Review Article

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Advances of chronic pain: better insights, better treatment

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Abstract: Pain is often referred to as the "fifth vital sign". It profoundly impacts both physical and psychological well-being, either as a primary condition or in conjunction with other systemic diseases. Pain typically results from complex neurophysiological processes, including peripheral and central sensitization, altered pain pathways, and maladaptive neuroplasticity, which can lead to persistent or chronic pain. Current pharmaceutical treatments, such as non-steroidal anti-inflammatory drugs (NSAIDs) and tricyclic antidepressants, often fall short of desired therapeutic outcomes. To improve efficacy, advanced drug delivery systems (DDS) with extended-release formulations and multimodal analgesia have shown promise. Surgical interventions are increasingly recognized for chronic pain resistant to conservative treatments, while exercise, psychological counseling, and strong social support have proven benefits. This review examines the mechanisms of chronic pain, current management approaches, and explores potential future advancements in analgesic strategies.
Keywords: Chronic pain; Neuropathic pain; Multimodal analgesia; Drug delivery, Neuromodulation

1. DEFINITION OF CHRONIC PAIN

In 2020, the International Association for the Study of Pain (IASP) redefined pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage," a definition applicable to both acute and chronic pain across various conditions [1]. While acute pain serves as a fundamental proprioceptive response necessary to alert the body to potential injury, chronic pain evolves into a persistent condition last at least three months that often resembles a disease in itself. Chronic pain not only leads to physical and psychological suffering but also imposes a significant economic burden on society. According to studies by the Centers for Disease Control and Prevention (CDC) in the United States and similar research in the UK, it is estimated that approximately 40% of the population in these regions suffers from chronic pain. Beyond the obvious physical and psychological impacts, chronic pain results in considerable financial costs. A report from 2010 estimated that the total economic burden of chronic pain, encompassing medical management and lost productivity, ranges between $560 and $635 annually, affecting nearly one in three Americans [2]. Given the profound personal and societal consequences, optimizing the treatment of chronic pain has become a critical and urgent healthcare priority.

2. CLASSIFICATION AND CLINICAL SYMPTOMS OF CHRONIC PAIN

"Pain," as defined, is an uncomfortable sensation reported by the patient. According to the cause of onset, chronic pain can be classified

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into three primary types: nociceptive pain, neuropathic pain, and nociplastic pain. These categories are distinguished based on their underlying pathogenesis and the location of the lesion [2]. Nociceptive pain primarily arises from actual or potential tissue damage outside the nervous system, manifesting in somatic and visceral diseases, often accompanied by additional symptoms. This type of pain is typically a protective response to tissue injury. Neuropathic pain, on the other hand, results from damage or dysfunction of the somatosensory system, often due to conditions such as nerve compression, diabetes, neuromas, ion channelopathies, cardiovascular diseases, and autoimmune disorders. The prevalence and recurrence rates of neuropathic pain have garnered attention, as it is estimated to affect approximately 5% of the global population. Besides, research from The Institute of Medicine indicated that chronic pain severity and related disability seem to increase with age, which suggests that the societal pressure caused by chronic pain might be influenced by the aging tendency of the population [3]. Neuropathic pain can be further categorized into peripheral and central neuropathic pain based on the location of damaged neurons. Typical manifestations include hyperalgesia (excessive pain induced by normal stimulation), allodynia (painful sensations triggered by usually non-painful stimuli), spontaneous pain, and paralgesia (reduced or absent pain sensation) [4]. Nociplastic pain refers to pain that arises without clear evidence of tissue injury or somatosensory system pathology. It is a relatively recent classification that recognizes pain syndromes where abnormalities in pain processing, often at the central nervous system level, contribute to the perception of pain. This category of pain includes conditions such as fibromyalgia and complex regional pain syndrome (CRPS), where pain persists despite the absence of an identifiable lesion [2].

2.1 Mechanism and Clinical Conditions of Neuropathic Chronic Pain

Chronic neuropathic pain arises from lesions in the nervous system itself, affecting both peripheral and central pathways. The pain information consolidated by neurons in the dorsal root ganglion (DRG) is transmitted to secondary interneurons in the spinal dorsal horn (SDH). In addition to neurons, glial cells, particularly in the central nervous system (CNS), contribute significantly to chronic pain mechanisms. As the highest regulatory center, various regions of the thalamus and multiple cortical areas are involved in the complex processing and regulation of pain perception [5]. The balance between excitatory and inhibitory signals along the pain conduction pathway is crucial for modulating pain intensity, and disruptions in this balance can lead to the amplification of pain, further complicating chronic pain conditions.

2.1.1. Pain Conduction Pathway in the Peripheral Nervous System (PNS)

Pain sensation follows an anatomical proprioceptive pathway, with pain receptors in the skin conveying signals via the PNS to the central nervous system [4]. Within sensory conduction, two main types of nerve fibers in the dorsal root ganglion (DRG), large diameter A-fibers and medium or small diameter C-fibers, play crucial roles. The gate-control theory stands as a classical hypothesis in pain regulation mechanisms, proposing that innocuous sensory input conveyed by large Aβ-fibers can inhibit the transmission of nociceptive signals from smaller C-fibers in the spinal cord, effectively closing the gate to pain perception [6–8] **(Fig. 1)**.

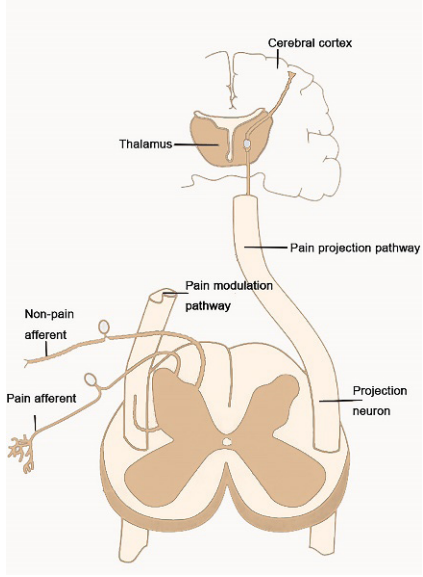

Figure 1. The pain conduction pathway from the peripheral to central nervous system.

C-fibers, characterized by their small diameter, are the principal contributors to the conduction of pain signals. These fibers express classic markers such as calcitonin gene-related peptide (CGRP), transient receptor potential vanilloid 1 (TRPV1),

and Isolectin IB4 (IB4). The expression of these molecules significantly increases during pain onset. Research has found that inhibiting C-fiber excitability using QX-314 or TRPV1 antagonist exhibited neuropathic pain relief [9, 10]. In contrast, A fibers are composed of larger diameter neurons identified by neurofilament 200 (NF200). They are generally non-nociceptive neurons, whereas sometimes they act in a distinct function in pain modulation. Specifically, Aβ-fibers function as inhibitors of allodynia, exerting their influence through feed-forward activation of spinal inhibitory neurons [11].

There is mounting evidence suggesting that A fibers and C fibers do not function independently but instead exhibit a dynamic interaction that collectively contributes to pain regulation. Research indicates that the interplay between Aβ-C fiber and C-C fiber interactions plays a critical role in the modulation of neuropathic pain, where A fibers can influence the excitability of C fibers and vice versa. Peripheral axotomy in rats increased the excitability of adjacent intact primary nociceptive neurons, and the excitability could be weakened by inhibition of GABA degradation [12]. Previous studies have explored the impact of C-fiber stimulation on the other branch spontaneous activity (SA) of DRG C-nociceptive neurons. In visceral inflammatory model rats, the cutaneous branch of C-nociceptors, which innervates both skin and viscera, exhibited hypersensitivity [13]. Moreover, topical applications of substances like capsaicin, peppermint oil, and mustard oil have been shown to alleviate inflammatory muscle pain induced by complete Freund's adjuvant (CFA) injection [13].

2.1.2. Central Nervous System (CNS) Lesions

Central neuropathic pain is usually caused by a lesion or disease affecting the central somatosensory nervous system, presenting a complexity that surpasses lesions in the peripheral nervous system due to its role in information integration. Common causes of central neuropathic pain include spinal cord injury, stroke, and multiple sclerosis (MS), with thalamic infarctions and lateral medullary lesions following stroke being prominent contributors [5, 14]. A recent study has highlighted the involvement of ventral tegmental area (VTA)-nucleus accumbens (NAc) circuits in mediating both acute and chronic pain, as demonstrated through the optogenetics technique. Activation of neurons in NAc was observed, and further research found the subsequent activation of its downstream VTA neurons. Selective activation or inhibition of VTA neurons could exacerbate or inhibit neuropathic pain caused by CCI surgery in mice [15]. Interestingly, in models of neuropathic pain and cancer-related pain, the activity of the dopaminergic reward pathway is significantly reduced, suggesting that alterations in reward processing may contribute to the pain experience [16].

2.1.3. The Imbalance of Excitation and Inhibition

At higher levels of the central nervous system, various brain nuclei secrete opposing excitatory and inhibitory neurotransmitters, maintaining a delicate balance in nervous system activity. Disruption of this balance can result in sensory abnormalities, including pain sensitization and pain suppression, contributing to the pathophysiology of chronic pain. Recent studies using optogenetic techniques have provided valuable insights into this balance. For instance, optogenetic activation of GABAergic neurons in the lateral parabrachial nucleus has been shown to selectively alleviate neuropathic pain without altering basal nociceptive processing. This suggests that targeted modulation of inhibitory circuits in specific brain regions may offer therapeutic potential for managing chronic pain while preserving normal pain sensitivity [17].

2.2. Abnormal Regulation of Ion Channels and Pain-Related Receptors

Ion channels are essential for nerve impulse transmission and play a key role in pain initiation and progression. Voltage-gated potassium channels (Nav), including Nav1.7, Nav1.8, and Nav1.9, along with the voltage-gated calcium channel Cav2.2, have been identified as key players in neuropathic pain, making them potential therapeutic targets [18]. Notably, Nav1.7 is specifically expressed in nociceptive neurons, and mutations or deficiencies in this channel result in congenital insensitivity to pain. While Nav1.7 can be selectively inhibited by tetrodotoxin (TTX), the systemic administration of TTX carries the risk of severe toxicity, limiting its clinical use. Consequently, researchers are actively exploring the development of novel local drug delivery systems to alleviate peripheral neuropathic pain without systemic side effects [19].

Additionally, N-methyl-D-aspartate receptors (NMDARs), found in both the central nervous system and peripheral tissues, are critical for higher brain functions such as learning and memory, as well as pain processing. When activated by glutamine, NMDARs allow the passage of Na^+, K^+, and Ca^{2+} ions, contributing to pain sensitization [20]. Research has shown that NMDAR antagonists can prevent central sensitization and reduce pain hypersensitivity, underscoring their potential for treating chronic pain [21].

2.3. The Relationship between Chronic Pain and Emotion

Recent research has shown that chronic pain is not only linked to sensory transduction disorders but also closely tied to affective disorders such as addiction, depression, and anxiety, contributing to psychological pain. A notable comorbidity is the frequent co-occurrence of chronic pain and depression, particularly in older adults, which worsens prognosis and increases the risk of additional health issues [22]. Neuroimaging studies highlight shared neurobiological changes in reward-related brain regions between chronic pain patients and drug addicts [5]. Depression, often linked to dysregulated neurotransmitter systems like serotonin and norepinephrine, involves brain areas crucial for pain processing, such as the ventral striatum and prefrontal cortex, which modulate both pain and mood [23]. Additionally, sleep deprivation has been identified as a risk factor for chronic pain, with a meta-analysis showing that disrupted sleep increases pain intensity and sensitization in both peripheral and central systems [24, 25].

2.4. Immune System and Chronic Pain

Chronic pain occurs in numerous immune-related diseases. Previous studies have found that the IgG-immune complex (IgG-IC) is a necessary factor to induce pain hypersensitivity [26, 27]. Fc-gamma receptor I (FcγRI) is the receptor that specifically binds to Fc domain of IgG, and it has been found mainly expressed in small-sized nociceptive neurons in DRG. It participated in the activation of sensory neurons evoked by the immune complex (IC), including an increase of calcium influx and neuronal excitability [28]. Specifically, further research showed that transient receptor potential canonical channel 3 (TRPC3) is the essential channel for mediating the current evoked by IC. The current was diminished once TRPC3 was silenced or inhibited. This progress relied on the activation of spleen-associated tyrosine kinase (Syk)-phospholipase C (PLC)-inositol trisphosphate (IP3) signaling pathway, a classic pathway for IgG-IC to activate FcγRI [29]. Moreover, FcγRI was found to be overexpressed in both the antigen-induced arthritis (AIA) joint pain model rats and the CCI model mice. Inhibition of FcγRI effectively suppressed the pain behavior and the associated downstream signaling pathways [30, 31]. These findings suggest immune receptors serve as probable treatment targets to ameliorate neuropathic pain.

Astrocytes and microglia cells act as immune cells of the nervous system, they are activated at pain condition and then release inflammatory factors such as interleukin 6 (IL-6), interleukin 1β (IL-1β) and tumor necrosis factor α (TNF-α), These factors play a pivotal role in chronic pain pathways by activating intracellular signaling cascades such as protein kinase A (PKA)-p38β mitogen-activated protein kinase (MAPK) pathway and the Janus kinases (JAKs)- signal transducer and activator of transcription 3 (STAT3) pathway. These pathways, through direct or indirect receptor binding on neurons and glia cells, contribute to the initiation and maintenance of chronic pain [32, 33].

Besides, Cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) are key enzymes in prostaglandin synthesis, which contribute to inflammation and pain. COX-2 is secreted by macrophages and synoviocytes, of which the expression is selectively increased in response to inflammatory and other physiologic stimuli and growth factors [34, 35].

2.5. Treatment of Chronic Pain

In contrast to the previous definition of pain, the latest edition places increased emphasis on the adverse effects on function, as well as on social and psychological well-being. This underscores the understanding that effective pain management necessitates a holistic approach, addressing not only the medical aspects but also encompassing psychological and social dimensions for comprehensive improvement [36].

2.6. Pharmaceutical Therapy

2.6.1. Current Analgesic Drug Treatment

Chronic pain management primarily relies on pharmaceutical interventions due to the complex

mechanisms of pain modulation in the nervous system **(Table 1)**. The IASP recommends first-line treatments based on systematic reviews and meta-analyses, including tricyclic antidepressants (TCAs), pregabalin, gabapentin, and serotonin-norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine and duloxetine, which target neuropathic pain by modulating neurotransmitter systems. These central acting analgesics provide value in many painful disorders, including low-back pain, fibromyalgia, postherpetic neuralgia, and neuropathic pain [37]. For conditions like trigeminal neuralgia, carbamazepine and oxcarbazepine are effective first-line treatments, targeting hyperactive neuronal firing. NSAIDs like ibuprofen and diclofenac reduce inflammation by inhibiting COX enzymes, which makes a lot of contributions to chronic pain. Therefore, NSAIDs are one of the most frequently used analgesics in the management of mild to moderate chronic pain, such as low back pain and chronic joint pain [35]. While tramadol and opioids (e.g., morphine) can provide analgesia for the persisting cancer pain according to the WHO cancer-pain management ladder, their use is limited by adverse effects, including respiratory depression, nausea, and addiction risks, making them less suitable for long-term management.

Table 1. Drug information and indications of analgesics in clinical.

Drug Name	Brand Name(s)	Drug Class	Dosage Form(s)	Year of Approval	Half-Life	Indications
Ibuprofen	Advil, Motrin, Nurofen	NSAID (COX-1/ COX-2 Inhibitor)	Oral tablets, oral suspension, topical gel	1969	2–4 hours	Acute pain, inflammation, arthritis, menstrual cramps
Diclofenac	Voltaren, Cataflam, Flector	NSAID (COX-2 Selective)	Oral tablets, gel, topical patch, injection	1973	1–2 hours	Inflammatory pain, osteoarthritis, rheumatoid arthritis, dysmenorrhea
Celecoxib	Celebrex	COX-2 Inhibitor	Oral capsules	1998	11 hours	Osteoarthritis, rheumatoid arthritis, acute pain, familial adenomatous polyposis
Paracetamol (Acetaminophen)	Tylenol, Panadol, Calpol	Analgesic, Antipyretic	Oral tablets, syrup, suppository	1950s	2–3 hours	Mild to moderate pain, fever, headache, musculoskeletal pain
Tramadol	Ultram, ConZip, Ryzolt	Opioid Analgesic	Oral tablets, extended-release capsules	1995	6–7 hours	Moderate to severe pain, neuropathic pain
Amitriptyline	Elavil	TCA	Tablet, oral solution	1961	10–50 hrs	Neuropathic pain, Fibromyalgia, Migraine
Nortriptyline	Pamelor, Aventyl	TCA	Capsule, oral solution	1964	18–44 hrs	Neuropathic pain, Chronic tension headaches
Imipramine	Tofranil	TCA	Tablet, capsule	1959	9–20 hrs	Chronic neuropathic pain, Migraine
Desipramine	Norpramin	TCA	Tablet	1964	12–30 hrs	Diabetic neuropathy, Postherpetic neuralgia
Clomipramine	Anafranil	TCA	Capsule	1989	32 hrs	Chronic headache (off-label), neuropathic pain
Protriptyline	Vivactil	TCA	Tablet	1967	54–92 hrs	Chronic neuropathic pain (off-label)
Duloxetine	Cymbalta	SNRI	Capsule (delayed-release)	2004	12 hrs	Diabetic neuropathy, Fibromyalgia, LBP
Venlafaxine	Effexor, Effexor XR	SNRI	Tablet, capsule (XR)	1993	5 hrs (IR); 11 hrs (XR)	Neuropathic pain, Fibromyalgia, Migraine

(Continued)

Drug Name	Brand Name(s)	Drug Class	Dosage Form(s)	Year of Approval	Half-Life	Indications
Milnacipran	Savella	SNRI	Tablet	2009	8 hrs	Fibromyalgia
Levomilnacipran	Fetzima	SNRI	Extended-release capsule	2013	12 hrs	Off-label for chronic pain
Morphine	MS Contin, Kadian, Roxanol	Opioid Analgesic	Oral tablets, extended-release tablets, injection	1941	2–4 hours	Severe pain, cancer pain, palliative care
Fentanyl	Duragesic, Sublimaze, Actiq	Opioid Analgesic	Transdermal patch, lozenge, injection, buccal tablet	1968	3–7 hours	Severe pain, cancer pain, post-surgical pain
Oxycodone	OxyContin, Percocet, Roxicodone	Opioid Analgesic	Oral tablets, extended-release tablets, oral solution	1976	3–4 hours	Moderate to severe pain, chronic pain management
Gabapentin	Neurontin, Gralise	Anticonvulsant, Neuropathic Pain	Oral capsules, tablets, oral solution	1993	5–7 hours	Neuropathic pain, postherpetic neuralgia, seizures
Pregabalin	Lyrica	Anticonvulsant, Neuropathic Pain	Oral capsules, oral solution	2004	6 hours	Neuropathic pain, fibromyalgia, seizures
Lidocaine	Xylocaine, Lidoderm, EMLA	Local Anesthetic	Topical gel, patch, injection	1948	1–2 hours (topical)	Local anesthesia, acute pain relief, postherpetic neuralgia
Capsaicin	Zostrix, Capzasin	Topical Analgesic	Cream, gel, patch	1981	Variable	Musculoskeletal pain, neuropathic pain, arthritis
Carbamazepine	Tegretol, Carbatrol, Epitol	Anticonvulsant, Neuropathic Pain	Oral tablets, extended-release tablets	1968	25–65 hours	Trigeminal neuralgia, neuropathic pain, seizures
Botulinum Toxin Type A	Botox, Dysport, Xeomin	Neuromuscular Blocker	Injection	1989 (Botox)	3–6 months	Chronic pain (including migraine, spasticity, neuropathic pain)
Methadone	Dolophine, Methadose	Opioid Analgesic	Oral tablets, oral solution, injection	1947	15–60 hours	Chronic pain, opioid dependence, detoxification

For peripheral neuropathic pain, treatments such as 8% capsaicin patches, lidocaine patches, and botulinum toxin A injections offer localized pain relief. Local anesthetics (LAs) such as bupivacaine and lidocaine block voltage-gated sodium channels, alleviating peripheral pain. Although LAs were previously difficult to administer systemically due to their short duration and toxicity, extended-release formulations now allow for more effective and localized delivery, reducing side effects. [4, 38].

2.6.2. Limitations of Existing Drug Formulations for Chronic Pain Treatment

Pain management in clinical practice utilizes a wide range of drug formulations, tailored to the type, severity, and duration of pain. Common formulations include oral tablets and capsules, widely used for various pain types, including NSAIDs, opioids, and antidepressants. For those unable to take oral medications, liquid solutions, oral disintegrating tablets,

and syrups offer an alternative. Injectable forms such as intravenous, intramuscular, and subcutaneous injections are commonly used in acute pain management, with a rapid onset of action.

For localized relief, topical formulations such as creams, gels, patches, and sprays are applied directly to the skin. These can provide targeted relief for conditions like muscle or joint pain with minimal systemic effects. Transdermal patches are designed for continuous drug release, offering sustained pain relief. Sublingual and buccal formulations, including sublingual tablets and sprays, provide rapid absorption for immediate pain relief, particularly in breakthrough pain scenarios. Extended-release and controlled-release formulations offer prolonged effects, reducing the frequency of dosing.

Other innovative options like nasal sprays and inhalers allow for quick onset of action, particularly for breakthrough or post-surgical pain. Each formulation has specific advantages, and the choice depends on factors such as the patient's condition, the nature of the pain, and the required onset and duration of relief.

3. DEVELOPMENTAL DRUG DELIVERY SYSTEM IN ANALGESIA

Traditional formulations suffer from numerous limitations concerning drug action duration, efficacy, release rate, stability, and bioavailability. With ongoing advancements in drug delivery systems (DDS) research and an increasing demand for more effective pain management, novel DDS approaches have been developed to address these limitations. These include extended-release/controlled-release drug delivery systems, which offer the advantage of prolonged drug action and more consistent therapeutic effects. Additionally, in situ local drug delivery systems have emerged, enabling targeted drug release at the site of pain or injury, thereby minimizing systemic side effects and enhancing efficacy. For post-surgical pain management, the Enhanced Recovery After Surgery (ERAS) guidelines recommend a multimodal analgesia approach, incorporating scheduled doses of NSAIDs and acetaminophen. These treatment protocols can be further optimized through the use of novel DDS technologies, which provide better control over drug release and can reduce reliance on opioids, ultimately improving recovery outcomes [39].

3.1. Extended-Release/Controlled-Release DDS

Extended/controlled-release Drug Delivery Systems (DDS) encompass a category of formulations where the active drug is dispersed in a suitable carrier, and its release occurs gradually at a constant or modulated rate within a specified release medium. These systems are designed to reduce the frequency of drug administration, often halving the dosing schedule compared to traditional formulations, which significantly improves patient adherence to treatment regimens.

Designated as modulated release preparations by the United States Pharmacopeia (USP), extended/controlled-release DDS offer advantages over traditional drug formulations. Notably, they maintain a more stable blood concentration, thereby mitigating the 'peak-trough' phenomenon commonly observed with immediate-release preparations. This results in more consistent therapeutic effects, reduced fluctuations in drug plasma levels, and a decrease in the occurrence of toxic side effects. Additionally, extended-release DDS can enhance drug bioavailability, allowing for maximized therapeutic efficacy with lower doses.

The combination of extended-release DDS with various analgesic drugs has demonstrated significant therapeutic benefits. For example, ibuprofen, a widely used type of NSAIDs, is favored for its excellent safety profile, effectiveness, and low risk of adverse effects. It is available over-the-counter (OTC) in a 200 mg regular-release preparation with a recommended frequency of 4–6 hours. However, for the management of chronic pain conditions, such as osteoarthritis and lumbar disc herniation, the need for prolonged analgesic effects is critical. Recent innovations have led to the development of a novel ibuprofen quick-sustained release dual-layer tablet, which extends the drug's therapeutic duration to over 12 hours. This innovative formulation exhibits similar initial release properties to standard ibuprofen regular release tablets but maintains effective therapeutic blood concentrations over a 12-hour dosing interval, showcasing distinct extended-release properties [40].

Tramadol, a synthetic opioid, is commonly used in the treatment of neuropathic pain. Under administration, tramadol is metabolized in the liver by the enzyme debrisoquine 4-hydroxylase (CYP2D6), leading to the formation of its active metabolite, O-demethyltramadol, which binds to opioid

receptors and exerts analgesic effects. Variations in the CYP2D6 genotype can significantly affect tramadol metabolism. Individuals with poor metabolizer genotypes may require higher tramadol doses to achieve effective pain relief compared to those with normal metabolism [41]. Since its introduction in 1995, tramadol was initially prescribed in conventional formulations with a dosing frequency of 4–6 times per day. The development of DDS has enabled a reduction in dosing frequency, allowing for once-daily administration with a dosage range of 100–400 mg. Clinical studies have demonstrated significant improvements in the bioavailability of extended-release tramadol formulations, resulting in more stable blood concentrations and reduced adverse effects compared to both the placebo group and the immediate-release preparation group [42].

3.2. In Situ Local DDS

Local administration of drugs, particularly LAs, offers a targeted approach to pain relief, especially in cases where systemic or cardiovascular adverse effects may arise. The pharmacokinetic of LAs are predominantly influenced by physical and chemical properties, such as the oil/water partition coefficient. Due to their lipophilic nature, LAs can easily traverse nerve membranes in their molecular form. The duration of the drug's effect primarily relies on its ability to bind to hemoglobin in the bloodstream. Only the free drug can cross from the blood into the target site, where it exerts its therapeutic effect. Upon binding with hemoglobin, a drug reservoir is formed, extending the duration of action. However, the chemical structure of some LAs may result in hydrolysis and poor protein binding, leading to a shorter duration of action and an increased potential for toxicity, despite a faster onset of analgesia. The inherent LAs pose significant limitations to their application as effective analgesics. To address these limitations, novel strategies have been developed, such as the use of polymeric materials like poly (lactide-co-glycolide acid) (PLGA) to encapsulate drugs like bupivacaine into nanoparticles. These methods extend the drug's action time while reducing toxic side effects and improving bioavailability, making them particularly suitable for neuropathic pain management.

For example, Exparel®, a liposomal formulation of bupivacaine, has demonstrated extended analgesic effects for up to 72 hours after injection, offering prolonged pain relief with reduced adverse effects [38]. In a chronic compression of dorsal root ganglion (CCD) mice model, PLGA-bupivacaine nanoparticles exhibited sustained release, providing long-lasting analgesia for up to 35 days [43]. Moreover, combining nanoparticles facilitates the simultaneous delivery of multiple drugs, optimizing the effects of multimodal analgesia [44].

The application of implants for long-term, stable drug release has also shown promise in chronic pain treatment. The characteristics of these implants make them indispensable for managing chronic and long-term conditions, improving patient compliance. Xaracoll®, for instance, utilizes Collarx® technology to form a collagen matrix that acts as a slow-release carrier for bupivacaine. It was approved by the US Food and Drug Administration (FDA) in August 2020. After being placed directly at the surgical site, this implant provides controlled release of the drug for up to 24 hours, immediately releasing bupivacaine during the procedure [45].

Another notable development is SABER-Bupivacaine (Posimir®), a depot formulation of bupivacaine that has been approved by the FDA in February 2021. This formulation is designed for pain management following arthroscopic subacromial decompression, with a mean release rate of approximately 10 mg/h, providing pain relief for up to 72 hours after injection [46, 47].

In the field of topical administration, microneedles offer a novel and efficient approach for drug delivery. For example, a microneedle array loaded with ziconotide, a potent analgesic, demonstrated effective pain relief for 6 hours in chronic pain rat models, with promising biosecurity results [48].

4. NON-PHARMACEUTICAL THERAPIES

4.1. Surgical Treatment

Pharmacological treatments, while effective for many patients, often fall short in managing chronic pain conditions such as lumbar disc herniation and arthritis. In cases where conservative therapies are insufficient and clinical symptoms persistent, surgery becomes an important therapeutic option. Surgical interventions can alleviate progressive neurological deficits and provide substantial relief, ultimately improving patients' quality of life.

Neuromodulation through surgery primarily involves the use of electrical stimulation delivered by

implanting electrodes into the PNS (e.g., DRG) and the CNS (spinal cord and brain). The foundational principle of neuromodulation, particularly spinal cord stimulation (SCS) and peripheral stimulation, is based on the gate control theory. This theory proposes that nociceptive signals, transmitted by Aδ and C fibers, can be inhibited by the activation of Aβ fibers, thereby reducing pain perception. Modulating the activity of Aβ fibers can thus effectively manage neuropathic pain [49, 50].

Beyond this, controlling ectopic electrical activity in neurons plays a critical role in the development and persistence of chronic pain. Various types of invasive neuromodulation techniques have demonstrated significant analgesic effects by modulating neuronal excitability and altering the interactions between neurotransmitters and their corresponding receptors through the application of specific electrical signals. Depending on the implantation site, stimulation frequency, and intensity, neuromodulation therapies can be categorized into spinal cord stimulation (SCS), brain stimulation, and peripheral stimulation **(Table 2)**. Notably, these therapies not only provide alleviation of chronic pain but also contribute to improving the quality of life (QoL) of patients, which is also important for a sustainable treatment.

Table 2. Recent types of neuromodulations to neuropathic pain alleviation.

Types of Neuromodulation		Mechanism	Implanting position	Stimulate formulation	Indications
Spinal cord stimulation (SCS)	Conventional SCS	Activation of Aβ fibers and inhibitory interneurons according to the Gate Theory	The epidural space posterior to spinal cord columns	Low frequency (40–80 Hz), high pluse width (200–500 μs), high amplitude (3.5–8.5 mA)	Chronic pain
	High frequency SCS			Short duration (30 μs) High frequency (10000 Hz) Low amplitude (1–5 mA)	CRPS, FBSS, Peripheral neuropathy
	Brust SCS			500 Hz, 1 ms with 1 ms intervals 40 times per second, 5 consecutive waves	
	Closed loop SCS		The epidural space on the lateral aspect of the segment of the spinal cord corresponding to the site of pain	100–300 Hz, 50–1000 μs, with 60 μs interval	Chronic leg and back pain
	Dorsal root ganglion stimulation (DRG-S)		Dorsal root ganglion	Low frequency (4–20 Hz), 80–300 μs with 600 pulses, 20–250 μA	More adaptive to regional neuropathic pain versus SCS

(Continued)

Types of Neuromodulation		Mechanism	Implanting position	Stimulate formulation	Indications
Brain stimulation	Deep brain stimulation (DBS)	Deliver an electrical current to the specific brain area	The sensory thalamus, periaqueductal or periventricular grey matter, and the anterior cingulum		Better therapeutic effect to headache
	Motor cortex stimulation (MCS)	Implanted electrodes on the surface of brain to stimulate the motor cortex and fibers underneath	Motor cortex		CRPS, phantom pain, facial pain, post-stoke pain, and brachial plexus avulsion
Peripheral stimulation		Deliver electrical stimulation to peripheral nerve percutaneously	Peripheral nerve	An implantable electrode contact, a microprocessor receiver, an external or internal miniaturized pulse generator placed percutaneously	More specific to limb neuropathic pain, such as post-stroke shoulder pain, low back pain, phantom limb pain and post-traumatic nerve pain

For non-invasive surgery, techniques such as radiofrequency ablation (RFA) and chemical destruction are commonly used to directly damage and ablate diseased nerve fibers in order to alleviate intractable neuropathic pain, such as trigeminal neuralgia. However, these procedures may result in the loss of normal sensory function, an inevitable drawback [49]. Discectomy and decompression surgery are widely employed to treat chronic pain, particularly in cases where conservative treatments like physical therapy or medication fail to provide relief. These procedures are typically indicated for patients suffering from conditions such as herniated discs, spinal stenosis, or degenerative disc disease, which lead to compression of the spinal nerves [51]. Discectomy involves the removal of the damaged portion of a disc that is compressing on nearby nerves, while decompression surgery relieves pressure on the spinal cord or nerve roots by removing bone spurs, thickened ligaments, or disc fragments. Both surgeries aim to alleviate pain, restore function, and improve the patient's quality of life by addressing the root cause of the pain, often linked to nerve irritation or compression. While the success rates for these procedures are generally favorable, outcomes can vary depending on the severity of the condition and the patients' overall health [52–54]. These surgeries are typically considered when other non-surgical treatments have not provided sufficient relief.

The effectiveness of postsurgical outcomes is significantly influenced by the duration of preoperative symptoms [55]. However, in the case of neck pain, clinical studies suggest that there are no significant differences in outcomes between surgical intervention and conservative treatments [56]. While surgery can provide substantial pain relief, there is also a potential risk of persistent postoperative pain. For example, joint replacement surgery for knee and hip osteoarthritis has been associated with approximately 38% of patients experiencing ongoing pain following arthroplasty [57].

4.2. Physical Mitigation Therapy: Modulation of Neuronal Excitability

4.2.1. Transcranial Magnetic Stimulation (TMS)

Transcranial magnetic stimulation (TMS) is a non-invasive neuromodulatory technique that stimulates

neurons in the brain's surface or deeper regions using a powerful magnetic field generated by an electromagnetic coil. The high-frequency electrical current passing through the coil induces an electromagnetic field that can penetrate the brain tissue, resulting in neuronal depolarization. This depolarization can evoke responses such as muscle twitches or modulate neuronal plasticity, which contributes to the amelioration of chronic pain, particularly within the CNS. Repetitive TMS (rTMS) has been shown to produce lasting local changes in brain activity, extending beyond the stimulation period. This improvement marks an evolution from the original TMS method [58]. TMS has demonstrated particular efficacy in treating neuropathic pain types associated with post-stroke central pain and trigeminal neuralgia. However, its effectiveness is less pronounced in cases of neuropathic pain originating from more peripheral anatomical sources, such as traumatic peripheral neuropathy [49].

Several clinical studies concentrated on exploring the pathophysiology of migraine and other headaches with TMS, and have achieved better results. Evidence showed that TMS significantly increases the rest motor threshold (RMT) of migraineurs, which represents the excitability of a central core of neurons, and the target muscle in the primary motor cortex and excitability of brainstem or spinal cord motor neurons [59]. It can also act as a tool to understand or monitor therapeutic analgesia interventions [60]. A recent study demonstrated that rTMS effectively reversed the imbalance of primary somatosensory cortex and primary motor cortex microcircuitry and contributed to alleviating nociceptive hypersensitivity in the spared nerve injury mice model. It might improve the analgesic mechanism of TMS, provide a further basis for the treatment of chronic pain [61].

4.2.2. Transcranial Direct Current Stimulation (tDCS)

Transcranial direct current stimulation (tDCS) is a therapy that provides a subthreshold modulation of neuronal excitability through the application of low-intensity electrical currents, which can be either positively or negatively charged. Unlike other neuromodulation techniques, the effects of tDCS are longer-lasting, often extending for several minutes after stimulation, and the therapy is applied to the surface of the scalp. tDCS influences the neuronal network by interacting with key neurotransmitters such as GABA, serotonin, dopamine, and acetylcholine. It also modulates the N-methyl-D-aspartate receptors (NMDARs), which are involved in neuroplasticity, thus improving mechanisms such as emotional appraisal of pain, descending pain inhibition, and modulation of the endogenous opioid system [62]. In addition to its therapeutic effects, tDCS offers significant practical advantages over more invasive therapies. It is cost-effective, requires less day-to-day maintenance, and is associated with fewer side effects, contributing to an overall improvement in patients' QoL. Patients who received active tDCS showed a reduction in pain intensity, number of attacks, and medication at the end of interventions and up to 8 weeks after the treatment [63]. However, the analgesic effect of primary motor cortex stimulation of tDCS seems to be weaker than rTMS [64].

4.2.3. Transcutaneous Electrical Nerve Stimulation (TENS)

TENS is a non-invasive method for alleviating pain via the application of low-intensity electrical stimulation. TENS devices are available in various forms, including compact battery-powered portable units and larger stationary models, both of which consist of leads and adhesive electrodes. Besides activating Aβ fibers, research has shown that TENS can significantly increase the expression of opioid and cannabinoid receptors. It also reduces the wind-up phenomenon and potentiation of spinal dorsal horn neurons by modulating NMDA receptors. Furthermore, TENS has been shown to modulate levels of pro-inflammatory cytokines, influence neuroimmune interactions, and promote neural plasticity, contributing to its analgesic effects [50]. A meta-analysis exhibited low-certainty evidence of a difference between TENS compared to sham TENS in reducing neck pain. Further well-designed researches are necessarily needed to more comprehensively evaluate its therapeutic effect on chronic pain treatment [65].

5. FOCUSED ULTRASONIC STIMULATION AND LASER TREATMENT

Focused Ultrasound Stimulation (FUS) is a non-invasive technique that utilizes powerful ultrasonic waves to deliver targeted energy to specific regions of the brain. The high penetration capability of FUS allows for the thermal ablation of tissue, transient disruption of the blood-brain barrier, and the potential to

either excite or inhibit neuronal activity. Additionally, FUS can enhance connectivity between different brain regions. These mechanisms suggest that FUS could serve as a potential non-invasive neurosurgical therapy for chronic pain management. However, clinical research on the use of FUS for chronic pain treatment remains limited and requires further investigation [66].

5.1. Photobiomodulation Therapy (PBMT)

PBMT is a non-thermal and non-ionizing light therapy that applies light amplification via stimulated emission of radiation (LASER), as well as low-intensity red and/or near-infrared light-emitting diodes (LEDs). The primary mechanism of PBMT in alleviating chronic pain involves its biological effects on tissues, such as promoting cell proliferation, accelerating healing processes, enhancing tissue regeneration, preventing cell death, and exhibiting anti-inflammatory activity. Furthermore, PBMT directly interacts with the terminals of Aδ and C fibers when applied to peripheral nerves, leading to the depolymerization of microtubules and the acceleration of the electron transport chain. These actions contribute to pain relief. PBMT is effective in treating both acute and chronic musculoskeletal pain as well as fibromyalgia. [67].

5.2. Acupuncture

Low-quality evidence suggests that acupuncture may offer some sensory improvement in low back pain, although its effects on functional improvement are limited [68]. Interestingly, studies have found no significant differences between true acupuncture and sham acupuncture, the latter involving skin stimulation without actual needle penetration [69]. Acupuncture has also been shown to provide preventive effectiveness in chronic and episodic migraine. Patients who underwent staged acupuncture therapy experienced greater relief from headache symptoms compared to those in the placebo group. Long-term studies, particularly those lasting over one year, are still lacking to fully assess the efficacy of acupuncture in treating chronic migraines [70].

5.3. Exercising and Psychological Treatment

According to the latest perspective from pain research by the International Association for the Study of Pain (IASP), psychosocial factors are recognized as modifiers of the pain experience rather than equal contributors [36]. There is growing evidence suggesting that physical exercise is beneficial in alleviating chronic pain through health improvement and the enhancement of sleep quality [71]. Additionally, massage therapies, such as effleurage, kneading, friction, stretching, and petrissage, have been found to contribute to pain relief in conditions like temporomandibular disorders and low back pain [68, 72].

Cognitive behavioral therapy (CBT) is one of the most commonly used psychological interventions for chronic pain. Its efficacy has been assessed as a standalone therapy or when combined with other management strategies across various pain disorders. However, the results suggest that this approach has limited efficacy in alleviating pain, indicating the requirement for additional pharmacological interventions to effectively manage neuropathic pain. [73, 74].

Conclusion

Chronic pain, characterized by its prolonged duration, high incidence, and susceptibility to recurrence, presents significant challenges in clinical management. Traditional drug delivery methods, such as oral administration and intravenous injection, have limitations due to their short duration of action and potential systemic side effects. The development of extended-release and controlled-release DDSs offers a promising solution for pain management, providing longer-lasting relief with fewer doses. In addition to pharmaceutical therapies, both invasive and non-invasive surgeries have proven effective in alleviating chronic pain in clinical settings. Furthermore, exercise, a positive attitude, and appropriate psychological counseling are essential components of a comprehensive pain management strategy. To further enhance treatment approaches, ongoing research into new mechanisms of chronic pain, as well as innovative therapies such as gene therapy and the development of monoclonal antibodies, are critical areas of focus.

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Conflict of Interest Disclosures

The authors have no conflicts of interest to declare.

Abbreviations

NSAIDs: Non-steroidal Anti-inflammatory Drugs; **DDS:** Drug Delivery System; **IASP:** the International Association for the Study of Pain; **CDC:** the Center for Disease Control and Prevention; **GDP:** Gross Domestic Product; **PNS:** Peripheral Nervous System; **CNS:** Central Nervous System; **DRG:** dorsal Root Ganglion; **CGRP:** Calcitonin gene-related peptide; **TRPV1:** Transient Receptor Potential Vanilloid 1; **IB4:** Isolectin IB4; **NF200:** Neurofilament 200; **SDH:** Spinal Dorsal Horn; **IL-6:** Interleukin 6; **IL-1β:** Interleukin 1β; **TNF-α:** Tumor Necrosis Factor α; **HIV:** Human Immunodeficiency Virus; **MS:** Multiple Sclerosis; **VTA:** Ventral Tegmental Area; **NAc:** Nucleus Accumbens; **TRPM8:** Transient receptor potential melastatin 8; **TRPA1:** Transient receptor potential ankyrin 1; **NMDARs:** N-methyl-D-aspartate receptors; **TCAs:** Tricyclic Antidepressants; **LAs:** Local Anesthetics; **DDS:** Drug Delivery System; **ERAS:** Enhanced Recovery After Surgery; **USP:** the United States Pharmacopeia; **OTC:** Over-The-Counter; **PLGA:** Poly (Lactide-co-Glycolide acid); **CCI:** Chronic Constriction Injury; **FDA:** the US Food and Drug Administration; **SABER:** Sucrose Acetate Isobutyrate Extended-Release; **CBT:** Cognitive Behavioral Therapy.

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