Recent Developments in the Management of Post-Traumatic Pain

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ABSTRACT

A variety of analgesic options are currently available for the treatment of acute and chronic post-traumatic pain (PTP). These include non-steroidal anti-inflammatory drugs (NSAIDs), opioids, and adjuvant analgesics (i.e., antidepressants, anticonvulsants, N-methyl-D-aspartate receptor antagonists), as well as muscle relaxants and local anesthetics. Unfavorable safety profiles have limited the use of many of these drugs in PTP management, however, and PTP often remains inadequately treated. Contemporary research has focused on the development of more efficacious pharmaceuticals with fewer associated side-effects, as well as on the use of non-pharmaceutical approaches, such as neurofeedback, to facilitate or enhance analgesia. This review discusses these advances in detail, providing an overview of the recent developments in the management of PTP.

Keywords: post-traumatic pain, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, adjuvant analgesics, neurofeedback, electroencephalogram (EEG), pain management

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INTRODUCTION

Post-traumatic pain (PTP) patients comprise an extremely large and diverse population. Treatment options are typically prescribed or recommended on a case-by-case basis depending on the type of pain exhibited. PTP can present clinically in a variety of forms, including localized inflammatory (head, neck, back, or limbs), widespread inflammatory (musculoskeletal), neuropathic, or syndromic (e.g., complex regional pain syndromes, post-traumatic stress disorder, fibromyalgia (FM)). Severe acquired brain injury (ABI) and traumatic brain injury (TBI) are also frequently associated with an abnormally exaggerated subjective response to painful stimuli (hyperpathia), the treatment of which presents significant clinical challenges (for a review, see Ofek and Defrin [1]). Pain duration is also an important consideration in PTP management, as chronic pain is commonly the result of alterations in the molecular pathways mediating acute pain [2]. Despite its prevalence and frequent severity, PTP remains inadequately treated in many cases. Individualized optimization of pharmacologic and non-pharmacologic analgesic use is a primary goal (and challenge) of PTP management.

A variety of pharmacologic agents are currently available for the management of PTP, including non-steroidal anti-inflammatory drugs (NSAIDs), adjuvant analgesics, opioids, muscle relaxants, and local anesthetics (Table 1). Advances in basic and clinical research have greatly expanded analgesic options for PTP management. Studies on NSAIDs and opioids have led to the development of drugs with improved efficacy and safety profiles. Adjuvant analgesics, drugs that have primary indications other than pain, are being used more frequently for the clinical management of PTP, and novel neuromodulatory mechanisms are being developed as non-pharmacologic methods for enhancing analgesia. This review discusses these advances in detail, providing an overview of the recent developments in the management of PTP.

NON-Steroidal anti-INFLAMmatory Drugs (NSAIDs)

NSAIDs are among the most widely used and prescribed drugs worldwide [3], and are central to the treatment of acute PTP. Their mechanism of action is reduced prostaglandin production through inhibition of peripheral and central cyclooxygenase (COX). COX-1 is constitutive, involved in gastric mucosal protection and required for normal physiologic function of stomach, kidney, and platelets, whereas COX-2 is inducible and involved in the inflammatory response. Non-selective COX inhibitors affect both COX-1 and COX-2 production [4]. This large and diverse group of NSAIDs includes salicylates, oxicams, propionic acids, acetic acids, naphthylalkalones, and fenamates. NSAID use is associated with a ceiling effect, or a dosage beyond which efficacy is not increased. Patients who no longer experience the analgesic effects of a particular NSAID after long-term use are often encouraged to switch to a different analgesic agent. The analgesic effects of these drugs last an average of only 4–6 h, requiring multiple doses for continuous pain relief. Given the constitutive effects of COX-1, it is not surprising that prolonged and continuous usage of non-selective COX
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<td>3. Codeine</td>
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<td>Amitriptyline</td>
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<td>Increase in potassium conductance (2)</td>
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<td>Carbonic anhydrase isoenzyme inhibition (2)</td>
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<td>Carbamazepine</td>
<td>Na⁺ ion channel inactive state stabilization (1)</td>
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Patients exhibited an increased incidence of cardiovascular events in individuals recovering from coronary artery bypass surgery. Inhibitors, such as valdecoxib (and its intravenous prodrug, parecoxib), were assessed for their analgesic effects in another COX-2 inhibitor, celecoxib [11]. In 2005, Nussmeier and colleagues [12] observed similar increased cardiovascular toxicity in a study of patients receiving celecoxib. A greater risk of recurrent colonic polyp prevention was confirmed in a study of patients treated with rofecoxib compared with the control group treated with naproxen. The significance of these findings was complicated by the absence of a placebo group, however, as it was unclear whether the detrimental effect was due to an increased risk of gastrointestinal toxicity, bleeding, or adverse cardiovascular events, and liver and renal dysfunction [5].

It has long been acknowledged that selectively inhibiting COX-2 while leaving COX-1 unaffected could potentially yield the same anti-inflammatory benefits with reduced toxicity and gastrointestinal side-effects. The first two selective COX-2 inhibitors, celecoxib (Celebrex, Celebra) and rofecoxib (Vioxx), were approved by the US Food and Drug Administration (FDA) in 1999 [6]. However, studies examining the gastrointestinal safety of these drugs appeared to produce mixed results. The Celecoxib Long-Term Arthritis Safety Study (CLASS) reported a gastrointestinal protective effect of celecoxib at the 6-month analysis [7], but further investigation determined that these effects were not present at the 12-month analysis [8]. In contrast, the Vioxx Gastrointestinal Outcomes Research (VIGOR) study found that rofecoxib resulted in a lower incidence of upper gastrointestinal toxicity than naproxen after long-term use [9]. It has been proposed that the discrepancy in gastrointestinal benefit between the CLASS and VIGOR studies can be explained in part by the continued use of low-dose aspirin in CLASS patients but not in VIGOR patients, as aspirin is a non-selective COX inhibitor [6].

The VIGOR study also revealed a surprisingly higher incidence of myocardial infarction in patients treated with rofecoxib compared with the control group treated with naproxen. The significance of these findings was complicated by the absence of a placebo group, however, as it was unclear whether the detrimental effect was due to an increased risk from rofecoxib or a beneficial effect from naproxen, or was an artifact of the study design [9]. Despite its improved gastrointestinal profile, rofecoxib was withdrawn from the market in 2004 after a trial designed to test its efficacy in recurrent colonic polyp prevention confirmed an association with increased cardiovascular toxicity [10]. A greater risk of cardiovascular events was also observed in a similar study of patients receiving celecoxib [11]. In 2005, Nussmeier and colleagues [12] assessed the analgesic effects of another COX-2 inhibitor, valdecoxib (and its intravenous prodrug, parecoxib), in individuals recovering from coronary artery bypass surgery. Patients exhibited an increased incidence of cardiovascular endpoints at 30 days after receiving a total of only 10 days of COX-2 inhibition.

The results of these four large clinical trials confirm the association between selective COX-2 inhibitors and cardiovascular toxicity. Despite these findings, a novel dual-acting COX-2 and carbonic anhydrase (CA) inhibitor known as CG100649 is currently undergoing phase II clinical trials in the United States and Europe [13, 14]. Developed for the treatment of osteoarthritis, rheumatoid arthritis, and acute pain, CG100649 has shown efficacy in the treatment of induced arthritis, inflammation, and thermal hyperalgesia in animal models. CG100649 exhibits a high binding affinity for CA, with dissociation occurring in tissues with low CA activity (e.g., inflamed joints). It was expected that the high affinity of CG100649 for CA would affect the drug's distribution profile, as tissues and cells highly enriched with CAs, such as the gastrointestinal tract, blood, and kidney, would show reduced COX-2 inhibition due to substantial CA uptake of CG100649 [14]. Whole-body radiography (WQBPI) studies in rats supported this hypothesis; tissues with the highest CA activity (liver, lung, kidney, and bone marrow), as well as whole blood, showed the highest radioactivity [15]. Although the efficacy and safety trials conducted to date have produced encouraging results, it is still unclear whether CG100649 will exhibit an improved cardiovascular safety profile compared with other selective COX-2 inhibitors.

Because a wide variety of analgesic therapies are currently available for the treatment of PTP, it is questionable whether the use of selective COX-2 inhibitors is indicated for PTP management. Furthermore, improvements in gastroprotective therapy have reduced the risks associated with non-selective COX inhibitor use, lessening the need for selective COX-2 inhibition. Proton pump inhibitors (e.g., omeprazole), H2 blockers (e.g., famotidine), and prostaglandin analogs (e.g., misoprostol) have shown particular efficacy in protecting patients from adverse gastrointestinal events during NSAID therapy [4].

### ADJUVANT ANALGESICS

Advances in the area of adjuvant analgesics have occurred rapidly over the last 20 years, far surpassing those made in

<table>
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<td>Skeletal muscle relaxant</td>
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<td>Cyclobenzaprine</td>
<td>5-HT2 receptor antagonist</td>
</tr>
<tr>
<td>Local anesthetic</td>
<td>N/A</td>
<td>Lidocaine 5% patch</td>
<td>Na+ ion channel blockade</td>
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</table>

*aNon-steroidal anti-inflammatory drug.  
bCyclooxygenase.  
cN-methyl-D-aspartate.  
dSelective serotonin/norepinephrine reuptake inhibitor.  
eVoltage-gated calcium ion channel.  
fGamma-amino butyric acid-A.  
gGamma-amino butyric acid-A.
other analgesic therapies [16]. Adjuvant analgesics are a diverse group of drugs that were originally developed for a primary indication other than pain. Although a few of these medications are currently used as primary analgesics for specific pain conditions, the majority are used to enhance analgesia [17]. Some of the most recent advances in adjuvant analgesic therapy for PTP are discussed below.

Antidepressants

Antidepressants have been used in the treatment of chronic PTP for the last several decades, including pain associated with post-herpetic neuralgia, painful diabetic neuropathy, post-surgical pain, and FM [18, 19]. Tricyclic antidepressants (TCAs), such as amitriptyline (Elavil), have been the primary focus of antidepressant analgesic research. The mechanism of action of TCAs is non-selective inhibition of the uptake of noradrenaline (norepinephrine) and serotonin, as well as blocking of sodium channels. TCAs exhibit the greatest analgesic efficacy of all antidepressants, with amitriptyline being considered the current analgesic antidepressant gold standard [20]. Although TCAs possess significant pain-reducing properties, they are also associated with a variety of adverse effects, including sedation, confusion, blurred vision, and postural hypotension [21]. The most common side-effects associated with TCA use (e.g., dry mouth, constipation, ocular side-effects, urinary hesitancy) are related to the drugs' anticholinergic properties [22].

A new class of antidepressants, selective serotonin reuptake inhibitors (SSRIs), became available in the late 1980s and includes medications such as fluoxetine, paroxetine, sertraline, and citalopram. Although these drugs produce fewer side-effects, they are also less effective at reducing chronic pain [23]. Newer antidepressants with distinct pharmacological characteristics are becoming more widely used in clinical practice. These include mirtazapine (noradrenergic and specific serotoninergic antidepressant) and reboxetine (noradrenaline reuptake inhibitor). Although clinical data are still limited, these drugs exhibit antinoceptive properties and possess significant therapeutic potential for the treatment of PTP (for a review, see [24]).

Serotonin–norepinephrine reuptake inhibitors (SNRIs) are a class of antidepressants whose mechanism of action is dual inhibition of serotonin and norepinephrine reuptake. In contrast to SSRIs, which act more selectively on the neurotransmitter serotonin, SNRIs target and increase the levels of both serotonin and norepinephrine. These agents block serotonin and norepinephrine transporters but, unlike TCAs, do not concomitantly block receptors for these neurotransmitters [25]. SNRIs such as venlafaxine (Effexor), nefazodone (Serzone), and duloxetine (Cymbalta) have proven effective for the management of PTP, exhibiting improved safety profiles compared with SSRIs [26–29].

Because of the widespread, long-term use of antidepressant medications as analgesics, a more complete and detailed discussion of the role of these drugs in PTP management is beyond the scope of this review. Readers are referred to a timely review by Mico et al [20] for further discussion of the role of antidepressants in post-traumatic analgesia.

Anticonvulsants

Unlike acute pain, chronic pain is conditioned and sustained by mechanisms of peripheral and central sensitization. Pharmaceuticals that target the molecular mechanisms underlying this sensitization are able to discriminate between acute and chronic pain transmission [30]. Anticonvulsants target molecular pathways involved in central sensitization and have thus become an integral part of the clinical management of chronic PTP.

Traditional anticonvulsants, such as carbamazepine (Tegretol), oxcarbazepine (Trileptal), and valproic acid (Depakene), have been used as analgesics since the 1960s [31]. More recent anticonvulsant and antimigraine drugs (e.g., lamotrigine (Lamictal) and topiramate (Topamax)) have demonstrated even greater analgesic efficacy and are considered to be as effective as the antidepressant amitriptyline for the treatment of PTP. Gabapentin (Neurontin) and pregabalin (Lyrica) are two of the most commonly prescribed anticonvulsants for the treatment of PTP, particularly chronic neuropathic pain [32]. Indicated for the management of epileptic seizures since 1993 and 2004 (respectively), these adjuvant analgesics exert their therapeutic effects by binding to, and decreasing the activity of, the alpha-2-delta subunit of the voltage-gated calcium ion channel [33]. Overstimulation of this subunit is thought to play an important role in the hypersensitization process, suggesting a mechanism of action for the drugs’ analgesic properties [34]. Gabapentin and pregabalin have proven effective for several forms of PTP, including FM [35, 36], postoperative pain stress disorder [37, 38], postoperative pain [39], and several forms of neuropathic pain [40–43].

At least 30 randomized clinical trials involving ~2350 patients have investigated the use of gabapentin and pregabalin for postoperative traumatic pain relief in adults. Dauri et al [39] conducted a systematic review of these studies (22 on gabapentin, eight on pregabalin) in 2009. By compiling the results of the previous studies, the group was able to conclude that gabapentin and pregabalin reduce post-surgical pain and opioid consumption when compared with placebo. However, they also found that comparisons between gabapentin/ pregabalin and other standard postoperative treatment protocols were insufficient; a generalized statement regarding the superior postoperative analgesic efficacy of these drugs could not be made because of lack of conclusive evidence. This observation raises the question of whether gabapentin and pregabalin should be considered a preferred method of treatment for the management of surgically induced PTP.

Tzellos and colleagues conducted a similar analysis in 2008 [40], systematically reviewing studies investigating the use of gabapentin and pregabalin for spinal cord injury (SCI)-induced neuropathic pain. Their assessment of five previously published studies (two on pregabalin, three on gabapentin) revealed that both drugs appear to be effective for reducing SCI pain. Their analysis also highlighted the lack of studies directly comparing the efficacy and safety profiles of gabapentin and pregabalin in
SCI pain management. Performing a systematic review allowed the group to identify apparent differences between the two drugs, however, providing clinically relevant comparative data. Their findings suggest that pregabalin is more efficacious than gabapentin for the management of SCI-induced neuropathic pain, but that it is also associated with an increased risk of adverse events.

In 2002, a neuropathic pain study group led by M G Serpell [41] assessed the analgesic efficacy of gabapentin in ~300 patients with a wide variety of neuropathic pain syndromes. Patients exhibited at least two of the following symptoms: allodynia, burning pain, shooting pain, or hyperalgesia. The results of this study indicated that gabapentin reduces pain and improves some quality-of-life measures in a diverse group of neuropathic pain syndromes. Importantly, gabapentin was well tolerated throughout the 8-week study, with the most common adverse events being mild to moderate dizziness and somnolence.

Although such a broad neuropathic pain study has not yet been conducted for pregabalin, independent studies have demonstrated its efficacy in reducing neuropathic pain associated with SCI [44], post-herpetic neuralgia [42], and painful diabetic neuropathy [17, 41]. In June 2007, pregabalin was approved by the FDA for the treatment of FM, a complex chronic widespread pain syndrome believed to be associated with trauma [45], particularly of the cervical spine [46, 47]. Preclinical and clinical data suggest that pregabalin exhibits improved analgesic and absorption profiles compared with gabapentin, with similar rates of the same adverse events (e.g., dizziness and somnolence) [48]. Pregabalin has also been shown to be effective in the treatment of gabapentin-resistant nociceptive inflammatory pain [30]. These findings suggest that pregabalin is more than a structural and functional analog of gabapentin, and broaden its indications for the management of PTP. Present suggestions for anticonvulsant treatment of chronic PTP are lamotrigine as the first choice, followed by gabapentin or carbamazepine/oxcarbazepine [49].

In conjunction with the section of this article on antidepressant medications, a complete discussion of the importance of anticonvulsants as a treatment option for the clinical management of PTP is beyond the scope of this review. Readers are referred to timely reviews by Wiffen et al [31] and Finnernup et al [49] on the use of anticonvulsants as analgesic medications.

NMDA receptor antagonists

N-methyl-D-aspartate receptors (NMDARs) are glutamate-gated ion channels that are widely expressed throughout the central nervous system (CNS). Because of their high permeability to calcium ions, NMDARs play key roles in the excitatory synaptic transmission and subsequent neurotoxicity involved in neuropathic and chronic inflammatory pain [50]. Post-injury activation of NMDARs in the dorsal horn of the spinal cord facilitates the development of allodynia, the abnormal generation of pain in response to low threshold inputs [51]. The central role of NMDARs in pain response has made them a primary pharmaceutical target for the treatment of PTP.

The analgesic properties of NMDAR antagonists, such as ketamine, dextromethorphan, amantadine, and memantine (Namenda), have been studied extensively over the last several years. These agents have demonstrated significant potential for the treatment of neuropathic pain syndromes, including post-herpetic neuralgia, SCI-induced central neuropathic pain, peripheral neuropathy, and painful diabetic neuropathy [52]. In addition to the typical intravenous and oral administration of these drugs, Lynch et al [53] reported long-term reductions in perceived pain with minimal adverse events in an open-label study of 2% amitriptyline/1% ketamine topical cream in neuropathic pain syndromes. Reductions in neuropathic pain using low-dose intranasal ketamine have also been reported [54]. Dextromethorphan, ketamine, and memantine have proven effective for the treatment of phantom limb pain [55–57] and/or pain associated with FM [58, 59], and co-administration of an NMDAR antagonist (memantine) and a calcium ion channel blocker (pregabalin) has recently been proposed as an analgesic and neuroprotective strategy for the treatment of FM-associated chronic pain [60]. A summary of the known analgesic efficacies of clinically relevant NMDAR antagonists is provided in Table 2.

Despite the successful analgesic use of NMDAR antagonists, these drugs are not equally efficacious for the treatment of all types of PTP (for a review, see [61]). For example, memantine, an amantadine derivative, has been proposed for the treatment of neuropathic pain for its improved safety profile and relatively rapid onset of action compared with other NMDAR antagonists. Clinical trials conducted to date have met with limited success, however, and the routine use of memantine is currently not indicated for neuropathic pain treatment [62]. In contrast, neramexane, an NMDAR antagonist similar to memantine, showed positive results for chronic pain analgesia in preclinical and clinical trials [63–65]. A recent review on the use of NMDAR antagonists for postoperative pain also reported drug-dependent variations in analgesic efficacy. Although the co-administration of ketamine and morphine is not recommended, evidence suggests that low-dose ketamine infusion and the administration of dextromethorphan may be able to provide postoperative pain relief [66].

The combined results from analgesic studies of NMDAR antagonists highlight two important considerations. First, each NMDAR antagonist exhibits efficacy for treating only certain types of pain. Dextromethorphan is a prime example, as it reduces pain associated with FM and painful diabetic neuropathy but has no analgesic benefit for post-herpetic neuralgia [67]. This observation suggests that different forms of chronic PTP are mediated by different, albeit similar, molecular mechanisms. Determining which molecules and pathways play the most critical roles in each type of pain may illuminate more effective targets for pain reduction.

Second, the analgesic relief achieved by patients with a particular form of PTP varies depending on the NMDAR antagonist being administered. For example, ketamine and dextromethorphan, but not memantine, are effective at reducing...
neuropathic pain. These results may be explained by the molecular organization of NMDARs. Each NMDAR is a heteromeric complex incorporating different subunits of three possible subtypes: NR1, NR2, and NR3. Each subtype has several possible isoforms (eight, four, and two, respectively), generating a total of 14 possible subunits. It is now known that NMDAR antagonists exhibit different binding affinities for different subunits [50]. In a contemporary review of NMDAR physiology, Wu and Zhuo [52] suggest that targeting NMDAR subunit NR2B will provide the safest, most effective relief for various forms of neuropathic pain.

Despite their analgesic properties, the use of NMDAR antagonists in PTP management is currently limited by their association with adverse psychotropic affects, including sedation, confusion, and motor incoordination [68]. High-dose administration of high-affinity NMDAR antagonists (e.g., ketamine, dextromethorphan) can also cause over-antagonization of the glutamatergic system, leading to neurodegeneration and an exacerbation of acute pain [69, 70]. Recent research in the area of NMDAR antagonism has focused primarily on the reduction of these adverse events. (S)-norketamine, the (S) enantiomer of norketamine, is a primary metabolite of ketamine, which also acts as an NMDAR antagonist. Oral administration of this compound produces dose-dependent analgesic effects in animal models of human neuropathic and chronic inflammatory pain. Impaired motor function was observed at doses ~10-fold greater than those required for antinociception, suggesting an improved safety profile compared with other NMDAR antagonists [71]. A novel non-competitive NMDAR antagonist known as CNS 5161 HCl was also recently evaluated for use in the treatment of human neuropathic pain. Forst et al [72] reported indications of analgesic activity in diabetic neuropathic patients after the administration of 500 µg of CNS 5161 HCl. The compound was well tolerated at this dosage, with the most commonly reported side-effects being increasing blood pressure, mild visual disturbances, and headaches.

Regardless of their analgesic potential, the broad use of NMDAR antagonists for the treatment of PTP will ultimately depend on the development of (1) NMDAR subunit-specific antagonists with superior analgesic efficacy, and (2) moderate-affinity antagonists with improved clinical safety profiles.

### OPIOIDS

Opioid analgesics reduce pain by interacting with CNS mu-, kappa-, and delta-opioid receptors, components of the endogenous vertebrate pain suppression system [73]. This mechanism of action renders opioids one of the most potent classes of clinically available analgesics. Opioid analgesics have been the mainstay approach for acute and chronic cancer pain for the last several decades, and pain specialists are now turning their attention to the use of these drugs for the management of chronic non-malignant pain [4].

Numerous studies have explored the efficacy of opioids in the treatment of neuropathic pain (for reviews, see [74–76]). Current research and clinical observations indicate that neuropathic pain is generally unaffected by opioid treatments, whereas intermediate-term studies indicate significant analgesic efficacy of opioids compared with placebo. A similar systematic review by Schmidt and Schmidt [75] also

### Table 2. Clinically Relevant NMDAR Antagonists and their Known Analgesic Efficacies

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<td>[93–96]</td>
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</tr>
<tr>
<td>Memantine</td>
<td>CRPS</td>
<td>Yes</td>
<td>[112]</td>
</tr>
<tr>
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<td>FM</td>
<td>Yes</td>
<td>[59]</td>
</tr>
<tr>
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<td>PHN</td>
<td>Yes</td>
<td>[106]</td>
</tr>
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<td>PLP</td>
<td>Yes</td>
<td>[55, 56, 107]</td>
</tr>
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<td>[110]</td>
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<tr>
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<td>Yes</td>
<td>[54]</td>
</tr>
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<td>2% amitriptyline/4% ketamine cream</td>
<td>NP</td>
<td>Yes</td>
<td>[53]</td>
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CBP, chronic back pain; CNP, central neuropathic pain; CRPS, complex regional pain syndrome; FM, fibromyalgia; NH, neurogenic hyperalgesia; NP, neuropathic pain; PDN, painful diabetic neuropathy; PHN, post-herpetic neuralgia; PLP, phantom limb pain; PNP, peripheral neuropathic pain; POP, postoperative pain; SCIIP, spinal cord injury-induced pain; TNP, trigeminal neuropathic pain.
reported a lack of consensus regarding the efficacy of opioids in neuropathic pain management. The authors suggested that new randomized, placebo-controlled, double-blind clinical trials be performed with tighter control of study variables in order to minimize interstudy discrepancies.

NMDAR antagonists are often co-administered with opioids in order to extend their duration, enhance their analgesic effects, and prevent tolerance with long-term use [77]. For example, in a systematic review of 37 trials, Subramaniam and colleagues [78] reported that low-dose ketamine safely reduces opioid consumption and, in some cases, provides additional analgesic benefit. However, because of the adverse events associated with adjuvant analgesic use (see the section on Adjuvant analgesics), it has been suggested that these drugs be co-administered only when patients cannot obtain satisfactory pain relief from a primary pain medication (e.g., NSAIDs, opioids) [17]. Cannabinoids, drugs that share the same target as delta-9-tetrahydrocannabinol (delta-9-THC), the psychoactive ingredient in cannabis, have demonstrated analgesic efficacy for the treatment of neuropathic pain in humans and animal models. Recent research supports the concurrent use of cannabinoids in combination with opioid and adjuvant analgesics in order to limit the required doses of these drugs [79].

Despite their strong analgesic properties, opioids are often either underused or prescribed at suboptimal doses due to association with a variety of adverse effects, including nausea and vomiting, constipation, respiratory depression, dizziness, cognitive impairment, urinary retention, and myoclonus [5]. The potential for tolerance, physical dependence, withdrawal, addiction, misuse, and abuse of these drugs raises additional concerns for both patients and clinicians regarding opioid use in the treatment of chronic PTP. Rates of opioid abuse and addiction have increased over the last decade [80, 81], emphasizing the need for opioid analgesics with decreased propensity for tolerance and dependence. Co-administration of a mu-opioid receptor agonist and a delta-opioid receptor antagonist has been shown to attenuate the occurrence of tolerance and dependence [82]. These observations have led to the development of opioid ligands with mixed agonist/antagonist opioid receptor affinity. Preclinical trials have demonstrated the antinociceptive efficacy and reduced propensity for tolerance of these drugs, and suggest that they may produce fewer respiratory and gastrointestinal side-effects than pure mu-receptor antagonists [81]. If these results are confirmed by clinical trials, the favorable safety profile of these novel opioid analgesics will promote their use in the clinical management of chronic PTP, where the long-term use of traditional opioid medications bears significant patient risk.

NEUROFEEDBACK

Despite the plethora of pharmacologic analgesics currently available, chronic PTP remains inadequately treated in many cases [83]. Sensitization of neuronal networks in the dorsal horn of the spinal cord (i.e., central sensitization) plays a critical role in the modulation of chronic pain [84]. Available evidence indicates that cortical processing of pain signals is also altered in chronic pain states. Unlike acute pain, the experience of chronic pain engages brain networks related to cognitive and emotional processing [85, 86].

A variety of techniques have been used to study correlations between pain and cephalic physiology, including functional magnetic resonance imaging (fMRI), positron emission tomography (PET), repetitive transcranial magnetic stimulation (rTMS), and electroencephalograms (EEG). EEG has proven to be particularly effective for studying nociceptive processing, as EEG bandwidth strengths are correlated with fluctuations in pain experience. Specifically, research using acute (induced) pain models indicates that, although an increase in pain produces an increase in the strength of all EEG frequencies, beta frequencies increase more relative to the other bandwidths, and the relative strengths of slower frequencies (predominantly alpha, but also theta in some studies) decrease [87].

Preliminary research suggests that EEG bandwidth activity also reflects the cortical processing of nociceptive signals during chronic pain states [88–90]. In these studies, patients utilized EEG operant conditioning to alter the relative power of EEG frequency bands, leading to a reduction in their chronic pain. This technique, commonly referred to as neurofeedback, is a relatively new analgesic approach. In a contemporary commentary, Jensen et al [87] speculated on the potential therapeutic applications of neurofeedback if further research confirms the correlation between chronic pain and EEG bandwidth strength. The idea that chronic pain can be reduced at the supraspinal (cortical) level regardless of the degree of central sensitization in the CNS bears significant therapeutic potential. Neurofeedback may prove to be particularly beneficial for patients whose pain does not respond to pharmacological therapies that target central sensitization pathways (e.g., anticonvulsants, NMDAR antagonists).

CONCLUSIONS

Numerous options are currently available for the treatment of acute and chronic PTP. Although much progress has been made toward improving the safety and efficacy of these analgesic approaches, several issues still remain. The long-term safety profiles of NSAIDs and opioids are a primary concern among clinicians, and the adverse events associated with NMDAR antagonists and adjuvant analgesics currently limit their use as PTP treatment options. Contemporary research is focused largely on the development of more efficacious analgesic pharmaceuticals with fewer side-effects, as well as on the enhancement of non-pharmaceutical neuromodulatory treatment options.

Sensitivity to acute pain, susceptibility to chronic pain, and response to analgesia vary widely between subjects [91]. The significant influence of genetic factors on this variability is now widely appreciated, and animal models are a powerful tool for discovering genes related to human pain variability. Given the complexity of the nervous system and the variety of clinical presentations of PTP, adequate clinical management will likely require more individualized treatment strategies that combine multiple pharmacologic and non-pharmacologic analgesic...
approaches. By using animal models to identify genes that contribute to variable pain sensitivity, susceptibility, and analgesic safety and efficacy through allelic variation, we move toward the long-term goal of developing improved methods of individualized PTP diagnosis, prognosis, counseling, treatment, and prevention.

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REFERENCES


