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Review Article

Neurogenic inflammation as a novel treatment target for chronic pain syndromes

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ABSTRACT

Chronic pain syndrome is a heterogeneous group of diseases characterized by several pathological mechanisms. One in five adults in Europe may experience chronic pain. In addition to the individual burden, chronic pain has a significant societal impact because of work and school absences, loss of work, early retirement, and high social and healthcare costs. Several anti-inflammatory treatments are available for patients with inflammatory or autoimmune diseases to control their symptoms, including pain. However, patients with degenerative chronic pain conditions, some with 10-fold or more elevated incidence relative to these manageable diseases, have few long-term pharmacological treatment options, limited mainly to non-steroidal anti-inflammatory drugs or opioids. For this review, we performed multiple PubMed searches using keywords such as "pain," "neurogenic inflammation," "NGF," "substance P," "nociception," "BDNF," "inflammation," "CGRP," "osteoarthritis," and "migraine." Many treatments, most with limited scientific evidence of efficacy, are available for the management of chronic pain through a trial-and-error approach. Although basic science and pre-clinical pain research have elucidated many biomolecular mechanisms of pain and identified promising novel targets, little of this work has translated into better clinical management of these conditions. This state-of-the-art review summarizes concepts of chronic pain syndromes and describes potential novel treatment strategies.

1. Introduction

Chronic pain persists past the normal healing period and thus lacks the acute warning function of physiological nociception (Nicholas et al., 2019). The biopsychosocial model recognizes chronic pain as a combination of physical dysfunction, beliefs, coping strategies, distress,

Abbreviations: BDNF, brain-derived neurotrophic factor; CGRP, calcitonin gene-related peptide; CNS, central nervous system; EMA, European Medicine Agency; FDA, Food and Drug Agency; Glu, glutamate; IL, interleukin; JAKs, Janus kinases; mAbs, monoclonal antibodies; NK-1, neurokinin-1; NMDA-Rs, *N*-methyl-D-aspartate receptors; MrgprB, Mas-related G-protein–coupled receptor; NGF, nerve growth factor; NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; PNS, peripheral nervous system; RPOA, rapidly progressive OA; SP, substance P; $T_{1/2}$, long plasma elimination time; T_{max}, maximal concentration; TNF, tumor necrosis factor; TrkA, *tropomyosin receptor kinase A*.

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illness, behavior, and social interactions (Gatchel et al., 2007; Meints and Edwards, 2018). One in five adults in Europe may experience chronic pain (Breivik et al., 2015), and the scarcity of new and effective analgesics has an ongoing individual impact. It is also noteworthy that the new International Classification of Diseases (ICD-11) has now included chronic pain as a separate entity. Significant disease burden, absences, loss of work, early retirement, and high social and healthcare costs are important effects, as well. Given the biopsychological nature of chronic pain, management is challenging and requires a multidisciplinary approach including psychological, sociological, and pharmacological interventions or physiotherapy to improve quality of life (Kerns et al., 2011). The four main unmet needs related to chronic pain are awareness, prevention, efficacious therapies, and multimodal plus interdisciplinary care. Several therapeutic strategies focus with limited scientific evidence solely on targeting anatomical structures. Although basic science and pre-clinical pain research have elucidated many biomolecular mechanisms of pain and identified promising novel targets, little of this work has translated into better clinical management of chronic pain. This objective of this state-of-the-art review was to summarize current concepts of chronic pain syndromes and to describe potential novel treatment strategies.

2. Literature search

This review was written with the aim of reporting on the conference, "Pain and Neurogenic Inflammation in Clinical Medicine 2020," organized by the corresponding author of this article. Each author presented the relevant advancements in their field of expertise. Because of the broad scope of the review, we performed multiple PubMed searches using keywords such as "pain," "neurogenic inflammation," "NGF," "substance P," "nociception," "BDNF," "inflammation," "CGRP," "osteoarthritis," and "migraine." In certain instances, the subsections offer broad summaries of a specific topic.

3. Results

3.1. Nociception and development of chronic pain

The pathophysiology of persistent pain includes peripheral and central, neuronal, neuroimmune, and vascular mechanisms. Inflammatory responses are critical in many chronic pain conditions and may contribute to neuropathic and inflammatory pain (Teasell, 2001; Baral et al., 2019). Recently, there has been a significant drive to identify molecular mediators of pain-related functional plasticity leading to chronicity and to understand the interplay between the periphery and the central nervous system (CNS). The pathophysiology of pain is complex, and the CNS plays a crucial role in its development.

Nociceptive afferent neurons are specialized sensory neurons mediating the response to noxious stimuli. Their somas lie in the dorsal root ganglion or trigeminal ganglion. They extend their axons to almost all regions of the body, including deep somatic tissues like muscles, joints, and bones (Pinho-Ribeiro et al., 2017). These neurons are quite heterogeneous in neurotransmitter and receptor expression (Carlton, 2014). They can be classified based on content of neuropeptides, such as substance P (SP) or calcitonin gene-related peptide (CGRP), or expression of the high-affinity nerve growth factor (NGF) receptor *tropomyosin receptor kinase A* (TrkA) or voltage-gated channels (Gold and Gebhart, 2010). Nociceptors respond to noxious events that may lead to tissue damage, and nociceptive sensory neurons are essential for acute and chronic pain signaling in humans. Acute pain has an important protective role, warning the organism of imminent danger, and it can be recurrent because of persistent stimuli. After 12 weeks, assuming that a lesion has healed, acute pain can transition into chronic pain, with more prominent peripheral and central sensitization, and pathophysiological changes in the peripheral nervous system (PNS) as well as in the CNS (Schneiderhan et al., 2017). The resultant pain usually persists beyond its biological usefulness and compromises quality of life (Grichnik and Ferrante, 1991). Chronic pain is not an extension of acute pain but rather a result of persistent nociceptor activation experienced over time (Grichnik and Ferrante, 1991).

Peripheral sensitization can be defined as an increased sensitivity to afferent nerve stimuli following tissue insult or inflammation (Gold and Gebhart, 2010) (Fig. 1). Central sensitization, in contrast, is a condition of the CNS associated with chronic pain development and its maintenance. Sensitization manifests thus as a persistent state of reactivity with a lowered threshold for pain stimuli. This reduced threshold develops because of temporal summation, in which post-synaptic action potentials generated by the same stimulus in the same population of nociceptors add up (or summate), eliciting a stronger outcome (Staud et al., 2003; Rhudy et al., 2011). A further crucial step to sensitization is the "awakening" of "sleeping" nociceptors, which do not respond to thermal or mechanical stimuli in non-inflamed tissues. This "awakening" is termed spatial summation, in which action potentials are generated by the same stimulus in more than one nociceptor (Reid et al., 2015). Together, these mechanisms synergize to cause the psychophysical phenomenon of hyperalgesia, an increase in pain sensation related to thermal or mechanical stimuli. The result also can be changes in pain threshold as well as in the temporal and spatial manifestation of pain.

The mechanisms responsible for central sensitization differ from those triggering peripheral sensitization. Central sensitization results from CNS changes that can alter the response to sensory inputs, even in the absence of noxious stimuli (Latremoliere and Woolf, 2009). Nociceptors are thus a vital bodily defense, providing protective sensitivity to transient threats. The pivotal role of nociceptors for the generation of pain is strikingly obvious in individuals with congenital insensitivity to pain (Nagasako et al., 2003). At first, these individuals manifest with structural small fiber neuropathy and premature death of nociceptors resulting from TrkA mutation, consequently reducing or ceasing NGF signaling through TrkA (Indo et al., 1996). A loss of function mutation in the *SCN9A* gene coding for Nav1.7 voltage-gated channels then also may impede action potential propagation in nociceptive terminals (Shields et al., 2018). Of note, in people with the Nav1.7 channelopathy, no overt structural neuropathy is noted and the ability to detect thermal stimuli remains intact.

3.2. Peripheral nociception, inflammation, and neurogenic inflammation

Peripheral inflammation or injury induces the release of neurotransmitters from central terminals and increases the excitability of neurons in the dorsal horn of the spinal cord, including the upper cervical spinal cord, and in the spinal trigeminal subnucleus caudalis. Once tissue integrity has been breached, the peripheral nociceptive nervous system recruits further lines of defense. In the hyperacute phase of tissue damage, a combination of pro-nociceptive mediators, including prostaglandins, bradykinin, and protons, is released and excites nociceptors through G-protein–coupled receptors or ligand- and temperature-gated ion channels, notably the capsaicin receptor TRPV1 (Schumacher, 2010; Amaya et al., 2013; Gouin et al., 2017). The intensity of the nociceptor discharge is closely related to the magnitude of the perceived ongoing pain (Koltzenburg and Handwerker, 1994; Dubin and Patapoutian, 2010). Nociceptor sensitization sets in after initial excitation (Gold and Gebhart, 2010), and the consequent sensitization of the CNS may also contribute to inflammation. Protein kinases, including ERK and P38 of the mitogen-activated protein kinase family, are involved in the sensitization of both the CNS and PNS. For example, inflammatory mediators activate ERK and P38 in the primary sensory and second order dorsal root ganglion neurons, resulting in posttranslational, translational, and transcriptional regulation. This effect ultimately manifests as inflammatory pain (Ji et al., 2018). Nociceptive neurons and parts of the immune system interact to regulate this sensation of pain. Vascular and non-vascular inflammatory responses following activation of primary sensory neurons orchestrate this phenomenon. The subsequent

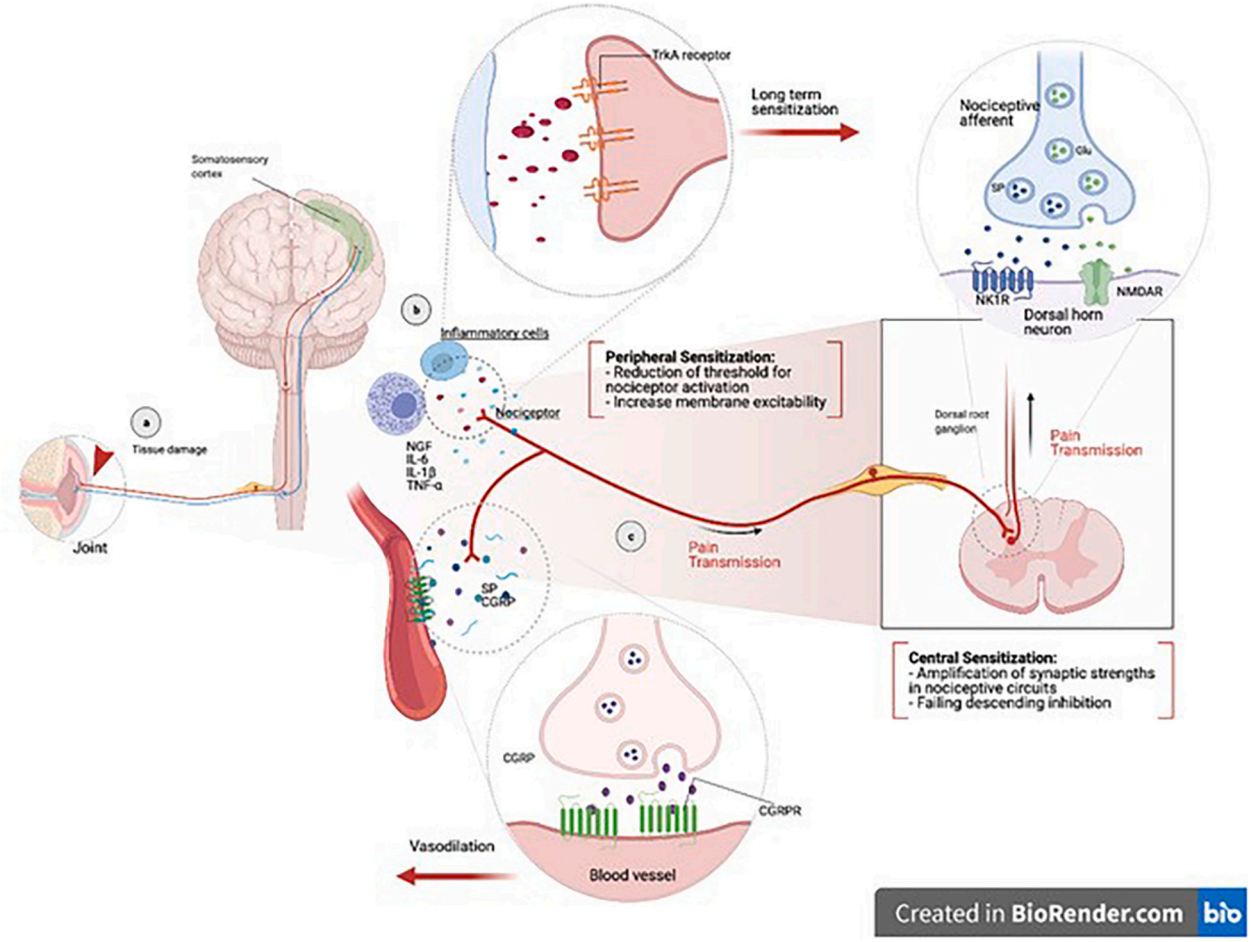

Fig. 1. Principles of central and peripheral sensitization. Nociceptive afferent neurons extend through the spinal cord via the dorsal horn. The dorsal horn integrates information from descending cerebral nociceptive pathways back to the brain after tissue damage or noxious stimuli from the periphery. This injury activates both immune cells and neurons. The former release pro-inflammatory mediators, such as IL-6, IL-1β, and TNF-α, and also NGF. NGF binds to TrkA receptors on nociceptive terminals and leads to long-term sensitization. Nociceptors can also release CGRP after anti-dromal transport following binding to CGRP receptors with consecutive peripheral vasodilation. Nociceptive signals induce neuronal depolarization, and action potentials travel to the CNS after the release of glutamate (Glu) and SP. Because many forms of synaptic plasticity rely on Glu signaling, unsurprisingly, most if not all primary sensory afferents involved in pain signaling rely on this neurotransmitter.

release of vasoactive and inflammatory polypeptides, such as CGRP or SP, from peripheral nociceptive terminals is a pivotal facilitator (Helyes et al., 1997; Geppetti et al., 2008; Iyengar et al., 2017). Repetitively stimulated nociceptive fibers during chronic pain induce anti-dromal transport with the subsequent release of SP or CGRP at the nociceptor. These neurotransmitters activate lymphocytes, mast cells, or macrophages, which then cause further upregulation of inflammation and nociception (Berczi et al., 1996).

Peripheral nociceptor terminals express receptors and ion channels that detect molecular mediators released during inflammation (Pinho-Ribeiro et al., 2017). Upon activation, immune cells further release a number of pro-inflammatory cytokines including interleukin (IL)-5, IL-6, IL-1β, IL-17A, tumor necrosis factor (TNF)α, serotonin, histamine, NGF, and interferon-γ (Aich et al., 2015; Pinho-Ribeiro et al., 2017). These compounds with little excitatory capacity rapidly sensitize the transduction of nociceptors (Schaible et al., 2011; Yam et al., 2018). Persistent inflammation thus results in additional changes in expression patterns in primary nociceptive neurons. In contrast, upregulation of pro-analgesic ion channels and receptors induces downregulation of anti-nociceptive mechanisms (Xu and Yaksh, 2011; Pinho-Ribeiro et al., 2017). Among a vast selection of neuron-associated mediators, NGF is pivotal to triggering this process. This neurotrophin was originally found to regulate growth and differentiation of embryonic sympathetic and sensory neurons (Levi-Montalcini et al., 1996). It also is a pleiotropic molecule in adults, involved in immune system functions, bone metabolism, chronic pain, and CNS disorders such as Alzheimer's disease (Levi-Montalcini et al., 1996; Mufson et al., 2019). Blocking NGF in inflamed tissue can prevent nociceptor sensitization, but neurons treated with NGF (patch clamp) show increased discharge of action potentials (McMahon et al., 1995; Zhang and Nicol, 2004). Overall, blocking the cascade of events resulting from nociceptor activation can downregulate neurogenic inflammation. Despite agreement that this phenomenon contributes to the magnitude of classical signs of tissue inflammation, controversy persists about whether neurogenic inflammation in turn contributes to nociceptor sensitization.

3.3. *The central nervous system and chronic pain*

Different forms of functional, chemical, and structural plasticity lead to the sensitization of the central nociceptive system, with subsequent pain hypersensitivity under both normal and pathological conditions (Woolf and Salter, 2000; Latremoliere and Woolf, 2009). Inflammation and nerve injury can lead to augmented membrane excitability, synaptic efficacy, and reduced inhibition that can eventually alter nociceptive pathway neurons. These functional plasticity changes include structural remodeling and reorganization of synapses with sprouting of the

terminal branches, cells, and circuits (Kuner, 2010; Bushnell et al., 2013). Anatomical and transcriptional changes therefore cement the temporal and spatial summation. Central sensitization can contribute to different types of pain, including neuropathic pain (Yunus, 2007), migraine (Burstein and Jakubowski, 2004), and fibromyalgia (Desmeules et al., 2003).

Among the triggers of central sensitization, a number of neurotransmitters, such as glutamate (Glu), SP, and CGRP (Liu et al., 1997; Chang et al., 2019; Zieglgansberger, 2019), play a central role, acting on post-synaptic neurons of the spinal cord (Kangrga et al., 1990; Westlund, 2006). Because many forms of synaptic plasticity rely on Glu signaling, unsurprisingly, most if not all primary sensory afferents involved in pain signaling rely on this neurotransmitter (Osikowicz et al., 2013; Fernandez-Montoya et al., 2017). Of note, Glu binds to receptors on post-synaptic neurons, and activation of *N*-methyl-D-aspartate receptors (NMDA-Rs) is crucial in initiating and maintaining central sensitization (Woolf and Thompson, 1991). In addition, during the first stages of central sensitization, an increased density and activity of these excitatory receptors can lead to postsynaptic hyperexcitability (Ultenius et al., 2006; Latremoliere and Woolf, 2009).

SP, CGRP, and brain-derived neurotrophic factor (BDNF), together with their receptors, also can contribute to central sensitization. Thus, several molecules released following nociceptor afferent activity can initiate separately or in concert a series of intracellular pathways that may eventually lead to hypersensitivity. For example, the co-release of SP with Glu also participates in central sensitization and thus contributes to modulation of nociception and pain (Salter, 2004; Latremoliere and Woolf, 2009). In addition, SP and CGRP play key roles in a variety of non-neuronal signaling mechanisms at this site (Ren and Dubner, 2008; Ji et al., 2019). The central amygdala, a limbic structure rich in CGRP-binding sites, is activated by direct nociceptive input via the parabrachial nucleus (Neugebauer, 2015; Miyazawa et al., 2018). These afferents bypass the thalamocortical route (Neugebauer, 2015; Miyazawa et al., 2018). Parabrachial–central amygdala synapses release Glu and CGRP, and strong painful stimuli may then preferentially release CGRP (Okutsu et al., 2017). CGRP also significantly increases the amplitude of excitatory postsynaptic currents induced by NMDA-Rs, but not the amplitudes mediated by α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (Hildebrand et al., 2014; Okutsu et al., 2017). CGRP- and SP-induced potentiation of synaptic NMDA-R function is expected to have a potent impact on strengthening the nociception–emotion link in persistent pain (Hildebrand et al., 2014; Shinohara et al., 2017). Of note, the enhanced temporal summation in pain implicates central NMDA-R mechanisms (Price et al., 1994; Vierck Jr. et al., 1997), and administration of the NMDA antagonist ketamine reduces pain and temporal summation (Graven-Nielsen et al., 2000). CGRP receptor antagonists, on the other hand, attenuate noxious stimulation–induced neuronal responses and pain-related behaviors (Hirsch et al., 2013). Despite these important advances in our understanding, these findings have yet to move into clinical translation. However, the notion of the emotional basis of chronic pain opens up a new horizon of opportunities for developing novel treatment strategies.

3.4. Treatment strategies for neurogenic inflammatory pain

Current pharmaceutical regimens for treating chronic pain are mostly limited to symptom management. Only a few compounds such as nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, antidepressants, and anti-epileptics are available to manage pain, frequently with poor efficacies. In part, severe adverse events restrict their long-term use (Hefti et al., 2006). Presenting yet another unrecognized and unmet need in pain management are the emotional and psychological aspects. It is now clear that the chronicity of pain involves learning and psychosocial factors (Boersma and Linton, 2005; Edwards et al., 2016). The limbic system stores autobiographical memories of adverse stimuli with no simple mechanism for erasing them (Engen and Anderson, 2018). Experience-based adoption of dreadful expectancies contributes to contextual fear conditioning (Beckers et al., 2013; Lonsdorf et al., 2017). Opioids, such as morphine, that target the Mu opioid receptor are among the most common treatments for acute pain management, but chronic usage leads to tolerance and physical dependence. Thus, alternative Mu opioid receptor agonists that do not induce tolerance and dependence need to be identified (Berger and Whistler, 2010; Kreek et al., 2019; Miyachi et al., 2021). The opioid crisis in the United States has undoubtedly shown the limits of such therapies, and the need for non-addictive drugs is pressing. Although a recent study has shown that Europe as whole is not facing a similar opioid crisis (Hauser et al., 2021), medicine is facing a "silver tsunami" because the incidence of many degenerative chronic pain syndromes increases with age. For example, osteoarthritis (OA) affects more than 300 million people worldwide, and the problem will become a severe one for medicine in aging societies by the year 2050. Chronic degenerative pain syndromes have a prevalence of 20% and more. Key mediators of chronic pain, such as SP, CGRP, and NGF, are promising candidates for treating neurogenic pain. Targeted therapies against CGRP and NGF, for example, offer novel treatment options for migraine and OA. Below, we discuss in detail the current treatments for these two forms of neurogenic pain.

3.5. Targeting CGRP to treat migraine

Migraine is a chronic, debilitating neurovascular disorder that the World Health Organization has classified as the second most disabling worldwide, with a prevalence of 15%–18% (Group, 2017). Current research also points to a sex disparity in migraine, with a higher prevalence in women, likely because of sex steroid hormone differences (Al-Hassany et al., 2020). Despite intensive research, however, its pathogenesis remains controversial. Migraines have both a vascular and a neurogenic component, including intra- or extracranial vasodilation and the release of vasoactive peptides, such as CGRP (Russell et al., 2014). CGRP consists of 37 amino acids present in two isoforms, α-CGRP and β-CGRP. CGRP and its canonical receptor, a heterodimer consisting of calcitonin-like receptor and receptor activity-modifying protein 1, are widely expressed in both the CNS and the PNS (Ho et al., 2010) as well in the trigeminovascular system (Iyengar et al., 2019). CGRP binding its receptor triggers vasodilation, but whether vasodilation causes migraine or is an epiphenomenon is unclear. Of note, CGRP plasma levels positively correlate with headache intensity and timing (Juhasz et al., 2003), and CGRP intravenous infusion causes migraine-like symptoms in migraine patients (Lassen et al., 2002).

The acute treatment of migraine relies on compounds specifically developed for the disease, such as the triptans (reviewed in de Vries et al., 2020). In contrast, prophylactic treatment has relied on drugs originally developed for other disorders, such as antihypertensive or antiepileptic drugs. Unfortunately, all of these compounds are only moderately effective, with side effects that limit adherence (Kawata et al., 2021). The identification of CGRP as causative in migraine events has led to the development of different therapeutic strategies to specifically treat or prevent migraine. Four monoclonal antibodies (mAbs) targeting CGRP or its receptor have been approved by the U.S. Food and Drug Agency (FDA) or the European Medicine Agency (EMA) for the prophylactic treatment of migraine (Table 1). With their extended time to reach the maximal concentration (T_{max}) and long plasma elimination time ($T_{1/2}$), mAbs have proven to be effective. mAbs are relatively large molecules that usually do not cross the blood–brain barrier, so that they are more likely to act outside of the brain. Sites of action include the meningeal vasculature and certainly also the trigeminal ganglion, which is not protected by the blood–brain barrier (Eftekhari et al., 2015). The results of a recent retrospective longitudinal study suggested that patients discontinued use of prophylactic therapies when they initiated CGRP receptor antagonist therapy with erenumab. Adherence to these novel therapies is higher than to the older medications, suggesting an increased real-world effectiveness (Hines et al., 2021). However, a

Table 1
Current experimental and approved migraine treatments.

Reference	Molecule	Clinical phase	Target	Route of administration
Gepants				
(1)	Rimgegepant (Biohaven)	FDA approval for the acute treatment of migraine	CGRP receptor antagonists	Oral
(2)	Ubrogepant (Allergan/ Abbvie)	FDA approval for the acute treatment of migraine	CGRP receptor antagonists	Oral
(3)	Atogepant (Allergan. Abbvie)	Clinical phase for the prophylactic treatment of migraine	CGRP receptor antagonists	Oral
(4)	Olcegepant	Development phase completed (kinetics and toxicity)	CGRP receptor antagonists	
(4)	Telcagepant	Development phase completed (kinetics and toxicity)	CGRP receptor antagonists	
Antibodies				
(5, 6)	Eptinezumab (Alder/ Lundbeck)	FDA approval for the prophylactic treatment of migraine	Peptide (both a-CGRP and b-CGRP)	Intravenous
(7)	Fremanezumab (Teva)	FDA and EMA approval for the prophylactic treatment of migraine	Peptide (both a-CGRP and b-CGRP)	Subcutaneous
(8, 9)	Galcanezumab (Eli Lilly)	FDA and EMA approval for the prophylactic treatment of migraine	Peptide (both a-CGRP and b-CGRP)	Subcutaneous
(10, 11)	Erenumab (Amgen/ Novartis)	FDA and EMA approval for the prophylactic treatment of migraine	Canonical CGRP receptor	Subcutaneous

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proportion of migraine patients do not experience benefit from CGRP-targeted treatments, suggesting the involvement of other pathways in migraine. A preliminary study has indicated that those who do not benefit from their current CGRP-targeted therapy fare better by switching antibody class, but more rigorous double-blind studies are necessary (Ziegeler and May, 2020).

Gepants are small molecule CGRP receptor antagonists. The development of the so-called first-generation gepants was halted because of pharmacokinetic limitations or hepatotoxicity (Yao et al., 2013), but the second generation appears to be safe and tolerable, with several different compounds (atogepant, ubrogepant, rimegepant) already FDA approved. Zavegepant is currently under clinical investigation for acute treatment or prophylaxis of migraine. Gepants with different pharmacokinetics along with mAbs could provide a continuum between acute and prophylactic approaches. Although these drugs all are effective in prophylactic (mAbs and some gepants) or acute (gepants) migraine treatment, real-life efficacy, long-term safety, and durability of the effects remain to be established.

3.6. Targeting NGF to treat OA

OA affects about 9.6% of older men and 18% of older women (Woolf and Pfleger, 2003). Cartilage degradation is a hallmark of OA, with pain and reduced joint functionality. Treatment of OA pain remains an unmet medical need. This pain probably stems from the inflammatory response and release of inflammatory cytokines, including NGF. Indeed, NGF is present in subchondral bone of the human tibial plateau, cartilage, and synovium in OA and rheumatoid arthritis (Aso et al., 2019). Increased synovial NGF immunoreactivity, along with synovitis and morphological changes in chondrocytes, also has been associated with symptomatic knee OA (Stoppiello et al., 2014; Aso et al., 2020). It has become clearer that the NGF/TrkA pathway has a central role during the development of pain in OA (McNamee et al., 2010; Barker et al., 2020), which has prompted research into therapeutic strategies targeting NGF in both animal studies and clinical trials (reviewed in Wise et al., 2021). Preclinical studies have shown encouraging results.

Although several anti-NGF mAbs have been tested in the clinical setting, only fasinumab is currently in clinical development for treatment of painful lower extremity OA and low back pain (Table 2). Tanezumab is another anti-NGF mAb, but its testing was stopped by the manufacturer in late 2021. Initially, following a proof-of-concept study showing improvement in joint pain and functionality (Lane et al., 2010), tanezumab was administered intravenously with and without NSAIDs (Schnitzer et al., 2015). After the treatment, patients with knee or hip OA had significant pain reduction and improvement in joint function compared to either placebo or NSAID alone. In 2010, however, the clinical development program for anti-NGF antibodies was put on hold after several serious adverse events emerged resembling joint osteonecrosis or rapidly progressive OA (RPOA) in patients treated with higher doses of both NGF antagonists alone or combined with NSAID. A detailed analysis identified most of these events as RPOA. This disorder is considered to be an accelerated form of OA leading to joint replacement. After a second clinical hold because of unclear and suspected peripheral neuropathy, clinical trials were eventually continued. Additional phase III studies with fasinumab and tanezumab were continued with a subcutaneous formulation. As in the previous studies with an intravenous formulation, these results also showed significantly reduced joint pain, but adverse events including RPOA were still present with the

Table 2
Current experimental and approved osteoarthritis treatments.

Ref	Molecule	Clinical Phase	Target	Mechanisms
Small molecules				
(1)	ALE-0540	Pre-clinical phase – tested in L5/L6 ligation model of neuropathic pain (rat)	NGF receptor	Inhibition of NGF binding to TrkA or both p75 receptor and TrkA
(2)	PD 90780	Pre- clinical phase – In vitro testing	NGF	Inhibition of NGF binding to p75 receptor in vitro
(3)	Ro 08–2750	Pre- clinical phase – In vitro testing	NGF	Inhibition of NGF binding to p75 receptor in vitro
(4)	Y1036	Pre- clinical phase – In vitro testing	NGF	Inhibit NGF-TrkA signal transduction pathways in vitro
Peptidomimetic antagonists				
(5–7)	NGF analogs	Pre- clinical phase – In vitro testing	Small monomeric cyclic analogs mimicking β-turn regions of NGF	Inhibition of NGF binding to TrkA
TRK inhibitors				
(8)	K252a	Pre- clinical phase – In vitro testing	Trk	TRK inhibitor
(9)	ASP7962	Phase 2a in knee osteoarthritis	TrkA	TRK inhibitor
Antibodies				
(10, 11)	Tanezumab (humanized antibody)	Clinical trials in hip and knee OA, chronic low back pain	NGF	NGF sequestering therapy
(12)	Fasinumab (fully human antibody)	Clinical trials in hip and knee OA, chronic low back pain	NGF	NGF sequestering therapy
(13)	MNAC13 (monoclonal antibody)	Pre-clinical phase- animal studies (rat)	TrkA	Inhibition of NGF binding to TrkA

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higher dose. The mechanism behind the development of RPOA is not completely understood, and the FDA and EMA both rejected approval of tanezumab for the treatment of OA pain, leading to the termination of the clinical tanezumab program in 2021. However, targeting patients with chronic low back pain and excluding medium to severe OA might be a promising alternative strategy for anti-NGF regimens.

Fasinumab has completed phase II/III studies in patients with knee OA. Fasinumab also resulted in significant reduction in joint pain, with similar incidences of RPOA. Currently, studies with fasinumab at 1 mg every 4 weeks and 1 mg every 8 weeks are underway, and results should be reported soon. In summary, inhibition of NGF by systemic administration of antibodies appears to reduce pain and improve function in individuals with lower extremity OA. If fasinumab is approved, a longer acting non-opioid alternative will be available for the treatment of OA or perhaps chronic low back pain.

3.7. Substance P in chronic pain

CGRP and NGF have been successfully targeted in chronic pain pathologies. In contrast, SP has not been as promising, and the results of studies are variable, preventing definite conclusions. SP is expressed in the spinal ganglion and released after stimulation of primary nociceptive neurons. SP binds the neurokinin-1 (NK−1) receptor found in the CNS (Shults et al., 1984), on the trigeminal and spinal ganglia (Lee et al., 1985; Gibbins et al., 1987; Snijdelaar et al., 2000), and immune cells, such as lymphocytes, macrophages, and mast cells (Schaffer et al., 1998). SP leads to inflammation with vasodilation and edema after repetitive stimulation and anti-dromal transport with release at the nociceptor. In this way, SP causes neurogenic inflammation with recruitment of immune cells and the release of pro-inflammatory mediators (Pedersen-Bjergaard et al., 1991). Genetic studies have pointed towards the role of the SP/NK-1 pathway in the development of pain. For instance, the absence of the NK-1 receptor in mice does not alter the perception of acute pain, but pain wind-up was absent. Furthermore, African naked mole rats have limited SP fibers in the skin (Park et al., 2003) and are not susceptible to some types of pain (Park et al., 2008). Consequently, NK-1 receptor antagonists were developed with the idea of blocking SP neurotransmission (Mantyh, 2002). Although these antagonists showed promising results in animal models, results of clinical studies were disappointing (Borsook et al., 2012). Aprepitant is a SP/NK-1 receptor antagonist approved as an antiemetic drug. Surprisingly, aprepitant did not show attenuation of pain after 2 weeks of treatment in patients with post-herpetic neuralgia or a decrease of sensitization in a human model of electrical hyperalgesia (Chizh et al., 2007). This outcome raised the question of compound specificity in humans. Furthermore, blocking the NK-1 pathway might upregulate other neurotransmitters involved in nociception or activate alternative pathways such as NK-2 or NK-3. Findings of recent study suggest that SP released from primary afferents binds Mas-related G-protein–coupled receptor (MrgprB2) on mast cells, triggering the release of inflammatory mediators as well as immune cell recruitment (Green et al., 2019). Thus, SP-mediated nociception involves not only the NK-1 receptor but also MrgprB2,

suggesting that perhaps the other receptor should be a focus (Navratilova and Porreca, 2019). MrgprX2, the human homolog of MrgprB2, may be a promising new target for chronic pain.

3.8. Alternative targets for pain treatment

Despite our growing understanding of the pain landscape, novel treatment targets are necessary in light of the current scarcity of treatment options. Novel therapeutic regimens targeting more disease-specific key molecules of chronic pain will have to be a focus in neuroscience and interdisciplinary research in rheumatology, neurology, and pain medicine. The lack of disease-specific treatment targets for chronic pain syndromes is in astounding contrast to a "minority" of inflammatory autoimmune diseases with targeted therapies against TNF-α, IL-1β, IL-6, IL-12/23, IL-17, IL-23, CTLA4, CD20, PDE4, or Janus kinases (JAKs) (reviewed in Selmi et al., 2014; Sarzi-Puttini et al., 2019). Animal models of pain and the identification of novel therapeutic targets have led to development of new treatment strategies in the pre-clinical setting, but the translation into the clinic has been disappointing (Yezierski and Hansson, 2018). Nonetheless, evidence is gradually accumulating of beneficial effects in subtypes of pain syndromes. The poor translation between experimental models and clinical condition may trace to the clinical relevance of the model and assessment methods used (Vierck et al., 2008). Several studies also suggest that the inflammatory response has a critical role during neuropathic and inflammatory pain (Teasell, 2001; Baral et al., 2019) by enhancing the expression or release of prostaglandins, sympathetic amines, endothelin, and NGF (Vanderwall and Milligan, 2019). With neurogenic inflammatory pain, target molecules can be related to inflammation itself or to pain, and it is crucial to evaluate the underlying inflammatory mechanisms. One of the mediators of inflammation in pain is TNF-α, a classical pro-inflammatory cytokine that enhances release of second order pro-inflammatory cytokines, such as IL-6 and other mediators, amplifying the inflammatory response (Busch-Dienstfertig and Gonzalez-Rodriguez, 2013). Like several other cytokines, IL-6 exerts its effects through JAK/signal transducer activation (Busch-Dienstfertig and Gonzalez-Rodriguez, 2013). A meta-analysis revealed that JAK inhibitors (tofacitinib) used for joint pain from rheumatoid arthritis improve outcomes, but in several patients, pain persists even when inflammation is contained (Boyce et al., 2016). Patient-reported outcomes such as health assessment questionnaire responses, physical function, and patient assessment of pain showed significant improvements in patients treated with baricitinib alone and in combination with methotrexate as compared to methotrexate alone (Schiff et al., 2017; Taylor et al., 2017).

Therapies targeting inflammation in degenerative chronic pain syndromes have failed thus far. These chronic pain syndromes do not all rely on the same pathways as systemic inflammation, but anti-inflammatory regimens may be beneficial for some chronic pain syndromes. For example, anti-TNF-α antibodies have been tested in patients with knee OA, and the treatment was well tolerated, with a significant improvement in pain (Maksymowych et al., 2012). However, in another clinical trial, pain did not improve in patients with hand OA that had not responded to analgesics and NSAIDs (Chevalier et al., 2015). Thus, further studies are necessary to assess the therapeutic benefits of anti-inflammatory compounds.

Recently, the approach to pain has included revisiting old molecules, such as cannabinoids and capsaicin, and new synthetic compounds. Results of these studies suggest that cannabis and cannabis-based molecules may be effective and improve quality of life in a variety of chronic pain conditions (reviewed in McKenna and McDougall, 2020). Cannabinoid receptors are localized on the sensory nerve, and their dual ability to reduce inflammation and neuronal activity might be a crucial mechanism in modulating neurogenic inflammation and pain. The legal consumption of cannabis and its use for pain management are already approved in several countries, despite limited evidence of their efficacy in pain management (Hauser et al., 2018; Rice et al., 2021). Further clinical studies are needed to properly assess the benefits and pitfalls of cannabis-based therapies in pain management (Perrot and Trouvin, 2019). Another relevant treatment for pain is capsaicin, the active ingredient in chili peppers. Capsaicin targets the TRPV1 receptor, which is prominent on nociceptors containing neuropeptides, and more specifically, it is enriched in nociceptors expressing SP and CGRP (Chung and Campbell, 2016; Wang et al., 2019). Capsaicin may reduce release of neuropeptides that are active at neurogenic pain onset. A double-blind multicenter study recently showed that intra-articularly injected synthetic capsaicin yielded improvement in pain in patients with knee OA (Stevens et al., 2019). Of note, intra-articular injection of capsaicin did not cause side effects, as seen with the subcutaneous or intravenous administration of anti-NGF compounds. However, high doses of capsaicin can desensitize nociceptors, causing the loss of axon terminals (Pezet and McMahon, 2006).

Another emerging therapeutic target candidate for chronic pain is BDNF, a crucial modulator of nociception. Although BDNF expression can contribute to plasticity in spinal neurons during controllable pain, spinal injury or chronic pain can lead to an altered response to BDNF, triggering central sensitization and pain hypersensitivity (Grau et al., 2017). Sustained BDNF levels may show noxious properties with chronic pain (Nijs et al., 2015). Pro-inflammatory conditions in hyperalgesia also can induce upregulation of BDNF (reviewed in Cappoli et al., 2020). A recent study showed that BDNF also plays a role in OA, with synovial expression of the BDNF receptor TrkB associated with higher OA pain (Gowler et al., 2020). However, when administered as a pharmacological treatment in the CNS, BDNF showed anti-inflammatory effects, suggesting an anti-nociceptive role (Cirulli et al., 2000). Antibodies targeting BDNF reduced pain-like behavior in rat and mouse models of neuropathic pain (Zhou et al., 2000; Yajima et al., 2005). In rat models of OA, intra-articular BDNF injection exacerbated pain behavior, whereas sequestration of BDNF with TrkB-Fc antibodies reversed pain (Gowler et al., 2020). These results further indicate the contribution of the BDNF/TrkB pathway in chronic pain and its potential as therapeutic target.

Finally, the latest emerging target for pain is the gut microbiota (Lin et al., 2020). These microbes may modulate inflammatory response–associated pain both in the PNS and CNS and thus offer numerous therapeutic targets for chronic pain (Guo et al., 2019). Therefore, chronic pain management requires multiple treatment targets. Yaksh and colleagues have summarized other potential regimens (Yaksh et al., 2015). Pain management should thus involve a multidisciplinary approach and vision, combining pharmacological therapies with non-pharmacological and self-management strategies.

4. Discussion

Current pharmacological management of chronic pain is mostly symptomatic, not disease-modifying, and shows only limited efficacy and many adverse effects. A common finding is the low effect sizes of all monomodal treatment strategies, irrespective of medical, psychological, or physiotherapeutic approaches. New treatment strategies are urgently needed. At the same time, risk factors for the development of chronic pain are often ignored. In this review, we focused specifically on therapeutic strategies involving neuropeptide mediators of neurogenic inflammation. Research has targeted inhibiting neuropeptides such as CGRP, SP, and NGF or their receptors, with varying degrees of success. As several molecules come into action during neurogenic inflammation and chronic pain, redundancy in these molecules can limit the action of targeted treatments.

Pharmacological regimens, strategies to modify risk factors, and investment in prevention are of paramount importance. Patient education should thus be included in an interdisciplinary pain-management strategy. In addition, identification of new biomarkers could promote the development of new analgesics (Fig. 2). Finally, although most

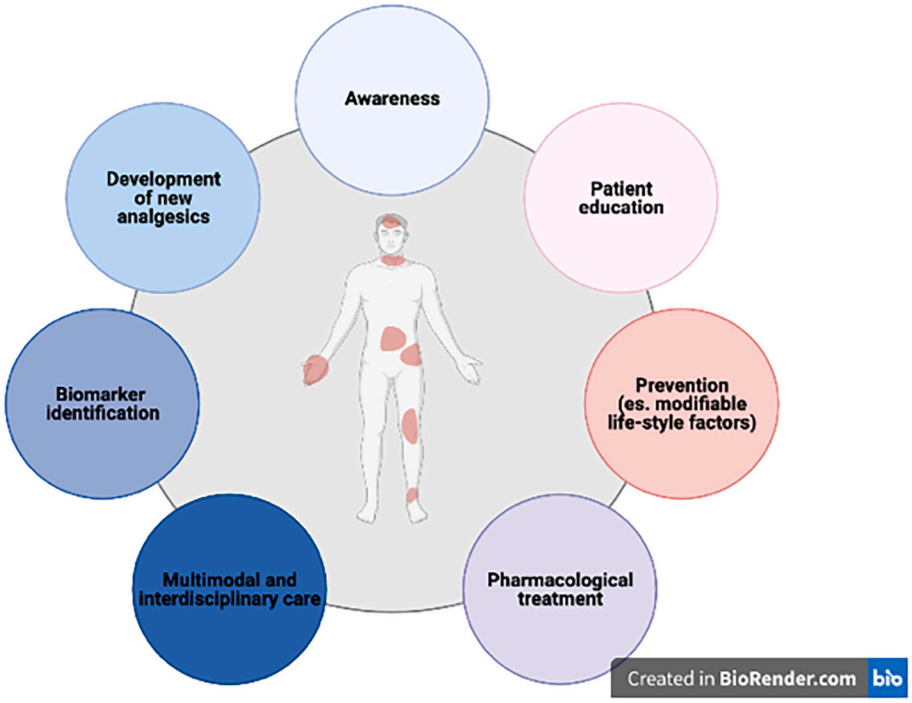

Fig. 2. Patient-centric and interdisciplinary pain-management strategy. Chronic pain management is challenging and requires a multidisciplinary approach including awareness, patient education in self-management approaches, and prevention, along with multimodal and interdisciplinary care that includes physiological, psychological, sociological, and pharmacological interventions. Identification of new biomarkers may also promote the development of new analgesics.

countries offer a limited multimodal and interdisciplinary care for chronic pain, the healthcare system should encourage a holistic and collaborative approach to providing better care to patients suffering from chronic pain. Perseverance in research, education, and advocacy are the main instruments to leverage in improving management for millions of patients with chronic pain.

Author contribution

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