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Review Article

Recent advances in pain management

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ABSTRACT

Pain is one of the most common complaints for which patients approach physicians. In spite of this there is a huge unmet need for developing medications for pain that are safe and efficacious. Owing to the heterogeneity of clinical pain and complex pathophysiology, target identification for drug development is difficult. Preclinical models have also proven unreliable for the development of novel analgesics. Recent advances in understanding the physiology of nociception has enabled the development of novel analgesics including abuse deterrent opioids, drugs targeting several receptors, ion channels and enzymes. This review will attempt to cover the physiology of nociception focusing on the novel targets, the challenges in development of novel analgesics and give an overview of the recently developed drugs and those in the pipeline for the management of pain.

Keywords: Nociception, Pain therapy, Recent Advances in pain therapy

INTRODUCTION

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage." Pain is the most common neurological complaint. Pain can be broadly classified as acute and chronic pain. Acute pain is usually a symptom of the underlying disease condition and has a protective role biologically while chronic pain lacks a biological protective role and is a disease condition in itself, presenting with symptoms of refractory pain, functional and psychological impairment, and disability.[1] An annual cost of 560–635 billion dollars is spent in direct treatment costs and lost productivity due to chronic pain causing a huge economic burden to the community.[2]

Pain (including widespread pain syndromes) can be due to inflammation or tissue damage, cancer, or lesions of the nervous system leading to spontaneous pain, hyperalgesia and allodynia. The available drugs like non-steroidal anti-inflammatory drugs (NSAIDS) and opioids with good analgesic efficacy are coupled with deleterious side effects. The adjuvant drugs used like amine reuptake inhibitors and anti-epileptics have poor analgesic efficacy with side effects that decrease the quality of life.

There is an unmet need for the development of novel effective and safe analgesics without abuse liability.

PHYSIOLOGY OF NOCICEPTION

The physiological process by which pain is perceived is known as nociception. Nociceptors have unmyelinated (C-

fibre) or thinly myelinated (Aδ-fibre) axons. Stimulation of afferent Aδ nociceptive fibres causes a sharp, well-localized pain sensation. Activation of nociceptive C fibres is associated with a dull, burning or aching, and poorly localized pain. Their cell bodies lie in the dorsal root ganglia of the spinal cord or in the trigeminal ganglia. The nociceptors express ion-channel receptors (belonging to the transient receptor potential (TRP) family of ion channel receptors) which convert the noxious stimuli into action potentials.

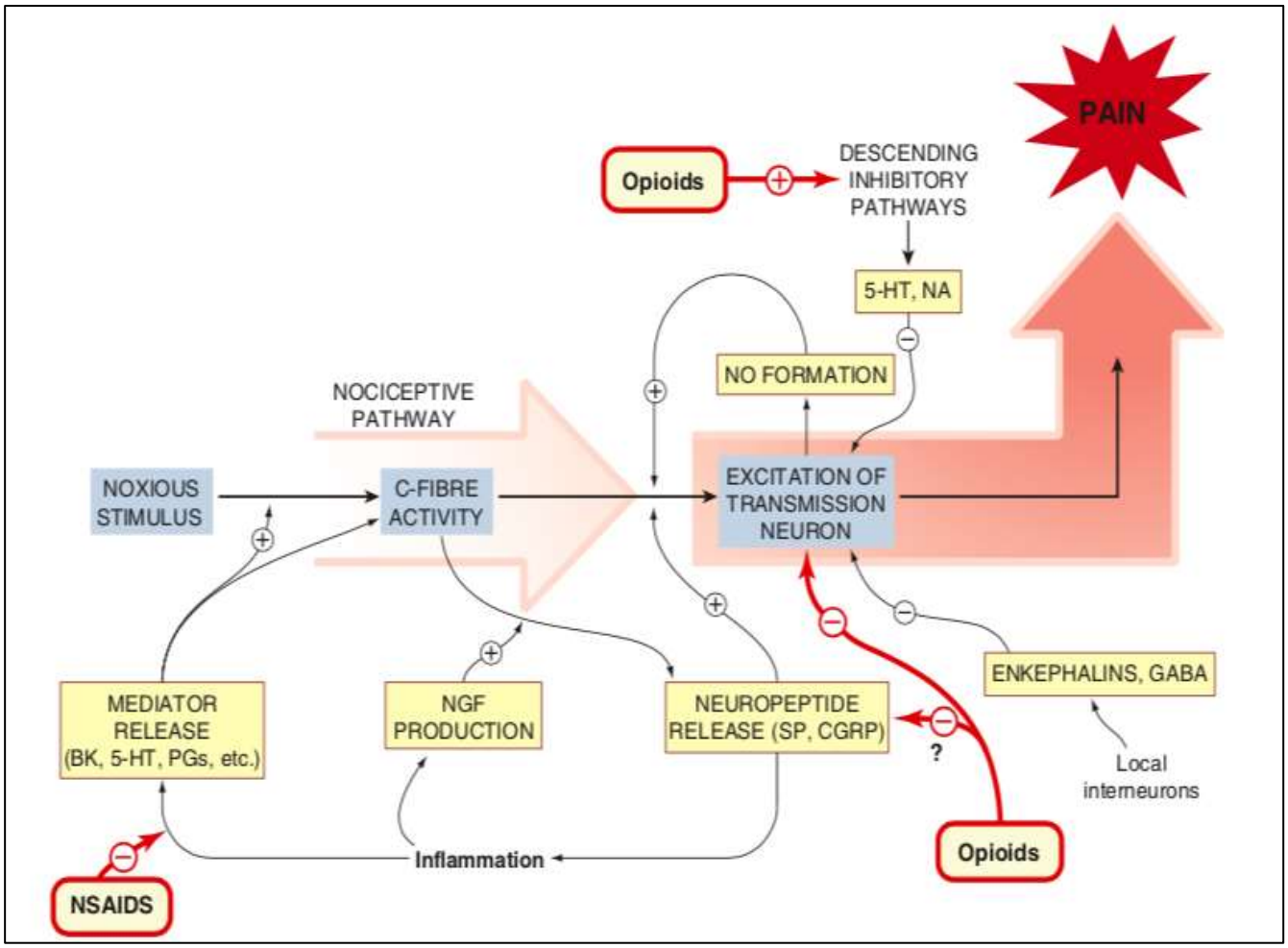

Figure 1: Modulation of nociceptive pathways.[3]

These ion channels are mostly voltage gated sodium channels. Action potentials that result from the transduction of noxious stimuli are conducted along the axon of the sensory neuron into the spinal cord where they synapse on the dorsal horn. Glutamate is released at this synapse. The release of neurotransmitters is modulated by N-type voltage gated calcium channels. The dorsal horn neurons send projections to supra-spinal areas in the brainstem, hypothalamus, and thalamus and then, through relay neurons, to the cortex where the sensation of pain is perceived. Glutamate and substance P are the major transmitters involved in pain transmission.

CENTRAL MODULATION OF PAIN[2]

Synaptic transmission in the spinal cord is regulated by the actions of both local inhibitory interneurons and projections that descend from the brainstem to the dorsal horn. The major inhibitory neurotransmitters in the dorsal horn of the spinal cord are opioid peptides, norepinephrine, serotonin (5-HT), glycine, and GABA. At the level of the spinal cord, cells located in the dorsal horn modulate the sensation of pain. Activation of non-nociceptive afferent fibres may suppress the nociceptive transmission in the spinal cord. This is the basis of "the gate control theory of pain". Descending inhibitory pathways from the brain further modulate pain transmission. The inhibitory pathways include opioid, noradrenergic and serotonergic systems.

CHRONIC PAIN[2]

On repeated painful stimuli to the nociceptors, the threshold for their activation is decreased. This is called

auto-sensitisation. As the painful stimulus continues there is increased membrane excitability. Finally gene alteration takes place leading to prolonged and increased perception of pain with even minor/ no stimulus. This property of the neurons to change is called neuronal plasticity.

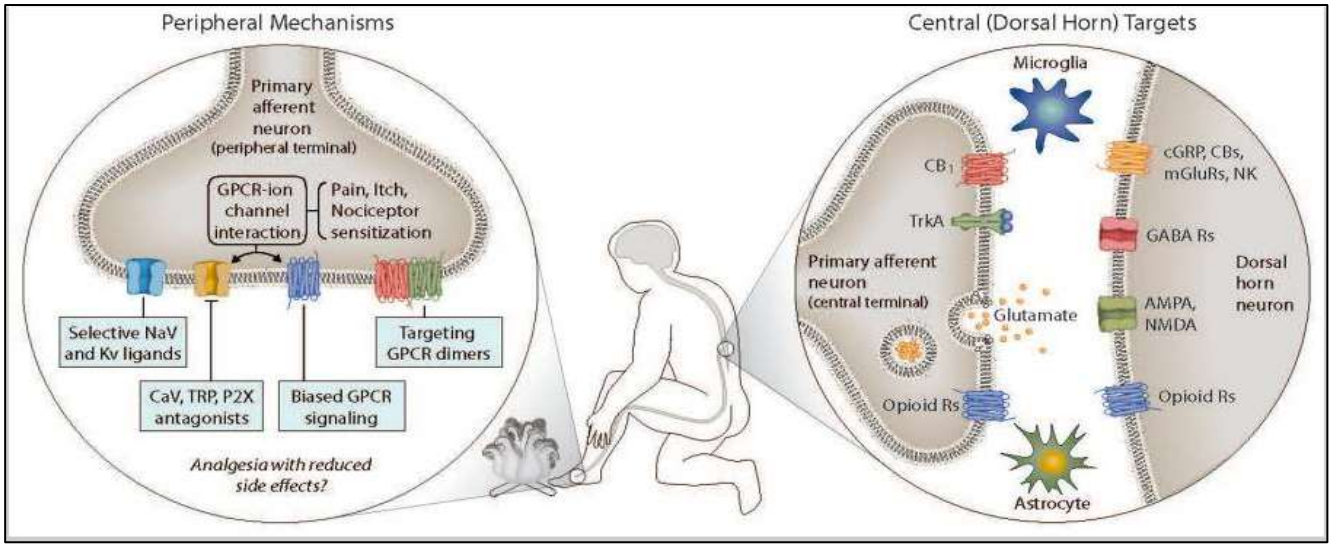

Figure 2: Newer targets being explored for development of analgesics.[4]

DRUGS ACTING ON OPIOID RECEPTOR LIKE RECEPTOR-1 (ORL-1)

ORL-1 is also known as nociception receptor. It is expressed in the central nervous system (CNS). On activation by its ligand nociceptin, it causes closure of voltage gated calcium channels and opening of potassium channels reducing excitability.[5] Cebranopadol is a low selectivity ORL-1 agonist and was found to be as effective as tapentadol and superior to placebo in phase 2 trials. Buprenorphine also has ORL-1 agonist activity.[6]

HISTAMINE RECEPTORS

The H3 receptor subtype (H3R) is an inhibitory autoreceptor located on both pre and postsynaptic neurons. Activation of H3Rs in the skin reduces calcitonin gene-related peptide (CGRP) and substance P release, leading to an anti-inflammatory response. The compound GSK189254 (H3 agonists) was found effective in animal models of neuropathic pain.[5]

DRUGS TARGETING G-PROTEIN COUPLED RECEPTORS

The receptor systems involved in pain pathways include cannabinoid receptors, angiotensin type 2 receptors and α2 adrenergic receptors.

Cannabinoid receptors agonists[7]

The CB1 and CB2 receptors have been investigated as potential targets for management of pain. CB1 receptors have severe psychomimetic effects and abuse potential but CB2 receptors showed promise as analgesics in preclinical trials. Olorinab, a highly potent CB2 agonist has completed phase 2a trials for treatment of visceral pain. Tedalinab, another potent and highly selective CB2 agonist has also shown analgesic and anti-inflammatory effects in phase 1 trials. Other molecules like LY2828360, S-777469, KHK6188 were discontinued for lack of efficacy in clinical trials.

Angiotensin type 2 receptor (AT2R) inhibitors

The AT2 receptors are expressed in the sensory neurons of humans and have been implicated in the development of neuropathic pain. AT2R inhibitors are being developed for the treatment of neuropathic pain. The molecule EMA-401 is now in phase 2b of clinical development. It is being investigated for the treatment of painful diabetic neuropathy (EMPADINE trial) and post herpetic neuralgia (EMPHENE trial).[7,8]

Alpha (α2) adrenergic receptors agonists

α2 adrenergic receptors inhibit the presynaptic release of neuropeptides in the spinal cord and bring about reduction in pain. Phase 2 trials of an inhaled formulation of dexmedetomidine showed efficacy in reducing postoperative pain but was accompanied by adverse effects like hypotension and bradycardia.[5]

Chemokine receptors

Chemokines activate and sensitize the sodium channels and TRPV1 receptors. They help in maintenance of pain. They're also implicated in the causation of opioid

tolerance and opioid induced hyperalgesia. CCR2 receptor antagonist AZD242 was developed and showed promise in preclinical rodent models but did not show any analgesic efficacy in human studies.[5]

DRUGS TARGETING ION CHANNELS

The transient receptor potential vanilloid 1 (TRPV1) channel, voltage gated sodium channels (NaV), calcium channels and potassium channels are expressed preferentially in primary nociceptors. These have been used as targets for development of analgesic agents.

TRPV 1 channels

The TRPV1 channel is activated by the vanilloid capsaicin, noxious heat and low pH and is one of the important receptors involved in nociception. Drugs targeting TRPV1 receptors had 2 main adverse effects-reduced sensitivity to noxious heat leading to accidental burns and increase in body temperature. After the failure of many agents targeting TRPV 1 channels, modality specific antagonists have now been developed. A modality specific antagonist inhibits activation of TRPV1 channels by capsaicin alone without affecting the temperature and pH. The NEO6860 is a modality specific antagonist and has completed its phase 2a proof of concept study.[5,6]

Sodium channels

Voltage gated sodium channels limited to neurons in the peripheral nervous system include Nav1.7, Nav1.8 and Nav1.9. These channels are targeted for development of analgesics as blockade of these channels will bring about pain relief without affecting the central nervous system.

Nav1.7– these channels are found in nociceptors and sympathetic neurons and their loss of function mutations lead to insensitivity to pain. A class of sulphonamide compounds highly selective for Nav1.7 are being tested for analgesic activity. A molecule GDC-0310 is in phase 1 trials. 2 molecules failed to produce analgesia comparable to standard drug treatment and one molecule was withdrawn before recruitment for phase 1 trials was started. Non sulphonamide agents which are less specific for Nav1.7 are also being tested. Vixotrigine is in phase 3 trials for the treatment of trigeminal neuralgia and in phase 2 trials for treatment of erythromelalgia. Another drug funapide is in phase 2 trials for post herpetic neuralgia (topical formulation).[9] The major adverse effect with drugs blocking Nav1.7 is anosmia since these are expressed in olfactory neurons.

Nav1.8- Nav1.8 channels are tetrodotoxin-resistant voltage-gated sodium channels that are expressed selectively in small diameter primary nociceptive neurons making them attractive drug targets. Only 1 drug PF-04531083 entered clinical trials and was terminated in phase 2.

Calcium channels

Voltage dependent calcium channels regulate cellular excitability and mediate release of synaptic vesicles. The commonly used therapeutic agents gabapentin and pregabalin target voltage dependent calcium channels but are effective only in a minority of patients. They act by affecting trafficking and recycling of calcium channel proteins. Newer and more selective agents are under development.

Cav2.2 channels– synaptic transmission in the brain and spinal cord is mediated by Cav2.2 (N-type) calcium channels. These can be blocked selectively by peptides from the venom of cone snails. One of these is ziconotide (synthetic copy of ω conotoxin). Ziconotide is administered intrathecally as a continuous infusion for the treatment of severe chronic pain for whom other treatments have failed. The dosing schedule is 2.4 μg/day titrated upward in increments of 2.4 μg no more than two or three times weekly to the maximum recommended intrathecal dose of 19.2 μg/day.[10] Following this another molecule TROX-1 was developed which was found successful in animal studies with efficacy similar to NSAIDs.[11] The compound CNV 2197944 is also a Cav2.2 blocker which is now in phase 2 clinical trials for the treatment of diabetic neuropathy and herpetic neuralgia.

Cav3.2 channels– these are T-type calcium channels capable of activating central neurons. Blockade of these channels produces analgesia in rats. But none of the molecules have entered clinical testing so far.

Potassium channels

In animal models of hyperalgesia and pain, it has been found that there is a down regulation of potassium channels. Enhancing current through potassium channels can inhibit neuronal activity and produce analgesia. The most promising channels are the Kv7 and K2P family of channels.

Kv7 channels– these are voltage gated channels that modulate action potential firing. The anti-epileptic agent retigabine acts by enhancing the Kv7 channels. Flupirtine– introduced as a non-opioid analgesic is also a potassium channel enhancer has now been withdrawn due to liver toxicity.

K2P channels– are responsible for the potassium conductance that causes the negative resting membrane potential. They exert a strong control over neuronal excitability. These channels are down regulated in animal models of neuropathic pain and nerve injury.

N-Methyl D-aspartate receptor

The N-Methyl D-aspartate receptor (NMDA) receptors are involved in the pathogenesis of chronic pain. They cause central sensitization and long term potentiation leading to

chronic neuropathic pain. Hey are also implicated in the development of opioid tolerance. Non-competitive ion blockers like ketamine are found to be effective but they have psychomimetic adverse effects. Glycine is an agonist that potentiates NMDA receptor action. Glycine antagonists do not cause psychomimetic and neurotoxic adverse effects associated with NMDA receptor antagonists. Glycine antagonists are being developed for neuropathy and inflammation.

ENZYMES AS ANALGESIC DRUG TARGETS

Microsomal prostaglandin E2 synthase 1

Microsomal prostaglandin E2 synthase-1 (mPGES 1) is responsible for PGE2 production during inflammation as the terminal enzyme in the prostanoid pathway, acting downstream of cyclooxygenase. PGE2 is a major inflammatory sensitizer of nociceptors, and mPGES1 inhibition reduces inducible PGE synthesis without suppressing prostacyclin generation.[12] Two mPGES1 inhibitors were developed and they produced analgesia comparable to diclofenac in a guinea pig model of knee joint pain. But human trials have been discontinued. mPGES1 inhibition can be used for the management of inflammatory pain, without the adverse cardiovascular (myocardial infarction) and gastrointestinal bleeding adverse effects of COX2 inhibitors.

NERVE GROWTH FACTOR INHIBITORS

Nerve growth factor (NGF) is a part of a family of neurotrophins and it binds to tyrosine kinase A(TrkA) receptor. Activation of the TrkA receptors at the nociceptive nerve endings results in an increase in TRPV1 and NaV1.8 channel activity. The NGF-TrkA complex plays a role in the development of both inflammatory and neuropathic pain. Humanized anti-NGF antibodies have been developed. The drugs in clinical development are tanezumab, fulranumab and fasinumab.[13-16] Tanezumab has received fast track designation from USFDA for its approval in the treatment of chronic low back pain. Fulranumab and fasinuab are in phase 2 clinical trials.

NICOTINIC ACETYLCHOLINE RECEPTOR AGONISTS

Agonists at nicotinic acetylcholine receptors, based on epibatidine (an alkaloid from frog skin, which is a potent nicotinic agonist) show potent analgesic effects in animal models. They cause release of multiple mediators and also activate descending inhibitory pathways from the brainstem. Epibatidine and tebanicline were developed but were stopped in phase 2 clinical trials because of unacceptable adverse effects.

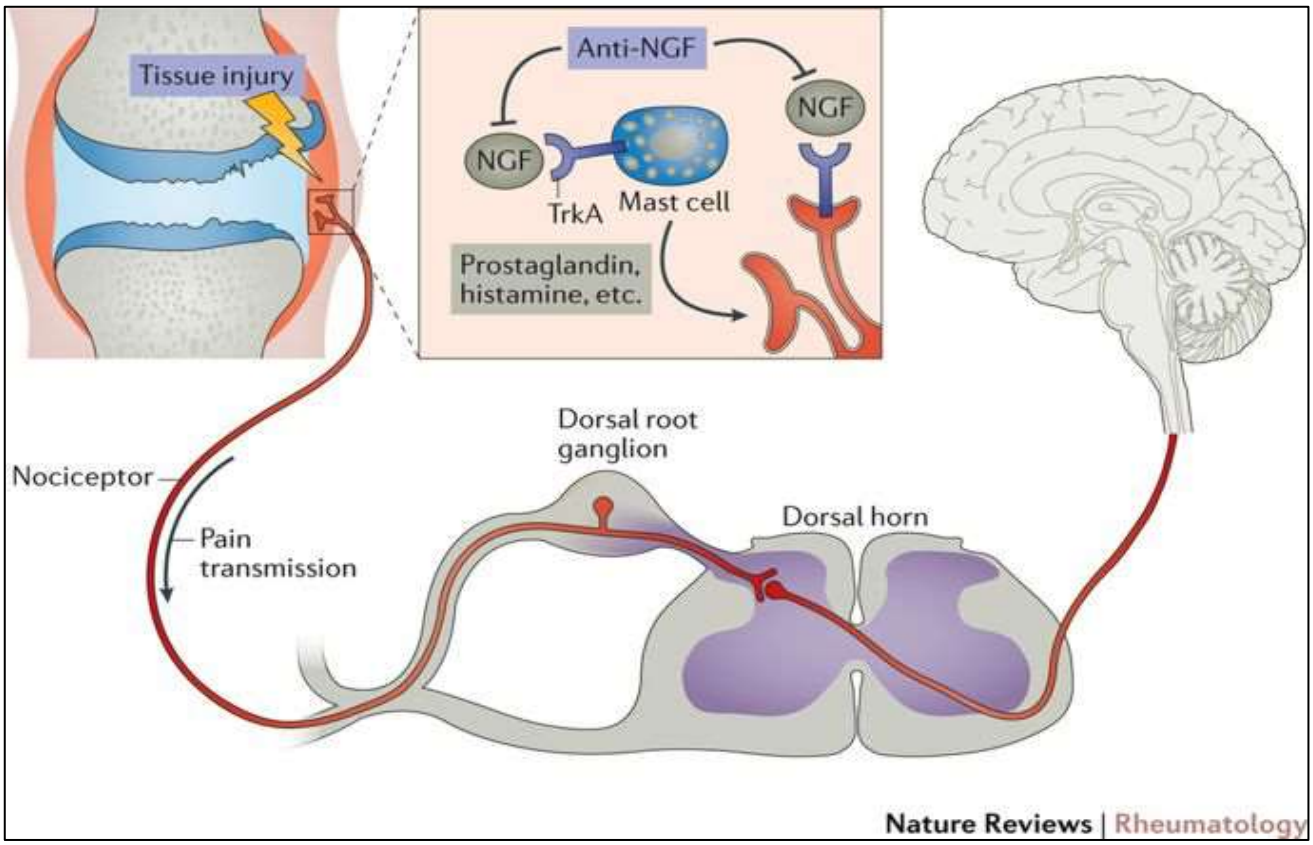

Figure 3: The NGF pathway of nociception.[16]

CHALLENGES IN THE DEVELOPMENT OF NOVEL ANALGESICS

Pain is a subjective experience that is influenced by various factors. To convert that into objective scores that is comparable between subjects is not simple. There are high levels of placebo and nocebo responders in chronic pain trials, this serves as a confounding factor. There are no predictive biomarkers for pain or target engagement. Improvement in these areas is critical to improve trial designs. Also the preclinical models most commonly used are rodents. The response to noxious stimuli evoked in lower animals may not be relevant in clinical pain conditions. Many of the pain models are not good surrogates of human diseases. Because of these reasons many molecules which showed good preclinical efficacy could not be replicated in human clinical trials.

INTERVENTIONAL PAIN MANAGEMENT[2]

The commonly used interventions for pain management include: nerve blocks like occipital nerve block, sphenopalatine ganglion block for headache and facial pain, coeliac plexus block for pancreatitis, epidural corticosteroid injection for radiculopathy, percutaneous disc decompression– disc herniation, spinal cord stimulation, motor cortex stimulation and intrathecal drug delivery systems.

Table 1: Receptor targets for novel drugs.

Targets	Drugs
Opioid receptor like receptor-1	Cebranopedal Buprenorphine
Histamine receptors	Gsk189254
Cb2 receptor agonists	Orolinab Tedalinab
AT2r inhibitors	Ema-401
α2 agonists	Dexmedetomidine
Chemokine receptors	Azd242
Trpv1 antagonists	Neo6860
Sodium channel blockers	Vixotrigine Funapide
Calcium channel blockers	Ziconotide
Potassium channel openers	Flupirtine
NMDA antagonists	Ketamine
Microsomal prostaglandin E2 synthase-1	-
Nerve growth factor inhibitors	Tanezumab Fulranumab Fasinumab
Nicotinic acetylcholine receptor agonists	Epibatidine Tebanicline

CONCLUSION

There are several promising emerging targets for the management of pain. There ae challenges in identifying molecular targets and appropriate preclinical models. Trial designs should be more robust to avoid confounding. The target population should also be carefully selected to avoid failure of molecules. Pharmacotherapy should be combined with effective adjuvant techniques and a multimodal management will ensure better management of pain.

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