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REVIEW ARTICLE

Targeting Opioid-Induced Hyperalgesia in Clinical Treatment: Neurobiological Considerations

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Abstract Opioid analgesics have become a cornerstone in the treatment of moderate to severe pain, resulting in a steady rise of opioid prescriptions. Subsequently, there has been a striking increase in the number of opioid-dependent individuals, opioid-related overdoses, and fatalities. Clinical use of opioids is further complicated by an increasingly deleterious profile of side effects beyond addiction, including tolerance and opioid-induced hyperalgesia (OIH), where OIH is defined as an increased sensitivity to already painful stimuli. This paradoxical state of increased nociception results from acute and long-term exposure to opioids, and appears to develop in a substantial subset of patients using opioids. Recently, there has been considerable interest in developing an efficacious treatment regimen for acute and chronic pain. However, there are currently no well-established treatments for OIH. Several substrates have emerged as potential modulators of OIH, including the N-methyl-D-aspartate and γ-aminobutyric acid receptors, and most notably, the innate neuroimmune system. This review summarizes the neurobiology of OIH in the context of clinical treatment; specifically, we review evidence for several pathways that show promise for the treatment of pain going forward, as prospective adjuvants to opioid analgesics. Overall, we suggest that this paradoxical state be considered an additional target of clinical treatment for chronic pain.

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Key Points

- Opioid analgesic medications induce a paradoxical state of increased pain sensitivity, known as opioid-induced hyperalgesia, which likely interferes with patients' overall treatment outcomes.
- A unanimous method of diagnosing and treating opioid-induced hyperalgesia in clinical practice remains indeterminate.
- There are several promising avenues of research that may lead to an effective pharmacological treatment paradigm for opioid-induced hyperalgesia.

1 Introduction

In 1870, English physician T. Clifford Albutt chronicled the first documented observation of increased pain sensitivity, or hyperalgesia, resulting from opioid exposure. He stated "At such time, I have certainly felt it a great responsibility to say that pain, which I know is an evil, is less injurious than morphia, which may be an evil. I have much reason to suspect that a reliance upon hypodermic morphia only ended in a curious state of perpetuated pain". In his discourse, he questioned whether morphine "tends to encourage the very pain it pretends to relieve" [1]. Over 140 years later, we are only beginning to unravel the enigmatic mechanisms underlying this paradoxical phenomenon and are ultimately coming to the realization that Albutt's observations were likely accurate.

Predicated from a sample of non-institutionalized adults in the US, an estimated 100 million people suffer from some form of chronic pain [2], with an approximate 25

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million experiencing moderate to severe, debilitating pain [3]. Encompassing a range of chronic pain states, estimates of cost range from US$560 to US$635 billion each year [2]. It is notable that the estimated 33 % prevalence rate for chronic pain in the US appears to be higher when compared with other countries; for instance, sample estimates for India were approximately 13 % [4], while another study reported chronic pain in 22 % of women versus 17 % of men in a Danish sample [5]. Further, an Australian study reported chronic pain in 19 % of their primary care sample [6], while a Canadian study reported similar estimates in 2011 [7].

The assertion by the US Joint Commission on Accreditation of Health Care Organizations that pain be considered "the fifth vital sign" has resulted in an increased focus on providing treatment for chronic non-cancer pain. This assertion has been criticized by some, as pain is more accurately perceived as a subjective, multidimensional symptom rather than an objective sign [8]. Nonetheless, limited availability of alternative therapies often leaves opioid pharmacotherapy as the only viable option, the result of which has been a dramatic increase in prescription of high-dose opioids for chronic pain.

Opioids have become the most frequently prescribed drug class, surpassing 259 million prescriptions in 2012 in the US [9]; this increase in number of prescriptions has given rise to a drastic increase in the rate of opioid addiction, along with a striking increase in the number of deaths due to prescription opioids. Of particular concern is that the majority of fatal opioid overdoses (50–80 %) have occurred in patients with a history of chronic pain [10] on prescribed opioid regimens [11]. Particularly disconcerting is that opioid prescription is at its highest in spite of reports questioning the efficacy of long-term opioids for chronic pain, and supporting a dose-dependent risk in misuse, addiction, overdose, and death [3, 12]. In fact, one observational study reported that 90 % of patients presenting to a pain management center were already on an opioid regimen [13], suggestive of either inadequate pain relief, addiction, or both. A solid estimate of patients presenting with chronic pain and a comorbid opioid use disorder (OUD) is not available, is likely dependent on duration and dose of opioid prescription [14], and reportedly ranges between 3–40 % [15]. Furthermore, OUD has an estimated economic cost of US$72.5 billion in healthcare services in the US [16], and those who abuse this drug class generate an average annual healthcare cost that is 8.7 times higher than non-abusers [17].

Opioids are associated with multiple adverse effects that include respiratory depression, constipation, cardiovascular issues such as hypotension and bradycardia, and a high abuse liability [18]. Furthermore, opioids elicit a paradoxical state of increased pain sensitivity, known as opioid-induced hyperalgesia (OIH). OIH manifests as an increased pain sensitivity that leads to higher opioid consumption, and in turn putatively diminishes overall pain relief [19, 20]. Further, OIH may interfere with the patient's overall chronic pain treatment outcome and has the potential to propagate addiction. Thus, it has been suggested that OIH be considered a treatment target in addition to analgesia to ultimately improve management of patients treated with opioids [21–23].

The purpose of this review is to evaluate what is currently known about the neurobiological substrates of OIH, to encapsulate the human studies on pharmacological treatments for OIH, and to recommend future considerations for addressing OIH in clinical settings. To provide background for our review, we first provide definitions for OIH and similar phenomena such as tolerance and sensitization. We then summarize the recent advances on the neurobiological mechanisms of OIH, and address issues related to assessment of OIH in preclinical and clinical studies. Several relevant systematic reviews of OIH have been published recently [20–22, 24–26]; our review extends the previous work by providing an updated evaluation of the field with a focus on viable clinical treatment targets.

2 Methods

Between August 2014 and April 2015, a search of PubMed, EMBASE, and Google Scholar was conducted to retrieve articles related to OIH. Specifically, both original reports and past review articles pertaining to OIH's definition, prevalence, measurement, relationship to other opioid-induced phenomena, underlying neurological substrates, and treatment paradigms were sought. Search terms included the following: opioid-induced hyperalgesia, pain, opioid use disorder, NMDA receptor, GABA receptor, glia, gabapentinoids, neurosteroids, and cannabinoids. All terms were filtered by either animal or human studies when relevant.

3 Definition and Theories of Opioid-Induced Hyperalgesia (OIH)

Following opioid exposure, OIH contrasts analgesia (relief from pain) and antinociception (decreased pain sensitivity), and manifests as subjectively perceived increased pain sensitivity to an already painful stimulus. OIH frequently includes allodynia, which is pain evoked by a stimulus that is not under normal circumstances considered painful [22, 27]. Perhaps most notable is that this increased pain sensitivity is diffuse and often manifests beyond the area of

original pain, is independent of the condition that the opioids were initially prescribed for, and persists or even worsens after dose escalation of opioids [28–30].

There are several prominent theories underlying OIH. Perhaps the most intensely debated theory, though recently largely unsupported, is that OIH is a causative factor in analgesic tolerance (see Sect. 3.2). Specifically, the increased pain sensitivity that one experiences after opioid treatment causes the need for increasing doses of opioids, thus reflective of tolerance [31–33]. A second theory has postulated a role for pronociceptive opioid metabolites, specifically resulting from morphine biotransformation. However, recent studies have suggested otherwise (see Sect. 4.4). A third prevalent theory is that OIH is an adaptive response that serves as a systems-level opponent process in response to opioid analgesia after prolonged opioid treatment. That is, as the body works to retain homeostasis, one's adaptive response to exogenously elicited analgesia is to create an opposing state of hyperalgesia in an effort to regain physiological equilibrium [19, 34–36]. Finally, a fourth theory that is gaining popularity, and is related to the aforementioned opponent process, is that OIH is the result of a glial-regulated immune response (see Sect. 4.2) [37, 38].

3.1 Prevalence of OIH in Humans

OIH is observed in patients who utilize opioids with both acute and chronic administration, though its overall prevalence remains indeterminate. The closest estimates indicate that a disconcerting proportion of patients present with what may be OIH; for instance, Mercadante et al. [39] reported nearly 14 % of 81 patients with cancer experienced diffuse pain not otherwise explained by patient history or disease progression, which was unresponsive to morphine titration and alleviated only by rotation to methadone. Ackerman [40] described a similar outcome in 28 % of a sample of 197 patients with chronic pain receiving opioids. While some studies suggest that OIH develops after chronic opioid use [41–43], both rodent [44, 45] and human studies [46–49] have documented OIH within hours of acute opioid administration. Studies using shorter-acting opioids such as remifentanil, sufentanil, fentanyl, and morphine provide the most suspicion of OIH [49–56]; however, there is documentation of this phenomenon in patients receiving long-acting opioids (e.g., methadone or buprenorphine) as well [23, 43, 57–60].

Though ample preclinical studies spanning over three decades provide evidence for OIH, clinical studies have several notable limitations which challenge accurate assessment and thus prevalence estimates of OIH. Of primary concern is the fact that studies investigating OIH often utilize different measures of pain (e.g., thermal or cold stimulation) that may not be related to clinical pain, so interpretation and comparison between studies becomes difficult. These limitations led some authors to question the validity of OIH in humans [20, 25, 61]. Secondly, the numerous populations under study likely influence the evaluation of OIH. Specifically, a majority of existing clinical studies of OIH focus on several cohorts: healthy volunteers receiving acute opioids while undergoing human experimental pain testing [62–65], those with acute pain following various surgical procedures [51–53, 66, 67], patients suffering from chronic pain [41, 68–70] or chronic illnesses such as cancer [50, 71–74], and populations of individuals with OUD [23, 43, 57–60]. Third, OIH does not manifest in all patients receiving opioids; individual differences, including psychological factors, likely play a role in whether one develops OIH following opioid exposure, though research on this topic is needed. Finally, distinguishing OIH from tolerance and opioid withdrawal remains a challenge in clinical settings, as these phenomena share similar features, but are indeed distinct (Sects. 3.2, 3.3; Table 1). For instance, many studies assessing OIH, particularly under surgical contexts, are often criticized for not accurately measuring OIH but rather opioid tolerance and/or withdrawal. Specifically, a hallmark outcome of these studies is an increase in postoperative opioid consumption following abrupt termination of an acute, fast-acting opioid, indicative of tolerance and/or withdrawal rather than OIH [20, 25]. As outlined in Tables 1 and 2, OIH, opioid tolerance, opioid withdrawal, and OUD have distinct clinical features and thus can be separated.

3.2 OIH versus Tolerance

OIH is often associated with development of analgesic tolerance, defined as decreased analgesic potency following prolonged opioid administration [18, 75]. While it has been commonly believed that analgesic tolerance and OIH are synonymous, both preclinical and clinical studies have indicated that OIH is unrelated to prior opioid analgesia or tolerance [42, 68, 76–78]. In an attempt to elucidate the clinical ambiguity between tolerance and OIH, Chen et al. [30] distributed a survey to 1408 US practitioners consisting of targeted questions that assessed their clinical experiences with opioid treatment. The results identified a significant knowledge gap in the differentiation of tolerance versus OIH; the distinguishing factor was the finding that increasing opioid dose overcomes tolerance, but leaves OIH unresolved [30]. Most striking is the finding that a hyperalgesic patient subject to upward dose titration experiences a significant worsening of diffuse hyperalgesic symptoms as the opioid dose increases [18]. As such, effectively treating chronic pain while adjusting for tolerance and attempting to define and avoid hyperalgesia

Table 1 Distinguishing between opioid tolerance, withdrawal, opioid use disorder, and opioid-induced hyperalgesia: definitions, symptoms, and known solutions

Condition	Definition	Symptoms	Solution
Tolerance	A decreased analgesic response to a stable dose of opioid	Reappearance of pain with the same intensity as prior to treatment	Upward dose titration Opioid rotation
Withdrawal	A physiological reaction to the abrupt discontinuation of an opioid or following the administration of an opioid antagonist after recent opioid use	Dysphoric mood, gastrointestinal disturbances, muscle aches, lacrimation or rhinorrhea, pupillary dilation, sweating, piloerection, yawning, fever, insomnia	Downward dose titration Detoxification Opioid treatment
Opioid use disorder[a]	A pervasive and problematic pattern of opioid use occurring within a 12-month period, despite negative consequences	Recurrent use resulting in physical and interpersonal deficits, tolerance, withdrawal, drug craving and seeking, changes in mood and personality	Downward dose titration Detoxification Opioid maintenance Rehabilitation programs
Opioid-induced hyperalgesia	A state of diffuse increased pain sensitivity to a stimulus of stable intensity, independent of disease progression	Significant worsening of original pain; diffuse pain that is independent of original pain and worsens with upward dose titration	Promising: Opioid rotation Opioid cessation Adjuvant pharmacotherapies

Definitions adapted from the National Council on Alcoholism and Drug Dependence, Inc. [81, 82], the National Institute on Drug Abuse: the Neurobiology of Drug Addiction [81], and the DSM-5 [80]

[a] Formally opioid abuse and opioid dependence (DSM-4; [79])

Table 2 Criteria for diagnosing opioid-induced hyperalgesia in clinical populations[a]

1. Increased pain intensity during chronic opioid treatment
2. Absence of disease progression
3. Absence of clinical or pharmacological opioid withdrawal
4. Elimination of opioid tolerance (assessed by changes in pain following upward dose titration) as a causative factor
5. Decreased pain intensity following opioid dose reduction
6. Elimination of pseudoaddictive behavior

[a] Adapted from Eisenberg et al. [25]

becomes a difficult clinical problem (see Table 2 for suggested criteria for diagnosing OIH).

3.3 OIH's Relationship to Addiction

An additional complexity is OIH's unexplored relationship with OUD. In the Diagnostic and Statistical Manual of Mental Disorders 4 (DSM-IV) [79], opioid use was diagnosed as either abuse or dependence, with the former being a less severe or early phase manifestation of the latter. However, the DSM-5 has combined abuse and dependence into a single diagnosis of OUD, measured on a continuum ranging from mild to severe. According to the DSM-5, OUD is defined as a pervasive pattern of opioid use despite significant consequences [80]. OUD includes criteria clusters for impaired control over drug use, social impairment, risky use, and pharmacological criteria that includes tolerance and withdrawal (Table 1) [80–82]. It is important to note that for individuals who are taking opioids under proper medical supervision, tolerance and withdrawal are expected and thus should be weighted appropriately when considering a diagnosis of OUD.

It is possible that OIH may increase the likelihood of developing OUD. Specifically, OIH manifests as increased pain sensitivity, which could lead a patient to believe that they must consume more opioid than truly required to treat the original underlying pain condition. Furthermore, it is not clear if the hyperalgesia seen during opioid withdrawal is synonymous with OIH seen during continuous use, as preclinical studies have demonstrated a mechanistic difference [78, 83–86]. In the case of opioid withdrawal syndrome, hyperalgesia appears after abrupt termination of opioid use. For instance, in preclinical paradigms using discontinuous morphine delivery (i.e., multiple injections), hyperalgesia may be intensified by 'mini-withdrawal' episodes when compared with chronic administration paradigms [35, 87–89]. However, in the case of OIH, increased nociception persists or even worsens following continuous treatment with any one opioid [29, 42]. Further, case reports suggest that OIH typically dissipates after opioid cessation [50, 90]; however, only a handful of studies have

investigated this directly, the results of which suggest that more than 1 month of abstinence is necessary for pain responses of former opioid users to approach that of healthy control participants. Specifically, Compton [91] reported the resolution of OIH in former opioid users abstinent for an average of 1 year, although Pud et al. [60] reported no change in reduced cold pressor pain tolerance after 1 month of opioid cessation in a similar population.

Opioid overuse pain syndrome (OOPS) has recently been proposed by Mehendale et al. [8] to classify a subset of opioid users with chronic non-cancer pain who do not adequately respond to high doses of opioids, show signs of inappropriate use/OUD, have decreasing function despite opioid use, favor pharmacological treatments, and demonstrate OIH. Of particular importance, OOPS takes into consideration the biopsychosocial aspects of pain, noting that opioids also alleviate depression and anxiety related to pain catastrophizing, while also propagating euphoria. As such, the authors postulate that opioids may actually be treating the psychological response to pain more so than the physical pain itself. Such a diagnosis may be warranted in patients with chronic non-cancer pain who demonstrate the need for multidimensional treatment beyond the sole use of opioids, the latter of which should only be managed by a highly trained pain management physician as a last resort. In fact, it is recommended here that patients are tapered off opioids completely, and referred to other pharmacological and psychological interventions [8].

One should also note the distinction between OIH and pseudoaddiction, the latter representing scenarios in which a patient presents with drug-seeking behaviors/reports of increased pain as a result of insufficient treatment. In such a case, these behaviors cease once an effective pain management regimen is established [92].

4 The Neurobiology of OIH

Potential mechanisms underlying OIH have emerged from the escalating amount of attention this phenomenon has received over the past several decades. Perhaps most intriguing is the finding that OIH occurs independently of opioid receptors [42, 77, 93–96], and is not a consequence of either prior or concurrent opioid receptor activity [42]. As such, research spanning nearly two decades has focused on understanding how OIH manifests without direct involvement of the opioid receptor system, the main findings of which are summarized in the following sections.

4.1 Central Sensitization in OIH

Prolonged opioid exposure leads to positive system adaptation, or central sensitization, that includes allodynia, hyperalgesia, and an expansion of the receptive field, which results in secondary hyperalgesia. In nociceptive pathways, sensitization specifically references increased synaptic transmission/efficacy in somatosensory neurons of the spinal dorsal horn, and thus pain hypersensitivity, following peripheral noxious as well as innocuous stimuli [97, 98]. Importantly, as central sensitization results in reduced nociceptive thresholds and the consequential phenotypic expression of pain, it is likely an important mechanism for the development of OIH [98, 99]. Specifically, OIH may result from sensitization of primary afferent neurons as well as microglia [98], resulting in neuroplastic changes of receptor systems in the peripheral and central nervous system that lead to enhanced production, release, and spread of excitatory neurotransmission. This, in turn, results in the suppressed reuptake or increased release of neurotransmitters such as glutamate and substance P, subsequent sensitization of pain pathways, and ultimately manifests as amplified subjective nociceptive responses [32, 33, 89, 97, 100].

For instance, cells in the dorsal horn that express G-protein coupled neurokinin-1 receptors (NK-1) have been shown to project to supraspinal areas that facilitate pain processing, and an upregulation of this receptor has been implicated in OIH [101]. The endogenous ligand for NK-1, substance P is an excitatory neurotransmitter synthesized by primary afferent nociceptors [102], and is released in the dorsal horn after noxious stimulation [103]. Importantly, substance P has a documented role in central sensitization-induced hyperalgesia accompanying inflammatory pain [100]. For instance, in pathological pain states, there is increased substance P release in primary afferents following noxious stimulation, resulting in the internalization of NK-1 receptors in both superficial regions and deep layers of the dorsal horn. Although this is the theorized neuronal substrate of inflammatory pain, this mechanism has been hypothesized to play a role in the neuronal plasticity associated with OIH [104]. For example, preclinical studies have shown that substance P administration evokes chemical, thermal, and mechanical hyperalgesia following either intermittent or chronic exposure to morphine. Further, OIH evoked by both systemic and intrathecal morphine elicits substance P activity and increases spinal NK-1 receptor expression, suggesting a strong role for central sensitization in this paradoxical pain state [33, 89, 100].

In addition to the sensitization of afferent pathways, descending facilitation of nociception from the rostroventral medulla (RVM) has also been implicated in OIH. Specifically, this descending feedback has been found to increase spinal levels of the endogenous opioid peptide dynorphin [105–107]. Though originally proposed to be antinociceptive, dynorphin has more recently been found to be a

paradoxically pronociceptive kappa-opioid receptor agonist, modulating synaptic transmission via non-opioid receptor mechanisms [107]. That is, dynorphin potentiates pronociception that is naloxone-insensitive by increasing neuronal receptive field size and sensitizing N-methyl-D-aspartate (NMDA) receptors, resulting in the increased release and subsequent binding of excitatory neurotransmitters (i.e., glutamate) as well as cytokines [108], and consequent release of intracellular calcium [107, 109]. For instance, preclinical studies indicate that intrathecal administration of dynorphin produces mechanical, tactile, and cold allodynia, and mechanical hyperalgesia that is blocked by NMDA receptor antagonism (MK-801 or LY235959), but is unresponsive to opioid receptor blockade. Additionally, dynorphin antiserum obfuscates morphine-induced hyperalgesia [107, 110, 111]. The results of these studies suggest a role for central sensitization involving endogenous opioids in the descending, facilitative control of OIH.

4.2 Neuroimmune Mechanisms

Microglia are activated in response to drugs of abuse, including opioids, through activation of the toll-like receptor 4 (TLR4). As suggested by multiple studies, microglial activation results in reduction of the analgesic efficacy of opioids by development of tolerance and hyperalgesia. Specifically, microglia activation results in the release of pro-inflammatory cytokines [tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 and others], chemokines, lipid mediators of inflammation, matrix metalloproteases, excitatory amino acids, and nitric oxide [36, 38, 112–118], all of which enhance neuronal activation. The release of pro-inflammatory cytokines results in increased number and conductance of alpha-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) and NMDA receptors, and down-regulation of gamma-aminobutyric acid (GABA) receptors [36, 38]. Thus, the consequence is neuronal hyperexcitability and pain enhancement [36, 116, 117, 119, 120]. This pronociceptive microglial activity suggests that OIH may be a neuroinflammatory response initiated in opposition to analgesia, resulting from prolonged exposure to exogenous opioids [34, 38, 117, 118]. Thus, it is plausible that these proinflammatory mediators (cytokines and chemokines) may be clinically assessed as a biomarker of microglial activation and thus potentially OIH [37, 112, 115, 121] (Fig. 1).

Opioids have been shown to have direct actions on brain and spinal microglia [38, 115, 117, 119, 122–125]. Specifically, microglia express opioid receptors, though the behavioral significance of this remains unclear [113]. Of particular interest to microglia's role in neuroexcitatory opioid effects is TLR4, where morphine, buprenorphine, oxycodone, meperidine, methadone, fentanyl, and remifentanil are thought to exert significant agonist activity [36, 38, 114–116, 119, 120, 122, 126]. TLRs are innate immune pattern recognition receptors found primarily on microglia, and following inflammation, this receptor's activity is increased throughout the CNS. TLR4 stimulation is fundamental in the downstream activation of inflammatory transcription factors and release of proinflammatory factors [36, 117, 118, 127, 128] (Fig. 1).

TLR4 agonists reportedly enhance pain, whereas antagonizing TLR4 activity by blockade of either TLR4 or downstream signaling, or the use of TLR4 knockout mice, show potentiated morphine analgesia and attenuated morphine tolerance [117]. Furthermore, TLR4 binds (−)- and opioid receptor-inactive (+)- ligands nonstereoselectively; thus, studies have found that (+)- and (−)- naloxone and (+)-naltrexone stereoisomers block TLR4 signaling to suppress glial activation and neuropathic pain [36, 38, 116, 119, 120, 122, 129, 130]. While these studies indicate a potential role for TLR4 activation in OIH, other studies report conflicting evidence. For instance, a mouse model of OIH employed by the Kest lab utilizes concomitantly administered naltrexone in both acute and chronic models of OIH induced by either morphine [42] or fentanyl [44]. That is, while morphine analgesia is prevented in this paradigm, OIH persists in the presence of NTX, conceivably narrowing the possibility of morphine working directly via TLR4 to mediate hyperalgesia. However, further research is needed to determine the precise role, if any, that TLR4 has in OIH.

4.3 Neurotransmitter Mechanisms

Both the glutamate and GABA neurotransmitter systems have been implicated in the development and maintenance of OIH. Their proposed role in modulating opioid effects is summarized in the following sections.

4.3.1 Glutamate

The majority of research regarding the systems modulating OIH implicates a role for the NMDA receptor, for which glutamate is the endogenous ligand. The NMDA receptor system has a well-documented role in neural and behavioral plasticity, long-term potentiation, learning, and memory. In 1991, Trujillo and Akil [131] indicated a likely role for the NMDA receptor in the development of opioid tolerance and dependence, resulting from neural adaptations after repeated morphine exposure. As such, it is an excellent candidate receptor system for the study of the mechanism underlying opioid-induced effects, including OIH [131, 132].

NMDA receptors play a primary role in central sensitization and consequent inflammatory pain, although a knowledge base for the role it plays in peripheral

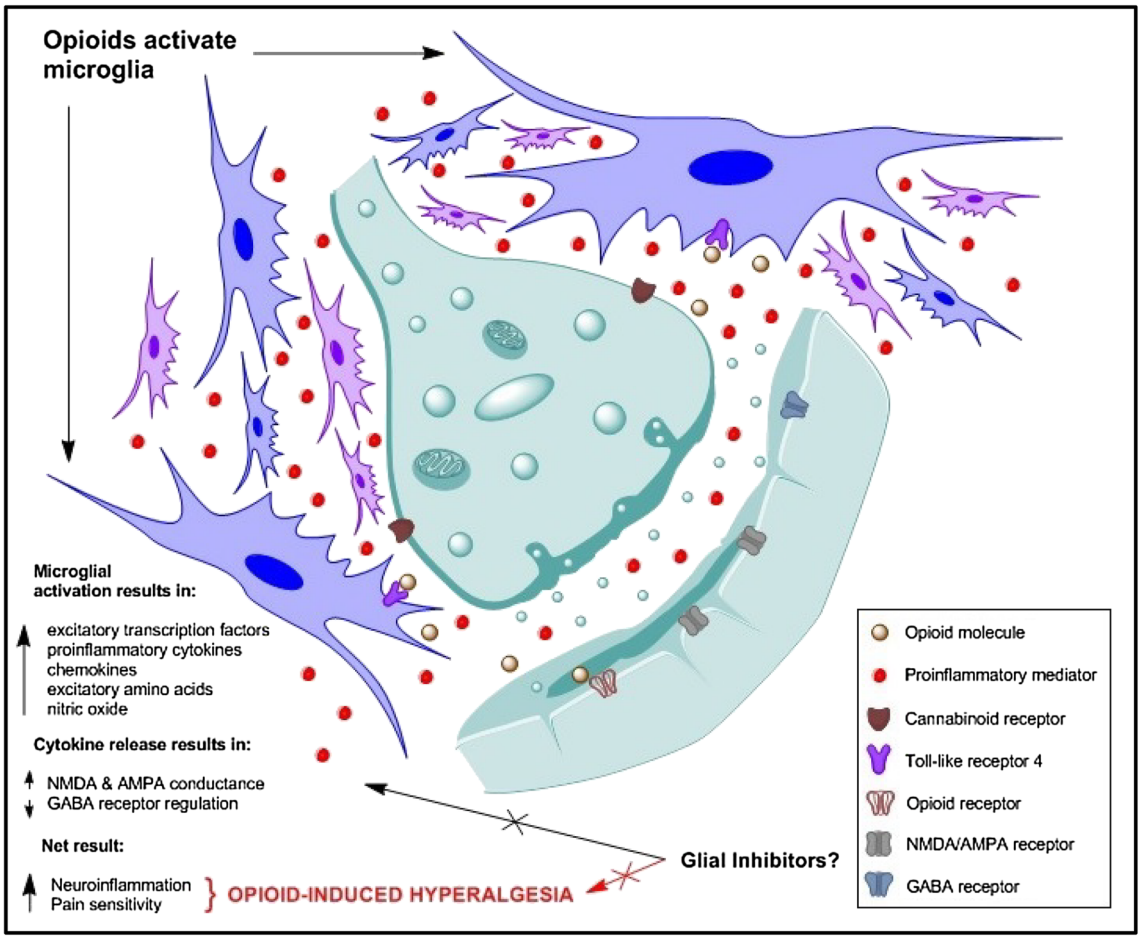

Fig. 1 Neuroimmune mechanisms of opioid-induced hyperalgesia. Opioids activate microglia, which in turn causes an increase in excitatory transcription factors, excitatory amino acids, nitric oxide, cytokines, and chemokines. The net result of this neuroimmune activity is inflammation, an increase in pain sensitivity, and thus the putative modulation of OIH. Pharmacological agents that inhibit microglial activation may attenuate OIH. *AMPA* alpha-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate, *GABA* gamma-aminobutyric acid, *OIH* opioid-induced hyperalgesia, *NMDA N*-methyl-D-aspartate. Figure is created by C. A. Arout using ChemBioDraw Ultra 14.0 (Cambridge Software, USA)

sensitization and OIH is not comprehensively established [46, 133–135]. As opioids do not have any binding affinity for NMDA receptors and NMDA receptor antagonists do not negatively affect acute opioid analgesia, it is implausible that opioids directly interact with this receptor system [31]. However, NMDA receptors are present in particularly dense concentrations in areas of the CNS that modulate pain signaling such as dorsal root ganglia, superficial layers of the dorsal horn laminae, the thalamus, and the hippocampus [93]. NMDA receptors in the spinal dorsal horn [31, 136, 137] and RVM [32, 33] appear to be particularly associated with OIH. Thus, several NMDA receptor antagonist compounds have been found to reduce OIH in both animal and human research, further illustrating a substantial role for this system in the modulation and potential treatment of this nociceptive state [39, 42, 46, 64, 88, 93, 138, 139].

4.3.2 GABA

The GABA receptor system and the opioid receptor system are closely intertwined, both neuroanatomically and functionally. For instance, GABA neurons express opioid receptors, particularly μ-opioid receptors, in multiple regions of the central nervous system critical to nociception [140, 141]. It has been suggested that chronic opioid administration leads to a downregulation of GABA receptors, resulting in decreased inhibition of pain signaling [36, 142].

Opioids exert their analgesic effects by inhibition of GABAergic neurons in the periaqueductal gray (PAG), a region critical to pain processing. Furthermore, opioid inhibition of GABA indirectly results in increased excitatory activity, and likely contributes excitatory opioid

effects, including OIH [140, 143, 144]. For instance, a recent preclinical study demonstrated that morphine induces hyperalgesia by downregulating the K+/Cl- co-transporter KCC2, resulting in altered Cl- homeostasis in the dorsal horn. The authors suggest the clinical application to be the restoration of $GABA_A$ inhibition to restore Cl- homeostasis in the dorsal horn, as this was effective in preventing OIH induced by morphine [78].

Another promising avenue of research is revealed in neurosteroids acting via the GABA receptor system. Neurosteroids bind to $GABA_A$ receptors to modulate a number of therapeutic effects (reviewed in Sect. 6.3.), including neuropathic pain [145–147]. As such, the GABA receptor system serves as a promising target of treatment in patients with OIH and warrants further investigation.

4.4 Opioid Metabolites

Subsequent to the finding that morphine metabolites possessed pronociceptive properties, it was initially thought that opioid metabolites mediate OIH. However, more recent preclinical studies have suggested otherwise. For instance, mice possess a variant UDP-glucuronosyltransferase (UGT) isoform involved in glucuronidation, which allows only for the formation of M3G and no M6G following morphine administration [148]. Thus, M6G is likely uninvolved in OIH, as mice do not produce this metabolite but nonetheless exhibit hyperalgesia [149]. Further, Swartjes et al. [93] demonstrated an indirect relationship between OIH and blood plasma concentrations of M3G in mice. Specifically, the group found that trough plasma levels of M3G corresponded to peak levels of morphine, at which point hyperalgesia worsened. This finding was detrimental in that it suggests morphine itself as the mediator of OIH; however, human studies have reported conflicting results regarding subjective pain relief and the ratio of morphine to its metabolites [150–152]. Swartjes et al. [93] also reported that mice lacking the ability to export M3G from the liver into systemic circulation ($MRP3^{-/-}$ mice) also develop OIH after an acute morphine administration. Further, Arout et al. [45] reported that while morphine in combination with the opioid receptor antagonist naltrexone resulted in significantly less activation in the PAG during a hyperalgesic state, naltrexone combined with M3G resulted in no such reduction of activity. Finally, other opioids shown to produce hyperalgesia, such as fentanyl, do not yield any known pronociceptive metabolites [44, 153]. As such, a rationale for opioid metabolites in the modulation of hyperalgesia induced by administration of the parent opioid is implausible.

5 Prospective Treatments for OIH

It is possible that OIH manifests as an adverse reaction to one particular opioid in an individual; as such, clinical findings indicate that opioid rotation [154] is sometimes sufficient to eliminate hyperalgesia and allodynia [39, 50, 71, 155]. Other studies suggest that downward dose titration [156–159] or complete discontinuation following detoxification [72, 91] is the most efficacious way to relieve this opioid-induced increased pain sensitivity. However, opioid discontinuation is not always a viable option; therefore, a solution that attenuates OIH such that the patient may continue benefitting from chronic opioids is needed. If a way to treat OIH can be elucidated, this will allow clinicians to continue prescribing opioids without concern over paradoxically increasing the very symptom they set out to treat: pain. Thus, adding adjuvant medications to opioids that target the receptor systems thought to underlie their hyperalgesic effects appears most promising (Table 3).

As reviewed above, there are a multitude of receptor pathways implicated in the modulation of OIH. Thus far, a host of animal studies have found that OIH is reversible by the NMDA receptor antagonists MK-801 [31, 42, 160–165], ketamine, or traxoprodil [93]. Human studies have found similar results by adding adjuvant ketamine [46, 54, 88, 166], as well as gabapentinoids such as pregabalin [49, 55] or gabapentin [23], or the cyclooxygenase-2 inhibitor parecoxib [48, 167], as reviewed in the subsequent sections. However, more recent research has shown that manipulating these substrates does not unequivocally resolve OIH. As such, other more recent studies have begun targeting other receptor systems in attempt to attenuate OIH in clinical treatment.

5.1 NMDA Receptor Antagonists

5.1.1 Ketamine

Ketamine is a potent noncompetitive NMDA receptor antagonist, first used for surgical anesthesia, and later found to produce analgesia through a possible opioid receptor-mediated mechanism [134, 168, 169]. There is an abundance of preclinical and clinical literature describing the ability of ketamine to reverse various pain states, ranging from chronic neuropathic pain contexts to OIH [170–172]. A wealth of literature details ketamine's use as an adjuvant to several opioids in a perioperative context; for example, it has been found to significantly reduce the amount of postoperative opioid consumption, attenuate incisional hyperalgesia (Table 3), and in some cases

Table 3 Clinical pharmacological studies investigating opioid-induced hyperalgesia

Medication	Mechanism	Citation	Population	Design	Assessment	Main findings
Dextromethorphan	NMDAR antagonism	Compton et al. 2008 [203]	MM patients $N = 40$ Aged 18–55 years	Randomized, double-blind, placebo-controlled	CPT + ES	Had no effect on OIH; noted sex differences in pre-methadone CPT tolerance: DEX worsened female CPT
Gabapentin	Actions at GABA-B receptors, GLT-1, noradrenergic receptors, and $\alpha 2\delta$ Ca^{2+} channels	Compton et al. 2010 [23]	MM patients $N = 26$ Aged 18–55 years	Randomized, double-blind, placebo-controlled	CPT	Decreased hyperalgesia
Ketamine	NMDAR antagonism	Angst et al. 2003 [88]	Opioid naïve healthy volunteers receiving remifentanil $N = 10$ Aged 20–35 years	Randomized, double-blind, crossover, placebo-controlled	HP + ES	Abolished extension of hyperalgesic skin area seen after remifentanil
		Hang et al. 2011 [166]	Laparoscopic cholecystectomy patients receiving remifentanil $N = 54$ Aged 18+ years	Randomized, placebo-controlled	VAS	Effective in preventing postoperative remifentanil-induced hyperalgesia
		Hong et al. 2011	Laparoscopic gynecologic surgical patients receiving remifentanil $N = 40$ Age range not specified	Randomized, double-blind, placebo-controlled	VAS	Reduced postoperative hyperalgesia and morphine consumption
		Joly et al. 2005 [46]	Abdominal surgery patients receiving remifentanil $N = 75$ Age range not specified	Randomized, double-blind, placebo-controlled	von Frey + PPT	Effective in preventing postoperative remifentanil-induced hyperalgesia; reduced postoperative morphine consumption
		Koppert et al. 2003 [64]	Healthy volunteers receiving remifentanil $N = 13$ Aged 20–40 years	Randomized, double-blind, crossover, placebo-controlled	ES	Enhanced remifentanil analgesia; abolished hyperalgesia
		Luginbühl et al. 2003 [62]	Healthy volunteers receiving remifentanil $N = 14$ Age range not specified	Randomized, double-blind, crossover, placebo-controlled	ES + PPT	Did not prevent remifentanil-induced hyperalgesia on PPT; increased analgesia on ES
		Yalcin et al. 2012 [54]	Abdominal hysterectomy patients receiving remifentanil $N = 90$ Aged 35–70 years	Randomized, placebo-controlled	PPT	Effective in preventing postoperative remifentanil-induced hyperalgesia and reducing postoperative morphine consumption

Table 3 continued

Medication	Mechanism	Citation	Population	Design	Assessment	Main findings
Ketamine + pregabalin	NMDAR antagonism; actions at α2δ Ca^{2+} channels	Martinez et al. 2014 [49]	Hip arthroplasty patients receiving sufentanil $N = 142$ Aged 18–80 years	Randomized, double-blind, placebo-controlled	VAS	Ketamine alone reduced the area of postoperative secondary hyperalgesia; each drug alone and the combination reduced postoperative morphine consumption; neither drug alone or the combination reduced postoperative pain intensity
Parecoxib	COX inhibition	Tröster et al. 2006 [167]	Healthy volunteers receiving remifentanil $N = 15$ Aged 20–45 years	Randomized, double-blind, crossover, placebo-controlled	ES	Enhanced remifentanil analgesia and prevented postinfusion remifentanil-induced hyperalgesia
		Lenz et al. 2011 [48]	Healthy volunteers receiving remifentanil $N = 16$ Aged 21–50 years	Randomized, double-blind, crossover, placebo-controlled	ES + CPT	Reduced the area of pinprick hyperalgesia, but not CPT pain
Pregabalin	Actions at α2δ Ca^{2+} channels	Lee et al. 2013 [55]	Laparoendoscopic urologic surgery patients receiving remifentanil $N = 90$ Aged 20–65 years	Randomized, double-blind, placebo-controlled	VAS	A single preoperative dose of pregabalin decreased hyperalgesia
Propranolol	Adrenergic antagonism	Chu et al. 2012 [47]	Healthy volunteers receiving remifentanil $N = 10$ Aged 18–32 years	Randomized, double-blind, crossover, placebo-controlled	ES + HP	Reduced magnitude of ES hyperalgesia; HP hyperalgesia was not evident

COX cyclooxygenase, *CPT* cold pressor test, *DEX* dextromethorphan, *ES* electrical stimulation, *GABA-B* gamma-aminobutyric acid B subtype, *GLT-1* glutamate transporter 1, *HP* heat pain, *MM* methadone maintenance, *NMDAR N*-methyl-D-aspartate receptor, *OIH* opioid-induced hyperalgesia, *PPT* pressure pain test, *VAS* Visual Analogue Scale

enhance analgesia in both animal and clinical investigations [66, 134, 138, 173–180].

How precisely ketamine induces analgesia is somewhat nebulous; it demonstrates activity at several different receptor systems in addition to the NMDA and opioid receptor systems, and affects multiple neurotransmitter pathways including both the cholinergic and monoamine systems. Additionally, it is not entirely clear if the pain relieving properties are due to analgesia, or antihyperalgesia [134, 169]. Further, it has been suggested that ketamine's analgesic properties may be partially mediated by its active metabolite, norketamine. Norketamine has a longer half-life than ketamine itself, is yielded in higher concentrations than ketamine following biotransformation, and is proposed to significantly contribute to ketamine's analgesic effects [181–183]. Nonetheless, ketamine's use in clinical practice for pain is limited, despite promise in studies of chronic pain [184], as well as clinically applied and experimental pain models of OIH (Table 3), in part due to its cardiovascular and psychotropic side effects [172, 185]. Further, ketamine is administered intravenously in clinical practice, as oral formulations are not commercially available; thus, use of this drug for chronic pain management is currently challenging and warrants further research.

5.1.2 Dextromethorphan

An antitussive drug, dextromethorphan is typically used as an over-the-counter cough suppressant, but has shown promise in pain suppression. Dextromethorphan antagonizes the spinal NMDA receptor system, and may manipulate opioid effects via this mechanism [186, 187]. Several studies have shown mixed results with dextromethorphan as an adjuvant medication in treating opioid tolerance [188–191] and withdrawal symptoms [192–197]. Numerous studies have cited dextromethorphan's ability to reduce intra- and post-operative morphine consumption [198–200], while others have not replicated these findings [201, 202]. Accordingly, Compton et al. [203] sought to determine if dextromethorphan would alleviate OIH in methadone maintenance patients. Following a 5-week trial, this group found no effect of dextromethorphan on OIH, as assessed by the cold pressor test and electrical stimulation pain measures [203] (Table 3). To date, no other clinical trials have investigated dextromethorphan in the context of OIH during concurrent opioid use.

5.1.3 Other NMDA Receptor Antagonists

While Swartjes and colleagues [93] attenuated hyperalgesia in rodents by administration of ketamine, they found additional evidence for the novel NR2B selective NMDA receptor antagonist traxoprodil in reversing hyperalgesia. Others have illustrated analgesic actions of this compound in rodents [204]. Such findings suggest a promising role for the NR2B subunit in particular in the development of OIH; this subunit densely populates both spinal and supraspinal sites such as the dorsal root ganglia, superficial layers of the dorsal horn laminae, the thalamus, hippocampus, and cortex [93]. Perhaps most appealing is that, in comparison with ketamine and other potent NMDA receptor antagonists, due to its selectivity for the NR2B subunit, traxoprodil appears to have limited psychotropic side effects. Thus, traxoprodil may be a plausible option for preventing or alleviating OIH. However, it is unexplored in this context, as only four animal studies [172, 204–206] have examined its potential use for the treatment of acute and chronic hyperalgesic states. The results of these studies suggest that although less potent when compared with ketamine, traxoprodil may be clinically efficacious for pain relief; further, it possesses few or no side effects when administered at analgesic doses.

Several studies have demonstrated OIH in patients enrolled in methadone maintenance treatment [23, 43, 57–60]. However, other studies have documented a reduction in OIH after patients were rotated onto methadone treatment. For instance, Axelrod and Reville [71] reported the success of methadone in reducing OIH in the case of a young girl suffering from cancer pain, who had previously been treated unsuccessfully with a multitude of other opioids. Additionally, Mercadante and colleagues [39] reported an individual case in which adjuvant methadone effectively reduced fentanyl-induced hyperalgesia. More recently, Mercadante et al. [39] reported the successful rotation of 12 patients to methadone, whose pain was originally unaffected by morphine. Methadone exhibits weak NMDA receptor-antagonistic properties; as such, it is plausible that a subset of patients that develop OIH resulting from other opioids may benefit from rotation to methadone. However, methadone's potential efficacy for OIH remains to be tested in randomized, controlled studies.

5.2 Gabapentinoids

There are two gabapentinoids that are used clinically: pregabalin and gabapentin. Pregabalin was designed as an antiepileptic drug and manipulates a multitude of neurotransmitters including glutamate, norepinephrine, and substance P [207]. A host of clinical research has elucidated a role for pregabalin in alleviating both postoperative pain and neuropathic pain, and in 2004, pregabalin was approved by the FDA for the treatment of the latter [208]. Subsequently, one study has directly investigated the potential effect of pregabalin in patients receiving opioids. Specifically, Lee et al. [55] reported the attenuation of putative OIH in patients receiving intraoperative

high-dose remifentanil by a single preoperative dose of pregabalin. A second study by Martinez et al. [49] combined pregabalin with ketamine, and reported that while patients who received only ketamine or pregabalin both demonstrated a significant decrease in postoperative morphine requirement, the combination of the two resulted in a significantly larger decrease in postoperative morphine. Thus, the combination of ketamine and pregabalin putatively offers a larger clinical benefit than the two in isolation (Table 3). As the impact of pregabalin on OIH is unclear, future studies should further investigate any potential benefit.

The anticonvulsant drug gabapentin was originally designed as an analog of GABA for the treatment of spasticity. Since, it has shown promise in chronic pain states, although its mechanism for this indication is not clear. It appears as though gabapentin may inhibit NMDA receptors, calcium channels, and peripheral nerves through GABA-mediated pathways. While a host of literature exists describing the ability of gabapentin to effectively treat neuropathic pain, clinical pharmacological studies regarding its impact on OIH are nearly nonexistent [209]. In fact, there is only one direct investigation of gabapentin this context. Specifically, Compton et al. [23] found that gabapentin effectively reduced OIH over the course of 1 week, as measured by cold pressor test latencies, in former opioid addicts currently maintained on methadone replacement (Table 3). These promising findings need to be replicated in different clinical samples that display OIH.

5.3 Propranolol

A β-adrenergic antagonist, propranolol was first administered to treat hypertension, and later found to attenuate anxiety. Following the results of a genetic study linking the β-adrenergic receptor to OIH [210], speculation arose regarding the clinical therapeutic effect of propranolol in treating OIH. Accordingly, Chu et al. [47] conducted a clinical trial in which propranolol effectively eliminated secondary hyperalgesia in healthy volunteers receiving remifentanil infusion and undergoing experimental pain testing (Table 3). As such, propranolol may prove useful in precluding OIH; however, further studies are needed.

5.4 Cyclooxygenase Inhibitors

Cyclooxygenase (COX) is an enzyme that is important for the formation of prostaglandins, which are hormones with a large role in sustaining homeostasis and mediating physiological effects in the body [211]. One proposed function of prostaglandins is to regulate inflammation; accordingly, several studies have sought to investigate whether inhibition of this system would affect OIH by utilizing NSAIDs that directly target COX. Specifically, two experimental pain investigations in healthy volunteers found that administration of one such drug, parecoxib, differentially affected experimentally induced OIH following remifentanil infusion [48, 167] (Table 3). Further, Tröster et al. [167] reported that parecoxib augmented remifentanil-induced analgesia. Thus, COX inhibitors such as parecoxib may have therapeutic potential in alleviating OIH.

6 Future Considerations in OIH

6.1 Glial Targets

To date, all approved medications for pain work by manipulating neuronal activity; however, more recent preclinical studies have suggested that other mechanisms be considered. Specifically, Hathway et al. [212] demonstrated hyperalgesia resulting from microglial central sensitization following brief, low-frequency stimulation of C-fibers in the dorsal horn, preventable by minocycline pretreatment. Importantly, these findings may have important implications for OIH; that pathological as well as physiological stimuli, the latter of which does not result in tissue damage, can lead to a microglial-regulated central sensitization state that is akin to that postulated in aberrant chronic pain [98, 212]. Further, co-administration of glial inhibitors has been found to potentiate opioid analgesia [117, 213, 214]; while their effects on OIH in clinical populations remain to be extensively studied, opioid administration does result in increased proinflammatory cytokine release and subsequent analgesic opposition [115]. Thus, it is feasible that glial inhibitors may attenuate OIH.

In light of the growing recognition that microglia play an important role in the development of nociception, this system may serve as a novel treatment target for OIH. Accordingly, numerous groups are studying the potential of inhibiting the glial system to enhance treatment of pain. For instance, the glial inhibitor ibudilast (MN166) has shown promise in the treatment of allodynia in neuropathic pain in an animal model [215, 216]. Considering that neuropathic pain and OIH share similar neurobiology, it is quite possible that targeting this system in treatment would reduce OIH and, in turn, increase the efficacy of opioid treatment. Further, another study reported an ability of this drug to induce a >3-fold increase in morphine analgesic potency [214]. Though the majority of research on ibudilast is in the preclinical stage, it has completed safety testing in humans [217, 218] and is thus of interest for the treatment of OIH.

A host of other glial-modifying agents have undergone animal testing in models of pain, the results of which are

reviewed in Hameed et al. [127]. Minocycline has also shown promise in studies of pain, particularly in an animal model of morphine effects. Though minocycline has non-selective actions at both neuronal and glial cell types within the nervous system [219], its anti-inflammatory actions are theorized to be a result of its inhibitory influence on the latter [220, 221]. Studies have shown this tetracycline antibiotic microglial inhibitor to reduce negative aspects of morphine treatment (respiratory depression, tolerance, and reward) while augmenting analgesia [213, 222]. This is of particular interest for treatment of OIH in populations with opioid addiction; it is possible the minocycline could alleviate OIH while also potentially dampening the risk of addiction resulting from long-term opioid treatment. Appropriately, there is currently one ongoing clinical trial investigating the effects of this drug on OIH in opioid-maintained patients (NCT02359006; ClinicalTrials.gov). Interestingly, minocycline is also reported to have neuroprotective effects [219, 222, 223]. Studies should be undertaken to examine the role of these drugs in alleviating OIH, as a host of literature highlights a potential role of glia in both pain and opioid-induced effects [38, 113, 115, 117, 212].

6.2 Cannabinoid Targets

Since the successful cloning of the cannabinoid receptors in the early 1990s [224, 225], many studies have examined the therapeutic potential of the cannabinoids in the treatment of chronic pain. Several studies have found no pain relieving benefits of delta-9-tetrahydrocannabinol (THC). For instance, Attal et al. [226] reported negative findings of oral THC in patients with chronic neuropathic pain. Interestingly, Wallace et al. [227] reported a dose-dependent analgesic effect of inhaled cannabis on experimental capsaicin-induced pain in a study of healthy volunteers. Specifically, they found no effect with a low dose, and analgesia resulting from a medium dose. Other studies have found negative results in postoperative acute pain patients, where oral or smoked cannabis yielded no benefit and in some cases enhanced pain [227–230]. Redmond et al. [231] also reported no effect of nabilone in healthy volunteers undergoing experimental pain testing. These sporadic negative findings are perhaps due to differences in formulation, administration, and potentially a lack of effectiveness for said acute pain conditions. Overall, it seems that studies of cannabis under acute pain paradigms and in healthy volunteers do not yield reliable results [227–231].

In the context of chronic pain, preliminary results indicate that agonists of this receptor system effectively reduce pain resulting from various conditions such as cancer, neuropathic pain, rheumatoid arthritis, multiple sclerosis, fibromyalgia, and HIV, putatively via anti-inflammatory properties [232–242]. For example, Eisenberg et al. [243] reported successful use of inhaled cannabis for the treatment of chronic neuropathic pain; a single dose was found to reduce pain by 45 % within 20 min, lasting for approximately 90 min with minimal adverse reactions. Unfortunately, generalizability of such findings is complicated by variations in cannabis products employed, ranging from crude herbal cannabis to several pharmaceutically developed products (described in [244]). Additionally, there are a limited number of large-scale randomized clinical trials examining efficacy and determining risk–benefit [244]. With that said, a function for cannabinoids in pain is mechanistically logical, as this receptor system densely populates regions intricately involved in pain processing such as the PAG, RVM, the dorsal spinal cord, and microglia [244, 245]. As such, the cannabinoid system may yield interesting results when combined with opioid therapy to reduce pain sensitivity, thus potentially eliminating OIH. In fact, Narang et al. [233] found that the combination of dronabinol and opioids resulted in increased pain relief when compared with participants utilizing only opioids; this synergy between THC and opioids has been supported by some investigations [246], but not others [247]. However, no studies have evaluated the effect of cannabis on OIH. Future studies should investigate a potential relationship between opioids, the cannabinoid system, and OIH, such that cannabinoids may be used as adjuvants to long-term opioid treatment to attenuate OIH.

6.3 Neurosteroids

Neurosteroids are steroidal hormones that are synthesized in the brain, and exert inhibitory effects mainly via $GABA_A$ receptors, glycine, and L- and T-type calcium channels [145–147, 248–251]. Among the most common neurosteroids are progesterone, pregnanolone, and allopregnanolone. Studies have revealed neurosteroids to have a therapeutic role in a number of conditions such as epilepsy, drug withdrawal-induced seizures, anxiety, premenstrual syndrome, stress, depression, and alcohol withdrawal. Furthermore, it is possible that some neurosteroids are produced in the nervous system in response to injury, exerting anti-inflammatory effects at the site of insult [145, 251]. Of particular relevance to pain and opioid research is neurosteroids' role in modulating neuronal plasticity and related activities of the nervous system, as well as their role in the sexual dimorphism of pain processing [145].

Subsequent to the finding that neurosteroids produce anesthesia in rat models and thus suppress pain sensation [252–254], neurosteroids have been found to promote analgesia [251, 255], and have documented efficacy in the

treatment of neuropathic pain [145]. Whereas lower levels of testosterone or progesterone have been associated with low nociceptive thresholds, injecting these steroidal hormones has been found to elicit analgesia [251, 256–260]. Several studies have also found that higher levels of progesterone decrease anesthetic [261] and postoperative analgesic requirements [262]. For instance, Lee et al. [262] found that parturient women with higher than average serum progesterone levels required less anesthesia and postoperative analgesic during cesarean delivery.

Due to their neuroprotective and antinociceptive effects [146], neurosteroids are a possible treatment target for alleviating OIH. Allopregnanolone in particular has shown promise in treating neuropathic pain (reviewed in [145]), and thus may be a potential candidate to attenuate OIH. While clinical use of neurosteroids is complicated by low bioavailability following rapid inactivation during metabolism, they have a favorable adverse effect profile and are markedly safer than currently available analgesics [145]. An interesting speculation lies in the potential connection between the aforementioned putatively dysregulated Cl- homeostasis in OIH [78] and the use of neurosteroids to treat OIH; while the authors suggested the use of benzodiazepines to restore the GABA inhibition induced by opioids [78], this combination is hazardous in clinical practice and is increasingly advised against [263]. Thus, neurosteroids could potentially achieve the same restoration of GABA inhibition while minimizing hazardous contraindications.

7 Concluding Remarks

This review highlights the importance of OIH in hindering the analgesic effects of opioids, especially with long-term opioid use. Additionally valuable would be considering OIH, in addition to analgesia, as a treatment target in the drug development process. Presently, clinical studies of OIH focus primarily on identifying this phenomenon in opioid-receiving populations, and determining its clinical relevance in regard to tolerance. To a lesser extent, there are studies investigating prevalence and methods to treat it; however, several methodological issues are present. Of primary concern is that while numerous investigations study OIH, it is not unequivocally recognized by clinicians due to a lack of a valid assessment tool to reliably separate OIH from tolerance or withdrawal, and aid in their diagnosis of suspected OIH. As a result, there are only a few studies examining the prevalence of OIH in clinical samples. Similarly, there is no consensus among researchers or practitioners as to the most appropriate method to detect OIH, as studies comparing the sensitivity and specificity of paradigms for detecting OIH are nearly nonexistent [264]. Furthermore, it has been reported that manipulations producing profound OIH on one pain assay may show no hyperalgesic liabilities on other assays, suggesting that OIH is both drug and modality specific. Animal studies also suggest that it is influenced by varying genetic backgrounds [265–268] and epigenetic factors [269], which needs to be further investigated in future human studies [270].

Secondly, most reports on successful treatment of OIH are case studies; there are few controlled experiments, and the few that exist are performed mostly in populations undergoing surgical procedures and subsequent short-term opioid treatment. In these scenarios, most patients are anesthetized with the short-acting opioid remifentanil, and subsequently given morphine in response to what is occasionally identified as remifentanil-induced hyperalgesia. While acute treatment of surgical pain is the scenario in which opioids were intended for, it is no longer the primary use, is not the sole context contributing to the rise in addiction, and thus does not accurately represent the modern day opioid-using population. Further, it is controversial as to whether these scenarios truly represent OIH, or are a manifestation of hyperalgesia resulting from opioid withdrawal. Future research should assess clinical manifestations of OIH in patients maintained on long-acting opioids for chronic pain conditions. Comprehensive analyses evaluating OIH in the entirety of opioid-consuming populations, using validated measures of pain with clinical relevance, are desperately needed, such that pain medicine can be fully informed with regard to this paradoxical, complicated state. OIH, in addition to analgesia, must be considered an aspect of chronic pain treatment, such that the efficacy of opioid therapy is increased by reducing the incidence of OIH in clinical practice. As highlighted by this review, there are several avenues of research that may prove fruitful in treating OIH via adjuvant pharmacotherapies. Perhaps the most promising route concerns glial mechanisms of inflammatory pain. As this area of study continues to bustle with new findings in the relationship between opioids and glia, we in the scientific community must address potential microglial inhibitors that may serve as effective adjuvants to opioids. Secondly, as the medical use of cannabinoids expands, we will likely see an increase in the number of patients reporting cannabis use for pain relief. As such, research is needed to assess the efficacy of cannabinoids in reducing OIH.

Finally, OIH has been shown to manifest differently in females as compared with males, yet preclinical and clinical studies including both sexes are strikingly limited. Most studies utilize only males to eliminate hormonal influences, a variable that is proving to be of increasing importance in the effective treatment of chronic pain. The sexual dimorphism of OIH and pain in general is a

fundamental characteristic that must not be ignored; future studies must be diligent in including both male and female participants, such that we may obtain the most accurate understanding of this paradoxical state of nociception.

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Compliance with Ethical Standards

Conflict of interest I. L. Petrakis reports a conflict of interest due to her role as a consultant for Alkermes. C. A. Arout, E. Edens, and M. Sofuoglu declare no conflicts of interest.

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References

1. Albutt C. On the abuse of hypodermic injections of morphia. Practitioner. 1870;3:327–30.
2. Gaskin DJ, Richard P. The economic costs of pain in the United States. J Pain. 2012;13(8):715–24.
3. Reuben DB, Alvanzo AAH, Ashikaga T, Bogat GA, Callahan CM, Ruffing V, et al. National Institutes of Health Pathways to Prevention Workshop: the role of opioids in the treatment of chronic pain. Ann Intern Med. 2015;162(4):295–300.
4. Dureja GP, Jain PN, Shetty N, Mandal SP, Prabhoo R, Joshi M, et al. Prevalence of chronic pain, impact on daily life, and treatment practices in India. Pain Pract. 2014;14(2):E51–62.
5. Ekholm O, Kurita GP, Højsted J, Juel K, Sjøgren P. Chronic pain, opioid prescriptions, and mortality in Denmark: a population-based cohort study. PAIN®. 2014;155(12):2486–90.
6. Henderson JV, Harrison CM, Britt HC, Bayram CF, Miller GC. Prevalence, causes, severity, impact, and management of chronic pain in Australian general practice patients. Pain Med. 2013;14(9):1346–61.
7. Schopflocher D, Taenzer P, Jovey R. The prevalence of chronic pain in Canada. Pain Res Manag. 2011;16(6):445.
8. Mehendale AW, Goldman MP, Mehendale RP. Opioid overuse pain syndrome (OOPS): the story of opioids, prometheus unbound. J Opioid Manag. 2013;9(6):421–38.
9. Paulozzi LJ, Mack KA, Hockenberry JM. Vital signs: variation among states in prescribing of opioid pain relievers and benzodiazepines—United States, 2012. Morb Mortal Wkly Rep. 2014;26:563–8.
10. Paulozzi LJ. Prescription drug overdoses: a review. J Saf Res. 2012;43(4):283–9.
11. Manchikanti L, Abdi S, Atluri S, Balog CC, Benyamin RM, Boswell MV, et al. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: part I—evidence assessment. Pain Phys. 2012;15(3 Suppl):S1–65.
12. Sullivan MD, Howe CQ. Opioid therapy for chronic pain in the United States: promises and perils. PAIN®. 2013;154(Supplement 1):S94–S100.
13. Manchikanti L, Damron K, McManus C, Barnhill R. Patterns of illicit drug use and opioid abuse in patients with chronic pain at initial evaluation: a prospective, observational study. Pain Physician. 2004;7(4):431–7.
14. Edlund MJ. The role of opioid prescription in incident opioid abuse and dependence among individuals with chronic non-cancer pain: the role of opioid prescription. Clin J Pain. 2014;30(7):557–64.
15. Abuse NIoD. Prescription drug abuse: chronic pain treatment and addiction. 2014. Available from: http://www.drugabuse.gov/publications/research-reports/prescription-drugs/chronic-pain-treatment-addiction. Accessed 18 Dec 2014.
16. Fraud CAI. Prescription for peril: how insurance fraud finances theft and abuse of addictive prescription drugs. Washington, DC: Coalition Against Insurance Fraud; 2007.
17. White AG, Birnbaum HG, Mareva MN, Daher M, Vallow S, Schein J, et al. Direct costs of opioid abuse in an insured population in the United States. J Manag Care Pharm. 2005;11(6):469.
18. Benyamin R, Trescot AM, Datta S, Buenaventura R, Adlaka R, Sehgal N, et al. Opioid complications and side effects. Pain Physician. 2008;11(2 Suppl):S105–20.
19. Ossipov MH, Lai J, Vanderah TW, Porreca F. Induction of pain facilitation by sustained opioid exposure: relationship to opioid antinociceptive tolerance. Life sci. 2003;73(6):783–800.
20. Tompkins DA, Campbell CM. Opioid-induced hyperalgesia: clinically relevant or extraneous research phenomenon? Curr Pain Headache Rep. 2011;15(2):129–36.
21. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. Pain Physician. 2011;14(2):145–61.
22. Chu LF, Angst MS, Clark D. Opioid-induced hyperalgesia in humans: molecular mechanisms and clinical considerations. Clin J Pain. 2008;24(6):479–96.
23. Compton P, Kehoe P, Sinha K, Torrington MA, Ling W. Gabapentin improves cold-pressor pain responses in methadone-maintained patients. Drug Alcohol Depend. 2010;109(1):213–9.
24. Lee JS, Kim SG, Jeong HJ, Kim JH, Yang YH, Jung WY. Difference of the naltrexone's effects in social drinkers by spicy food preference. J Korean Med Sci. 2014;29(5):714–8.
25. Eisenberg E, Suzan E, Pud D. Opioid-induced hyperalgesia (OIH): a real clinical problem or just an experimental phenomenon? J Pain Symptom Manag. 2014;49(3):632–6.
26. Raffa RB, Pergolizzi Jr JV. Opioid-induced hyperalgesia: is it clinically relevant for the treatment of pain patients? Pain Manag Nurs. 2013;14(3):e67–e83.
27. Heger S, Maier C, Otter K, Helwig U, Suttorp M, Berger A. Morphine induced allodynia in a child with brain tumour. BMJ. 1999;319(7210):627–9.
28. Low Y, Clarke CF, Huh BK. Opioid-induced hyperalgesia: a review of epidemiology, mechanisms and management. Singapore Med J. 2012;53(5):357–60.
29. Holtman JR Jr, Jellish WS. Opioid-induced hyperalgesia and burn pain. J Burn Care Res. 2012;33(6):692–701.
30. Chen L, Sein M, Vo T, Amhmed S, Zhang Y, Hilaire KS, et al. Clinical interpretation of opioid tolerance versus opioid-induced hyperalgesia. J Opioid Manag. 2014;10(6):383–93.
31. Mao J, Sung B, Ji R-R, Lim G. Chronic morphine induces downregulation of spinal glutamate transporters: implications in morphine tolerance and abnormal pain sensitivity. J Neurosci. 2002;22(18):8312–23.
32. Vanderah TW, Ossipov MH, Lai J, Malan TP Jr, Porreca F. Mechanisms of opioid-induced pain and antinociceptive tolerance: descending facilitation and spinal dynorphin. Pain. 2001;92(1–2):5–9.
33. Vanderah TW, Suenaga NM, Ossipov MH, Malan TP Jr, Lai J, Porreca F. Tonic descending facilitation from the rostral

ventromedial medulla mediates opioid-induced abnormal pain and antinociceptive tolerance. J Neurosci. 2001;21(1):279–86.
34. Simonnet G, Rivat C. Opioid-induced hyperalgesia: abnormal or normal pain? Neuroreport. 2003;14(1):1–7.
35. Ossipov MH, Lai J, King T, Vanderah TW, Malan TP, Hruby VJ, et al. Antinociceptive and nociceptive actions of opioids. J Neurobiol. 2004;61(1):126–48.
36. Li Q. Antagonists of toll like receptor 4 maybe a new strategy to counteract opioid-induced hyperalgesia and opioid tolerance. Med Hypotheses. 2012;79(6):754–6.
37. Watkins LR, Wiertelak EP, Goehler LE, Mooney-Heiberger K, Martinez J, Furness L, et al. Neurocircuitry of illness-induced hyperalgesia. Brain Res. 1994;639(2):283–99.
38. Watkins LR, Hutchinson MR, Rice KC, Maier SF. The "toll" of opioid-induced glial activation: improving the clinical efficacy of opioids by targeting glia. Trends Pharmacol Sci. 2009;30(11):581–91.
39. Mercadante S, Ferrera P, Arcuri E, Casuccio A. Opioid-induced hyperalgesia after rapid titration with intravenous morphine: switching and re-titration to intravenous methadone. Ann Palliat Med. 2012;1(1):10–3.
40. Ackerman WE 3rd. Paroxysmal opioid-induced pain and hyperalgesia. J Ky Med Assoc. 2006;104(9):419–23.
41. Chu LF, Clark DJ, Angst MS. Opioid tolerance and hyperalgesia in chronic pain patients after one month of oral morphine therapy: a preliminary prospective study. The Journal of Pain. 2006;7(1):43–8.
42. Juni A, Klein G, Kest B. Morphine hyperalgesia in mice is unrelated to opioid activity, analgesia, or tolerance: evidence for multiple diverse hyperalgesic systems. Brain Res. 2006;1070(1):35–44.
43. Compton P, Canamar CP, Hillhouse M, Ling W. Hyperalgesia in heroin dependent patients and the effects of opioid substitution therapy. J Pain. 2012;13(4):401–9.
44. Waxman AR, Arout C, Caldwell M, Dahan A, Kest B. Acute and chronic fentanyl administration causes hyperalgesia independently of opioid receptor activity in mice. Neurosci Lett. 2009;462(1):68–72.
45. Arout CA, Caldwell M, McCloskey DP, Kest B. C-Fos activation in the periaqueductal gray following acute morphine-3beta-D-glucuronide or morphine administration. Physiol Behav. 2014;10(130):28–33.
46. Joly V, Richebe P, Guignard B, Fletcher D, Maurette P, Sessler DI, et al. Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. Anesthesiology. 2005;103(1):147–55.
47. Chu LF, Cun T, Ngai LK, Kim JE, Zamora AK, Young CA, et al. Modulation of remifentanil-induced postinfusion hyperalgesia by the β-blocker propranolol in humans. Pain. 2012;153(5):974–81.
48. Lenz H, Raeder J, Draegni T, Heyerdahl F, Schmelz M, Stubhaug A. Effects of COX inhibition on experimental pain and hyperalgesia during and after remifentanil infusion in humans. Pain. 2011;152(6):1289–97.
49. Martinez V, Cymerman A, Ben Ammar S, Fiaud J, Rapon C, Poindessous F, et al. The analgesic efficiency of combined pregabalin and ketamine for total hip arthroplasty: a randomised, double-blind, controlled study. Anaesthesia. 2014;69(1):46–52.
50. Sjøgren P, Jensen N-H, Jensen TS. Disappearance of morphine-induced hyperalgesia after discontinuing or substituting morphine with other opioid agonists. Pain. 1994;59(2):313–6.
51. Cooper D, Lindsay S, Ryall D, Kokri M, Eldabe S, Lear G. Does intrathecal fentanyl produce acute cross-tolerance to iv morphine? Br J Anaesth. 1997;78(3):311–3.
52. Chia Y-Y, Liu K, Wang J-J, Kuo M-C, Ho S-T. Intraoperative high dose fentanyl induces postoperative fentanyl tolerance. Can J Anesth. 1999;46(9):872–7.
53. Guignard B, Bossard AE, Coste C, Sessler DI, Lebrault C, Alfonsi P, et al. Acute opioid tolerance: intraoperative remifentanil increases postoperative pain and morphine requirement. Anesthesiology. 2000;93(2):409–17.
54. Yalcin N, Uzun ST, Reisli R, Borazan H, Otelcioglu S. A comparison of ketamine and paracetamol for preventing remifentanil induced hyperalgesia in patients undergoing total abdominal hysterectomy. Int J Med Sci. 2012;9(5):327.
55. Lee C, Lee H-W, Kim J-N. Effect of oral pregabalin on opioid-induced hyperalgesia in patients undergoing laparo-endoscopic single-site urologic surgery. Korean J Anesthesiol. 2013;64(1):19–24.
56. Koppert W, Schmelz M. The impact of opioid-induced hyperalgesia for postoperative pain. Best Pract Res Clin Anaesthesiol. 2007;21(1):65–83.
57. Compton P, Charuvastra V, Ling W. Pain intolerance in opioid-maintained former opiate addicts: effect of long-acting maintenance agent. Drug Alcohol Depend. 2001;63(2):139–46.
58. Doverty M, White JM, Somogyi AA, Bochner F, Ali R, Ling W. Hyperalgesic responses in methadone maintenance patients. Pain. 2001;90(1):91–6.
59. Doverty M, Somogyi AA, White JM, Bochner F, Beare CH, Menelaou A, et al. Methadone maintenance patients are cross-tolerant to the antinociceptive effects of morphine. Pain. 2001;93(2):155–63.
60. Pud D, Cohen D, Lawental E, Eisenberg E. Opioids and abnormal pain perception: New evidence from a study of chronic opioid addicts and healthy subjects. Drug Alcohol Depend. 2006;82(3):218–23.
61. Fallon M, Colvin L. Opioid-induced hyperalgesia: fact or fiction? Palliat Med. 2008;22(1):5–6.
62. Luginbühl M, Gerber A, Schnider TW, Petersen-Felix S, Arendt-Nielsen L, Curatolo M. Modulation of remifentanil-induced analgesia, hyperalgesia, and tolerance by small-dose ketamine in humans. Anesth Analg. 2003;96(3):726–32.
63. Holtman J, Johnson J, Kelly T, Wala E. (663): Opioid-induced abnormal pain sensitivity. The Journal of Pain. 2007;8(4):S16.
64. Koppert W, Sittl R, Scheuber K, Alsheimer M, Schmelz M, Schüttler J. Differential modulation of remifentanil-induced analgesia and postinfusion hyperalgesia by S-ketamine and clonidine in humans. Anesthesiology. 2003;99(1):152–9.
65. Compton P, Athanasos P, Elashoff D. Withdrawal hyperalgesia after acute opioid physical dependence in nonaddicted humans: a preliminary study. J Pain. 2003;4(9):511–9.
66. Lee SH, Cho SY, Lee HG, Choi JI, Yoon MH, Kim WM. Tramadol induced paradoxical hyperalgesia. Pain Physician. 2013;16(1):41–4.
67. Hina N, Fletcher D, Poindessous-Jazat F, Martinez V. Hyperalgesia induced by low-dose opioid treatment before orthopaedic surgery: An observational case-control study. Eur J Anaesthesiol. 2015;32(4):255–61.
68. Suzan E, Eisenberg E, Treister R, Haddad M, Pud D. A negative correlation between hyperalgesia and analgesia in patients with chronic radicular pain: is hydromorphone therapy a double-edged sword? Pain Physician. 2013;16(1):65–76.
69. Hooten WM, Lamer TJ, Twyner C. Opioid-induced hyperalgesia in community-dwelling adults with chronic pain. Pain. 2015;156(6):1145–52.
70. Pivec R, Issa K, Naziri Q, Kapadia BH, Bonutti PM, Mont MA. Opioid use prior to total hip arthroplasty leads to worse clinical outcomes. Int Orthop. 2014;38(6):1159–65.

71. Axelrod DJ, Reville B. Using methadone to treat opioid-induced hyperalgesia and refractory pain. J Opioid Manag. 2007;3(2):113–4.
72. Monterubbianesi MC, Capuccini J, Ferioli I, Tassinari D, Sarti D, Raffaeli W. High opioid dosage rapid detoxification of cancer patient in palliative care with the Raffaeli model. J Opioid Manag. 2012;8(5):292–8.
73. Pirbudak L, Sevinc A, Maralcan G, Kilic E. Pain management with intrathecal clonidine in a colon cancer patient with opioid hyperalgesia: case presentation. Agri : Agri (Algoloji) Derneği'nin Yayin organidir = J Turk Soc Algol. 2014;26(2):93–6.
74. Kaye AD, Alian AA, Vadivelu N, Chung KS. Perioperative dilemma: challenges of the management of a patient on mega doses of morphine and methadone. J Opioid Manag. 2014;10(1):69–72.
75. Dumas EO, Pollack GM. Opioid tolerance development: a pharmacokinetic/pharmacodynamic perspective. The AAPS J. 2008;10(4):537–51.
76. Yoburn BC, Cohen AH, Inturrisi CE. Pharmacokinetics and pharmacodynamics of subcutaneous naltrexone pellets in the rat. J Pharmacol Exp Ther. 1986;237(1):126–30.
77. Juni A, Klein G, Pintar J, Kest B. Nociception increases during opioid infusion in opioid receptor triple knock-out mice. Neuroscience. 2007;147(2):439–44.
78. Ferrini F, Trang T, Mattioli T-AM, Laffray S, Del'Guidice T, Lorenzo L-E, et al. Morphine hyperalgesia gated through microglia-mediated disruption of neuronal Cl- homeostasis. Nat Neurosci. 2013;16(2):183–92.
79. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.
80. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA: American Psychiatric Association; 2013.
81. Abuse NIoD. The neurobiology of drug addiction. 2007. Available from: http://www.drugabuse.gov/publications/teaching-packets/neurobiology-drug-addiction/section-iii-action-heroin-morphine. Accessed 13 Nov 2014.
82. National Council on Alcoholism and Drug Dependence I. Signs and symptoms. 2014. Available from: https://ncadd.org/learn-about-drugs/signs-and-symptoms. Accessed 22 Dec 2014.
83. Harris AC, Hanes SL, Gewirtz JC. Potentiated startle and hyperalgesia during withdrawal from acute morphine: effects of multiple opiate exposures. Psychopharmacology. 2004;176(3–4):266–73.
84. Dunbar SA, Karamian I, Yeatman A, Zhang J. Effects of recurrent withdrawal on spinal GABA release during chronic morphine infusion in the rat. Eur J Pharmacol. 2006;535(1):152–6.
85. Dunbar SA, Karamian I, Zhang J. Ketorolac prevents recurrent withdrawal induced hyperalgesia but does not inhibit tolerance to spinal morphine in the rat. Eur J Pain. 2007;11(1):1–6.
86. Manchikanti L. Opioid-induced hyperalgesia method is a clinically relevant issue. Ann Palliat Med. 2012;1(1):2–3.
87. Gutstein HB. The effects of pain on opioid tolerance: how do we resolve the controversy? Pharmacol Rev. 1996;48(3):403–7.
88. Angst MS, Koppert W, Pahl I, Clark DJ, Schmelz M. Short-term infusion of the mu-opioid agonist remifentanil in humans causes hyperalgesia during withdrawal. Pain. 2003;106(1–2):49–57.
89. Li X, Clark JD. Hyperalgesia during opioid abstinence: mediation by glutamate and substance p. Anesth Analg. 2002;95(4):979–84.
90. Sjøgren P, Thunedborg L, Christrup L, Hansen S, Franks J. Is development of hyperalgesia, allodynia and myoclonus related to morphine metabolism during long-term administration?: Six case histories. Acta Anaesthesiol Scand. 1998;42(9):1070–5.
91. Compton MA. Cold-pressor pain tolerance in opiate and cocaine abusers: correlates of drug type and use status. J Pain Symptom Manag. 1994;9(7):462–73.
92. Weissman DE, Haddox JD. Opioid pseudoaddiction—an iatrogenic syndrome. Pain. 1989;36(3):363–6.
93. Swartjes M, Mooren R, Waxman AR, Arout C, van de Wetering K, den Hartigh J, et al. Morphine-induced hyperalgesia develops without involvement of morphine-3-glucuronide and is prevented by selective and non-selective *N*-methyl-D-aspartate antagonists. Mol Med. 2012;18(1):1320–6.
94. Woolf CJ. Intrathecal high dose morphine produces hyperalgesia in the rat. Brain Res. 1981;209(2):491–5.
95. Yaksh T, Harty G, Onofrio B. High dose of spinal morphine produce a nonopiate receptor-mediated hyperesthesia: clinical and theoretic implications. Anesthesiology. 1986;64(5):590–7.
96. Sakurada T, Watanabe C, Okuda K, Sugiyama A, Moriyama T, Sakurada C, et al. Intrathecal high-dose morphine induces spinally-mediated behavioral responses through NMDA receptors. Mol Brain Res. 2002;98(1):111–8.
97. Ji R-R, Kohno T, Moore KA, Woolf CJ. Central sensitization and LTP: do pain and memory share similar mechanisms? Trends Neurosci. 2003;26(12):696–705.
98. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011;152(3 Suppl):S2–15.
99. Mao J. Opioid-induced abnormal pain sensitivity: implications in clinical opioid therapy. Pain. 2002;100(3):213–7.
100. King T, Gardell LR, Wang R, Vardanyan A, Ossipov MH. Role of NK-1 neurotransmission in opioid-induced hyperalgesia. Pain. 2005;116(3):276–88.
101. Nichols ML, Allen BJ, Rogers SD, Ghilardi JR, Honore P, Luger NM, et al. Transmission of chronic nociception by spinal neurons expressing the substance P receptor. Science. 1999;286(5444):1558–61.
102. McCarthy PW, Lawson SN. Cell type and conduction velocity of rat primary sensory neurons with substance P-like immunoreactivity. Neuroscience. 1989;28(3):745–53.
103. Duggan AW, Morton CR, Zhao ZQ, Hendry IA. Noxious heating of the skin releases immunoreactive substance P in the substantia gelatinosa of the cat: a study with antibody microprobes. Brain Res. 1987;403(2):345–9.
104. Takeda Y, Chou KB, Takeda J, Sachais BS, Krause JE. Molecular cloning, structural characterization and functional expression of the human substance P receptor. Biochem Biophys Res Commun. 1991;179(3):1232–40.
105. Gardell LR, Wang R, Burgess SE, Ossipov MH, Vanderah TW, Malan TP Jr, et al. Sustained morphine exposure induces a spinal dynorphin-dependent enhancement of excitatory transmitter release from primary afferent fibers. J Neurosci. 2002;22(15):6747–55.
106. Wang Z, Gardell LR, Ossipov MH, Vanderah TW, Brennan MB, Hochgeschwender U, et al. Pronociceptive actions of dynorphin maintain chronic neuropathic pain. J Neurosci. 2001;21(5):1779–86.
107. Laughlin TM, Vanderah TW, Lashbrook J, Nichols ML, Ossipov M, Porreca F, et al. Spinally administered dynorphin A produces long-lasting allodynia: involvement of NMDA but not opioid receptors. Pain. 1997;72(1–2):253–60.
108. Laughlin TM, Bethea JR, Yezierski RP, Wilcox GL. Cytokine involvement in dynorphin-induced allodynia. Pain. 2000;84(2):159–67.
109. Lai J, Ossipov MH, Vanderah TW, Malan TP Jr, Porreca F. Neuropathic pain: the paradox of dynorphin. Mol Interv. 2001;1(3):160–7.
110. Vanderah TW, Gardell LR, Burgess SE, Ibrahim M, Dogrul A, Zhong CM, et al. Dynorphin promotes abnormal pain and spinal

opioid antinociceptive tolerance. J Neurosci. 2000;20(18):7074–9.
111. Vanderah TW, Laughlin T, Lashbrook JM, Nichols ML, Wilcox GL, Ossipov MH, et al. Single intrathecal injections of dynorphin A or des-Tyr-dynorphins produce long-lasting allodynia in rats: blockade by MK-801 but not naloxone. Pain. 1996;68(2–3):275–81.
112. Deleo JA, Tanga FY, Tawfik VL. Neuroimmune activation and neuroinflammation in chronic pain and opioid tolerance/hyperalgesia. Neuroscientist. 2004;10(1):40–52.
113. Coller JK, Hutchinson MR. Implications of central immune signaling caused by drugs of abuse: mechanisms, mediators and new therapeutic approaches for prediction and treatment of drug dependence. Pharmacol Ther. 2012;134(2):219–45.
114. Hutchinson MR, Bland ST, Johnson KW, Rice KC, Maier SF, Watkins LR. Opioid-induced glial activation: mechanisms of activation and implications for opioid analgesia, dependence, and reward. Scientific World J. 2007;7:98–111.
115. Hutchinson MR, Coats BD, Lewis SS, Zhang Y, Sprunger DB, Rezvani N, et al. Proinflammatory cytokines oppose opioid-induced acute and chronic analgesia. Brain Behav Immun. 2008;22(8):1178–89.
116. Hutchinson MR, Lewis SS, Coats BD, Rezvani N, Zhang Y, Wieseler JL, et al. Possible involvement of toll-like receptor 4/myeloid differentiation factor-2 activity of opioid inactive isomers causes spinal proinflammation and related behavioral consequences. Neuroscience. 2010;167(3):880–93.
117. Eidson LN, Murphy AZ. Blockade of toll-like receptor 4 attenuates morphine tolerance and facilitates the pain relieving properties of morphine. J Neurosci. 2013;33(40):15952–63.
118. Jacobsen J, Watkins LR, Hutchinson MR. Discovery of a novel site of opioid action at the innate immune pattern-recognition receptor TLR4 and its role in addiction. Int Rev Neurobiol. 2013;118:129–63.
119. Hutchinson MR, Zhang Y, Shridhar M, Evans JH, Buchanan MM, Zhao TX, et al. Evidence that opioids may have toll-like receptor 4 and MD-2 effects. Brain Behav Immun. 2010;24(1):83–95.
120. Lewis SS, Hutchinson MR, Rezvani N, Loram LC, Zhang Y, Maier SF, et al. Evidence that intrathecal morphine-3-glucuronide may cause pain enhancement via toll-like receptor 4/MD-2 and interleukin-1β. Neuroscience. 2010;165(2):569–83.
121. Watkins LR, Maier SF, Goehler LE. Immune activation: the role of pro-inflammatory cytokines in inflammation, illness responses and pathological pain states. Pain. 1995;63(3): 289–302.
122. Hutchinson MR, Zhang Y, Brown K, Coats BD, Shridhar M, Sholar PW, et al. Non-stereoselective reversal of neuropathic pain by naloxone and naltrexone: involvement of toll-like receptor 4 (TLR4). Eur J Neurosci. 2008;28(1):20–9.
123. Narita M, Miyatake M, Narita M, Shibasaki M, Shindo K, Nakamura A, et al. Direct evidence of astrocytic modulation in the development of rewarding effects induced by drugs of abuse. Neuropsychopharmacology. 2006;31(11):2476–88.
124. Horvath RJ, DeLeo JA. Morphine enhances microglial migration through modulation of P2X4 receptor signaling. J Neurosci. 2009;29(4):998–1005.
125. Takayama N, Ueda H. Morphine-induced chemotaxis and brain-derived neurotrophic factor expression in microglia. J Neurosci. 2005;25(2):430–5.
126. Hutchinson MR, Northcutt A, Hiranita T, Wang X, Lewis S, Thomas J, et al. Opioid activation of toll-like receptor 4 contributes to drug reinforcement. J Neurosci. 2012;32(33):11187–200.
127. Hameed H, Hameed M, Christo PJ. The effect of morphine on glial cells as a potential therapeutic target for pharmacological development of analgesic drugs. Curr Pain Headache Rep. 2010;14(2):96–104.
128. Wang X, Loram LC, Ramos K, de Jesus AJ, Thomas J, Cheng K, et al. Morphine activates neuroinflammation in a manner parallel to endotoxin. Proc Natl Acad Sci USA. 2012;109(16): 6325–30.
129. Antonilli L, Petecchia E, Caprioli D, Badiani A, Nencini P. Effect of repeated administrations of heroin, naltrexone, methadone, and alcohol on morphine glucuronidation in the rat. Psychopharmacology. 2005;182(1):58–64.
130. Stevens C, Aravind S, Das S, Davis R. Pharmacological characterization of LPS and opioid interactions at the toll-like receptor 4. Br J Pharmacol. 2013;168(6):1421–9.
131. Trujillo KA, Akil H. Inhibition of morphine tolerance and dependence by the NMDA receptor antagonist MK-801. Science. 1991;251(4989):85–7.
132. Trujillo KA. Effects of noncompetitive *N*-methyl-D-aspartate receptor antagonists on opiate tolerance and physical dependence. Neuropsychopharmacology. 1995;13(4):301–7.
133. Mao J, Price DD, Mayer DJ. Mechanisms of hyperalgesian and morphine tolerance: a current view of their possible interactions. Pain. 1995;62(3):259–74.
134. De Kock M, Lavand'homme P, Waterloos H. 'Balanced analgesia'in the perioperative period: is there a place for ketamine? Pain. 2001;92(3):373–80.
135. Du J, Zhou S, Coggeshall R, Carlton S. N-methyl-d-aspartate-induced excitation and sensitization of normal and inflamed nociceptors. Neuroscience. 2003;118(2):547–62.
136. Sluka K, Audette K. Activation of protein kinase C in the spinal cord produces mechanical hyperalgesia by activating glutamate receptors, but does not mediate chronic muscle-induced hyperalgesia. Mol Pain. 2006;2(13):1–9.
137. Gladding CM, Raymond LA. Mechanisms underlying NMDA receptor synaptic/extrasynaptic distribution and function. Mol Cell Neurosci. 2011;48(4):308–20.
138. Guignard B, Coste C, Costes H, Sessler DI, Lebrault C, Morris W, et al. Supplementing desflurane-remifentanil anesthesia with small-dose ketamine reduces perioperative opioid analgesic requirements. Anesth Analg. 2002;95(1):103–8.
139. Zhao Y-L, Chen S-R, Chen H, Pan H-L. Chronic opioid potentiates presynaptic but impairs postsynaptic *N*-methyl-D-aspartic acid receptor activity in spinal cords implications for opioid hyperalgesia and tolerance. J Biol Chem. 2012;287(30):25073–85.
140. Kalyuzhny AE, Wessendorf MW. Relationship of μ-and δ-opioid receptors to GABAergic neurons in the central nervous system, including antinociceptive brainstem circuits. J Comp Neurol. 1998;392(4):528–47.
141. Kalyuzhny AE, Dooyema J, Wessendorf MW. Opioid-and GABAA-receptors are co-expressed by neurons in rat brain. Neuroreport. 2000;11(12):2625–8.
142. Watkins LR, Hutchinson MR, Ledeboer A, Wieseler-Frank J, Milligan ED, Maier SF. Norman cousins lecture. Glia as the "bad guys": implications for improving clinical pain control and the clinical utility of opioids. Brain Behav Immun. 2007;21(2):131–46.
143. Cohen GA, Doze VA, Madison DV. Opioid inhibition of GABA release from presynaptic terminals of rat hippocampal interneurons. Neuron. 1992;9(2):325–35.
144. Vaughan CW, Ingram SL, Connor MA, Christie MJ. How opioids inhibit GABA-mediated neurotransmission. Nature. 1997;390(6660):611–4.
145. Patte-Mensah C, Meyer L, Taleb O, Mensah-Nyagan AG. Potential role of allopregnanolone for a safe and effective therapy of neuropathic pain. Prog Neurobiol. 2014;113:70–8.

146. Schumacher M, Mattern C, Ghoumari A, Oudinet J, Liere P, Labombarda F, et al. Revisiting the roles of progesterone and allopregnanolone in the nervous system: resurgence of the progesterone receptors. Prog Neurobiol. 2014;113:6–39.
147. Melcangi RC, Panzica GC. Allopregnanolone: state of the art. Prog Neurobiol. 2014;113:1–5.
148. Zelcer N, van de Wetering K, Hillebrand M, Sarton E, Kuil A, Wielinga PR, et al. Mice lacking multidrug resistance protein 3 show altered morphine pharmacokinetics and morphine-6-glucuronide antinociception. Proc Natl Acad Sci USA. 2005;102(20):7274–9.
149. van Dorp EL, Kest B, Kowalczyk WJ, Morariu AM, Waxman AR, Arout CA, et al. Morphine-6beta-glucuronide rapidly increases pain sensitivity independently of opioid receptor activity in mice and humans. Anesthesiology. 2009;110(6):1356–63.
150. Hammoud HA, Aymard G, Lechat P, Boccheciampe N, Riou B, Aubrun F. Relationships between plasma concentrations of morphine, morphine-3-glucuronide, morphine-6-glucuronide, and intravenous morphine titration outcomes in the postoperative period. Fundam Clin Pharmacol. 2011;25(4):518–27.
151. Samuelsson H, Hedner T, Venn R, Michalkiewicz A. CSF and plasma concentrations of morphine and morphine glucuronides in cancer patients receiving epidural morphine. Pain. 1993;52(2):179–85.
152. De Gregori S, Minella CE, De Gregori M, Tinelli C, Ranzani GN, Govoni S, et al. Clinical pharmacokinetics of morphine and its metabolites during morphine dose titration for chronic cancer pain. Ther Drug Monit. 2014;36(3):335–44.
153. Li X, Angst MS, Clark JD. A murine model of opioid-induced hyperalgesia. Mol Brain Res. 2001;86(1):56–62.
154. Fine PG, Portenoy RK. Establishing "Best Practices" for opioid rotation: conclusions of an expert panel. J Pain Symptom Manag. 2009;38(3):418–25.
155. Juba KM, Wahler RG, Daron SM. Morphine and hydromorphone-induced hyperalgesia in a hospice patient. J Palliat Med. 2013;16(7):809–12.
156. Vorobeychik Y, Chen L, Bush MC, Mao J. Improved opioid analgesic effect following opioid dose reduction. Pain Med (Malden, Mass). 2008;9(6):724–7.
157. Wilson GR, Reisfield GM. Morphine hyperalgesia: a case report. Am J Hosp Palliat Care. 2003;20(6):459–61.
158. de Conno F, Caraceni A, Martini C, Spoldi E, Salvetti M, Ventafridda V. Hyperalgesia and myoclonus with intrathecal infusion of high-dose morphine. Pain. 1991;47(3):337–9.
159. Vorobeychik Y, Chen L, Bush MC, Mao J. Improved opioid analgesic effect following opioid dose reduction. Pain Med. 2008;9(6):724–7.
160. Juni A, Cai M, Stankova M, Waxman AR, Arout C, Klein G, et al. Sex-specific mediation of opioid-induced hyperalgesia by the melanocortin-1 receptor. Anesthesiology. 2010;112(1):181–8.
161. Juni A, Klein G, Kowalczyk B, Ragnauth A, Kest B. Sex differences in hyperalgesia during morphine infusion: effect of gonadectomy and estrogen treatment. Neuropharmacology. 2008;54(8):1264–70.
162. Waxman AR, Juni A, Kowalczyk W, Arout C, Sternberg WF, Kest B. Progesterone rapidly recruits female-typical opioid-induced hyperalgesic mechanisms. Physiol Behav. 2010;101(5):759–63.
163. Laulin JP, Celerier E, Larcher A, Le Moal M, Simonnet G. Opiate tolerance to daily heroin administration: an apparent phenomenon associated with enhanced pain sensitivity. Neuroscience. 1999;89(3):631–6.
164. Laulin JP, Larcher A, Celerier E, Le Moal M, Simonnet G. Long-lasting increased pain sensitivity in rat following exposure to heroin for the first time. Eur J Neurosci. 1998;10(2):782–5.
165. Laulin JP, Larcher A, Célèrier E, Moal ML, Simonnet G. Long-lasting increased pain sensitivity in rat following exposure to heroin for the first time. Eur J Neurosci. 1998;10(2):782–5.
166. Hang L-H, Shao D-H, Gu Y-P. The ED50 and ED95 of ketamine for prevention of postoperative hyperalgesia after remifentanil-based anaesthesia in patients undergoing laparoscopic cholecystectomy. Swiss Med Wkly. 2011;141:w13195.
167. Tröster A, Sittl R, Singler B, Schmelz M, Schuttler J, Koppert W. Modulation of remifentanil-induced analgesia and postinfusion hyperalgesia by parecoxib in humans. Anesthesiology. 2006;105(5):1016–23.
168. Smith DJ, Pekoe GM, Martin LL, Coalgate B. The interaction of ketamine with the opiate receptor. Life Sci. 1980;26(10):789–95.
169. Persson J. Ketamine in pain management. CNS Neurosci Ther. 2013;19(6):396–402.
170. Max MB, Byas-Smith MG, Gracely RH, Bennett GJ. Intravenous infusion of the NMDA antagonist, ketamine, in chronic posttraumatic pain with allodynia: a double-blind comparison to alfentanil and placebo. Clin Neuropharmacol. 1995;18(4):360–8.
171. Laulin J-P, Maurette P, Corcuff J-B, Rivat C, Chauvin M, Simonnet G. The role of ketamine in preventing fentanyl-induced hyperalgesia and subsequent acute morphine tolerance. Anesth Analg. 2002;94(5):1263–9.
172. Swartjes M, Morariu A, Niesters M, Aarts L, Dahan A. Nonselective and NR2B-selective N-methyl-D-aspartic acid receptor antagonists produce antinociception and long-term relief of allodynia in acute and neuropathic pain. Anesthesiology. 2011;115(1):165–74.
173. Tverskoy M, Oz Y, Isakson A, Finger J, Bradley EL Jr, Kissin I. Preemptive effect of fentanyl and ketamine on postoperative pain and wound hyperalgesia. Anesth Analg. 1994;78(2):205–9.
174. Lavand'homme P, De Kock M, Waterloos H. Intraoperative epidural analgesia combined with ketamine provides effective preventive analgesia in patients undergoing major digestive surgery. Anesthesiology. 2005;103(4):813–20.
175. Roytblat L, Korotkoruchko A, Katz J, Glazer M, Greemberg L, Fisher A. Postoperative pain: the effect of low-dose ketamine in addition to general anesthesia. Anesth Analg. 1993;77(6):1161–5.
176. Wong C-S, Liaw W-J, Tung C-S, Su Y-F, Ho S-T. Ketamine potentiates analgesic effect of morphine in postoperative epidural pain control. Reg Anesth Pain Med. 1996;21(6):534–41.
177. Fu ES, Miguel R, Scharf JE. Preemptive ketamine decreases postoperative narcotic requirements in patients undergoing abdominal surgery. Anesth Analg. 1997;84(5):1086–90.
178. Menigaux C, Fletcher D, Dupont X, Guignard B, Guirimand F, Chauvin M. The benefits of intraoperative small-dose ketamine on postoperative pain after anterior cruciate ligament repair. Anesth Analg. 2000;90(1):129.
179. Menigaux C, Guignard B, Fletcher D, Sessler DI, Dupont X, Chauvin M. Intraoperative small-dose ketamine enhances analgesia after outpatient knee arthroscopy. Anesth Analg. 2001;93(3):606–12.
180. Zakine J, Samarcq D, Lorne E, Moubarak M, Montravers P, Beloucif S, et al. Postoperative ketamine administration decreases morphine consumption in major abdominal surgery: a prospective, randomized, double-blind, controlled study. Anesth Analg. 2008;106(6):1856–61.

181. White PF, Way WL, Trevor AJ. Ketamine-its pharmacology and therapeutic uses. Anesthesiology. 1982;56:119–36.
182. Holtman JR Jr, Crooks PA, Johnson-Hardy JK, Hojomat M, Kleven M, Wala EP. Effects of norketamine enantiomers in rodent models of persistent pain. Pharmacol Biochem Behav. 2008;90(4):676–85.
183. Fanta S, Kinnunen M, Backman JT, Kalso E. Population pharmacokinetics of S-ketamine and norketamine in healthy volunteers after intravenous and oral dosing. Eur J Clin Pharmacol. 2015;71(4):441–7.
184. Bredlau AL, Thakur R, Korones DN, Dworkin RH. Ketamine for pain in adults and children with cancer: a systematic review and synthesis of the literature. Pain Med. 2013;14(10):1505–17.
185. Way WL. Ketamine-its pharmacology and therapeutic uses. Anesthesiology. 1982;56(2):119–36.
186. Weinbroum AA, Rudick V, Paret G, Ben-Abraham R. The role of dextromethorphan in pain control. Can J Anesth. 2000;47(6):585–96.
187. Ramasubbu C, Gupta A. Pharmacological treatment of opioid-induced hyperalgesia: a review of the evidence. J Pain Palliat Care Pharmacother. 2011;25(3):219–30.
188. Elliott K, Kest B, Man A, Kao B, Inturrisi CE. *N*-methyl-D-aspartate (NMDA) receptors, mu and kappa opioid tolerance, and perspectives on new analgesic drug development. Neuropsychopharmacology. 1995;13(4):347–56.
189. Popik P, Kozela E, Danysz W. Clinically available NMDA receptor antagonists memantine and dextromethorphan reverse existing tolerance to the antinociceptive effects of morphine in mice. Naunyn-Schmiedeberg's Arch Pharmacol. 2000;361(4):425–32.
190. Salehi M, Zargar A, Ramezani MA. Effects of dextromethorphan on reducing methadone dosage in opium addicts undergoing methadone maintenance therapy: A double blind randomized clinical trial. J Res Med Sci. 2011;16(10):1354.
191. Chen S-L, Lee S-Y, Tao P-L, Chang Y-H, Chen S-H, Chu C-H, et al. Dextromethorphan attenuated inflammation and Combined Opioid Use in Humans Undergoing Methadone Maintenance Treatment. J Neuroimmune Pharmacol. 2012;7(4):1025–33.
192. Koyuncuoğlu H, Saydam B. The treatment of heroin addicts with dextromethorphan: a double-blind comparison of dextromethorphan with chlorpromazine. Int J Clin Pharmacol Ther Toxicol. 1990;28(4):147–52.
193. Rosen MI, McMahon TJ, Woods SW, Pearsall HR, Kosten TR. A pilot study of dextromethorphan in naloxone-precipitated opiate withdrawal. Eur J Pharmacol. 1996;307(3):251–7.
194. Bisaga A, Gianelli P, Popik P. Opiate withdrawal with dextromethorphan. Am J Psychiatry. 1997;154(4):584.
195. Akerele E, Bisaga A, Sullivan MA, Garawi F, Comer SD, Thomas AA, et al. Dextromethorphan and quinidine combination for heroin detoxification. Am J Addict. 2008;17(3):176–80.
196. Malek A, Amiri S, Habibi Asl B. The therapeutic effect of adding dextromethorphan to clonidine for reducing symptoms of opioid withdrawal: a randomized clinical trial. Int Sch Res Not. 2013;2013:1–5.
197. Lin SK, Pan CH, Chen CH. A double-blind, placebo-controlled trial of dextromethorphan combined with clonidine in the treatment of heroin withdrawal. J Clin Psychopharmacol. 2014;34(4):508–12.
198. Grace RF, Power I, Umedaly H, Zammit A, Mersiades M, Cousins MJ, et al. Preoperative dextromethorphan reduces intraoperative but not postoperative morphine requirements after laparotomy. Anesth Analg. 1998;87(5):1135–8.
199. Weinbroum A, Lalayev G, Yashar T, Ben-Abraham R, Niv D, Flaishon R. Combined pre-incisional oral dextromethorphan and epidural lidocaine for postoperative pain reduction and morphine sparing: a randomised double-blind study on day-surgery patients. Anaesthesia. 2001;56(7):616–22.
200. Weinbroum AA, Gorodetzky A, Nirkin A, Kollender Y, Bickels J, Marouani N, et al. Dextromethorphan for the reduction of immediate and late postoperative pain and morphine consumption in orthopedic oncology patients. Cancer. 2002;95(5):1164–70.
201. McConaghy P, McSorley P, McCaughey W, Campbell W. Dextromethorphan and pain after total abdominal hysterectomy. Br J Anaesth. 1998;81(5):731–6.
202. Rose JB, Cuy R, Cohen DE, Schreiner MS. Preoperative oral dextromethorphan does not reduce pain or analgesic consumption in children after adenotonsillectomy. Anesth Analg. 1999;88(4):749–53.
203. Compton PA, Ling W, Torrington MA. CLINICAL STUDY: Lack of effect of chronic dextromethorphan on experimental pain tolerance in methadone-maintained patients. Addict Biol. 2008;13(3–4):393–402.
204. Taniguchi K, Shinjo K, Mizutani M, Shimada K, Ishikawa T, Menniti FS, et al. Antinociceptive activity of CP-101,606, an NMDA receptor NR2B subunit antagonist. Br J Pharmacol. 1997;122(5):809–12.
205. Nishimura W, Muratani T, Tatsumi S, Sakimura K, Mishina M, Minami T, et al. Characterization of *N*-methyl-D-aspartate receptor subunits responsible for postoperative pain. Eur J Pharmacol. 2004;503(1–3):71–5.
206. Boyce S, Wyatt A, Webb J, O'donnell R, Mason G, Rigby M, et al. Selective NMDA NR2B antagonists induce antinociception without motor dysfunction: correlation with restricted localisation of NR2B subunit in dorsal horn. Neuropharmacology. 1999;38(5):611–23.
207. Taylor CP, Angelotti T, Fauman E. Pharmacology and mechanism of action of pregabalin: the calcium channel alpha2-delta (alpha2-delta) subunit as a target for antiepileptic drug discovery. Epilepsy Res. 2007;73(2):137–50.
208. Tassone DM, Boyce E, Guyer J, Nuzum D. Pregabalin: a novel gamma-aminobutyric acid analogue in the treatment of neuropathic pain, partial-onset seizures, and anxiety disorders. Clin Ther. 2007;29(1):26–48.
209. Rose M, Kam P. Gabapentin: pharmacology and its use in pain management. Anaesthesia. 2002;57(5):451–62.
210. Liang D-Y, Shi X, Li X, Li J, Clark JD. The β2 adrenergic receptor regulates morphine tolerance and physical dependence. Behav Brain Res. 2007;181(1):118–26.
211. Ricciotti E, FitzGerald GA. Prostaglandins and Inflammation. Arterioscler Thromb Vasc Biol. 2011;31(5):986–1000.
212. Hathway GJ, Vega-Avelaira D, Moss A, Ingram R, Fitzgerald M. Brief, low frequency stimulation of rat peripheral C-fibres evokes prolonged microglial-induced central sensitization in adults but not in neonates. Pain. 2009;144(1–2):110–8.
213. Hutchinson MR, Northcutt AL, Chao LW, Kearney JJ, Zhang Y, Berkelhammer DL, et al. Minocycline suppresses morphine-induced respiratory depression, suppresses morphine-induced reward, and enhances systemic morphine-induced analgesia. Brain Behav Immun. 2008;22(8):1248–56.
214. Hutchinson MR, Lewis SS, Coats BD, Skyba DA, Crysdale NY, Berkelhammer DL, et al. Reduction of opioid withdrawal and potentiation of acute opioid analgesia by systemic AV411 (ibudilast). Brain Behav Immun. 2009;23(2):240–50.
215. Hama AT, Broadhead A, Lorrain DS, Sagen J. The antinociceptive effect of the asthma drug ibudilast in rat models of peripheral and central neuropathic pain. J Neurotrauma. 2012;29(3):600–10.
216. Ellis A, Wieseler J, Favret J, Johnson KW, Rice KC, Maier SF, et al. Systemic administration of propentofylline, ibudilast, and

(+)-naltrexone each reverses mechanical allodynia in a novel rat model of central neuropathic pain. J Pain. 2014;15(4):407–21.
217. Rolan P, Hutchinson M, Johnson K. Ibudilast: a review of its pharmacology, efficacy and safety in respiratory and neurological disease. Expert Opin Pharmacother. 2009;10(17):2897–904.
218. Rolan P, Gibbons JA, He L, Chang E, Jones D, Gross MI, et al. Ibudilast in healthy volunteers: safety, tolerability and pharmacokinetics with single and multiple doses. Br J Clin Pharmacol. 2008;66(6):792–801.
219. Kim H-S, Suh Y-H. Minocycline and neurodegenerative diseases. Behav Brain Res. 2009;196(2):168–79.
220. Sumracki NM, Hutchinson MR, Gentgall M, Briggs N, Williams DB, Rolan P. The effects of pregabalin and the glial attenuator minocycline on the response to intradermal capsaicin in patients with unilateral sciatica. PloS One. 2012;7(6):e38525.
221. Popiolek-Barczyk K, Rojewska E, Jurga AM, Makuch W, Zador F, Borsodi A, et al. Minocycline enhances the effectiveness of nociceptin/orphanin FQ during neuropathic pain. BioMed Res Int. 2014;2014:762930.
222. Ledeboer A, Sloane EM, Milligan ED, Frank MG, Mahony JH, Maier SF, et al. Minocycline attenuates mechanical allodynia and proinflammatory cytokine expression in rat models of pain facilitation. Pain. 2005;115(1):71–83.
223. Li W-W, Setzu A, Zhao C, Franklin RJ. Minocycline-mediated inhibition of microglia activation impairs oligodendrocyte progenitor cell responses and remyelination in a non-immune model of demyelination. J Neuroimmunol. 2005;158(1):58–66.
224. Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature. 1990;346(6284):561–4.
225. Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. Nature. 1993;365(6441):61–5.
226. Attal N, Brasseur L, Guirimand D, Clermond-Gnamien S, Atlami S, Bouhassira D. Are oral cannabinoids safe and effective in refractory neuropathic pain? Eur J Pain (Lond, Engl). 2004;8(2):173–7.
227. Wallace M, Schulteis G, Atkinson JH, Wolfson T, Lazzaretto D, Bentley H, et al. Dose-dependent effects of smoked cannabis on capsaicin-induced pain and hyperalgesia in healthy volunteers. Anesthesiology. 2007;107(5):785–96.
228. Buggy DJ, Toogood L, Maric S, Sharpe P, Lambert DG, Rowbotham DJ. Lack of analgesic efficacy of oral Δ-9-tetrahydrocannabinol in postoperative pain. Pain. 2003;106(1):169–72.
229. Beaulieu P. Effects of nabilone, a synthetic cannabinoid, on postoperative pain. Canadian journal of anaesthesia =. Journal canadien d'anesthesie. 2006;53(8):769–75.
230. Kraft B, Frickey NA, Kaufmann RM, Reif M, Frey R, Gustorff B, et al. Lack of analgesia by oral standardized cannabis extract on acute inflammatory pain and hyperalgesia in volunteers. Anesthesiology. 2008;109(1):101–10.
231. Redmond WJ, Goffaux P, Potvin S, Marchand S. Analgesic and antihyperalgesic effects of nabilone on experimental heat pain. Curr Med Res Opinion. 2008;24(4):1017–24.
232. Blake D, Robson P, Ho M, Jubb R, McCabe C. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. Rheumatology. 2006;45(1):50–2.
233. Narang S, Gibson D, Wasan AD, Ross EL, Michna E, Nedeljkovic SS, et al. Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. J Pain. 2008;9(3):254–64.
234. Notcutt W, Price M, Miller R, Newport S, Phillips C, Simmons S, et al. Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 'N of 1'studies. Anaesthesia. 2004;59(5):440–52.
235. Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. BMJ. 2004;329(7460):253.
236. Wade DT, Robson P, House H, Makela P, Aram J. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. Clin Rehabil. 2003;17(1):21–9.
237. Abrams DI, Jay CA, Shade SB, Vizoso H, Reda H, Press S, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology. 2007;68(7):515–21.
238. Karst M, Salim K, Burstein S, Conrad I, Hoy L, Schneider U. Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial. JAMA. 2003;290(13):1757–62.
239. Holdcroft A, Maze M, Dore C, Tebbs S, Thompson S. A multicenter dose-escalation study of the analgesic and adverse effects of an oral cannabis extract (Cannador) for postoperative pain management. Anesthesiology. 2006;104(5):1040–6.
240. Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. J Pain. 2008;9(2):164–73.
241. Ellis RJ, Toperoff W, Vaida F, Van Den Brande G, Gonzales J, Gouaux B, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacology. 2008;34(3):672–80.
242. Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. Pain. 2004;112(3):299–306.
243. Eisenberg E, Ogintz M, Almog S. The Pharmacokinetics, efficacy, safety, and ease of use of a novel portable metered-dose cannabis inhaler in patients with chronic neuropathic pain: a phase 1a study. J Pain Palliat Care Pharmacother. 2014;28(3):216–25.
244. de Vries M, van Rijckevorsel DC, Wilder-Smith OH, van Goor H. Dronabinol and chronic pain: importance of mechanistic considerations. Expert Opin Pharmacother. 2014;15(11):1–10.
245. Martin WJ, Patrick SL, Coffin PO, Tsou K, Walker JM. An examination of the central sites of action of cannabinoid-induced antinociception in the rat. Life Sci. 1995;56(23):2103–9.
246. Naef M, Curatolo M, Petersen-Felix S, Arendt-Nielsen L, Zbinden A, Brenneisen R. The analgesic effect of oral delta-9-tetrahydrocannabinol (THC), morphine, and a THC-morphine combination in healthy subjects under experimental pain conditions. Pain. 2003;105(1–2):79–88.
247. Seeling W, Kneer L, Büchele B, Gschwend J, Maier L, Nett C, et al. Delta (9)-tetrahydrocannabinol and the opioid receptor agonist piritramide do not act synergistically in postoperative pain. Der Anaesthesist. 2006;55(4):391–400.
248. Majewska MD. Neurosteroids: endogenous bimodal modulators of the $GABA_A$ receptor mechanism of action and physiological significance. Prog Neurobiol. 1992;38(4):379–94.
249. Belelli D, Lambert JJ. Neurosteroids: endogenous regulators of the GABA(A) receptor. Nat Rev Neurosci. 2005;6(7):565–75.
250. Mitchell EA, Gentet LJ, Dempster J, Belelli D. GABAA and glycine receptor-mediated transmission in rat lamina II neurones: relevance to the analgesic actions of neuroactive steroids. J Physiol. 2007;583(3):1021–40.
251. Poisbeau P, Keller AF, Aouad M, Kamoun N, Groyer G, Schumacher M. Analgesic strategies aimed at stimulating the endogenous production of allopregnanolone. Front Cell Neurosci. 2014;8:174.
252. Cashin MF, Moravek V. The physiological action of cholesterol. Am J Physiol Leg Content. 1927;82(2):294–8.

253. Selye H. Anesthetic effect of steroid hormones. Exp Biol Med. 1941;46(1):116–21.
254. Selye H, Masson G. Additional steroids with luteoid activity. Science. 1942;358(96):2494.
255. Pathirathna S, Brimelow BC, Jagodic MM, Krishnan K, Jiang X, Zorumski CF, et al. New evidence that both T-type calcium channels and GABAA channels are responsible for the potent peripheral analgesic effects of 5alpha-reduced neuroactive steroids. Pain. 2005;114(3):429–43.
256. Kavaliers M, Wiebe JP. Analgesic effects of the progesterone metabolite, 3α-hydroxy-5α-pregnan-20-one, and possible modes of action in mice. Brain Res. 1987;415(2):393–8.
257. Frye CA, Duncan JE. Progesterone metabolites, effective at the $GABA_A$ receptor complex, attenuate pain sensitivity in rats. Brain Res. 1994;643(1):194–203.
258. Frye CA, Rhodes ME, Walf A, Harney JP. Testosterone enhances aggression of wild-type mice but not those deficient in type I 5α-reductase. Brain Res. 2002;948(1):165–70.
259. Frye CA, Walf AA, Rhodes ME, Harney JP. Progesterone enhances motor, anxiolytic, analgesic, and antidepressive behavior of wild-type mice, but not those deficient in type 1 5α-reductase. Brain Res. 2004;1004(1):116–24.
260. Pednekar JR, Mulgaonker VK. Role of testosterone on pain threshold in rats. Indian J Physiol Pharmacol. 1995;39(4):423–4.
261. Erden V, Yangn Z, Erkalp K, Delatioglu H, Bahçeci F, Seyhan A. Increased progesterone production during the luteal phase of menstruation may decrease anesthetic requirement. Anesth Analg. 2005;101(4):1007–11.
262. Lee J, Lee J, Ko S. The relationship between serum progesterone concentration and anesthetic and analgesic requirements: a prospective observational study of parturients undergoing cesarean delivery. Anesth Analg. 2014;119(4):901–5.
263. Gudin JA, Mogali S, Jones JD, Comer SD. Risks, management, and monitoring of combination opioid, benzodiazepines, and/or alcohol use. Postgrad Med. 2013;125(4):115–30.
264. Krishnan S, Salter A, Sullivan T, Gentgall M, White J, Rolan P. Comparison of pain models to detect opioid-induced hyperalgesia. J Pain Res. 2012;5:99.
265. Mogil JS, Wilson SG, Bon K, Eun Lee S, Chung K, Raber P, et al. Heritability of nociception I: responses of 11 inbred mouse strains on 12 measures of nociception. Pain. 1999;80(1):67–82.
266. Mogil JS, Wilson SG, Bon K, Eun Lee S, Chung K, Raber P, et al. Heritability of nociception II.Types' of nociception revealed by genetic correlation analysis. Pain. 1999;80(1):83–93.
267. Liang DY, Liao G, Lighthall GK, Peltz G, Clark DJ. Genetic variants of the P-glycoprotein gene Abcb1b modulate opioid-induced hyperalgesia, tolerance and dependence. Pharmacogenet Genomics. 2006;16(11):825–35.
268. Liang DY, Liao G, Wang J, Usuka J, Guo Y, Peltz G, et al. A genetic analysis of opioid-induced hyperalgesia in mice. Anesthesiology. 2006;104(5):1054–62.
269. Liang DY, Li X, Clark JD. Epigenetic regulation of opioid-induced hyperalgesia, dependence, and tolerance in mice. J Pain. 2013;14(1):36–47.
270. Doehring A, Oertel BG, Sittl R, Lötsch J. Chronic opioid use is associated with increased DNA methylation correlating with increased clinical pain. PAIN®. 2013;154(1):15–23.