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Title

Medication overuse headache and opioid-induced hyperalgesia: A review of mechanisms, a neuroimmune hypothesis and a novel approach to treatment.

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Key words

Medication overuse headache, opioid-induced hyperalgesia, codeine, glia, cytokines, ibudilast

Abbreviations

5HT	Serotonin
CGRP	Calcitonin gene-related peptide
CNS	Central nervous system
IL-1β	Interleukin 1 beta
IL-6	Interleukin 6
MOH	Medication overuse headache
MD2	Myeloid differentiation protein-2
NMDA	*N*-methyl D-aspartate
NSAIDs	Non-steroidal anti-inflammatory drugs
PBMCs	Peripheral blood mononuclear cells
TLR	Toll-like receptor
TLR-4	Toll-like receptor 4
TNFα	Tumor necrosis factor alpha

Abstract

Introduction. Patients with chronic headache who consume large amounts of analgesics are often encountered in clinical practice. Excessive intake of analgesics is now considered to be a cause, rather than simply a consequence of frequent headaches, and as such the diagnosis "medication overuse headache" has been formulated. Despite the prevalence and clinical impact of medication overuse headache the pathophysiology behind this disorder remains unclear and specific mechanism-based treatment options are lacking.

Discussion. Although most acute headache treatments have been alleged to cause medication overuse headache, here we conclude from the literature that opioids are a particularly problematic drug class consistently associated with worsening headache. Medication overuse headache may not be a single entity, as each class of drug implicated may cause medication overuse headache via a different mechanism. Recent evidence indicates that chronic opioid administration may exacerbate pain in the long-term by activating Toll-Like Receptor-4 on glial cells, resulting in a pro-inflammatory state that manifests clinically as increased pain. Thus, from the available evidence it seems opioid overuse headache is a phenomenon similar to opioid-induced hyperalgesia, which derives from a cumulative interaction between central sensitisation, due to repeated activation of nociceptive pathways by recurrent headaches, and pain facilitation due to glial activation.

Conclusion. Treatment strategies directed at inhibiting glial activation may be of benefit alongside medication withdrawal in the management of medication overuse headache.

Introduction

Patients with a prior history of a primary benign headache disorder who develop chronic daily headache associated with high frequency of analgesic intake form a high proportion of patients at specialist headache clinics.[1-4] Over the past few decades it has been proposed that excessive intake of analgesics and/or other symptomatic headache treatments may actually be a cause, rather than simply a consequence of frequent headaches, and as such the disorder "medication overuse headache" is recognised in the International Classification of Headache Disorders. Opioid analgesics in particular appear to be strongly associated with the development of medication overuse headache (MOH).[5] Little is known in regard to the pathophysiology of MOH,[6] thus mechanism-based specific treatments are lacking. Current practice is to withdraw the overused medication, a process that can be considerably distressing and difficult for patients, sometimes requiring hospital admission.

MOH in patients consuming opioids is likely to share pathophysiological features with opioid-induced hyperalgesia, a phenomenon in which opioids paradoxically increase pain sensitivity. The relatively recent discovery that microglia and astrocytes are able to facilitate nociceptive transmission once activated following opioid exposure provides a possible mechanism for the characteristic exacerbation of headache seen in this disorder. Drugs that target glial attenuation therefore represent novel treatment strategies that may be able to reduce headache burden and make detoxification procedures easier and more successful.

Medication overuse headache

According to the revised second edition of the International Classification of Headache Disorders, MOH should be diagnosed in patients with A) headache on ≥ 15 days per month, B) regular overuse of acute headache treatments for > 3 months and C) for whom headache has developed or has markedly worsened during medication overuse.[7] MOH is not a unitary entity, thus the threshold defining 'overuse' is dependent upon the class of drug consumed. Medication intake on ≥ 10 days per month is considered overuse for ergotamine, triptans, opioids and combination preparations, whereas intake on ≥ 15 days per month is required to meet the criteria for overuse of simple analgesics (non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, and paracetamol) or a combination of acute headache treatments. MOH in a patient who is over-consuming opioid analgesics is termed opioid overuse headache.[8]

MOH is a global health issue which impacts significantly on the quality of life of affected individuals, and imposes a large economic burden upon society.[9] It is reported to be the third most common form of headache encountered in clinical practice, following only tension-type headache and migraine,[10, 11] accounting for between 25-60% of patients seen in specialist headache centres.[1, 2, 11, 12]

Although medication overuse is a known risk factor, alone it is neither necessary nor sufficient to induce chronic daily headache.[13] When patients receive opioids or other analgesics for non-headache indications, those without a history of headache do not develop MOH, whereas those with a history of episodic headache frequently progress to experience chronic daily headache.[14, 15]

Causative agents in MOH

While virtually all drugs used in the symptomatic treatment of headache have been reported to induce MOH [16] from the primary literature it is clear that opioids are one medication class most strongly associated with progression to chronic headache.

In both clinic-based studies and longitudinal population-based studies, opioids are consistently associated with the development of chronic daily headache.[15, 17, 18] As part of the American Migraine Prevalence and Prevention study, the probability of transformation from episodic migraine to chronic migraine over one year was modelled in relation to medication use, using paracetamol users as a reference group. In unadjusted analyses, preparations containing opioids doubled the risk of chronic migraine, while medications such as triptans and NSAIDs did not significantly increase the likelihood of headache transformation. The probability of progression to chronic migraine was also found to correlate with elevated monthly opioid dose.[18] Barbiturate use is also associated with headache progression,[18] however MOH remains highly prevalent in territories where barbiturates are not longer used in headache management. These findings are supported by the results of the Frequent Headache Epidemiology study which found that opioid use, following adjustment for age, sex, primary headache diagnosis and number of pain medications consumed, was significantly associated with chronic daily headache, whereas use of aspirin or ibuprofen was in fact protective against headache progression.[17] To assess the hypothesis that opioids play a definitive role in inducing MOH, Bigal and colleagues have also employed Hills criteria of causation to demonstrate that a causal relationship between excessive opioid use and progression from episodic migraine to chronic daily headache is plausible.[5]

Pathophysiology of MOH

Despite the high prevalence and clinical impact of MOH the mechanisms contributing to the development of this disorder remain unclear.[19] While current research suggests several factors could play role in the pathophysiology of MOH, at present it is only possible to summarise mechanisms that appear to be associated with, or may predispose patients to, this condition.[6, 16] Insights gained from preclinical studies have been discussed recently in comprehensive reviews by Meng and colleagues[20] and Bongsebandhu-phubhakdi and Srikiatkhachorn.[21] Clinically, it seems that both behaviour and biology contribute to the initiation and maintenance of MOH and successful long-term treatment of this disorder depends upon adequate treatment of both elements.[22]

Psychological and behavioural factors. A number of psychological states and behaviours appear to be important in the development and perpetuation of medication overuse. Such factors include anxiety disorders, depressive disorders and obsessional drug-taking and/or dependence-related behaviours.[22, 23]

Genetic studies. A hereditary susceptibility to MOH, and therefore a genetic component to the pathogenesis of this disorder, has been proposed on the basis of epidemiological data.[6] The risk of developing MOH appears almost three times greater in individuals with a family history of MOH,[24] and further to the hypothesized link between substance abuse/dependence and MOH, patients with MOH are also more likely to have relatives who suffer from drug overuse or substance abuse.[24] A small number of studies have investigated potential molecular genetic factors related to dopamine and serotonin transport or substance abuse that may be involved in MOH,[25-28] yet at present this knowledge has not lead to the identification of new treatment targets.

Endocrine and neurotransmitter abnormalities. Depletion of serotonin (5HT) in platelets[29] and up-regulation of the pro-nociceptive $5HT_2$ receptor[30] have been demonstrated in MOH. Furthermore, in a

small pilot study, 5HT blood levels in MOH patients were reported to increase significantly following withdrawal of the overused analgesics, corresponding with clinical headache improvement.[31] It has been hypothesised that further suppression of an already abnormal 5HT-dependent antinociceptive system in patients with pre-existing headache by analgesic overuse may lead to the headache chronification seen following medication overuse.[32]

The endocannabinoid system has also been investigated in related to MOH as it is involved in modulating pain and plays a role in addiction and reward.[33] The activity of an endocannabinoid membrane transporter[33] and levels of endocannabinoids in the platelets are both reduced in MOH sufferers.[34]

Few studies have looked at the endocrine function of patients with MOH. Increased levels of orexin-A and corticotrophin-releasing hormone were found in the cerebrospinal fluid of patients with MOH, and these levels were correlated with monthly drug intake and dependence scores on a self-completed questionnaire.[35] The authors suggest such results could be interpreted as either a compensatory response to chronic pain or a hypothalamic response to stress deriving from the chronic pain.[35] Opioids, especially at high doses, cause suppression of gonadotrophin secretion and cortisol release.[36-38] One study in MOH patients, who did not take opioids, showed reduced growth hormone and thyroid-stimulating hormone response and increased adrenocorticotropic hormone and cortisol responses compared to controls.[39] However, endocrine responses specifically in opioid overuse headache have not been reported.

Acquired central sensitisation. There is growing evidence that central sensitization plays a significant role in the general process of headache chronification. Several features of chronic daily headache,

including increased headache frequency, expansion of the headache area and cutaneous allodynia, which are often observed in MOH, imply sensitisation of the trigeminal nociceptive neurons.[40] In MOH, facilitation of pain processing has been established in a range of studies using psychophysical and electrophysiological techniques. Recently Perrotta and colleagues found the threshold and temporal summation threshold of the nociceptive withdrawal reflex to be markedly reduced in patients with MOH. Psychophysical measurements also exposed enhanced pain perception following single and repeated stimulation in MOH patients as compared to episodic migraineurs. It appears the abnormalities observed were related, at least in part to medication overuse, as withdrawal of the overused medication was associated with an improvement in neurophysiological findings.[19] Ayzenberg and colleagues also observed pain facilitation of trigeminal and somatic nociceptive systems in MOH patients, which normalized after withdrawal treatment.[41]

Pharmacological factors. In addition to the above endogenous factors, causative mechanisms by which the wide range of agents alleged to cause MOH need to be elucidated. Although there may be a unifying mechanism by which structurally and pharmacologically unrelated analgesics may promote central sensitisation, it may be that different mechanisms exist for differing drugs and groups of drugs. One class of analgesics for which there is a demonstrated mechanism for causing pain facilitation is the opioid class.

Opioid-Induced Hyperalgesia

It is well known that tolerance and dependence develop after prolonged exposure to opioids and there is extensive literature on the neuronal mechanisms involved in these phenomena.[42-45] More recently, an additional unwanted consequence of opioid use which may contribute to reduced opioid efficacy, a paradoxically enhanced sensitivity to pain termed opioid-induced hyperalgesia,[46] has been demonstrated in animals and suggested in some human studies. Opioid-induced hyperalgesia has been defined by controlled, pre-clinical animal studies as a reduction in pain threshold from baseline following extended exposure to opioids.[47] In a clinical context it has been described as increased sensitivity to stimuli that normally provoke pain or a general exacerbation of pain in the absence of new tissue damage, subsequent to opioid intake.[46]

Pre-clinical evidence of opioid-induced nociceptive sensitivity

Many laboratories have clearly demonstrated thermal hyperalgesia and/or mechanical allodynia following both acute and chronic administration of opioids, including morphine, heroin, fentanyl and remifentanil, using a range of animal models[48-52]

Clinical evidence of opioid-induced hyperalgesia

While opioid-induced hyperalgesia is well documented in pre-clinical models, data from human studies remain controversial, as conflicting results have been reported.[46] Clinical and experimental evidence of opioid-induced hyperalgesia in man derives from studies in a number of diverse populations, namely, chronic pain patients receiving long-term opioid therapy, patients receiving peri-operative opioids, [53] opioid-addicted or maintained patients[54, 55] and healthy volunteers taking part in investigational studies using experimental pain models, although the demonstration of OIH may be model-dependent.[56] A

recent systematic review which evaluated clinical studies investigating opioid-induced hyperalgesia found that the strongest evidence supporting the existence of opioid-induced hyperalgesia came from studies in healthy volunteers, which involved assessment of secondary hyperalgesia following an opioid infusion.[47] In this review the authors conclude that evidence to date is insufficient to either support or refute the existence of opioid-induced hyperalgesia in humans, with the exception of opioid-induced hyperalgesia precipitated by opioid infusions in healthy volunteers.[47] However, the extent to which these experimental findings relate to clinical practice remains unclear.

Opioid-induced hyperalgesia in chronic pain patients receiving opioids. Chronic pain patients often experience a reduction in opioid analgesic efficacy over time, which may at least in part be due to opioid-induced hyperalgesia in additional to tolerance.[57] A range of individual cases and case series have described hyperalgesia associated with opioid administration and a reduction in pain following detoxification from the causative opioid medication.[58-63] At least two studies have prospectively evaluated the association between opioid dose and hyperalgesia in chronic pain patients, observing the development of hyperalgesia when initiating opioid treatment and increases in pain thresholds following opioid tapering. [64, 65] However, more recent evidence from one of these groups in a large prospective non-headache population suggests that tolerance and hyperalgesia may be separate phenomena.[66]

Codeine and opioid-induced hyperalgesia

To date there are no pre-clinical or clinical published data examining whether codeine can cause opioid-induced hyperalgesia. Our group conducted a small pilot trial comparing the cold pain tolerance and thresholds of non-headache pain patients receiving on average 83 mg (range 30-180 mg) of codeine

daily for 3 months or more with a control group of chronic pain patients taking paracetamol and/or non-steroidal anti-inflammatory drugs.[67] In this cohort hyperalgesia was not observed, yet this may be a result of our modest sample size.[67]

While larger doses of opioids more commonly lead to opioid-induced hyperalgesia, both ultra-high and ultra-low doses of opioids have been reported to cause nociceptive sensitization.[68] Thus, despite the fact that only a small fraction of the pro-drug codeine converted in the body to morphine[69] it is plausible that it too has potential to enhance pain sensitivity. This is important in terms of our hypothesis as many headache patients develop MOH following the overuse of combination analgesics that contain codeine[11, 70, 71] on a background of repeated glial activation due to recurrent headaches.

Possible mechanisms of opioid-induced hyperalgesia

Whilst opioid-induced hyperalgesia was first reported in a peer-reviewed journal over 60 years ago,[72] the molecular mechanisms and pathophysiology underlying this disorder remain unclear. Many hypotheses regarding the development of opioid-induced hyperalgesia have been put forward, including sensitization of peripheral nerve endings or second order neurons, enhanced descending facilitation of nociceptive pathways and increased production, release and decreased re-uptake of neurotransmitters involved in nociception.[46]

Many studies investigating the mechanisms involved in opioid-induced hyperalgesia have focused upon the increased amounts of or responses to various excitatory neurotransmitters through neuroplasticity, often examining the role of the glutaminergic *N*-methyl *D*-aspartate (NMDA) receptor.[46] In pre-clinical studies NMDA antagonists such as ketamine, magnesium and the experimental compound MK-801

prevent and/or reverse hyperalgesia following exposure to sufentanil or fentanyl.[73-75] Alternatively, it has been speculated that biologically active glucuronide metabolites may play a role in morphine-induced hyperalgesia.[76, 77] The metabolite morphine-3-glucuronide, which is known to possess very little affinity for any of the opioid receptor subtypes,[78, 79] is able to stimulate potent neuro-excitatory effects on behaviour when administered to rodents,[80, 81] yet this hypothesis does not explain opioid-induced hyperalgesia following administration of opioids which do not form glucuronide metabolites such as fentanyl.[75]

Although in the past it has been postulated that opioid receptor activation is a prerequisite for opioid-induced hyperalgesia, triple knock out mice lacking μ, δ and κ opioid receptors or rodents concurrently receiving the opioid receptor antagonist naltrexone also develop opioid-induced hyperalgesia, indicating that it develops independently of opioid receptor activity and therefore opioid analgesia.[75, 77]

Each of the studies discussed above, and the vast majority of the literature investigating opioid-induced hyperalgesia, has focused upon neuronal mechanisms by which opioids may increase pain sensitivity. However, in more recent times the pivotal role of neuroimmune activation and neuroinflammation in the pathogenesis of opioid-induced hyperalgesia has been described.[82]

Neuroimmune interactions in pain

Traditionally our understanding of pain has focused almost exclusively upon neurons, as neuronal circuits are fundamental in the processing, integration and transmission of nociceptive signals.[83] Recognition of the importance of neuroimmune interactions has come to provide a significant

conceptual advance in the understanding of nociceptive processing[84] and thus, has brought to light many novel targets with the potential to further improve the clinical management of pain.

Over the last two decades evidence has been mounting that astrocytes and microglia, in addition to neurons, play a vital role in pain modulation, including the initiation and maintenance of pathological pain.[85-87] It is likely that other glial cell types are also involved in pain facilitation, however research to date has focused upon astrocytes and microglia, as they are the most amenable to study.[88, 89]

An incontrovertible wealth of pre-clinical data show when exposed to stimuli, such as central nervous system (CNS) trauma, ischaemia, neurodegeneration or the immunological components of pathogens, microglial cells rapidly become 'activated', i.e. they develop an ability to perform a function beyond that which they are able to perform in the baseline state.[90] Subsequently, astrocytes become activated in response to the same range of stressors as microglia, as well as substances released by the activated microglial cells.[91]

Activation of astrocytes and/or microglia translates to increased production of mediators such as pro-inflammatory cytokines (e.g. interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNFα)),[92] chemokines[93], arachidonic acid and prostaglandins, excitatory amino acids, adenosine triphosphate, reactive oxygen species, nitric oxide and nerve growth factors.[92] Such inflammatory substances are able to increase neuronal excitability both directly and indirectly. [92]. In addition to the neuronal effects, these pro-inflammatory mediators also stimulate further glial cells, generating a positive feedback loop. After a stimulus has resolved, experimental evidence suggests microglia remain "primed", entering a sensitised state in which they do not actively produce pro-inflammatory substances, yet they over-respond to subsequent stimuli, increasing pro-inflammatory cytokine release

and exaggerating pain.[94-96]

Activation of spinal microglia and astrocytes has been demonstrated in virtually every clinically relevant animal model of an enhanced pain state[88] with similar results reported for trigeminal pain models.[97] Moreover, glial-attenuating pharmacological interventions are able to block the phenotypic transformation of glial cells into the activated state and prevent both allodynia and hyperalgesia across a diverse range of pre-clinical pathological pain models.[98-103]

It is now clear that glia-to-neuron signaling via toll-like receptor 4 (TLR-4) can play a causal role in the initiation and maintenance of pathological pain.[104-107] The toll-like receptors (TLRs) are a family of innate immune pattern recognition receptors, which respond to a wide variety of pathogen-derived and tissue damage-related ligands.[108] The TLR-4 receptor, which is primarily expressed upon microglia,[109] is an important contributor to activation of these cells, although expression on astrocytes, endothelial cells and neurons has also been reported.[110, 111] For a complete review of the role of TLRs in chronic pain, see review by Nicotra et al.[112]

The relevance of TLR signalling in human pain states is currently unknown largely due to the inaccessibility of pertinent tissue. Recently we have documented indirect evidence of clinical TLR involvement by studying peripheral blood mononuclear cells (PBMCs), which share many similarities with immune cells of the CNS.[113] PBMCs were isolated from human samples, stimulated *ex vivo* with TLR agonists and the subsequent release of IL-1β was measured. PBMCs from chronic pain patients released a significantly higher amount of TLR agonist stimulated IL-1β, as compared to that of pain-free individuals, and was higher again in chronic pain patients on opioids. These findings are, suggestive of immune alterations in human pain states and enhancement by opioids. [114]

Opioid-Induced Glial Activation

Glial activation is now also known to occur in response to opioid exposure.[107] Pre-clinically opioid-induced glial activation is known to oppose opioid analgesia and enhance opioid adverse effects including tolerance, dependence, reward and respiratory depression.[115, 116] Interestingly, opioid-induced glial activation is mediated through activation of TLR-4, exposing the potential to separate the beneficial actions of opioids from their unwanted adverse effects.[92] Pre-clinical studies have demonstrated that while morphine administration results in analgesia via agonism at the μ-opioid receptor on the neurons, it is also activates glial cells via TLR-4, resulting in the production of neuroexcitatory mediators.[117] The initial additive result is a reduction in pain, yet with prolonged opioid administration glial activation increases, as does subsequent pain facilitation, working against the analgesic effects of morphine, presenting clinically as opioid tolerance and then hyperalgesia.[118] This dual activity at both neuronal and glial cells is common with other clinically relevant opioids.[115] It has recently been demonstrated that morphine-3-glucuronide has TLR-4 agonist activity, indicating that codeine and morphine metabolites may contribute to this action.[119] For a detailed discussion regarding the role of TLR-4 in opioid-induced glial activation see review by Watkins at al.[92]

Despite the established body of pre-clinical evidence human trials are yet to conclusively demonstrate the impact of central immune signalling on the action of opioids in patient groups or healthy volunteers.[82]

Pro-inflammatory central immune signalling hypothesis of MOH

As discussed previously, headache pain resulting from regular consumption of opioid analgesics is a complication specific to patients with pre-existing headache, indicating there is a unique predisposing factor among this population.[14, 120] Within this group of MOH patients, the vast majority first present with episodic migraine or tension-type headache[121] as opposed to other forms of primary headache such as cluster headache.[122] We hypothesise this selective propensity to develop MOH stems from altered pro-inflammatory central immune signalling in patients with migraine and tension-type headache, or the presence of underlying central sensitisation, which renders them particularly susceptible to the effects of opioid-induced glial activation.

Evidence from preclinical models supports a role for neuron to glia interactions in migraine pain.[123] Glial cells are known to release a range of inflammatory cytokines, such as IL-1β, IL-6 and fractalkine, when exposed to calcitonin gene-related peptide (CGRP), a product released by neurons during migraine.[123] The cumulative glial activation resulting from CGRP release and opioid exposure is likely to be greater than that caused by CGRP alone, potentially explaining the exacerbation of migraine pain following opioid use.

The role of the immune system and central immune signalling in particular in tension-type headache is less clear. However, tension-type headache is generally considered a disorder of acquired central sensitisation of unknown cause,[124] thus, regardless of the source, the nociceptive sensitivity originally exhibited by this patient group could predispose them to headache chronification due to further pain facilitation brought about by opioid-induced glial activation. Of note, the tricyclic antidepressant amitriptyline, is the principal drug with proven efficacy in the prophylactic treatment of tension-type headache[125] but its mechanism of action is this condition is unclear[126]. Recently amitriptyline has been found to possess strong TLR-4 inhibitory activity.[107] While amitriptyline does not alter baseline pain

sensitivity it is able to potentiate morphine analgesia, as are other inhibitors of TLR-4 signalling.[107] These findings raise the possibility that attenuation of glial activation via TLR-4 blockade could contribute to the efficacy of this medication in tension-type headache.

The secretion of cytokines and other pro-inflammatory mediators, such as IL-1β, IL-6, TNF-α and nitric oxide, by activated glial cells seems likely to play a role in the transformation of episodic headache to chronic headache in general, and to MOH in particular as discussed by Meng and Cao.[127] This review also highlights the ability of stressful life events to amplify pain signals and contribute to headache chronification via glial activation.[127] Tumor necrosis factor-α, a substance released by activated glia known to mediate chronic pain states, is elevated in chronic headache patients with both migrainous and tension-type headache phenotypes.[128] and serum S100β, a protein derived from glial cells, is also raised in children with migraines.[129] Moreover, a study which identified a unique genomic expression pattern in MOH patients that responds to medication withdrawal used gene ontology of the samples obtained to determine that a significant number were involved in brain and immunological tissues, including the TLR signaling pathway, again alluding to altered immune activity in MOH.[130]

It is likely that opioid-overuse headache is related to opioid-induced hyperalgesia and is similarly mediated by glial activation in a susceptible patient population. It is plausible that opioid overuse may only lead to chronic headache in patients with pre-existing headache disorders, as the glial cells of headache suffers may be primed for activation, due to either repeated exposure to nociceptive signals as a consequence of the headache condition, or an underlying immune abnormality. Alternatively central sensitisation could increase the baseline pain sensitivity in these patients and further pain facilitation due to opioid-induced glial activation may be sufficient to transform episodic bouts of

headache into chronic headache disorder. See Figure 1 for a diagrammatical representation of the hypothesis.

Figure 1. (a) Neurons in basal state & glial cells quiescent. (b) Recurrent nociceptive impulses during episodic headaches sensitise neurons which release pro-inflammatory mediators that activate glial cells. Activated glial cells then release further pro-inflammatory mediators increasing pain sensitivity & headache frequency. After stimulus ceases glia remain primed. (c) Patient consumes opioids. Opioids agonise μ-opioid receptor to reduce pain. Opioids bind to TLR-4 to activate glia. Pro-inflammatory glial response is exaggerated as glial cells are primed. Long-term the net result is pain facilitation leading to chronic headache. (d) Ibudilast attenuates glial activation to reduce pain facilitation. μ-opioid receptor effects are not altered. Reduction in pain breaks cycle of opioid intake/glial activation/increased headaches. Abbreviations: IL-1β: interleukin 1β, IL-6: interleukin 6, TNFα: tumor necrosis factor α, ROS: reactive oxygen species, PGs: prostaglandins, NO: nitric oxide, EAA: excitatory amino acids, TLR-4: toll-like receptor 4.

Glial involvement in headache following opioid exposure has been evaluated pre-clinically using a rodent model of headache and morphine administration. In this study the authors were able to demonstrate that pre-exposure to an opioid results in facial allodynia, a surrogate for headache pain, during application of inflammatory "soup" to the dura in doses that fail to produce allodynia in opioid-naïve rats.[131] When low-dose inflammatory soup was applied following morphine administration but prior to a dose of inflammatory soup able to reliably produce robust facial allodynia, no pain facilitation was observed, mirroring the clinical observation that MOH does not develop *de novo* in those without a pre-existing headache condition.[131] The exacerbation of head pain observed was

attributed to opioid-induced glial activation as co-administration of the glial attenuator ibudilast with morphine was able to prevent facial allodynia.[132]

We have conducted docking simulations to explore the possibility that other headache treatments could activate glial cells, as opioid do, to worsen headache. *In silico* docking assessments using Vina[133] and previously published TLR4/Myeloid differentiation protein-2 (MD2) pdb files, indicate the energy requirement for codeine to bind to MD2, a protein required for TLR-4 activation, is over 100 fold lower than that of paracetamol, ibuprofen, sumatriptan and butabarbital. Furthermore, the non-codeine headache drugs bind at a site that is not characterised as important in the activation of the TLR-4/MD2 complex, indicating they are unlikely to trigger glial activation.

Taken together these findings suggest TLR-4 mediated glial activation may be specific to opioids among headache treatments and hence may be amenable to specific therapy directed to this pathway.

Potential treatment strategies targeting glial activation

From the arguments given above, we propose that pharmacological approaches that aim to control glial regulation of nociception may be of benefit in the clinical management of opioid overuse headache. Although it is agreed that medication withdrawal is essential, it is recognised that in many patients withdrawal is difficult but can be achieved through a comprehensive, multidisciplinary approach. [134] However, there is controversy whether this is the only treatment approach,[135] or whether additional medication can reduce headache burden before medication withdrawal to make the process easier.[136]

Currently no drug available for human use was developed specifically to target glial cells,[90] however a number of medications marketed for other indications have been found to attenuate activated glia and therefore may represent novel treatments for MOH. Conventional immunosuppressive agents are unlikely to be beneficial in the management of MOH because of paradoxical TLR activation.[137] The

medications licensed for use in humans for other conditions that have been shown to have glial inhibitory properties include minocycline and ibudilast.

Minocycline, a tetracycline derivative that possesses anti-inflammatory effects that are independent of its antimicrobial actions;[90] selectively disrupts activation of microglial cells to prevent allodynia without directly effecting either astrocytes and neurons.[138] Given that it is an already licenced, reasonably tolerated drug it could be considered as a treatment worth exploring for opioid overuse headache. However animal studies suggest that minocycline only has a significant inhibitory effect on glia when given before glial stimulation and is far less effective in reversing enhanced pain states, relative to drugs that also inhibit astrocyte activity.[138, 139] These properties do not make it appealing for treating existing opioid overuse headache.

Ibudilast, a relatively non-selective phosphodiesterase inhibitor that has been licensed for more than 20 years in Japan for the treatment of asthma,[140] may be a more promising treatment option for opioid overuse headache. In recent times it has been found to have glial attenuating properties, in particular the ability to inhibit TLR-4 signalling[117] and, unlike minocycline, it is effective in reversing allodynia when given after the glial activating stimulus.[102] For a review of the pharmacology of ibudilast, see Rolan et al.[141]

Emerging data from human studies also support the use of ibudilast in neuroinflammatory conditions. A 2 year clinical trial in multiple sclerosis provides some evidence that ibudilast has activity in the brain as it was able to reduce white matter loss.[142] Intriguingly and of relevance, although no conclusions can be made regarding efficacy in headache, a recent trial (clinicaltrials.gov identifier NCT00723177) has produced encouraging results following administration of ibudilast to human opioid addicts.[143] During

this double-blind, placebo-controlled study, heroin dependent subjects were able to withdraw from opioids with greater easer when receiving ibudilast,[143] indicating ibudilast may play a role in reversing the adaptive changes associated with long-term opioid use. Ibudilast doses used in these trials (up to 80 mg/day) have been well tolerated. [142] [141] We are currently conducting a randomised, double-blind, placebo-controlled trial of ibudilast in the treatment of MOH in patients who overuse opioids, see clinicaltrials.gov identifier NCT01317992 for more information regarding this study.

Ideally however a new drug with glial inhibitory properties that is without other actions would be most appropriate for evaluation. One potential candidate is (+)-naltrexone. This enantiomer of the orally available long acting selective μ-receptor antagonist (-)-naltrexone, which is licensed for use in humans for the management of opioid and alcohol addiction, is devoid of μ-receptor antagonism but is a potent TLR-4 antagonist. In preclinical studies (+)-naltrexone has been found to potentiate acute morphine analgesia, block opioid reward,[144] decrease the development of analgesic tolerance and hyperalgesia[117] and reverse allodynia.[106]. Studies to enable its use in humans are currently in progress.

Summary

MOH remains a significant clinical problem worldwide. Opioids are strongly associated with, and probably causally related to, the development of MOH. There is convincing preclinical evidence that opioids cause hyperalgesia through activation of glial cells via TLR-4 stimulation. Furthermore, evidence is emerging that in humans chronic pain is associated with increased TLR-4 sensitivity. This provides sufficient evidence to trial glial attenuators and/or TLR-4 antagonists as a potential disease-modifying treatment options in this area of high unmet medical need.

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Conflict of interest statement

PR is a coholder of a provisional (?) patent on the use of ibudilast in MOH (I will clarify with Kirk)

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