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REVIEW ARTICLE

The dynamic interaction between pain and opioid misuse

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In 2014, drug overdose surpassed automobile accidents as the number one cause of accidental death for the first time in the history of the United States. The overdose epidemic is largely driven by opioids, and genuine prescription opioid analgesics play the biggest role in this phenomenon. Despite advancements in abuse deterrent formulations, prescription drug monitoring programmes and clinical assessments for the detection of abuse potential, drug overdoses continue to escalate. The Center for Disease Control has recently issued new guidelines for opioid prescription, yet even these recommendations have their shortcomings. Furthermore, undertreated pain in patients with comorbid substance use disorder poses a major clinical challenge, particularly for patients on opioid replacement therapy. Despite the seemingly obvious interaction between the presence of pain and the abuse of pain-relieving opioids, there is surprisingly little mechanistic data to further our understanding of this vitally important topic. The need for novel pain interventions that minimize abuse liability is critical. Without a fundamental characterization of pain neurobiology and the interaction between chronic pain and the brain's reward system, we are unlikely to make progress in the alleviation of the opioid epidemic.

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Abbreviations

CDC, Center for Disease Control; DHT, digital health technology; POAs, prescription opioid analgesics; SUD, substance use disorder; VTA, ventral tegmental area

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Introduction

The opioid epidemic is one of the greatest health challenges of the 21st century. In the United States, drug overdose is the leading cause of accidental death, and the majority of these fatalities are due to opioids (Rudd *et al.,* 2016). The foundation of this epidemic was laid in the 1990s, in response to what was considered an epidemic in untreated pain. Pain was introduced as the 'fifth vital sign', and both professional and consumer interest groups advocated the use of prescription opioid analgesics (POAs) to address the crisis of untreated pain (Campbell, 1995). The timely emergence of oxycodone on the prescription drug market facilitated the adoption of opioids as a first-line treatment and initiated a highly competitive market for these drugs. POAs are undeniably useful in the treatment of acute pain. However, in light of the abuse and overdose epidemic, substantial controversy has arisen over opioids for chronic pain, and many health care providers are beginning to call into question their Hippocratic oaths. Modern clinical practice faces a huge challenge when it comes to meeting patients' analgesic needs while minimizing their exposure to the adverse risks of opioids.

At any given time, between 30 and 40% of the US population is experiencing either acute or chronic pain (Tsang *et al.,* 2008; Chou, 2009; Johannes *et al.,* 2010; Institute of Medicine, 2011). Given these findings, it may not be surprising that there is a concurrent prevalence of legitimate opioid analgesic prescriptions, with this class of pharmaceuticals being prescribed more frequently than any other category of drugs (Paulozzi *et al.*, 2014). Unfortunately, patients with diagnosed pain and a legitimate opioid prescription are particularly at risk for physical dependence, misuse and transition to illicit opioids such as heroin (Ballantyne and Mao, 2003; Cicero *et al.,* 2015; Fishbain *et al.,* 2008; Hedegaard *et al.,* 2015). It is also worth noting that 60% of POA overdoses occur in patients with genuine prescriptions from a single doctor (Centers for Disease Control and Prevention, 2012). Together, these data suggest a substantial interaction between opioid misuse and the presence of ongoing pain.

Much attention in the literature has been paid to pain as a pre-existing condition in opioid abuse and misuse (Martell *et al.,* 2007; Fishbain *et al.,* 2008; Wasan *et al.,* 2009). Pain is a trigger for self-medication and is, without question, a significant risk factor for opioid misuse (Alford *et al.,* 2016; Amari *et al.,* 2011). However, one of the challenges hindering our understanding of opioid risks in pain patients is the lack of consensus in the definition of terms such as misuse, problematic use, aberrant use and abuse (Chabal *et al.,* 1997; Compton *et al.,* 1998; Robinson *et al.,* 2001; Butler *et al.,* 2007; Larance *et al.,* 2011; Nikulina *et al.,* 2016). These assessment discrepancies may lead to clinician confusion and inconsistent patient treatment. Even when these assessments are used accurately, clinicians are often unable to predict abuse and addiction liability. For instance, chronic pain patients frequently develop tolerance and physical dependence, often in the absence of a substance use disorder (SUD) diagnosis, yet still resort to aberrant behaviours such as dose escalation in order to control poorly alleviated pain (Back *et al.,* 2009). Even if there were universal agreements on the definitions of misuse and abuse, efforts to use self-report assessments to identify pain patients who may be at risk of opioid misuse have been ineffective (Chou, 2014). An important first step in adequately identifying opioid risk is the characterization of the neurobiological interaction between chronic pain and opioid use. Given the role of the brain's reward circuitry in opioid addiction (Martin-Soelch *et al.,* 2001; Ross and Peselow, 2009), this circuit is an ideal target to study pain-induced vulnerability to opioid abuse risk.

Pain neurobiology and reward

The mesolimbic reward pathway has long been recognized for its role in motivated behaviour. The two major players in this system are the forebrain nucleus accumbens (NAc) and the midbrain ventral tegmental area (VTA). These structures have reciprocal connections; neurons in the VTA project rostrally to the NAc, where they release the neurotransmitter **dopamine**, and inhibitory neurons in the NAc feed back onto the VTA by releasing **GABA**. Salient stimuli induce phasic burst firing of dopamine neurons in the VTA, and this firing is sufficient to produce motivated behaviour such as reward seeking (Kim *et al.,* 2013; Tsai *et al.,* 2009). Opioids, like other drugs of abuse, activate the structures within the mesolimbic reward pathway *via* three types of opioid receptors: **μ**, **Δ** and **κ**. Binding of opioid agonists within this circuitry elicits the release of dopamine in the NAc. Activation of the **μ receptor** is largely responsible for encoding dopamine-dependent reward and reinforcement, for both opioids and other reinforcers (Devine *et al.,* 1993; Xiao and Ye, 2008; Le Merrer *et al.,* 2009; Giuliano *et al.,* 2013). In contrast to μ receptor activation, **κ receptor** activation in this pathway blocks the rewarding effects of μ receptor agonists, leading to diminished dopamine transmission in the NAc (Niikura *et al.,* 2010; Ehrich *et al.,* 2015). These changes in dopamine transmission are likely to underlie the dysphoria and other negative side effects elicited by κ receptor activation (Land *et al.,* 2009; Al-Hasani *et al.,* 2015; Donahue *et al.,* 2015). Thus, endogenous and exogenous activation of μ and κ receptors in the mesolimbic pathway seems to elicit a 'push-and-pull' effect on reward and aversion. It is also worth noting that pain relief itself is rewarding, a phenomenon that is attributed to the activation of this system (Becker *et al.,* 2012; Navratilova *et al.,* 2012).

Data from both human and animal studies indicate that chronic pain induces dramatic changes in the functionality of the reward system, both directly through diminished dopaminergic neurotransmission and indirectly through dysregulation of the opioid receptor systems (Narita *et al.,* 2004; Hipolito *et al.,* 2015; Martikainen *et al.,* 2015; Taylor *et al.,* 2015). During persistent inflammatory pain, μ receptors in this circuitry are desensitized, which may be due to a pain-induced increase in the release of endogenous opioid peptides (Schrepf *et al.,* 2016). There is also a top-down management of these processes by the hippocampus, given the role this structure plays in the reinstatement of drug-seeking behaviour (Portugal *et al.,* 2014). Pain-induced alterations in the reward pathway, including the altered value of reward and opioids (Loggia *et al.,* 2014), could play a vital

role in the vulnerability of patients to opioid misuse and abuse. Despite recent efforts to characterize pain-induced sensitivity to opioids, many unanswered questions remain. Although heroin abuse has recently been linked to several genetic polymorphisms (Hancock *et al.,* 2015; Nelson *et al.,* 2016), these have not specifically been studied in pain patients. The identification of 'abuse vulnerable' genetic markers or implementation of other biological screening tools would be of great utility, given the relative inadequacy of self-report and physician assessments of abuse liability (Chou, 2014).

Pain and substance use disorder

Treating chronic pain while avoiding abuse potential is particularly problematic for patients with a previous history of abuse. This is not a small problem, given that 5–17% of the US population has a diagnosed SUD (SAMHSA, 2015; Warner *et al.,* 1995). Unfortunately, nearly half of chronic pain patients with SUD diagnoses report that opioids, prescribed to relieve their pain, were the root cause of their disorder (Jamison *et al.,* 2000). It is well established that prior substance abuse (including nicotine and alcohol) is a strong predictor of opioid misuse/abuse (Turk *et al.,* 2008; Novy *et al.,* 2012). However, there is a significant risk of under-treating people with serious pain, particularly if the SUD diagnosis concerns opioids. In fact, 80% of **methadone** maintenance patients report recent pain, and 37% report chronic pain (Hser *et al.,* 2001; Prater *et al.,* 2002; Rosenblum *et al.,* 2003). It is particularly this population that is at the most risk: the presence of pain creates a vicious downward spiral (Garland *et al.,* 2013), where pain triggers hypervigilance and catastrophizing, leading to self-medication. The relative low cost and abundance of heroin (compared with POAs) is an important motivating factor when patients transition from POAs to illicit drugs (Cicero *et al.,* 2015). This cascade of events substantially increases the risk for abuse and overdose, given the unpredictable purity of illicit fentanyl and heroin (US Drug Enforcement Agency, 2016; Mars *et al.,* 2015). A recent meta-analysis, however (Dennis *et al.,* 2015), concluded that the presence of pain has no effect whatsoever on the consumption of illicit opioids. These discrepancies in the literature further highlight the need for mechanistic investigations into the neurobiology of opioid-treated pain in populations with prior opioid exposure.

The future of opioid therapy

Opioids are the most powerful analgesics known to man, and their continued use in the treatment of severe pain is inevitable. Blanket restriction of opioid therapy in pursuit of curbing the opioid abuse epidemic is not a desirable or realistic goal. What is clear, however, is that opioid therapy of the future must look very different from how it does today. Although the resolution of this crisis is a long way off, concerted efforts to address this issue are underway. In March of 2016, the Center for Disease Control (CDC) released a new set of opioid prescribing recommendations to guide general practitioners, who write the bulk of POA prescriptions. The three-prong approach by the CDC includes (i) using non-opioids for most cases of chronic pain, (ii) when prescribing opioids, using the lowest effective dose, and (iii) ensuring that patients who are treated with opioids are closely monitored (Dowell *et al.,* 2016).

In line with the CDC's first goal, much attention has returned to traditional non-opioid therapeutics such as non-steroidal anti-inflammatory drugs, antidepressants, anticonvulsants or some combination of these (Wolkerstorfer *et al.,* 2016), as well as early intervention with non-opioids to prevent pain chronicity entirely (ED Management, 2016). The development of novel non-opioid therapies is of great interest in academia and industry alike, and several classes of non-opioid drugs are in various stages of preclinical research and early stage clinical trials. For instance, the endocannabinoid system has received a great deal of attention as a novel analgesic target. A number of studies reliably demonstrate the analgesic efficacy of inhibiting enzymes that degrade endogenous cannabinoids (thereby enhancing endogenous cannabinoid activity), across a wide variety of pain states (Kinsey *et al.,* 2009; Sakin *et al.,* 2015; Wilkerson *et al.,* 2017). Over the last decade, evidence for the efficacy of non-pharmacological interventions for chronic pain management has also grown substantially. Two such approaches include cognitive behavioural therapy and mindfulness meditation practice. A recent meta-analysis of mindfulness for pain relief revealed that although pain intensity is not affected by this intervention, perceived pain control is significantly improved (Bawa *et al.,* 2015). Recent advances in this field indicate that the neural mechanisms underlying the efficacy of mindfulness are distinct from those of placebo effects (Zeidan *et al.,* 2015). A major drawback of psycho-behavioural pain management strategies, however, is the relative inaccessibility of these interventions in rural areas, in which opioid use disorders have a particularly high prevalence (Dunn *et al.,* 2016). Furthermore, these alternative approaches are also less likely to be covered by health insurance, creating a socio-economic disparity in non-pharmacological pain intervention (Harris *et al.,* 2012).

Novel opioid-based strategies have also received significant attention lately, consistent with the CDC's second goal of using the lowest effective dose. For instance, adjunct therapies such as cannabinoids are gaining notoriety because of their ability to produce synergistic analgesia and opioid sparing (Cox *et al.,* 2007; Abrams *et al.,* 2011; Johnson *et al.,* 2013). Under this type of adjunctive therapy, tolerance and dose escalation can be prevented, and overall opioid consumption is substantially reduced (Smith *et al.,* 2007; Haroutounian *et al.,* 2016). Analgesic synergy has been observed across a wide variety of cannabinoid and opioid agonists, species and administration routes (Cichewicz and McCarthy, 2003; Roberts *et al.,* 2006; Kazantzis *et al.,* 2016). The mechanisms of this generalized synergy are not completely understood, although there are several points of crosstalk between these receptors including overlapping G-protein signalling cascades and possible hetero-dimerization (Scavone *et al.,* 2013). Likewise, the mechanisms of opioid sparing remain to be elucidated, but are at least partially mediated by overall analgesic

requirements, given the self-tapering nature of patients' opioid dosing after the initiation of cannabis therapy (Boehnke *et al.,* 2016; Haroutounian *et al.,* 2016). Peripherally restricted opioid agonists are also undergoing intense investigation, because of their inability to produce the adverse effects mediated by the central nervous system (Albert-Vartanian *et al.,* 2016). Although this approach has great potential utility in clinical practice, to date, there is only one peripherally restricted opioid undergoing Phase II clinical trials (κ receptor agonist JNJ-38488502; Olesen *et al.,* 2013). Along similar lines, opioid receptor agonists with biased intracellular signalling properties are currently being explored for their potential to produce analgesia in the absence of undesirable side effects. For instance, the μ agonist **PZM21** selectively activates Gi-coupled cascades without β arrestin recruitment, resulting in analgesia without respiratory depression, the development of tolerance or abuse liability (Manglik *et al.,* 2016). Although the promise of biased agonists is quite strong, there will be a substantial latency before these types of therapies move out of preclinical investigation. Finally, abuse deterrent formulations have been effective in limiting the abuse liability of specific prescription opioids such as oxycontin. Unfortunately, this approach is also associated with the unintended consequence of diverting users to illicit opioid use, ultimately enhancing overdose mortality (Alpert *et al.,* 2017). Conversely, packaging interventions such as blister packs have consistently been shown to increase patient adherence and compliance to prescriptions, and in some countries, this is a federally mandated practice for opioids (Australian Government Department of Health, 2008; Conn *et al.,* 2015).

The CDC's third recommendation, to closely monitor those who are prescribed opioids, places a significant burden on primary care physicians, who write the vast majority of opioid prescriptions. This is incredibly problematic, given that primary care physicians currently only have 13–16 min to spend with each patient, are inadequately educated about pain and are already experiencing professional burnout on an epidemic scale (Doorenbos *et al.,* 2013; Peckham, 2016; West *et al.,* 2016). To relieve some of this burden, state-level prescription opioid monitoring systems have been implemented in 49 US states and have successfully limited opioid diversion and inappropriate prescriptions (Prescription Drug Monitoring Program Center of Excellence at Brandeis, 2014; US Government Accountability Office, 2002). For example, in the state of Kentucky, after the implementation of a state-wide monitoring programme, the average time for law enforcement to investigate alleged 'doctor shopping' dropped from 156 to 16 days. Unfortunately, there is conflicting evidence whether or not monitoring programmes actually diminish emergency department overdoses or opioid deaths (Paulozzi *et al.,* 2011; Li *et al.,* 2014; Maughan *et al.,* 2015; Patrick *et al.,* 2016). What these studies have clearly revealed, however, is that monitoring programmes vary considerably from state to state, and it is only the most rigorous programmes with near real-time data reporting that are the most effective at preventing overdose (Patrick *et al.,* 2016). Applying these rigorous principles to an integrated or federal drug monitoring programme could potentially improve the efficacy of prescription monitoring and relieve some burden on primary care physicians.

Despite the merit in the CDC's recommendations for the prevention of opioid misuse, they do not address the problem of treating patients who already suffer from opioid use disorder. An accretion of evidence from the last two decades definitively supports simultaneous enrolment in opioid replacement therapy and structured psychosocial support programmes for the treatment of opioid dependence (Kosten and O'Connor, 2003; Montoya *et al.,* 2005; Copenhaver *et al.,* 2007). Despite the compelling evidence for this approach and the prevalence of comorbid pain in this population, simultaneous pain management in this context has received little attention. However, emerging evidence strongly supports the efficacy of this type of psychotherapeutic pain management component in opioid use disorder treatment. Specifically, a comprehensive suite of approaches (including cognitive behavioural therapy, acceptance-based approaches and messaging about the importance of avoiding substance abuse as a method of pain management) effectively lowers pain intensity and pain-related function, compared with standard substance abuse treatment (Ilgen *et al.,* 2016). Taken together, these data suggest that a multi-modal, concurrent approach to pain management and substance abuse treatment may be a highly efficacious approach to ameliorating these issues. Unfortunately, there are major barriers in the broad application of this approach. Firstly, although any primary care physician can prescribe opioid analgesics, only a physician or psychiatrist with specialty training in addiction can prescribe opioid replacement therapy (FDA, 2006). This factor significantly contributes to the excess demand for opioid maintenance therapy and extensive waiting lists for maintenance programmes (Gunderson *et al.,* 2011). The delayed latency for patients to participate in these programmes is significantly correlated with poor outcomes, including relapse and mortality (Peles *et al.,* 2013; Ilgen *et al.,* 2016). One possible strategy to offset the pitfalls of treatment latency may be the use of digital health technologies (DHTs), such as smartphone- or internet-based interventions. DHTs have consistently been shown to improve outcomes for tobacco and ethanol abuse, including in low-income populations (Tait and Christensen, 2010; Muench, 2014; Keoleian *et al.,* 2015). These results, combined with the pervasive use of smartphone technology (Dahne and Lejuez, 2015), the potential for individualized treatment and the cost-effectiveness of digital health interventions, strongly warrant the study of DHTs for opioid use disorder and comorbid pain.

Summary

It is critical that we implement novel pain treatment strategies based on our collective knowledge of the failure of opioids in the treatment chronic pain. It would be counterproductive to follow the opioid crisis with a backlash against opioids, thus re-igniting the generational cycle of undertreated pain, followed by rampant analgesic prescription. It is very likely that the future of pain treatment will include personalized, precision, hybrid approaches that are based on the neurobiology of chronic pain. Without a

fundamental understanding of pain-induced changes in the brain and how these adaptations interact with subsequent analgesic drug exposure, we are merely fishing for effective solutions to the opioid crisis. Achieving this goal will take a large, concerted effort across hospitals and research institutions and a significant pain-targeted investment from funding agencies.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan *et al.*, 2016), and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 (Alexander *et al.*, 2015).

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Conflict of interest

A.W.-P. has an equity interest in Habu Health, a cannabis informatics company. J.A.M. has no conflicts to disclose.

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