The Self-administration of Analgesic Drugs in Experimentally Induced Chronic Pain

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Abstract Systemically and centrally delivered opioids have been comprehensively studied for their effects both in analgesic and addiction models for many decades, primarily in subjects with presumptive normal sensory thresholds. The introduction of disease-based models of persistent hypersensitivity enabled chronic evaluation of opioid analgesic pharmacology under the specific state of chronic pain. These studies have largely (but not uniformly) reported reduced opioid analgesic potency and efficacy under conditions of chronic pain. A comparatively limited set of studies has evaluated the impact of experimentally induced chronic pain on self-administration patterns of opioid and non-opioid analgesics. Similarly, these studies have primarily (but not exclusively) found that responding for opioids is reduced under conditions of chronic pain. Additionally, such experiments have also demonstrated that the condition of chronic pain evokes self-administration or conditioned place preference for non-opioid analgesics. The consensus is that the chronic pain alters responding for opioid and non-opioid analgesics in a manner seemingly related to their respective antiallodynic/antihyperalgesic properties under the specific state of chronic pain.

Keywords Chronic pain · Reinforcement · Opioid · Analgesic · Self-administration · Conditioned place preference

Contents

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1 Introduction

The experience of chronic pain is increasingly recognized as a public health concern to the USA alongside a global public health matter. The intense and comprehensive search to improve our understanding of the complex mechanistic changes associated with various chronic pain syndromes continues alongside global efforts to optimize delivery and use of currently available chronic pain medications. These investigations have been enabled for decades by the use of well-established animal models of sensory function and analgesic pharmacology. Our knowledge of sensory plasticity, neuroanatomical, and physiological changes has been greatly advanced in the last several decades by the introduction of a wide variety of animal models specific for pain conditions including inflammation (Colpaert et al. 1980), nerve injury (Bennett and Xie 1988; Seltzer et al. 1990; Kim and Chung 1992; Decosterd et al. 2002), tumor invasion (Wacnik et al. 2001; Sasamura et al. 2002), chemotherapeutic exposure (Polomano et al. 2001; Authier et al. 2003), and muscle pain (Kehl et al. 2000; Sluka et al. 2001), among many others. Many of these have been reviewed extensively previously (Gregory et al. 2013; Wang and Wang 2003) and in this collection of essays. With the establishment of each of these models, acute opioid pharmacology has been widely assessed (Sasamura et al. 2002; Kehl et al. 2000; Hylden et al. 1991; Mao et al. 1995; Bian et al. 1995; Yaksh et al. 1995; Ossipov et al. 1997; Nichols et al. 1995; Fairbanks et al. 2000; Yamamoto and Sakashita 1999; Wacnik et al. 2000; Yaksh 2002; Petraschka et al. 2007). We have significant knowledge of how opioids either reduce or fail to reduce hypersensitivity under these particular acute conditions, but minimal information on how subjects respond to these agents chronically.

We also have a substantial literature of opioid pharmacology in models of addiction that spans many decades (Koob and Le Moal 2008). Quite understandably, it is this extensive knowledge base of the neurobiology of addiction that is consulted when considering the impact of opioid pain medications on central nervous system (CNS) centers of reward and addiction (Ballantyne and LaForge 2007; Bailey et al. 2010). The vast majority of studies of opioid reward and addiction, however, have taken place in naïve subjects with presumptive normal sensory thresholds. This notation is important because what has been learned through the last 20 years of specific pain condition

modeling is that the central (Urban and Gebhart 1999; Kuner 2010; Zieglgansberger et al. 2005) and peripheral nervous systems (PNS) (Koltzenburg et al. 1999) are altered under conditions of persistent hypersensitivity. CNS alterations in subjects with chronic pain have been suggested to account for corresponding changes in chronic pain subjects' overall response to opioids ranging from analgesic effect to the propensity to transition to an addictive state. It is essential, therefore, to consider the total opioid pharmacology in the context of the chronic pain condition of interest. A comparatively limited number of studies of opioid responding under conditions of chronic pain have, in fact, demonstrated altered responding for opioids in either an enhanced or reduced responding direction. This chapter reviews and compares the observations from these studies to provide a comprehensive description of what has been learned to date. Taken collectively, the data tend to converge upon a general pattern that the state of analgesia, regardless of the reinforcing effects of the drug under normal conditions, is, in and of itself, reinforcing under conditions of established chronic pain.

2 Adjuvant-Induced Arthritis

Some of the earliest work evaluating analgesic self-administration in a model of chronic pain came out of efforts to characterize the establishment of a model of arthritic chronic pain. In order to assess whether complete Freund's adjuvant (CFA)-treated subjects would demonstrate a preference for analgesics, Colpaert et al. (1980) instituted a two bottle choice paradigm where rats had available to them either a bottle containing suprofen (a clinically used NSAID, since discontinued) or a bottle containing an alternative sweet solution. In this first study, arthritic rats demonstrated increased intake of the suprofen-containing solution relative to control rats. It is important to note that NSAIDS are not thought to be reinforcing in normal subjects (Hoffmeister and Wuttke 1975). Colpaert and colleagues followed this report with a similarly designed study (Colpaert et al. 1982) demonstrating that arthritic rats self-administered oral fentanyl significantly more than control rats comparable to the outcomes observed with suprofen. Taken together, these results suggested that the analgesic state itself, rather than the opioid, serves as the reward. Consistent with that proposal, Colpaert et al. (2001) later showed increased fentanyl consumption (two bottle choice model) in rats with mycobacterial-induced inflammation. However, in this case, they observed attenuation of the elevation in fentanyl consumption when the rats were provided with concurrent, non-contingent delivery of dexamethasone. This outcome suggested that the rats chose fentanyl for analgesic purposes rather than for its other rewarding properties. One aspect not represented in the design of this initial series was an assessment of chronic pain. However, it is noteworthy that the time course of the elevation in suprofen self-administration in arthritic rats relative to control rats closely followed the time of maximal elevation in paw and joint diameter (Colpaert et al. 1980). Once the paw and joint diameter elevation decreased, so declined the elevation in suprofen intake. This time-course correspondence between elevation in

fentanyl intake and paw and joint diameter was even tighter in the fentanyl study (Colpaert et al. 1982), as was the time course of body weight decrease and vocalizations, measures interpreted to be indicative of pain.

Shortly thereafter, a third study conducted by Lyness et al. (1989) compared the self-administration of intravenous morphine (5.0 mg/kg/injection, 24-h access) in rats with CFA versus vehicle-injected controls. In this experiment, the tail pressure test was applied to document the development of mechanical hyperalgesia and it was systematically shown that the self-administered morphine resulted in an anti-hyperalgesic response. However, in contrast to the previous studies, the rats with established chronic inflammatory pain self-administered significantly *less* morphine than control rats. Further, non-contingent delivery of indomethacin (an NSAID) by the experimenter significantly reduced morphine self-administration specifically in the arthritic, but not the control rat. Finally, as the pathology of the inflammation resolved, the arthritic rats began to escalate morphine intake to a level more comparable to that of control. These outcomes were interpreted by the authors as suggestive of the state of chronic pain resulting in an apparent *reduction* in the reinforcing properties of morphine, which, in this case, were able to be dissociated from the motivation for analgesic relief.

3 Neuropathic Pain

The nerve injury models of neuropathic pain (Bennett and Xie 1988; Seltzer et al. 1990; Kim and Chung 1992; Decosterd et al. 2002) were developed in the late eighties and early nineties and shortly thereafter a number of studies demonstrated that the opioid analgesics in these models were reduced in potency (Mao et al. 1995; Bian et al. 1995; Yaksh et al. 1995; Ossipov et al. 1997; Nichols et al. 1995; Fairbanks et al. 2000; Yamamoto and Sakashita 1999; Yaksh 2002; Petraschka et al. 2007) with some dependence on route of administration (Bian et al. 1995; Nichols et al. 1995; Lee et al. 1995). The introduction of these models enabled the evaluation of opioid self-administration under conditions of neuropathic pain, as had been previously assessed under conditions of inflammatory pain. Kupers and Gybels (1995) used the two bottle choice fentanyl self-administration protocol established by Colpaert to compare fentanyl self-administration between subjects with partial sciatic nerve ligation (Seltzer et al. 1990) and adjuvant arthritis (*Mycobacterium butyricum*) (Colpaert et al. 1980) as well as their respective controls. In the adjuvant arthritis model, an elevation in fentanyl consumption in the 3rd week corresponded precisely with the time of elevation in spontaneous pain indicators (paw elevations and shaking) measured in a separate group of arthritic rats. Von Frey thresholds decreased and signs of spontaneous pain elevated by 1 week post-surgery in neuropathic rats as expected. However, in contrast to the arthritic adjuvant experiments, fentanyl consumption did not elevate in neuropathic rats (not tested behaviorally) and, in fact, remained comparable to that of controls throughout the four-week testing period. The authors attributed these outcomes to

potential reduction in analgesic effectiveness of opioids under conditions of chronic pain, although opioid analgesic pharmacology was not assessed in this particular study.

In a later report, Martin and colleagues described their comprehensive and systematic evaluation of opioid self-administration of four clinically relevant prescription opioids (morphine, fentanyl, hydromorphone, methadone) and the gold standard opioid reinforcer heroin in rats with L5/L6 spinal nerve ligation (Kim and Chung 1992). In this study, the development of mechanical hypersensitivity was confirmed by von Frey threshold analysis by days 5–7 post-surgery for each subject included in the study and monitored twice weekly for the duration to ensure persistent hypersensitivity. Nerve-injured and sham-operated control rats were then trained to maintain lever pressing behavior for varying doses of i.v.-infused opioid reward (1 dose per hour within a 4-h session). Dose–response curves for each opioid were constructed and compared between the neuropathic and control conditions. Sham-operated rats developed standard inverted U-shaped dose–response curves that are characteristic of fixed-ratio drug self-administration experiments. In the case of the neuropathic rats, the inverted U-shaped dose–response curve was shifted rightward for all the opioids, meaning that the lower doses that were effective in eliciting operant responding behavior in control rats were ineffective in neuropathic rats. In other words, at the lower opioid dose range, rats with chronic pain did not respond with behavior indicative of addiction. The higher doses that did elicit responding in neuropathic rats were notably comparable to those that reverse neuropathic mechanical allodynia. Further, and importantly, non-contingent delivery of a dose of intrathecal clonidine (an alpha-2 adrenergic agonist) that alleviates nerve injury-evoked mechanical hypersensitivity significantly reduced heroin-maintained responding in nerve-injured, but not control, subjects. Taken together, these data support the proposal that the antihyperalgesic effects of opioids contributed to the motivation to maintain responding in subjects with chronic pain. That interpretation is consistent with the prior views advanced by Colpaert et al. (1980, 2001), Lyness et al. (1989), and Kupers and Gybels (1995).

Martin and colleagues further demonstrated in a separate study that rats with chronic neuropathic pain (Kim and Chung 1992) (but not normal rats) will develop maintained responding for intrathecally delivered clonidine, although not for adenosine (Martin et al. 2006). Spinal clonidine-maintained responding in nerve-injured rats (Martin et al. 2006) was extinguished either by inclusion of the alpha-2 adrenergic receptor antagonist idazoxan with intrathecal clonidine or substituting saline for the clonidine intrathecal infusion. Since clonidine is typically considered to have minimal abuse liability (Martin et al. 2006) and humans do not abuse clonidine for euphoric effect, it is thought that the rats with chronic pain likely self-administered spinal clonidine for its analgesic properties. It is noteworthy that a similar pattern was later observed where nerve-injured (but not control) rats demonstrated conditioned place preference [a model often used as a measure of reward (Tzschentke and Schmidt 1995)] in a chamber associated with intrathecally delivered clonidine, but not adenosine (King et al. 2009). This difference was proposed to be explained by the observation that adenosine reduces evoked hyperalgesia in

human subjects with neuropathic pain but not spontaneous ongoing pain (Eisenach et al. 2003). Taken together, these observations are supportive of the proposal that operant measures may be able to distinguish between analgesics effective for spontaneous and ongoing pain versus hypersensitivity evoked by sensory stimuli.

4 Neuropathic Pain, CFA, Vincristine

Consistent with the work of both Kupers and Gybels (1995) and Martin et al. (2007), we (Wade et al. 2013) recently demonstrated that mice with chronic pain induced by either nerve injury (Fairbanks et al. 2000), adjuvant arthritis, or chronic exposure to the chemotherapeutic vincristine do not establish oral fentanyl-maintained responding in contrast to their respective controls with normal sensory thresholds. In these experiments, all mice were given the opportunity to lever press for oral fentanyl reward (active lever) or no reward (control lever) in daily 2-h sessions for a 3–4-week period following the establishment of chronic hyperalgesia. Importantly, and consistent with similar observations in rat (Martin et al. 2007), mice with nerve injury, paw inflammation, or chemotherapy exposure demonstrated food-maintained responding indicating that the failure to develop opioid-maintained responding was specific for the drug and not indicative of a generalized inability to acquire the behavior. These studies are distinguished from the previous reports in that the development of opioid-maintained responding in control versus chronic pain conditions was monitored daily during the initiation and maintenance phases of all chronic pain conditions.

5 Long-Access Self-administration

It is noteworthy that the prior studies (Martin et al. 2007; Wade et al. 2013) evaluating opioid self-administration under conditions of chronic pain might best be characterized as short-access sessions, meaning that the subjects had access to the opioid in increments of 1–4 h. Wade et al. (2012) have since expanded analysis to evaluate the self-administration of intravenous oxycodone in CFA-treated rats in long-access sessions (12 h in duration). Consistent with the prior reports, responding for oxycodone is significantly diminished in CFA-treated rats versus saline-injected controls under conditions of long-access sessions over a period of at least 13 days. Further, evaluation of the motivation for reward by examining breakpoints under a progressive ratio of reinforcement was conducted at the conclusion of the study. It was observed that the breakpoint (the limit in the lever presses necessary to receive the next reward) is significantly lower in animals with CFA-induced inflammation relative to controls.

6 Cannabinoid-Maintained Responding in Neuropathic Pain

Consistent with the proposal that the self-administration method of operant conditioning may be an effective approach to evaluate potential analgesics with greater sensitivity than standard reflex measures (Colpaert et al. 2001; Martin et al. 2007), Gutierrez et al. (2011) conducted a comparison of CB2 receptor-selective agonist (*R, S*)-AM1241-maintained responding between neuropathic and control rats (both sham-operated and naïve). Using the spared nerve injury (SNI) model in this case, mechanical hypersensitivity was established and the rats were allowed to enter 4 consecutive daily sessions with the opportunity to press two levers, one of which resulted in delivery of i.v.-infused (*R*, *S*)-AM1241. A key observation is that naive rats did not develop lever preference for (*R*, *S*)-AM1241, whereas rats with established neuropathic pain significantly increased preference for the lever associated with (*R, S*)-AM1241. Neuropathic rats were further evaluated for sensory thresholds 15–20 min following the operant session when it was observed that mechanical hypersensitivity was significantly alleviated, indicating that a sufficient amount of drug was self-administered to achieve an antiallodynic/antihyperalgesic effect. Such a paired set of observations (measurement of operant responding and sensory thresholds within the same subjects) provides strong evidence in support of the proposal that the state of analgesia is a reinforcing condition. Additionally, two important observations were introduced by this study: First, when the reinforcer was switched to vehicle, neuropathic rats ceased responding for reward and showed an allodynic response to presentation of von Frey fibers. Interestingly, the removal of the cannabinoid did not result in an initial elevation in lever responding prior to extinction. This pattern contrasts with that typically observed with abused drugs in rats with presumptive normal sensory thresholds. Second, subjects that received sham operation as a control for the nerve injury demonstrated comparable active lever responding for CB2 receptor-selective cannabinoid as did neuropathic animal during the FR1 schedule, although their mechanical withdrawal thresholds (at normal sensory levels) were not affected by the drug session. Consideration must be made that sham-operated controls (while viewed as a control for neuropathic pain) perhaps should not be considered "pain-free" control subjects given the fact that, by definition, they undergo surgical procedures involving muscle damage and skin incision and can be presumed to have experienced post-operative pain. The motivation for sham-operated, but not naïve subjects to lever press for cannabinoid reward, may be associated with analgesic effects not detectable by the reflex methods. It is also noteworthy that the responses of the sham-operated subjects were less than those of the neuropathic rats with increased schedules of reinforcement (e.g., FR6), suggesting that the neuropathic rats worked harder for (*R*, *S*)-AM1241 than sham-operated controls. These data indicate that, although the sham subjects may be representative of a post-operative pain state, the response to pain

was distinguishable between the two populations, as might be expected. These observations highlight the limitations of the sensory reflexes in fully detecting chronic pain responses and feature the operant self-administration model as an approach to screen potentially clinically relevant analgesic medications.

7 Analgesic-Induced Conditioned Place Preference

In contrast to operant studies of self-administration of analgesics under conditions of neuropathic pain, which have been comparatively limited, recent years have seen an increase in studies involving the conditioned place preference (CPP) model of reward to examine a variety of analgesic substances [e.g., clonidine and lidocaine in chronic pain models of inflammation and nerve injury (He et al. 2012)]. Some of the recent studies using CPP to assess non-opioid analgesic drugs have been recently reviewed (Navratilova et al. 2013) and a pattern similar to the previously described self-administration studies has emerged, consistent with the long-standing proposal that relief from pain is a rewarding state. Interestingly, however, studies of morphine-induced CPP yield notably contrasting results. Morphine-induced CPP has been shown to be significantly reduced in neuropathic rats (Ozaki et al. 2004) and mice (Niikura et al. 2008) relative to their sham-operated counterparts as well as reduced in mice with established CFA-(Betourne et al. 2008) and carrageenan-induced (Suzuki et al. 1996) inflammation and hindpaw thermal hyperalgesia. Morphine-induced CPP has been demonstrated to be reduced in mice with either formalin-induced inflammation (Suzuki et al. 1996; Narita et al. 2005) or neuropathic pain (sciatic nerve ligation) (Petraschka et al. 2007; Ozaki et al. 2002, 2003). In contrast, a recent study (Cahill et al. 2013) reported that low doses (1, 2 mg/kg, sc) of morphine significantly induced CPP in nerve-injured (spared nerve injury model), but notably not in control rats. These doses were demonstrated to be antiallodynic using von Frey mechanical stimulation and it is suggested that the analgesic rather than the hedonic properties may account for the rewarding effects. It is noteworthy that higher doses (4, 8 mg/kg) were less effective, consistent with the inverted U-shaped dose–response curves typical of opioid agonists in operant self-administration studies. The difference between this most recent report (Cahill et al. 2013) of morphine-induced CPP in chronic pain versus the prior morphine-induced CPP literature in various states of chronic pain (Ozaki et al. 2002, 2003, 2004; Niikura et al. 2008; Betourne et al. 2008; Suzuki et al. 1996; Narita et al. 2005) is not clear. However, taken collectively, these results are in agreement that under the condition of chronic pain, the reward properties of morphine are altered relative to normal control subjects.

8 Studies on CNS Alterations Under Conditions of Chronic Pain

At this point, two general themes should be evident from accumulated evidence from 30 years of operant studies of opioid responding in chronic pain states: (1) opioid responsiveness is frequently diminished (although sometimes increased) under conditions of chronic pain and (2) the state of pain relief is, itself, a reinforcing event. It should follow that chronic pain-induced alterations in the CNS could contribute to such alterations in pharmacological response. This question is an area of increasing investigation and, while a comprehensive review is beyond the scope of this chapter, some featured observations will be noted for consideration. It is increasingly recognized that persistent chronic pain causes functional (Low et al. 2012) and structural alterations throughout the CNS, some of which can result in cognitive deficits that are reversible with effective pain treatment (Seminowicz et al. 2011). Given the operant behavior reviewed here demonstrating altered responding for analgesics under conditions of chronic pain, it might be expected that some of these changes take place in the CNS locations where reward and addiction intersect with modulation of pain and/or are directly mediated. In fact, a literature is emerging that examines molecular and functional alterations at some of these centers under conditions of persistent chronic pain. For example, peripheral nerve injury results in altered DNA methylation in pre-frontal cortex (Alvarado et al. 2013; Tajerian et al. 2013), a brain region that contributes to the affective component of pain (Tracey and Bushnell 2009; Schweinhardt and Bushnell 2010) and is also known to contribute to the development of addiction (Goldstein and Volkow 2011). It has been well established that the mesolimbic dopaminergic system projecting from the ventral tegmental area (VTA) to the nucleus accumbens (NAcc) drives the rewarding effect of morphine (Koob 1992; Nestler 1996; Narita et al. 2001). Specifically, opioids are thought to inhibit GABAergic interneurons in the VTA which in turn disinhibit dopamine cells in the VTA resulting in elevated dopamine levels in NAcc. Not surprisingly, a number of mechanistic studies of alterations in VTA and in NAcc under conditions of chronic pain have emerged.

8.1 NAcc

In normal mice, morphine-induced CPP results in a elevation of dopamine in NAcc; this elevation is reduced under conditions of chronic pain (Narita et al. 2005). However, in formalin-treated mice, inhibition of morphine-induced CPP is also accompanied by a decrease in NAcc dopamine levels, a decrement that can be reversed with intrathecal delivery of an immunoneutralizing antibody to dynorphin, suggesting involvement of the kappa opioid system (Narita et al. 2005). Similar observations were recently reported by Taylor et al. (2013) who observed that chronic constriction injury also led to an overall reduction in basal and morphine-stimulated

dopamine levels in the NAcc. Through fMRI, Baliki et al. (2010) have shown that patients with chronic low back pain present a distinct pattern of connectivity within the NAcc that corresponds to the magnitude of chronic spontaneous pain. They have further shown that anticipation of relief of pain (analgesia) results in activation of NAcc core (Baliki et al. 2013). These data are congruent with a recent study (Navratilova et al. 2012) of peripheral nerve block (PNB)-induced CPP in rats with incisional pain (Brennan et al. 1996). In this experiment, incised rats were injected 24 h post-surgery with lidocaine to induce peripheral nerve block in a paired chamber manner to evoke CPP. Lidocaine-mediated analgesia results in place preference presumably from relief of the ongoing spontaneous pain. This observation suggests that relief of post-surgical spontaneous pain is also rewarding, consistent with the previous interpretation of the observations of Colpaert et al. (1980, 1982, 2001), Lyness et al. (1989), Kupers and Gybels (1995), Martin et al. (2006), and Gutierrez et al. (2011).

8.2 VTA

Extracellular signal-related kinase (ERK) derives from the serine/threonine protein kinases and contributes to the cellular processes involving protein phosphorylation and gene expression. ERK activity in the reward centers of the brain has been examined under conditions of non-contingent chronic morphine administration with and without chronic pain. Berhow et al. (1996) showed that ERK activity increased in the VTA following implantation of a morphine pellet (75 mg, 5-day time course) and this ERK activity subsequently increased tyrosine hydroxylase activity, a biomarker for increased dopamine production in the reward centers. Ozaki et al. (2004) have similarly evaluated this pathway as a mechanism underlying their observation that neuropathic pain reduces morphine CPP (Ozaki et al. 2002). They observed that rats with neuropathic pain exhibit decreased ERK activity (lower levels of p-ERK) in the VTA compared to their sham-operated controls (Ozaki et al. 2004). Complementarily, morphine-induced CPP was also inhibited as a result of i.c.v. injection of a specific MEK inhibitor, PD98059, which blocks ERK activity. These data suggest a mechanism for the reduction of opioid-induced CPP in neuropathic pain.

8.3 Intracranial Self-stimulation of the VTA

To determine whether the alterations in opioid responding under conditions of neuropathic pain were due to a concomitant change in the dopaminergic input from the VTA to the NAcc and/or the ability of opioid agonists to modulate these inputs, Ewan and Martin (Ewan and Martin 2011) applied a model of intracranial self-stimulation (ICSS) specifically to the VTA. It has been demonstrated that rats will

develop and maintain lever pressing for electrical stimulation to the VTA, which results in elevation of dopamine in the NAcc (Hernandez and Shizgal 2009). Nerve-injured subjects revealed equivalent stimulation–response curves as controls, suggesting that the effects of nerve injury on opioid reinforcement may be specific to opioids and not general reinforcers. In support of that proposal, the ICSS-potentiating effects of morphine and heroin (but not cocaine) were both reduced in neuropathic rats compared to controls. These data in essence identify a mechanism of diminished opioid responding to the VTA and illustrate the specificity of the effect to the opioid system.

9 Summary and Conclusions

Taken collectively, the 30 years of operant studies of analgesic drugs (both opioid and non-opioid) suggest two organizing principles. First, by and large, states of chronic pain induced by diverse manipulations (inflammation, nerve injury, tumor invasion, or chemotherapeutic exposure) tend to reduce opioid self-administration. It seems that alterations in opioid sensitivity of dopaminergic neurons projecting from the VTA to the NAcc are a likely explanation for this phenomenon. Second, subjects with established chronic pain tend to seek the state of analgesia. The analgesic state itself is a rewarding stimulus. Evidence in support of this principle is found in elevated ingestion of oral analgesics (both opioid and non-opioid), reduced responding for one analgesic when another is provided non-contingently, and the self-administration of non-opioid analgesics and CPP of non-opioid analgesics, and some analgesic doses of opioids under conditions of chronic pain. This phenomenon is consistent with the human clinical experience where it is common that patients appropriately seek pharmacological treatment for relief of their malignant or chronic pain (Walsh 1984). Sometimes, the manner of that pursuit resembles inappropriate drug-seeking behavior (Marks and Sachar 1973; Weissman and Haddox 1989; Kirsh et al. 2002; Weissman 2005; Lusher et al. 2006). This phenomenon, termed "pseudoaddiction" (Weissman and Haddox 1989), is often resolved by adequate pain management (Marks and Sachar 1973; Weissman and Haddox 1989; Kirsh et al. 2002), not unlike reduced opioid self-administration with non-contingent delivery of the non-opioid analgesics reported in the aforementioned chronic pain rodent models (Colpaert et al. 2001; Lyness et al. 1989; Martin et al. 2007).

The question is often asked, what is the percentage of chronic pain patients that develop an opioid addiction and how does that compare to the general population? There is considerable variability in the clinical data responding to this question (Ballantyne and LaForge 2007). However, some patterns have emerged that merit attention. An evidence-based structured review (Fishbain et al. 2008) of sixty-seven studies is well recognized (Garland et al. 2013; IOM 2011; Minozzi et al. 2012) as having contributed useful progress toward this question. Within this review, 24 studies comprising 2,507 chronic pain patients exposed to opioids found that the abuse/addiction rate was 3.27 % (range 0–45 %). A number of variables [e.g., history

of prior non-opioid (Pletcher et al. 2006) and opioid substance abuse, mental illness, duration on opioids (Edlund et al. 2007)] are identified as likely to influence the establishment of opioid misuse/addiction following implementation of chronic opioid analgesic therapy for chronic pain. Taking at least one of these into consideration, the data were analyzed separately for those chronic pain patients without a prior history of substance abuse/addiction. The abuse/addiction rate to opioid medication was 0.19 % when considering only subjects without a prior history of abuse and addiction. These values are sometimes compared to the prevalence of addiction in the general population (~10 %) (Fishbain et al. 2008); perhaps a more useful comparison would be to more recent data collected from a survey (Huang et al. 2006) of 43,000 adults which revealed that the prevalence specifically of prescription opioid non-medical use to be 4.7 % and conversion to opioid addiction as 1.4 %.

This same review (Fishbain et al. 2008) also considered seventeen studies representing 2,655 chronic pain patients that evaluated aberrant drug-related behaviors (ADRBs, e.g., unauthorized dose escalation, aggressively requesting medication, hoarding medication, among others); these can be indicators of the development of addiction. The percentage of chronic pain patients exposed to opioids that displayed ADRB (11.5 %, range 0–44.6 %)) was reduced to 0.59 % when assessing only subjects without a prior history of substance abuse and addiction. As mentioned above, behaviors associated with pseudo-addiction can resemble ADRBs; this possibility was not considered by the reviewed studies and so the prevalence noted in the structured review may be an overestimate, as the authors noted. Further, it is noteworthy that the distinctions between definition and/or diagnosis of opioid abuse versus true opioid addiction are often obscured in the broader social and clinical discussion (Fields 2011). Therefore, the question posed above is highly complex and whether reliable conclusions can be drawn from or compared between the existing clinical literature remains controversial (Ballantyne and LaForge 2007; Minozzi et al. 2012; McAuliffe 2012).

The ongoing search to further our understanding of the neurobiological mechanisms underlying potential chronic pain-induced alteration of analgesic self-administration is essential. Such information may help guide and optimize chronic medication management for specific forms of chronic pain.

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