Mechanism-based nonopioid analgesic targets

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Acute pain management has historically been dominated by opioids, whose efficacy is overshadowed by the risks of addiction, tolerance, and dependence, culminating in the global opioid crisis. To transcend this issue, we must innovate beyond opioid-based μ receptor treatments, identifying nonopioid analgesics with high efficacy and minimal adverse effects. This Review navigates the multifaceted landscape of inflammatory, neuropathic, and nociplastic pain, emphasizing mechanism-based analgesic targets tailored to specific pain conditions. We delve into the challenges and breakthroughs in clinical trials targeting ion channels, GPCRs, and other molecular targets. We also highlight the intricate crosstalk between different physiological systems and the need for multimodal interventions with distinct pharmacodynamics to manage acute and chronic pain, respectively. Furthermore, we explore emerging strategies, including gene therapy, stem cell therapy, cell type–specific neuromodulation, and AI-driven techniques for objective, unbiased pain assessment and research. These innovative approaches are poised to revolutionize pain management, paving the way for the discovery of safer and more effective analgesics.

Overview

Effective pain management is crucial to improving the quality of life for people with acute and chronic pain. Traditional analgesics, like opioids, NSAIDs, serotonin-norepinephrine reuptake inhibitors (SNRIs), and gabapentinoids, are commonly used, but have profound limitations, including variable efficacy and adverse effects. Opioids that activate the μ receptors have long been the cornerstone in treating acute pain (Figure 1A). However, their use is hampered by high risk of abuse and dependency and both limited efficacy in managing chronic pain and serious adverse effects (1). The opioid crisis has had a devastating impact, with over 60 million people globally affected by opioid addiction and more than 100,000 annual opioid overdose deaths (2). These limitations underscore the urgent need for safer, more effective analgesics with minimal abuse potential.

Addressing pain mechanisms before pain management

Acute nociceptive pain arises from the activation of nociceptors, which are high-threshold Aδ- and C-fiber sensory neurons innervating tissues to detect harmful/noxious stimuli. Nociceptors convert noxious stimuli into action potentials that propagate through the dorsal root ganglion (DRG) to the spinal dorsal horn, where the nociceptive input signal can be amplified or inhibited by local interneurons and descending regulation. The integrated signal is then relayed to the brain stem and higher-order brain regions, which process sensory-discriminative, affective, and cognitive dimensions of pain (Figure 1B) (3–6).

Under healthy conditions, pain is protective, serving as a vital warning system to detect danger and prevent injury from damaging stimuli, a process termed nociceptive pain. However, pain can transition into debilitating pathological forms due to inflammation, nerve damage, or dysregulated pain processing in the CNS. These conditions often present with hyperalgesia (heightened sensitivity to noxious stimuli), allodynia (pain in response to normally innocuous stimuli), and spontaneous pain. Effective management of pathological pain requires: avoiding reliance on opioid (specifically μ) receptor signaling (Figure 1, A and B); targeting specific regions and mechanisms (Table 1) underlying different pain conditions (Table 2); acknowledging the complex interactions among different biological systems; and preserving the fundamental protective elements of nociceptive function, especially in chronic pain conditions.

Inflammatory pain. Inflammatory pain arises from the immune system's response to tissue injury, pathogen infections, or immune disorders (7). While inflammation was evolutionarily developed as a protective process — recruiting immune cells to eliminate pathogens, clear cellular debris, and promote wound healing — it can transition into persistent pain under chronic inflammatory conditions. Tissue damage activates the innate and adaptive immune systems, recruiting macrophages, mast cells, DCs, neutrophils, and T cells that release proinflammatory cytokines, chemokines, growth factors, and reactive oxygen species, many of which directly sensitize nociceptors by lowering their activation thresholds, causing hyperalgesia and allodynia (Figure 1C) (7). This peripheral sensitization, localized at the inflammation site, is a hallmark of inflammatory pain. Another important consideration is inflammatory priming, where an initial inflammatory insult "primes" nociceptors and immune cells, sensitizing them to subsequent stimuli (8). This priming may then lead to exaggerated painful responses to even mild inflammatory triggers (hyperalgesic priming), contributing to recurrent inflammatory pain (9).

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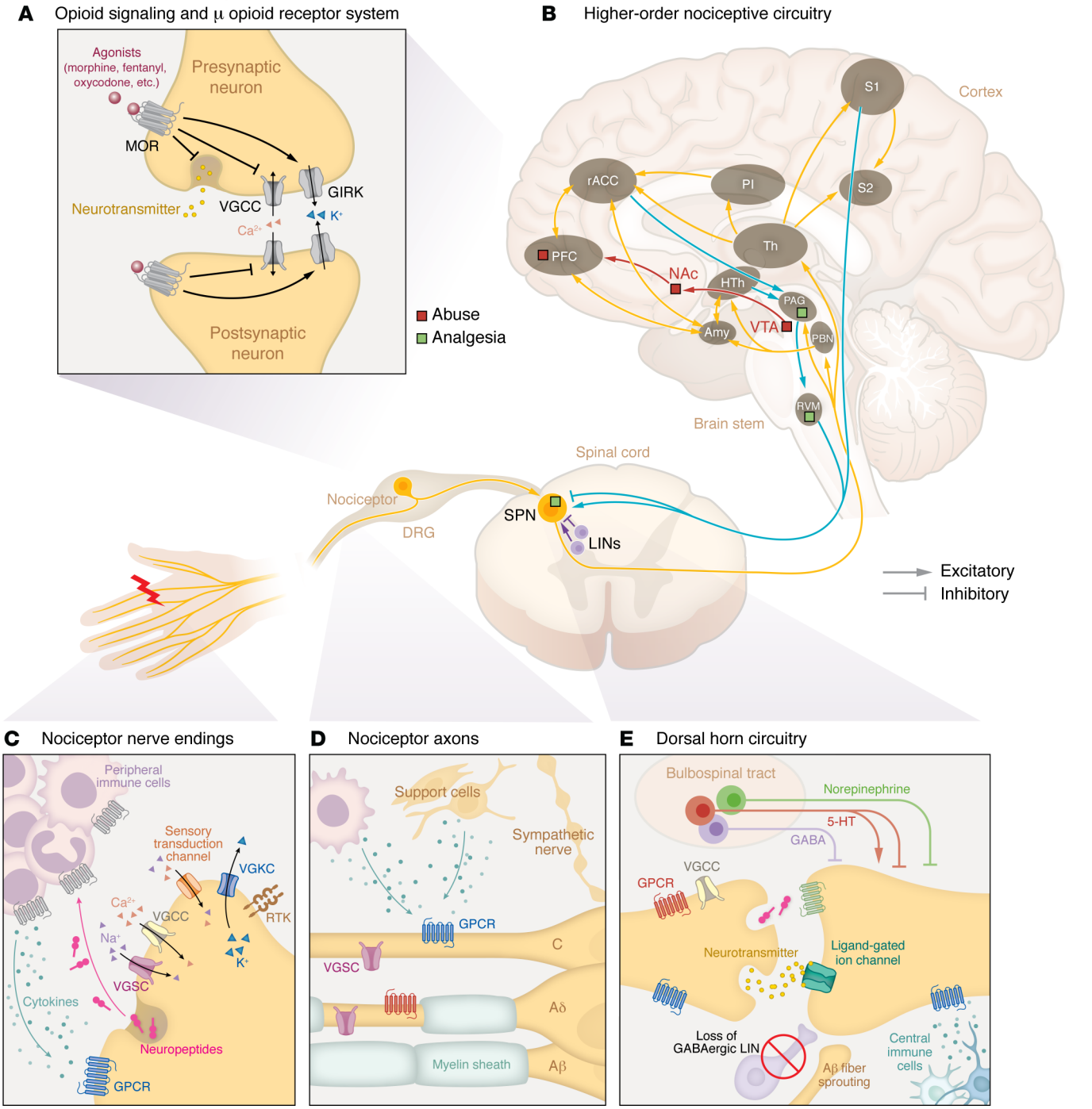

Figure 1. Molecular and circuit architecture of pain processing. (**A**) Activating the μ-opioid receptor (MOR) signaling system produces inhibitory effects on pain-initiating signal transmission but is also associated with adverse effects. See Table 1 for details. (**B**) Neural circuitry underlying nociceptive signal processing. Nociceptor afferents transmit signals from the periphery through the DRG to the spinal dorsal horn, where local interneurons (LINs) modulate the signals before relaying to higher-order brain structures via spinal projection neurons (SPNs). These structures include the parabrachial nucleus (PBN), periaqueductal gray (PAG), hypothalamus (HTh), thalamus (Th), prefrontal cortex (PFC), rostral anterior cingulate cortex (rACC), posterior insular cortex (PI), amygdala (Amy), and primary and secondary somatosensory cortices (S1, S2), constituting the ascending pathway (yellow). Descending pathways (blue) from the rACC, PAG, and rostral ventromedial medulla (RVM) modulate pain by inhibiting or facilitating spinal nociceptive transmission. The ventral tegmental area (VTA), nucleus accumbens (NAc), and PFC are implicated in the reward and abuse potential of opioids (red), whereas the PAG, RVM, and dorsal horn are primary sites for opioid-induced analgesia (green). (**C**) Peripheral tissue injury or pathogen invasion recruits immune cells that release proinflammatory cytokines, leading to heightened nociceptor excitability, which in turn drives neuropeptide release and amplifies inflammation. (**D**) Direct damage to nerves by injury or disease results in nociceptor hyperexcitability, demyelination, sympathetic nerve sprouting, and recruitment of peripheral immune cells to the site of injury that contribute to pain. Nonneuronal support cells secreting cytokines may exacerbate pain development. (**E**) Increases in ligand-gated ion channel activity, decreases in inhibitory GPCR signaling, loss of inhibitory LINs, and sprouting of nonnociceptive A fibers to the superficial dorsal horn can promote pain signaling. Recruitment of central immune cells (e.g., microglia and astrocytes) and a top-down regulation of serotonergic (5-HT), noradrenergic, and GABAergic projections via the bulbospinal tract also modulate CNS pain signals.

Table 1. General strategies for pain relief

Anatomical targets	Strategy	Molecular and cellular targets
Sensory nerve endings	Block signals evoked by external noxious stimuli.	Sensory transduction channels such as TRPV1 at nociceptor endings (Figure 1C)
Sensory neuron axons	Block action potential generation or propagation in nociceptors.	Voltage-gated ion channels such as Nav1.7, Nav1.8 in nociceptor axons (Figure 1D)
DRG	Modulate transcript expression in the primary sensory neuron soma to regulate proteins involved in peripheral sensitization, ectopic activity, and pain amplification.	Voltage-gated ion channels, ligand-gated receptors, and GPCRs expressed in DRG neurons, immune cells, and satellite glia attenuate neuroinflammation and nociceptor sensitization
Dorsal horn circuitry	Block nociceptive signal processing in the superficial dorsal horn of the spinal cord by targeting nociceptor–to–spinal projection neurons and modulating local interneurons.	Cav2.2 and postsynaptic receptors such as NMDA at synapses along the nociceptive pathway, particularly between primary sensory and second-order spinal neurons (Figure 1E)
Higher-order nociceptive circuitry	Modulate nociceptive signals in higher-order brain regions, such as cortex and descending pathways from the brain stem.	Modulation of descending pathways, including 5-HT, GABAergic, and noradrenergic inputs from the PAG, RVM, and locus caeruleus to the spinal dorsal horn (Figure 1, B and E). While serotonin exerts both pro- and antinociceptive effects depending on receptor subtype (e.g., activation of the excitatory 5-HT_3 receptor amplifies pain transmission, whereas the inhibitory 5-HT_{1A} receptor attenuates nociceptive signaling), activation of α_2-adrenergic and GABAergic receptors suppresses pain transmission (3, 6)
	Binding of opioid agonists to MORs activates the Giα subunit, leading to reduced cAMP levels and suppression of PKA activity. This disrupts SNARE protein function, impairing vesicle fusion and neurotransmitter release. Additionally, MOR activation decreases calcium influx through VGCCs and enhances potassium outflow through the activation of inwardly rectifying potassium (GIRK) channels, leading to neuronal hyperpolarization (Figure 1A).	MORs in various brain and spinal areas, including the PAG, RVM, and spinal dorsal horn (green in Figure 1B). Dependence and addiction are primarily associated with the activation of these receptors in the mesolimbic reward pathway primarily composed of nucleus accumbens, ventral tegmental area, and prefrontal cortex (red in Figure 1B) (201)

Cav2.2, N-type calcium channel; 5-HT, serotonergic; PAG, periaqueductal gray; RVM, rostral ventromedial medulla; MOR, μ-opioid receptors; VGCC, voltage-gated calcium channel.

Immune cells can exert both pronociceptive and antinociceptive effects. For example, macrophages activated by an acute injury or infection initially adopt proinflammatory phenotypes, releasing cytokines that sensitize nociceptors. Over time, they transition to antiinflammatory states, producing reparative mediators like IL-10 and thrombospondin-1, which counteract sensitization by modulating signaling pathways in peripheral terminals including PKA signaling (10). In a diet-induced diabetic-like neuropathy, macrophages recruited to the nerve help delay axonal degeneration (11). Managing inflammatory pain requires, therefore, understanding of the timing and context of the immune responses critical for determining the balance between pain sensitization and resolution. The goal is to selectively dampen pathological pain while preserving nociceptive protection and reparative immune functions.

Neuropathic pain. Neuropathic pain is caused by damage or disease affecting the somatosensory system. Unlike acute inflammatory pain, it is entirely pathological and typically persistent, lacks protective function, and is often accompanied by debilitating comorbidities like depression, anxiety, sleep disorders, and cognitive impairments (12–14). Spontaneous pain, a hallmark of neuropathic conditions, is more prevalent than stimulus-evoked pain (15). Mechanistically, neuropathic pain is multifaceted. Peripheral hyperexcitability due to aberrant ion channel expression, ectopic spontaneous discharges, and altered intracellular signaling pathways plays key roles (Figure 1D). Meanwhile, central sensitization enhances synaptic efficacy in the CNS through increased NMDA receptor activation and diminished GABAergic inhibition in the spinal dorsal horn (16–19). Structural plasticity, including synaptic reorganization, nonnociceptive Aβ fibers sprouting into central nociceptive pathways (20), activation of normally silent projection neurons (21), and expansion of peripheral nerve endings (22), extends hypersensitivity beyond the original injury site. Altered connectivity and plasticity in higher-order circuitry and bulbospinal descending control further exacerbate pain perception, reinforcing its chronic nature (Figure 1E).

"Neuropathic pain" encompasses a wide range of conditions with diverse etiologies, symptoms, and mechanisms (Table 2). Peripheral nerve injury–induced neuropathic pain involves aberrant axonal regeneration and spontaneous ectopic activity in injured axons (18, 19). By contrast, metabolic neuropathies, like diabetic peripheral neuropathy, arise from hyperglycemia-induced oxidative stress, resulting in nerve damage and pain (23). Similarly, neurotoxin-induced peripheral neuropathy, as seen in chemotherapy-induced peripheral neuropathy (CIPN), is associated with mitochondrial dysfunction and neurodegeneration (24). Conversely, central neuropathic pain, resulting from CNS damage, involves distinct mechanisms like loss of inhibitory control and cortical circuit reorganization (25). Neuropathic pain may cause paresthesia, dysesthesia, and itch, or negative symptoms like numbness and loss of touch or temperature sensations, reflecting its complex nature. The diverse etiologies highlight the need to contextualize neuropathic pain subtypes and identify specific pathophysiology to develop targeted therapies.

Nociplastic pain. "Nociplastic pain," previously termed dysfunctional pain, describes conditions like fibromyalgia and complex regional pain syndrome type I (CRPS-I), where chronic pain occurs without apparent tissue damage or disease and is often accompanied by fatigue, sleep disturbances, cognitive impairments, and mood disorders (26). Patients often exhibit resistance to traditional

Table 2. Classification of pain

Category	Etiology	Clinical examples
Nociceptive pain	Pain arising from actual or threatened damage to nonneural tissue due to the activation of high-threshold nociceptor sensory neurons.	Only a clinical issue if it causes tissue damage triggering inflammatory responses
Inflammatory pain	Pain triggered by an immune response to tissue damage or infection. Acute inflammatory pain serves a protective role, promoting healing. However, chronic inflammation constitutes a pathological condition.	Post-tissue injury, rheumatoid arthritis, osteoarthritis
Peripheral nerve injury–induced neuropathic pain	Pain resulting from direct damage to peripheral nerves due to trauma, surgery, or other mechanical insults.	Peripheral nerve compression (neuropraxia), crush (axonotmesis), transection (neurotmesis), limb amputation, neuromas, trigeminal neuralgia, postsurgical pain, small-fiber neuropathy, complex regional pain syndrome type II
Metabolic neuropathy	A neuropathy caused by metabolic imbalances that damage peripheral nerves. Commonly associated with conditions like diabetes, hypothyroidism, or vitamin deficiencies, it also leads to numbness, tingling, and pain in the extremities, due to impaired nerve function from prolonged metabolic dysfunction.	Diabetic peripheral neuropathy, small-fiber neuropathy, hypothyroid neuropathy, vitamin deficiency neuropathy
Neurotoxin-induced peripheral neuropathy	Exposure to neurotoxins, such as chemotherapy agents (e.g., paclitaxel or vincristine) or environmental toxins, that directly damage peripheral nerves, causing degeneration and hyperexcitability. Specific neurotoxic agents can lead to an alteration in different molecular pathways, affecting microtubule function, axonal transport, and mitochondrial integrity.	Chemotherapy-induced peripheral neuropathy, alcoholic neuropathy, heavy-metal neuropathy
Infection-induced neuropathic pain	Following acute infection, viruses can remain dormant in sensory ganglia and then reactivate, causing axon damage, leading to neuropathic pain.	Postherpetic neuralgia, HIV-associated neuropathy
Central neuropathic pain	Pain that results from damage to or disease of the CNS involving loss of inhibitory controls, increased excitatory neurotransmission, and reorganization of neural circuits at spinal or cortical levels.	Brain injuries, spinal cord injuries, strokes, multiple sclerosis
Nociplastic pain	Pain arising in the absence of a clear injury or inflammation, often associated with psychological and emotional factors.	Fibromyalgia, complex regional pain syndrome type I, migraine, chronic primary bladder/pelvic pain syndrome, chronic temporomandibular pain
Visceral pain	Pain arising from internal organs, typically caused by inflammation though it can be associated with nociplastic pain like irritable bowel syndrome.	Inflammatory bowel disease, irritable bowel syndrome
Mixed pain	Complex pain conditions involving both neuropathic and inflammatory components require further classification to guide treatment choices.	Cancer pain, chronic low back pain

analgesics like NSAIDs and opioids, while drugs targeting neuropathic pain, including gabapentinoids and SNRIs, offer only limited efficacy (27, 28). Consequently, first-line treatments prioritize nonpharmacological approaches like cognitive-behavioral therapy, given the strong psychological and emotional factors (29, 30). Nociplastic pain mechanisms remain the least understood and appear highly heterogeneous, primarily involving central sensitization (28), though peripheral alterations have also been suggested (31, 32), with genetic predisposition and environmental factors potentially also contributing to the development of nociplastic pain (33). Moreover, increased levels of proinflammatory cytokines (e.g., IL-6, IL-8, and TNF-α) are observed in both fibromyalgia and CRPS-I (34, 35), suggesting a potential immune contribution to the pathogenesis. These complexities, along with the lack of a well-defined etiology, make preclinical modeling challenging. Commonly used animal models (36, 37), like intramuscular acid injection, replicate only certain aspects of the clinical symptoms of fibromyalgia, leaving uncertainty whether they faithfully reproduce the pathophysiology.

The absence of reliable biomarkers further complicates diagnosis, and targeted therapies remain elusive. Current clinical studies largely rely on hemodynamic imaging (for example, functional MRI [fMRI]), leaving neural dynamics underexplored. Integrating complementary neuroimaging modalities to enhance spatiotemporal resolution, like fMRI-electroencephalography or -polysomnography fusion, alongside epigenetic and serological features (28, 33), could facilitate identification of bona fide biomarkers. Given the high prevalence of sleep disturbances in patients, potential biomarkers may also emerge during sleep (38). Furthermore, connectomics-based brain mapping (39) could refine pain classification for more precise diagnosis. These insights could inform the development of more physiologically relevant preclinical models to understand mechanisms, which are necessary to develop target-based therapies. Notably, a recent study showed that IgG transfer from fibromyalgia patients induces mechanical and thermal pain in mice, likely through binding to satellite glia and sensory neurons in the DRG, leading to nociceptor sensitization (40). This suggests immune components as viable therapeutic targets, and offers a more translational approach for modeling nociplastic pain.

Multisystem involvement and multimodal intervention. Pain is a complex sensory experience involving multiple systems. For instance, peripheral nerve injury from trauma triggers immune activation in several distinct ways. Initially, damage to nonneuronal tissues like skin recruits immune cells releasing proinflammatory mediators that sensitize nociceptors, causing an acute inflammatory component of the nerve injury pain (Figure 1, C and D). Persistent inflammation, however, may sustain pain, as seen in patients

with chronic pain, in whom mast cell infiltration correlates with pain severity (41). Mechanistically, this may stem from inadequate production of antiinflammatory mediators like IL-4 and IL-10 (42), and/or prolonged T cell activation that amplifies pain signals (43). Conversely, the somatosensory system modulates immune function especially in chronic inflammation conditions like arthritis and colitis (44, 45). Neurons can interact directly with immune cells, as seen in a CIPN model where TLR on nociceptors activates immunity through MyD88 signaling (46). Additionally, sensory neurons release neuropeptides from their peripheral terminals, which act upon cognate receptors on immune cells (Figure 1C), leading to neurogenic inflammation (47). Calcitonin gene–related peptide (CGRP) released by nociceptors acts on bacteria-infected tissues to inhibit neutrophil recruitment (48), while the neurokinin-1 (NK1) receptor, activated by nociceptor-derived substance P, contributes to cutaneous inflammation (49). Similar phenomena are implicated in fibromyalgia (50). Such bidirectional neuron-immune communications can pathologically stabilize inflammatory and sensitized states, resulting in chronic pain. Beyond the periphery, injury or disease can drive CNS immune responses through microglia and astrocytes, further exacerbating central pain signaling (Figure 1E). However, the contribution of spinal microglial activation to neuropathic pain appears to be sexually dimorphic (51–53). Similarly, a recent study showed that meningeal regulatory T cells mediate a female-specific antinociceptive effect via δ-opioid receptors, a mechanism dependent on sex hormones rather than their canonical immune-regulatory role (54).

The autonomic system, particularly sympathetic nerves, contributes to neuropathic pain through signaling molecules like norepinephrine or by aberrant sprouting into the somatosensory system (55). In the same system, vascular movements have also been implicated in driving ectopic activity in the DRG via Piezo2 channels (56). Nonneuronal support cells including Schwann cells, satellite glia, and fibroblasts can promote pain development by secreting proinflammatory mediators and growth factors (Figure 1D) (57–60). Chronic pain may also affect the endocrine system, with hypothalamic-pituitary-adrenal axis dysregulation altering stress hormones like cortisol, affecting pain perception and inflammation as seen in fibromyalgia (61, 62). Similarly, in diabetes, hyperglycemia induces oxidative stress through the formation of glycation end products, which interact with neuronal and endothelial receptors, promoting nerve damage and neuropathic pain (63). Psychosocial factors also participate in shaping pain expression (64), with preclinical studies showing that pain-related behaviors can be socially transferred through higher-order cognitive circuitry, including the cingulate cortex (65).

The multisystem nature of pain underscores why therapies targeting only a single system often fail to fully alleviate the pain symptoms (66). This complexity emphasizes the need for multimodal approaches, either by combination of drugs that target a comprehensive spectrum of pathological changes across different physiological systems or by identification of a single compound that acts on multiple selected targets (67). While current clinical data suggest that such combinations often fail to produce synergistic effects (68), this could be due to the lack of mechanistic guidance on optimal drug pairings and the limitations of trial duration. By understanding the interplay among the engaged systems, future therapeutic strategies can better address the multifactorial nature of chronic pain, leading to more effective pain management.

Considerations for treating acute and chronic pain. Pain is a dynamic process that can transition from acute to chronic phases, each governed by distinct mechanisms. Acute pain typically results from the rapid peripheral sensitization of nociceptors due to inflammatory mediators released at the injury site. This sensitization enhances neuronal firing, leading to increased neurotransmitter release from the central terminals of nociceptors, which in turn amplifies pain signals to the brain. In contrast, chronic pain involves maladaptive plasticity within both the periphery and the CNS, often marked by irreversible physiological and anatomical changes. Notably, not all patients develop chronic pain, even after similar initial insults (69). This suggests that genetic and epigenetic factors drive long-term changes in gene expression that contribute to pain chronicity in susceptible individuals (70, 71). Critically, even if the pain primarily originates from one system, it can recruit other systems over time, evolving into a "mixed" pain condition. Persistent inflammation has been observed in chronic neuropathic conditions long after the initial trigger-induced inflammation has resolved (72). Likewise, while rheumatoid arthritis has a clear inflammatory origin, pain may persist despite eventual diminished tissue inflammation (66), with recent evidence suggesting that synovial fibroblasts contribute to pain persistence through interactions with sensory neurons (60).

The transition from acute to chronic pain also involves spatial shifts in pathophysiology. Following peripheral injury, central sensitization develops, while peripheral immune cells and proinflammatory cytokines may also infiltrate the CNS through a compromised blood-brain barrier (BBB), further amplifying pain signaling (43, 73). Understanding the spatiotemporal dynamics and mechanistic nature of pain progression is therefore crucial for effective intervention. We stress the need for longitudinal studies rather than heterogeneous patient cohorts to better capture pathological progression in individual patients. Furthermore, we must explore targeted therapies during the acute phase to prevent maladaptive changes from becoming entrenched, offering a neuroprotective strategy rather than merely suppressing established symptoms (Figure 2).

Defining the underlying pathophysiology is essential for developing particular pharmacokinetic and pharmacodynamic strategies tailored to different pain states. For instance, postoperative pain or acute injury could be effectively treated with the oral or topical administration of short-acting antiinflammatory agents or ion channel blockers, while chronic pain with centralized components may require long-term targeted genetic modulation via neuraxial routes (Figure 2). Effective treatment depends not only on drug selection but also on delivery routes (Figure 3A), which influence drug bioavailability and target specificity. Despite efforts to develop more potent analgesics, their clinical efficacy remains limited if pharmacokinetic barriers exist, such as plasma protein binding and restricted BBB penetration. To overcome these challenges, a series of innovative technologies facilitating drug delivery have been developed (Figure 3B). For example, zinc and magnesium oxide nanoparticles exhibit intrinsic analgesic properties by depositing Zn^{2+} or Mg^{2+} ions into CNS synapses, thereby reducing ionotropic NMDA receptor activity (74, 75). Nanoparticle formulations of Zn^{2+} or Mg^{2+} also improve CNS penetration compared with ion administration alone. Additionally, nanoparticle-based carriers

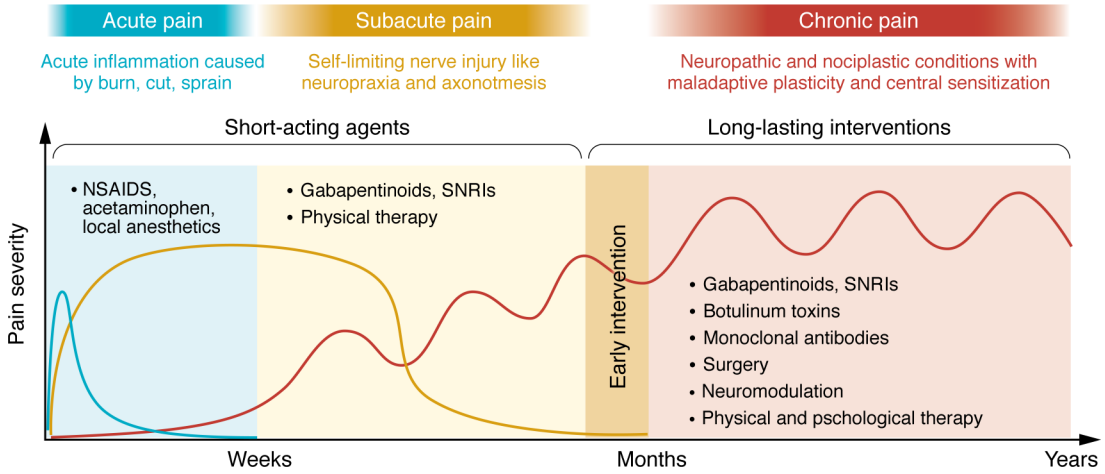

Figure 2. Acute and chronic pain demand distinct therapeutic strategies. Pain can be broadly categorized into acute, subacute, and chronic phases, each defined by distinct pathophysiological mechanisms and requiring tailored therapeutic strategies. This timeline illustrates the transition from short-acting symptomatic relief to more durable, disease-modifying interventions. Acute pain, typically mediated by nociceptor activation and inflammation, is commonly managed with short-acting agents such as NSAIDs, acetaminophen, and local anesthetics. Subacute pain – often resulting from injuries with regenerative potential, such as nerve compression (neuropraxia) or crush injuries (axonotmesis) – may resolve spontaneously and can be managed with gabapentinoids, SNRIs, and physical therapy. Chronic pain, particularly under neuropathic or nociplastic conditions (see Table 2), is frequently paroxysmal and recurrent, necessitating long-lasting interventions. Current options include pharmacotherapies, surgical interventions, neuromodulation, and multimodal physical and psychological therapies, though their efficacy remains limited and variable. Emerging approaches (see Figure 4B) may offer more targeted and sustained relief. Importantly, early interventions during the acute/subacute phase may help prevent the development of maladaptive plasticity, offering a neuroprotective strategy rather than merely suppressing symptoms once chronic pain is established.

enhance the efficacy of local anesthetics, prolonging their duration and reducing systemic toxicity (76).

Target-based pain management

In this section, we review molecular targets across anatomical sites for pain management (Table 1). The landscape of preclinical and clinical investigation is constantly advancing, and we have endeavored to highlight those select clinical trials that have resulted in promising clinical success or relative failure. We also discuss some promising targets being validated in preclinical research, as these may lay the groundwork for future clinical development. Clinical trial data were sourced from ClinicalTrials.gov and the International Clinical Trials Registry Platform, where we selected pain-related trials that targeted molecules including ion channels, GPCRs, enzymes, transporters, and others.

Ion channels. Voltage-gated sodium channels (VGSCs; referred to individually as Nav; Table 3) have been at the epicenter of drug design for the development of novel pain-killing drugs for several decades. Their role in membrane depolarization controls multiple aspects of neuronal excitability (i.e., action potential threshold, height, and width) (77). Furthermore, peripheral sensory neurons preferentially express a subset of VGSCs (Nav1.7, Nav1.8, and Nav1.9) that work in tandem to facilitate nociception (78). The importance of VGSCs in nociception is supported by the profound antinociception exerted by local anesthetics like lidocaine that nonselectively block VGSCs. However, their lack of subtype selectivity precipitates many undesired side effects, including loss of motor function and hypoesthesia. Therefore, considerable efforts have been expended to design potent analgesics with specificity for "nociceptive" VGSCs: Nav1.7, Nav1.8, and Nav1.9. So far, efforts have failed to develop a clinically viable molecule with subtype selectivity for VGSCs, with one notable exception: Vertex Pharmaceuticals was recently granted FDA approval for their selective Nav1.8 blocker suzetrigine (VX-548). The clinical success of suzetrigine provides evidence that Nav1.8 is a driver of pain and efficient blockade of Nav1.8 is sufficient in attenuating pain. However, the clinical trial data suggest that there is still room for improvement, as its greatest efficacy, which was limited, was observed in postsurgical pain (79) and diabetic neuropathy but not for sciatica, highlighting the importance of targeting the specific mechanisms underlying different pain conditions. On the other hand, TV-45070, a topical Nav1.7 blocker, has shown some promise, but failed to meet predetermined primary endpoints in postherpetic neuralgia patients (80, 81). Systemic administration of Nav1.7 blockers has failed to produce a clinical candidate either because of poor pharmacokinetics (82) or because they engaged Nav1.7 to produce analgesia but also precipitated effects on sympathetic neurons, leading to hypotension (83, 84). Curiously, a novel triple-acting (Nav1.7/1.8/1.9) molecule, ANP-230, has shown effectiveness in preclinical models in rodents (67, 85), which may be a useful strategy rather than targeting a single channel. Sodium channels are powerful determiners of nociceptor excitability; however, only relatively recently have we begun to tap into the clinical potential of selective VGSC blockade targeted at single or multiple specific subtypes. Ongoing efforts to explore other selective Nav inhibitors, some of which are actively recruiting participants for phase I/II clinical trials (86, 87), will hopefully result in an expansion of Nav channel inhibitors for treating pain. Selective Nav channel blockers may serve as key nonopioid pain relief options in the future.

The voltage-gated calcium channel (VGCC; referred to individually as Cav; Table 3) family represents a promising target for pain management, given its well-established role in regulating neuronal

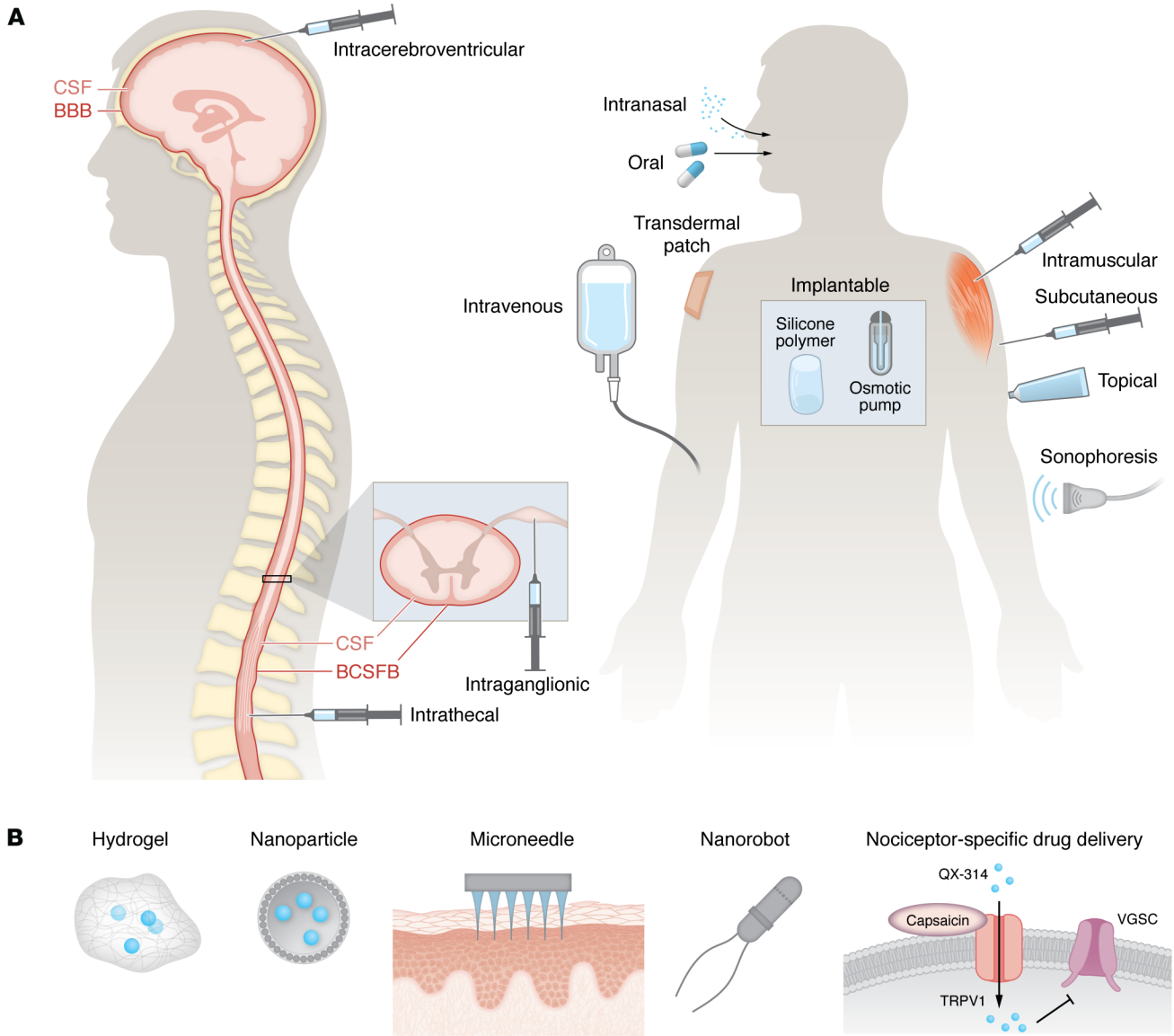

Figure 3. Drug delivery routes and techniques that enhance delivery efficacy and pharmacokinetics. (**A**) Oral administration is most common but suffers from first-pass metabolism and limited CNS penetration. Intranasal delivery offers rapid absorption via the olfactory and trigeminal pathways, enhancing brain access. Parenteral routes, including subcutaneous, intramuscular, and intravenous injections, provide faster onset but with systemic exposure and potential side effects. For localized pain control, topical and transdermal patch formulations minimize systemic effects while allowing sustained drug release. Sonophoresis enhances transdermal penetration using ultrasound waves (187). Intrathecal and intracerebroventricular delivery bypass the blood–cerebrospinal fluid barrier (BCSFB) and blood-brain barrier (BBB), allowing direct access to the cerebrospinal fluid (CSF). Intraganglionic administration is an effective route as the DRG is a primary site for the initiation of pain triggering signals and lies outside the BCSFB (188). Implantable systems, including silicone polymer–based depots and osmotic pumps, enable controlled, long-term drug release (189). (**B**) Biodegradable hydrogels offer sustained drug release, providing localized delivery with minimal systemic side effects (190). These hydrophilic networks respond to environmental triggers such as pH or temperature to control drug release (191). Nanoparticles, including lipid-based, polymeric, and inorganic variants, improve drug solubility, stability, and targeted tissue penetration while overcoming biological barriers (192). Engineered microneedles enable painless, transdermal drug delivery, bypassing the stratum corneum, improving bioavailability for molecules and biologics (193). Nanorobots, driven by magnetic, light, acoustic, or chemical propulsion, hold promise for precision-targeted drug delivery, actively navigating biological environments to reach specific tissues (194). There is also a targeted pain-specific local analgesia strategy involving coadministration of membrane-impermeant sodium channel blockers such as QX-314 or BW-031 with agonists that activate large-pore channels selectively expressed in nociceptors (e.g., capsaicin-TRPV1). This approach facilitates drug entry only into nociceptors, effectively blocking their activity while preserving motor and tactile function (195, 196).

excitability and synaptic transmission (88). VGCCs are classified into 3 main types — Cav1 (L type), Cav2 (P/Q type, N type), and Cav3 (T type) — each playing distinct roles in neuronal function. Among these, the N-type calcium channel (Cav2.2) has garnered the most attention as a pain target due to its crucial role in mediating synaptic neurotransmitter release between primary sensory neurons and spinal dorsal horn neurons. A variety of ω-conotoxins have been developed to block Cav2.2 in preclinical pain models. Some,

Table 3. Approved and ongoing clinical trials targeting ion channels

Target	Mechanism	Compound	Pain state (see also Table 2)	Clinical trial phase
VGSCs				
Nav1.7	Inhibition of sodium channel flux antagonizing action potential generation. Nav1.7 is responsible for a rapid tetrodotoxin-sensitive inward sodium current in nociceptors. Nav1.7 has a negatively shifted steady-state inactivation and slow closed-state inactivation (202). These kinetic properties allow Nav1.7 to contribute to action potential threshold.	Funapide	Osteoarthritis (NCT02068599), postherpetic neuralgia (80), postsurgical pain (NCT04826328)	Phase II
		AZD3161	Nociceptive pain (NCT01240148)	Phase I
		DSP-2230	Nociceptive pain (ISRCTN80154838)	Phase I
		PF-05089771	Diabetic peripheral neuropathy (NCT02215252)	Phase II
		Vixotrigine	Small-fiber neuropathy and trigeminal neuralgia (203, 204)	Phase II
		iN1011-N17	Postherpetic neuralgia (NCT06218784)	Phase I
Nav1.8	Nav1.8 contributes to the slowly developing tetrodotoxin-resistant (205) current in nociceptors. It is responsible for most of the sodium influx during action potential generation and heavily underlies action potential electrogenesis (206).	ODM-111	Chronic neuropathic pain (ISRCTN84512888)	Phase I
		PF-06305591	Nociceptive pain (NCT01776619)	Phase I
		VX-150	Small-fiber neuropathy (NCT03304522)	Phase II
		Suzetrigine	Acute and chronic pain (NCT05558410, NCT05661734, NCT06176196)	FDA-approved for acute pain
			Diabetic peripheral neuropathy (NCT06628908)	Phase III
		VX-993	Acute pain (NCT06619847)	Phase II
		LTG-001	Acute postsurgical pain (NCT06774625)	Phase II
		JMKX-000623	Diabetic peripheral neuropathy (NCT06221241)	Phase II
Nav1.9	Nav1.9 produces an ultra-slow inactivating and tetrodotoxin-resistant sodium current in sensory neurons (207). It also has a high degree of activity at resting membrane potential, suggesting it may help amplify subthreshold fluctuations (208).	ANP-230	Familial infantile episodic limb pain. This molecule is unique in that it is capable of inhibiting Nav1.7, Nav1.8, and Nav1.9 (67, 85)	Phase I/II
Broad VGSCs	Tetrodotoxin is a potent inhibitor of a subset of VGSCs. Tetrodotoxin binds extracellularly to the pore-forming chain of the VGSC at the selectivity filter and prevents influx of sodium ions, thus reducing cellular excitability. Tetrodotoxin is highly selective for VGSCs; however, it blocks Nav1.1, Nav1.2, Nav1.3, Nav1.4, Nav1.6, and Nav1.7 with nanomolar concentrations, whereas Nav1.5, Nav1.8, and Nav1.9 are blocked with micromolar concentrations (209).	Tetrodotoxin	Cancer pain (210)	Phase III
VGCCs				
Cav2.2	Blocking of N-type channel sensory neuron terminals in the spinal dorsal horn, inhibiting neurotransmitter release (88).	Ziconotide	Mixed pain with chronic and refractory features (211)	FDA-approved
		CNV2197944	Diabetic neuropathy (NCT01893125), postherpetic neuralgia (NCT01848730)	Phase II
Cav3.2	Blocking of Cav3.2, which participates in modulating sensory neuron excitability (88).	Z944	Inflammatory pain (212)	Phase Ib
Cav$\alpha_2\delta$	Interfering with the trafficking of the $\alpha_2\delta$ subunit to the cell membrane and thus modulating VGCCs to reduce calcium influx and neurotransmitter release in the spinal dorsal horn circuitry (90, 91).	Gabapentin, pregabalin	Various neuropathic pain conditions (91)	FDA-approved
			Fibromyalgia (27)	Pregabalin is FDA-approved for fibromyalgia; gabapentin may be used off-label
		Mirogabalin	Peripheral neuropathic pain (213)	Approved (Japan)
		Crisugabalin (HSK16149)	Diabetic neuropathy (214)	Phase III
VGKCs				
Kv7.2/7.3	Activation of Kv7 channels decreases excitability in peripheral sensory neurons (215).	Flupirtine	Excitability of human peripheral myelinated axons in vivo (216)	Phase I
		ICA-105665	Acute nociceptive pain (NCT00962663)	Phase I
Sensory transduction channels				
TRPV1	TRPV1 antagonism (101).	XEN-D0501	Diabetic neuropathy (NCT03278158)	Phase II
		ACD440 gel	Peripheral neuropathic pain (NCT05416931)	Phase II
	Agonists leading to TRPV1 desensitization (101).	Qutenza	Diabetic neuropathy, postherpetic neuralgia, CIPN (217, 218)	FDA-approved
		CNTX-4975	Osteoarthritis knee pain (219)	Phase III
		Resiniferatoxin	Osteoarthritis knee pain (220)	Phase III
TRPA1	TRPA1 antagonism (101).	LY3526318	Osteoarthritis (NCT05080660), chronic lower back pain (NCT05086289), diabetic neuropathy (NCT05177094)	Phase II
Synaptic transmission				
NMDA receptors	NMDA antagonist acting at both presynaptic terminals and postsynaptic spinal neurons (106).	Ketamine	Neuropathic and other severe pain conditions (221)	FDA-approved as a general anesthetic; also used off-label to manage various pain conditions
		NYX-2925 (222)	Diabetic neuropathy (NCT04146896), fibromyalgia (NCT04147858)	Phase II

such as ziconotide, have reached the market. However, considerable drawbacks exist, particularly due to severe side effects like dizziness, nausea, and ataxia, as well as challenges in drug delivery methods, as intrathecal administration is required to bypass the BBB (89).

The calcium channel auxiliary protein $\alpha_2\delta$ subunit is also a major target for neuropathic pain. Trafficking of this auxiliary subunit is upregulated by axon damage, enhancing VGCC function, leading to increased neurotransmitter release and pain signaling (90, 91). Gabapentinoids (i.e., gabapentin and pregabalin) target the $\alpha_2\delta$ subunit and are widely used for neuropathic pain management with potential applicability for fibromyalgia (27, 91). However, responses vary substantially across individuals and pain conditions, and these medications are associated with cognitive and sedative adverse effects (92).

Potassium channels are responsible for potassium efflux resulting in membrane hyperpolarization, reducing neuronal excitability (93). Thus, enhancement of the efflux of potassium ions in nociceptors would be an attractive strategy for treating pain (94). There has been one notable success in this investigational landscape, flupirtine. Flupirtine is an aminopyridine that enhances currents through the voltage-gated potassium channels (VGKCs; referred to individually as Kv; Table 3) KCNQ (Kv7) and G protein–gated inwardly rectifying potassium (GIRK) channels and decreases currents through NMDA receptors (95, 96). The multimodal mechanism of action of flupirtine resulted in considerable analgesia in clinical trials across various pain modalities, contributing to its initial success (97, 98). However, severe hepatotoxicity led to its withdrawal from the market (99). Other potassium channel modulators being developed for epilepsy and ALS may have analgesic efficacy similar to that of flupirtine without its adverse effects (100).

Another straightforward strategy for alleviating pain triggered by external stimuli is to directly target molecular pain triggers, namely peripherally expressed sensory transduction channels (Table 3). Extensive preclinical research has focused on these channels, particularly the transient receptor potential (TRP) channel family (101) and mechanosensitive Piezo2 channels (102, 103). However, translating these findings into the clinic has proven challenging. Many of these channels are broadly expressed across various sensory cell types, meaning they are not exclusively linked to pain but are also essential for other physiological functions. Consequently, systemic inhibition can lead to side effects, and clinical success has been limited. One achievement is localized/topical modulation of TRPV1, which has shown efficacy in treating both inflammatory and neuropathic pain. Topical application mitigates the risk of off-target effects, preserving basal sensory functions while offering anatomically defined pain relief, an advantage over systemic administration, which can disrupt key protective functions of nociceptive pain and alter thermoregulation (101). It is important to recognize that distinct sensory cell types may contribute to different pain conditions, such that the precise targeting of specific cell populations (104) may be a useful strategy.

Postsynaptic ionotropic receptors (Table 3), NMDA, AMPA, and GABA type A ($GABA_A$), are also options for pain management, as they play critical roles in processing and relaying pain-initiating signals from the spinal cord to higher-order circuits (5). Synaptic transmission involving these receptors produces both excitatory and inhibitory signals through glutamatergic and GABAergic synapses, respectively. Therefore, analgesia can be achieved through antagonizing excitatory (NMDA and AMPA) and agonizing inhibitory ($GABA_A$) receptors, especially via the α_2 subunit (105–107). These receptors are particularly pertinent in the context of inflammatory and neuropathic pain, where both sensitization and disinhibition in the CNS are key mechanistic features (16, 18, 19). However, owing to their broad involvement in general neurotransmission across the central and peripheral nervous systems, targeting these receptors for analgesia can lead to serious side effects, limiting their clinical applicability.

GPCRs. Among the myriad of receptors that populate nociceptor cell membranes, ion channels represent only a subset of pharmacologically exploitable molecules. Another major group are GPCRs, which transform extracellular stimuli into intracellular signaling cascades that modulate cellular responses depending on their associated G protein (Table 4). In neurons, strong changes in output, either excitatory or inhibitory, are typical following GPCR activation. GPCRs participate in nociceptive signal processing in varying capacities. From a preclinical perspective, there have been great advancements in understanding how they modulate pain signaling. For example, neuropeptide Y receptors 1 (NPY1R) and 2 (NPY2R) are Gi-coupled GPCRs that, in preclinical models, antagonize neuronal hyperexcitability in the spinal dorsal horn, reducing nociception (108, 109). However, clinical exploitation of these GPCRs has not been realized. This does not imply that NPYR1 and NPYR2 are not important for human nociception; rather, clinical data on these have yet to materialize. There have been some forays into GPCR modulation of pain in patients. Novartis Pharmaceuticals' angiotensin II type 2 receptor antagonist EMA401 was developed to inhibit AGTR2, as AGTR2 was discovered to contribute to neuropathic pain (110). EMA401 was administered to participants with postherpetic neuralgia, who reported a decrease in their pain metrics; however, hepatotoxicity resulted in early termination of the trial (111). AstraZeneca developed a small-molecule negative allosteric modulator of the CCR2 receptor, AZD2423. Although it had high target engagement, there were no appreciable changes in reported pain scores in a double-blind placebo-controlled clinical trial (112). Pfizer attempted to leverage the modulation of nociceptive signaling with a cannabinoid receptor 2 (CB2) agonist, olorinab (ADP-371). CB2 agonism is a powerful modulator of nociceptive input into the spinal cord (113). In preclinical models of colitis, olorinab reversed abdominal hypersensitivity (114), which mirrored earlier reports of CB2-mediated analgesia in rodents. Unfortunately, olorinab did not reach the desired primary endpoint in a phase IIb clinical trial (115), although it did reduce average reported abdominal pain scores in patients with moderate to severe colitis-related pain.

Cannabis-based medicines, particularly cannabidiol (CBD) and tetrahydrocannabinol (THC), have been used for some neurological conditions (116) owing to their interactions with a wide variety of molecular targets. Preclinical studies indicate that THC exerts analgesia primarily through activation of the CB1 and CB2 GPCRs, while CBD modulates pain thorough a multitarget mechanism, including serotoninergic receptors ($5\text{-}HT_{1A}$), TRP channels (117, 118), sodium channel blockade, and potassium channel activation (119, 120). Although there is some evidence for analgesic activity in chronic pain conditions, like fibromyalgia (121, 122), no canna-

Table 4. Approved and ongoing clinical trials targeting GPCRs

Target	Mechanism	Compound	Pain state (see also Table 2)	Clinical trial phase
Angiotensin receptors				
AGTR1/2	Inhibition of angiotensin II type 1 and type 2 receptors is efficacious in models of inflammatory and neuropathic pain. AGTR1 antagonists may have a stronger influence on the CNS, whereas AGTR2 expressed by macrophages is a primary driver of pain phenotypes in the periphery (223, 224).	EMA401	Postherpetic neuralgia and painful diabetic neuropathy (111)	Phase II
Cannabinoid receptors				
CB1/CB2	Agonism of the cannabinoid system (113).	Sativex	Multiple sclerosis (NCT01606176, NCT01604265), spinal cord injury (NCT01606202)	Phase III
		ORG-28611	Postsurgical dental pain (NCT00782951)	Phase II
Bradykinin receptors				
B1R, B2R	Antagonism of the bradykinin receptor system attenuates pain-like behaviors in animals. However, efforts in humans have yet to find success past phase II clinical trials (225).	BAY2395840 (B1R)	Diabetic nerve pain (NCT05219812)	Phase II
		MK0686 (B1R)	Postoperative dental surgery pain (NCT00533403)	Phase II
		RGH-478 (B1R)	Osteoarthritic knee pain (EUCTR2011-000931-10-HU)	Phase II
		BI-113823 (B1R)	Osteoarthritic knee pain (NCT01207973)	Phase I
		Fasitibant (B2R)	Osteoarthritis of the knee (NCT02205814)	Phase II
Chemokine receptors				
CCR2	CCR2 expression increases in neurons following injury. CCL2 released by neighboring astrocytes suggests an interaction between peripheral nociceptors and astrocytes that promotes nociceptor hyperexcitability that maintains pain states (226).	AZD2423	Post-traumatic neuralgia (112) and diabetic polyneuropathy (NCT01201317)	Phase II
Serotonin receptors				
5-$HT_{1B/1D}$, 5-HT_{1F}, 5-HT_2	Agonism on the Gi/o-coupled 5-$HT_{1B/1D}$ receptor (123).	Zolmitriptan	Acute migraine (123)	FDA-approved
	Agonism on the Gi/o-coupled 5-HT_{1F} receptor (125).	Lasmiditan	Acute migraine (125)	FDA-approved
	Antagonism on the Gq-coupled 5-HT_2 receptor (125).	Cyclobenzaprine	Fibromyalgia (125)	Phase III
Adrenergic receptors				
α_2AR	Agonism on the Gi/o-coupled α_2-AR (227).	Lofexidine	Opioid withdrawal–induced pain (227)	FDA-approved

binoid-based therapies have been approved for pain management. Further studies with well-designed CBD/THC formulations or their analogs are needed to evaluate their therapeutic potential and long-term safety for pain management.

Serotonin and α_2-adrenergic receptors are promising targets for pain modulation. 5-$HT_{1B/1D}$ and 5-HT_{1F} receptor agonists are FDA-approved for acute migraine (123, 124), while a 5-HT_2 receptor antagonist showed promise for fibromyalgia in a phase III trial (125). α_2-Adrenergic agonists, including clonidine, dexmedetomidine, and tizanidine, offer strong analgesic/anesthetic effects, but clinical utility is limited by sedation and hypotension (126). Current efforts focus on subtype-selective adrenergic α_2 agonists to minimize side effects. PS75, a functionally selective α_{2A} agonist, has analgesic efficacy with minimal sedation in animal models (127), suggesting potential for safe analgesic therapy.

Enzymes, transporters, and others. Enzymes and transporters have long been recognized for pain management (Table 5). NSAIDs like ibuprofen and aspirin are widely available over the counter because of their relatively safe profile at low doses. These drugs inhibit COX-2, an enzyme that produces prostaglandins, key mediators of inflammatory pain (128). Acetaminophen, a widely used, nonabusable painkiller, is a weak inhibitor of COX-2 in the CNS (129), but whether this is responsible for how it alleviates pain is uncertain. While COX-2 inhibitors are effective for many mild acute pain conditions, they exhibit limited efficacy in neuropathic and nociplastic pain, suggesting that these conditions involve prostaglandin E_2–independent mechanisms. Antidepressants and SNRIs represent another traditional pain therapeutic that acts on a broad spectrum of molecules, modulating descending and ascending aminergic pain pathways. They show efficacy in some neuropathic and nociplastic conditions, especially those with strong centralized components (130). However, systemic delivery often causes off-target effects, and their efficacy varies across pain subtypes and individuals. Improving target specificity and minimizing adverse effects is critical to advancing pain management beyond these traditional pharmacotherapies.

Monoclonal antibody (mAb) therapies (Table 5) represent a potential transformative approach for pain management by targeting the immune-somatosensory interactions underpinning many pain conditions as discussed above. Unlike conventional drugs, mAbs

Table 5. Approved and ongoing clinical trials targeting enzymes, transporters, and others

Compounds	Targets	Mechanisms	Pain state (see also Table 2)	Clinical trial phase
NSAIDs				
Ibuprofen, aspirin, ketorolac, etc.	Nonselective but primarily COX-1/2	NSAIDs inhibit COX-1 and/or COX-2 both centrally and peripherally, reducing prostaglandin production (128).	Various acute pain conditions (128)	FDA-approved
Antipyretics				
Acetaminophen	Nonselective but primarily COX-2 in the CNS	COX-2 in the brain, leading to reduced prostaglandin synthesis (129) and other mechanisms.	Fever, mild headaches	FDA-approved
Tricyclic antidepressants				
Amitriptyline	Broad targets including serotonin, norepinephrine, and ion channels	Inhibition of monoamine reuptake, antagonism of receptors, modulation of ion channels, antiinflammatory and neurotrophic effects (228).	Various neuropathic and nociplastic pain conditions (228)	FDA-approved for treating depression, but also prescribed off-label for neuropathic pain and fibromyalgia (228)
Serotonin-norepinephrine reuptake inhibitors				
Duloxetine, venlafaxine, milnacipran, esreboxetine (AXS-14)	Serotonin and/or norepinephrine	SNRIs enhance the activity of descending inhibitory pain pathways in the bulbospinal pathway by inhibiting norepinephrine and serotonin reuptake (130).	Diabetic peripheral neuropathy, fibromyalgia (229, 230) (duloxetine and venlafaxine)	FDA-approved (duloxetine) FDA-approved for mood and anxiety disorders, but commonly used off-label for pain management (venlafaxine)
			Fibromyalgia (27) (milnacipran)	FDA-approved
			Fibromyalgia (231) (esreboxetine)	Phase III
Tropomyosin receptor kinase receptors				
PF-06273340	TrkA/B/C	Tropomyosin receptor kinase A binds the trophic factor NGF and promotes neuronal survival. Activation of TrkA also leads to hyperexcitability in mature nociceptors. Blockade of this pathway reduces nociceptor excitability in preclinical models (233).	Ultraviolet-induced inflammatory pain (232)	Phase I
Monoclonal antibodies				
Tanezumab, fulranumab, fasinumab	NGF	Inhibition of NGF, which is released by immune cells in response to tissue damage, where it binds to TrkA receptors on nociceptors, leading to their sensitization (237).	Osteoarthritis knee pain (234); cancer pain (235), chronic low back pain (236) (tanezumab)	Phase III
			Diabetic peripheral neuropathy, postherpetic neuralgia (238) (tanezumab)	Phase II
			Osteoarthritis knee pain (239) (fulranumab)	Phase III
			Osteoarthritis knee pain (133, 134); chronic low back pain (133) (fasinumab)	Phase III
Tocilizumab, sarilumab	IL-6	Inhibition of the activity of IL-6, a proinflammatory cytokine released by immune cells upon tissue damage, which is involved in both peripheral and central sensitization (241).	Rheumatoid arthritis (240) (tocilizumab) Rheumatoid arthritis (242) (sarilumab)	FDA-approved for rheumatoid arthritis but not for pain management
Adalimumab, golimumab, certolizumab pegol, infliximab	TNF-α	Inhibition of TNF-α released by macrophages, Schwann cells, and other immune cells at the site of injury, which promotes both peripheral and central sensitization (244).	Rheumatoid arthritis (243) (adalimumab) Rheumatoid arthritis (245) (golimumab) Rheumatoid arthritis (246) (certolizumab pegol)	FDA-approved for rheumatoid arthritis but not for pain management
			Rheumatoid arthritis (247) (infliximab)	FDA-approved for rheumatoid arthritis but not for pain management
			Chronic low back pain (248) (infliximab)	Phase III
Galcanezumab, erenumab, eptinezumab, fremanezumab	CGRP	CGRP is found in nociceptors, where it can amplify pain signals through peripheral sensitization and neurogenic inflammation. Although the exact mechanism in migraine is poorly understood, vasodilation and central sensitization are thought to be involved (141).	Migraine (142)	FDA-approved
Proteinase-activated receptor				
MEDI0618	PAR2	PAR2 is activated by proteases and promotes pain by sensitizing sensory neurons and enhancing inflammatory signals. It acts in both the periphery and spinal cord, amplifying pain through neuropeptide release and TRP channel activation (249).	Migraine (NCT06602479)	Phase II
			Osteoarthritis (NCT04198558)	Phase I
Neurotransmitter release				
Botox (onabotulinumtoxinA), Dysport (abobotulinumtoxinA)	SNARE proteins	Botulinum toxin is a potent inhibitor of vesicular acetylcholine release and precipitates flaccid muscle paralysis through persistent SNARE protein cleavage. However, there is also evidence that botulinum toxin prevents vesicular fusion in peripheral and central neuron synapses, suggesting that the analgesic effect observed in migraine may extend to other pain states (250).	Chronic migraine in adolescents (NCT01662492) (Botox)	FDA-approved
			Chronic migraine (NCT06047444) (Dysport)	FDA-approved
			Episodic migraine (NCT06047457) (Dysport)	FDA-approved

NSAID, nonsteroidal antiinflammatory drug; PAR2, proteinase-activated receptor-2.

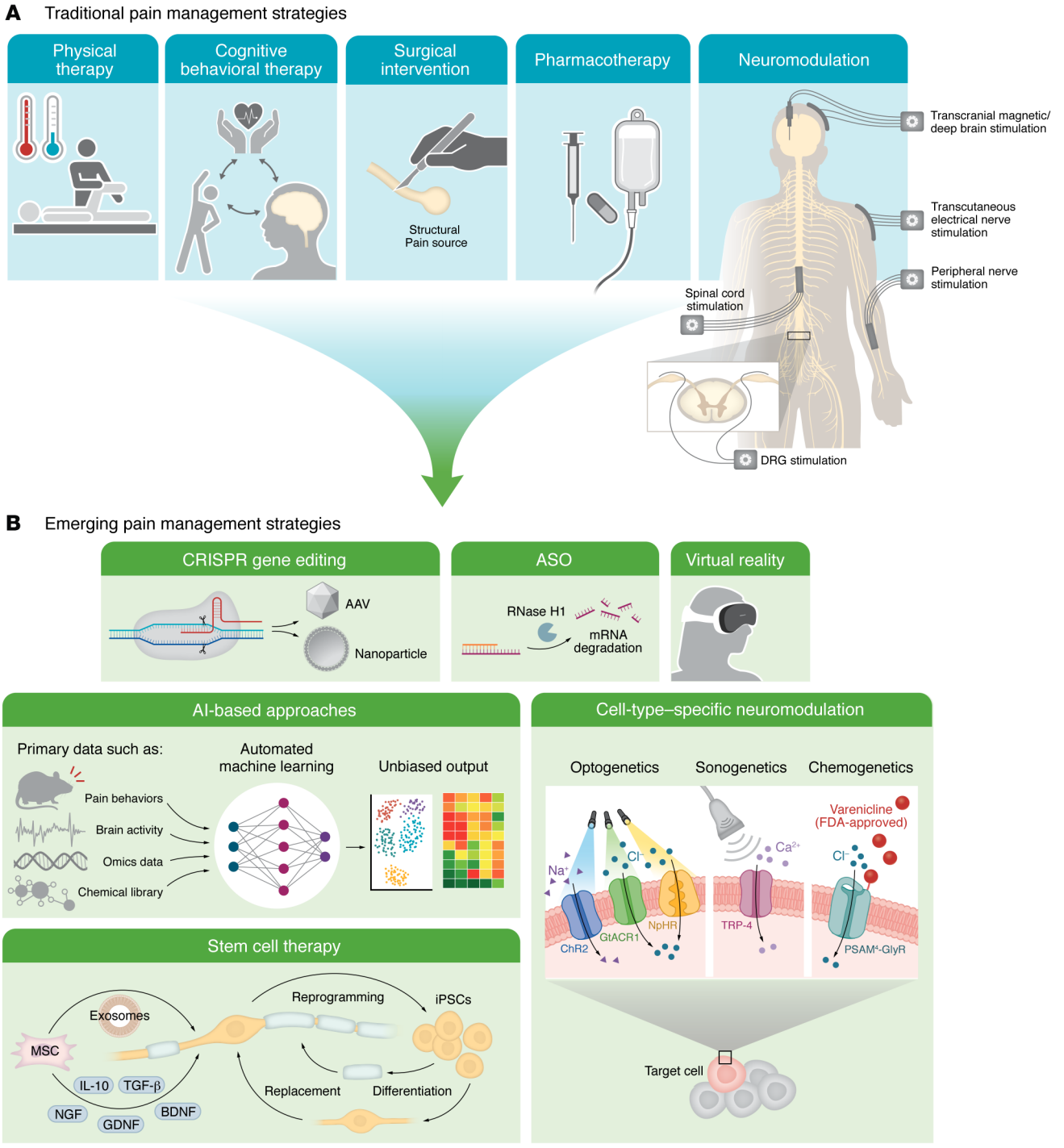
A Traditional pain management strategies
Physical therapy
Cognitive behavioral therapy
Surgical intervention
Structural Pain source
Pharmacotherapy
Neuromodulation
Transcranial magnetic/ deep brain stimulation
Transcutaneous electrical nerve stimulation
Peripheral nerve stimulation
Spinal cord stimulation
DRG stimulation
B Emerging pain management strategies
CRISPR gene editing
AAV
Nanoparticle
ASO
RNase H1
mRNA degradation
Virtual reality
AI-based approaches
Primary data such as:
Pain behaviors
Brain activity
Omics data
Chemical library
Automated machine learning
Unbiased output
Cell-type–specific neuromodulation
Optogenetics
Sonogenetics
Chemogenetics
Varenicline (FDA-approved)
Na+
Cl−
Ca2+
ChR2
GtACR1
NpHR
TRP-4
PSAM4-GlyR
Target cell
Stem cell therapy
Exosomes
MSC
IL-10
TGF-β
NGF
GDNF
BDNF
Reprogramming
iPSCs
Replacement
Differentiation

Figure 4. Current and emerging technologies for pain management. (**A**) Traditional approaches encompass pharmacotherapy, physical therapy (manual therapy, cryo-/thermotherapy), psychotherapy, surgery, and electrical neuromodulation, which are selected based on specific pain conditions. Physical and psychological (cognitive-behavioral therapy) therapies are often recommended for conditions resistant to conventional pharmacotherapy, like fibromyalgia (26). Surgical excision may address structural pain sources such as neuromas (197). Neuromodulation is typically reserved for refractory chronic pain unresponsive to standard treatments (198). In practice, multimodal approaches combining several strategies are common. (**B**) Emerging approaches aim to offer tailored, mechanism-based pain relief. CRISPR delivered through an adeno-associated virus (AAV) or nanoparticle allows precise editing of "pain genes" at the DNA level for permanent effects. Antisense oligonucleotides (ASOs) are short, single-stranded DNA or RNA strands that bind to specific mRNA transcripts, either degrading them via RNase H–mediated cleavage or blocking their translation, thereby transiently preventing production of pain-related proteins. Stem cell therapy using mesenchymal stem cells (MSCs) promotes tissue repair and reduces inflammation by secreting neurotrophic factors (NGF, GDNF, BDNF) and antiinflammatory cytokines (IL-10, TGF-β). MSC-derived exosomes may also serve as natural nanocarriers for delivering drugs or siRNAs (199). Patient-derived induced pluripotent stem cells (iPSCs) can be differentiated into DRG neurons and Schwann cells to repair or replace damaged tissues. Advanced neuromodulation leverages cell-specific genetic tools. Optogenetics can directly modulate neuronal activity with various opsins responsive to light of different wavelengths, inducing excitatory (ChR2) or inhibitory (GtACR1 or NpHR) effects. Sonogenetics couples ultrasound stimulation with mechanosensitive channels such as TRP-4, offering noninvasive deep tissue neuromodulation. Humanized $PSAM^4$-GlyR chemogenetics using an FDA-approved agonist offers translational promise. AI/ML techniques not only enable automated unbiased analysis of pain behaviors, neuroimages, neural activity, and omics integration, but also advance drug discovery, and the modeling of cellular and circuit pain processes via AI-powered virtual cells (AIVCs). Finally, virtual reality that engages sensory and cognitive pathways can be an adjunctive therapy for certain chronic pain (200), like complex regional pain syndrome (CRPS) (ClinicalTrials.gov NCT04849897).

offer unparalleled specificity and extended half-life, which minimizes off-target effects and enables sustained therapeutic effects with less frequent dosing (131). In preclinical models, anti-NGF antibodies reduce pain in cancer pain models in rodents (132). One anti-NGF antibody produced by Regeneron Pharmaceuticals, fasinumab, had clinical success in two separate trials in patients with low back pain and osteoarthritic knee pain (133, 134). However, treatment-associated adverse joint events were observed in participants with knee osteoarthritis (133). Another example is the CCL17 inhibitor GSK3858279 developed by GlaxoSmithKline. Instead of direct modulation of CCL17's cognate receptor CCR4, GSK3858279 binds CCL17, preventing CCL4/CCL17-mediated immune cell activation, thus reducing pain (135, 136). In a phase I clinical trial for safety and efficacy in patients with knee osteoarthritis, weekly administration of GSK3858279 was well tolerated and significantly decreased pain scores (137), though in another trial in healthy participants, GSK3858279 did not reach desired primary endpoints (138), displaying that GSK3858279's efficacy is dependent on the presence of a preexisting chronic inflammatory pain state. Additional efforts include AbbVie's lutikizumab, an anti–IL-1α/β antibody. Like anti-NGF therapies, lutikizumab, a dual–variable domain immunoglobulin, was expected to bind and sequester IL-1α/β, reducing proinflammatory signaling and pain in inflammatory pain conditions (139, 140). In a phase II clinical trial in knee osteoarthritis, lutikizumab was, however, unable to significantly impact either the joint inflammation or its associated pain (141).

Although mAbs have shown promising clinical applications, particularly for anti-CGRP antibodies for treating migraine (142), challenges remain. Most mAbs are unable to cross the BBB, and their efficacy in treating neuropathic and nociplastic pain remains underexplored. Additionally, high production costs and the requirement for parenteral administration present logistical and economic barriers.

Another consideration for treating neuropathic pain is targeting not receptors but epigenetic factors that impact gene expression. Genetic reprogramming occurs in neurons along the "pain pathway" following a neuropathic insult (70, 71), and antagonizing this process may reduce pain. Inhibition of histone deacetylases (HDACs) prevented genetic repression in preclinical models of neuropathic pain and reduced pain hypersensitivity, suggesting that genetic expression changes may contribute to the initiation of neuropathic pain (143, 144). Regency Pharmaceuticals tested this concept using the HDAC6 inhibitor ricolinostat in patients with painful diabetic neuropathy (145). However, the HDAC6 inhibition did not significantly decrease patient pain scores after 12 weeks of treatment.

Emerging novel technologies for pain management

While various conventional approaches to pain management are available depending on specific pain contexts (Figure 4A), emerging technologies are revolutionizing the way we can approach mechanism-based pain treatment (Figure 4B).

Gene therapy using CRISPR-based techniques (146) or antisense oligonucleotides (ASOs) (147) is being explored to directly modulate pain-associated genes such as *SCN9A* (encoding Nav1.7) and *KCNA2* (Kv1.2) for targeted pain relief in preclinical models (148–150). CRISPR genomic editing can potentially provide a long-lasting effect after a one-time intervention, which may be particularly beneficial for refractory chronic pain conditions with strong genetic components. In contrast, ASOs act at the RNA level, allowing a reversible and tunable modulation for acute pain (Figure 2). While CNS delivery remains a major challenge, advancements in viral vectors and lipid nanoparticles (146) are bringing them closer to clinical pain management.

Stem cell therapy, unlike traditional strategies that mainly manage symptoms, offers an opportunity to address the root cause of pathological conditions like traumatic injuries by repairing damaged tissues. Mesenchymal stem cells have shown therapeutic benefits in conditions including spinal cord injury, chronic low back pain, and diabetic neuropathy, owing to their antiinflammatory and neurotrophic properties (151). Early proof-of-concept work is also exploring direct replacement of damaged sensory neurons using organoids derived from induced pluripotent stem cells (iPSCs) (152), often combined with bioengineered scaffolds like hydrogels to enhance integration and regeneration (153).

Advanced neuromodulation techniques, such as optogenetics and sonogenetics, are valuable for studying pain mechanisms and developing new treatments (154–157). Unlike conventional electrical neuromodulation, which lacks cell type specificity, they offer superior spatiotemporal precision by using light or ultrasound

paired with targeted genetic tools. However, clinical translation faces major challenges, including efficient delivery of opsins to human neurons and the need for advanced optics to reach deep tissues. While sonogenetics allows deeper tissue penetration, its reliance on mechanosensitive proteins raises concerns about off-target effects from endogenous channel expression. Nevertheless, progress in viral vectors and gene-editing technologies is narrowing the gap to clinical applications. Notably, a humanized chemogenetic system, PSAM^4-GlyR (158), has been recently characterized, which offers a greater translational potential over conventional Designer Receptors Exclusively Activated by Designer Drugs (DREADDs), with faster chloride channel conductance, all-human receptor components, and an FDA-approved agonist, varenicline.

The emergence of artificial intelligence–based (AI-based) methods is transforming pain research by enabling precise diagnosis, biomarker identification, and the discovery of novel therapies. In preclinical research, machine learning–based (ML-based) techniques such as DeepLabCut (159) have been applied to objectively phenotype pain behaviors (160, 161). Unsupervised algorithms like Motion Sequencing (MoSeq) are also emerging to uncover hidden behavioral patterns invisible to human observation (162, 163). In clinical settings, ML is increasingly used to identify potential biomarkers from neuroimaging data and brain activity recorded from patients with chronic pain (164, 165). ML further aids in analyzing transcriptomic (166–169), proteomic (170, 171), and interactomic (172–174) datasets and GWAS (175, 176) to identify context-specific pain-related genes and pathways. Moreover, AI supports drug development and identification of novel analgesic compounds through virtual screening and de novo molecular design (177, 178). Emerging tools such as AI-powered virtual cells (AIVCs) (179) simulate nociceptor function, circuit connections, and neuroimmune crosstalk, allowing prediction of analgesic efficacy in silico. These innovations accelerate pain research by bridging computational models and experimental studies to guide pain management strategies, though the need for high-quality, representative datasets, and the risk of overfitting or poor generalizability, remain issues that must be addressed.

Charting the future: pathways forward

While many promising targets have been or are being identified for pain management, fewer than 10% of candidate drugs gain approval (180). This high failure rate is largely due to the limited efficacy in humans compared with animal models, severe adverse events, and poor pharmacokinetics (181). Addressing these challenges requires a comprehensive understanding of the molecular, cellular, and circuit mechanisms underlying each pain condition and differentiating pain modalities (e.g., thermal, mechanical, and spontaneous pain). A deeper understanding of species differences, including insights from studies using primary human DRGs (52, 168, 182), is crucial to improve the translational relevance and impact of preclinical studies. Additionally, sex differences in pain mechanisms, particularly in conditions with pronounced bias such as fibromyalgia, might necessitate sex-specific therapeutic strategies (51–54, 183). Developing preclinical models that closely replicate human pain conditions is essential, as many current models fail to capture the complexity of clinical pain — particularly its chronic nature. This includes utilizing in vivo longitudinal imaging approaches to investigate behavioral and neuronal changes (21, 22, 184), and in vitro modeling using patient-derived iPSCs to generate human sensory neurons and CNS organoids (185, 186), capturing key aspects of individual susceptibility to chronic pain development. For clinical research, it is vitally important to improve trial design, as limitations including underpowered studies, short trial durations that fail to capture the chronic features, and mismatches between preclinical and clinical conditions (e.g., testing of a drug validated in traumatic injury on diabetic neuropathy patients) can profoundly impact outcomes. It is also important to adopt advanced imaging techniques and ML-based phenotypic approaches to identify precise biomarkers for pain diagnosis and treatment rather than relying only on patient self-reporting. This is especially critical for nonverbal populations, including infants and individuals with cognitive impairments. By integrating cutting-edge technologies, refining preclinical models, and enhancing clinical methodologies, the field can begin to address and overcome key barriers more effectively to improve pain management, which could pave the way for safer, more effective, and personalized precision therapies, as well as lead to the elimination of prescription opioids.

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