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Novel Pharmacological Nonopioid Therapies in Chronic Pain

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Abstract

Purpose of Review Opioid use and abuse has led to a worldwide opioid epidemic. And while opioids are clinically useful when appropriately indicated, they are associated with a wide range of dangerous side effects and whether they are effective at treating or eliminating chronic pain is controversial. There has long been a need for the development of nonopioid alternative treatments for patients that live in pain, and until recently, only a few effective treatments were available. Today, there are a wide range of nonopioid treatments available including NSAIDs, acetaminophen, corticosteroids, nerve blocks, SSRIs, neurostimulators, and anticonvulsants. However, these treatments are still not entirely effective at treating pain, which has sparked a new exploration of novel nonopioid pharmacotherapies.

Recent Findings This manuscript will outline the most recent trends in novel nonopioid pharmacotherapy development including tramadol/dexketoprofen, TrkA inhibitors, tapentadol, opioid agonists, Nektar 181, TRV 130, ßarrestin2, bisphosphonates, antibodies, sodium channel blockers, NMDA antagonists, TRP receptors, transdermal vitamin D, AAK1 kinase inhibition, calcitonin gene-related peptide (CGRP), TRPV4 antagonists, cholecystokinin, delta opioid receptor, neurokinin, and gene therapy.

Summary The pharmacotherapies discussed in this manuscript outline promising opioid alternatives which can change the future of chronic pain treatment.

Keywords Chronic pain · Pain treatment · Nonopioid

Introduction

Chronic pain is a unique disorder that requires a completely different set of considerations compared to the management of acute pain. Acute pain can be managed by symptom control, whereas chronic pain requires a more specific, targeted pharmacological intervention. The use of opioids as a panacea for all forms of pain has been demonstrated to not be appropriate for chronic pain disorders because it does not address the complex physiologic mechanisms specific to chronic pain. The mechanism of chronic pain disorders is caused by either neuropathic pain, which involves damage to the central or peripheral nervous system, or general dysfunction of pain processing throughout the central nervous system [1]. Various

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mechanisms have been proposed to help explain the pathophysiology of chronic pain including peripheral sensitization to nociceptor stimuli, central sensitization, ectopic excitability, primary sensory degeneration, and disinhibition. Development of pharmacological therapies acting on molecular targets of these mechanisms is promising for drug discovery and future therapy in chronic pain disorders [2].

Additionally, opioid therapy in chronic pain treatment has not been demonstrated to improve function in patients suffering from chronic pain. Multiple studies have cited the total increase in morbidity and mortality associated with opioid therapy in the context of chronic pain [3–5]. Opioid-induced hyperalgesia, a paradoxical effect of treatment, has been cited as a major problem in the long-term use of opioids for the treatment of chronic pain [6]. Many mechanisms of opioid-induced hyperalgesia have been studied and proposed, several of which are closely associated with the mechanisms underlying chronic pain. [7].

Though many recent advances have been made in the area of pain, research funding for pain by the National Institutes of Health for chronic pain has been described as disproportionate considering the level of economic impact and morbidity it causes in the USA [8]. A report by the NIH estimated the 2016 fiscal year research expenditures into chronic pain at $410 million, which is approximately 2.2% of the NIH budget [9]. Clinical trials demonstrating long-term efficacy and safety of opioid use in the context of chronic pain are also woefully lacking, and current research is insufficient to provide strong recommendations in the long-term management of chronic pain with opioid treatment [10–12].

The crisis of pain has reached epidemic levels in many countries around the world and is associated with wide socioeconomic, psychosocial, and public health impact [13, 14]. Accompanying this pain crisis, society has also seen an epidemic of opioid misuse, particularly in North America. The opioid crisis itself has become a great burden with increased rates of mortality and morbidity with opioid overdose rates rising to present times as the leading cause of preventable death in the USA within the last decade [15, 16]. Patients with chronic pain are seen by healthcare providers in every specialty, and much progress has been made in awareness, diagnosis, and management. However, much more is needed to be discovered in improving patient outcomes in pain management. This review is set out to highlight the importance of pain recognition, the undertreatment of pain, molecular targets, and novel pharmacological nonopioid therapies for use in the treatment of chronic pain disorders.

Undertreatment of Pain

The opioid crisis is now at its peak in the USA. In 2016, the DEA announced an order stating that opioid production must decrease by 25% in the year 2017. As healthcare providers have long depended on opioids to treat patients that experience pain, it remains possible that this DEA-enforced decrease in the availability of opioids could trigger an opposing effect: undertreatment of pain. Several population groups are at an increased risk of experiencing pain and its consequences as well as receiving inadequate treatment for pain. Studies have routinely demonstrated that women, children, the elderly, and ethnic and racial minorities are regularly those more affected by undertreated of pain [17]. Women have a greater prevalence of chronic pain than men, and they are more likely to be undertreated for this pain as a result of misdiagnosis, delays incorrect diagnosis, and a higher incidence of poorly understood disorders of chronic pain like fibromyalgia. Women are also more likely to suffer from comorbid conditions that exacerbate pain like depression [17].

Children can also be undertreated for pain. They require a modified pain control regimen compared to adults, and unfortunately, healthcare providers lack sufficient evidence-based recommendations for children's dosages for many analgesic medications. Improper pharmacologic treatment can result in the undertreatment or overtreatment of pediatric pain [17]. The elderly are also at increased risk for inadequate pain control. Data from studies of long-stay nursing home residents (LSNH) have shown that more than 40% of LSNH residents experience persistent pain and that a fifth of these patients are not medicated at all despite their pain [18].

Regarding ethnic and racial minorities, physicians often prescribe lower doses of pain medications to African American patients compared to white patients with similar self-reported pain levels. Lower rates of clinician-assessed pain evaluations and higher rates of inadequate pain treatment have been found for African Americans across all different types of pain. Elderly African Americans with cancer pain in nursing homes were found to have a 63% greater likelihood of receiving no analgesic medications than their white counterparts. Hispanics are at an increased risk for both pain and undertreatment of pain. This has been attributed to overall lower education, lower income levels, higher rates of obesity, lack of health insurance, lack of a dependable income source, limited English proficiency, and resultant poor communication with healthcare providers. Primary interview accounts of Native Americans living in the USA suggest that they are at higher risk of underdiagnosis and undertreatment of pain as a result of cultural practices of minimizing pain complaints [17].

In 2000, in response to growing pressure from both academic and professional healthcare groups advocating for the improvement in pain assessment and treatment, the Joint Commission introduced new standards to address pain management. This resulted in healthcare providers implementing a protocol that promoted quantitative assessment of patient's self-reported pain and a greater emphasis on achieving

immediate pain relief. This led to increased use of opioids in the hospital setting. Researchers attributed a subsequent rise in trauma center mortality rates to overuse of opioids and sedatives as a result of compliance with the new standards [19].

The Joint Commission revised their pain standards in 2016. Changes included calling for the identification of psychosocial risk factors that potentially influence patients' self-reported pain, increased monitoring of opioid prescribing patterns, encouraging nonpharmacologic pain treatment options, and changes to promote the safe use of opioids both during and after hospitalization [19].

Overall, the undertreatment of pain remains a significant issue, and healthcare providers must remain vigilant in their treatment of patients that experience pain, even when opioids are becoming less available and less widely used. Healthcare providers are increasingly utilizing nonopioid analgesics for their patients, but until recently, NSAIDs and acetaminophen were the most widely known. Several advances have been made to identify novel nonopioid pain medications, and we will discuss them in detail below.

Novel Nonopioid Pharmacological Therapies in Chronic Pain

Although opioids have been the drug of choice for pain management, there are novel nonopioid options that are becoming available. Furthermore, combining drugs with different mechanisms at multiple sites of action could yield better pain relief with fewer side effects. More recently, multimodal analgesia has been developed and involves the use of drugs in an additive or synergistic fashion, including a broad spectrum of action, greater efficacy, better compliance, and a better efficacy/safety ratio. As a result, analgesic combinations are recommended by the World Health Organization (WHO), American Pain Society (APS), and American College of Rheumatology (ACR) and are commonly used in clinical practice. Developing effective analgesics that lack the high abuse potential and serious side effects remains the most pressing need in chronic pain, and the development of new medications and new combinations of drugs is starting to gain traction.

Tramadol/Dexketoprofen

This is a new combination of dexketoprofen (a nonsteroidal anti-inflammatory drug (NSAID)) plus tramadol (an opioid) [20•]. The NSAID dexketoprofen is an anti-inflammatory and analgesic drug. It inhibits both COX1 and COX 2. It is as effective as a double dose of racemic ketoprofen but with a faster onset of analgesia coupled with rapid pain relief. It has both peripheral and central anti-inflammatory activity. Inhibition of prostanoid synthesis is the most important analgesic mode of action. NSAIDs also affect the synthesis and activity of other neuroactive substances that are believed to play an important role in processing nociceptive input within the dorsal horn. They have a better safety profile including a lower risk of GI bleeding. Tramadol, a weak opioid, provides double analgesic activity in the spinal cord as an opioid and, at the same time, on the descending modulatory pathways. Tramadol efficacy for the management of moderate-to-severe pain was found to be comparable to that achieved using equianalgesic doses of parenteral morphine or alfentanil.

Combining these two different analgesics in fixed doses in a single tablet can provide better pain relief than either drug alone [21]. The antinociceptive effect of this combination occurred at doses lower than those necessary for each drug alone. The effective synergistic dose ratio was identified as dexketoprofen/tramadol at 1:3, respectively. A single oral dose of dexketoprofen 25 mg plus tramadol 75 mg provided good levels of pain relief with long duration of action [22]. Its efficacy has been shown in moderate-to-severe acute pain mandibular molar tooth extraction, joint replacement surgery such as total hip arthroplasty, soft tissue surgery, abdominal hysterectomy, low back pain, and osteoarthritis. The adverse event rates are low including mild or moderate nausea, vomiting, or dizziness. Thus, the combination of dexketoprofen and tramadol is rational from both pharmacokinetic and pharmacodynamic standpoints. The increased clinical benefits of this combination are not accompanied by an increase in the number and/or severity of adverse events.

TrkA Inhibitors

Tropomyosin receptor kinases (Trks) are cell surface receptor kinases that are highly expressed in neurons and play an important role in cell signaling. The Trk family is comprised of TrkA, TrkB, and TrkC [23]. Trks play important roles in pain sensation as well as tumor cell growth. All three of the Trks' polypeptides are composed of three distinct topological domains: an extracellular domain, a transmembrane domain, and a cytoplasmic kinase domain. Activation of the receptor occurs when a complementary neurotrophic partner binds with the extracellular domain of these kinases. Binding results in dimerization and subsequent autophosphorylation, thereby initiating the intracellular signaling pathway. One pathway of particular interest of particular interest is the NGF/TrkA pathway because it plays a central role in the biology of chronic pain. Activation of the receptor tyrosine kinase TrkA by NGF triggers intracellular signaling cascades and protein expression that increases the sensitivity of nociceptors leading to chronic sensitization and pain. The NGF produced by target tissues or tumor cells activates TrkA receptors expressed on the terminals of C-fibers. Three categories are known to be important in nociceptive transmission: thin myelinated A-delta fibers, nonpeptidergic unmyelinated (C-) fibers, and peptidergic unmyelinated (C-) fibers. Peptidergic C-fibers

and the majority of A-delta fibers express TrkA, corresponding to approximately 40% of adult DRG cells, and are responsive to inhibition of the NGF/TrkA pathway, which has been validated clinically using NGF-neutralizing monoclonal antibodies that are currently in phase II–III trials for osteoarthritis pain. The small molecule inhibitors of TrkA are an alternative intervention modality for the treatment of chronic pain.

A TrkA inhibitor is used in the treatment of chronic pain such as osteoarthritis, bone cancer or sarcoma related pain, and bone fracture pain. ARRY-470, a TrkA inhibitor, has been shown to significantly attenuate tumor-induced pain [24]. One study reported that early and sustained administration of a Trk inhibitor blocked neuroma formation and sensory nerve fiber sprouting and reduced bone cancer pain-related behaviors by 50–60% [24]. The Trk inhibitor has a 50:1 plasma to CSF ratio; therefore, the antihyperalgesic actions of this drug appear to occur primarily outside the blood brain barrier. It takes around 6–8 h for a full analgesic effect. The drug's safety and efficacy are still being studied.

Tapentadol

Tapentadol extended-release (ER) is a centrally acting opioid analgesic approved for the treatment of severe, chronic pain. It exhibits a dual mechanism of action, one as a mu receptor agonist and the other as a noradrenaline reuptake inhibitor. As both effects contribute synergistically to the ability to control pain, the drug has analgesic efficacy comparable to other strong opioids with greater affinity for the mu receptor, albeit with a seemingly lower incidence of side effects, in particular, the GI effects. The most common reasons for initiating therapy with tapentadol ER were insufficient analgesia, the emergence of adverse effects, and a decline in quality of life. Tapentadol ER might be especially useful in these mixed types of pain. Its use was associated with significant decrease in pain intensity, improved quality of life, increase in compliance rates, and decrease in anxiety and depression rates [25]. The analgesic efficacy and safety of tapentadol for the palliation of cancer pain in adults concluded that pain relief and toxicity were comparable between tapentadol and oxycodone/morphine.

Studies have demonstrated that the treatment therapy with tapentadol should be started at a dose of 25 to 50 mg/day, allowing the use of rescue morphine [26•]. This dose can be gradually titrated up to a maximum of 200 mg. In patients with prior tolerance to opioids, treatment can start at higher doses of 100 to 150 mg/day. The most widely used mean dose is approximately 25–450 mg/day. Conversion ratios for tapentadol ER to oxycodone/morphine/fentanyl are 10:2:3:0.03. Maintenance of pain control during the first week and improved analgesia as tapentadol ER doses can be titrated based on effectiveness and individual tolerance [26•].

Tapentadol has few mild adverse reactions such as dizziness, loss of appetite, and nausea and vomiting. Different studies in patients with the nonmalignant disease have revealed that tapentadol is better tolerated than oxycodone or controlled-release morphine [26•]. Efficacy was similar to oxycodone with better GI tolerability profile than oxycodone and morphine. This favorable side effect profile could make it a suitable option for elderly, delicate, or cognitively impaired patients. Furthermore, tapentadol appears to be correlated with fewer confusion episodes or altered levels of consciousness. Related to its better tolerance profile and efficacy comparable to strong opioids, tapentadol is considered to be one of the alternative options for cancer pain in several clinical practice guidelines. It also showed a reduction in the use of adjuvant treatments, such as paracetamol, anticonvulsants, and antidepressants.

Withdrawal rates appear to be lower than for other strong opioids, such as morphine and fentanyl. Tapentadol in the community is a safe and effective alternative for moderate–severe cancer pain. One study showed that the proportion of patients with anxiety or severe depression decreased from 32 to 8% after 3 months of treatment [25].

Additional benefits in physical well-being and other quality-of-life domains hampered by pain, such as sleep, autonomy, libido, hygiene, self-care, independence, and social activities, were seen. Pain intensity significantly declined from baseline in all. It reduced the use of antidepressants and other psychoactive drugs. In another study, the proportion of patients with suicidal ideation declined from 25 to 8%. Overall, a tendency toward a greater feeling of "substantial improvement" was seen with the use of tapentadol.

Opioid Agonists

CR845 is a peripherally selective kappa opioid agonist that acts by selectively targeting peripheral kappa opioid receptors. It is designed to treat acute and chronic pain and pruritus by its proposed mechanism of action. In a phase 2b, randomized, double-blind, placebo-controlled trial conducted in patients with osteoarthritis of the hip or knee experiencing moderate-to-severe pain [27]. A reduction in mean joint pain scores was observed in all patients with an encouraging safety profile. Hence, there is a significant potential of CR845 as a new therapeutic approach for the treatment of chronic inflammatory pain. Apart from its usefulness in patients with osteoarthritis (OA) of the knee or hip experiencing moderate-to-severe pain, it is also used in patients undergoing laparoscopic hysterectomy or bunionectomy procedures. CR845 treatment resulted in statistically significant reductions in pain intensity and opioid-related side effects. It also decreased the use of rescue medication for pain control.

Another Cara Therapeutics report stated that CR845 was "observed to be well-tolerated, without incurring the

dysphoric and psychotomimetic side effects that have been reported with centrally acting (CNS-active) kappa opioid receptor agonists" [28]. It also lacks the respiratory depression and abuse liability of mu opioid receptor agonists. Three tablet strengths of CR845 include 1.0, 2.5, and 5.0 mg, that should be dosed twice daily over 8 weeks. All tablet strengths are reported to be well tolerated with no drug-related serious adverse events (SAEs). The most common adverse events associated with this drug are dry mouth and constipation. There are no associated clinically significant changes in serum sodium levels.

Nektar 181

NKTR-181 is a long-acting, selective mu opioid agonist. It is the first full mu opioid agonist molecule designed to provide potent pain relief without the high levels of euphoria and is used to treat patients suffering from chronic pain [29]. It is used in the treatment of chronic lower back pain. Patients on NKTR-181 experienced a 65% reduction in pain score when used as twice-daily dosing of NKTR-181 tablets. The effective dose was NKTR-181 (100 to 400 mg twice daily) for 12 weeks. The studies showed sustained pain relief and general improvements in sleep patterns, as well as an overall improvement in quality of life.

NKTR-181 has a novel molecular structure which allows it to have low permeability across the blood-brain barrier. This slows its entry into the brain and attenuates dopamine-associated euphoria. It does not cause euphoria, which in turn, can lead to abuse and addiction with standard opioids. It also has significantly lower abuse potential than oxycodone. The inherent properties of NKTR reduce its rate of entry into the brain compared to standard mu opioids, regardless of route of administration. Thus, NKTR-181 may be a major advance toward safer opioid therapy for the treatment of moderate-to-severe chronic pain.

The US Food and Drug Administration (FDA) has granted the investigational medicine NKTR-181 Fast Track designation for the treatment of moderate-to-severe chronic pain. NKTR-181 is an investigational product only and has not been approved for use by the FDA or any other regulatory agencies.

TRV 130 (Oliceridine)

Oliceridine (TRV130) is a novel μ-receptor G-protein pathway selective (μ-GPS) modulator. It was designed to improve the therapeutic window of conventional opioids by activating G-protein signaling while causing low β-arrestin recruitment to the μ receptor [30].

The dual signaling profile of conventional opioids (activating both G protein and β-arrestin signaling is associated with analgesia but also with adverse events (AEs) that greatly restrict their clinical utility). The most important and prevalent of these AEs are nausea, vomiting, and respiratory effects. AEs associated with conventional opioids frequently have a substantial impact on the treatment of postoperative pain, with potential adverse effects on patient safety, pain control, hospital length of stay, re-hospitalization rates, and overall cost of care.

With conventional opioids, clinicians often face the challenge of finding the optimal balance between pain control and ORAES (e.g., patients with chronic obstructive pulmonary disease, obesity, renal impairment, sleep apnea, or advanced age), an exercise that can be particularly relevant in high-risk patients. A novel therapy with opioid-like efficacy and improved safety and tolerability would, therefore, satisfy an important unmet medical need.

It is used in patients with moderate-to-severe pain following abdominoplasty. A phase IIb study demonstrated that oliceridine produced rapid and meaningful relief of moderate-to-severe acute pain and was well tolerated [31]. Oliceridine treatment produced statistically significant analgesia compared to placebo. Analgesia with oliceridine was similar to morphine over 24 h, and analgesia occurred more rapidly with oliceridine, with greater reductions from baseline.

Oliceridine demonstrated a favorable safety and tolerability profile. Statistically significant differences in the prevalence of nausea, vomiting, and respiratory effects were seen between the oliceridine and morphine groups, with a lower prevalence in patients treated with either oliceridine regimen than in those treated with morphine [31]. The differentiated performance characteristics of oliceridine may be a consequence of biased ligand pharmacology. As a μ-GPS, oliceridine activates the μ receptor in a differential manner, with a preference toward the G-protein pathway (associated with analgesia) over the β-arrestin pathway (associated with ORAEs and inhibition of G-protein-mediated analgesia). Additionally, unlike morphine, oliceridine has no known active metabolites; the latter property may allow for more predictable performance, regarding analgesic efficacy and dose-related ORAEs, that is directly linked to the plasma concentration of the parent compound. These results suggest that oliceridine, by activating G-protein-mediated analgesia and mitigating β-arrestin-mediated ORAEs, may have a wider therapeutic window and offer effective, rapid analgesia with fewer ORAEs.

Oliceridine is an investigational agent not yet approved by the US Food and Drug Administration.

ßarrestin2

The overall response to opioid receptor activation is the result of several signaling cascades. Analgesia is attributed to the Gai/o signaling cascade, while many of the unwanted side effects are attributed to ßarrestin2 downstream signaling. ßarrestin2 is a G-protein-coupled receptor (GPCR) signaling regulator protein. ßarrestin2-mediated signaling contributes to

the undesirable side effect profile of morphine such as constipation, tolerance, and dependence [32]. ßarrestin2 knockout (KO) mice display and enhanced antinociceptive response to morphine treatment plus resistance to developing tolerance to morphine-mediated analgesia as well as reduced levels of opioid-induced respiratory depression, constipation, and dependence [32, 33••]. Further animal models [34] confirmed that rats with attenuated levels of ßarrestin2 from siRNA knockdown showed enhanced analgesia and reduced naloxone-induced withdrawal symptoms [33••]. In an attempt to replicate this KO physiology in a human model, researchers have developed ligands that can activate a specific receptor and induce some but not all of the downstream signal cascades. This is referred to as functional selectivity and is thought to occur by the ligand inducing different conformations of the receptor upon binding. Functionally selective ligands directed at the Mu opioid receptor (MOR) are in development with one, TRV130, currently in phase III clinical trials. Evidence suggesting ßarrestin2 signaling cascade mediates kappa opioid receptor (KOR) associated dysphoria, and aversion has led to further research into ligand-biased ßarrestin2 attenuation at the KOR. Animal models have demonstrated analgesia without the KOR side effects of anhedonia or motor dysfunction. Caveats to these promising findings include the lack of any ßarrestin2-mediated side effect profile attenuation when full MOR agonists or high doses of morphine are used even in KO models. Furthermore, while TRV130 produces analgesia in vivo, it fails to show any attenuation of ßarrestin2 recruitment in vitro. This suggests that adverse side effects may be downstream of and not directly mediated by ßarrestin2. Also, results from an earlier phase II trial of TRV130 failed to demonstrate a reduction in the opioid-associated side effects [33••].

Bisphosphonates

Bisphosphonates (BPs) have a potential role in the treatment of pain associated with complex regional pain syndrome type I (CRPS-I) [35]. Through a yet-to-be-determined mechanism, BPs have demonstrated efficacy in long-term pain management associated with CRPS-I. CRPS-I is characterized by pain, usually in an extremity, that develops following a traumatic injury or insult to that extremity. Animal studies suggest that the release of inflammatory neuropeptides and cytokines acts as both an inciting and sustaining event in the disease pathophysiology. CRPS-I is characterized by a reduction in bone density and demineralization of the bones in the affected limbs. While BPs do reduce bone resorption by inhibiting osteoclastic activity, studies have demonstrated that the associated bone loss is unrelated to increased osteoclast-mediated bone resorption. It follows that the role of BPs in moderating the clinical manifestations of CRPS-I is not due to BPs' antiosteoclastic properties, but likely by a more complex interaction between BPs and biochemical events inciting and sustaining the syndrome. Randomized controlled trials have demonstrated IV alendronate, clodronate, pamidronate, neridronate, and oral alendronate to be effective in reducing overall pain and improving the quality of life in patients with CRPS-I when compared to placebo. While promising, these studies have their limitations. The population sizes have been small, with the largest study including only 82 people. Additionally, there were no standardized criteria for the diagnosis of CRPS used by the studies. Of significance, because most of these studies included patients with longstanding CRPS-I, the potentially confounding interaction between the efficacy of BPs and the duration of the disease could not be properly assessed. This is of importance in understanding the mechanism of BPs in the disease process because the rate of uptake of BPs by the skeleton varies throughout the course of the disease, with the most uptake occurring in the later stages and by a mechanism likely different from that seen in the earlier stages [35].

Antibodies

Nerve growth factor (NGF) is a neurotrophin released from peripheral tissue following a noxious stimulus (tissue-damaging event). NGF binds tropomyosin-related kinase A (trkA), a tyrosine kinase receptor that is selectively expressed on C-fibers and Aδ peripheral nerve terminals. Binding leads to internalization of the NGF-trkA complex and retrograde transport to the dorsal root ganglion cell bodies causing modification and/or increase in the expression of various receptors involved in nociception. Interfering with this pathway has shown promising results in altering the initiation and maintenance of pain. Pharmacotherapy with anti-NGF antibodies promoting the sequestration of free NGF has demonstrated the most promising experimental and clinical evidence for reducing pain by interfering with this pathway (when compared to inhibition of trkA function or prevention of NGF binding and trkA activation).

To date, five phase III clinical trials involving the monoclonal anti-NGF antibody tanezumab in the treatment of osteoarthritis (OA) associated joint pain demonstrated a statistically significant reduction in pain when compared to treatment with a placebo drug. Other anti-NGF antibodies, fulranumab and fasinumab have also been found to provide considerable pain relief in patients with chronic hip or knee OA. In addition to showing significant analgesia when compared to placebo-controlled treatment, multiple studies have found tanezumab to have superior efficacy over active control treatment with an NSAID or opioid. Clinical trials have also established the efficacy of anti-NGF therapy for pain associate with other chronic conditions. Tanezumab was found to be superior to both placebo and NSAID therapy for the treatment of chronic lower back pain (CLBP), with patients reporting less intense

pain and improvements in physical function. In several proof-of-concept, clinical trials, patients with diabetic neuropathy and interstitial cystitis also reported significant reductions in pain when treated with tanezumab [36]. In June of 2017, the FDA granted Fast Track designation for tanezumab for the treatment of pain associated with OA and CLBP [37].

Sodium Channel Blockers

For years, the mainstay treatment for trigeminal neuralgia has been sodium channel blockers, specifically carbamazepine and oxcarbazepine, which need to be titrated to effect over time and also have significant side effect profiles. Nine isoforms of sodium channel blockers have been elicited, of which three are important in pain, Nav1.7, 1.8, and 1.9. Nav1.7 is thought to act as a threshold for the firing of action potentials and is suited as a target for novel selective sodium channel blockers [38]. Zakrzewska et al. look at a novel sodium channel blocker, BIIB074, a Nav1.7 sodium channel blocker, and its safety and efficacy in the treatment of trigeminal neuralgia [39]. BIIB074 can inhibit the firing of trigeminal neurons. Specifically, the authors looked at the efficacy of this drug without titration. In phase 2 trials, patients received 150 mg of BIIB074 three times daily for 3 weeks. No severe side effects were noted, and the most common side effects were headache, pyrexia, nasopharyngitis, sleep disorders, and tremors. The primary endpoint for treatment failure was not significantly lower than placebo, but there will be continued research into this nonopioid, nontitratable sodium channel blocker for the treatment of trigeminal neuralgia [39]. BIIB074 has selectivity for the sodium channel Nav1.7 which is a major sodium channel in the nociceptive system. None of these sodium channels exist in the brain. Because of this selectivity, CNS depression of excitability side effects is nonexistent. Nav1.7 has also been implicated in genetic studies as a link to chronic pain syndrome when gain of function mutations is evident, as well as the inability to feel pain when loss of function mutations are evident [40].

NMDA Antagonists

Fibromyalgia is a complicated disease process that involves increased sensitivity of the spinal cord neurons resulting in perceived pain in the brain. C and A-delta fibers receive nociceptive input and which in turn depend on NMDA receptor activity. Various studies have shown that there is an increase in glutamate in the brain in patients with fibromyalgia. Low-level, non-noxious stimuli are perceived as pain when relayed to the brain. Glutamate is a known excitatory molecule and binds to the NMDA receptor with glycine to activate it potentiating the excitatory pathway. There are many NMDA antagonists on the market which have various effects on the modulation of the pain pathways related to NMDA. Ketamine is a noncompetitive NMDA antagonist, with more selectivity in the S form. Ketamine also acts on opioid, muscarinic, non-NMDA glutamate receptors, and GABA, and has local anesthetic properties. Ketamine has been shown to decrease pain in the short term in those with fibromyalgia and chronic regional pain syndrome [41]. Dextromethorphan has also been studied alongside ketamine in fibromyalgia patients. Both showed a reduction in pain that was highly significant, and both had statistically significant side effects of dizziness, nausea, and sedation [42]. Memantine is a noncompetitive NMDA antagonist that reduces glutamate and prevents calcium entry. This drug also dissociates from the channel and does not cause significant NMDA activity in relation to normal synaptic function. Compared to placebo, there was a significant reduction in pain in patients with fibromyalgia receiving memantine [43]. Amantadine has weak NMDA antagonist activities with variable results on neuropathic pain but has not been studied in patients with fibromyalgia. Guaifenesin also has some NMDA antagonist activity but showed no difference in pain outcomes compared to placebo [41].

TRP Receptors

Cytosolic calcium is a key molecule in the regulation of muscle contraction, neuronal depolarization, platelet aggregation, cell proliferation, and apoptosis. TRP channels are calcium permeable and play a role in calcium homeostasis within cells as well as cell organelles [44]. The structure of the TRP family of receptors contains six membrane-spanning helices with a pore-forming loop between the last two. The N and C segments are in the cytosol. The largest group of nociceptive pain receptors is the TRP family of receptors, specifically TRPV1 and TRPA1. Activation of these channels leads to an influx of sodium and calcium resulting in depolarization which triggers an action potential to transmit information to the spinal cord and brain [44]. These TRP channels have been implicated in many pain pathways, including inflammatory pain, neuropathic pain, visceral pain, and pain related to cancer and migraines. TRPV1 is most prominently associated with inflammatory pain. Antagonists to this receptor have been shown to mitigate thermal pain from inflammation related to noxious stimuli from heat. TRPA1 is also associated with inflammatory pain in mechanical and cold hyperalgesia as well as inflammation from allergic contact dermatitis [44]. TRPV1 and TRPA1 are also seen in neuropathic pain pathways specifically related to diabetic and chemotherapeutic neuropathies. Blockade of these receptors appears to attenuate neuropathies. These receptors are also associated with visceral pain, and silencing those receptors may attenuate visceral pain in irritable bowel syndrome [44]. Chronic pain is multidimensional and a common symptom of cancer. TRPV1 is associated with bone cancer, and pharmacological or genetic blockage of that receptor has been shown to potentiate analgesia. In addition,

antagonists to that receptor have been shown to potentiate the effects of morphine on pain control in mice [44]. This receptor is a potential target for future antagonists in developing a multimodal approach to chronic pain treatment without reliance on opioids.

Palmitoylethanolamide

Cannabis acts on cannabinoid (CB) receptors in the central nervous system and immune system and acts on CB1 and CB2 receptors which are nociceptive receptors in the dorsal horn and peripheral immune system. Cannabis has been shown to reduce pain in individuals suffering from chronic pain. Cannabis compounds have central side effects of asthenia, confusion, somnolence, and GI effects. Palmitoylethanolamide is a cannabimimetic that is hypothesized to reduce pain through endocannabinoid effects on the immune system to reduce inflammation. It does not bind to the classical receptors but may indirectly stimulate endocannabinoids and phytocannabinoids through its agonistic effects on the TRPV1, PPAR-alpha, and cannabinoid receptors. Palmitoylethanolamide (PEA) has been shown to reduce the inflammatory markers of COX, eNOS, and iNOS and by reducing mast cell activation. A large meta-analysis by Artukoglu et al. showed that PEA might be effective in the treatment of chronic pain although a large amount of heterogeneity exists in randomized trials, and they were not able to demonstrate a likely cause (Artukoglu et al. 2017). The trials that were examined varied among three end points for chronic pain and the causes of chronic pain which may underestimate the benefits of PEA. Serious adverse events were reported in the trials, but less serious side effects were not necessarily reported. There still needs to be research done on PEA particularly with randomized and placebo-controlled trials so that efficacy and tolerability can be determined. Also, adverse events within the literature should be examined, dose tolerability should be examined, and effects on acute and chronic pain should be compared. Much more research needs to be done on PEAs as a potential option for nonopioid pain management, but thus far, the data looks promising.

Transdermal Vitamin D

Vitamin D is a group of fat-soluble secosteroids, the most important of which are D3 (cholecalciferol) and D2. There are a limited number of foods that contain vitamin D, the major source of which is derived from the synthesis of cholecalciferol from cholesterol on the skin via sun exposure. Vitamin D3 pills can also be taken orally as a supplement. As such, there are several studies that show a relationship between low levels of vitamin D3 and chronic pain [45]. The most striking of which is osteomalacia, a disease where the bones become soft due to low levels of phosphate, calcium, and vitamin D [46, 47]. Cholecalciferol has also reduced neuropathic pain in patients with type II diabetes and a low vitamin D status [48]. Recently, a randomized control trial reported that vitamin D3 could be safely delivered through the dermal route, which could be useful in treating vitamin D3 deficiency, suggesting that a route other than oral can be safe for treating conditions related to vitamin D [49]. Finally, a 2017 single-arm open-label research study investigating vitamin D supplementation in patients with chronic lower back pain found vitamin D to be effective at relieving patient back pain when administered 60,000 IU, orally, once a week for 8 weeks [50]. Side effects of vitamin D include kidney stones, muscle weakness, bone pain, weight loss, extreme thirst, frequent urination, and fatigue. It also has several drug interactions including steroids, cholestyramine, phenytoin, antacids, and calcium supplements. Overall, there is growing evidence to support vitamin D as a treatment for chronic pain. Whether this becomes a recommended treatment adopted by a majority of physicians will require more research.

AAK1 Kinase Inhibition

Neuropathic pain is a consequence of lesions in the somatosensory system mainly related to diabetes and post-herpetic neuralgias. Therefore, people with neuropathic pain experience hyperalgesia, allodynia, and spontaneous pain. The mainstay of treatment for neuropathic pain is SSRIs, SNRIs, and the gabapentin family of drugs which essentially work on the noradrenergic system which is a potent inhibitor of the dorsal horn in the spinal cord. Although these drug classes have been marketed for years for neuropathic pain, there are still many patients who do not respond to these treatments. AAK1 knockouts were identified as potential pain targets in mice due to the reduced response to persistent pain when that gene was knocked out [51]. Kostich et al. identified novel AAKI inhibitors and monitored the response to pain in the mouse model. Their results show that mice fail to develop allodynia. No tolerance was noted in continued treatment with inhibitors. AAKI is linked to the noradrenergic pathway as well, as are the most common prescribed classes of medication for treatment of neuropathic pain. AAKI does not use the opioid pathway of inhibition; rather, it may work synergistically with opioids regarding the antinociception noradrenergic pathway. Pregabalin and gabapentin are limited by their side effect profiles, particularly sedation and cognitive impairment at the expense of only minor pain control in many patients. In mice, the doses of gabapentin tested which had significant efficacy also caused significant motor impairment. AAKI inhibitors, on the other hand, were tested at efficacious doses and did not show any marked motor impairment [51]. This study shows that selective AAKI inhibitors can be identified without dose-limiting side effects as a potential target for neuropathic pain.

Calcitonin Gene-Related Peptide

Migraines manifest themselves as chronic pain and sensory disturbance that happens episodically over time. The role of calcitonin gene-related peptide (CGRP) in migraine pathophysiology has gained interest as a novel target for antagonists for acute treatment as well as prevention of migraines. CGRP is a 37-amino acid neuropeptide in a family that includes adrenomedullin, amylin, and calcitonin with a wide array of functions within the central and peripheral nervous system. CGRP is released from perivascular nerve terminals when noxious stimuli are present. This release causes vasodilation which suggests a role in neurogenic inflammation. Schou et al. looked at a meta-analysis of CGRP in the role of nonheadache pain and chronic pain [52]. The results of their study identify that CGRP is involved in somatic, visceral, inflammatory, and neuropathic pain. Somatic pain showed a correlation of CGRP levels. This review suggests that CGRP may play a role in transmitting pain, particularly somatic, from tendon and joint pain. CGRP may also have a pro-inflammatory role in the periphery as well as central sensitization. This process has not been fully elicited, but potential antagonistic targets to this molecule may have a future role in the management of chronic pain. Efficacy and safety have already been established in migraines, and this should pave the way for future studies involving other types of chronic pain [52].

TRPV4 Antagonists

The transient receptor potential vanilloid 4 (TRPV4) is a gated Ca^{2+} channel expressed in neurosensory cells of the central nervous system. It is stimulated by changes in pH, osmolarity, mechanical stress, and cellular swelling [53, 54]. Agonism of TRPV4 has been found to induce hyperalgesia through the release of nociceptive neuropeptides substance P (SP) and CGRP. Deletion of the TRPV4 gene showed evidence of reducing hyperalgesia and mechanical visceral pain [54–56]. Intrathecal injections of antisense oligodeoxynucleotides against TRPV4 mRNA have been shown to reduce hyperalgesia caused by paclitaxel-induced neuropathy in animal models [57].

Recent structure-activity relationship studies have found that selective antagonists of the TPRV4 receptor showed an analgesic effect in animal models [58–60]. In models of general trigeminal irritant pain and visceral pain, daughter compounds of GSK205 have been shown to attenuate pain behavior via dual inhibition of TRPV4 and TRPA1 [61]. In models of dorsal root ganglion compression, TRPV4 was shown to act on a MAPK pathway [62]. The topical anesthetic butamben acts on TRPV4 and has also been shown to also have an analgesic effect in micromolar concentrations [63–65]. Though it has been difficult to design ligands to selectively probe TPRV4 over other PRV receptors, TPRV4 research remains a promising area due to its effects on modulation of inflammation and analgesia.

Cholecystokinin

The neuropeptide cholecystokinin (CCK) is found in high concentrations in tissues important for the modulation of pain including cortical gray matter, hypothalamus, periaqueductal gray matter (PAG), and ventromedial thalamus [66, 67]. CCK has been shown to block morphine-induced analgesia in animal models in a dose-dependent manner [68, 69]. This blockade is reversed by proglumide, a CCK receptor antagonist [70]. Coadministration of opioids with proglumide and lorglumide enhances and potentiates the analgesic effect of the opioid and prevents the development of tolerance [71–73]. Multivalent drugs targeting both opioid and CCK pharmacophores have been proposed and demonstrate increased receptor affinity and biological activity [74–77]. Recent work in diabetic polyneuropathy has shown the combination of proglumide and celecoxib; a selective COX-2 inhibitor reduces hyperalgesia and allodynia with synergism and interaction indexes of 0.45 ± 0.03 and 0.39 ± 0.08, respectively [78]. Antihyperalgesic effects in chronic pain models have even been observed in CCK inhibition with tricyclic antidepressants (desipramine), partial opiate agonists (tramadol), triptans (rizatriptan), and even benzodiazepines [79–82]. This evidence further indicates the role of CCK in pain modulation and its potential as an adjunct therapy in chronic pain to reduce opioid dose and side effects.

Delta Opioid Receptor

The δ-opioid receptor (DOR) shares a common pathway with μ (MOR), κ (KOR), and opioid-like receptor 1 (ORL1) in the modulation of pain [83]. Classically, DOR, a seven-transmembrane protein receptor, interacts with inhibitory G-proteins to decrease neuron activity and the transmission of pain. This is accomplished through the activation of the $K_{ir}3$ inward rectifying potassium channel, causing hyperpolarization and inhibition of neural activity [84]. As chronic pain is associated with comorbid mood disorders, the DOR makes an attractive molecular target due to its anxiolytic and antidepressant effects [85, 86]. Antagonism of the DOR through the small molecule antagonist naltrindole, DOR knockout, and DOR antisense DNA showed the prevention of morphine tolerance and dependence with retention of analgesia [87–89]. Peptidomimetic and nonpeptide molecules that combine MOR agonist and DOR antagonist activity reduce tolerance and extends the duration of analgesia [90–95]. Therapy including selective DOR and dual active DOR/MOR compounds remains a compelling area of investigation for the reduction of opioid use [96–98]. The recent discovery of δ-

opioid receptor-selective positive allosteric modulators (δ PAMs) was not only a useful tool to probe molecular mechanisms of pain but also exhibited cooperativity and increased binding affinity of ligands at the orthosteric site [99]. Very recently, inhibition of the phosphatase and tensin homolog (PTEN)-regulated checkpoint increased the delivery of the DOR to the neuronal surface, further increasing the efficacy of DOR antagonists [100]. Although the DOR is less often studied than the MOR, a robust set of tools exists to assist further clinical advances in DOR-targeted intervention [101].

Neurokinin

The neurokinin receptor (NK) is expressed in the dorsal horn of the spinal cord and is activated by SP [102]. Studies suggest that NK is vital in the activation of the ascending limb of the spinobulbospinal pain pathway which is involved in the development of opioid-induced hyperalgesia and antinociceptive tolerance [103–105]. Furthermore, inhibition of NK-1 reduces the thermal nociception and mechanical allodynia associated with chronic neuropathic pain [106]. Studies including antagonism and ablation of NK receptor-containing cells in the rostral ventromedial medulla (RVM) concluded that the NK receptor is involved in the maintenance of hyperalgesia and conduction of the pain pathway [107, 108]. Additionally, NK receptor inhibitors in combination with μ/δ agonists have been shown to have antinociceptive properties, reduce tolerance, and have less impact on the reward pathway leading to addiction [109–113]. NK receptor inhibitors are a promising class of compounds for chronic pain therapy due to their ability to reduce tolerance and paradoxical opioid-induced hyperalgesia.

Gene Therapy

The use of viral vectors is an established method of modifying gene expression in nervous tissues. Studies using herpes simplex virus (HSV) and adeno-associated virus (AAV) viral vectors to alter tissue-specific function through gene transfer have demonstrated significant pain reduction when employed in the setting of various pain-generating conditions. Advantages to this method of treatment include the longevity of the benefit, as opposed to multiple daily dosing of medications, and high specificity of the target tissue, potentially avoiding side effects common with current pharmacotherapy resulting from systemic administration.

Research has revealed that peripheral noxious stimulation, as well as direct nerve injury, can result in downregulation of voltage-gated potassium (Kv) channels. This is thought to contribute to the development of neuropathic pain. Studies conducted by Fan et al. [114] demonstrated that AAV-mediated transfer of Kv genes resulted in attenuation of this downregulation in an animal model of neuropathic pain and was associated with significant pain relief [115].

Gene therapy using replication-deficient HSV vectors expressing preproenkephalin (vHPPE), a natural opioid, has been studied in a post-herpetic neuralgia (PHN) rat model. Treatment with vHPPE resulted in prolonged duration relief of PHN hypersensitivity. HSV-mediated enkephalin expression reduced VZV-induced nocifensive behaviors in the rat PHN model, and when administered prophylactically, PHN-associated nocifensive behaviors failed to develop [116]. In 2011, a multicenter, dose escalation, phase I clinical trial involves NP2, a replication-defective HSV-based vector that expresses preproenkephalin in 10 subjects with intractable focal pain caused by cancer. NP2 was injected intradermally in subjects with intractable focal pain caused by cancer. NP2 was injected intradermally into the dermatome that corresponded to the radicular distribution of pain. Patients that received the middle and high doses of NP2 reported pain relief, and NP2 was well tolerated in all subjects [117].

Three pro-inflammatory cytokines, tumor necrosis factor alpha (TNFα) and interleukin-1 and 6 (IL-1, 6), are associated with neuropathic pain in addition to chronic morphine tolerance and withdrawal. Consequently, anti-inflammatory medications like NSAIDs are often used as a therapy. Studies have since demonstrated that HSV vector delivered gene therapy promoting the upregulation of anti-inflammatory molecules (IL-4, 10, TNF-soluble receptor) resulted in both attenuation of the tolerance and withdrawal side effect profile and reduced overall pain behaviors in a murine model of neuropathic pain induced by partial spinal cord injury.

Summary and Conclusions

The pharmacotherapies discussed in this manuscript outline promising opioid alternatives which can change the future of chronic pain treatment. As more research and development are conducted, it is likely that more novel pharmacotherapies will continue to be developed. Healthcare providers have a unique role in our worldwide opioid epidemic in that they can directly influence how they treat their patients. It is the healthcare providers who support these novel nonopioid pharmacotherapies that will truly overturn the epidemic and foster the continued development of novel nonopioid treatments for chronic pain.

Compliance with Ethical Standards

Conflict of Interest Elyse M. Cornett, Brendon Hart, Shilpadevi Patil, Andrew Pham, and Kenneth F. Mancuso declare no conflict of interest. Alan D. Kaye is a speaker for Depomed, Inc. and Merck, Inc.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance.

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