A comprehensive review on pain: Model, target, therapy, and prospect (Review)

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Abstract. Pain serves as both a protective physiological response essential for species survival and a global health issue affecting human well-being and societal development. The present review systematically summarized and analyzed the research progresses on pain through a multidimensional analytical framework encompassing animal models, molecular targets, therapeutic approaches and future prospects. In animal modeling, neuropathic pain paradigms have evolved from traditional mechanical compression to composite models that combine dynamic displacement and chemical stimulation. Cancer-induced pain models employ orthotopic tumor transplantation to recapitulate bone metastasis and soft tissue invasion mechanisms and visceral pain models combine inflammatory mediators with mechanical distension to replicate clinical manifestations. The above animal models are the main models of pain, each with its own characteristics and applicable scope. The studies of molecular targets have identified voltage-gated ion channel, G protein-coupled receptor signaling cascades, and inflammation-related enzymes as critical analgesic targets, providing a molecular basis for the design of new analgesic drugs. New targets for treating pain are still being studied. Clinical treatment strategies are showing a trend of multimodal integration, with breakthroughs in opioid optimization and non-opioid innovation in drug therapy, precise analgesia achieved through neuromodulation techniques in intervention therapy, and strengthened chronic pain management dimensions through physical and psychological interventions. Although there are a number of means for treating pain, the research on drugs that can truly cure pain has still a long way to go. The future research and development of analgesics will focus on in-depth analysis of pathological mechanisms, adverse reactions of opioid drugs, personalized analgesic strategies, and interdisciplinary transformation.

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Abbreviations: AWR, abdominal withdrawal reflex; cAMP, cyclic adenosine monophosphate; CBT, cognitive behavioral therapy; CSNRC, chronic spinal nerve root compression; DSS, dextran sulfate sodium; IDDS, intrathecal drug delivery system; MPQ, McGill pain questionnaire; NOP, nociceptin opioid peptide; NOS, nitric oxide synthase; NRS, numeric rating scale; NSAIDs, nonsteroidal anti-inflammatory drugs; ODI, Oswestry disability index; SCS, spinal cord stimulation; SNL, spinal nerve ligation; TENS, transcutaneous electrical nerve stimulation; TMS, transcranial magnetic stimulation; TNF-α, tumor necrosis factor-α; TRP, transient receptor potenti; TRPM, transient receptor potential melastatin; TRPP, transient receptor potential polycystin

Key words: pain, model, target, therapy, prospect

Contents

1. Introduction

Pain, recognized as one of humanity's most fundamental physiological and psychological experiences, has been designated by the international medical community as the 'fifth vital sign' following blood pressure, temperature, respiration, and pulse (1).

With global aging populations and increasing burdens of chronic diseases, the prevalence of pain has risen steadily and severely compromised patients' quality of life (2). This highlights the urgent need for innovative analytical approaches. To address this, the present study used the integration of multi-pathway analysis to establish a systematic analytical framework, aiming to advance precision diagnosis and treatment of pain.

Definition of pain. In medical science, pain is defined as a complex feeling that extends beyond mere physiological tissue injury. It involves intricate interactions among psychological, emotional and social factors (3). The International Association for the Study of Pain revised its definition in 2020, emphasizing that pain is 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' (4). This definition transcends traditional biological perspectives, underscoring the subjectivity and variability of pain. Individual perceptions of pain are influenced by multiple factors, including physiological status, psychological cognition, cultural background, and social environment (5).

Classification of pain. Modern medicine classifies pain into three categories (6): i) Nociceptive pain: Arising from direct or potential tissue injury. Nociceptive pain is generally unrelated to nerve distribution but is associated with pathological damage causing the pain, such as degenerative changes, trauma, muscle spasm, or visceral disorders (7-10). ii) Neuropathic pain: Resulting from peripheral or central nervous system lesions. It is typically linked to abnormal sensory perception caused by damage to nerves responsible for pain signal transduction and transmission (11). Clinically, neuropathic pain often manifests as spontaneous, persistent severe pain (12). iii) Central sensitization-induced pain: Caused by central nervous system sensitization in the absence of overt tissue damage or neurological lesions (13).

Clinical evaluation, management and medical significance. The clinical evaluation and management of pain must incorporate both objective and subjective dimensions. Quantitative tools such as the visual analogue scale (VAS) or numeric rating scale (NRS) are commonly used to quantify pain assessment, while multidimensional instruments such as the McGill pain questionnaire (MPQ) further analyze pain characteristics, emotional experiences and effects on quality of life (14). For neuropathic pain, definitive diagnosis requires combined neuroelectrophysiological testing. Therapeutic strategies emphasize concurrent use of pharmacological and non-pharmacological interventions (15). For chronic pain, multidisciplinary collaboration models have become mainstream, aiming to restore functional capacity through comprehensive medical, psychological and social support interventions rather than solely pursuing 'pain-free' outcomes (16). The medical significance of pain lies not only in its role as a pathological warning signal but also in its status as a critical global public health issue. The resulting socioeconomic burdens and diminished quality of life demand systematic solutions (17).

Research objectives and innovations. The present review aimed to achieve three interrelated and clinically oriented goals, while addressing the limitations of traditional reviews and opening up new perspectives for pain research. However, existing research has mostly focused on analyzing analgesic mechanisms through a single pathway (18-20). To overcome this limitation, the present review integrated multi-channel analysis methods and established a systematic analysis framework. The present review innovatively combined research methods such as in-depth analysis of molecular mechanisms, optimization of transformation models and interdisciplinary technology integration. In summary, the aims and innovations of these summaries and analyses are to bridge the gap between basic research and clinical practice, providing theoretical support for developing personalized pain management strategies and constructing a precise pain diagnosis and treatment system, to accelerate the transformation and application of mechanism oriented therapies and ultimately to promote pain management research into a new era of high-efficiency, low toxicity and personalized treatment.

2. Methods

To comprehensively review the research progress on models, mechanisms, therapies and prospect of pain, the present review conducted a search in existing scientific databases using the terms 'pain model', 'pain mechanism', 'pain therapy', 'pain prospect'. Relevant literature on pain was obtained from both online and offline databases, covering the period from 1987-2025, totaling 334 references. Online databases included Elsevier (https://www.elsever.com/), PubMed (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (https://www.webofscience.com/), Google Scholar (https://scholar.google.com/), Wiley (https://www.wiley.com/), EMBASE (https://www.embase.com/), SpringerLink (https://link.springer.com/), Cochrane Library (https://clinicaltrials.gov/) and China national knowledge infrastructure (CNKI) (https://www.cnki.net/). Other related references were sourced from pharmacopoeias and other articles. To ensure a comprehensive review, the literature search strategy was designed to encompass both modern scientific research and historical scholarly works. For official pharmacopoeias (such as Chinese Pharmacopoeia) and articles from non-mainstream journals, specific inclusion criteria were established. These sources were included based on their recognized historical importance, foundational role in theory development, or provision of unique data not available in peer-reviewed journals. Figs. 1-6 were drawn by BioGDP (https://biogdp.com/) in this paper.

3. Models of pain

The selection of experimental animals for pain models demonstrates remarkable diversity (Data S1). Primate species exhibit high anatomical and physiological similarity to humans, enabling superior simulation of human disease progression and serving as ideal candidates for chronic pain modeling. Notably, their advanced nervous systems, including complex cortical pain processing pathways and homologous pain-related brain regions (such as the anterior cingulate cortex and insula), allow for the study of subjective pain-like experiences (such as pain-related anxiety or cognitive modulation of pain) that are difficult to replicate in

lower-order species; this unique advantage makes primates invaluable for validating the translational potential of novel analgesics targeting central pain mechanisms, especially for chronic conditions such as post-herpetic neuralgia where human cognitive and emotional factors strongly influence pain outcomes. However, their demanding husbandry conditions, limited availability, high costs and ethical constraints have restricted their widespread adoption. Successful pain studies have been conducted using large mammals such as pigs, dogs and cats (21), though their adoption is limited by substantial practical and ethical challenges, further limiting their scalability. Rodents are the most widely used models due to their physiological similarity to humans, low cost, ease of handling and scalability, enabling reliable mechanistic and translational studies (22). Additionally, zebrafish, fruit flies and nematodes (23,24) demonstrate significant promise in pain genetics and molecular mechanism studies. Their well-characterized genome sequences, controllable genetic manipulations, simple body architectures and short life cycles offer unique advantages for investigating pain-related cellular and molecular pathways, warranting broader application in this field.

Since experimental animals cannot express pain directly as can humans, specific assessment methods are needed to indirectly judge their pain status. Clinical evaluation of pain in patients relies on methods such as medical interviews, physical examinations and standardized questionnaire assessments. However, experimental animals cannot verbally communicate discomfort during nociceptive stimulation, so pain assessment for them mainly falls into two categories: Naturalistic readouts based on spontaneous behaviors and stimulus-evoked readouts via calibrated interventions.

Spontaneous behaviors. Spontaneous behaviors refer to unprovoked behavioral manifestations that reflect animals' inherent responses to pain. These include foot withdrawal reflexes, excessive grooming, scratching, vocalization, reduced exploratory activity, increased immobility and changes in facial expression. In pathological pain states, animals further exhibit hyperalgesic symptoms (characterized by enhanced responsiveness to stimuli and reduced reaction thresholds), where mild provocation can induce spontaneous defensive behaviors such as foot withdrawal, licking, or abdominal retraction.

Stimulus-evoked readouts. Unlike naturalistic readouts, stimulus-evoked readouts require active induction of behavioral alterations using specialized equipment, instruments, or reagents with calibrated stimuli. This approach converts pain perception into numerically representable outcomes, enabling indirect objective assessment of pain intensity and sensitivity. Common stimulus-evoked assessment methods for pain sensitivity in animals include mechanical, thermal, and cold hyperalgesia tests, as well as specialized detection protocols. i) Mechanical hyperalgesia assessment: Mechanical pain thresholds are determined using Von Frey filaments applied to the plantar or abdominal regions, with the threshold defined as the minimum stimulus intensity eliciting a rapid withdrawal reflex (25). ii) Thermal hyperalgesia assessment: Thermal pain thresholds are assessed by irradiating the animal's paw with a radiant heat source and recording the latency to withdrawal (26). Cold hyperalgesia assessment: For cold hyperalgesia evaluation, animals are placed on a 4˚C thermal plate, and withdrawal responses (foot withdrawal, licking, jumping) are measured by latency or frequency within a specified time frame (27). iii) Specialized detection method: The abdominal withdrawal reflex (AWR) experiment evaluates visceral sensitivity and pain thresholds through gradual pressure inflation of the rectum. Metrics such as the pressure required to elicit abdominal muscle contractions and arching of the spine, or the number of contractions observed under fixed pressure over time, are recorded to assess changes in visceral nociception.

The classification of pain models is mainly based on three core dimensions: Etiological source, pathological mechanism characteristics and technology construction. Integrating longitudinal disease evolution, horizontal mechanistic interactions and cross-validated assessments, the four pain models (neuropathic pain, cancer-induced pain, visceral pain and inflammatory pain animal models) constitute a systematic framework. This approach maintains the distinctiveness of each model while collectively illuminating the dynamic pain network, offering a stratified and multi-faceted perspective for exploring mechanisms and devising treatments.

The present study systematically reviewed the preparation methods and experimental cycles of commonly used pain models across four major categories: neuropathic pain model, cancer-induced pain model, visceral pain model and inflammatory pain animal model. The present review summarized the evaluation criteria along with their advantages and limitations. The novelty of the present review lies in its emphasis on the hierarchical, multi-dimensional framework for pain model classification and analysis. Unlike typical pain model reviews that predominantly focus on individual model types, the present review highlighted the established framework, integrating etiological sources, pathological mechanisms and construction technologies, enabling effective cross-validation across different pain types. By constructing such an interconnected analytical framework, the present review goes beyond the scope of traditional reviews that merely catalog models and their parameters; it provided a translational research tool to bridge gaps between different pain model systems, guiding researchers to design more comprehensive experiments and promoting the development of targeted analgesic strategies applicable to multiple pain conditions. To visually demonstrate the classification framework and representative examples of these models, schematic diagrams are specifically illustrated in Fig. 1.

Neuropathic pain model. Neuropathic pain arises from damage or dysfunction of the peripheral or central somatosensory nervous system, commonly occurring secondary to trauma, ischemia, metabolic disorders, or toxin exposure (28). Modern medical research has identified three primary mechanisms underlying radicular neuropathic pain: Mechanical compression, neural root inflammatory response and neurohumoral response. Establishing an idealized animal model is crucial for studying these mechanisms, as it serves as an excellent experimental platform for exploring various clinical treatment strategies, testing novel drugs and conducting fundamental experimental research. In the process of researching neuropathic pain models, there are also some research bottlenecks:

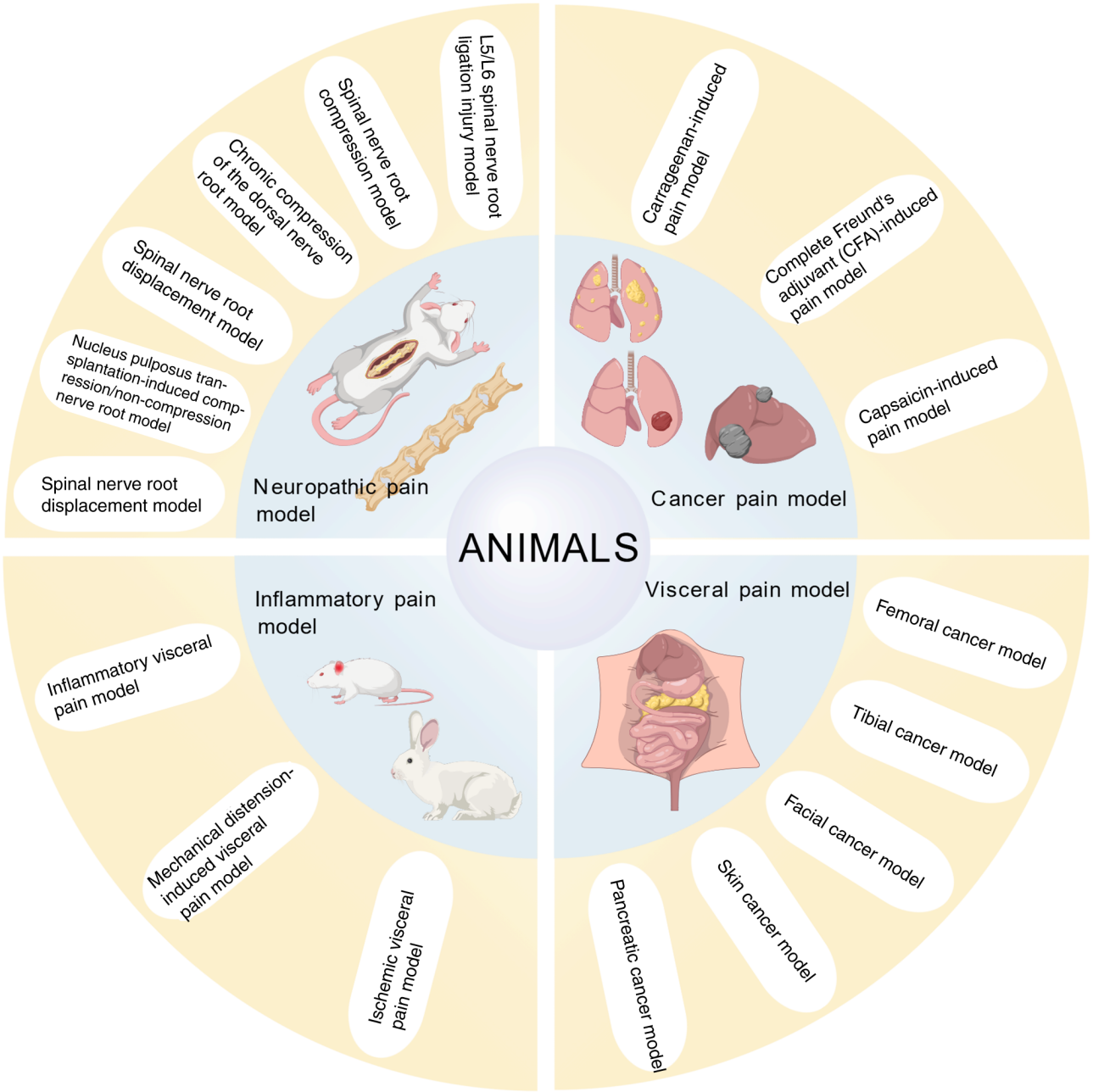

Figure 1. Classification of different animal models of pain.

i) Ethical concerns (severity of pain induction). ii) Lack of full human translation (rodent models cannot capture subjective aspects of pain). The present review systematically summarized the current modeling methods, technical features and methodological advantages and limitations of mainstream neuropathic pain models (Table I), providing a structured reference framework for researchers to screen models based on experimental objectives. In Table I, SD rats were mainly selected as experimental animals and the indicator was mechanical pain threshold.

L5/L6 spinal nerve root ligation (SNL) injury model. The SNL injury model was first established by Kim and Chung (29). This model employed Sprague-Dawley (SD) rats as experimental subjects. The modeling procedure involved: ligation of the L5 and L6 spinal nerves following exposure via a dorsal surgical approach. The SNL model induces reliable neuropathic pain phenotypes, including mechanical hyperalgesia and allodynia, which closely mirror clinical radicular pain (30,31).

Subsequent studies by Huang *et al* (32) compared the effects of preserving compared with resecting paravertebral muscle groups on neuropathic pain, muscle damage and inflammatory markers. Their findings confirmed that SNL models retaining paravertebral muscles effectively reduce postoperative muscle injury and inflammatory responses, thereby enhancing reproducibility and clinical relevance. This model's strengths include precise nerve root segment localization, facilitating nerve root-specific studies, and controllable surgical trauma, meeting animal ethics requirements.

Table I. Characteristics of different types of neuropathic pain models.

Authors, year	Type	Animal	Method	Time	Indicators	Advantages	Disadvantages	(Refs.)
Bennett *et al*, 1988; Zhang *et al*, 2019	Sciatic nerve chronic constriction injury pain model	ICR mice	Sciatic nerve ligation	14 days	Spontaneous pain, mechanical pain threshold, thermal pain threshold, cold pain threshold	Simple operation, stable pain sensitivity	Variable ligation tightness causing inconsistent injury severity	(45,46)
Kim *et al*, 1992	SNL pain model	SD rats	L5/L6 SNL	16 weeks	Mechanical pain threshold, thermal pain threshold	Consistent ligation position and degree	Relatively complex procedure, severe trauma with high infection risk	(29)
Zhu *et al*, 2018	SNL pain model	ICR mice	L5 spinal nerve ligation	17 days	Mechanical pain threshold, thermal pain threshold	Consistent ligation position and degree	Relatively complex procedure, severe trauma with high infection risk	(47)
Meng *et al*, 2020	Spinal cord injury	SD rats	Weight-drop impact on central spinal cord	28 days	Mechanical pain threshold	Cost-effective implementation, clinically relevant pathogenesis	Difficult impact localization, potential rebound-induced secondary injury	(48)
Shih *et al*, 2017	CPSP pain model	SD rats	Collagenase injection into thalamic ventral posterolateral nucleus	4 weeks	Mechanical pain threshold, thermal pain threshold	High hemorrhage stability, high success rate, low mortality	Chronic minor vascular leakage, Minimal hematoma mass effect	(49)
Lu *et al*, 2018	CPSP pain model	SD rats	Autologous blood injection into thalamic ventral posterolateral nucleus	35 days	Mechanical pain threshold	Clinically consistent intracerebral hemorrhage progression	Needle track blood reflux impairing hematoma formatio	(50)
Li *et al*, 2019	Infraorbital nerve chronic constriction injury pain model	SD rats	Infraorbital nerve ligation	35 days	Mechanical pain threshold	Simplified procedure mimicking clinical trigeminal compression-induced allodynia	Technically demanding with significant tissue damage	(51)

Table I. Continued.

Authors, year	Type	Animal	Method	Time	Indicators	Advantages	Disadvantages	(Refs.)
Cao *et al*, 2013	Infraorbital nerve transection pain model	SD rats	Partial transection of lateral infraorbital nerve	35 days	Mechanical pain threshold	Consistent injury severity, prolonged pain sensitivity duration	Variable ligation tightness causing inconsistent injury severity	(52)

CPSP, central post-stroke pain; ICR, institute of cancer research; SD, Sprague Dawley; SNL, spinal nerve ligation.

However, technical challenges of SNL models persist: standardized ligation procedures directly affect reproducibility, as minor deviations in parameters such as ligature tension, fixation position, or surgical technique may induce inter-individual variability, representing the primary technical bottleneck for this model. Furthermore, the model inherently induces moderate to severe neuropathic pain, raising ethical concerns regarding animal welfare. Its primary translational limitation lies in the fundamental species differences in pain processing; rodent models cannot capture the multidimensional subjective experience of human chronic neuropathic pain. Compared with chronic compression models, the SNL model offers superior technical reproducibility due to its straightforward surgical approach but demonstrates lower pathophysiological fidelity in simulating the gradual progression of clinical degenerative disorders. While highly suited for studying acute nerve injury mechanisms and screening analgesic efficacy, its utility for evaluating long-term therapeutic interventions may be limited by the static nature of ligation-induced injury.

Spinal nerve root compression model. The chronic spinal nerve root compression model (CSNRC) was first established by Wang *et al* (33). This model used SD rats as experimental subjects. Experimental validation confirms that mechanical compression in this model induces axonal demyelination of the nerve root and activates interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) inflammatory cytokine cascades mediated by spinal dorsal horn microglia, ultimately triggering classic neuropathic pain phenotypes such as mechanical allodynia and spontaneous pain (34). These pathological characteristics exhibit significant correlation with clinical radicular pain caused by lumbar spinal stenosis and intervertebral disc herniation, establishing this model as a reliable platform for investigating chronic compressive nerve injury. The CSNRC model demonstrates significant technical advancements over traditional nerve ligation approaches. Furthermore, the model enables quantifiable stratification of neural injury severity through precise adjustments to the compression device thickness (0.3-0.5 mm). Additionally, its reversible compression design provides a dynamic investigative platform for studying decompression therapeutics. Postoperative material displacement may introduce experimental deviations, indicating that procedural stability optimization remains a critical challenge requiring resolution.

Ethical considerations must be noted due to the persistent pain state induced by chronic compression. More importantly, while the model replicates structural compression, it cannot model the complex psychosocial factors that markedly influence chronic pain perception and disability in human patients. In contrast to ligation models that create acute axonal injury, compression models such as CSNRC provide superior pathophysiological fidelity for degenerative conditions by mimicking the progressive nature of clinical nerve root compression. They exhibit clinical relevance for spinal stenosis research and offer unique advantages for testing decompression therapies and chronic drug interventions. However, this enhanced fidelity comes at the cost of technical reproducibility, as the requirement for microscopic precision in compression device placement introduces greater procedural variability compared with ligation techniques. The progressive nature of compression in the CSNRC model may offer improved predictive validity for long-term drug efficacy against chronic neuropathic pain compared with acute injury models. However, its ability to forecast clinical outcomes remains constrained by the same fundamental limitations of rodent models: simplified neuroanatomy, lack of comorbid conditions, and an inability to assess the effect of therapy on pain-related quality of life and affect.

Chronic compression of dorsal root ganglia model (CCDRG). The CCDRG model was optimized by Zhang *et al* (35). This model involved implanting customized stainless steel rods into the L5 intervertebral foramen to induce sustained compression of dorsal root ganglia. Experimental evidence confirms that the CCDRG model triggers abnormal neuronal discharges in compressed dorsal root ganglia, leading to mechanical hyperalgesia and spontaneous pain behaviors. Its pathological mechanisms involve increased neuronal excitability, inflammatory factor release and glial cell activation, demonstrating significant correlation with clinically observed radicular pain caused by intervertebral foramen stenosis (36). The advantage of this model is its minimally invasive foraminal approach, which achieves ganglia-specific compression without spinal canal opening, thereby reducing surgical infection risks while preserving neural pathway integrity. A study has shown that compared with traditional nerve root exposure models, the CCDRG model increases postoperative survival rates by ~30% and more accurately simulates the chronic compressive pathology of intervertebral disc herniation (35).

However, anatomical differences in the intervertebral foramen of different sizes of rats require custom steel rod sizes, resulting in higher experimental costs and potential implant displacement-key technical bottlenecks that can affect the stability of experimental data. From an ethical standpoint, the chronic nature of the compression involves prolonged animal suffering. A fundamental limitation for clinical translation is the model's inability to account for the top-down neuromodulatory and psychological components that are integral to the human chronic pain experience.

Spinal nerve root displacement model. The spinal nerve root displacement model was developed by Finskas *et al* (37) and employs biomechanical stimulation of nerve roots through intervertebral disc puncture. Some studies demonstrate that mechanical traction in this model induces abnormal neuronal discharges in dorsal root ganglia, leading to ipsilateral hindpaw mechanical hyperalgesia and motor dysfunction, with pain characteristics closely mimicking the pathological progression of nerve root edema secondary to clinical intervertebral disc herniation (38). Mechanistic investigations reveal a positive correlation between puncture depth and disc degeneration rate, with radicular pain arising from dual mechanisms: Enhanced mechanical stimulation due to reduced intervertebral space height and peripheral sensitization triggered by elevated pro-inflammatory cytokines (IL-6, TNF-α) in dorsal root ganglia. This combined structural injury and inflammatory activation makes the model an ideal platform for studying dynamic nerve root compression mechanisms. Compared with traditional static compression models, its advantages lie in simulating the pathophysiological process of post-herniation nerve root displacement, retaining vascular supply system integrity, and exhibiting pronounced laterality-specific pain behavioral indices. However, precise control of the puncture angle and bony fixation stability of the puncture needle are critical technical factors ensuring experimental reproducibility. Ethical oversight is crucial given the invasive disc puncture procedure. The model's translational relevance is constrained by the inherent inability of rodent models to replicate the human subjective pain experience and the complex brain-level changes associated with chronic pain.

Nucleus pulposus transplantation model. The autologous nucleus pulposus transplantation model, co-developed by Shamji *et al* (39) and Kim *et al* (40), focuses on exploiting the chemical irritative effects of autologous disc tissue. This model employs SD rats as experimental subjects. Experimental validation confirms that transplanted nucleus pulposus tissue directly activates transient receptor potential vanilloid (TRPV) 1 channels in dorsal root ganglia by releasing inflammatory mediators such as IL-6 and prostaglandin E2 (PGE2), inducing classic neuropathic pain manifestations (41). Cho *et al* (42) demonstrated through model modifications that even without mechanical compression, chemical stimulation from nucleus pulposus tissue alone can activate satellite glial cells in dorsal root ganglia, upregulate the nuclear factor kappa B (NF-κB) signaling pathway and ultimately induce inflammatory radicular pain. These pathological features closely resemble non-compressive radicular pain in clinical disc herniation patients, providing a critical experimental platform for studying chemically mediated radicular pain mechanisms. The model reduces immune rejection by using autologous tissue. It also simulates mechanical compression and chemical stimulation, and includes stable, quantifiable behavioral indicators of pain. However, individual differences in the absorption rate of the nucleus pulposus may affect the duration of the inflammatory response, so preoperative magnetic resonance imaging (MRI) is needed to assess the severity of disc degeneration to enhance experimental consistency. The model's limitation for translational research stems from the rodent nervous system's simplified processing of nociception compared with humans, failing to incorporate the supraspinal and psychosocial determinants of chronic pain.

Spinal nerve root chemical stimulation model. Zhao *et al* (43) established the spinal nerve root chemical stimulation model, which uses formaldehyde to simulate non-compressive radicular pain by mimicking chemical inflammatory mediators. Experimental evidence confirmed that formaldehyde-induced chemical stimulation activated transient receptor potential ankyrin (TRPA)1 channels in dorsal root ganglia, triggering neuropeptide release (CGRP, substance P) and resulting in persistent mechanical hyperalgesia with behavioral characteristics highly analogous to clinical discogenic radiculitis (44). This model transcends traditional mechanical compression frameworks by elucidating inflammation-mediated radicular pain mechanisms via controlling chemical stimulation. Compared with autologous nucleus pulposus transplantation models, its advantages includes eliminating mechanical compression variables to focus on chemical pathogenicity, strong dose-response controllability of formaldehyde concentration and minimal surgical trauma with high procedural standardization. However, technical challenges persist: Different chemical stimulants may activate divergent pain signaling pathways, requiring multi-group controlled experiments to validate specific inflammatory mediators' nociceptive roles, a critical bottleneck for broader model application. The core translational limitation shared by all rodent models is their inability to emulate the complex, subjective and emotionally charged nature of human chronic pain, which is profoundly influenced by higher-order brain functions and psychosocial context. Contemporary neuropathic pain modeling has evolved from singular mechanical compression to multidimensional pathological mechanism simulations, with various models demonstrating marked specificity and complementarity in pain mechanism research. The L5/L6 ligation model provides an ideal platform for investigating acute nerve injury mechanisms through precise nerve root localization, while chronic compression models (CSNRC, CCDRG) more closely approximate the progressive pathological processes of clinical degenerative disorders. Recently developed dynamic compression models (spinal nerve root displacement) and chemical stimulation models (nucleus pulposus transplantation/formaldehyde stimulation) have transcended traditional mechanical injury paradigms, offering novel perspectives for deciphering inflammation-mechanics interactions in radicular pain pathogenesis (45-47). Current model systems still face critical bottlenecks between mechanistic fidelity and clinical translatability. On one hand, significant neuroanatomical disparities between rodents and humans, such as nerve root

vascular supply patterns and spatial distribution of dorsal root ganglia, may compromise pathological translation of mechanical stimuli. On the other hand, overreliance on reflexive nociceptive behavioral metrics in model evaluation fails to capture the affective-cognitive dimensions of chronic pain.

A critical and universal limitation is the inherent inability of models to replicate the human subjective pain experience, which is shaped by complex cortical processing, psychological state and social factors. All models involve ethically significant pain induction, necessitating rigorous justification and mitigation of suffering. The selection between ligation and compression models involves fundamental trade-offs: While ligation offers technical simplicity and reproducibility for acute injury studies, compression models provide superior pathophysiological fidelity for chronic degenerative conditions (48-50). Similarly, chemical stimulation models excel in isolating inflammatory mechanisms but lack the mechanical component central to a number of clinical conditions. The optimal model choice therefore depends on the specific research objectives, whether prioritizing mechanistic isolation, clinical relevance, therapeutic testing applicability, or technical practicality.

A paramount consideration that underpins all model selection is their documented track record in predicting clinical efficacy. The high failure rate of neuropathic pain drugs transitioning from robust preclinical results to successful human trials highlights a pervasive translational crisis. This disconnect is multifactorial, stemming from over-reliance on reflexive pain measures in animals that do not capture the multidimensional human pain experience, fundamental species differences in drug metabolism and pharmacokinetics, and the absence of common comorbidities (such as anxiety or depression) in animal models that markedly modulate drug response in patients (51,52). Therefore, while animal models remain indispensable for mechanistic insight and initial screening, researchers must interpret preclinical efficacy data with caution. Future model development must prioritize the integration of outcome measures that bridge this translational gap, such as non-reflexive pain behaviors, functional outcomes, and if possible, measures of affective pain components. Furthermore, employing a battery of models that capture different aspects of the human condition, rather than relying on a single model, may provide a more realistic and predictive preclinical assessment of therapeutic potential. Future model development should prioritize constructing large-animal chronic compression models to enhance anatomical comparability, integrating advanced behavioral assessments such as functional neuroimaging and conditioning place aversion and engineering transgenic animals for spatiotemporally controlling activation of specific pain pathways.

Cancer-related pain model. Cancer-related pain is caused by malignant tumors themselves, metastatic lesions, or anti-tumor therapies (53), commonly observed in a number of patients with advanced-stage cancers. Bone cancer pain results from bone metastasis in various advanced malignancies, which is a primary pain inducer. Injecting controlled quantities of tumor cells into different anatomical sites enables the development of multiple cancer pain models, including facial, cutaneous and visceral cancer pain. Rodent bone cancer pain models currently represent the most widely used chronic cancer pain paradigms. Rats, owing to their larger body mass and skeletal structure, permit controllable ranges for tumor cell injection volumes, making them prevalent in bone cancer pain model preparation. Based on tumor type and modeling site, the following systematically summarized and compared construction methods, characteristics and methodological advantages/limitations of prevalent cancer pain models, providing researchers with a reference framework for model selection aligned with experimental objectives (Table II).

Femoral cancer pain model. The femoral cancer model replicates clinical pathological features of metastatic bone pain through orthotopic tumor cell inoculation into rodent femoral marrow cavities. A study indicated that model construction required consideration of three key factors: Animal strain, tumor cell type and inoculation technique (54). Critical femoral cancer model replication technologies involved precise cell inoculation and systematic validation. Surgical procedures require anesthesia-assisted exposure of the femoral intercondylar fossa, followed by slow marrow cavity infusion of cell suspensions using 26G microinjectors, with bone wax sealing post-injection to prevent cell leakage. Pain behavioral assessments employ dynamic monitoring: Von Frey filament testing reveals 40-60% reductions in mechanical withdrawal thresholds post-modeling; tail compression tests show markedly elevated pressure sensitivity correlating positively with radiographic bone destruction severity. Radiographic verification identifies periosteal thickening at 14 days and pathological fractures at 21 days via X-ray, while micro-CT quantifies bone microstructure parameters to establish structural-pain correlations (55). Histopathological analyses confirms tumor cell infiltration and osteoclast activation, with molecular assays demonstrating upregulated spinal dorsal horn glial fibrillary acidic protein and IL-1β expression, indicating neuroinflammatory involvement in pain maintenance.

Tibial cancer pain model. The tibial cancer pain model was served as a critical tool for investigating cancer-induced bone pain mechanisms and therapeutic strategies. The most prevalent model involves intratibial marrow cavity injection of breast carcinoma cells, effectively mimicking human metastatic the pathological features and pain behaviors of bone cancer. The core mechanisms of the model involves tumor cell-induced osteolysis and neuroinflammation (56,57). The model also facilitates analgesic intervention evaluation: Electroacupuncture attenuated pain via autophagy-mediated NLRP3 suppression or NRG1/ErbB2 signaling modulation of glial activation, while opioids paradoxically promoted tumor angiogenesis through μ opioid receptor (MOR) upregulation. Despite standardized operability and clear pathology, strict control of inoculation parameters and postoperative infection prevention remain essential for model stability and reproducibility.

Facial cancer pain model. In preclinical facial cancer pain research, the Walker-256 tumor cell-induced rat model has become predominant (58). Derived from rat mammary carcinoma and maintained via intraperitoneal passage, these cells form facial tumors demonstrating local tissue

Table II. Characteristics of different types of cancer pain models.

Authors, year	Type	Animal	Method	Time	Indicators	Advantages	Disadvantages	(Refs.)
Schwei *et al*, 1999	Femoral cancer pain model	B6C3-Fe-a/a, C3H/HeJ mice	Injection of fibrosarcoma cells into distal femoral marrow cavity	21 days	Spontaneous pain, mechanical pain threshold	High stability, mass reproducibility possible	Technically demanding, requires precise tumor cell concentration control	(72)
Wang *et al*, 2019	Tibial cancer pain model	SD rats	Injection of Walker 256 cells into tibial marrow cavity	21 days	Spontaneous pain, mechanical pain threshold	High viability and invasiveness of Walker 256 cells	High *in vivo* culture costs, prolonged experimental cycles	(73)
Kopruszinski *et al*, 2018	Facial cancer pain model	Wistar rats	Injection of Walker 256 cell suspension into right vibrissal pad	6 days	Spontaneous pain, mechanical pain threshold, thermal pain threshold	High viability and invasiveness of Walker 256 cells	High *in vivo* culture costs, prolonged experimental cycles	(58)
Huang *et al*, 2019	Cutaneous cancer pain model l	SD rats	Subcutaneous injection of Walker 256 cells into hindpaw plantar region	17 days	Mechanical pain threshold, thermal pain threshold	High viability and invasiveness of Walker 256 cells	High *in vivo* culture costs, prolonged experimental cycles	(74)
Wang *et al*, 2017	Pancreatic cancer pain model	BALB/c-nu mice	Orthotopic implantation of SW1990 cells into pancreas	14-28 days	Spontaneous pain, mechanical pain threshold	High stability, mass reproducibility possible	Technically demanding, requires precise tumor cell concentration control	(75)

SD, Sprague Dawley.

infiltration, neural compression and inflammatory mediator release, closely resembling clinical head/neck cancer pain mechanisms. Key evaluation metrics included thermal hyperalgesia, mechanical allodynia and spontaneous face-grooming behaviors (59). Conditioned place preference testing quantifies pain relief motivation through analgesic-paired environment preference, while comorbid anxiety-like behaviors facilitates the study of pain-emotion interactions (60). The model has validated analgesics (morphine, bosentan and pregabalin) and revealed peripheral endothelin receptor-trigeminal sensitization linkages (61). Despite its usefulness, interspecies differences limit translational relevance, prompting recent attempts to engraft human carcinoma cells in immunocompromised hosts, though applications remained exploratory. Overall, the Walker-256 facial cancer model, with standardized protocols, phenotype clarity and clinical pain mimicry, remain indispensable for mechanistic and therapeutic investigation.

Cutaneous cancer pain model. Malignant melanoma, a highly aggressive and lethal form of skin cancer, exhibits extremely high mortality rates as most patients are diagnosed at advanced stages (62). Although pain is not a primary clinical symptom, 7% of patients experience pain, with >50% of metastatic melanoma cases requiring palliative care and morphine treatment due to neuropathic pain components (63). However, current models predominantly target limb skin, lacking successful constructions for other anatomical regions. Furthermore, a toe cancer model developed ulceration and hemorrhage 14 days post-inoculation (64), precluding oral herbal analgesic evaluation while remaining valuable for injectable drug mechanism

studies. The plantar skin cancer model has emerged as a novel paradigm for cancer pain following bone cancer and chemotherapy models. Despite its limited variety, it provides critical platforms for mechanistic and therapeutic exploration. Xie and Wang (65) established a validated toe skin tumor model through murine left hindpaw plantar tumor cell injections, demonstrating pain behavior alterations. Intrathecal amiloride administration elevated thermal pain thresholds, alleviated thermal hypersensitivity and suppressed spinal dorsal horn acid-sensing ion channel 3 protein expression, offering novel clinical therapeutic insights. Tabata *et al* (66) constructed melanoma pain models via hindlimb subcutaneous melanoma cell inoculation, revealing that tropomyosin receptor kinase A (TrkA) inhibitory peptides reduced paw edema and melanoma-induced pain through TrkA receptor modulation.

Pancreatic cancer pain model. The establishment of pancreatic cancer pain model is fundamental for investigating pathogenesis and therapeutic strategies. Current models include chemically induced, transplanted tumor, genetically engineered, organoid and diabetes-associated composite paradigms (67). Ectopic grafts facilitate tumor monitoring but poorly replicate tumor microenvironments, whereas orthotopic injections improve emulated clinical pathology despite surgical complexity (68). Patient-derived xenograft model preserved tumor heterogeneity by engrafting human tumors into immunocompromised mice, though host stromal cell replacement occurs during passaging (69). Genetically engineered models simulate pancreatic carcinogenesis through clustered regularly interspaced short palindromic repeats-associated protein 9-mediated mutations, providing human-like tumor progression for mechanistic/targeted therapy studies despite high costs and technical demands. Organoid models reconstructed 3D tumor architectures from patient tissues, enable orthotopic transplantation to recapitulate malignant transformation with high fidelity and personalized potential, though standardization and microenvironmental completeness required refinement (67-69). Diabetes-associated composite models combine high-fat diets with streptozotocin-induced type 2 diabetes, followed by luciferase-tagged pancreatic cancer cell implantation. Integrated with bioluminescence imaging, these models illuminated metabolic-tumor interactions by dynamically visualizing hyperglycemia-driven tumor growth (70). Modern cancer pain models have transcended traditional tumor transplantation methods, establishing a three-dimensional framework focused on bone-derived pain, soft tissue invasion pain and neuroinvasive pain (71). In bone metastasis models, lower limb bone injection systems successfully replicate clinical intermittent severe pain and mechanical hyperalgesia by simulating osteolytic processes, while spinal metastasis models complete the research toolkit for vertebral metastatic pain. Notably, the neuroinvasive triple-negative breast cancer model, established via MDA-MB-231 cell injection into nerve bundles, achieved breakthrough precision in neuropathic cancer pain simulation, with mechanical allodynia phenotypes persisting one month longer than conventional models (72,73). However, current bone cancer evaluation systems overly focus on osteoclast activity indicators, inadequately reflecting astrocyte-CXCL12/CXCR4 signaling-mediated pain sensitization within tumor microenvironments. Additionally, existing pain assessment criteria fail to distinguish neural mechanisms between resting spontaneous pain and movement-associated pain (74,75).

Visceral pain model. Appropriate experimental visceral pain models are prerequisites for mechanistic investigations. Advances in anatomical and neurobiological research have enabled the development of multiple visceral pain models, laying foundations for basic/clinical studies. Effective models must simulate clinical pathophysiological features while ensuring reproducibility, operability and cost-effectiveness. Visceral pain exhibited unique characteristics due to sparse sensory neuron distribution and complex convergent nociceptive pathways: i) Diffuse localization with ambiguous pain origins, ii) referred pain at distant somatic sites, iii) organ-specific pain susceptibility linked to nociceptor distribution, iv) autonomic/motor reflexes and v) non-correlation with visceral damage (76). Visceral pain exhibits characteristics of ambiguous localization, referred pain and non-fully injury-associated features, owing to sparse sensory neuron distribution, peripheral cross-innervation of nociceptive afferent fibers, and complex multichannel nociceptive pathways (77). The construction of visceral pain model must meet requirements for clinical pathophysiological similarity, high reproducibility and operational feasibility. Current models are categorized into inflammatory, mechanical distension, ischemic and electrical stimulation types based on modeling stimuli (78). The present review systematically summarized and compared the construction methods, characteristics and advantages/limitations of major visceral pain models to guide researchers in selecting appropriate models based on experimental objectives (Table III).

Inflammatory visceral pain model. The inflammatory visceral pain model simulates pain through chemical or biological stimulation-induced local inflammation (79,80). An acute pancreatitis model employed retrograde sodium taurocholate injection into the pancreatic duct or subcapsular punctures to replicate biliary pancreatitis pathology but suffered from high surgical trauma and mortality (81,82). Sigmoid colon pain model induced localized inflammation using 5% formaldehyde submucosal injection, eliciting abdominal licking and arching within 45 min, with self-limiting inflammation facilitating self-controlled drug studies (83,84). In ulcerative colitis model, dextran sulfate sodium (DSS) drinking *ad libitum* or 2,4,6-trinitrobenzenesulfonic acid (TNBS)/ethanol rectal administration induced bloody stools and mucosal damage, with TNBS offering superior reproducibility despite interindividual DSS intake variability (85-87). A neonatal colorectal inflammation model established chronic visceral hypersensitivity through dilute acetic acid enemas in pups, mirroring irritable bowel syndrome pathophysiology by single-injury induction (88). A bladder pain model used intravesical mustard oil or acrolein to provoke dysuria, though murine urethral injury risks exist. A cyclophosphamide-induced acrolein metabolite model improved mimicking of natural bladder mucosa irritation mechanisms (89-91).

Mechanical distension pain model. Mechanical distension model replicated organ expansion or obstruction via physical stimuli. The gastroduodenal distension model triggered teeth

Table III. Characteristics of different types of visceral pain models.

Authors, year	Type	Animal	Method	Time	Indicators	Advantages	Disadvantages	(Refs.)
Wang *et al*, 2021	Capsaicin-induced inflammatory pain model	C57BL/6J mice	Gastric gavage of capsaicin	7 days	Spontaneous pain	Simple operation without surgery/ injection	High individual variability requiring strict dose control; mild inflammatory marker changes	(101)
Yao *et al*, 2020	Stress pain model	SD rats	Senna leaf extract gavage + physical stress	14 days	Colorectal distension and abdominal withdrawal	Mimics IBS under stress conditions	Divergence from multifactorial IBS etiology; stability needs improvement	(102)
Felice *et al*, 2014	Neonatal maternal separation pain model	SD rats	Maternal separation rearing	10 days	Colorectal distension and abdominal withdrawal	Non-invasive, high operability	Requires neonatal pups; long modeling cycle; low success rate	(103)
Wu *et al*, 2018	Colitis pain model	SD rats	TNBS enema	4 weeks	Colorectal distension and abdominal withdrawal	Direct colonic action with minimal systemic effects	Long modeling cycle; high mortality if improperly operated	(104)
Liu *et al*, 2020	Pancreatitis pain model	SD rats	DBTC tail vein injection	7 days	Spontaneous pain, Mechanical pain threshold	Simple implementation	Significant systemic impacts; uncontrolled ethanol intake in drinking water	(105)
Furuta *et al*, 2018	Interstitial cystitis pain model	F344 rats	Hydrochloric acid bladder perfusion	2 weeks	Spontaneous pain	Direct bladder action with minimal systemic effects	Urethral catheterization-induced trauma affecting behavioral performance	(106)
Deng*et al*, 2024	Acetic acid writhing pain model	C57/BL6 mice	Intraperitoneal acetic acid injection	21 days	Spontaneous pain	Rapid behavioral responses, high reproducibility	Uncontrolled diffusion rate/ direction of acetic acid	(107)

DBTC, dibutyltin dichloride; IBS, irritable bowel syndrome; SD, Sprague Dawley; TNBS, 2,4,6-Trinitrobenzenesulfonic acid.

grinding and back arching by inflating intragastric balloon catheters, though invasive surgery restricted application (92). Colorectal distension (CRD) involved anal balloon inflation to induce abdominal contractions and pelvic lifts, with inflammatory priming enhancing pain sensitivity, albeit with intestinal perforation risks at excessive pressures (93-94). Neonatal repetitive CRD in pups induced persistent visceral hypersensitivity in adulthood, serving as a tool for chronic pain mechanism research (95).

Ischemic visceral pain model. An ischemic visceral pain model simulated myocardial ischemia via coronary artery occlusion, yet vascular anatomical variations caused significant behavioral heterogeneity, limiting its use to qualitative studies (96). An electrical stimulation model applied controlled parameters to visceral nerves to evoke pain but lacked physiological relevance (97). A specialized maternal separation model induced gut hypersensitivity and anxiety-like behaviors in neonatally separated rodents through hypothalamic-pituitary-adrenal (HPA) axis dysregulation and intestinal barrier disruption, making them ideal for irritable bowel syndrome research (98-100). In summary, inflammatory models excels in drug screening despite low specificity, mechanical distension models improve approximate physiological stimuli and maternal separation models facilitated chronic pain mechanism exploration. Future advances require

multimodal assessment systems integrating imaging and molecular biomarkers to enhance translational value.

Inflammatory-driven, ischemia-induced and functional disorder paradigms have become mainstream modeling frameworks in visceral pain research. In gut-brain axis dysfunction studies, programmed colorectal distension techniques have established gold-standard evaluation systems by quantifying viscerosomatic pain correlation indices (101). Innovative mechano-chemical pancreatic stimulation models (35 mmHg sustained pressure combined with dynamic pH monitoring) precisely replicate the synergistic effects of mechanical stress and acidic microenvironments in pancreatitis pain. The research highlighted the bladder chemo-optogenetic platform and successfully constructed reversible neuromodulation frameworks for visceral pain pathways (102,103). Current model systems face dual bottlenecks in mechanistic resolution: Intestinal mechanical stimulation models struggle to specifically regulate enteric glial-TRPA1 ion channel signaling networks, while chronic pancreatic injury models exhibit 48-72 h temporal discrepancies between peripheral stellate cell activation and central sensitization markers (104). Technological advances such as Sox10-CreERT2-mediated conditional gene editing of enteric glial subsets, development of bidirectional gut-brain modulation models and deployment of miniaturized multimodal biosensor arrays enabling synchronized autonomic rhythm and visceral pain threshold tracking (sampling frequency ≥100 Hz) will propel visceral pain research toward precision modulation and systemic integration (105).

Inflammatory pain model. Inflammatory pain arises from tissue injury or infection-triggered inflammatory responses, commonly observed in arthritis, postoperative inflammation, or infectious diseases. Inflammatory mediators (prostaglandins, bradykinin and cytokines) activate peripheral nociceptors, inducing pain sensitization and central nervous system remodeling. Clinical manifestations included redness, swelling, heat and dysfunction, with characteristic 'protective' features and sensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs)/glucocorticoids (106). While inflammatory and visceral pain overlap in mechanisms, they differ fundamentally: Visceral pain exhibits diffuse localization and referral, whereas inflammatory pain is typically well-localized and injury-associated. The inflammatory pain model simulates acute/chronic inflammatory states via local injections of specific irritants into skin, plantar surfaces, muscles, or joints (107). These models induce acute inflammation through neutrophil chemotaxis and sustained pain via macrophage infiltration, with pain modulation mechanisms closely linked to opioid peptide analgesia (108). Table IV systematically summarized and compared the construction methods, characteristics, and advantages/limitations of major inflammatory pain models to guide researchers in selecting appropriate models based on experimental objectives.

Carrageenan-induced pain model. Local carrageenan injection triggers biphasic inflammation: Acute neutrophil-dominant phase (24-48 h) transitions to chronic monocyte/macrophage phase over two weeks. The model induces thermal/mechanical hypersensitivity at injection sites and secondary hyperalgesia in remote areas, pathologically resembling rheumatoid arthritis (109).

Complete Freund's adjuvant (CFA) model. CFA injection into tails or joint cavities elicits stronger persistent inflammation than carrageenan. The CFA model exhibits injection site swelling, 60-70% reduced hindlimb weight-bearing, and 40% decreased wheel-running activity. Previous studies confirmed electroacupuncture combined with spinal orphanin FQ receptor antagonists modulates such pain, validating acupuncture analgesia in chronic inflammation (110,111).

Capsaicin-induced pain model. Local capsaicin injection activates TRPV1 channels, provoking neurogenic inflammation. The model features 50% thermal hyperalgesia and 80% mechanical allodynia around injection site with secondary mechanical hypersensitivity distally (112). Transient C-fiber depolarization-induced hypoalgesia at injection cores provides unique insights into spatiotemporal pain conduction dynamics (109). The classic CFA chronic inflammatory model establishes the temporal correlation between macrophage M1 polarization phenotypes and mechanical hyperalgesia through dynamic TNF-α/IL-1β expression profiling (28 days) (113). The IL-23 local sensitization model pioneered a γδT cell-IL-17A signaling axis-driven neural sensitization purification system, overcoming traditional adjuvant model heterogeneity (114). The TLR4/ATP bimodal stimulation model achieves molecular-level spatiotemporal synchronization of NLRP3 inflammasome activation and neuropeptide (CGRP, substance P) release via two-photon intravital imaging. Cross-species neutrophil metabolic cycle displays impaired biological validity in chronic inflammatory microenvironment reconstruction (rodents <8 h vs. humans 5-90 days) (115-117). A peripheral innervation model exhibits clinical phenotype disconnects, as synovial C-fiber density (<25%) inadequately explains rheumatoid pain persistence. The lactate-ASIC3 signaling axis in pain regulation lacks standardized paradigms from metabolic reprogramming perspectives. Emerging solutions include dorsal root ganglion organoid-chip models co-cultured with polarized macrophages, microelectrode arrays for neuro-immune interaction kinetics, optogenetic delivery systems (TRPV1-liposome carriers) for submillimeter IL-6 control in joints and humanized chemokine models (IL8-CXCR1 transgenics) to establish cross-species pain translation metrics, collectively advancing inflammatory pain research toward personalized precision medicine (118,119).

Other pain models. Somatic pain can be simulated using the formalin model (97). Injection of 1% formalin into the dorsal surface of the right hindpaw in rodents induces biphasic pain responses: Phase I (immediate pain lasting for10 min post-injection) and Phase II (delayed pain commencing 15-20 min post-injection and persisting 1 h). Phase II, which is commonly used in experimental studies, involves distinct mechanisms from Phase I. NSAIDs effectively attenuate Phase II pain but fail to modulate phase I responses. Species-specific behavioral differences are observed: Rats exhibit paw withdrawal, whereas mice displayed licking behaviors. Phase II pain is now recognized as peripherally mediated inflammatory pain

Table IV. Characteristics of different types of inflammatory pain models.

Authors, year	Type	Animal	Method	Time	Indicators	Advantages	Disadvantages	(Refs.)
Melo-Carrillo *et al*, 2013	Dural neuroinflammation pain model	Wistar rats	Inflammatory stimulant injection into dura mater via cranial drilling	16 days	Spontaneous pain	Closely mimics clinical manifestations	Technically complex with significant animal trauma	(112)
Burgos-Vega *et al*, 2019	Dural neuroinflammation pain model	ICR mice	Inflammatory stimulant injection into dura mater via cranial sutures	7 days	Spontaneous pain	Minimal animal injury	Requires high precision, suitable only for mice	(113)
Sufka *et al*, 2016	Nitroglycerin-induced pain model	SD rats	Intraperitoneal injection of nitroglycerin	2 weeks	Spontaneous pain	Simple, cost-effective, anesthesia-free	Systemic effects limit intracranial vascular specificity	(114)
Philpott *et al*, 2020	Intra-articular injection pain model	Wistar rats	Sodium iodoacetate injection into knee joint cavity	14 days	Mechanical pain threshold	Rapid implementation with low animal stress	Dose-dependent effects difficult to control	(115)
Shi *et al*, 2020	Joint immobilization pain model	New Zealand rabbits	6-week left hindlimb knee extension fixation	6 weeks	Mechanical pain threshold	Non-invasive joint protection	Fixation device detachment risks experimental validity	(116)
Katri *et al*, 2019	Meniscus resection pain model	Lewis rats	Medial collateral ligament transection with meniscectomy	44 days	Mechanical pain threshold, cold pain threshold	Severe/ persistent osteoarthritis induction	Surgical variability affects injury severity consistency	(117)
He *et al*, 2024	CFA-induced arthritis pain model	SD rats	Complete Freund's Adjuvant (CFA) injection into right hindpaw plantar region	42 days	Spontaneous pain	Gold standard for rheumatoid arthritis research	Prolonged modeling period; systemic inflammation affects model stability	(118)
Bai *et al*, 2025	Collagen-induced arthritis pain model	SD rats	Bovine type II collagen emulsified with Incomplete Freund's Adjuvant (IFA)	28 days	Spontaneous pain	Mimics human RA autoimmune mechanisms	Collagen purity/emulsion quality affects success; multi-dose immunization	(119)
Koo *et al*, 2002	Ankle joint overloading pain model	SD rats	Mechanical ankle overextension with 180˚ inversion	7 days	Spontaneous pain	No chemical inducers required	Short pain duration requiring rapid assessment; operator-dependent	(120)

Table IV. Continued.

Authors, year	Type	Animal	Method	Time	Indicators	Advantages	Disadvantages	(Refs.)
Wu *et al*, 2023	Carrageenan-induced Inflammation pain model	SD rats	1% carrageenan injection into left hindpaw plantar region	7 days	Spontaneous pain	Rapid inflammatory response	Transient hypersensitivity; unsuitable for chronic studies	(121)

CFA, complete Freund's adjuvant; ICR, institute of cancer research; IFA, incomplete Freund's adjuvant; RA, rheumatoid arthritis; SD, Sprague Dawley.

associated with central sensitization, making this model valuable for investigating tissue injury-induced hyperalgesia mechanisms (120).

Pain behavioral assessments evaluate nociceptive thresholds by applying acute noxious stimuli to elicit withdrawal reflexes. These methods simulate physiological acute pain but lack pathological validity, precluding standalone model development. They are primarily employed to verify threshold changes in existing pain models (121).

Mechanical nociceptive response testing predominantly utilized the Von Frey test (122). Originally developed by Maximilian Von Frey in the 19th century, this method applies calibrated filaments to the plantar surface in ascending force order to determine mechanical withdrawal thresholds. Alternatively, fixed-force filaments delivered repetitive stimuli to quantify withdrawal frequency/duration. Chaplan *et al* (25) subsequently optimized threshold determination protocols. Current practice favors electronic Von Frey systems for standardized force application. Colorectal distension via transanal balloon inflation simulates visceral pain, with pain thresholds assessed through AWR scoring.

However, behavioral interpretation introduce subjectivity. Thermal/cold nociception assessments are widely adopted in rodents. The tail-flick test measures heat avoidance latency by applying thermal stimuli to the tail (123). The hot plate test eliminates restraint-induced stress by observing escape behaviors on a heated surface. The Hargreaves test quantifies hindpaw withdrawal latency to radiant heat (124). Cold sensitivity evaluation substituted hot water with ice baths in tail-flick paradigms. Acetone droplet application induces cold allodynia in hypersensitive rats but elicits nonspecific responses (mechanical/chemical irritation) in mice (125). Semiconductor-cooled plates dominate cold pain studies, minimizing ambient temperature artifacts while retaining mechanical stimulation limitations (126). Recent advances in rodent pain assessment methodologies continue to refine precision and translational relevance.

4. Targets of pain

The convergence of structural biology and computational pharmacology has shifted to pain targets from single-receptor antagonism to multidimensional regulatory systems. Traditional targets such as MOR employ allosteric modulation strategies that stabilize receptor-G protein-biased conformations, addressing the analgesia-addiction dissociation challenge. Discoveries at neuroimmune interfaces drive the paradigm shift from neuron-centric to tripartite neuron-glial-immune network modulation. This section systematically elaborated conformational control of classical membrane receptors, ion channel subtype-specific drug design breakthroughs, mechanistic insights into neuroimmune interface targets and epigenetic modulation strategies, establishing a theoretical framework for multidimensional analgesic development.

Ionotropic channel receptors

Voltage-gated ion channels

Voltage-gated sodium channel. Voltage-gated sodium channels, transmembrane protein complexes comprising an α-subunit and β-subunits, are classified into nine subtypes (Nav1.1-1.9) based on α-subunit variations. These channels mediate action potential generation/conduction and are critically involved in neuropathic pain pathogenesis. Specifically, Nav1.3, Nav1.7, Nav1.8, and Nav1.9 play pivotal roles in nociceptive signaling. Nav1.3 is predominantly expressed in embryonic/neonatal central nervous system (CNS) with minimal adult expression, but its upregulation following peripheral/central nerve injury is associated with neuropathic pain. miR-30b downregulation under neuropathic conditions reduces SCN3A mRNA inhibition, elevating Nav1.3 expression to enhance neuronal excitability (127). Nav1.7 is predominantly expressed in small C-fiber nociceptors of dorsal root ganglia (DRG), mediating action potential generation in an endogenous opioid-independent manner. Its unique slow activation/inactivation kinetics enabled ramp current generation, lowering action potential thresholds and amplifying subthreshold depolarizations to critically regulate pain transduction (128,129). Nav1.8, a tetrodotoxin-resistant sodium channel enriched in trigeminal ganglia and DRG nociceptors, represents a high-selectivity analgesic target (130). Co-expressed with Nav1.7/1.8 in small DRG neurons, Nav1.9 participates in familial episodic pain syndromes and GM-CSF-induces hyperalgesia through Jak2-Stat3 pathway co-activation (131). Pharmacological blockade of Nav1.7/1.8 channels reduces ectopic discharges and elevates peripheral firing thresholds to alleviate pain (132), with Nav1.7-selective inhibitors emerging as promising next-generation analgesics through therapeutic index optimization (133).

Voltage-gated Ca^{2+} channel. Voltage-gated Ca^{2+} channel regulates cytosolic Ca^{2+} levels to influence cellular excitability and signaling, with N-type and T-type subtypes implicated in pain pathophysiology. The N-type blocker ziconotide, approved

by the U.S. Food and Drug Administration (FDA) for intrathecal administration in severe chronic pain, exhibits potent analgesia limited by narrow safety margins. T-type channels in central/peripheral neurons mediated somatic/visceral pain transduction, making their modulators potential analgesics (134).

Voltage-gated K^+ channel. Potassium voltage-gated channel subfamily KQT member 4 (KCNQ) validates analgesic targets, as evidenced by retigabine's efficacy in chronic inflammatory/neuropathic pain models (135). Genetic studies of inherited erythromelalgia identified KCNQ2-encoded Kv7.2 channels as peripheral determinants of pain susceptibility (136), suggesting intrinsic analgesic mechanisms beyond conventional modulation (137). Flupirtine, a retigabine analog targeting Kv7.2, has been clinically used since 1984 despite adverse effects. Cryo-EM structures of apo-state human Kv7.2 and ligand-bound complexes with retigabine/ztz240 provided molecular blueprints for improved KCNQ agonist design (138). While numerous pharmaceutical efforts focused on KCNQ openers, only retigabine and flupirtine have reached clinical application, underscoring the need for optimized subtype-selective agents.

Mechanosensitive ion channel-TREK-1. As a key member of the K2P potassium channel family, TREK-1 is regulated by G protein-coupled receptors (GPCRs) and enriched in small sensory neurons (139). TREK-1 knockout mice exhibit enhanced thermal sensitivity and mechanical allodynia, with diminished osmotic pain responses particularly in PGE2-sensitized models (140), establishing TREK-1 as a promising multitarget analgesic candidate.

Ligand-gated ion channels

Acid-sensing ion channel (ASIC). ASIC, a proton (H^+)-activated cation channel expressed in both peripheral and central nervous systems, plays critical roles in pain signal transmission and modulation. The ASIC family comprises ASIC1-ASIC4 subtypes, with ASIC1 predominating in spinal neurons and brain regions such as the cerebral cortex and hippocampus (141). Duan *et al* (142) demonstrated that intrathecal administration of ASIC1a-specific inhibitors or antisense oligonucleotides in CFA-induced inflammatory rats markedly reduced thermal/mechanical hyperalgesia via ASIC1a downregulation. Stauntonia PTS extract inhibited ASIC currents and downregulated ASIC3 protein expression, exhibiting analgesic effects in animal models. Key active compounds YF-33 and YF-49 show dose-dependent ASIC current suppression and potent analgesia (143). Paeoniflorin alleviates pain by inhibiting ASIC-mediated H^+-activated currents through adenosine A1 receptor interaction, shortening Phase II pain duration in formalin tests (144). Dexmedetomidine concentration-dependently inhibited ASIC electrophysiological activity via α2-adrenergic receptors (α2-ARs), mitigating acid-induced nociceptive behaviors through peripheral α2A-Ars (145). These findings highlighted diverse pharmacological strategies targeting ASICs for pain management.

α4B2 nicotinic acetylcholine receptor. The α4β2 nicotinic acetylcholine receptor (nAChR), a ligand-gated ion channel widely expressed in the CNS/PNS, modulates pain signaling through acetylcholine, dopamine, γ-aminobutyric acid (GABA) and norepinephrine regulation. Its agonists/partial agonists exhibit analgesic efficacy in neuropathic/inflammatory pain models, reversible by nAChR antagonists (146). However, novel α4β2 nAChR-targeted analgesics remained preclinical, necessitating further development.

N-methyl-D-aspartate (NMDA) receptor. NMDA receptor, an ionotropic glutamate receptor abundant in spinal dorsal horn neurons, is a validated mediator of pathological pain and hyperalgesia across formalin, CFA, carrageenan and neuropathic models. Studies have revealed NMDA receptor expression on spinal keratinocytes and involvement in astrocyte activation during sciatic nerve injury-induced neuropathic pain. Li *et al* (147) demonstrated NMDA receptor participation in spinal microglial activation and neuroactive substance release during acute peripheral inflammatory pain, expanding their therapeutic potential.

Purinergic receptor. ATP-gated P2X receptor facilitates K^+ efflux and Na^+/Ca^{2+} influx through seven subtypes (P2X1-7) expressed on neurons, immune cells and cancer cells. P2X3 mediates acute pain in sensory neurons, P2X4 neuropathic pain in glia and P2X7 inflammatory pain in immune cells (148). Emerging evidence positions purinergic signaling via P2X receptors as a dual therapeutic target for cancer progression and pain. Franceschini and Adinolfi (148) proposed combining standard chemotherapeutics with P2X2/3/4/7 antagonists to simultaneously address tumor growth and cancer-related pain.

Capsaicin receptor. The transient receptor potential (TRP) channel constitutes a family of cellular channel proteins initially discovered in *Drosophila* photoreceptors, where TRP mutations abolished sustained light-induced responses while permitting transient voltage currents. TRP channels are expressed across multiple tissues, with their activation via diverse stimuli triggering cation influx to modulate cellular states. The TRP family comprises six subfamilies: Canonical (TRPC), melastatin (TRPM), vanilloid (TRPV), ankyrin (TRPA), polycystin (TRPP) and mucolipin (TRPML) (149). Among them, TRPV1, TRPA1 and TRPM8 play pivotal roles in analgesic mechanisms. TRPV1 channel, recognized as a critical regulator of nociception, exhibits sensitivity to thermal and chemical stimuli. Activation induces inflammatory mediator/neurotransmitter release from nociceptive nerve terminals to generate pain signals, positioning TRPV1 antagonists as validated analgesic agents (150). TRPA1 channel, activated by reactive oxygen species and cold temperatures, represents emerging therapeutic targets through their involvement in mechanical/allodynic pain pathways (151). TRPM8 channel, cold-sensitive thermoreceptors, paradoxically mediate analgesia when they activate their agonists in neuropathic pain management (152,153). Preclinical studies confirm TRPV1's therapeutic relevance across cancer, neuropathic, postoperative and musculoskeletal pain models. Its selective expression in primary nociceptors underpinned targeted intervention strategies. Emerging approaches include potassium current enhancers to suppress nociceptive signaling and Cav2.2/Cav3.2 calcium channel blockade, demonstrating complementary analgesic potential (154).

GPCRs

Opioid receptor. Opioid receptors, a class of GPCRs, include multiple subtypes such as central MOR, δ-opioid receptor (DOR), κ-opioid receptor (KOR) and peripheral Mrg opioid

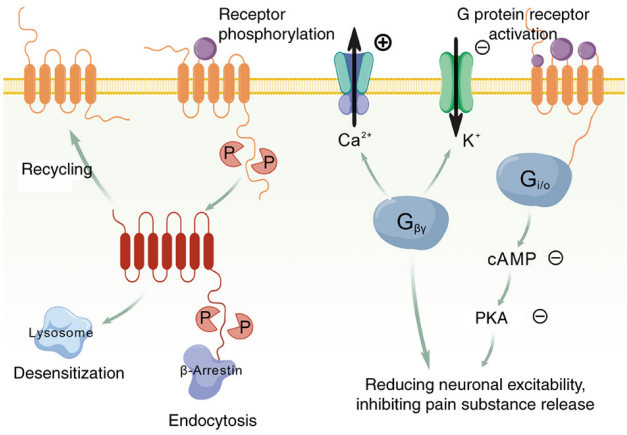

Figure 2. Signal transduction diagram after activation of μ-opioid receptor. cAMP, cyclic adenosine monophosphate; PKA, protein kinase A.

receptor, all of which modulated pain signaling (155). Despite severe adverse effects on the central and enteric nervous systems, opioids remained the gold standard for acute pain management. MOR, expressed in both central and peripheral nervous systems (Fig. 2), is clinically targeted by agonists for analgesia. The δ-opioid receptor agonist SNC80 exerts dose-dependent analgesic and anti-depressant effects in rodents and suppresses acid-induced writhing responses as well as chemically evoked nociceptive behaviors via systemic administration. While κ-opioid receptor agonists are widely used in preclinical pain studies, their clinical analgesic efficacy in humans remains suboptimal (156). As a specialized opioid receptor subtype, Mrg receptor constitutes a novel GPCR family selectively expressed in small-to-medium neurons of trigeminal and DRG in mammals. The murine Mrg family comprises 50 members categorized into four classes (A-D), whereas humans possessed seven Mrg receptors (MrgX1-7). MrgC receptor activation enhances morphine's analgesic potency and duration through MOR G-protein modulation. Wang *et al* (157) demonstrated that intrathecal administration of the selective MrgC agonist BAM8-22 (3 nmol) potentiated morphine analgesia and induced a leftward shift in morphine's dose-response curve.

Metabotropic glutamate receptor. Metabotropic glutamate receptors (mGluRs), members of GPCR family, encompass eight distinct subtypes. These receptors act as modulators of neuronal excitability and synaptic transmission, expressed at both presynaptic and postsynaptic sites in the nervous system. Their activation produces either analgesic or pain-sensitizing effects, depending on their anatomical location and downstream signaling cascades. Early studies demonstrated that mGluRs played a role in pain transmission. For instance, the competitive mGluR antagonist L-AP3 inhibited the activation of spinal dorsal horn neurons induced by repeated topical application of mustard oil, suggesting that persistent pain caused by such applications can be suppressed by blocking mGluR-mediated signaling pathways (158). Additionally, systemic administration of the non-competitive mGlu5 antagonist MPEP reversed mechanical hyperalgesia induced by inflammatory mediators such as CFA and carrageenan. Oral administration of MPEP exhibited gastrointestinal protective effects superior to those of NSAIDs such as indomethacin and diclofenac sodium. Furthermore, peripheral administration of MPEP markedly reduced CFA-induced inflammatory hyperalgesia, highlighting the critical role of peripheral mGlu5 expression in pain modulation (158). These preclinical findings collectively established mGluRs as promising targets for developing novel analgesics to treat chronic inflammatory and neuropathic pain. Future studies in animals and humans will further elucidate the therapeutic potential of mGluRs in chronic pain management.

Adenosine receptor. Adenosine receptors, extracellular GPCRs, comprise four subtypes (A1R, A2AR, A2BR and A3R) and participate in physiological, non-physiological and pathological processes as part of endogenous signaling pathways. Extensive research indicates that systemic administration of A1R agonists alleviates pain in preclinical models of inflammatory and neuropathic pain, with early reports proposing A1R agonists as potential analgesics. A2AR is expressed on peripheral inflammatory and immune cells, regulating anti-inflammatory responses and serving as a therapeutic target in inflammatory and immune disorders. Similarly, A2BR is expressed on peripheral inflammatory and immune cells and its activation enhances pro-inflammatory activities, though its role in pain remains poorly characterized. A3R is expressed in multiple organs and peripheral tissues, including cells involved in inflammatory responses. Intrathecal injection of the selective A3R agonist IB-MECA produces analgesia, while the selective A3R antagonist MRS 1220 blocks adenosine-induced analgesia following intrathecal administration (159). These discoveries highlight adenosine receptors as valuable targets for novel analgesic development.

Cannabinoid receptor. Cannabis has been used for pain relief for over four centuries, but its analgesic mechanisms have remained unclear until the discovery of cannabinoid receptors. The first cannabinoid receptor (CB1) was cloned from a cDNA library, followed by CB2, cloned from HL-60 cells. CB1 receptor is abundantly expressed in the CNS and sparsely in peripheral tissues, whereas CB2 receptor is predominantly localized to immune cells, with lower expression in microglia, DRG, spinal cord, and specific brain regions (160). In the CNS, CB1 receptor modulated pain transmission in regions such as the spinal dorsal horn, periaqueductal gray matter, dorsal raphe nucleus and ventral posterolateral thalamus, mediating cannabinoid-induced analgesia. Peripherally, cannabinoid analgesia involved both CB1 and CB2 receptors. Intrathecal administration of CB2-selective agonists effectively attenuated pain in multiple inflammatory pain models, while selective CB2 activation avoids CNS-related side effects (hypomotility, catalepsy, hypothermia, cognitive impairment) associated with CB1 modulation (134).

Glucagon-like peptide-1 receptor. The glucagon-like peptide-1 receptor (GLP-1R), a member of GPCR family, is specifically expressed in microglia of the spinal dorsal horn and markedly upregulated during peripheral nerve injury. Intrathecal administration of GLP-1R agonists, such as GLP-1 (7-36) and exenatide, reduce pain hypersensitivity by 60-90% in models of formalin-induced pain and peripheral neuropathy. This

analgesic effect is completely abolished by GLP-1R antagonists or genetic knockout of GLP-1R. Furthermore, GLP-1R agonists alleviate persistent and neuropathic pain via GLP-1R activation (161). The identification of this novel signaling pathway in the spinal dorsal horn, implicated in diverse pain hypersensitivities, offers a promising avenue for exploring pain mechanisms and developing innovative analgesics.

Imidazoline I2 receptor. In 2011, Li *et al* (162) identified imidazoline I2 receptor as a novel target for analgesic. The I2 receptor or I2 binding site referred to multiple proteins with high affinity for (3H)-idazoxan and (3H)-2-BFI. It was found that I2 receptor-targeting drugs exerted analgesic effects in rat models of inflammatory and neuropathic pain, particularly in chronic pain (163). Early research found that selective I2 receptor ligands alone lacked significant analgesia but potentiated the analgesic effects of opioids in acute pain models (163). Ongoing investigations into I2 receptor will provide critical insights for developing next-generation analgesic.

Enzymes

P38 mitogen-activated protein kinase (MAPK). The p38 MAPK signaling system serves as a central regulatory network for cellular responses to environmental stressors, playing pivotal roles in maintaining homeostasis, mediating stress responses and modulating inflammatory processes (164). This pathway integrates diverse stressors and ligand signals through apoptosis-associated receptors or GPCR, triggering intricate intracellular cascade reactions. The signaling cascade involves multi-level regulatory mechanisms including small GTPase activation and adaptor protein interactions, ultimately activating kinase family members at the MAP3K level (165). The p38 MAPK family comprises 20 distinct MAP3K-related kinases encoded by separate genes, which phosphorylated substrates by recognizing Ser-Xaa-Ala-Xaa-Ser/Thr motifs (148). Based on sequence characteristics and inhibitor sensitivity, these kinases are categorized into p38α/β and p38γ/δ subgroups (166). Activated p38 MAPK regulates cellular functions by phosphorylating downstream effectors such as MAPK activating protein kinases or directly modulating key factors including phospholipase A2 and heat shock proteins and activating transcription factor 2, ETS transcription factor 1, C/EBP homologous protein and myocyte enhancer factor 2C (Fig. 3) (167). Pathologically, aberrant p38 MAPK activation in neural tissues promotes release of pro-inflammatory mediators such as TNF-α and IL-1β (168). These cytokines enhance nociceptive sensitization, incision length and abnormal discharges through ion channel modulation and synaptic plasticity alterations. Sustained pathway activation induces cascading amplification of pain signals, forming the pathological basis of chronic pain (164). NSAIDs and botanical extracts exert analgesic effects via p38 MAPK modulation (169). For instance, the traditional Chinese medicine An-Gong-Niu-Huang-Wan suppresses COX-2, IL-1β, TNF-α, PGE2 and NO expression by inhibiting p38 MAPK and phosphoinositide 3-kinase/protein kinase B signaling (170). Daphnetin, a natural coumarin derivative, demonstrates potent spinal p38 MAPK inhibition in neuropathic pain models, offering novel therapeutic insights (171). These findings elucidate pharmacological mechanisms of traditional remedies while advancing targeted drug development.

Cyclooxygenase (COX). COX is a rate-limiting enzyme that synthesizes prostaglandins from arachidonic acid. It exists as two classical isoforms, COX-1 and COX-2, which regulate diverse physiological and pathological processes. Lu *et al* (172) demonstrated that cerebral COX-1 modulated late-stage neuropathic pain following sciatic nerve injury, while COX-2 governed early-phase pain initiation. Zhou *et al* (173) identified COX-2 as a downstream effector in ephrinBs-EphBs-mediated spinal pain signaling. The COX-3, a novel cyclooxygenase family member, expands therapeutic targets for analgesic research (174).

Nitric oxide synthase (NOS). NOS comprises three isoforms: Neuronal, inducible and endothelial. NO generated through these enzymes exerts multifaceted biological effects in pain pathophysiology. Intrathecal NO precursors/donors exacerbated thermal hyperalgesia and tactile allodynia in neuropathic rats, reversible by NOS inhibitors (174). Kuboyama *et al* (175) established the critical role of NOS/NO signaling in spinal microglial activation and nerve injury, inducing tactile allodynia using knockout mice and providing mechanistic insights into neuropathic pain.

Other targets

Canonical NF-κB. The NF-κB signaling pathway bifurcates into canonical and non-canonical branches. The canonical pathway, activated by pro-inflammatory cytokines (TNF-α and IL-1β) through IL-1 receptor, Toll-like receptors and TNF receptor, initiated via TNF receptor (TNFR) 1 trimerization and subsequent recruitment of TNF receptor-associated death domain/receptor-interacting protein 1. This triggers TNF receptor-associated factor 2/5 and cIAP1/2-mediated ubiquitination, assembling LUBAC-TAK1-NEMO/IKK complexes. Linear ubiquitination of the NF-κB essential modulator activates the inhibitor of nuclear factor κB kinase, which in turn phosphorylates IκBα, enabling NF-κB dimer (RelA/p50) nuclear translocation and inflammatory gene transcription (Fig. 4) (176,177). NF-κB's five family members (RelA/p65, RelB, c-Rel, p50/p105 and p52/p100) crucially regulated pain hypersensitivity through cytokine amplification. In gouty arthritis models, astragaloside IV suppresses NF-κB-mediated IL-2/IL-6/TNF-α expression to alleviate monosodium urate-induced inflammation (178). Migraine studies demonstrated traditional Chinese medicine's inhibition of NF-κB ameliorated vascular dysfunction and central sensitization (179). Acupuncture modulated this pathway in rheumatoid arthritis to achieve anti-inflammatory and immunoregulatory analgesia (180). Pharmacological interventions targeting NF-κB included dezocine, a κ-opioid receptor modulator that attenuated remifentanil-induced hyperalgesia via TLR4/NF-κB/TRPA1 axis inhibition (181). Metformin alleviated radiation-induced dermatitis pain by suppressing p38 MAPK/NF-κB-driven IL-1β/IL-6/TNF-α overproduction (182).

GABA receptor. GABA receptor expressed by inhibitory interneurons in spinal dorsal horn laminae I-III regulate pain transmission through GABA type A receptor (GABAA) and GABA type B receptor (GABAB) activation in primary afferents and dorsal horn neurons (183). GABAA receptors,

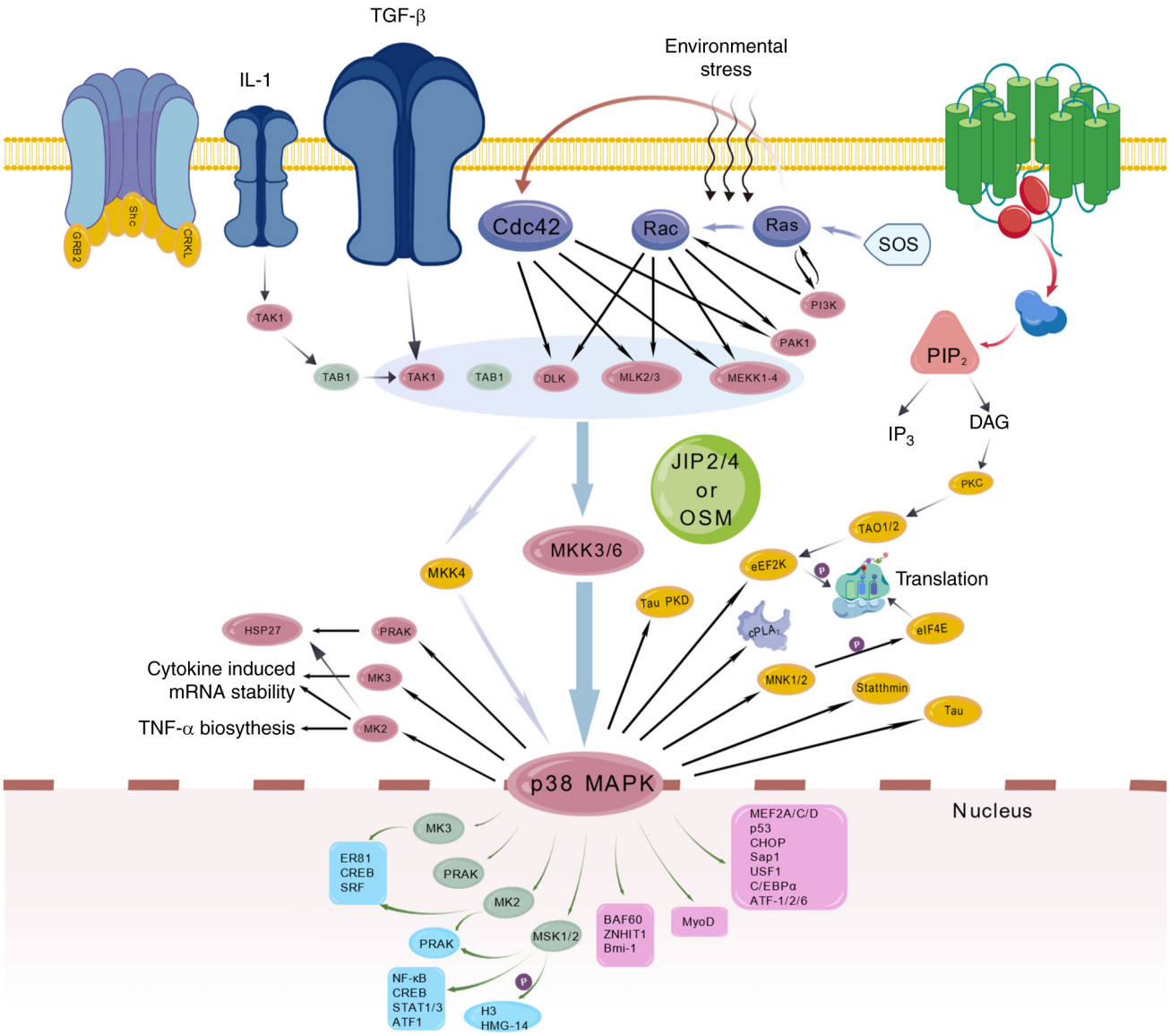

Figure 3. Signaling pathway of P38 MAPK. ATF-1/2/6, activating transcription factor 1/2/6; BAF60, brahma-associated factor 60; BMI-1, B-cell specific moloney murine leukemia virus integration site 1; C/EBPα, CCAAT/enhancer-binding protein α; CHOP, C/EBP homologous protein; Cdc42, cell division cycle 42; CREB, cAMP response element-binding protein; DAG, diacylglycerol; DLK, dual-leucine zipper-bearing kKinase; eEF2K, eukaryotic elongation factor 2 kinase; eIF4E, eukaryotic initiation factor 4E; ER81, ETS-related protein 81; GAB2, GRB2-associated binding protein 2; GSKL, glycogen synthase kinase-like; H3, histone 3; HSP27, heat shock protein 27; HMG-14, high mobility group protein 14; IL-1, interleukin-1; IP_3, inositol trisphosphate; JIP2/4, JNK-interacting protein 2/4; MAPK, mitogen-activated protein kinase; MEF2A/C/D, myocyte enhancer factor 2A/C/D; MEKK1-4, mitogen-activated protein kinase kinase kinase 1-4; MKK3/6, mitogen-activated protein kinase kinase 3/6; MKK4, mitogen-activated protein kinase kinase 4; MLK2/3, mixed lineage kinase 2/3; MK2, mitogen-activated protein kinase-activated protein kinase 2; MK3, mitogen-activated protein kinase-activated protein kinase 3; MNK1/2, MAP kinase interacting serine/threonine kinase 1/2; MyoD, myoblast determination protein; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; OSM, oncostatin M; PAK1, p21-activated kinase 1; PIP_2, phosphatidylinositol 4,5-bisphosphate; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; PLA_2, phospholipase A_2; PRAK, p38-regulated/activated protein kinase; SAP1, serum response factor accessory protein 1; SOS, son of sevenless; SRF, serum response factor; STAT1/3, signal transducer and activator of transcription 1/3; TAB1, TGF-β activated kinase 1 binding protein 1; TAK1, TGF-β activated kinase 1; TAO1/2, thousand and one amino acid kinase 1/2; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; USF1, upstream stimulatory factor 1; ZNHIT1, zinc finger HIT domain-containing protein 1.

predominantly localized in DRG, induce neuronal depolarization to block nociceptive signaling. However, their widespread CNS distribution caused benzodiazepine-related side effects (sedation, motor impairment and addiction), limiting clinical utility in chronic pain. Most CNS $GABA_A$ receptors are benzodiazepine-sensitive, composed of 2α, 2β and 1γ2 subunits, with benzodiazepine binding sites formed by γ2 and α1/α2/α3/α5 subunits. Knock-in mouse models revealed that benzodiazepine-induced sedation/amnesia/convulsion relate to α1 subunits, while analgesia involved α2 > α3 > α5 subunits. Selective activation of spinal α2/α3 subunits of the GABA receptor minimizes adverse effects and thus represents a novel analgesic strategy (184). Studies on sinomenine demonstrated that its analgesic effect is completely reversed by bicuculline, a $GABA_A$ receptor antagonist, indicating modulation via the $GABA_A$ receptor (185). $GABA_B$ receptors modulated peptidergic primary afferents and dorsal horn neurons. The agonist baclofen alleviated chronic pain, spinal injury, and trigeminal neuralgia. Early evidence showed systemic/intrathecal baclofen produces analgesia in acute/chronic pain models (186).

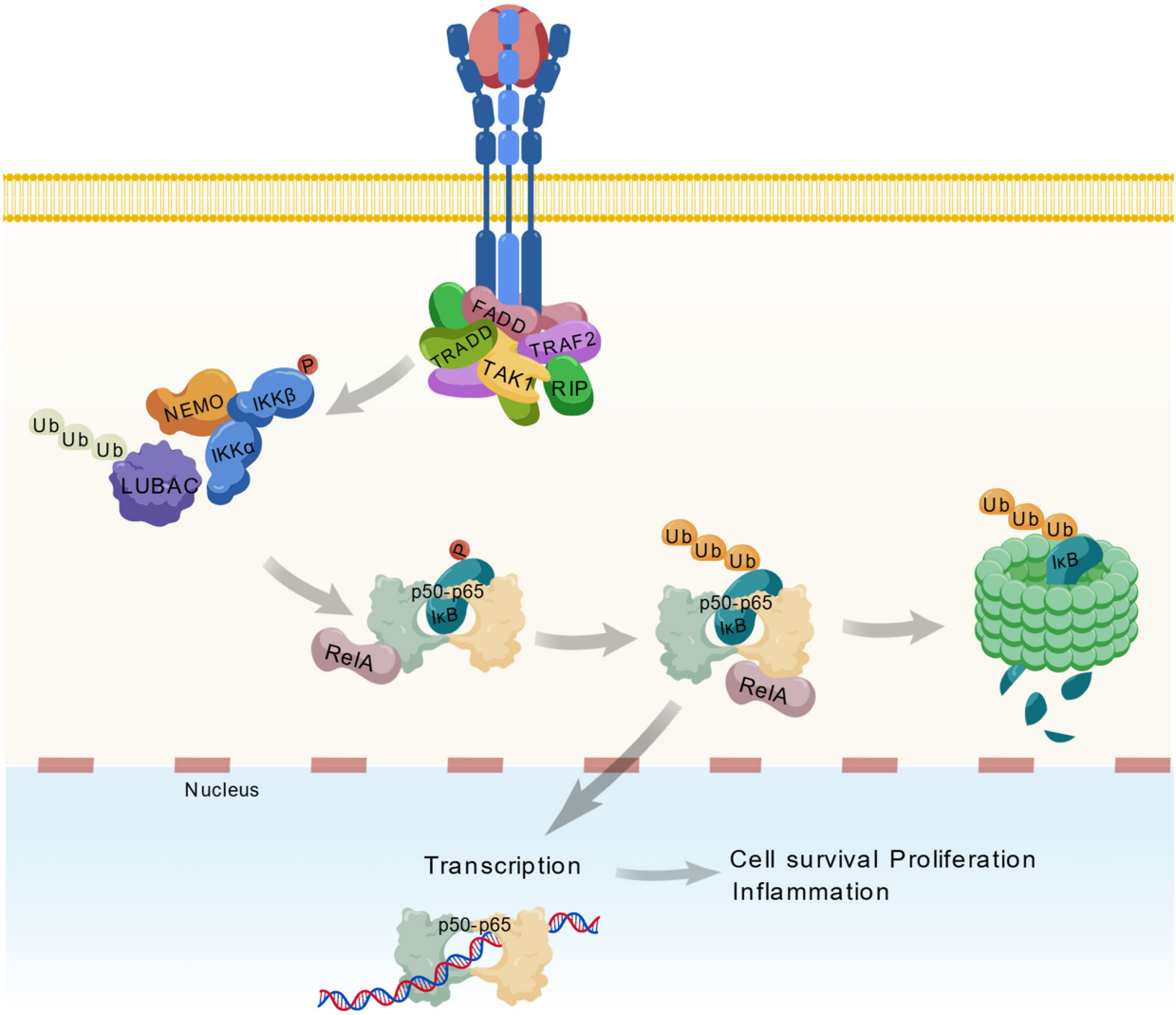

Figure 4. Signaling pathway of NF-κB. FADD, fas-associated protein with death domain; IκB, inhibitor of κ-B; IKKα, IκB kinase α; IKKβ, IκB kinase β; LUBAC, linear ubiquitin chain assembly complex; NEMO, NF-κB essential modulator; NF-κB, nuclear factor κB; p50, NF-κB subunit p50; p65, NF-κB subunit p65; RIP, receptor-interacting protein; TAK1, transforming growth factor-β-activated kinase 1; TRADD, TNF receptor-associated death domain; TRAF2, TNF receptor-associated factor 2; Ub, ubiquitin.

TNF-α receptor (TNFR). TNF-α, a proinflammatory cytokine released during tissue injury, mediates chronic neuropathic pain via TNFR1/TNFR2. Post-nerve injury, TNF-α upregulation in affected nerves enhances Aδ fiber firing through TNFR1/2 activation, while TNFR-neutralizing antibodies attenuated CCI-induced pain (187). TNFR1-knockout mice lacked thermal hyperalgesia but reduced mechanical/cold pain, whereas TNFR2-knockouts exhibited weak mechanical/cold sensitivity (188), confirming different roles in neuropathic pain pathogenesis. Current research mainly focuses on four-dimensional target innovations: i) Membrane receptor conformational dynamics, ii) ion channel microdomain targeting, iii) neuroimmune interface modulation and iv) epigenetic regulation. These advances established multidimensional intervention systems from molecular conformations to epigenetic memory. However, some researches were constrained by three major bottlenecks: The inability of single-target modulation to block multi-pathway compensatory effects in pain signaling, low translational efficiency due to species-specific differences in preclinical models and the dual challenges of blood-brain/blood-nerve barrier penetration for neuroimmune-targeted drugs. Future investigations should focus on breakthroughs in multitarget coordination technologies and organoid-chip validation platforms. A prioritized recommendation involves exploring the mechanosensitive channel properties of astrocytic gap junction protein Cx43 to develop mechanoresponsive analgesics, potentially providing novel therapeutic avenues for tissue fibrosis comorbid with chronic pain.

5. Treatments of pain

Drug therapy

Opioids. Opioids exert analgesic effects through opioid receptors in the central and peripheral nervous systems. The endogenous opioid system, one of the most extensively studied innate pain modulatory systems, established opioids as the gold standard for moderate-to-severe pain management (189). This system

comprised four 7-transmembrane GPCRs: MOR, KOR, DOR and NOP. Among them, MOR, a GPCR, mediates analgesia via G protein pathway activation that inhibits neuronal excitation and promotes hyperpolarization (190). Current opioid research prioritizes developing low-adverse-effect agents through strategies including biased agonists, multifunctional ligands, allosteric modulators (191) and MOR splice variant-targeting drugs (192). Anatomically, MOR is distributed extensively across pain pathways-peripheral nociceptors, spinal dorsal horn, thalamic nuclei, periaqueductal gray (PAG) and rostral ventromedial medulla-forming multidimensional regulatory networks integrating cognitive-emotional components in cortical/hippocampal/coeruleus regions (193). Comparatively, KOR/DOR/NOP receptors exhibit lower expression and weaker analgesia despite overlapping distributions. Their localization in respiratory centers underlie MOR-mediated respiratory depression (194). In reward circuits, MOR activation in ventral tegmental area-nucleus accumbens dopaminergic projections disinhibited GABAergic neurons to enhance dopamine release and addiction potential (195). Molecularly, opioid receptors signal through inhibitory G protein and β-arrestin pathways. Gi/o activation inhibits adenylate cyclase (AC) to reduce cyclic adenosine monophosphate (cAMP) while modulating ion channels: Gβγ subunits suppress N-type Ca^{2+} channels and activate G protein-coupled inwardly rectifying potassium channel (GPCIRPC) to decrease neuronal excitability (196). In PAG, MOR analgesia arises from disinhibition of glutamatergic descending pathways via GABAergic interneuron suppression (197). A study revised classical views by demonstrating G protein-mediated respiratory inhibition via GPCIRPC-induced hyperpolarization in β-arrestin knockout models (198). Oligomerization receptor critically modulated functionality. μ/δ heterodimers altered ligand affinity/surface density to modify analgesia (199), while μ/NOP heteromers attenuated signaling (200). Post-activation phosphorylation recruited β-arrestins for desensitization/internalization, contributing to acute tolerance. Chronic tolerance involved compensatory upregulation of cAMP/Ca^{2+}/protein kinase C pathways and transcriptional plasticity (163,195). To address the opioid crisis, novel strategies focused on biased agonists like TRV130 that preferentially activated G protein over β-arrestin pathways, reducing respiratory depression/nausea (201-203). PZM21 has reduced side effects, though lower potency, compared with morphine (204). Further optimization seeks enhanced G protein/β-arrestin signaling bias to maximize therapeutic indices.

Non-opioid analgesics. Non-opioid analgesics are commonly used as adjunctive therapy for moderate-to-severe cancer pain, enhancing analgesia while reducing opioid-related adverse effects such as constipation, nausea, vomiting, excessive sedation and respiratory depression. These agents primarily included NSAIDs and acetaminophen (APAP), suitable for mild-to-moderate pain. NSAIDs alleviate inflammatory pain by inhibiting COX to suppress prostaglandin synthesis, whereas the mechanism of APAP remains incompletely understood, potentially involving central inhibition and prostaglandin synthesis blockade. Limitations included gastrointestinal bleeding, cardiovascular risks, and hepatotoxicity.

APAP. APAP, an acetanilide-class antipyretic-analgesic, is the most widely used over-the-counter analgesic for fever and mild-to-moderate pain management. A study suggested that APAP acted via central COX-3 inhibition to reduce cerebral PGE2 production (205). APAP serves as first-line therapy for mild cancer pain and is formulated with opioids as second-line agents. Rapid oral absorption and hepatic metabolism characterize APAP, while hepatotoxic intermediates necessitate dosage control; this is especially important in polypharmacy. The recommended maximum daily dose is ≤2000 mg/d, especially for NSAID-contraindicated patients.

NSAIDs. NSAIDs, fundamental in pain management, exert antipyretic, analgesic, anti-inflammatory effects via prostaglandin synthesis inhibition. Prostaglandins mediate bone resorption in metastatic lesions, making NSAIDs effective for bone metastasis pain. Traditional NSAIDs exhibited frequent side effects, while selective COX-2 inhibitors reduced gastrointestinal toxicity, platelet inhibition and acute kidney injury risks. NSAID-induced renal medullary prostaglandin suppression impairs opioid metabolite clearance, potentially causing drowsiness, confusion, or myoclonus. Renal function monitoring was critical during NSAID-opioid coadministration.

Bisphosphonates. Bone metastases, common in advanced breast, lung, prostate cancers, and multiple myeloma, requires prompt intervention. Bisphosphonates (pamidronate, ibandronate and zoledronic acid) inhibit osteoclast-mediated bone destruction, promote remineralization and reduce skeletal-related events (SREs) such as pathological fractures (206). Despite efficacy, osteonecrosis of the jaw occurs ~0.01% of users after months of therapy. SREs (bone pain, fractures and spinal compression) severely impair quality of life and indicated disease progression. While bisphosphonates reduce SRE incidence, 50% patients remain unresponsive (207). Emerging research highlights the RANKL/osteoprotegerin system as a central pathway regulating osteoclast differentiation and bone metabolism (208).

Denosumab. Denosumab, a monoclonal antibody targeting RANKL, suppresses osteoclast activation, reduces bone resorption, and increases bone density (209). Compared with zoledronic acid, denosumab delays first SRE onset, reduces recurrence risk and improves controlled bone metastasis progression in breast, prostate and solid tumors (210). Advantages included renal safety without monitoring requirements. However, hypocalcemia and jaw necrosis are notable risks. Clinical decisions must balance efficacy, cost, and patient-specific factors.

Caffeine. Caffeine, a xanthine alkaloid and central stimulant, counteracted opioid-induced sedation per recent guidelines (211). While enhancing NSAID analgesia in non-cancer pain, its role in cancer pain remains under investigation. A double-blind RCT in 41 advanced cancer patients showed intravenous caffeine (200 mg/d) reduced NRS scores by 0.833 (95% CI: 0.601-1.066) vs. 0.350 (95% CI: 0.168-0.532) with placebo (P=0.038), though clinical significance was marginal (NRS improvement <1). Further trials were needed to validate utility (212).

Glucocorticoids. Glucocorticoids suppress proinflammatory cytokines/chemokines implicated in neuroglial activation and cancer pain (213). Recommended for postoperative pain adjuncts (214), they alleviate tumor-related edema (215). In a multicenter phase III trial, methylprednisolone (16 mg/d) improved fatigue, appetite and satisfaction in advanced cancer patients despite limited direct analgesia (216). Anti-inflammatory and anti-edema mechanisms supported further exploration in cancer pain.

Ketamine. Ketamine, an NMDA receptor antagonist and opioid receptor modulator, provided central/peripheral analgesia monoamine reuptake inhibition and ion channel ($Na^+/K^+/Ca^{2+}$) modulation (217). Combined with epidural or subcutaneous morphine, low-dose ketamine enhanced analgesia duration and efficacy in refractory cancer pain, though peripheral mechanisms remained unclear (218). Ketamine is positioned as a feasible option for severe cases, with controllable adverse reactions (nausea, sedation), making it an important alternative for refractory cancer pain. Optimal dosing routes require further study.

Platelet-activating factor (PAF) receptor. PAF mediates neuropathic pain, with intrathecal PAF inducing thermal hyperalgesia and mechanical allodynia reversible by antagonists (CV-3988, TCV-309 and WEB2086) (219,220). In murine osteolytic cancer pain models, PAF synthase/LPCAT2 upregulation is associated with spontaneous/evoked pain behaviors. Intrathecal PAF antagonists or siRNA-mediated receptor knockdown alleviated pain (221). Synergy with morphine enhances analgesia while reducing constipation, suggesting PAF antagonists as novel adjuncts for intractable cancer pain.

Adjuvant analgesics

Antidepressants. Chronic pain induces both physical suffering and psychological distress, particularly depression, which markedly hinders cancer pain rehabilitation. Antidepressants play critical roles in neuropathic and cancer pain management by inhibiting monoamine reuptake to elevate synaptic neurotransmitter levels. Common agents included tricyclic anti-depressants (TCAs), selective serotonin reuptake inhibitors (fluoxetine, sertraline) and serotonin-norepinephrine reuptake inhibitors (venlafaxine, duloxetine). Adverse effects (constipation, urinary retention) necessitate cautious dosing initiation and gradual titration. Sedating TCAs benefited patients with anxiety or sleep disorders, typically administered at night. Abrupt discontinuation risks withdrawal symptoms, requiring tapered cessation.

Antiepileptics. Neuropathic pain affects 1/3 cancer patients due to tumor compression, infiltration, or treatment-related neural injury. Pregabalin and gabapentin, first-line agents for neuropathic pain, block voltage-gated calcium channels to reduce neurotransmitter release. Pregabalin offers advantages over gabapentin in dosing frequency, efficacy and tolerability, though dizziness and peripheral edema remain common (222). It is worth mentioning that a number of neuropathic pain drugs fail in clinical trials despite strong preclinical results. Therefore, the successful launch of each drug must undergo preclinical and clinical trials. Only when the results of pre- and post-clinical studies are effective and consistent, can it be successfully marketed.

Topical agents. Lidocaine alleviates cancer-related cutaneous allodynia via rapid tissue penetration and with minimal systemic effects, localized irritation being the primary adverse event (223). Cannabinoid nasal sprays [δ9-Tetrahydrocannabinol (THC) 2.5 mg/l, Cannabidio (CBD) 2.7 mg/100 ml] demonstrate analgesic, antiemetic and appetite-stimulating effects at 1-4 sprays/day, despite regulatory controversies (224).

Cannabinoids. Cannabinoids exert analgesia via presynaptic receptor activation, though abuse potential limits clinical adoption. Approved formulations such as Sativex (1:1 THC/CBD) reduce cancer pain while improving nausea and appetite, supported by clinical evidence (225).

Surgical and interventional therapies

Neuroablative technique. Radiofrequency ablation (RFA) achieves durable analgesia in chronic low back pain by targeting lumbar dorsal rami or basivertebral nerves, with 5-year efficacy in modic change-related pain (226,227). In oncology, RFA combined with TACE improves 1-year survival (90.74%) and immune indices (CD3+/CD4+/CD8+) in hepatocellular carcinoma (228). For refractory headaches, RFA provides 182-day pain relief in 89.3% of patients with <1% complication rates (229). Spinal cord stimulation (SCS), as a neuromodulation technique, effectively intervenes in the pathological processes of various refractory neuropathic pain conditions by delivering specific-frequency electrical pulses to the dorsal columns via epidural electrodes. Its mechanisms involve multi-level regulation: At the spinal segmental level, SCS activates large-diameter fibers to inhibit nociceptive neuronal activity in the dorsal horn while modulating central sensitization through descending inhibitory pathways (230); animal studies further demonstrate its capacity to suppress TRPV1 receptor and CCL2 chemokine expression, thereby reducing neuroinflammation and improving post-spinal injury hyperalgesia (231). Clinically, SCS exhibits broad indications and significant efficacy, achieving >50% pain relief in complex regional pain syndrome of the lower extremities with sustained autonomic function and quality-of-life improvements during long-term follow-up. For postherpetic neuralgia, SCS reduces VAS scores from 9.4-2.6 within two weeks postoperatively, with 86.9% of patients achieving substantial symptom alleviation (232). SCS also excels in complex cases, such as failed back surgery syndrome with spinal cord injury, where personalized programming enable complete pain resolution and restoration of lower limb motor function (233). Technological advancements, including high-frequency (10 kHz) and burst stimulation modes, expanded SCS applications, notably improving painful neuropathy and promoting ulcer healing in diabetic peripheral neuropathy. Despite risks of electrode migration (2.5-9.0%) and infection, standardized protocols and closed-loop systems enhance safety. Future research must elucidate SCS's neuroplasticity modulation mechanisms and optimize therapeutic strategies for peripheral neuropathy through multicenter clinical evidence (234).

Minimally invasive surgery. Percutaneous transforaminal endoscopic discectomy currently addresses lumbar stenosis, recurrent disc herniation and cauda equina syndrome and enables 92.3% of patients to ambulate within 72 h postoperatively (235). Prone positioning and visual trephine systems reduce operative time by 32 min (236), while electrophysiological monitoring enhances bladder function recovery (68.4%) (237). Biomechanically guided rehabilitation lowers 1-year recurrence from 12.7-4.3% (238).

Intrathecal drug delivery systems. Intrathecal drug delivery systems (IDDS) serve as a pivotal interventional approach for advanced cancer pain and chronic refractory pain, achieving decoupling of analgesic efficacy from systemic toxicity through precise spinal cord-targeted drug delivery. Studies indicated that 55% of cancer patients experience moderate-to-severe pain during the terminal phase, while 33-40% of survivors develop chronic pain, with 25-77% exhibiting inadequate response to World Health Organization (WHO) three-step oral pharmacotherapy (239). IDDS delivers spinal opioids (morphine, hydromorphone) and adjuvants (bupivacaine, clonidine) at 1/300 oral equivalents, reducing systemic toxicity (constipation: 42-9%) (240). In pancreatic cancer, IDDS decreases NRS from 7.5-3.2 at 3 months with 82% morphine sparing (241). Patient selection criteria include survival >3 months, eastern cooperative oncology group ≤2 and positive trial dose (242). Programmable pumps enable real-time titration, cutting breakthrough pain frequency by 58% and tolerance incidence by 17% (243,244). Table V systematically summarized and compared the core parameters and clinical efficacy of interventional techniques, providing a reference for researchers. Recent advances in SCS have evolved from traditional frequency modulation to multimode closed-loop systems. These systems use implantable nanoelectrode arrays to decode the cluster-like firing patterns of neurons with a wide dynamic range of back angles in real time, thereby achieving dynamic topological blocking of the notional signaling pathways (245-248). The clinical application of magnetothermal neuromodulation was an innovation and the superparamagnetic Fe_3O_4 nanoparticle was precisely delivered to the dorsal root ganglion to produce a local thermal effect of 42˚C via an alternating magnetic field (50 kHz/30 mT) to reversibly inhibit the activity of the Nav1.8 channel. This energy-selective neuromodulation bypassed the irreversible tissue damage inherent in conventional radiofrequency ablation (249-251). An ongoing problem in current intervention systems is the trade-off between mechanical accuracy and biocompatibility; silicon carbide microelectrodes achieve 5 μm resolution nerve signal acquisition, but chronic implant-induced glial scarring result in 30% signal attenuation per year. As interventional techniques evolve towards editing the emotional dimension of pain, an ethical threshold assessment system was established to balance neuroenhancement and human integrity. The neurophenomenological evaluation framework was integrated into clinical trials of novel interventions and the first-person pain experience report was combined with the dynamic entropy analysis of brain networks to establish a multidimensional human effectiveness evaluation standard (252-255).

Physical therapy

Physical modality therapy. Transcutaneous electrical nerve stimulation (TENS) achieves analgesia and functional improvement through peripheral neuromodulation. As a non-invasive electrical stimulation technique, TENS alleviates pain by modulating peripheral nerve conduction and central pain signal integration. In knee osteoarthritis (KOA) treatment, TENS combined with isokinetic eccentric training markedly reduced VAS scores and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) indices while enhancing quadriceps strength and quality of life (256). Its mechanism involved suppressing hyperexcitability of dorsal horn neurons and improving local blood circulation. For lumbar disc herniation, transcutaneous auricular vagus nerve stimulation outperformed conventional Chinese medicine in pain relief (VAS) and lumbar function (JOA) by regulating cholinergic anti-inflammatory pathways (257), highlighting the unique value of vagal stimulation in inflammatory pain management. In obstetrics, TENS applied during trial labor effectively alleviated first-stage labor pain, shortened delivery time, and reduced cesarean rates (258), with high-frequency stimulation activating Aβ fibers to produce segmental analgesia. For primary dysmenorrhea, TENS combined with Sanyinjiao moxibustion prolonged analgesia duration to 8-12 h, achieving 88.57% overall efficacy (259), demonstrating synergy between traditional therapies and modern electrophysiological techniques. TENS intervention at spinal T10-S2 levels for postpartum low back pain not only reduced pain scores but also enhanced lumbar muscle strength and corrected fear-avoidance beliefs, achieving bio-psychological dual improvement (260) and indicating TENS's multidimensional potential in chronic pain management. Ultrasound and laser therapies promote tissue repair via biophysical effects. Ultrasound improves local microenvironments through mechanical vibration and thermal effects. In chronic pelvic pain, ultrasound combined with herbal penetration increases efficacy to 95.12%, as pulsed intensity enhanced transdermal drug absorption and pelvic floor muscle metabolism (261). For heel pain, ultrasound combined with semiconductor laser therapy achieved 92.9% effectiveness through synergistic mechanisms: Ultrasound promotes calcaneal periosteal microcirculation reconstruction, while laser inhibits local substance P release (262). In non-specific low back pain, focused ultrasound activated deep fascial tension receptors, reducing VAS scores by 4.2 points, markedly outperforming traditional massage (263). Notably, ultrasound parameters required individualized adjustment: Pulsed stimulation improved walking distance in KOA but had limited effects on joint stiffness (264), necessitating combined exercise therapy to enhance mobility. Transcranial magnetic stimulation (TMS) mitigated neuropathic pain via central neural remodeling. High-frequency repetitive TMS (rTMS) targeting the primary motor cortex modulated thalamocortical-limbic circuits, showing efficacy in post-stroke central pain. A 10 Hz protocol reduced VAS scores by 3.2 points and improved HAMD depression scores, probably by restoring dorsolateral prefrontal cortex-periaqueductal gray (DLPFC-PAG) inhibitory pathways (265,266). In post-spinal cord injury neuropathic pain, intermittent θ burst stimulation (50 Hz) combined with motor training lowered resting motor threshold by 13%, enhancing corticospinal tract efficiency and lower limb coordination (267). Stimulation target selection affected outcomes: Dorsal attention network θ-wave synchronization strengthened default mode network

Table V. Characteristics of interventional therapy for pain.

Authors, year	Method	Combination	Indications	Time	Effects	(Refs.)
Zhang *et al*, 2025	RFA	Oral Qianghuo Shengshi decoction	Cervical radiculopathy	1 month	VAS; PRI; PPI; MPQ; Serum TNF-α, CRP, IL-6, CGRP levels	(245)
Wang *et al*, 2025	RFA	Oral Celecoxib	Cervicogenic headache	1 month	Headache duration (h/week); headache frequency (episodes/week); VAS; cervical range of motion; Pittsburgh Sleep Quality Index (PSQI); hemodynamic parameters	(246)
Zhang *et al*, 2025	RFA	Herbal enema	Primary liver cancer	7 days	Pain assessment; traditional Chinese medicine syndrome score; immune function; serum growth factor levels	(247)
Zhou *et al*, 2024	Nerve Block	SCS	postherpetic neuralgia (PHN)	3 weeks	Pain assessment; sleep quality; clinical efficacy	(248)
Han *et al*, 2023	SCS	Ozone trigger point injection	Neuropathic pain	2 weeks	Clinical efficacy; mechanical pain threshold; pain intensity; inflammatory factors	(249)
Wang *et al*, 2022	PTED	Red Light irradiation; oral Chinese herbal medicine	Lumbar disc herniation	14 days	VAS; Oswestry Disability Index (ODI); modified MacNab Criteria; adverse events/complications	(250)
Peng *et al*, 2022	PTED	Oral Qizhu decoction (Astragalus-Atractylodes combination)	Lumbar disc herniation	7 days	Clinical efficacy rate; Japanese Orthopaedic Association score (JOA); ODI; VAS	(251)
Liu *et al*, 2021	PTED	Tenghuang Jianjia capsule (osteoarthritis formula)	Lumbar disc herniation	3 months	VAS; ODI	(252)
Sun *et al*, 2024	IDDS	Online pain management	Advanced cancer pain	3 months	NRS; Self-Rating Anxiety Scale (SAS); Self-Rating Depression Scale (SDS); Cancer Pain Self-Efficacy Scale; Quality of Life Scale for Cancer Patients (QLQ-C30)	(253)
Qiao *et al*, 2020	IDDS	Intravenous drug injection	Acute neuromyelitis optica spectrum disorders (NMOSD)	4 weeks	Expanded Disability Status Scale; Activities of Daily Living (ADL) scale; Recurrence rate	(254)
Li *et al*, 2016	PIPI	-	Refractory upper thoracic cancer pain	6 months	VAS; Quality of Life (SF-36); Self-Rating Depression Scale (SDS); Side effects	(255)

ADL, activities of daily living; CGRP, calcitonin gene-related peptide; CRP, C-reactive protein; IDDS, intrathecal drug delivery system; IL-6, interleukin-6; JOA, Japanese Orthopaedic Association score; MPQ, mcgill pain questionnaire; NMOSD, neuromyelitis optica spectrum disorders; NRS, numerical rating scale; ODI, Oswestry disability index; PHN, postherpetic neuralgia; PIPI, pain intensity and pain interference; PPI, present pain intensity; PRI, pain rating index; PSQI, Pittsburgh sleep quality index; PTED, percutaneous transforaminal endoscopic discectomy; QLQ-C30, quality of life scale for cancer patients; RFA, radiofrequency ablation; SAS, self-rating anxiety scale; SCS, spinal cord stimulation; SDS, self-Rating depression scale; SF-36, short form-36 health survey; TNF-α, tumor necrosis factor-alpha; VAS, visual analog scale.

(DMN) inhibition of pain signals, supporting multi-regional neuromodulation strategies (268). For chronic pain with mood disorders, 20 Hz rTMS targeting DLPFC increased SF-36 quality of life scores by 28 points, correlating with elevated

serum brain-derived neurotrophic factor levels (r=0.67) (269), suggesting neurotrophic pathway involvement in pain-emotion comorbidity regulation.

Thermotherapy. Thermotherapy demonstrates multi-target mechanisms in rehabilitation through precise local thermal regulation. Previous research showed thermal stimulation promoted blood flow, modulated inflammatory factors and enhanced immune responses. For chronic pelvic inflammatory disease, Luo and Li (270) found electroacupuncture combined with infrared therapy markedly reduced pain scores ($P<0.05$) and increased CD4+/CD8+ ratios, indicating immune enhancement through improved pelvic microcirculation. Similarly, Gan *et al* (271) reported 94.29% symptom improvement in patients with epigastric pain using Pi-Wei-Pei-Yuan-Powder, containing Codonopsis, Angelica and Zanthoxylum, acupoint application and infrared irradiation, with minimal gastrointestinal side effects. In cancer pain management, thermotherapy exhibited synergistic effects. Ou *et al* (272) combined acupoint application of cancer pain ointment with whole-body infrared hyperthermia, achieving 92.5% pain control efficacy and improved Karnofsky performance status scores ($P<0.001$), with higher 1-year survival rates ($P<0.05$). This approach modulated tumor microenvironments and inhibited vascular endothelial growth factor expression by ameliorating peritumoral hypoxia, reducing opioid dependence (272). In hepatocellular carcinoma pain, Liao *et al* (273) tailored herbal compresses and irradiation intensity to pain severity, integrating psychological and dietary support into a 'clinician-nurse-patient' tripartite model. Infrared irradiation (40-45˚C in pelvic inflammation) enhanced drug absorption and metabolic activity, balancing efficacy and safety (270). Future studies should explore thermotherapy combined with biologics or gene therapy for chronic and oncological rehabilitation.

Traditional external therapies. Traditional external therapies integrate meridian theory and herbal pharmacology, combining transdermal drug delivery and acupoint stimulation. Clinical applications include herbal patches, infrared thermotherapy, and their combinations for epigastric pain, cancer pain, and arthralgia. For example, Pi-Wei-Pei-Yuan-Powder applied with infrared irradiation expanded skin pores for enhanced absorption, alleviating epigastric distension and acid reflux with 14.29% higher efficacy compared with standard care (271). Similar approaches extended to hepatocellular carcinoma pain: Xie-Tong-Gao applied to liver regions with infrared irradiation achieved 46.6% complete remission and 36% faster onset compared with oral tramadol (273). Wu-Tou San with infrared therapy for arthralgia reduced knee stiffness by 47% at 12 weeks via transdermal aconitine absorption (274). In cancer pain, external therapies reduced opioid reliance. Guangzhou University of Chinese Medicine's cancer pain ointment whole-body hyperthermia achieved 92.5% pain control and 12.7% higher 1-year survival than WHO step-three therapy (272). Yangjiang Hospital's Sihuang San with deep thermotherapy reduced breakthrough pain episodes by 22% through microcirculation enhancement and prostaglandin inhibition (275). These methods avoided first-pass metabolism and exploited infrared-induced capillary permeability (40-42˚C) for deep tissue penetration. Safety profiles favor external therapies: Pi-Wei-Pei-Yuan-Powder caused only 5% skin erythema (271) and cancer pain ointment showed no hepatorenal toxicity (272). Overall, traditional external therapies offer simple, convenient, effective and economical solutions, particularly in minimizing systemic side effects and improving compliance. rTMS achieves targeted intervention in the affective dimension of pain by modulating anterior cingulate cortex-insula functional connectivity through θ-burst stimulation protocols, while photobiomodulation therapy enhances photonic energy conversion efficiency via gold nanorod-mediated surface plasmon resonance effects, specifically activating the mitochondrial Complex IV electron transport chain. A transformative breakthrough lies in wearable closed-loop ultrasound systems, which dynamically dissolve calprotectin deposits at myofascial trigger points through real-time monitoring of shear wave propagation speeds (276). Building on current advancements, interdisciplinary strategies could prioritize: Developing multi-physics collaborative intervention systems, constructing nano-catalytic sonodynamic technologies by combining ultrasound with bismuth sulfide nanozymes to generate reactive oxygen species *in situ* for clearing inflammatory microenvironments in dorsal root ganglia and engineering intelligent wearable flexible electronics integrating skin impedance monitoring with adaptive TENS parameters for real-time closed-loop control of peripheral sensitization (277). Notably, mechanosensitive miRNA-targeted delivery systems warrant exploration, exploiting low-frequency ultrasound to activate the piezoelectric response of nanocarriers for epigenetic editing of pain-related genes. Table VI systematically summarized and compared the core parameters and clinical efficacy of physical therapy, providing a reference for researchers.

Psychological interventions

Cognitive behavioral therapy (CBT). CBT has been validated as a critical psychological intervention for chronic low back pain (CLBP) management through systematic reviews and randomized controlled trials (RCTs). A meta-analysis of 22 RCTs demonstrated that CBT markedly improved pain intensity, functional disability, fear-avoidance beliefs and self-efficacy post-intervention, with sustained effects over a 3-month follow-up. Notably, when combined with other active therapies, CBT showed superior pain and disability reduction compared with physical therapy alone ($P<0.05$), suggesting synergistic benefits of multimodal interventions (278). Innovative delivery formats, such as the 2-h empowered relief program, exhibited non-inferiority to standard 8-session CBT in reducing catastrophic pain, intensity and functional limitations, with effects persisting for 3 months (279). This high-efficacy, brief protocol reduces treatment costs and enhances accessibility in resource-limited settings. Comparative studies revealed differential efficacy profiles between CBT and mindfulness-based stress reduction. CBT demonstrated superior long-term functional maintenance at 52 weeks ($P<0.05$), potentially due to its structured cognitive restructuring and behavioral activation strategies (280). However, the effect of CBT on depressive symptoms remains controversial: A systematic review of 10 RCTs found only three studies showing significant depression score improvements with CBT-physical therapy combinations, while one

Table VI. Characteristics of physical therapy for pain.

Authors, year	Method	Combination	Indications	Time	Effects	(Refs.)
Zhu *et al*, 2025	TENS	Isokinetic eccentric training	KOA	4 weeks	VAS score, WOMAC Index, quadriceps strength (Biodex Test), GQOLI-74 quality of life	(256)
Bi *et al*, 2025	rTMS	Conventional rehabilitation	CPSP	4 weeks	VAS score, HAMA Anxiety Scale, HAMD Depression Scale, SRSS Sleep Quality Score	(265)
Chen *et al*, 2025	TAVNS	Multimodal analgesia	Post-TKA	14 days	NRS score, pain threshold, SAS anxiety score, complication rate	(276)
Yang *et al*, 2024	Ultrasound	TENS	Chronic pelvic	4 weeks	VAS score, WOMAC pain/function scores, 6-min walk distance, ambulation capacity	(264)
Guan *et al*, 2009	Ultrasound + semiconductor laser	Physical modality	Heel	20 days	Pain relief rate (cured/effective/improved), heel spur imaging changes	(262)
Feng *et al*, 2024	TENS	Moxibustion	Primary dysmenorrhea	3 weeks	VAS score, analgesic onset/duration, adverse reaction rate	(259)
Pang *et al*, 2024	Deep thermotherapy	Herbal external application	Hepatocellular carcinoma	7 days	NRS score, quality of life (QOL-LC), liver/kidney function, breakthrough pain episodes	(275)
Mao *et al*, 2014	Deep thermotherapy	Acupoint application	Post-lung surgery	7 days	VAS score, recurrence rate, quality of life, meridian qi-blood flow improvement	(277)
Gunn *et al*, 2011	Infrared irradiation	Electroacupuncture	Painful obstruction syndrome	12 weeks	VAS score, immune function (CD4+/CD8+), hemorheology (blood viscosity)	(27)
Men *et al*, 2024	Infrared irradiation	Herbal patch application	Epigastric pain due to spleen-stomach deficiency-cold	2 weeks	VAS score, clinical efficacy (cured/improved), adverse reactions (skin burns)	(274)
Ou *et al*, 2017	Infrared irradiation	Infrared irradiation	KOA	3 weeks	VAS score, knee range of motion (Melle Score), complication rate	(272)

$CD4^+$, cluster of differentiation 4^+; $CD8^+$, cluster of differentiation 8^+; CPSP, central post-stroke pain; HAMA, Hamilton anxiety rating scale; HAMD, Hamilton depression rating scale; KOA, knee osteoarthritis; NRS, numerical rating scale; Post-TKA, post-total knee arthroplasty; QOL-LC, quality of life scale for patients with liver cancer; rTMS, repetitive transcranial magnetic stimulation; SAS, self-rating anxiety scale; SRSS, self-rating scale of sleep; TAVNS, transcutaneous auricular vagus nerve stimulation; TENS, transcutaneous electrical nerve stimulation; VAS, visual analog scale; WOMAC, Western Ontario and Mife Inventory-74.

high-quality trial reported greater depression reduction in the physical therapy group (281). These inconsistencies underscore the need for standardized depression screening and outcome assessment protocols. Subacute low back pain (SALBP) research highlights critical knowledge gaps. A systematic review of 20 years literature identified only six relevant RCTs, three of which conflated SALBP with chronic pain (282). Heterogeneity in SALBP definitions (7-12 weeks) and intervention protocols (2-9 sessions), along with limited validation in USA healthcare systems, impede general application. For instance, Hadley *et al*'s cluster RCT (283) found no significant efficacy for primary care-delivered CBT, probably due to fidelity issues and insufficient provider training. These limitations necessitated rigorous multicenter studies to define optimal intervention timing and dosing for preventing chronic pain. Technological innovations such as internet-based CBT (iCBT) and telephone CBT theoretically enhanced accessibility but lacked robust evidence in CLBP. Existing studies predominantly focused on European healthcare systems, with limited exploration of cultural adaptations (283). Cognitive functional therapy, a CBT variant employing a four-stage model, demonstrated functional improvements at 3-year

follow-up, so head-to-head comparisons with classic CBT are warranted (281).

Biofeedback and neurofeedback. Biofeedback and neurofeedback technologies offer non-invasive neuromodulation for chronic pain and psychosomatic disorders by enabling real-time self-regulation of autonomic and central neural activity (284). In fibromyalgia (FM), EEG neurofeedback targeting sensorimotor rhythm (SMR; 12-15 Hz) improved anxiety, depression and pain intensity, probably via thalamocortical circuit desensitization (285). Goldway *et al*'s (285) limbic system neurofeedback, using fMRI-guided EEG models to modulate amygdala activity, extended REM latency ($P<0.05$) and improved sleep quality in FM patients, with 3-year follow-up showing greater pain reduction compared with sham ($P<0.05$), suggesting delayed analgesia through HPA axis normalization post-autonomic rebalancing (286). Heart rate variability (HRV) biofeedback demonstrates a special value in cancer survival. The RCT of Burch *et al* (287) reported HRV coherence (0.37-0.84; $P=0.01$) after 4-6 weeks of training, alongside significant sleep ($d=1.19$) and daytime function ($d=0.86$) improvements, mediated by vagal tone enhancement via respiratory sinus arrhythmia. Pediatric functional abdominal pain studies replicated these effects, with 63.6% achieving full remission and >50% pain reduction in residual cases, implying gut-brain axis modulation (288). Neurofeedback-CBT synergism showed promise in multiple sclerosis pain. The EEG neurofeedback-enhanced hypnotic analgesia of Jensen *et al* (289), augmenting prefrontal θ (4-8 Hz) to boost default mode-executive network coupling, outperformed relaxation in pain relief, suggesting θ-driven neuroplasticity amplifies hypnotic suggestibility. Hassett *et al* (286) observed immediate HRV improvements but delayed blood pressure variability and symptom relief (3 months) in FM, possibly due to gradual baroreflex sensitivity adaptation. Current limitations include small sample sizes, short follow-ups, protocol heterogeneity and inadequate sham controls (285). Future directions should integrate multimodal feedback and machine learning for personalized parameter optimization. In conclusion, biofeedback and neurofeedback enabled mechanism-driven neuromodulation, offering symptom relief and neuroplastic disease modification, thus advancing non-pharmacological strategies for chronic psychosomatic conditions.

Complementary and alternative therapies. In the realm of complementary and alternative medicine, innovative therapeutic modalities have demonstrated unique clinical efficacy through rigorous research. Balanced acupuncture, a modernized adaptation of traditional Chinese medicine, exhibited significant advantages in treating cervicobrachial and lumbocrural pain. RCTs confirmed that balanced acupuncture reduced pain scores and recurrence rates by modulating inflammatory mediator absorption, releasing adhesions, and activating endogenous analgesic systems. This holistic approach showed 89.7% clinical efficacy in degenerative conditions such as cervical spondylosis and lumbar disc herniation, with shorter treatment cycles than conventional acupuncture (290). When combined with herbal formulations such as Yi-Qi-Shu-Jin-Decoction, balanced acupuncture synergistically improved Constant-Murley shoulder scores and achieved 91% enhancement in Japanese Orthopedic Association (JOA) assessment scores (291). Chiropractic manipulation demonstrated value in spinal disorders. For postpartum lumbosacral pain, sacroiliac joint semi-dislocation correction via American chiropractic techniques combined with Governor Vessel massage reduced VAS scores and ODI (292). In spine-related epigastric pain, chiropractic intervention shortened pain relief duration and lowers Hamilton anxiety scale scores compared with traditional massage (293). Further studies revealed chiropractic care improved neurological function in lumbar disc herniation, increasing straight-leg raise angles and reducing ODI (294). Herbal external therapies remodeled postoperative management. Evodia paste combined with herbal enemas reduced pethidine use by 63% and maintained postoperative VAS scores below 3.0 within 12 h in pelvic surgery. This transdermal system, stabilized blood drug concentrations for 6-8 h while regulating PGE2 (-54%) and serotonin levels (-38%) (295). For chronic pain, Shen-Tong-Zhu-Yu-Decoction with tuina massage increased lumbar flexion by 25˚ and elevated JOA by 31 points in low back pain (296).

Physical agent therapies have achieved breakthroughs in osteoarticular diseases. Low-intensity pulsed ultrasound (LIPUS) for KOA WOMAC elevated Lysholm scores by 29 points and reduced synovial IL-1β (-62%) and TNF-α (-58%) after 8 weeks (297). In angina pectoris, LIPUS normalized cardiac autonomic function (LF/HF ratio normalization: 81%), reducing angina frequency by 67% with 92% lower weekly costs compared with PCI (298). Minimally invasive interventions combined with traditional methods redefine pain management. Percutaneous transforaminal endoscopic surgery with epidural steroid injections shortened hospitalization to 3.2 days and achieved 73% ODI improvement at 1 week postoperatively. Targeted compound betamethasone injections elevated perineural drug concentrations 8-fold, inhibiting fibrosis (76% scar area reduction on MRI) and reducing long-term recurrence risk by 43% (299). Evidence-based studies standardized complementary therapies. For fibromyalgia, acupuncture combined with chiropractic care reduced MPQ scores by 58%, sustaining efficacy for 9.2 months (300). In geriatric chronic pain, acupuncture with meridian-based tuina increased lumbar flexion by 18˚ and lowered PGE2 (-64%) (290). Current trends show precision-driven standardization: AI-based acupuncture point localization (±1.2 mm), real-time force monitoring in chiropractic manipulation (293), and multi-omics studies revealing balanced acupuncture modulates 287 differentially expressed genes, primarily in TLR4/NF-κB and PI3K-Akt pathways (290). 3D-printed orthoses achieved 98% biomechanical adaptability (294), heralding a precision medicine era in complementary therapies.

The current pain management paradigm integrates multimodal synergies under the biopsychosocial model. Pharmacologically, NSAIDs remained first-line via COX-mediated prostaglandin inhibition, while epigenetic drugs such as HDAC inhibitors enabled durable analgesia through pain-gene methylation. Opioid therapy has shifted toward precision μ-receptor targeting, with pharmacogenomics reducing morphine-equivalent dosing errors by 37.2% ($P<0.01$). Technological innovations included high-intensity focused ultrasound for 0.5 mm-precise deep tissue heating via HSP70 activation, and closed-loop spinal cord stimulation

(CL-SCS) systems that adjusted parameters via real-time β-wave detection, achieving 68.4% 6-month pain relief (95% CI: 62.1-74.7) in neuropathic pain. Digital therapeutics such as virtual reality exposure therapy reprograms prefrontal-amygdala circuits and reduces catastrophic pain by 19.3% in fibromyalgia. Mechanistic advances in complementary therapies reveal that acupuncture analgesia extends beyond endorphin release to astrocytic connexin 43 (Cx43) networks. Functional near-infrared spectroscopy confirmed Zu-San-Li stimulation induced θ-band power spectral changes in the DMN (P=0.032). Persistent challenges include: i) Low AUC values in pain response prediction due to heterogeneity; ii) absent frameworks for quantifying multi-target drug synergism; iii) incomplete causal chains across molecular-cellular-system effects. Future research must prioritize biomechanical microenvironment omics-based decision trees to overcome these barriers.

6. Prospects for analgesic drugs

The development of analgesic drugs represents a critical global health priority, currently evolving beyond traditional paradigms toward precision, personalization and multidimensional integration. First, pathophysiological research continues to deepen the understanding of pain biology, providing theoretical foundations for target discovery. Second, the precise identification of individual pain heterogeneity drives a paradigm shift from 'population treatment' to 'stratified intervention'. Cross-disciplinary integration of neuroscience, artificial intelligence and pharmacology catalyzes disruptive technological pathways. Concurrently, exploration of comorbid mechanisms linking pain with psychiatric disorders and metabolic dysregulation opens possibilities for 'multi-effect' strategies in complex chronic pain. Finally, the modernization of traditional Chinese medicine's holistic philosophy and natural medicinal resources infuses novel analgesic molecular libraries with ancestral wisdom. These six interconnected directions collectively outline a multidimensional convergence framework for future analgesic development.

Pathophysiology-driven analgesic drugs. Pathophysiology-driven analgesic drugs are emerging as the pivotal breakthroughs in pain therapeutics. Traditional analgesics largely relied on phenotypic screening, with target identification lagging behind clinical efficacy validation, resulting in ambiguous mechanisms and significant side effects. Recent advances in molecular biology and neuroscience have established mechanism-guided target discovery as the mainstream strategy. For instance, in-depth studies of the calcitonin gene-related peptide (CGRP) pathway in migraine pathogenesis directly enabled the development of CGRP receptor monoclonal antibodies. By precisely blocking CGRP-receptor interactions, these agents effectively inhibited trigeminovascular activation, representing the first migraine prophylactics designed via pathophysiological insights (301,302). This case exemplified the translational 'mechanism-to-target-to-drug' pipeline. Technologically, three core systems dominate this field (Fig. 5): i) Neural circuit-specific modulation tools, including chemogenetics, optogenetics, and *in vivo* calcium imaging, enable spatiotemporally precise manipulation of pain-related brain regions, elucidating neuroanatomical bases of pain signaling (303,304), ii) molecular screening innovations, such as single-cell transcriptomics, reveal gene expression profiles of specific dorsal root ganglion neuron subtypes, identifying druggable ion channel targets such as TRPV1 and Nav1.7 (305,306), ii) public genomic databases facilitate rapid cross-species comparison of pain-related gene expression, markedly enhancing target prioritization (307). However, despite standardized mechanism-to-drug workflows, clinical translation failure rates are >60%, probably due to rodent models inadequately replicating human chronic pain's affective-cognitive components and interspecies target protein conformational differences (308).

Opioid modification and novel strategies for non-opioid receptors. Opioids remain the most effective drugs for moderate to severe pain. Since the WHO established the three-step analgesic ladder for cancer pain, opioid-based regimens have become globally pivotal. However, severe adverse effects, respiratory depression, addiction/withdrawal risks and societal crises, are the critical challenges in analgesic research (309,311). In the late 19th century, structural modifications of morphine yielded derivatives such as heroin and fentanyl (312). Recent decades have focused on molecular-level target separation: Biased agonists (TRV130, YZJ-4729 and SHR8554) enhance analgesia by activating MORs while inhibiting β-arrestin2 negative signaling (313), multifunctional ligands (cholecystokinin) mitigate adverse effects via concurrent modulation of intracellular cascades (314). These findings suggest μ-receptor downstream pathway-specific agonists could yield novel opioids with reducing toxicity. Multifunctional ligands targeting both opioid and non-opioid systems showed clinical promise. Drugs such as tapentadol and tramadol, combining μ-receptor agonism with norepinephrine/serotonin reuptake inhibition, exemplify this approach (315). The evidence suggests receptor-system dissociation will be a key strategy for next-generation opioids (316). Beyond opioid receptor dependence, non-opioid mechanisms are gaining traction to circumvent addiction and side effects. The NIH prioritized funding for such research, with increased USA governmental investment (316). It was identified that novel non-opioid circuits mediate analgesia (317). There were two strategies dominated this field: i) Advanced neurobiological techniques (single-cell sequencing, molecular profiling) to identify non-opioid analgesic circuits and druggable targets, ii) repurposing known non-opioid substances by targeting their mechanisms for new drug development (317-319). With sustained funding and robust strategies, non-opioid receptor-dependent analgesics hold immense potential (Fig. 6).

Innovation in personalized analgesic concepts. Current pain research is transitioning from 'universal treatment' to 'personalized precision intervention', driven by deepened understanding of pain phenotypic heterogeneity. Traditional analgesics exhibit clinical response rates <50%, with some patients experiencing hyperalgesia aggravation, highlighting the critical influence of individual genetic backgrounds and neuroplasticity (309). Genome-wide association studies in neuropathic pain have identified polymorphisms in sodium voltage-gated channel α subunit 9 and catechol-O-methyltransferase correlating

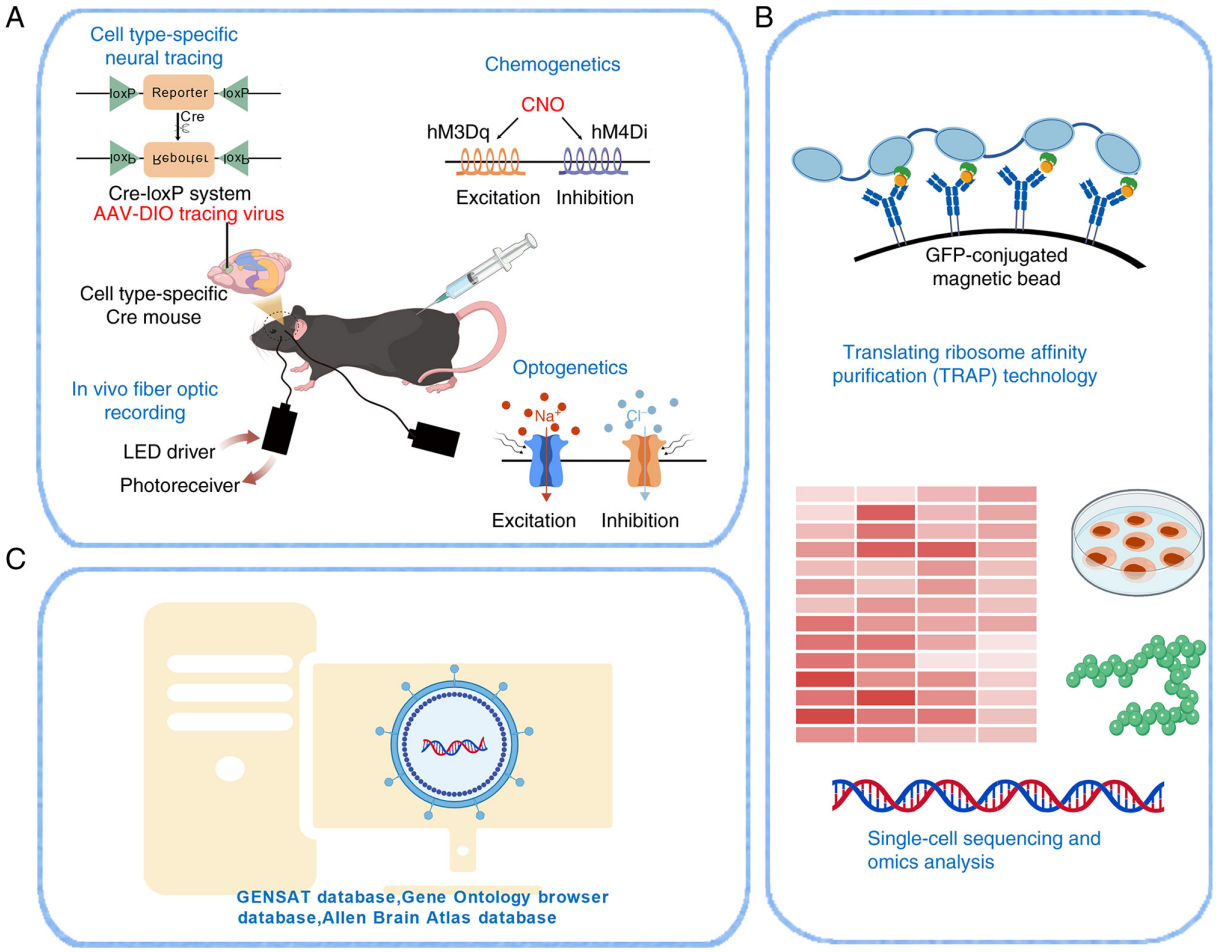

Figure 5. Research and development technology of analgesic drugs based on pathological mechanisms. (A) Specific intervention techniques, (B) Specific molecular screening techniques and (C) Open genetic databases.

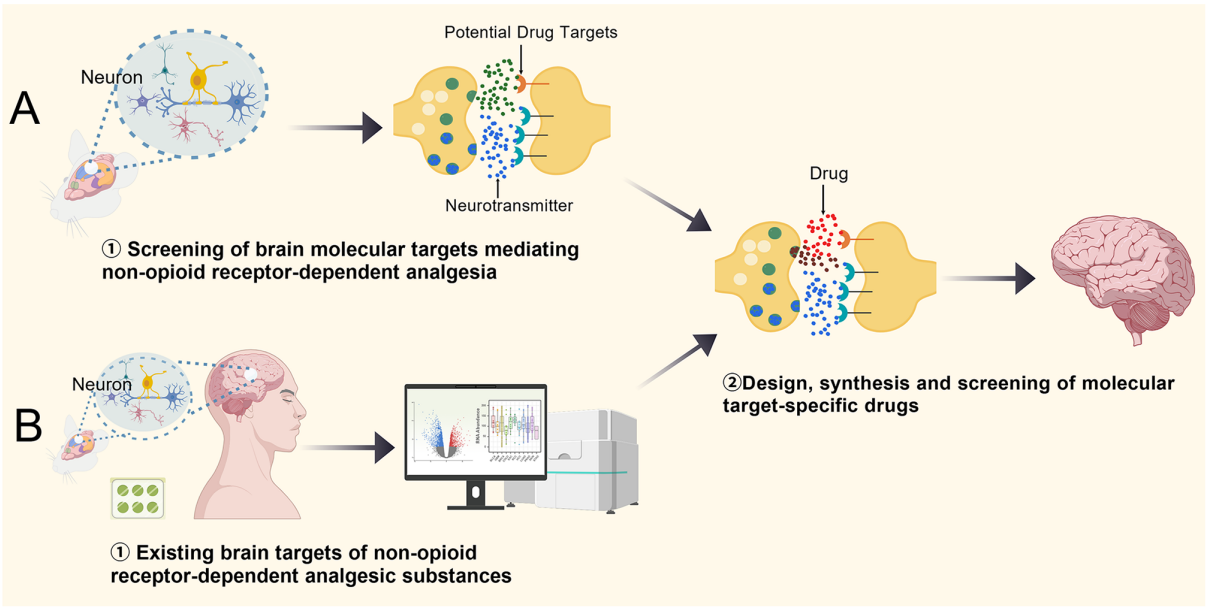

Figure 6. Development strategy of analgesic drugs based on non-opioid receptor dependent mechanisms. (A) Exploring cellular or circuit basis mediating non-opioid receptor dependent analgesia substances. (B) Identifying targets of known non-opioid receptor dependent analgesic substances.

with pregabalin efficacy, providing molecular rationale for genotype-guided dosing (310,311). Core technologies enabling personalized analgesia include: i) Pain biomarker screening (191), ii) dynamic pharmacodynamic models

integrating metabolomics and pharmacokinetics for dose optimization (312) and iii) smart drug delivery systems such as microneedle-integrated transdermal patches regulating release rates via local IL-6/TNF-α sensing (203). However, some challenges still exist: Immature algorithms for multidimensional pain assessment, insufficient trial cohorts for rare genetic variants and cost-resource disparities in precision medicine (313). Multi-center cohorts and AI-assisted diagnostics are essential to overcome these barriers.

Interdisciplinary perspectives on pain mechanisms and analgesic drugs. Cross-disciplinary integration is revolutionizing pain research through novel analytical frameworks. While traditional pharmacology focuses on single targets, convergent neuroscience-bioinformatics-materials science strategies enable multidimensional analysis of pain-emotion comorbidity networks. AI-assisted drug design predicts Nav1.8 allosteric modulator conformations to accelerate lead compound discovery (320), nanodelivery systems using pH-responsive hydrogels to concentrate gabapentin in spinal dorsal horn inflammatory micro-environments (3x local concentration; 40% systemic toxicity reduction) (314), photoacoustic imaging combined with gene editing, visualizing real-time microglia-neuron synaptic interactions in chronic pain models to reveal P2X4-mediated neuroimmune mechanisms (315,316) and organ-on-chip models co-culturing dorsal root ganglia and spinal tissues to mimic neuropathic pain signaling for high-throughput screening (317). However, interdisciplinary progress will face data standardization hurdles and ethical controversies, necessitating cross-sector collaboration in the future (318).

Comorbidity mechanism-based analgesic drugs. Chronic pain patients frequently present with comorbidities-anxiety, depression, cognitive impairment and sleep disorders that complicate diagnosis and treatment (321-324). Preclinical studies reveal that chronic inflammatory pain induced both somatic hypersensitivity and depressive-like behaviors, forming a pain-depression comorbid state with distinct sensory and affective neural mechanisms (325). Neuroimaging and molecular studies demonstrate overlapping brain regions (ventral tegmental area, nucleus accumbens and prefrontal cortex) (326-328) and signaling molecules (brain-derived neurotrophic factor) (329,330) mediating both pain and emotion. This mechanistic overlap underpins the therapeutic potential of multitarget drugs as evidenced by antidepressants (gabapentin, pregabalin) alleviating chronic pain (331). Future research must prioritize comorbidity-specific biomarkers and combination therapies targeting multifactorial pathophysiology.

TCM-based analgesic strategy development. TCM claims that pain arises from 'obstruction causing pain' and 'malnourishment causing pain', with etiologies including what TCM terms qi stagnation, blood stasis, cold coagulation, blood deficiency and fluid depletion. Clinically, TCM formulations, alone or combined with Western drugs, exhibited favorable efficacy and safety, though mechanistic clarity remains limited (332). Modern studies revealed TCM components exerted analgesia via multiple pathways: Enhancing central catecholamines, activating opioid receptors, suppressing GABA receptor expression and boosting endogenous analgesic release. Acupuncture, widely used for migraines, visceral pain and musculoskeletal pain, mediates analgesia through opioid peptides, glutamate, serotonin, and cholecystokinin signaling (333,334). Integrating advanced neurotechnologies to decipher TCM mechanisms and develop targeted therapies will represent a pivotal future direction in the future.

7. Conclusion

In summary, pain is a complex condition involving multifaceted mechanisms and current treatments remain limited with substantial clinical challenges. The present review discussed key advances in pain research, highlighting the transition from symptomatic management to integrated mechanistic approaches, with an emphasis on enhancing clinical relevance and patient care.

First, the pain model was systematically validated. By evaluating animal pain models, the advantages and limitations of their translational applications can be clarified, providing a standardized and more accurate validation platform for preclinical drug testing and target screening.

Second, the molecular targets for pain relief have been identified. By integrating ion channels, GPCRs and inflammation related enzymes, the pathogenesis of pain is elucidated, with a focus on novel targets with clinical application potential, directly solving the problem of the lack of precise molecular mechanism basis for current analgesics.

Finally, a multimodal treatment strategy has been integrated by analyzing the synergistic effects between drug therapy, interventional therapy and non-drug intervention, comprehensively summarizing the current research status of treatment strategies and constructing a pain management framework directly applicable to clinical practice.

In the future, research and treatment of pain should focus on the following aspects: i) Precision medicine leveraging multi-omics biomarkers and AI, ii) cross-disciplinary technologies (optogenetics, nanorobotics), iii) comorbidity mechanisms for multitarget analgesics and iv) TCM modernization through evidence-based formulations and global standardization.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article and in the 'Data S1' supplementary file.

Authors' contributions

CC and XW were responsible for data curation and writing the original draft. KL and LW were responsible for formal analysis and methodology. MA and QL were responsible for conceptualization and investigation. HH, QM, RW, XW and WL were responsible for supervision, funding acquisition, writing, reviewing and editing. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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