g., HRV)	Autonomic nervous system status	Auxiliary assessment of autonomic-immune axis changes	Noninvasive and suitable for repeated measurements	Limited specificity and easily influenced by multiple physiological and contextual factors	Useful for supplementing the interpretation of vagal modulation, stress response, and symptom-cluster improvement
Inflammatory cytokines/neuropeptides and related biomarkers	Biological background signals	Supportive mechanistic readouts	Can be linked to hypotheses regarding neuroinflammation or analgesia	High variability, limited specificity and consistency, and inability to establish mechanisms on their own	Best used as supportive evidence to indicate whether symptom changes are accompanied by changes in the biological background

dence. The CSI tool is primarily used for phenotype screening, QST and CPM are employed to assess sensory processing and pain modulation, fMRI evaluates network-level mechanisms, and biomarkers provide supportive biological context. Future acupuncture studies should adopt a multidimensional assessment framework encompassing symptom scales, functional evaluations, phenotype screening, psychophysical testing, neuroimaging, and selected biomarkers. Such an approach may enhance mechanistic understanding, improve interpretation across multiple levels of evidence, and provide a more comprehensive evaluation of acupuncture efficacy [60, 71].

Standardization of electroacupuncture parameters and patient stratification: Electroacupuncture protocols vary greatly across clinical studies, with frequency, stimulation intensity, treatment duration, and session number all potentially influencing treatment outcomes [60]. Several patient-related factors, including consciousness state, disease duration, comorbid conditions, symptom fluctuation, and treatment tolerance, potentially affect clinical dosing strategies and limit the direct translation of preclinical stimulation parameters to human practice [60].

Standardization of electroacupuncture parameters should extend beyond frequency, intensity, and treatment course to include comprehensive reporting of intervention details. The STRICTA guideline recommends specifying the treatment rationale, needle depth, stimulation method, session frequency, treatment course, and control procedures. Nevertheless, many randomized trials on acupuncture for CP still report incomplete details on needle depth, treatment context, and sham acupuncture design. This omission is significant because sham acupuncture is not always inert; touch stimulation, structured care process, and personal expectations may affect analgesic responses, potentially reducing differences among treatment groups [72]. Inadequate reporting hampers reproducibility, inter-study comparisons, and mechanistic interpretation, as it adds difficulty to discern whether observed effects are attributable to acupuncture itself or to the way the treatment was delivered.

Emerging studies have explored the influence of different electroacupuncture parameters on treatment outcomes. Nonetheless, clinical parameter ranges should not be assumed to correspond directly to preclinical electroacupuncture models, where stimulation conditions in animal experiments are more tightly controlled and may not fully reflect awake patients' experiences. For instance, in older adults with chronic non-specific low back pain, randomized trials have manipulated electroacupuncture frequency as an independent variable, suggesting that the parameter selection can significantly affect results [72]. Simultaneously, data-mining analyses in conditions such as osteoarthritis further indicate significant heterogeneity in clinical parameter combinations, emphasizing the need for more reproducible parameter windows and more consistent reporting standards.

From a mechanistic perspective, low-frequency and high-frequency electroacupuncture may recruit different endogenous analgesic systems. The clinical relevance of these mechanistic differences depends on the tolerability and sustainability of stimulation intensity, session structure, and cumulative treatment dose in awake patients over extended treatment courses [60]. Accordingly, future studies should avoid inferring mechanisms only from a single pain score. Instead, trials should simultaneously assess stimulation parameters, potential mechanistic targets, and clinical outcomes to strengthen the correspondence between treatment parameters, underlying mechanisms, and therapeutic efficacy [62].

In addition to stimulation parameters, baseline patient characteristics are also critical determinants of treatment heterogeneity, particularly in populations with a high burden of CS-associated features. In such patients, sufficient treatment duration, higher session frequency, or a more "desensitization-oriented" strategy may be more likely to yield benefit than a low-dose, short-course intervention. For instance, in fibromyalgia cohorts, indicators of central amplification such as temporal summation have been shown to predict acupuncture response, suggesting that patients with a higher baseline burden of CS-associated features may require longer or more intensive treatment [56]. In contrast, the predictive value of temporal summation appears less stable in chronic low back pain, suggesting that stratification

tools cannot be universally applied across distinct pain conditions and highlighting the need for disease-specific or phenotype-specific stratification approaches [70].

Based on current evidence, a feasible strategy is to predefine the range of electroacupuncture frequency and intensity at the study design stage, report these parameters comprehensively, and explicitly justify how the selected clinical dosing scheme relates to or differs from preclinical parameter settings. At the statistical analysis stage, baseline CS-associated phenotypes, QST characteristics, emotional comorbidity, disease duration, and other key clinical variables should be included in stratified analyses or interaction tests, so that clinical treatment heterogeneity can be converted into interpretable findings [73-75]. In populations with a high burden of CS-associated features, concurrent observation of pain reduction and shifts in QST indicators toward a desensitization pattern could help advance acupuncture analgesia from an experience-based therapy toward a more precision-oriented intervention [56, 76].

More importantly, future precision-oriented study designs should incorporate responder analysis at the protocol stage, rather than treating it only as a post hoc exploratory approach. In CP acupuncture research, recording central sensitization phenotype, pain distribution, emotional comorbidity, coping style, and prior treatment response prior to enrollment, combined with prespecified subgroup analyses or interaction tests, could enhance the identification of true responder populations. Precision-oriented acupuncture research should not focus solely on a single biomarker, but rather establish a testable link between patient phenotype, treatment parameters, proposed mechanisms, and clinical outcomes.

Conclusion

Contemporary CP management has shifted from single-treatment care toward multimodal care [60]. In this context, acupuncture should not be viewed only as a stand-alone analgesic therapy but rather as an integral part of broader pain management strategies. Current evidence suggests that acupuncture can relieve pain in the short term, especially electroacupuncture, and may modulate neuroinflammation and central sensitization-associated processes. This has important clinical implications, as many patients with CP also have poor sleep, fatigue, emotional disturbances, and functional limitations. Accordingly, reliance on pain scores alone to evaluate acupuncture's effect is insufficient. Integration with exercise-based rehabilitation, psychological intervention, and pharmacotherapy may yield more desirable results. Nonetheless, every related result must be explained with much careful thought. CP conditions differ in their predominant mechanisms, acupuncture studies also differ in stimulation parameters, treatment dose, and control design, and a large proportion of mechanistic evidence derives from animal studies. Translational assessment tools, including CSI, QST, CPM, fMRI, autonomic indices, and biomarkers, remain incompletely standardized [71].

Accordingly, future research should move beyond reliance on pain scores alone and incorporate disease specificity, phenotype stratification, standardized intervention parameter, and multidimensional endpoint designs. High-quality prospective studies that integrate symptom outcomes, functional measures, and mechanism-relevant readouts within the same framework will be essential for clarifying which patients are most likely to benefit from acupuncture and through which mechanisms such benefits occur [71, 77]. Establishing a reproducible association among phenotype, intervention parameters, mechanistic pathways, and clinical outcome will be pivotal for more rigorously testing the precision application and translational value of acupuncture in CP.

Disclosure of conflict of interest

None.

Abbreviations

CP, chronic pain; IASP, International Association for the Study of Pain; CS, central sensitization; MeSH, Medical Subject Headings; CSI, Central Sensitization Inventory; QST, quantitative sensory testing; CPM, conditioned pain modulation; fMRI, functional magnetic resonance imaging; DPMS, descending pain modulatory system; PAG, periaqueductal gray; RVM, rostral ventromedial medulla; PAG-RVM, periaqueductal gray-rostral ventromedial medulla; CP/CPPS,

chronic prostatitis/chronic pelvic pain syndrome; VAS, Visual Analog Scale; NRS, Numeric Rating Scale; LTP, long-term potentiation; TLR4, Toll-like receptor 4; NF-κB, nuclear factor kappa B; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; COX-2, cyclooxygenase-2; Iba1, ionized calcium-binding adapter molecule 1; GABA, gamma-aminobutyric acid; CONSORT, Consolidated Standards of Reporting Trials; STRICTA, Standards for Reporting Interventions in Clinical Trials of Acupuncture; CX3CL1, C-X3-C motif chemokine ligand 1; HRV, heart rate variability; MMCP, mixed-mechanism chronic pain.

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