# Chapter 1
# Opioid and Non-Opioid Drug Responding Under States of Chronic Pain: A Timeline Spanning 1980 to Present Day

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**Abstract** It has been long recognized that chronic pain is a significant public health concern. After many decades of research and development investment for alternatives, the most effective pharmacological tools for managing diverse chronic pains remain the opioid analgesics. Several serious side effects including, the risks of addiction or diversion of opioid-containing dosage forms to nonpatient populations render the use of opioid medication for treatment of pain complicated. At the same time, it been asserted repeatedly that patients with established chronic pain demonstrate reduced propensity to acquire addiction to opioids than the general population. For over 30 years, neuropharmacological studies in rodent models of opioid self-administration have suggested that responding for opioids is, in fact, significantly altered under conditions of established chronic pain, and often reduced. However, with the introduction of the sustained release opioid preparations, the expansion of opioid prescribing, and appropriately heightened concerns regarding opioid-related addiction and mortality by respiratory depression, this long-standing assertion that patients with chronic pain are less susceptible to addiction has been recently challenged. In response to this challenge the opportunity arises, perhaps, to consider that chronic pain is a generic term that refers to a broad spectrum of painful conditions; these pain conditions may have common neurobiological mechanisms, but also key distinctions. Understanding the neurobiology underlying distinct chronic pain conditions as they relate to opioid addiction may help to better predict the therapeutic window and side effect risks associated with chronic opioid therapy. Progress has been made in this area, but it is currently recognized that more specific information is greatly needed. As a primer to planning such future studies, the pres-

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C.A. Fairbanks, T.J. Martin (eds.), *Neurobiological Studies of Addiction in Chronic Pain States*, Contemporary Clinical Neuroscience 17,
DOI 10.1007/978-1-4939-1856-0_1

ent chapter is intended to summarize the prior three and a half decades of neuropharmacological studies that have systematically evaluated opioid (and non-opioid) analgesic responding in animal models of opioid addiction.

## Introduction

In 2011, the Institute of Medicine (IOM) report on chronic pain [1] importantly highlighted the prevalence of chronic pain in the USA and the associated economic costs. Additionally, the report systematically described the current complexities associated with treating chronic pain, particularly with opioid analgesics, the diversion of which has become a crisis parallel to and linked with chronic pain. Although the report appropriately acknowledges these very valid concerns regarding the use of opioids, the report also discusses concern surrounding the rising fear of analgesic medication that is prevalent both in the practitioner and patient population. Among a number of barriers to appropriate pain medication, the IOM report asserts that "Regulatory, legal, educational, and cultural barriers inhibit the medically appropriate use of opioid analgesics" [1]. Like all patients with neurological dysfunction, patients with chronic pain tend to seek medical treatment to improve their quality of life [2]. It is recognized that these patients sometimes encounter disapproval for seeking treatment and that they represent a stigmatized patient population. Although the introduction of the sustained release opioid preparations in the 1990s expanded access to high doses of opioids and more accessible media profiling of cases of conversion to addiction [3] may elevate cultural consciousness of risks, these barriers to pain management are not a recent phenomenon. The stigma and the debate about pain management has been ongoing for decades [2–4] just as patients with chronic pain have been seeking pharmacological management of their pain for decades [2]. What may confound the patient–practitioner interaction and contribute to a cycle of stigma and distrust is that patients with chronic pain may display similar characteristics as those that pursue prescription opioid with an intent to abuse [5–9]. This scenario, described as "pseudoaddiction" [3, 6], has been reported as often addressed when the chronic pain patient receives effective treatment [5–7]. There are parallels to this phenomenon in a subset of neuropharmacological studies in animal models of addiction that have studied responding for reinforcing drugs in animals with established chronic pain. In the last 30 years, there has been a limited but important set of studies that have evaluated how opioids are self-administered in animals with established chronic pain. In selected studies, opioid self-administration in chronic pain subjects is reduced when non-opioid analgesics are provided by the experimenter [10–12]. These studies suggest that, in these cases, the subjects' motivation for self-administration of opioids is for analgesic relief. In fact, a resounding theme across multiple studies and models of chronic pain is that the state of analgesia itself is a rewarding phenomenon, consistent with the clinical observation of pseudoaddiction. In this review, we will feature this literature to document the progression of knowledge acquired through

comprehensive and diligent consideration of self-administration of a spectrum of analgesic medications across a variety of animal models of established chronic pain.

## Analgesic Self-Administration in Chronic Pain Models

It was recognized [13] decades ago that there was an urgent need to establish an animal model of chronic pain in order to study the mechanisms of chronic pain and analgesic pharmacology. As part of the effort to develop and characterize such a model, the first studies that considered operant self-administration of analgesic medications emerged. Among the first models was a model of hindpaw inflammation induced by intraplantar injection of various mycobacteria. It was inferred that the resultant inflammation would evoke a chronic painful state, the question being how best to demonstrate that the condition was, in fact, interpreted as pain by the subject. In a report as early as 1980, Colpaert and colleagues hypothesized [14] that if the mycobacterial injection in the tail base were, in fact, hyperalgesic, that subjects might demonstrate a preference for oral analgesic drugs when presented with an option to choose between a bottle containing an analgesic and no analgesic drug. They tested this proposal by offering rats treated with chronic Freund's adjuvant (CFA) the option to drink fluid from a bottle with the nonsteroidal anti-inflammatory drug suprofen or a bottle with a control solution. Since NSAIDs do not demonstrate addictive properties in rats [15], an elevation in suprofen self-administration in rats with hindpaw inflammation might be reflective of motivation to self-medicate presumptive associated inflammatory pain. Consistent with their hypothesis, the CFA-treated subjects consumed more from the bottle containing the analgesic suprofen than did normal rats. Similar to these results using suprofen, Colpaert and colleagues [16] reported in 1982 observations that inflamed rats self-administered oral fentanyl more than noninflamed controls. These complementary studies with suprofen and fentanyl provided very early evidence to support the concept that analgesic relief may be a reinforcing condition. Measurements that are frequently used to assess hypersensitivity under conditions of chronic pain [17] were not taken in these experiments; the assertion that the subjects experienced chronic pain was based upon several indirect observations. Specifically, the rats with CFA-induced inflammation displayed a decrease in body weight and an increase in spontaneous vocalizations, which are suggestive of states of distress or discomfort. Furthermore, the peaks of the increases in both suprofen [14] and fentanyl [16] consumption in CFA-treated rats were matched by the peak increases in the diameters of the inflamed paws and joints. Finally, when the inflammation subsided, the analgesic self-administration reduced to control levels.

Almost 20 years later, Colpaert expanded this analysis to consider the impact of the addition of systemic analgesics in arthritic rats with elevated intake of opioid. In 2001 Colpaert and his colleagues [11] showed, again, that rats with chronic arthritis drank significantly more from a bottle with fentanyl than a control bottle.

In contrast to the early studies from the 1980s, these experiments included experimenter-delivered systemic administration of the anti-inflammatory glucocorticoid, dexamethasone. In dexamethasone-treated rats, the self-administration of fentanyl diminished over time. The effect was interpreted as support for the concept that, under conditions of chronic pain, elevated responding for fentanyl in rats with chronic inflammatory pain may be due to motivation to seek pain relief.

In 1989, a second research group [10] evaluated the propensity of CFA-treated rats to lever press for intravenous delivery of morphine relative to controls. Their observations were comparable to that of Colpaert and colleagues with some striking differences. In contrast to the findings of Colpaert, in these experiments the CFA-treated rats self-administered significantly *less* morphine than their control counterparts. However, similar to the findings of Colpaert, experimenter-delivered administration of indomethacin (an NSAID) further reduced morphine self-administration in CFA-treated subjects. Indomethacin had no effect on morphine self-administration in normal rats. As the inflammation subsided, the CFA-treated rats increased morphine-self-administration. That the self-administration response converged to the level of the normal subjects as the inflammation resolved is congruent with the findings of Colpaert, although the direction of the effect is in notable contrast. It is noteworthy that in this study, unlike the first studies of Colpaert, a nociceptive reflex measurement was taken (tail pressure test) to determine the magnitude of induced hypersensitivity and to verify that the self-administered levels of morphine were, in fact, analgesic. The secondary observations of this study were consistent with those of Colpaert in that provision of the NSAID reduced morphine self-administration suggesting that the state of analgesia may, in and of itself, be reinforcing. On the other hand, their main observation that morphine self-administration was reduced under the state of inflammation-induced hyperalgesia, perhaps for the first time, suggested that the very state of chronic hypersensitivity reduced the reinforcing properties of morphine.

## Other Pain Models

### *Nerve Injury*

It has also been long recognized that various conditions of chronic pain are not biologically equivalent. For example, the pharmacology of opioid analgesics under conditions of inflammation is thought to differ vastly from that under the state of neuropathic pain. While opioids tend to demonstrate enhanced analgesic potency in states of chronic inflammation [18–20], opioid analgesics under conditions of nerve injury show reduction in potency [21–29] depending on the route of administration [21, 23, 30]. The nerve injury based models of chronic neuropathic pain [31–34], introduced in the 1980s and 1990s, facilitated the further consideration of opioid-maintained responding. In 1995, Kupers and Gybels [35] compared oral fentanyl self-administration (two bottle choice method) between neuropathic [32] and

arthritic rats [14], as well as the appropriate corresponding control groups. Consistent with the data presented in the 1980s by Colpaert [16], rats with CFA-induced inflammation demonstrated an increase in preference of the fentanyl-containing bottle relative to control. This increase took place at a time that matched the peak of hypersensitivity measured in a separate group of CFA-treated rats. Conversely, the rats with partial sciatic nerve injury, while confirmed to be hyperalgesic, did not show an increase in preference for fentanyl over the course of the experiment, in contrast to the inflamed rats. The preference of the nerve-injured rats between the two bottles was similar to control rats. Kupers and Gybels ascribed this effect to the aforementioned purported lower efficacy/potency of opioids under conditions of neuropathic pain. It should be noted here, however, that whether or not oral fentanyl reversed mechanical hyperalgesia in these specific subjects was not evaluated.

Twelve years later the observation that morphine self-administration was altered under conditions of nerve injury was confirmed and significantly expanded. In 2007 Martin et al. [12] contributed an extensive analysis of the self-administration profiles of multiple doses of a spectrum of opioids in rats subjected to the Chung method [36] of nerve ligation. These experiments are reviewed elsewhere in this volume by the authors themselves (Chap. 2), but merit some description in this chapter of their contribution to this *Timeline* of related studies. Martin et al. compared maintained lever pressing behavior in neuropathic rats and their respective controls in response to presentation of multiple doses (one dose per hour for 4 consecutive hours) of the well-known reinforcer heroin and four widely studied opioid analgesics (morphine, fentanyl, hydromorphone, and methadone). Briefly, dose–response analysis for the aforementioned opioids in almost all cases demonstrated decreased efficacy/potency in neuropathic rats compared to controls. In other words, the lower doses that support maintained responding in normal rats were not effective in nerve-injured rats. Therefore, in these rats, the activity that is typically interpreted as a model of addiction was not present at those doses. In the case of heroin and methadone, higher doses resulted in responding in nerve-injured rats; notably, these higher doses alleviated hypersensitivity. These results are consistent with two phenomena previously described (1) that the state of neuropathic pain, unlike inflammatory pain, results in a reduction in the presumed motivation of subjects to lever press for opioid reward, a finding consistent with that of Kupers and Gybel [35] and (2) the remaining rewarding effects of higher doses of higher efficacy opioids may be a consequence of the subject's motivation to achieve relief from chronic pain, consistent with the previous studies. This second interpretation is supported by additional observations that experimenter delivered clonidine (an alpha 2 adrenergic receptor analgesic agonist) resulted in reduction of heroin-maintained responding in neuropathic (but not control) rats [12]. Note that this finding paralleled that of Colpaert [11] with dexamethasone-mediated reduction of escalation of fentanyl intake in CFA-treated rats and Kupers and Gybel's demonstration that indomethacin reduced morphine self-administration in nerve-injured rats [35]. These observations would suggest that subjects in a state of neuropathic pain would maintain lever pressing for a non-opioid analgesic. In fact, in a complementary study Martin et al. [37] observed that, unlike control rats, neuropathic rats lever pressed preferentially

for the alpha2 adrenergic receptor agonist clonidine (an analgesic) when delivered spinally via an indwelling intrathecal catheter. These data are congruent with that of Colpaert who, as mentioned before, demonstrated increased suprofen intake over control solution in CFA-treated rats.

The aforementioned studies [12, 38] that assessed opioid self-administration under conditions of chronic pain represent operant sessions where the subjects have access to the reinforcers for a short duration of time (1–4 h). Wade and colleagues [39] have recently presented their evaluation of the self-administration of intravenous oxycodone in rats treated with CFA during 12 h periods of time (long access). In agreement with the studies described above, rats with unilateral CFA inflammation respond for oxycodone significantly less than vehicle-treated controls. This effect was studied for 13 days of established tactile hypersensitivity. Additionally, at the end of the study period, an assessment of breakpoints of progressive ratio of reinforcement (the maximum in the lever presses required to earn the next drug infusion) was made. It was noted that CFA-treated subjects demonstrate notably lower breakpoints than control counterparts. These observations are consistent with the concept that the motivation to lever press for opioids is altered in rats with chronic pain.

### *Mice*

From the mid 2000s to present day, we [38] have also pursued studies of opioid self-administration under diverse conditions of established chronic hypersensitivity specifically in mice. These experiments revealed that mice with pre-established persistent hindpaw sensitivity resultant from either spinal nerve ligation [27], subcutaneous injection of CFA into the hindpaw, or repeated injections of vincristine fail to develop lever pressing preference for oral fentanyl, unlike normal control subjects. In these studies, subjects initiated daily 2 h self-administration sessions for 2–3 weeks following establishment of hindpaw hyperalgesia from one of the aforementioned treatments. During the session, pressing one lever resulted in delivery of either a 70-μL quantity of fentanyl available for oral consumption or a 20-mg food pellet. Pressing the other lever provided no reward. A noteworthy distinction is that while the mice with pre-established hypersensitivity did not develop maintained responding for opioid, they did develop food-maintained responding (similar to controls). Therefore, these data indicate that the reduction in opioid responding is directly related to drug treatment and is not evident with food reward.

### *Conditioned Place Preference*

Similar to studies of opioid self-administration, there are a few key early reports using conditioned place preference (CPP) as a model to consider opioid dependence under conditions of persistent pain. In 1988, using the CPP assay, Shippenburg

and colleagues [40] explored, for the first time in a systematic manner, the reward associated with opioids in subjects with inflammatory pain. They observed that, like previous reports [18–20], the opioids morphine and the kappa agonist U-69594 showed increased antinociceptive potency under conditions of inflammation versus the control condition. In contrast to the observations of Colpaert using the two bottle choice approach, Shippenburg and colleagues observed that subcutaneously delivered morphine did not result in increased time spent in the morphine-paired chamber relative to control subjects, despite the fact that the doses used were analgesic. The reasons for the contrast are not clear, but Shippenburg's study represents the first in a series of evaluations of morphine CPP conducted under conditions of chronic pain, as well as other non-opioid analgesic drugs [41]. More recent studies of CPP using non-opioid analgesic drugs appear to indicate a response reflective of the proposal that the analgesic condition is, itself, rewarding [42]. In contrast, many CPP reports using morphine reveal diverse outcomes. These are summarized in Table 1.1. Recent observations by Cahill et al. [43] showed that doses of subcutaneously delivered morphine in the range of 1–2 mg/kg did not induce CPP in normal rats but did result in a place preference in neuropathic rats. These same morphine doses reversed tactile hyperalgesia consistent with the proposal that the pain-relieving properties of morphine may be attributable to its effect in CPP. While these results are compellingly supportive of the emerging organizing principle that the state of analgesia corresponds to reward-associated responses in nerve-injured subjects, there are a series of studies that stand in notable contrast. Morphine-induced CPP has been shown to be reduced in mice with inflammation based hindpaw hypersensitivity induced by CFA [44] and carrageenan [45]. Morphine CPP has been systematically and repeatedly shown to be reduced in neuropathic rats [46] and mice [29, 47–49]. CPP induced by tramadol and its primary metabolite M1 has also been shown to be reduced in nerve-injured mice [50]. Morphine-induced CPP has also been demonstrated to be reduced in mice with formalin-induced inflammation [45, 51]. The differences between these results [44–49, 51] that reveal reduced morphine-induced CPP under conditions of chronic pain, versus that of Shippenburg [40] (no change), and the more recent report [43] of enhanced morphine-induced CPP in chronic pain are not well understood. Some of the key parameters are summarized in Table 1.1. Where consensus can be found is that, by and large, the state of chronic pain most often changes the tendency of rodents to show a place preference for noncontingent administration of morphine.

## Non-Opioid Reinforcing Analgesics: Cannabinoid

In addition to consideration of opioids, NSAIDS, and corticosteroid classes of medications, Gutierrez and colleagues [54] have compared the self-administration pattern of a selective agonist for the cannabinoid 2 receptor in neuropathic rats versus two distinct controls, sham-operated and naïve rats. Following the development of tactile allodynia, the rats were placed in daily sessions over 4 days where they could bar press either of two levers. Pressing one of the levers does not result in any

**Table 1.1** Studies of morphine-induced conditioned place preference in rodent

| Study | Species | Pain model | Dose of morphine and route of administration | Confirmed analgesic effect of morphine | Time in chamber during drug pairing | Morphine CPP outcome in subjects with chronic pain |
|---|---|---|---|---|---|---|
| Shippenburg [40] | Male Sprague Dawley rat, Charles River, Wiga, Germany | CFA, unilateral hindpaw injection | 0.3, 1, 3, 5 mg/kg, S.C. | Yes, paw pressure threshold (Randall-Selitto) | 60 min | No change |
| Sufka [52] | Male Sprague Dawley rat, Harlan, IN | CFA, unilateral hindpaw injection | 3, 10 mg/kg | Yes, hot plate | 60 min | Enhanced |
| Suzuki [45] | Male Sprague Dawley rats (Tokyo Experimental Animals) | Formalin, carrageenan | 2, 4, 8 mg/kg, S.C. | Yes, paw pressure threshold (Randall-Selitto) | 50 min | Suppressed |
| Oe [53] | Male ICR mice (Tokyo Experimental Animals) | PKC activator PDBU (1, 5, 10 nmol 5 day thermal hyperalgesia) | 3, 5, 10 mg/kg, S.C. | Yes, hot plate (55 °C) | 60 min | Suppressed |
| Ozaki [48] | Male Sprague Dawley rats (Tokyo Experimental Animals) | Partial sciatic nerve ligation | 4 or 8 mg/kg, S.C. | Not specifically assessed | 60 min | Suppressed |
| Ozaki [49] | Male, ICR mice (Tokyo Experimental Animals) | Partial sciatic nerve ligation | 3, 10, and 30 nmol/ mouse, I.C.V. | Yes, tail flick test | 60 min | Suppressed |
| Ozaki [46] | Male ICR mice (Tokyo Experimental Animals) | Partial sciatic nerve ligation | 2.5, 5, 10 mg/kg, S.C. | Not specifically assessed | 60 min | Suppressed |
| Niikura [47] | Mice: male and female C57BL/6J and 129S2/SvPas mixed background | Partial sciatic nerve ligation | 5 mg/kg, S.C. | Not specifically assessed | 60 min | Suppressed |
| Narita [51] | Rats: Sprague Dawley (Tokyo Experimental Animals) | Formalin unilateral hindpaw | 2, 4, 8 mg I.P. | Not specifically assessed | 60 min | Suppressed |
| Petraschka [29] | Male C57BL/6 mice (Charles River Laboratories, Wilmington, MA, USA) | Partial sciatic nerve ligation | 2.5, 5 mg/kg, S.C. | Yes, tail flick test | 30 min | Suppressed |
| Betourne [44] | Female C57BL/6 mice (Iffa Credo, L'Arbresle, France) | Cancer (melanoma cell) CFA | 10 mg/kg, I.P. | Yes, hindpaw licking | 20 min | Suppressed: cancer, CFA |
| | | Carrageenan | | | | No change: carrageenan |
| Cahill et al. [43] | Male Long Evans rat (Charles River, St. Constant, Quebec) | Chronic constriction injury | 1, 2, 4, 8 mg/kg, S.C. | Yes, effective by 30 min | 60 min | Enhanced |

outcome, pressing the other lever resulted in an intravenous infusion of the CB2 receptor agonist (*R*, *S*)-AM1241. Unlike the opioid analgesics, but similar to NSAID analgesics, normal rats did not develop a preference for either lever. Neuropathic rats, however, showed lever-pressing preference for (*R*, *S*)-AM1241 i.v. delivery (but not vehicle), which alleviated tactile hypersensitivity measured following conclusion of each session. These data suggest that the lever pressing responses in neuropathic rats could be associated with the analgesic response of (*R*, *S*)-AM1241 delivery. An important observation noted in this study was that sham-operated rats (a common control for nerve injury models) also displayed active lever discrimination for intravenous (*R*, *S*)-AM1241. It is not very common for studies to include both naïve and sham-operated controls and so these findings are important for consideration of what the sham-operated control may represent. Sham-operated controls receive the same experience as nerve-injured rats in terms of anesthesia, incision, and all mechanical aspects of the surgery except the nerve injury itself. One might expect that there should be an aspect of postoperative pain that may not be detected in the standard reflex measurements and may (or may not) persist into the time of self-administration experimentation. We have similarly observed [38] an effect on self-administration in sham-operated subjects that may be interpreted as intermediate between nerve injured and naïve subjects. The primary importance of the contribution of Gutierrez and colleagues is to demonstrate that, like other non-opioid analgesic agents, the CB2 selective receptor agonist induced a lever preference that appears to be closely associated with analgesic benefit.

## Conclusion

A prevalent observation from this review of over three decades of research appears to be that responding for opioids is different in subjects with chronic pain than subjects without chronic pain. As described above, that theme is observed repeatedly in many different experiments, across species, and pain-inducing conditions. These observations call for much greater investigation of opioid responding under conditions of chronic pain, identification and full characterization of the CNS altered systems so that the appropriate context can be considered when developing and optimizing patient pain management protocols. Currently, the discourse on patient response to opioid analgesics is primarily informed by our extensive decades-old literature on patient, nonhuman primate, and rodent responding to opioids under presumed pain-free conditions. Consideration of any alteration in the responding of chronic pain patients to opioid analgesics relative to the pain free human population has been acknowledged clinically for decades [2–4], but is eclipsed by our immensely greater knowledge and appropriate concern regarding the addictive properties of opioids in people without established chronic pain conditions. Second, experimental subjects with induced persistent pain, in many cases, appear to intentionally self-administer or seek the state of pain relief whether achieved by opioid or non-opioid analgesics. In other cases, opioid responding is diminished. This may be due to alterations in the reward pathways as is discussed further in this volume by Narita and colleagues in Chap. 4 of this volume. The general consensus of the literature

reviewed here is that pain relief is reinforcing or motivational. It is essential to significantly expand our consideration of the alterations in subjects' responding for opioid and other analgesics under diverse states of chronic pain in order to more fully address this public health concern from a scientific and objective platform.

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