Allodynia: Pathophysiology and emerging management strategies (Review)

BHARATH KANUMURI SAMPANGI and MURALIDHARAN PALAYYAN

Department of Pharmacology, Chettinad School of Pharmaceutical Sciences, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam, Tamil Nadu 603103, India

Received September 1, 2025; Accepted February 4, 2026

DOI: 10.3892/wasj.2026.444

Abstract. Allodynia is a painful condition in which normal sensations, such as a light touch, light pressure or mild changes in temperature, are experienced as extremely painful sensations. It results from disruptions in the body pain pathways and begins with overactive nerve endings and ion channels, such as transient receptor potential vanilloid 1, transient receptor potential ankyrin 1 and voltage-gated sodium channels such as Nav1.8, which are markedly affected by inflammation and glial cell activity. Over time, the nervous system itself becomes hypersensitive with the pain centers of the brain, including the anterior cingulate cortex and insula, influencing not only the physical but also the emotional experience of pain. Doctors use such instruments as sensory testing, nerve fiber analysis and advanced imaging for a better understanding on these changes. Medication providing temporary relief includes gabapentinoids, serotonin-norepinephrine reuptake inhibitors and tricyclic antidepressants, while some modified therapies are aimed at specific ion channels and immune pathways with promising results. Alongside the use of drugs, other methods such as spinal cord stimulation, repetitive transcranial magnetic stimulation, transcutaneous electrical nerve stimulation, cognitive behavioral therapy and mirror therapy aid in retraining the nervous system. Due to the individuality of the condition, the most effective treatment is a combination of medication and behavioral and rehabilitative treatments to restore the balance and to improve the quality of life of patients

Correspondence to: Dr Muralidharan Palayyan, Department of Pharmacology, Chettinad School of Pharmaceutical Sciences, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam, Tamil Nadu 603103, India
E-mail: muralidharanp@care.edu.in

Abbreviations: ACC, anterior cingulate cortex; BDNF, brain-derived neurotrophic factor; CBT, cognitive behavioral therapy; CGRP, calcitonin gene-related peptide; CIPN, chemotherapy-induced peripheral neuropathy; DRG, dorsal root ganglia; fMRI, functional magnetic resonance imaging; LTP, long-term potentiation; NGF, nerve growth factor; rTMS, repetitive transcranial magnetic stimulation; SCS, spinal cord stimulation; SNRIs, serotonin-norepinephrine reuptake inhibitors; TENS, transcutaneous electrical nerve stimulation; TNF-α, tumor necrosis factor-alpha; TRPA1, transient receptor potential ankyrin 1; TRPM8, transient receptor potential melastatin 8; TRPV1, transient receptor potential vanilloid 1

Key words: allodynia, central sensitization, neuropathic pain, nociceptors, ion channels, pain modulation

Contents

1. Introduction

The term ‘allodynia’ was introduced by Professor Paul Potter and it is derived from the Greek words ‘allos’, which means other and ‘odynia’ means pain. Allodynia is a health condition where pain is brought about by an event that is not considered painful, such as a simple touch or light temperature. The International Association for the Study Pain (IASP) identifies allodynia as a type of pain, which is triggered by a stimulus that does not normally cause pain. In the earlier period, it had been confused with hyperalgesia. Hyperalgesia refers to a heightened and excessive response to pain. As illustrated in Fig. 1, advances in pain science have clarified that allodynia and hyperalgesia are distinct phenomena with different underlying mechanisms, despite their clinical overlap (1). Allodynia is mainly a deviant activation of low-threshold mechanoreceptors, particularly Aβ fibers, which transmit non-nociceptive signals.

Pain disorders and allodynia are considered as a serious global health issue and ~20% of the population suffers from these conditions. Of these, neuropathic pain is one of the main causes of allodynia. It is estimated that 6.9 to 10% of the global population suffers with neuropathic pain and out of these cases, 15-50% have allodynia (2). Neuropathic pain generally develops as a result of injury or a malfunction in the peripheral nervous system and results in changes in pain signaling to and from the muscles, as well as increased sensitivity (3).

Allodynia is commonly observed blearious neurological and chronic pain disorders, which suggests that there are major alterations in processing. One such condition, trigeminal neuralgia, is a key example of a disorder commonly associated with stimulus-evoked allodynia. Trigeminal neuralgia can be defined as episodic, severe facial pain distributed over the trigeminal nerve distribution often of the great intensity, precipitated by even light touch or minor temperature changes. This connection highlights the more general relevance of allodynia that it is able to occur not only in systemic neuropathies, but also in localized nerve diseases, such as trigeminal neuralgia associated with allodynia (4).

Several other conditions are also shown to have a strong association with allodynia. For example, neuropathic pain and touch-evoked pain responses are common with the complication of diabetes and diabetic neuropathy (5). Postherpetic neuralgia (PHN), which follows the reactivation of the varicella-zoster virus, may result in persistent allodynia due to damage to the nerves (6). Phantom limb pain in amputees, caused by neuroma formation and maladaptive brain plasticity is another type of allodynia (7). In the case of migraines, individuals often develop cutaneous allodynia with minimal activity leading to pain such as brushing hair or wearing glasses (8). Those with fibromyalgia often experience the presence of mechanical allodynia to light touch (9). Complex regional pain syndrome (CRPS), which commonly occurs following an injury or surgery is another condition where allodynia is a critical factor and can result in prolonged and heightened pain (10). Multiple sclerosis is an example of a disease in which demyelination of central nervous system fibers can lead to allodynia (11). Central post-stroke pain and spinal cord injury additionally involve altered sensory processing as one of the contributors to the development of allodynia (12,13). Moreover, chemotherapy-induced peripheral neuropathy (CIPN), which is caused by neurotoxic agents, such as paclitaxel and oxaliplatin, often causes sensory disturbances such as allodynia owing to peripheral sensory neuron damage (14).

Despite the high prevalence of allodynia in these and other clinical conditions, it remains under study and is not yet fully understood. This is mainly due to the complex, multimodal nature of the condition, and the range of mechanisms involved in its development. A complete understanding of allodynia requires a more in-depth understanding of both peripheral and central sensitization processes and the role of different sensory fibers, nociceptors, ion channels and intracellular signaling pathways. Of particular interest are transient receptor potential (TRP) channels of which transient receptor potential vanilloid 1 (TRPV1) and transient receptor potential ankyrin 1 (TRPA1) are crucial in nociceptor plasticity and stress responses, as well as transcription factors, such as activating transcription factor (ATF)3 (15). Advances in two-photon calcium imaging and genetic approaches, including subtype-specific neuronal labeling and ablation studies, have revealed significant functional heterogeneity among polymodal nociceptors and their roles in nociceptive signal amplification (16).

Clinically, the correct diagnosis and management of allodynia require differentiation between different types, e.g., mechanical static, mechanical dynamic and thermal allodynia, which can be challenging. Specialized diagnostic tools, such as quantitative sensory testing (QST), intraepidermal nerve fiber density (IENFD) analysis, and neuroimaging techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography are key to determining the exact nature of the condition (17).

The aim of the present review was to provide comprehensive knowledge on allodynia that will include the classification of the condition, the pathophysiology of the condition, the molecular pathway, the diagnostic process and the treatment methods, both the traditional and the new ones. The methods of treatment are founded on long-established pharmacological treatments, including gabapentinoids and serotonin-norepinephrine reuptake inhibitors, (SNRIs) as well as topical anesthetics and new targeted treatments such as sodium channels (Nav1.7, Nav1.8), nerve growth factor (NGF) and angiotensin II type 2 receptors. Besides the pharmacological approaches, non-pharmacological protocols, which include transcutaneous electrical nerve stimulation (TENS), mirror therapy, repetitive transcranial magnetic stimulation (rTMS) and cognitive behavioral therapy (CBT) have also been examined to identify their potential to regulate pain and also help in rehabilitation. Another way to treat pain is by using spinal cord stimulation (SCS).

A new mini-review on allodynia is required as it is a complex disease, and it is difficult to diagnose and treat. Despite immense progress being made in the understanding of the condition, it does tend to be overlooked in the clinical setting. Recent advances on molecular mechanisms, particularly on peripheral and central sensitization, identify novel targets of treatment that are yet to be completely explored. The present review aimed to consolidate the most recent research, therapeutic approaches and diagnostic techniques in order to improve the outcomes of the patient, with in an aim to improve the diagnosis and to develop personalized strategies for treatment of allodynia.

2. Classification of allodynia

Allodynia is categorized according to the nature of the stimulus that causes pain, with various sensory modalities and types of stimuli as illustrated in Fig. 2. Dynamic mechanical allodynia is defined as pain generated by light, and moving stimuli such as brushing or mild stroking, and it is largely mediated by myelinated Aβ fibers. This subtype is commonly examined with soft brushes or cotton swabs (18). Static mechanical (tactile) allodynia is caused by sustained pressure or contact without movement and affects Aδ fibers (19). Thermal allodynia is characterized by pain reactions to modest temperature changes, such as cold or heat, which are primarily mediated by Aδ and C fibers (20).

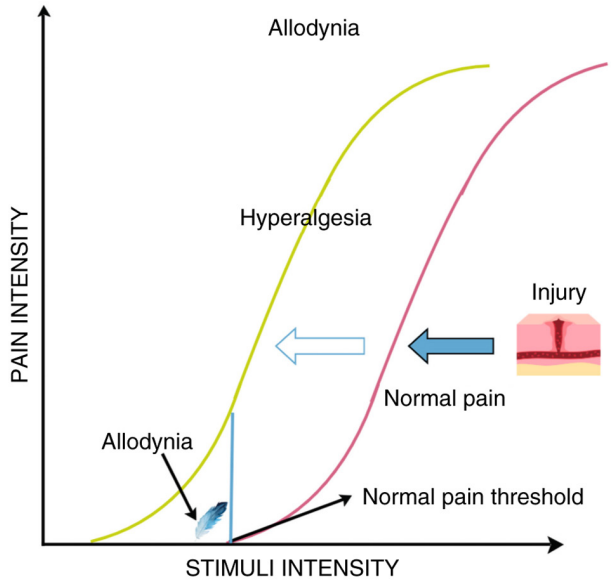

Figure 1. Difference between allodynia and hyperalgesia. The diagram aims to provide a sense of how pain perception can change following injury. Under normal conditions, pain only begins when some stimulus surpasses a threshold, as indicated by the pink curve. In hyperalgesia, which is indicated by the light green curve, the same stimulus causes a stronger pain response than normal. In allodynia, which is defined by the blue curve, touching stimuli, which are normally gentle and non-painful, elicit pain at levels below the normal threshold. Together, these altered responses illustrate the mechanisms through which nerve signaling can become distorted to enact enlarged, or misplaced, pain sensations in chronic pain states.

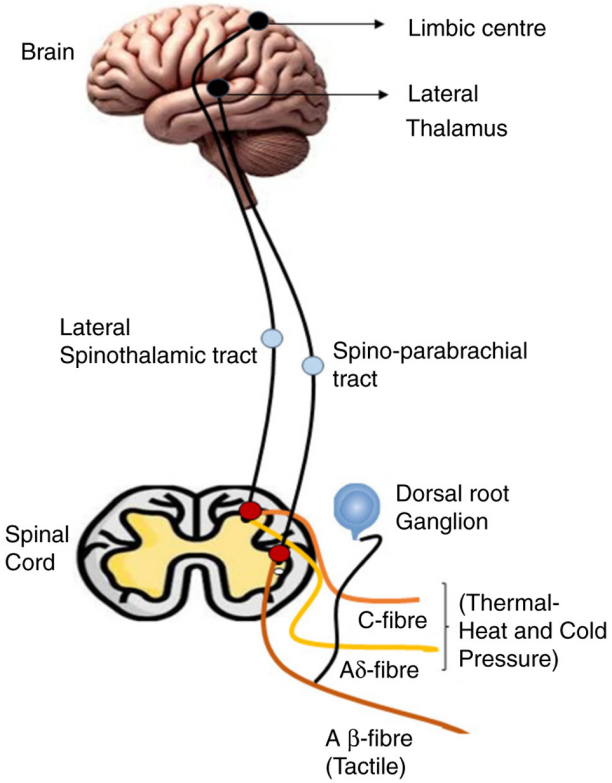

Figure 2. Schematic illustration of sensory modalities in allodynia. The image illustrates how different types of sensations such as touch, pressure and temperature travel from the body to the brain. Specialized nerve fibers (Aβ, Aδ and C-fibers) carry these signals through the spinal cord. Some follow the lateral spinothalamic tract to the lateral thalamus, aiding in the recognition and location of pain. Others follow the spino-parabrachial tract to the limbic center, where emotional responses to pain are processed. Together, these pathways explain not only how pain is perceived, but also the emotional reaction to pain.

Cold allodynia is typically observed in conditions including post-stroke pain and CIPN (21). Lastly, punctate allodynia is a mechanical subtype triggered by pinprick or monofilament stimulation that activates many nociceptive fibers (22). This categorization (presented in Table I) helps medical professionals and researchers to discover the underlying neuropathic processes and to choose an appropriate diagnostic and curative methods.

3. Polymodal nociceptors

Allodynia is rooted in the function of nociceptors, particularly polymodal types that respond to mechanical, thermal and chemical stimuli. First described by Bessou and Perl (23) in 1969, these neurons are primarily unmyelinated C fibers, with a smaller subset of lightly myelinated Aδ fibers. Both contribute to pain signal transmission at different conduction speeds, shaping the intensity and timing of pain perception.

Polymodal nociceptors have large activation thresholds under normal physiological conditions and become sensitive only in the presence of inflammation, tissue damage, or chemical mediators. This sensitization reduces their activation threshold and causes aberrant excitability, which contributes to the development of allodynia and hyperalgesia. When activated, polymodal nociceptors transmit action potentials through the dorsal root ganglia (DRG) to the central nervous system (CNS), where pain is perceived. Their peripheral terminals release neuropeptides such as substance P and calcitonin gene-related peptide (CGRP), which promote neurogenic inflammation and amplify local pain signaling.

Under normal physiological conditions, these neurons exhibit high activation thresholds; however, inflammation, tissue injury, or chemical mediators lower these thresholds and increase neuronal excitability, contributing to sensitization, allodynia and hyperalgesia (24). C fibers conduct slow, dull, and persistent pain signals (~0.6-1.1 m/sec), whereas Aδ fibers transmit faster, sharp pain (3-10 m/sec) (25).

Polymodal nociceptors adapt to various harmful stimuli through the dynamic expression of specific ion channels, TRPV1 for heat, TRPA1 for chemical or oxidative stress, and Piezo2 for mechanotransduction. These channels enable the integration and encoding of diverse noxious signals (26).

Electrophysiological techniques such as microneurography have allowed direct recordings from human nociceptors, enabling the classification of polymodal subtypes based on their stimulus responses. Among these, ‘silent’ nociceptors that are normally unresponsive to mechanical input, become active during inflammation and illustrating the system's adaptability (27). These insights underscore the complexity of nociceptor subtypes and their role in transforming environmental stimuli into persistent pain.

Polymodal nociceptors are located in both superficial and deep tissues ending in free nerve terminals. Their receptive fields may be distinct or overlapping, reflecting their integrative role in pain detection and amplification (24). This functional

Table I. Classification of allodynia based on stimulus modality.

Type of allodynia	Stimulus characteristic	Fiber type involved	Common diagnostic tools	Associated conditions
Dynamic mechanical allodynia	Light, moving stimuli (e.g., brushing, stroking)	Myelinated Aβ fibers	Soft brush, cotton swab	Neuropathic pain, fibromyalgia
Static mechanical allodynia	Steady pressure or touch without movement	Aδ fibers	Blunt probe, fingertip pressure	CRPS, PHN
Punctate allodynia	Pinprick or monofilament stimulation	Aδ and C nociceptive fibers	Von Frey filaments	Peripheral neuropathy, diabetic neuropathy
Thermal allodynia (cold/heat)	Minor cold or heat changes	Aδ and C fibers	Thermorollers, temperature-controlled probes	Post-stroke pain, chemotherapy-induced neuropathy

CRPS, complex regional pain syndrome; PHN, postherpetic neuralgia.

versatility enables them to contribute to both protective and pathological pain states, particularly in chronic conditions such as allodynia.

Recent research has identified zinc finger CCHC-type containing 12 (Zcchc12)-positive DRG neurons as key polymodal sensors involved in both thermal and mechanical pain. The ablation of these neurons significantly reduces sensitivity to both stimuli, underscoring their integrative role in nociception (28). As primary detectors and amplifiers of peripheral pain, polymodal nociceptors play a central role in the neurobiology of allodynia through their molecular adaptability and broad sensory responsiveness.

4. Peripheral mechanisms of allodynia

A number of types of allodynia originate from peripheral sensitization, marked by a lowered activation threshold and increased responsiveness of nociceptors to external stimuli. This heightened sensitivity often follows tissue injury or inflammation, where the release of inflammatory mediators alters nociceptor function.

Chemicals such as bradykinin, prostaglandins, ATP, serotonin, histamine and pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin (IL)-1β interact with ion channels on nociceptive terminals. Key channels involved in this process include voltage-gated sodium channels (Nav1.7 and Nav1.8), calcium channels and TRP channels, particularly TRPV1 and TRPA1, which collectively enhance neuronal excitability and pain signaling.

Sensory neurons become hyperexcitable when ion channels are upregulated, phosphorylated, or have more efficient membrane trafficking. During inflammation, the NGF binds to its receptor, tropomyosin receptor kinase A (TrkA), on nociceptors. This interaction triggers transcriptional upregulation of pain-related ion channels, amplifying peripheral nociceptive signaling (29).

Peripheral nerve injury can also lead to ectopic activity, the spontaneous generation of action potentials in damaged nerves or DRG neurons. This aberrant excitability arises from abnormal ion channel redistribution and pathological sprouting of Aβ fibers into the superficial dorsal horn. These low-threshold fibers may inappropriately activate pain pathways in response to normally non-painful stimuli, contributing to the development of allodynia (30).

Neuroimmune crosstalk arises when macrophages infiltrate sites of nerve injury or inflammation, releasing pro-inflammatory cytokines, such as TNF-α and IL-1β that sustain nociceptor sensitivity. Simultaneously, oxidative stress leads to the generation of reactive oxygen species, which impair mitochondrial function and further increase nociceptor excitability (31).

Mechanotransduction channels such as Piezo2, which normally mediate light-touch sensation, have also been implicated in mechanical allodynia. Sensitization or upregulation of Piezo2 enhances neuronal responsiveness to mechanical stimuli, and targeted deletion of Piezo2 in sensory neurons significantly reduces mechanical hypersensitivity in animal models, underscoring its role in pathological pain processing (32).

Peripheral sensitization is not merely a temporary electrical shift; it can cause long-term changes in nociceptor phenotype and gene expression. ATF3, a stress-response marker, is elevated in DRG neurons after nerve damage, which might indicate neuronal reorganization and the shift to chronic pain (33). Collectively, these molecular, electrophysiological and immunological alterations contribute to the onset and duration of allodynia by increasing nociceptor excitability at the peripheral level.

5. Central sensitization and spinal mechanisms

Central sensitization is a key driver of chronic pain and allodynia. It involves the increased excitability and synaptic efficiency of neurons within the CNS, particularly in the dorsal horn of the spinal cord. Sustained nociceptive input from peripheral sensitization lowers the activation threshold of these neurons, resulting in exaggerated responses to both painful and non-painful stimuli (34).

A defining feature of central sensitization is the abnormal recruitment of low-threshold Aβ fibers into pain pathways. These fibers, which normally transmit light touch, gain access to nociceptive circuits due to structural and functional plasticity. As a result, non-painful stimuli are misinterpreted as painful, a phenomenon that characterizes mechanical allodynia (35).

Central sensitization involves the activation of N-methyl-D-aspartate (NMDA) receptors, the increase in intracellular calcium levels, and the subsequent stimulation of protein kinases such as protein kinase C (PKC) and calcium/calmodulin-dependent protein kinase II (CaMKII). These changes enhance synaptic transmission and trigger long-term alterations in gene expression through transcription factors like cAMP response element-binding protein. Additionally, reduced inhibitory signaling via gamma-aminobutyric acid (GABA) and glycine receptors leads to disinhibition and heightened excitability within spinal circuits (36,37).

Chronic pain induces the activation of microglia and astrocytes, which results in the release of pro-inflammatory cytokines, such as IL-1β, TNF-α, various chemokines and brain-derived neurotrophic factor (BDNF). These glial-derived factors intensify excitatory neurotransmission and contribute to the persistence of central sensitization (38).

In allodynia, wide dynamic range neurons in the spinal cord typically involved in encoding stimulus intensity across both noxious and non-noxious inputs become excessively responsive. This pathological amplification of sensory input leads to the misinterpretation of harmless stimuli as painful, a defining feature of allodynia (39).

Supraspinal mechanisms play a crucial role in maintaining the central sensitization. Functional and structural changes in brain regions involved in pain processing and affective modulation, including the anterior cingulate cortex (ACC), insular cortex and thalamus, have been demonstrated in individuals with chronic allodynia and neuropathic pain, contributing to disrupted pain modulation and altered emotional processing (40,41).

Moreover, long-term potentiation (LTP)-like activity in these regions mirrors synaptic plasticity observed in learning and memory, thereby reinforcing the chronicity of pain (42,43). Together, these spinal and supraspinal adaptations constitute the neurobiological foundation of central sensitization, highlighting the integrated roles of neuronal and glial mechanisms in the development and persistence of allodynia.

6. LTP and structural plasticity in allodynia

LTP, a well-established mechanism of synaptic plasticity involved in learning and memory, has also emerged as a critical pathophysiological process in the development and persistence of chronic pain and allodynia. In nociceptive pathways, LTP refers to a sustained enhancement of synaptic strength following the high-frequency or prolonged stimulation of afferent nociceptors, particularly within the dorsal horn of the spinal cord. This heightened synaptic efficacy lowers the threshold for neuronal activation, thereby facilitating the transmission of both noxious and non-noxious sensory input as pain (44,45).

In pain pathways, LTP is primarily mediated by glutamatergic neurotransmission through NMDA receptors, which permit calcium influx into the postsynaptic neuron following sufficient depolarization (46). The increase in intracellular calcium activates second messenger systems, particularly PKC and CaMKII, which phosphorylate subunits of AMPA and NMDA receptors and modulate ion channel function. These molecular events facilitate synaptic plasticity and increase the excitability of dorsal horn neurons (47).

Glial activation, particularly in microglia and astrocytes, plays a central role in both the initiation and persistence of central sensitization. Upon activation, these glial cells release pro-inflammatory mediators, such as IL-1β, TNF-α and BDNF. BDNF binds to tropomyosin receptor kinase B receptors and disrupts inhibitory GABAergic transmission by altering the neuronal chloride gradient. This shift converts inhibitory signals into excitatory ones, a process known as disinhibition (48).

Structural alterations often accompany the functional changes associated with central sensitization. Aβ fibers, which typically transmit innocuous tactile input to laminae III-V of the dorsal horn, may aberrantly sprout into lamina II, the primary termination zone for nociceptive C fibers (49). This maladaptive reorganization allows low-threshold stimuli, such as light touch to engage pain pathways, thereby contributing to the development of mechanical allodynia. Additionally, supraspinal plasticity further amplifies and sustains chronic pain (50).

LTP-like processes have been identified in higher-order brain regions, such as the ACC and insula, where sustained nociceptive input amplifies the emotional and affective dimensions of pain. fMRI studies reveal that structural and functional alterations in these regions are closely linked to chronic pain and contribute to its persistence (51). These molecular, cellular and structural changes illustrate how LTP, originally a mechanism for learning and memory, becomes maladaptive in pain circuits, leading to distorted pain perception even after the initial injury or stimulus has resolved (52).

7. Differential diagnosis and clinical testing of allodynia

The diagnosis if allodynia requires an understanding of sensory disturbances and a focused clinical evaluation to distinguish it from conditions, such as hyperalgesia (exaggerated response to painful stimuli), dysesthesia (unpleasant abnormal sensation) and paresthesia (abnormal but not necessarily unpleasant sensation). Allodynia is pain caused by normally non-painful stimuli and is classified by stimulus type: Dynamic mechanical, static mechanical, thermal (heat or cold), or punctate. Assessment begins with a detailed history emphasizing pain quality, location and triggers, followed by bedside sensory testing with standard stimuli (53).

Mechanical dynamic allodynia is assessed with the tools, such as a cotton swab, soft brush, or gauze gently stroked across the skin. A painful response to this light tactile stimulation indicates dynamic allodynia. Mechanical static allodynia is evaluated by applying steady, non-moving pressure, commonly using the blunt end of a pen or a calibrated pressure algometer. Thermal allodynia is tested with cold metal instruments (e.g., a tuning fork or cold roller) or heat

stimulators to evaluate sensitivity to temperature extremes. The reported pain is compared to responses from unaffected contralateral or adjacent areas (54).

Basic laboratory evaluations help to identify the systemic or metabolic causes of allodynia. A complete blood count and basic metabolic panel assess general health, while an elevated erythrocyte sedimentation rate or elevated C-reactive protein levels may indicate inflammation or autoimmune disease. Hemoglobin A1c is used to screen for diabetes, a common cause of neuropathy. Vitamin B12, thiamine and thyroid-stimulating hormone levels help to detect nutritional or endocrine-related neuropathies (4).

QST is a standardized method used for assessing somatosensory function with reproducible stimuli. It employs tools such as von Frey filaments for mechanical thresholds, thermodes for thermal sensitivity, and pressure algometers for deep tissue pain (55). QST is widely used in clinical and research settings to identify sensory deficits and hypersensitivity with precision.

In suspected small fiber neuropathy, a skin biopsy provides histological evidence through the measurement of IENFD. A reduced IENFD indicates small fiber degeneration and serves as a diagnostic marker for conditions such as diabetic and chemotherapy-induced neuropathy that are commonly linked to allodynia (56).

Imaging is not routinely required, but may be indicated when central pathology is suspected. A computed tomography head scan can identify acute events such as stroke in aged patients, while an MRI is more sensitive for detecting demyelinating diseases (e.g., multiple sclerosis) or structural lesions affecting pain pathways. Imaging decisions should be guided by neurological findings and clinical context (40). In addition, validated screening tools such as the Douleur Neuropathique 4 questionnaire and the Leeds Assessment of Neuropathic Symptoms and Signs provide a standardized approach for identifying neuropathic pain features, including allodynia, in outpatient settings (57). These assessments combine symptom-based descriptors (e.g., burning and tingling) with simple bedside tests, such as evaluating responses to light touch and pinprick, making them both efficient and clinically practical.

Electromyography (EMG) is a diagnostic technique that assesses muscle activation by recording electrical activity using electrodes placed either on the skin or inserted into muscle fibers. While EMG does not evaluate sensory nerve function or directly measure nociceptive pathways, it plays a crucial role in differentiating the true muscular weakness from weakness due to motor neuron dysfunction. This is particularly critical when motor neuron degeneration is suspected. EMG is also valuable in localizing the site of neuropathy and in determining the association of motor component, thereby contributing to a more accurate and comprehensive neurological assessment (58).

Laser-generated heat pulses and contact-heat-evoked potentials are advanced neurophysiological techniques designed to assess thermal pain pathways. Unlike traditional somatosensory evoked potentials that rely on mechanical or electrical stimulation of sensory fibers, these methods utilize precisely controlled heat stimuli, delivered either via laser or contact heat devices, to selectively activate Aδ fibers responsible for transmitting thermal nociceptive signals. By recording the cortical responses elicited by these thermal stimuli, clinicians can objectively evaluate the integrity and function of small-diameter fibers involved in pain perception. These tools are especially valuable in diagnosing small fiber neuropathies and in research settings where a detailed assessment of thermal nociception is required (59).

8. Transcriptional and molecular markers in nociceptor plasticity

Transcriptional reprogramming within DRG neurons plays a key role in the development of allodynia. Among key molecular markers, ATF3 is widely recognized as an indicator of neuronal injury. Its expression rises rapidly following axotomy or neurotoxic insults, signaling stressed or regenerating sensory neurons. ATF3 activation through the c-Jun N-terminal kinase (JNK) pathway contributes to nociceptor hyperexcitability and peripheral sensitization (60).

ATF2, a downstream effector of p38 MAPK and JNK signaling, has been implicated in inflammatory and neuropathic pain pathways and regulates the expression of nociception-related genes such as TRPV1. Experimental studies suggest that modulation of ATF2 activity influences pain hypersensitivity, highlighting its role in chronic pain plasticity (61). Similarly, c-Jun activation promotes axonal regeneration and also contributes to hyperexcitability in the DRG via downstream effectors such as cytokines and neurotrophins.

Neurotrophic signaling is vital for maintaining nociceptor phenotype and promoting plasticity. NGF, through TrkA receptors, supports the survival of peptidergic neurons, while Ret receptor signaling favors non-peptidergic populations. Following injury, elevated NGF levels induce abnormal Aβ fiber sprouting and upregulate TRPV1 expression, contributing to mechanical and thermal allodynia (62). Zcchc12 protein is identified as a novel marker for a distinct subset of DRG neurons. Zcchc12-positive neurons respond to both mechanical and noxious heat stimuli (63).

The selective ablation of these neurons reduces heat sensitivity, indicating their role in integrating multiple nociceptive inputs. *In vivo* two-photon calcium imaging reveals increased polymodal nociceptor activity following neuropathic injury, accompanied by a reduction in modality-specific neuronal populations (64).

RNA-binding proteins such as human antigen R (HuR) regulate nociceptor plasticity at the post-transcriptional level. HuR stabilizes mRNAs encoding TrkA and IL-6 signaling components. The pharmacological inhibition of HuR reduces mechanical allodynia and neuroinflammation (65).

Metabolic regulators, such as liver kinase B1 (LKB1), which modulates AMP-activated protein kinase and cellular energy homeostasis, are also involved in nociceptor stress responses. The conditional deletion of LKB1 in sensory neurons induces spontaneous allodynia and alters pain thresholds, highlighting the link between metabolic balance and nociceptive function (66). Research has shown that T-box transcription factor 5 (Tbx5) plays a major role in the development of neuropathic allodynia (67). Following spinal nerve ligation, the expression of Tbx5 is upregulated

in the injured dorsal horn where it regulates the expression of TRPV1, which is a key ion channel involved in pain perception. This regulation is provided by epigenetic modifications in this case binding of Tbx5 to histone H3 lysine 9 acetylation H3K9Ac, causing activation of the gene. Tbx5 also interacts with transcription factors, such as GATA binding protein 4 (GATA4) and bromodomain-containing protein 4 (Brd4) that form a network that increases transcription of TRPV1 to contribute to the hypersensitivity to an allodynia. Furthermore, the signal that is expressed by Fbxo3 after nerve injury stabilizes the expression of Tbx5 and increases the expression of TRPV1. Targeting Tbx5 and its signaling pathways is a potential new pathway of therapeutic options in the treatment of neuropathic allodynia and other forms of chronic pain states (68).

9. Pain modulation and descending inhibitory pathways in allodynia

Allodynia is influenced not only by ascending nociceptive input, but also by descending pathways from the brainstem and cortex, which modulate pain transmission in the spinal dorsal horn (69).

Key structures, such as the periaqueductal gray (PAG), rostral ventromedial medulla (RVM) and locus coeruleus regulate spinal nociception through neurotransmitters such as serotonin, norepinephrine, GABA and endogenous opioids (70-72). The PAG-RVM-spinal axis controls pain via ON and OFF cells; ON cell hyperactivity contributes to chronic pain, while OFF cells inhibit nociceptive signals (73). In disorders such as neuropathy and fibromyalgia, impaired inhibition or excessive facilitation increases the spinal excitability and sensitizing responses to non-painful stimuli (74).

fMRI analyses have revealed reduced activity in inhibitory regions and heightened activation in facilitatory circuits in chronic pain (41). Diminished serotonergic and noradrenergic projections further weaken spinal inhibition, worsening sensitization (75). SNRIs, such as duloxetine and milnacipran alleviate allodynia by enhancing descending inhibitory neurotransmission through increased spinal serotonin and norepinephrine levels (76-78). Similarly, α2-adrenergic agonists such as clonidine boost noradrenergic tone and reduce neuropathic pain (79).

The limbic system, including the ACC, prefrontal cortex and amygdala, regulates the emotional aspects of pain and interfaces with descending pathways (80). Stress and emotional dysregulation can exacerbate allodynia via these top-down mechanisms. Psychological therapies such as CBT and mindfulness target top-down cortical-limbic-brainstem descending pain modulatory circuits to improve pain perception and quality of life (81). Thus, dysfunction of descending inhibition is central to chronic allodynia, and targeting these brainstem and cortical systems presents a promising treatment approach.

10. Therapeutic interventions in allodynia

Allodynia management involves in pharmacological and non-pharmacological strategies targeting the peripheral and central sensitization mechanisms, as summarized in Table II.

Pharmacological treatments. Gabapentinoids, including gabapentin and pregabalin, are lipophilic GABA analogs that inhibit calcium channels with the α2δ-1 subunit, reducing spontaneous neuronal discharges following nerve injury without affecting normal signal propagation. In burn-related neuropathic pain, they enhance descending noradrenergic activity from the locus coeruleus, suppressing pain transmission and potentially improving sleep. Preclinical and clinical studies suggest that gabapentinoids may reduce mechanical allodynia and thermal hyperalgesia following thermal injury. The randomized limited trials and observational studies report that pregabalin and gabapentin can alleviate neuropathic burn pain, reduce opioid use, and may also relieve postburn pruritus unresponsive to antihistamines (82,83).

Antidepressants such as SNRIs and tricyclic antidepressants (TCAs) may provide some relief, though they are more effective for hyperalgesia than allodynia. Antidepressants, particularly tricyclics such as nortriptyline and amitriptyline, require chronic administration to relieve neuropathic pain, including mechanical allodynia. In a mouse model, chronic, but not acute, treatment with these drugs suppressed allodynia, while fluoxetine was ineffective. The analgesic effect involved activation of the endogenous opioid system, specifically δ- and κ-opioid receptors. By contrast, gabapentin reduced allodynia through a separate, opioid-independent pathway. This highlights distinct mechanisms for antidepressants and anticonvulsants in managing neuropathic pain (43,84).

Sodium and calcium channel blockers, along with anticonvulsants, are commonly used to manage allodynia by increasing neuronal firing thresholds. Non-steroidal anti-inflammatory drugs (NSAIDs) have not demonstrated effectiveness in neuropathic pain. In the collagen-induced arthritis rheumatoid arthritis model, NSAIDs showed dose-dependent anti-inflammatory effects but failed to alleviate mechanical allodynia. Their limited impact on grip strength, a measure of functional ability, reflects this. Clinically, these findings suggest that NSAIDs alone are insufficient for managing arthritis-related pain and should be combined with other analgesics for effective relief (85).

Opioids provide limited benefit in neuropathic pain and may worsen symptoms over time; evidence supporting oxycodone is minimal. Opioids are frequently used to manage severe burn-related pain, yet few rodent studies compare their efficacy in burn-induced allodynia. A previous study evaluated the effects of morphine, oxycodone and hydrocodone on mechanical allodynia in the limb contralateral to a burn injury (86). Mice received oral opioid treatment (20 or 40 mg/kg) or saline twice daily following burn or sham injury and were assessed using von Frey filaments through day 28. Mechanical allodynia developed in the uninjured limb by day 21 post-burn. Hydrocodone significantly suppressed this contralateral allodynia, whereas morphine and oxycodone showed minimal benefit. These findings suggest that hydrocodone may be more effective in preventing burn-induced secondary allodynia, underscoring the need for further preclinical research to guide optimal opioid use in burn pain management.

Cannabis-based therapies remain controversial as current research has demonstrated limited efficacy, as well as potential adverse effects (87). Some research has been promising with cannabinoid-based medicines (CBMs), particularly those with

Table II. Mechanism-based pharmacological and non-pharmacological therapies for allodynia.

A, Pharmacological therapies

Authors, year of publication	Therapy/intervention	Mechanism of action	Clinical use/indication	(Refs.)
Jayabalan and Schnitzer, 2017	Tanezumab	NGF neutralization	Chronic musculoskeletal/allodynic pain	(94)
Kremer *et al*, 2018	Amitriptyline, Nortriptyline	SNRIs + Sodium channel blockade	Postherpetic and diabetic neuropathy	(84)
Patel *et al*, 2016	Gabapentin, pregabalin	Inhibition of α2δ subunit of voltage-gated calcium channels	Diabetic neuropathy, PHN, fibromyalgia	(83)
Andrew *et al*, 2014	EMA401	Angiotensin II type-2 receptor antagonism	CIPN, PHN	(105)
Bhaskar *et al*, 2011	Lidocaine (topical); Capsaicin 8% patch	Peripheral voltage-gated sodium channel inhibition; TRPV1 receptor desensitization	PHN, diabetic neuropathy	(91)
Bhattacharya *et al*, 2009	Carbamazepine, Vixotrigine, VX-548	Voltage-gated sodium channel blockade (Nav1.7, Nav1.8)	Trigeminal neuralgia, Diabetic Peripheral Neuropathy	(101)
Visser and Schug, 2006	Ketamine	NMDA receptor antagonism	CRPS, spinal cord injury pain	(93)

B, Non-pharmacological therapies

Authors, year of publication	Therapy/intervention	Mechanism of action	Clinical use/indication	(Refs.)
Radiansyah and Hadi, 2023	rTMS	Cortical neuromodulation	Fibromyalgia, chronic pain	(108)
Arcos-Holzinger *et al*, 2023	Virtual reality therapy	Cortical remapping and neuromodulation	CRPS	(115)
Omar Fadili *et al*, 2021	Mirror therapy	Cortical remapping	Phantom limb pain	(116)
Adler-Neal and Zeidan, 2017	Mindful Meditation, yoga	Mind-body modulation	Fibromyalgia	(117)
Suszyński *et al*, 2015	Desensitization, physical therapy	Functional restoration	Post-nerve injury	(118)
Ehde *et al*, 2014	CBT	Psychosocial and cognitive modulation	Fibromyalgia, migraine	(113)
Tashani and Johnson, 2009	TENS	Spinal gate control activation	Diabetic neuropathy, CRPS	(112)
Shrivastav and Musley, 2009	SCS	Neuromodulation	CRPS, central allodynia	(119)

NGF, nerve growth factor; SNRIs, serotonin-norepinephrine reuptake inhibitors; PHN, postherpetic neuralgia; CIPN, chemotherapy-induced peripheral neuropathy; TRPV1, transient receptor potential vanilloid 1; CRPS, complex regional pain syndrome; rTMS, repetitive transcranial magnetic stimulation; CBT, cognitive behavioral therapy; TENS, transcutaneous electrical nerve stimulation; SCS, spinal cord stimulation.

a mixture of both Δ9-tetrahydrocannabinol (D9-THC) and cannabidiol proving efficacious in conditions of pain reduction, such as diabetic neuropathy and PHN (88). For instance, drugs containing these two cannabinoids (i.e. Sativex) have had moderate success in assisting with pain relief and the quality of sleep (89). In spite of these positive findings, the results are still inconsistent with some studies showing no significant improvements. These mixed results have at times been attributed to variability in cannabinoid formulations, dosing strategies and patient demographics.

Moreover, the use of CBMs is not without issues. The psychoactive effects of D9-THC such as dizziness, cognitive

impairment and fatigue may limit the tolerability of these treatments particularly in patients who require long-term management. These negative effects, combined with concerns of study biases (from the psychoactive nature of D9-THC) are a contributing factor to the current controversy of CBM use for the treatment of allodynia. Although cannabinoids are promising, further in-depth research is required to clarify the role of cannabinoids in terms of identifying the best formulated, dosed and administered cannabinoids in order to control allodynia (90).

Topical therapies include 5% of lidocaine patches for localized neuropathic pain (e.g., PHN), and 8% of capsaicin patches, which desensitize TRPV1-expressing nociceptors, relieving static allodynia (91).

Opioid-sparing agents such as tramadol and tapentadol activate μ-opioid receptors and inhibit norepinephrine reuptake, providing dual-action analgesia for central and peripheral pain (92). Ketamine, an NMDA receptor antagonist, reverses central sensitization and is effective in refractory cases (93).

Monoclonal antibodies, such as tanezumab target NGF-TrkA signaling to reduce C-fiber sensitization in musculoskeletal allodynia (94). Mirogabalin, a newer α2δ ligand, exhibits improved CNS selectivity and efficacy in diabetic neuropathy and PHN (95).

CIPN is a major dose-limiting side-effect with no approved treatment. The selective inhibition of histone deacetylase 6 (HDAC6) using agents such as ACY-1083 and ACY-1215 has been shown to fully reverse cisplatin-induced mechanical allodynia, spontaneous pain, and numbness (96). This effect is linked to enhanced α-tubulin acetylation, improved mitochondrial transport and function and the restoration of intraepidermal nerve fiber density. These results support the inhibition of HDAC6 as a promising therapeutic option for CIPN with potential for rapid clinical translation (97).

Dual Na^+/Ca^{2+} blockers such as 820P for generalized neuropathic pain (98) and TRP channel modulators such as transient receptor potential melastatin 8 (TRPM8) antagonists, along with TRPA1 antagonist are under study for oxaliplatin-induced cold and mechanical allodynia (99).

TRP channels, particularly TRPV1-V4, TRPA1 and TRPM8, play a central role in pain perception by converting external stimuli into painful signals. In pathological states, their overactivation contributes to mechanical allodynia and thermal hyperalgesia. Endogenous lipid metabolites, primarily derived from arachidonic and linoleic acids via cyclooxygenase, lipoxygenase and cytochrome P450 pathways, are major modulators of TRP channels. These lipids can influence TRP activity either by directly binding to the channels or indirectly through G-protein coupled receptors. TRP channels thus function as lipid-sensitive sensors that integrate signals from multiple metabolic pathways, although the exact molecular mechanisms remain under investigation (100).

Sodium channel blockers, such as carbamazepine and lacosamide reduce neuronal excitability and are effective in trigeminal neuralgia and diabetic neuropathy (101). Newer selective voltage-gated sodium channel inhibitors are being explored for pain modulation. VX-548 (formerly suzetrigine), an orally bioavailable Nav1.8 blocker, has demonstrated analgesic efficacy in phase II (NCT04977336, NCT05034952) and phase III clinical trials (NCT05660538) for acute post-operative pain. However, its effectiveness for chronic neuropathic pain or mechanical and cold allodynia has not yet been established (102). By contrast, the selective Nav1.7 inhibitor PF-05089771 failed to meet predefined efficacy endpoints in a placebo-controlled clinical trial in patients with painful diabetic peripheral neuropathy, and its late-stage development for neuropathic pain indications was discontinued. Evidence for dual Nav1.7/1.8 inhibitors such as ASP9226 remains limited, and robust late-stage clinical data supporting their use in mechanical or cold allodynia are currently lacking (103,104).

Central sodium channel modulators (e.g., NRD135S.E1) and novel ligands such as Crisugabalin (HSK16149) are under investigation for PHN and diabetic neuropathy. Suzetrigine (MK-8189), a Nav1.8 blocker, has exhibited early efficacy in acute neuropathic pain (54).

EMA401, an angiotensin II type 2 receptor antagonist, reduces peripheral neuroinflammation (105). Mirtazapine, though primarily an antidepressant, has been shown to alleviate mechanical and thermal allodynia in neuropathic pain models (106). The repeated oral administration of mirtazapine (20-30 mg/kg) in rats with nerve injury significantly reduced allodynia, especially by day 14. This analgesic effect is linked to its ability to suppress proinflammatory cytokines (TNFα and IL-1β) and NF-κB activity in the brain, while enhancing the expression of the anti-inflammatory marker, IL-10. These findings suggest that mirtazapine may relieve allodynia through central neuroimmune modulation (107).

Non-pharmacological interventions. rTMS modulates cortical excitability and benefits patients with fibromyalgia and post-stroke pain (108). SCS is a procedure in which electrical impulses are delivered within the dorsal columns and this modulates pain in diseases, such as CRPS, and failed back surgery syndrome. It functions via two mechanisms to disrupt nociceptive pathways and to activate the pain inhibition systems, reducing abnormal pain processing. Studies have demonstrated that SCS exerts a significant suppressive effect on allodynia and hyperalgesia, with an increase in current perception threshold in affected areas, which appears to indicate reduced pain sensitivity. Additionally, SCS increases conditioned pain modulation with the possibility to restore the natural pain inhibition mechanisms of the body, which provides immense potential for the treatment of sensory abnormalities, such as allodynia (109,110).

Graded motor imagery and mirror therapy use cortical remapping and visual feedback to relieve movement-induced and tactile allodynia, particularly in CRPS and phantom limb pain (111). TENS activates Aβ fibers and engages spinal gate control mechanisms, reducing localized neuropathic pain (112). CBT addresses the emotional aspects of chronic pain, improving the coping and resilience in individuals with persistent allodynia (113).

Cingulotomy is a neurosurgical procedure that targets the anterior cingulate cortex, an area of the brain involved in processing both pain and emotions. In patients with allodynia, non-painful stimuli normally cause pain. This surgery can reduce the emotional distress and perception of pain signals. When the conventional treatments fail, it is considered as an alternative approach as it helps to modulate the response of

the brain to chronic pain and it can also improve the overall quality of life of patients (114).

11. Future research directions and unanswered questions

Future studies are required to focus on allodynia for a more in-depth understanding of the molecular and cellular mechanisms of peripheral and central sensitization, particularly the role of ion channels, such as Nav1.7, Nav1.8, TRPV1, TRPA1 and Piezo2, as well as the transcriptional markers, such as ATF3 and ATF2 involved in regulating nociceptor plasticity. Investigating neuroimmune crosstalk, glial activation and structural changes, such as Aβ fiber sprouting are required to explain this persistence of pain. There is also a need to refine diagnostic strategies through the improvement of quantitative sensory testing; intraepidermal nerve fiber density analysis and with advanced neuroimaging to better differentiate subtypes of allodynia to guide personalized treatment. Novel therapeutic targets, such as the NGF-TrkA signaling, angiotensin II type 2 receptors and epigenetic regulators need to be explored and non-pharmacological interventions, such as spinal cord stimulation, rTMS, TENS, mirror therapy and CBT should be optimized and combined with pharmacological treatments to improve rehabilitation and long-term outcomes.

However, despite progress, a number of questions remain unanswered. It is impossible to determine the reasons behind the development of allodynia in some individuals with nerve injury or with systemic disease and how the peripheral and central mechanisms work together on a temporal basis to perpetuate the hypersensitivity. The fact that Nav1.7 blockers were not effective in the clinical trials, even though there is ample genetic evidence for a target pain signaling circuit, is an indication that the understanding of the use of compensatory mechanisms and redundancy in pain signaling is required. Reliable biomarkers to predict response to treatment are still lacking and strategies to reverse maladaptive plasticity in nociceptive circuits remain underdeveloped. Furthermore, the emotional and brain cognitive aspects of pain induced by the brain regions, such as the anterior cingulate cortex and insula are not yet well incorporated into clinical practice. These shortcomings underscore the need to perform the mechanistic stratification of patients, longitudinal trials to determine the persistence of interventions, and translational research whereby the latest molecular findings are juxtaposed with an individualized therapeutic approach.

12. Conclusion

The present review aimed to provide a thorough discussion on allodynia, with a focus on pathophysiology, mechanisms, diagnosis, and new and forthcoming treatments. A condition in which normally non-painful stimuli are experienced as painful (allodynia) has been increasingly recognized as a key cause of the chronic pain disorders observed in the context of neuropathic injuries and related conditions, such as fibromyalgia, multiple sclerosis and diabetic neuropathy.

Key molecular mechanisms, particularly those involving ion channels, such as TRPV1, TRPA1, Nav1.7 and Nav1.8 are central to the sensitization process of nociceptors involved in peripheral and central sensitization. This is further compounded by the neuroimmune crosstalk and glial cell activation, which increases the duration of pain signals and exacerbates the experience of allodynia. A more in-depth understanding of these mechanisms may provide a prospect for the development of more specific therapies, as demonstrated in ongoing studies of particular ion channels, neuroimmune interactions and transcriptional factors, such as ATF3 and ATF2 (33,60,62).

Currently, the treatment techniques for allodynia are diverse, as medications such as gabapentinoids, SNRIs and TCAs provide some relief; however, these treatments focus mainly on neuropathic pain. Non-pharmacological methods such as spinal cord stimulation, rTMS, mirror therapy, CBT and TENS have shown positive results in modulating pain and in rehabilitation. However, more tailored treatment regimens are required as the condition remains very difficult to manage and is complex.

The unmet clinical need remains high, with numerous patients receiving inadequate symptom relief. Farther research is warranted to improve the diagnostic methods, as well as to investigate novel therapeutic opportunities, such as optimizing existing pharmacological therapies and combining interdisciplinary treatment approaches such as neuropsychological and neuro rehabilitative ones. Bridging the possible area between the molecular mechanisms of personalized care will be crucial in the improvement of the long-term outcomes of persons that suffer from allodynia.

In conclusion, although progress has been made in understanding the mechanisms involved in the pathophysiology of allodynia and in providing symptomatic relief, further more targeted and comprehensive interventions are warranted. The future of the management of allodynia is in the ongoing interdisciplinary research. including pharmacology, neuroscience, psycholog, and the latest methods of diagnostic techniques in order improve the outcomes of patients and promote personalized treatment strategies.

Acknowledgements

The authors would like to thank the Chettinad Academy of Research and Education (Deemed to be a university) for providing institutional support and research facilities that enabled the completion of this work.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Author's contributions

BKS performed the comprehensive literature search, collected and synthesized relevant articles, organized the structure and prepared the initial draft of the manuscript. MP supervised the study and conceptualized the study. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Viana F: Nociceptors: Thermal allodynia and thermal pain. Handb Clin Neurol 156: 103-119, 2018.
2. Cleveland Clinic: Allodynia: What It Is, Causes, Treatment & Types. https://my.clevelandclinic.org/health/symptoms/21570-allodynia.
3. Kumar A, Kaur H and Singh A: Neuropathic pain models caused by damage to central or peripheral nervous system. Pharmacol Rep 70: 206-216, 2018.
4. He Y and Kim P: Allodynia. StatPearls. StatPearls Publishing, Treasure Island, FL, 2023.
5. Obrosova IG: Diabetic painful and insensate neuropathy: Pathogenesis and potential treatments. Neurotherapeutics 6: 638-647, 2009.
6. Smith HS: Current therapy in pain. Elsevier Health Sciences, Philadelphia, PA, 2009.
7. Fieldsen D and Wood S: Dealing with phantom limb pain after amputation. Nurs Times 107: 21-23, 2011.
8. Ashkenazi A, Sholtzow M, Shaw J, Burstein R and Young WB: Identifying cutaneous allodynia in chronic migraine using a practical clinical method. Cephalalgia 27: 111-117, 2007.
9. Dellwo A: When Skin Hurts From a Touch With Allodynia and Fibromyalgia. Verywell health, 2025. https://www.verywellhealth.com/painful-to-touch-fibromyalgia-tactile-allodynia-3972954
10. Guthmiller KB, Dua A, Dey S and Varacallo MA: Complex regional pain syndrome. StatPearls [Internet]: StatPearls Publishing, Treasure Island, FL, 2025.
11. Pettigrew M: Hyperalgesia and Allodynia. ms Focus Magazine, 2016. https://msfocus.org/Magazine/Magazine-Items/Exclusive-Content/2022/Hyperalgesia-and-Allodynia
12. Greenspan DJ, Ohara S, Sarlani E and Lenz AF: Allodynia in patients with post-stroke central pain (CPSP) studied by statistical quantitative sensory testing within individuals. Pain 109: 357-366, 2004.
13. Lee S, Zhao X, Hatch M, Chun S and Chang E: Central neuropathic pain in spinal cord injury. Crit Rev Phys Rehabil Med 25: 159-172, 2013.
14. Sisignano M, Baron R, Scholich K and Geisslinger G: Mechanism-based treatment for chemotherapy-induced peripheral neuropathic pain. Nat Rev Neurol 10: 694-707, 2014.
15. Kaneko Y and Szallasi A: Transient receptor potential (TRP) channels: A clinical perspective. Br J Pharmacol 171: 2474-2507, 2014.
16. Girven KS and Sparta DR: Probing deep brain circuitry: New advances in in vivo calcium measurement strategies. ACS Chem Neurosci 8: 243-251, 2017.
17. Devigili G, Rinaldo S, Lombardi R, Cazzato D, Marchi M, Salvi E, Eleopra R and Lauria G: Diagnostic criteria for small fibre neuropathy in clinical practice and research. Brain 142: 3728-3736, 2019.
18. Samuelsson M, Leffler AS and Hansson P: Dynamic mechanical allodynia: On the relationship between temporo-spatial stimulus parameters and evoked pain in patients with peripheral neuropathy. Pain 115: 264-272, 2005.
19. Spicher CJ, Mathis F, Degrange B, Freund P and Rouiller EM: Static mechanical allodynia (SMA) is a paradoxical painful hypo-aesthesia: Observations derived from neuropathic pain patients treated with somatosensory rehabilitation. Somatosens Mot Res 25: 77-92, 2008.
20. Ran C, Kamalani GNA and Chen X: Modality-specific modulation of temperature representations in the spinal cord after injury. J Neurosci 41: 8210-8219, 2021.
21. Mohanan AT, Nithya S, Nomier Y, Hassan DA, Jali AM, Qadri M and Machanchery S: Stroke-induced central pain: overview of the mechanisms, management, and emerging targets of central post-stroke pain. Pharmaceuticals (Basel) 16: 1103, 2023.
22. Jensen TS and Finnerup NB: Allodynia and hyperalgesia in neuropathic pain: Clinical manifestations and mechanisms. Lancet Neurol 13: 924-935, 2014.
23. Bessou P and Perl E: Response of cutaneous sensory units with unmyelinated fibers to noxious stimuli. J Neurophysiol 32: 1025-1043, 1969.
24. Perl E, Kumazawa T, Lynn B and Kenins P: Sensitization of high threshold receptors with unmyelinated (C) afferent fibers. Prog Brain Res 43: 263-277, 1976.
25. Lawson S: Phenotype and function of somatic primary afferent nociceptive neurones with C-, Adelta-or Aalpha/beta-fibres. Exp Physiol 87: 239-244, 2002.
26. Dib-Hajj SD and Waxman SG: Translational pain research: Lessons from genetics and genomics. Sci Transl Med 6: 249sr4, 2014.
27. Ackerley R and Watkins RH: Microneurography as a tool to study the function of individual C-fiber afferents in humans: Responses from nociceptors, thermoreceptors, and mechanoreceptors. J Neurophysiol 120: 2834-2846, 2018.
28. Wu D, Chen Y, Li Z, Xie H, Wang S, Lu Y, Bao L, Zhang X and Li C: Zcchc12-containing nociceptors are required for noxious heat sensation. J Neurosci 42: 2690-2700, 2022.
29. García-Domínguez M: NGF in neuropathic pain: Understanding its role and therapeutic opportunities. Curr Issues Mol Biol 47: 93, 2025.
30. Tsuda M: Microglia in the spinal cord and neuropathic pain. J Diabetes Investig 7: 17-26, 2016.
31. Jomova K, Raptova R, Alomar SY, Alwasel SH, Nepovimova E, Kuca K and Valko M: Reactive oxygen species, toxicity, oxidative stress, and antioxidants: Chronic diseases and aging. Arch Toxicol 97: 2499-2574, 2023.
32. Szczot M, Liljencrantz J, Ghitani N, Barik A, Lam R, Thompson JH, Bharucha-Goebel D, Saade D, Necaise A, Donkervoort S, *et al*: PIEZO2 mediates injury-induced tactile pain in mice and humans. Sci Transl Med 10: eaat9892, 2018.
33. Tsujino H, Kondo E, Fukuoka T, Dai Y, Tokunaga A, Miki K, Yonenobu K, Ochi T and Noguchi K: Activating transcription factor 3 (ATF3) induction by axotomy in sensory and motoneurons: A novel neuronal marker of nerve injury. Mol Cell Neurosci 15: 170-182, 2000.
34. Gold MS and Gebhart GF: Nociceptor sensitization in pain pathogenesis. Nat Med 16: 1248-1257, 2010.
35. McKune CM, Murrell JC, Nolan AM, White KL and Wright BD: Nociception and pain. In: Veterinary Anesthesia and Analgesia: The Fifth Edition of Lumb and Jones: Chapter 29. John Wiley & Sons, Inc., 584-623. 2015.
36. Latremoliere A and Woolf CJ: Central sensitization: A generator of pain hypersensitivity by central neural plasticity. J Pain 10: 895-926, 2009.
37. Fang L, Wu J, Lin Q and Willis WD: Calcium-calmodulin-dependent protein kinase II contributes to spinal cord central sensitization. J Neurosci 22: 4196-4204, 2002.
38. Gao YJ and Ji RR: Targeting astrocyte signaling for chronic pain. Neurotherapeutics 7: 482-493, 2010.
39. Zurn CA, Beauchene C, Duan W, Guan Y and Sarma SV: Predicting wide-dynamic range neuron activity from peripheral nerve stimulation using linear parameter varying models. Annu Int Conf IEEE Eng Med Biol Soc 2021:4428-4431, 2021.
40. Maihöfner C, Schmelz M, Forster C, Neundörfer B and Handwerker HO: Neural activation during experimental allodynia: A functional magnetic resonance imaging study. Eur J Neurosci 19: 3211-3218, 2004.
41. Apkarian AV: Human brain imaging studies of chronic pain: Translational opportunities. In: Translational Pain Research: From Mouse to Man. Kruger L and Light AR (eds). CRC Press/Taylor and Francis, Boca Raton, FL, 2010.
42. Benbouzid M, Choucair-Jaafar N, Yalcin I, Waltisperger E, Muller A, Freund-Mercier MJ and Barrot M: Chronic, but not acute, tricyclic antidepressant treatment alleviates neuropathic allodynia after sciatic nerve cuffing in mice. Eur J Pain 12: 1008-1017, 2008.
43. Sindrup SH, Otto M, Finnerup NB and Jensen TS: Antidepressants in the treatment of neuropathic pain. Basic Clin Pharmacol Toxicol 96: 399-409, 2005.
44. Kuner R and Flor H: Structural plasticity and reorganisation in chronic pain. Nat Rev Neurosci 18: 20-30, 2017.

45. Lamprecht R and LeDoux J: Structural plasticity and memory. Nat Rev Neurosci 5: 45-54, 2004.
46. Gaiarsa JL, Ben-Ari Y, Kittler JT and Moss SJ: Long-term plasticity at inhibitory synapses: A phenomenon that has been overlooked. In: Kittler JT, Moss SJ, editors. The Dynamic Synapse: Molecular Methods in Ionotropic Receptor Biology. Boca Raton (FL): CRC Press/Taylor & Francis; 2006. Chapter 2.
47. Jones TL and Sorkin LS: Activated PKA and PKC, but not CaMKIIalpha, are required for AMPA/kainate-mediated pain behavior in the thermal stimulus model. Pain 117: 259-270, 2005.
48. Bonalume V: GABAA receptor as a novel regulator of peripheral pain sensitivity and local neuron-glia interaction. 2020. https://hdl.handle.net/2434/699522.
49. Wiese AJ and Yaksh TL: Nociception and pain mechanisms. In: Handbook of veterinary pain management: pp10-41. 2015. DOI: 10.1016/B978-0-323-08935-7.00002-8.
50. Baliki MN, Chialvo DR, Geha PY, Levy RM, Harden RN, Parrish TB and Apkarian AV: Chronic pain and the emotional brain: Specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. J Neurosci 26: 12165-12173, 2006.
51. Schweinhardt P, Glynn C, Brooks J, McQuay H, Jack T, Chessell I, Bountra C and Tracey I: An fMRI study of cerebral processing of brush-evoked allodynia in neuropathic pain patients. Neuroimage 32: 256-265, 2006.
52. Choucair-Jaafar N, Yalcin I, Rodeau JL, Waltisperger E, Freund-Mercier MJ and Barrot M: Beta2-adrenoceptor agonists alleviate neuropathic allodynia in mice after chronic treatment. Br J Pharmacol 158: 1683-1694, 2009.
53. Baron R, Binder A and Wasner G: Neuropathic pain: Diagnosis, pathophysiological mechanisms, and treatment. Lancet Neurol 9: 807-819. 2010.
54. Keam SJ: Suzetrigine: First approval. Drugs 85: 845-851, 2025.
55. Weaver KR, Griffioen MA, Klinedinst NJ, Galik E, Duarte AC, Colloca L, Resnick B, Dorsey SG and Renn CL: Quantitative sensory testing across chronic pain conditions and use in special populations. Front Pain Res (Lausanne) 2: 779068, 2022.
56. Raicher I, Ravagnani LHC, Correa SG, Dobo C, Mangueira CLP and Macarenco RSES: Investigation of nerve fibers in the skin by biopsy: technical aspects, indications, and contribution to diagnosis of small-fiber neuropathy. Einstein (Sao Paulo) 20: eMD8044, 2022.
57. Mulvey MR, Boland EG, Bouhassira D, Freynhagen R, Hardy J, Hjermstad MJ, Mercadante S, Pérez C and Bennett MI: Neuropathic pain in cancer: Systematic review, performance of screening tools and analysis of symptom profiles. Br J Anaesth 119: 765-774, 2017.
58. Sperry MM, Ita ME, Kartha S, Zhang S, Yu YH and Winkelstein B: The interface of mechanics and nociception in joint pathophysiology: Insights from the facet and temporomandibular joints. J Biomech Eng 139: 021003, 2017.
59. De Schoenmacker I, Berry C, Blouin JS, Rosner J, Hubli M, Jutzeler CR and Kramer JLK: An intensity matched comparison of laser-and contact heat evoked potentials. Sci Rep 11: 6861, 2021.
60. Nakagomi S, Suzuki Y, Namikawa K, Kiryu-Seo S and Kiyama H: Expression of the activating transcription factor 3 prevents c-Jun N-terminal kinase-induced neuronal death by promoting heat shock protein 27 expression and Akt activation. J Neurosci 23: 5187-5196, 2003.
61. Brandt MR, Beyer CE and Stahl SM: TRPV1 antagonists and chronic pain: Beyond thermal perception. Pharmaceuticals (Basel) 5: 114-132, 2012.
62. Jankowski MP and Koerber HR: Neurotrophic factors and nociceptor sensitization In: Kruger L, Light AR, editors. Translational pain research: From mouse to man. Boca Raton (FL): CRC Press/Taylor & Francis; 2010. Chapter 2.
63. Wang K, Wang S, Chen Y, Wu D, Hu X, Lu Y, Wang L, Bao L, Li C and Zhang X: Single-cell transcriptomic analysis of somatosensory neurons uncovers temporal development of neuropathic pain. Cell Res 31: 904-918, 2021.
64. Grienberger C, Giovannucci A, Zeiger W and Portera-Cailliau C: Two-photon calcium imaging of neuronal activity. Nat Rev Methods Primers 2: 67, 2022.
65. Sorge RE, Si Y, Norian LA, Guha A, Moore GE, Nabors LB, Filippova N, Yang X, Smith R, Chellappan R and King PH: Inhibition of the RNA regulator HuR by SRI-42127 attenuates neuropathic pain after nerve injury through suppression of neuroinflammatory responses. Neurotherapeutics 19: 1649-1661, 2022.
66. MacIver NJ, Blagih J, Saucillo DC, Tonelli L, Griss T, Rathmell JC and Jones RG: The liver kinase B1 is a central regulator of T cell development, activation, and metabolism. J Immunol 187: 4187-4198, 2011.
67. Zhu T, Qiao L, Wang Q, Mi R, Chen J, Lu Y, Gu J and Zheng Q: T-box family of transcription factor-TBX5, insights in development and disease. Am J Transl Res 9: 442-453, 2017.
68. Lai CY, Hsieh MC, Chou D, Lin KH, Wang HH, Yang PS, Lin TB and Peng HY: The transcription factor Tbx5-dependent epigenetic modification contributes to neuropathic allodynia by activating TRPV1 expression in the dorsal horn. J Neurosci 44: e0497242024, 2024.
69. Thomas Cheng H: Spinal cord mechanisms of chronic pain and clinical implications. Curr Pain Headache Rep 14: 213-220, 2010.
70. Mokhtar M and Singh P: Neuroanatomy, Periaqueductal Gray. StatPearls [Internet]. StatPearls Publishing, Treasure Island, FL, 2025.
71. Loyd DR and Murphy AZ: The role of the periaqueductal gray in the modulation of pain in males and females: Are the anatomy and physiology really that different? Neural Plast 2009: 462879. 2009.
72. Lubejko ST, Livrizzi G, Buczynski SA, Patel J, Yung JC, Yaksh TL and Banghart MR: Inputs to the locus coeruleus from the periaqueductal gray and rostroventral medulla shape opioid-mediated descending pain modulation. Sci Adv 10: eadj9581, 2024.
73. Peng B, Jiao Y, Zhang Y, Li S, Chen S, Xu S, Gao P, Fan Y and Yu W: Bulbospinal nociceptive ON and OFF cells related neural circuits and transmitters. Front Pharmacol 14: 1159753, 2023.
74. Fayaz A and Bhattacharjee A: Pain in Neurological Disorders. In: Neurology: A Queen Square Textbook. Howard R, Kullman D, Werring D and Zandi M (eds). 3rd Edition. Chapter 31. John Wiley & Sons, Inc., 1075-1096, 2024.
75. Bardoni R: Serotonergic modulation of nociceptive circuits in spinal cord dorsal horn. Curr Neuropharmacol 17: 1133-1145, 2019.
76. Marks DM, Shah MJ, Patkar AA, Masand PS, Park GY and Pae CU: Serotonin-norepinephrine reuptake inhibitors for pain control: Premise and promise. Curr Neuropharmacol 7: 331-336. 2009.
77. Sansone RA and Sansone LA: Serotonin norepinephrine reuptake inhibitors: A pharmacological comparison. Innov Clin Neurosci 11: 37-42. 2014.
78. Beyti B and Gancheva S: Pharmacological approaches for management of neuropathic pain in children. Scripta Scientifica Medica 57: 7-18, 2025.
79. Bahari Z and Meftahi GH: Spinal α2-adrenoceptors and neuropathic pain modulation; therapeutic target. Br J Pharmacol 176: 2366-2381, 2019.
80. Yang S and Chang MC: Chronic pain: structural and functional changes in brain structures and associated negative affective states. Int J Mol Sci 20: 3130, 2019.
81. Bose E: Mental Pathways to Pain Relief: A Review of Psychological Interventions for Chronic Pain. Inter J Neurobiol, 2024.
82. Gustafsson H, Flood K, Berge OG, Brodin E, Olgart L and Stiller CO: Gabapentin reverses mechanical allodynia induced by sciatic nerve ischemia and formalin-induced nociception in mice. Exp Neurol 182: 427-434, 2003.
83. Patel R and Dickenson AH: Mechanisms of the gabapentinoids and α2δ-1 calcium channel subunit in neuropathic pain. Pharmacol Res Perspect 4: e00205, 2016.
84. Kremer M, Yalcin I, Goumon Y, Wurtz X, Nexon L, Daniel D, Megat S, Ceredig RA, Ernst C, Turecki G, *et al*: A dual noradrenergic mechanism for the relief of neuropathic allodynia by the antidepressant drugs duloxetine and amitriptyline. J Neurosci 38: 9934-9954, 2018.
85. van Laar M, Pergolizzi JV Jr, Mellinghoff HU, Merchante IM, Nalamachu S, O'Brien J, Perrot S and Raffa RB: Pain treatment in arthritis-related pain: beyond NSAIDs. Open Rheumatol J 6: 320-330, 2012.
86. Emery MA, Shawn Bates ML, Wellman PJ and Eitan S: Hydrocodone is more effective than morphine or oxycodone in suppressing the development of burn-induced mechanical allodynia. Pain Med 18: 2170-2180, 2017.
87. Almuntashiri N, El Sharazly BM and Carter WG: Are cannabis-based medicines a useful treatment for neuropathic pain? A systematic review. Biomolecules 15: 816, 2025.
88. Petzke F, Tölle T, Fitzcharles MA and Häuser W: Cannabis-based medicines and medical cannabis for chronic neuropathic pain. CNS Drugs 36: 31-44, 2022.

89. Barnes MP: Sativex®: Clinical efficacy and tolerability in the treatment of symptoms of multiple sclerosis and neuropathic pain. Expert Opin Pharmacother 7: 607-615, 2006.
90. Mosley C, Gaynor J, Cital S and Brassard J: Cannabinoids for pain management. In: Cannabis Therapy in Veterinary Medicine. Cital S, Kramer K, Hughston L and Gaynor JS (eds). Springer, Cham. pp117-141, 2021. https://doi.org/10.1007/978-3-030-68317-7_5.
91. Bhaskar A and Mittal R: Local therapies for localised neuropathic pain. Rev Pain 5: 12-20, 2011.
92. Roulet L, Rollason V, Desmeules J and Piguet V: Tapentadol versus tramadol: A narrative and comparative review of their pharmacological, efficacy and safety profiles in adult patients. Drugs 81: 1257-1272, 2021.
93. Visser E and Schug SA: The role of ketamine in pain management. Biomed Pharmacother 60: 341-348, 2006.
94. Jayabalan P and Schnitzer TJ: Tanezumab in the treatment of chronic musculoskeletal conditions. Expert Opin Biol Ther 17: 245-254. 2017.
95. Zajączkowska R, Mika J, Leppert W, Kocot-Kępska M, Malec-Milewska M and Wordliczek J: Mirogabalin-A novel selective ligand for the a~ 2δ calcium channel subunit. Pharmaceuticals (Basel) 14: 112, 2021.
96. Krukowski K, Ma J, Golonzhka O, Laumet GO, Gutti T, Van Duzer JH, Mazitschek R, Jarpe MB, Heijnen CJ and Kavelaars A: HDAC6 inhibition effectively reverses chemotherapy-induced peripheral neuropathy. Pain 158: 1126-1137, 2017.
97. Cavaletti G, Canta A, Chiorazzi A, Ballarini E, Rodriguez V, Scuteri A, Nicolini G, Malacrida A, Cordella P, Stevenazzi A, *et al*: Protective effect of new histone deacetylase 6 inhibitors in a cisplatin-induced peripheral neurotoxicity murine model. Pain Rep 11: e1395, 2026.
98. Kutzsche J, Guzman GA, Willuweit A, Kletke O, Wollert E, Gering I, Jürgens D, Breitkreutz J, Stark H, Beck-Sickinger AG, *et al*: An orally available Cav2. 2 calcium channel inhibitor for the treatment of neuropathic pain. Br J Pharmacol 181: 1734-1756, 2024.
99. Marcotti A, Fernández-Trillo J, González A, Vizcaíno-Escoto M, Ros-Arlanzón P, Romero L, Vela JM, Gomis A, Viana F and de la Peña E: TRPA1 modulation by Sigma-1 receptor prevents oxaliplatin-induced painful peripheral neuropathy. Brain 146: 475-491, 2023.
100. Yoo S, Lim JY and Hwang SW: Sensory TRP channel interactions with endogenous lipids and their biological outcomes. Molecules 19: 4708-4744. 2014.
101. Bhattacharya A, Wickenden AD and Chaplan SR: Sodium channel blockers for the treatment of neuropathic pain. Neurotherapeutics 6: 663-678, 2009.
102. Jones J, Correll DJ, Lechner SM, Jazic I, Miao X, Shaw D, Simard C, Osteen JD, Hare B, Beaton A, *et al*: Selective inhibition of NaV1. 8 with VX-548 for acute pain. N Engl J Med 389: 393-405, 2023.
103. Schaffler K, He W, Passier P, Tracy K, Fakhoury A and Paul J: A phase I, randomized, double-blind, laser-evoked potential study to evaluate the analgesic/antihyperalgesic effect of ASP9226, a state-dependent N-type voltage-gated calcium channel inhibitor, in healthy male subjects. Pain Med 19: 2246-2255, 2018.
104. Minett MS, Falk S, Santana-Varela S, Bogdanov YD, Nassar MA, Heegaard AM and Wood JN: Pain without nociceptors? Nav1. 7-independent pain mechanisms. Cell Rep 6: 301-312, 2014.
105. Rice ASC, Dworkin RH, McCarthy TD, Anand P, Bountra C, McCloud PI, Hill J, Cutter G, Kitson G, Desem N, *et al*: EMA401, an orally administered highly selective angiotensin II type 2 receptor antagonist, as a novel treatment for postherpetic neuralgia: A randomised, double-blind, placebo-controlled phase 2 clinical trial. Lancet 383: 1637-1647, 2014.
106. Aghili SH, Manavi MA, Panji M, Farhang Ranjbar M, Abrishami R and Dehpour AR: Mirtazapine improves locomotor activity and attenuates neuropathic pain following spinal cord injury in rats via neuroinflammation modulation. Neurochem Res 49: 3326-3341. 2024.
107. Zhu J, Wei X, Feng X, Song J, Hu Y and Xu J: Repeated administration of mirtazapine inhibits development of hyperalgesia/allodynia and activation of NF-kappaB in a rat model of neuropathic pain. Neurosci Lett 433: 33-37, 2008.
108. Radiansyah RS and Hadi DW: Repetitive transcranial magnetic stimulation in central post-stroke pain: Current status and future perspective. Korean J Pain 36: 408-424, 2023.
109. Jeon YH: Spinal cord stimulation in pain management: A review. Korean J Pain 25: 143-150, 2012.
110. Kriek N, de Vos CC, Groeneweg JG, Baart SJ and Huygen FJPM: Allodynia, hyperalgesia,(quantitative) sensory testing and conditioned pain modulation in patients with complex regional pain syndrome before and after spinal cord stimulation therapy. Neuromodulation 26: 78-86, 2023.
111. Strauss S, Barby S, Härtner J, Pfannmöller JP, Neumann N, Moseley GL and Lotze M: Graded motor imagery modifies movement pain, cortical excitability and sensorimotor function in complex regional pain syndrome. Brain Commun 3: fcab216, 2021.
112. Tashani O and Johnson M: Transcutaneous electrical nerve stimulation (TENS) a possible aid for pain relief in developing countries? Libyan J Med 4: 62-65, 2009.
113. Ehde DM, Dillworth TM and Turner JA: Cognitive-behavioral therapy for individuals with chronic pain: Efficacy, innovations, and directions for research. Am Psychol 69: 153-166, 2014.
114. Deng Z, Pan Y, Li D, Zhang C, Jin H, Wang T, Zhan S and Sun B: Effect of bilateral anterior cingulotomy on chronic neuropathic pain with severe depression. World Neurosurg 121: 196-200, 2019.
115. Arcos-Holzinger M, Biebl JT, Storz C, Gutmann M, Azad SC, Holzapfel BM and Kraft E: Virtual reality in managing Complex Regional Pain Syndrome (CRPS): A scoping review. Front Neurol 14: 1069381, 2023.
116. Fadili O, Labouche B and Achour FR: The use of mirror therapy in the treatment of phantom limb pain in amputees. World J Adv Res Rev 10: 214-219, 2021.
117. Adler-Neal AL and Zeidan F: Mindfulness meditation for fibromyalgia: mechanistic and clinical considerations. Curr Rheumatol Rep 19: 59, 2017.
118. Suszyński K, Marcol W and Górka D: Physiotherapeutic techniques used in the management of patients with peripheral nerve injuries. Neural Regen Res 10: 1770-1772, 2015.
119. Shrivastav M and Musley S: Spinal cord stimulation for complex regional pain syndrome. Annu Int Conf IEEE Eng Med Biol Soc 2009: 2033-2036, 2009..