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The pain and health characteristics of skin injecting opioid users

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The Pain and Health Characteristics of Skin Injecting Opioid Users

by

Canyon Steinzig RN, PhD(C)

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

Nursing

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
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by

Canyon Steinzig RN, PhD(C)
Dedication and Acknowledgements

To my mom, Charlotte Ada Steintzig, the voice of intelligence in my life, and to my dad, Donald George Steintzig, who embodies the intelligence of listening.

This dissertation is the culmination of a great effort and I am thankful for the generosity of the numerous people who have helped me along the way. First, I want to thank the Betty Irene Moore Foundation for their generous fellowship that gave me this opportunity to fulfill my dream of obtaining a PhD, and the Alex Anognos Scholarship for supporting my research at San Francisco General Hospital. I also want to thank all of my classmates and professors who opened my mind to a new way of seeing the world. I am also grateful to Dr. Steve Paul for his kindness and devotion to the nursing students at UCSF. I strive to emulate this in my own career. He also helped me analyze and understand my study findings. I want to thank all the staff at San Francisco General Hospital ISIS clinic for their help and support with this work. I especially want to thank the patients who participated in the study, their openness inspires me. I cannot adequately thank my committee members for their patience in reading draft after draft and all of their generous support. I thank Dr. Sandra Weiss, for her kind clarity and succinct communication. I thank Dr. Peggy Compton, whose body of work is the source and inspiration for this project. I only hope to contribute some valuable piece to the better care of heroin users. I thank Dr. Martha Neighbor, who always
reminds me that research must have meaning to the patients. Finally, I thank my advisor, Dr. Kathleen Puntillo, who has never failed to meet me and pull me to a higher level. She is a truly remarkable person, with an energy and intellect that I hope to someday grasp. I thank her for guiding what has been a personal transformation, and I hope to make her proud. I want to thank Teri Gwin, who believed in me and took me under her wing as I became a teacher. I’m getting there. I thank Karen Wolf for seeing me as a great nurse would, with effortless care and understanding. I want to thank my family and friends, E&A, M&A, M&K, R&M, I&G, K&K, C&K and all the people of that little place over the hill who take care of each other. Finally, to Jeanne and Adeline, who make everything matter.
The Pain and Health Characteristics of Skin Injecting Opioid Users

ABSTRACT

Some opioid users are known to have a high prevalence of chronic pain as well as other physical and mental health problems. However, data remain limited on the pain experience of active skin injecting opioid users. The aims of this descriptive study were twofold: (1) to examine the overall prevalence of moderate to severe chronic pain (MSCP) as well as other health and pain characteristics of skin injecting opioid users who seek hospital care for treatment of a painful skin abscess related to injecting drugs, and; (2) to identify potential predictors of MSCP, including demographics, acute pain intensity, physical and mental health, and pain treatment characteristics. An urban sample of 91 adult English speaking patients was interviewed in an abscess treatment clinic at a large medical university. MSCP was defined as pain that was experienced within the last week, had persisted for more than 6 months, and was of moderate to severe intensity or interference. Any chronic pain within the last week was reported by 73% of patients and MSCP by 67%. Fifty-percent of all patients reported psychiatric diseases, including depression, anxiety and bipolar disorder. There were no characteristics under study that significantly predicted MSCP in this sample. However, this sample of skin-injecting opioid users was found to report extremely high rates of moderate to severe chronic pain as well as high levels of physical and psychiatric disease. Future research is warranted to investigate approaches aimed at achieving optimal, safe pain relief for this very vulnerable population.
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CHAPTER 1

Dissertation Introduction: The Pain and Health Characteristics of Skin Injecting Opioid Users

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Dissertation Introduction: The Pain and Health Characteristics of Skin

Injecting Opioid Users

Pain is a prevalent, undertreated and costly complaint that claims a large proportion of health care money and time. Despite recommendations from the American Pain Society (American Pain Society, 1995; the Veterans Administration’s “pain as a fifth vital sign” campaign (Health Care Advisory Board, 1998; Veterans Health Administration, 1999; Kirsch, Berdine & Zablotsky et al., 2000) and subsequent JCAHO support and advocacy for improved and formalized pain management (JCAHO, 2002), many pain problems remain unsolved (National Centers for Health Statistics, 2006).

Twelve percent of all prescriptions are related to pain management, and up to 20 percent of all outpatient visits are for complaints of pain (Schappert, 1992). Over 75 million Americans are thought to live with chronic pain, with the majority of pain experienced being moderate to severe in nature (Turk, Okifuji & Kalauokalani, 1999). In addition to the consequences for the individual such as alterations in health, mood, function, and work (Turk, 2002), there are broader implications for society at large, and it remains an expensive problem for an already over-burdened healthcare system, where the annual cost of untreated or undertreated pain has been calculated at over $100 billion per year (Turk, 2002).

Pain remains a problem for patients across a broad spectrum of society, but research has shown that some populations may be uniquely vulnerable to suffering from chronic pain. Some groups that are known to suffer inordinately
with pain include ethnic minorities (Anderson, Green & Payne, 2009; Edwards, Doleys, Fillingim, Lowery, 2001; Edwards, Fillingim, Keefe, 2001; Breitbart, Rosenfeld, Passik, et al., 1996; Cleeland, Gonin & Hatfield et al., 1994), those living with less privilege (Faucett, Gordo & Levine, 1995) and those living with certain disease states such as cancer (Portenoy, Ugarte, Fuller & Haas, 2004; Cleeland, Gonin & Baez et al., 1997; Potenoy, Kornblith & Wong et al., 1994) or AIDS (Vogl, Rosenfeld & Breitbart et al., 1999; Hewitt, McDonald & Portenoy et al., 1997; Breitbart, McDonald & Rosenfeld et al., 1996; Rosenfeld, Breitbart & McDonald et al., 1996). Furthermore, a review of the existing literature has identified a strong relationship between exposure to chronic methadone (Potter, Prather & Weiss, 2008; Sheu, Lussier & Rosenblum et al., 2008; Rosenblum, Herman & Chunki et al., 2003; Jamison, Kauffman & Katz, 2000) oral morphine (Hay et al., 2008) and worsening pain. Specifically, in both observational (Potter et al., 2008; Sheu et al., 2008; Rosenblum et al., 2003; Jamison et al., 2000) and experimental studies, humans (Hay et al., 2009; Compton, Athanasos & Elashoff, 2003; Compton, Charuvastra, Kintaudi & Ling, 2000) and animals (Bright & Bradley, 2000; Devillers, Boisserie, Laulin, Larcher & Simonnet, 1995) exposed to opioids have been shown to experience heightened pain responses or more chronic pain.

The focus of this dissertation has been to better understand the chronic pain prevalence, as well as the physical and mental health characteristics and pain treatment modalities, of skin injecting opioid users. Chapter 2 discusses research that articulates the physiologic mechanisms of the pain experience of
opioid-exposed animals and people. That chapter also provides an overview of the peripheral pain system followed by a detailed examination of the central and descending mechanisms by which the brainstem is involved in pain processing. The chapter concludes with a description of possible mechanisms by which chronic opioid exposure may lead to a worsened pain experience. The majority of existing research draws their conclusions from animal models, but there is a growing body of literature that stems from experiments with human subjects.

Chapter 3 of this dissertation relates to the relationship between opioid addiction and pain. The first section presents the literature which addresses the central brain mechanism of opioid addiction and also presents the literature which addresses the central brain mechanism of pain. The chapter concludes with a description of the overlapping central brain mechanisms of opioid addiction and pain that may make chronic opioid users especially vulnerable to worse pain experiences.

Chapter 4 presents the results of the dissertation study, “The pain and health characteristics of skin injecting opioid users with acute pain.” The overarching goal of this study was to improve the understanding of the pain and health experience of patients who inject opioids into their skin. The two specific aims of the study were to:

- examine the overall prevalence of moderate to severe chronic pain (MSCP) as well as other health and pain characteristics of skin injecting opioid users who seek hospital care for treatment of a painful skin abscess related to injecting drugs.
• identify potential predictors of MSCP including demographics, acute pain intensity, physical and mental health, and pain treatment characteristics.

Chapter 5 is a conclusion of the dissertation with a summary of the key findings and implications for future research and clinical practice.
References


Hewitt DJ, McDonald M & Portenoy RK et al. (1997). Pain syndromes and


www.cdc.gov/nchs.data.hus.hus06.pdf (accessed April 12, 2010).


Veterans Health Administration Memorandum.(1999). Pain as the Fifth Vital

Vogl D, Rosenfeld B, Breitbart W, Thaler H, Passik S, McDonald M & Portenoy
RK. (1999). Symptom prevalence, characteristics, and distress in AIDS
CHAPTER 2

Pain and Opioid Induced Hyperalgesia in Chronic Opioid Users

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INTRODUCTION

Acute (Ducharme, 2005; Puntillo, Neighbor, O'Neil & Nixon, 2003; Ducharme & Barber, 1995) and chronic pain (Maetzel & Li, 2002; Rustoen et al., 2004; Turk, 2002; Breivik, Collett, Ventafridda et al., 2006; Moulin, Clark & Speechley, 2003; Hensler et al., 2009) are known to be highly prevalent, costly, under assessed and under treated among those seeking care in hospitals, clinics or living in the community. Pain is a primary reason people seek medical and emergency care, with emergency department patient pain rates as high as 78% (Cordell et al., 2002; Tanabe & Buschmann, 1999) and in-patient pain rates close to that (Donovan & Miaskowski, 1992). In addition, certain groups of patients suffer inordinately from both acute and chronic pain. These include ethnic minorities, (Portenoy, Ugarte, Fuller, & Haas, 2004; Edwards, Fillingim & Keefe, 2001; Edwards, Doleys, Fillingim & Lowery, 2001; Faucett, Gordon & Levine, 1994; Cleeland, Gonin & Baez et al., 1997; Todd, Samaroo & Hoffman, 1993) the poor, (Saastamoinen, Leino-Arjas, Laaksonen & Lahelma, 2005; Eachus, et al., 1999; Lock, Allgar & Jones, 1999; Badley & Ibañez, 1994; Andersson, Ejlertsson & Leden et al., 1993) and women (Andersson et al., 1993), in addition to those with specific mental (Barry et al., 2009; Demyttenaere et al., 2004, Bair, Robinson, Katon & Kroenke, 2003) and physical (Lesage & Portenoy, 1999; Vogl et al., 1999; Portenoy & Thaler et al., 1994, Gonin & Hatfield, 1994) illnesses. There are sufficient data to suggest that some opioid-using patients are among those who suffer inordinately due to pain (Peles, Schreiber, Gordon & Adelson, 2005; Rosenblum, Herman, Chunki et al., 2003; Jamison, Kauffman & Katz,
2000). In fact there is a growing body of research which indicates a high prevalence of chronic pain in some opioid dependent methadone maintenance treatment program (MMTP) patients (Peles et al., 2005; Rosenblum et al., 2003; Jamison et al., 2000). Rates of 37% for severe, interfering chronic pain to 61% for any pain lasting more than 6 months have been reported. Typically, the reported pain has been at least moderate to severe in intensity and has been shown to severely interfere with multiple domains of the patient’s life. It is also known that a significant number of opioid dependent patients also belong to vulnerable populations and carry high rates of mental and physical health problems (Peles et al., 2005; Rosenblum et al., 2003; Jamison et al., 2000). Because some opioid exposed patients have been reported to have increased pain reports, many are likely to seek out care for their pain (Alford, Compton, Samet & Ann, 2006), increasing the imperative to understand their pain. Also, current research suggests that exposure to some opioids such as methadone (Davis & Inturissi, 1999) may influence human pain physiology.

There are many formal definitions of chronic opioid use, dependence and addiction. However, the relevant pain literature does not clearly define the terms. For the purposes of this paper, people are defined as addicted and dependent chronic opioid users if they are receiving methadone maintenance for opioid addiction replacement therapy, or are active illicit opioid users who experience withdrawal when abstaining from opioids.

The aim of this review is to describe the physiologic mechanisms that are known to play a role in the pain experience of chronic opioid dependent patients.
To achieve this, the paper will evaluate both animal and human studies that have described the processes by which these patients may come to experience high rates and intensities of pain. This paper will elucidate the alterations in the physiologic processes that may stem from opioid exposure. The first section will include a brief review of pain definitions and mechanisms by which opioids contribute to a heightened pain experience. The second section will provide a detailed explanation of the central descending pain inhibition and facilitation modulatory systems as they relate to transient, inflammatory, and neuropathic conditions. The third section will address the specific phenomena of opioid tolerance and hyperalgesia associated with chronic opioid use. Because the primary aim of this paper is to describe the role of the brain in pain modulation, discussions of peripheral and spinal mechanisms of pain transmission and control will be limited to opioid influences at the dorsal horn.

THE PAIN SYSTEM

Definitions and Pain Types

Pain involves chemical and electrical changes at the peripheral site of injury, nociceptive reflexes via peripheral and central transmission pathways, modulation at the dorsal horn of the spinal cord, and both modulation and interpretation in the brain (Miaskowski, 2004). Transient pain involves the electrical transmission of a noxious stimulus from the periphery to the brain that is usually sharp in nature and resolves immediately. Transient pain relates to the fact that it involves no tissue damage and no neuroplastic changes within the nervous system itself (Loeser & Melzack, 1999). Acute nociceptive pain is caused
by cutaneous, somatic or visceral tissue damage and resolves when the tissue heals, usually within days or weeks. Hyperalgesia and allodynia can accompany nociceptive pain, and they are caused by chemical changes at both the peripheral (PNS) and central nervous system (CNS). Hyperalgesia is increased sensitivity and pain perception from damaged tissue, and allodynia is an alteration in sensation whereby uninjured tissue becomes sensitized to previously non-painful stimuli. Allodynia is also referred to as secondary (relating to pain in uninjured tissue) hyperalgesia and is thought to be modulated by the CNS.

*Neuropathic pain* is that which is initiated from injury and pathology of the nervous system itself and is not part of a normal physiologic response to injured/healing tissue. It is seen in the setting of disease states that affect peripheral nerves such as diabetes, infection (e.g., herpes zoster), nerve compression, or nerve trauma. Neuropathic pain can also be caused by damage or dysfunction within the central nervous system (CNS), which includes the brain, brainstem, and spinal cord, and is then referred to as a type of *central pain*. This damage or dysfunction may have organic causes such as stroke, multiple sclerosis, tumors, epilepsy, brain or spinal cord trauma, or Parkinson's disease (Haddad, 2007; Loeser & Melzack, 1999). It also may have non-organic causes, such as depression (Maletic & Raison, 2009; Maletic et al., 2007) or chronic opioid exposure (Peles et al., 2005; Rosenblum et al., 2003; Jamison et al., 2000).
Pain System Physiology- Overview

A noxious stimulus leads to pain perception through a series of physiologic steps. *Transduction* is the manner by which mechanical, thermal or chemical stimuli, under the influence of neurotransmitters, are converted to electrical signals at nociceptors, i.e., free nerve endings. These nerves then transmit an electrical signal to the dorsal horn of the spinal cord (Vanderah, 2007; Campbell & Meyer, 2006; Coutaux, Adam & Willer, 2005; Riedel & Neeck, 2001).

Nociception can be produced at the peripheral nociceptor in 3 ways: first, by direct stimulation by heat or mechanical pressure; second, by direct action upon the nociceptor by a neurotransmitter; and third, by sensitization of dormant or sleeping nociceptors by transmitters and chemicals released during injury (Haddad, 2007; Riedel, 2001)

*Transmission* is the processing of noxious signaling (Riedel, 2001; Schaible, Del Rosso & Matucci-Cerinic, 2005; Schmelz & Petersen, 2001). Electrical signals from the periphery are relayed to second order neurons in the spinal cord prior to being conducted to the thalamus, limbic system and cortex via a set of pathways.

*Modulation* occurs at the second-order neurons within the dorsal horn. It is defined as a change in threshold in response to the primary inputs, whereby they become either more or less sensitive. That is, modulation can be facilitory or inhibitory (Schaible et al., 2005; Riedel, 2001; Schmelz, 2001).

*Perception* of pain takes place within higher order brain regions including the sensory cortex, providing a clear sense of discrimination and intensity to the
sensation (Schaible et al., 2005; Riedel, 2001; Schmelz, 2001). Again, before an impulse can be transmitted through the dorsal horn and perceived within the brain, it undergoes a great deal of modulation.

**Ascending Facilitory Pain Modulation in the Spinal Column Dorsal Horn**

When a secondary afferent neuron within the dorsal horn of the spinal cord demonstrates an increased responsiveness to inputs from a broader area in the periphery (i.e., they have expanded “receptive fields”), the phenomenon is facilitory and is called central sensitization (Ikeda, 2006). This sensitization of dorsal horn neurons contributes to the hyperalgesia and allodynia of injury (Millan, 1999) and is often termed “wind up” (Ikeda, 2006). Two of the most important neurotransmitters involved in the process of sensitization are glutamate and substance P, both of which interact with and excite second order dorsal horn neurons. Glutamate is released from primary afferents and binds specifically to both N-methyl-D-aspartate (NMDA)-type and non-NMDA excitatory amino acid receptors on second order neurons. Substance P is similar but binds to its own NK-1 receptors. Under non-painful conditions, the NMDA receptor is inactive, as it is physiologically blocked by a magnesium ion sitting in its ion channel, which impedes the influx of calcium to the cell. However, during continuous nociceptive activation from the primary afferent, non-NMDA glutamate (AMPA) receptor, NK-1 receptor, and surprisingly opioid receptor binding, force the removal of the magnesium from the NMDA receptor. With the magnesium blockade removed, calcium flows rapidly into and depolarizes the second order neuron, initiating an action potential and transmission toward the brain. Two important points can be
taken from the above description. The first is that peripheral pain fiber activation enhances central pain fiber activation. The second is that opioids can also promote central pain fiber activation (Ikeda, 2006; Millan 1999).

**Ascending Inhibitory Pain Modulation in the Spinal Cord Dorsal Horn**

Despite the role opioids can sometimes play to facilitate pain, they are (with GABA) predominantly inhibitory neurotransmitters within the dorsal horn. Opioids affect the pre-synaptic terminal of the primary afferent nociceptor via the mu-opioid receptor by blocking voltage gated calcium channels as well as by opening potassium channels. This potassium blocks the flow of calcium into the pre-synaptic terminal and results in the inhibition of neurotransmitter release as well as hyperpolarization and inhibition of the pain signal (Todd, 2002; LaMotte, Shain, Simone & Tsai, 1991). In addition to opioids, gamma amino butyric acid (GABA) exerts an inhibitory effect on nerves through enhanced chloride ion channel activation and subsequent membrane hyperpolarization. Both lead to inhibition of action potentials. GABA is identified as an inhibitory neurotransmitter found in 25-30% of dorsal horn neurons (Drew, Siddall & Duggan, 2004). Yet, GABA activation has been implicated in some inflammatory pain states, making easy generalizations about its role in pain difficult (Todd, 2002). As was mentioned above, generalizations regarding inhibition and excitation are even more difficult with regard to opioids and are a major point of discussion within this paper.

When a nociceptive stimulus is finally transmitted from the dorsal horn, an impulse travels to the brainstem, limbic system, thalamus and cortex. The brain is
the anatomic home of a complex descending modulatory system which has important implications for the pain experience of opioid users. An understanding of the relationship between opioids and pain is impossible without a clear view of opioid processes within what is called the central descending pain modulatory system and the role of opioids within it. The next section of the paper is an examination of that system

CENTRAL DESCENDING PAIN MODULATION

Overview

There are over forty years of research clearly linking the administration of opioids to the descending pain modulatory system. This section articulates the mechanisms of this system in an effort to better understand the pain experience of people who are chronically exposed to opioids. Since the late 1960’s the existence of a descending pain modulatory pathway in the brainstem has been continuously elucidated and refined (Fields & Vanegas et al.,1983; Fields & Basbaum, 1978, Fields & Anderson, 1978). There is now clear evidence for a pain inhibitory circuit which is initiated by nociceptive projections from the dorsal horn of the spinal cord to the level of the peri-aqueductal gray (PAG) region of the brainstem (Fields,1992). See figure 1. Stimulation of the PAG by either chemical or electrical impulses activates an endogenous opioid response via descending (efferent) projections from the PAG to the nucleus raphe magnus (NRM) in the rostral ventral medulla (RVM) and down the dorsolateral funiculus (DLF) pathway to the spinal cord. (See figure 2.) This in turn causes the release of serotonin (5-HT), a neuro-transmitter involved in many functions including pain, into the dorsal
horn (Fields, 1992), which then inhibits afferent (ascending) nociceptive transmission in the dorsal horn of the spinal cord. Thus, midbrain and brainstem activation is intimately involved in pain control (Fields, 1992). The following sections will clarify how the descending pain modulatory system is dependent upon endogenous opioids at the brainstem level, and how those opioid stimulated descending neurons use serotonin as the modulator of nociception when they reach the dorsal horn.

**Descending Modulation: Mechanism in the Rostral Ventral Medulla (RVM)**

**On/Off Cells**

Nociception is facilitated and inhibited by regions in the brainstem, and the final common structure for descending control, the RVM, plays an important role in this modulatory process (Fields, 2000; Zhou & Gebhart, 1990). A model of descending pain modulation and the role of “On” cells and “Off” cells found in the RVM is described in a previous review (Gebhart, 2004). Briefly, “On” cell firing in the medulla is associated with promotion of ascending nociceptive transmission, and “Off” cell firing is associated with attenuation of ascending nociceptive transmission. There are three important conditions related to descending pain modulation and On/Off Cells: tonic control, control during injury, and control related to exogenous or endogenous opioids. In the first condition, regarding tonic control, when an animal is not exposed to any nociceptive input, the descending PAG-RVM-DLF circuitry is the source of descending tonic inhibition of dorsal horn nociceptive neurons. This is why healthy skin does not hurt when touched (Vanegas, Barbaro, & Fields, 1984). In the second condition of
descending pain modulation, after an injury or exposure to a noxious stimulus in a rat model (Vanegas et al., 1984), “On” cells in the RVM activated projections to the dorsal horn via the DLF. That is, “On” cells in the RVM began to fire, and inhibitory “Off” cells stopped firing. This initiated a state of dis-inhibition. In other words, tonic inhibition described in the setting of non-painful healthy skin is reversed and is the reason why injured tissue hurts. More specifically, the response is a twofold input: (1) injury causes an increased facilitation leading to a heightened pain experience; and, (2) decreased inhibition occurs which also leads to heightened pain. “On” cell excitation and “Off” cell inhibition occur simultaneously (Vanegas et al., 1984), supporting the notion that they are under some form of yet to be elucidated reciprocal control. What is known is that a system that is normally inhibitory begins to facilitate pain transmission in the setting of injury, causing primary hyperalgesia.

Pain that extends to tissue that is proximal to damaged tissue but has not been damaged is called secondary hyperalgesia. Several animal studies by Urban and colleagues have shown that secondary hyperalgesia is inhibited by the experimental blockage or destruction of the descending modulating pathways in the RVM (Urban, Coutinho & Gebhart, 1999; Urban & Gebhart, 1999; Urban, Zahn & Gebhart, 1999; Urban, Jiang & Gebhart, 1996). This means that secondary hyperalgesia is modulated in a facilitory manner by cells within this pathway. Although this seems strange, in the setting of injury, secondary hyperalgesia can be thought of as a useful protective and splinting mechanism, serving to promote healing. One study (Urban & Gebhart, 1999) demonstrated
that this facilitation was specifically related to “On” cell activation within the RVM. Others found that when RVM cells were destroyed, secondary hyperalgesia was either reversed (Urban, 1996) or entirely inhibited (Urban, Zahn & Gebhart, 1999). In the third condition related to descending pain modulation, opioids inhibit “On” cells in the RVM. Specifically, when morphine is injected systemically (Fields & Anderson, 1978) or directly into the PAG (Cheng, Fields & Heinricher, 1986), “On” cells are completely inhibited, while “Off” cells typically demonstrate an increased rate of firing. Therefore, neither the “On” cell-induced facilitation nor the “Off” cell disinhibition of ascending nociceptive fibers in the dorsal horn occurs. This is perhaps the best model for why pain is relieved when injured patients receive an opioid agonist drug. Investigators have noted that opioid agonists binding to the PAG actually stop transmission of nociceptive information from the dorsal horn to the thalamus, cortex or other higher brain centers (Hernandez, Lopez, & Vanegas, 1989).

**Descending Modulation: Mechanisms in the Locus Coeruleus (LC)**

While much attention is paid to the RVM for its role in the descending modulatory system, there is evidence that the locus coeruleus (LC), a cluster of cells located in the dorsal wall of the upper pons, also contributes to descending modulation of inflammatory pain associated with actual injured tissue (inflammatory primary hyperalgesia) (Tsuruoka & Willis, 1996). (See figure 1.) Destructive lesions in the bilateral LC of rats had no effect on time to paw withdrawal, called withdrawal latency (WL), from a noxious heat stimulus prior to inflammation-induced hyperalgesia (Tsuruoka, 1996). However, after development
of an inflammatory injury induced hyperalgesia, the lesioned rats demonstrated significantly shorter WL than did non-lesioned sham operated rats. Additionally, it was observed that contra-lateral WL, i.e., from the non-inflamed foot, was unaffected by LC lesions, indicating that an intact LC only inhibits hyper-excited nociception from the primary injured tissue pool in the DH (Tsuruoka, 1996). This indicates that the intact LC contributes to an inhibitory part of the efferent pain modulation system to attenuate pain, but only in the setting of primary tissue hyperalgesia.

**Descending Modulation (facilitory and inhibitory) in Response to Inflammatory Pain**

There is evidence that inflammation initially contributes to the activation of descending facilitory modulators, initiating and worsening the pain experience. However, this facilitation is overshadowed by a stronger inhibitory modulation over time, which eventually relieves the pain. It is thought that much of this modulation is initiated in the PAG (Fields,1992; Gebhard, 2004). A study by Schaible and colleagues found that induced arthritis in cats, an experimental model of inflammation, increased dorsal horn activity and generated allodynia and hyperalgesia (Schaible, Neugebauer, Cervero & Schmidt, 1991). This increased pain was made worse by blocking PAG descending modulation (i.e., inhibiting the inhibitor). Pain was also found to be worse when non-injured tissue was stimulated, i.e., from secondary hyperalgesia. All this indicates that, for arthritis pain models, the PAG modulates in an inhibitory manner. Also, the same system inhibits the secondary hyperalgesia associated with inflammatory injury.
Opioid systems in the ventral PAG are also highly involved in inflammation-induced descending inhibition. Harasawa and colleagues (2000) and Hurley and Hammond (2000) found that opioid injection into the ventral PAG of rats inhibited hind paw withdrawal from noxious chemical stimuli, with greater and longer effect in animals undergoing chemical induced inflammation than in uninjured animals (Harasawa, Fields & Meng, 2000; Hurley & Hammond, 2000). This inhibition also affected, to a lesser extent, the contra-lateral paw, supporting the hypothesis that the opioid effect is due to the descending modulatory system and not to changes in the dorsal horn.

The PAG's opioid system's involvement in inflammatory pain, however, is not straight-forward. While the ventral PAG contains opioid receptors that are involved in the descending inhibition of inflammatory pain, opioid receptors in the dorsal PAG may be pain facilitory. In fact, the findings from several experiments by Morgan and colleagues indicate that inflammatory changes can antagonize descending inhibition from the PAG, and that this alteration is specifically related to an endogenous opioid facilitory effect on the dorsal PAG (Morgan, Gold, Liebeskind & Stein, 1991; Morgan, Sohn & Liebeskind, 1989; Morgan & Liebeskind, 1987).

The above results offer evidence that inflammatory injury either facilitates pain transmission or diminishes pain inhibition. It also appears that the inflammation-induced facilitory circuit is opioid dependent and operates within the dorsal PAG. It may be that early in inflammatory injury, the dominant process is dorsal inhibition of the inhibitor. This makes sense when remembering that acute
pain is fundamentally protective.

**Descending Modulation (facilitory and inhibitory) in Response to Neuropathic Pain**

As described earlier, the descending pain modulating system is typically in a state of tonic inhibition. This is not the case in the setting of neuropathic pain. It has been demonstrated that nerve injury pain is related to descending facilitation of pain from the brainstem regions (Heinricher, McGaraughty & Tortorici, 2001; Kovelowski et al., 2000). However, unlike with inflammation, the PAG may be less involved in neuropathic pain modulation and the RVM more involved. Specifically, cholecystokinin (CCK), known to be a physiological antagonist of opioid-mediated antinociception (Heinricher et al., 2001), may be involved in some chronic pain states where opioids have reduced effect. Specifically, it is known that hyperalgesia and allodynia caused by nerve injury are related to cholecystokinin (CCK) receptor activation in the RVM and that they are inhibited by CCK antagonism within the RVM (Heinricher et al., 2001; Kovelowski et al., 2000).

CCK (Wei & Pertovaara, 1999) as well as NMDA (Pertovaara, Wei, & Hamalainen, 1996) has a role in inhibiting/antagonizing the tonic descending inhibition of the RVM. A possible mechanism for this is that they both antagonize the ability of opioids to activate “Off” cells, which generates an “On” cell facilitory state. This, in effect, becomes a positive feedback loop between the RVM and the dorsal horn, whereby nociceptive transmission itself inhibits “Off” cells, allowing more nociceptive transmission and ever increasing mechanical
hyperalgesia and allodynia (Vanegas & Schaible, 2006; Wei, 1999; Pertovaara et al, 1996).

**Descending Pain Modulation: Summary**

Whether the descending pain modulatory system from the brainstem is inhibitory or facilitory depends upon, among other things, the type of injury and the neuronal pool involved (primary versus secondary). Neurons of the PAG, the NRM, and surrounding structures of the RVM are the primary efferent arms of a pain modulatory system which descends from the brainstem to the spinal cord. In the setting of inflammatory pain, the dominant findings are inhibitory modulation related to opioid action at the ventral PAG. In the setting of nerve injury, however, there is a dominant hyperalgesia related to CCK and NMDA activation. It is clear that, while the pain modulation system is complex and involves many specific regional messengers, opioids are highly involved in the modulation of pain. Therefore, the next section narrows the above discussion of pain modulation to the specific role that opioids play in contributing to heightened pain experiences, often referred to as opioid induced hyperalgesia (OIH).

**OPIOID TOLERANCE AND OPIOID INDUCED HYPERALGESIA**

Exposure to opioids over time causes three important physiologic changes. The first is called tolerance, which is defined as the diminishing effect of a drug over repeated use, i.e., a pharmacological tolerance. The second, physical dependence is defined by withdrawal symptoms upon abstinence from opioids. The third, opioid-induced hyperalgesia (OIH) is generally operationalized as the unique contribution of opioids toward lowered pain tolerance or
heightened pain sensitivity, and is often confused with pharmacologic tolerance. In fact, because all three have similar or overlapping clinical manifestations, it is difficult to fully distinguish between them (Thompson & Ray, 2003; Devillers et al, 1995; Martin & Inglis, 1965). The next section examines the mechanisms by which long term opioid use contributes to these phenomena.

**Opioid Tolerance, Dependence, OIH and the role of NMDA receptors**

Pain tolerance and opioid dependence are inherently related at the µ-opioid receptor. In addition to inhibiting acute pain, the binding of the µ-receptor by opioid agonists (e.g., morphine, heroin, and methadone) results in adaptation (i.e., increased excitability and nervous transmission). This adaptation occurs via a variety of neurotransmitters and pathways, including N-methyl-D-aspartate (NMDA) glutamate receptors, and is thought to contribute to the phenomenon of opioid induced hyperalgesia (OIH).

Opioid physical dependence and its manifestation (withdrawal symptoms upon abstinence) is highly influenced by the release of nor-epinephrine (NE) from brainstem sites (Thompson & Ray, 2003). Specifically, the rostral ventral medulla (RVM) and the locus coeruleus (LC) are known to be important sites of this release (Thompson & Ray, 2003; Cecchi, Khoshbouei, Javors & Morilak, 2002; Delfs, Zhu, Druhan & Aston-Jones, 2000; Christie, Williams, Osborne & Bellchambers, 1987). Withdrawal occurs because continuous opioid use suppresses activity in the LC and the RVM, which when left uninhibited during abstinence, become hyper-excited (Christie, Williams et al., 1987). This excited state is NE dependent and is hypothesized to contribute to what has been
framed as the stress induced anxiety of opioid withdrawal, with very similar manifestations as other forms of stress induced anxiety (Delfs et al., 2000).

According to Cecchi and colleagues (2002), this process then influences physical dependence by driving the organism to relieve the anxiety through opioid-induced suppression of NE induced excitation (Cecchi et al., 2002).

Much of the research into the development of opioid tolerance and OIH has focused on the contribution of the NMDA glutamate receptors and their contribution to heightened or facilitated nociceptive transmission known as sensitization or “wind up.”. Antagonists to NMDA receptors diminish OIH or reduce opioid tolerance. Examples of such antagonists are ketamine, dextromethorphan, and MK-801 in addition to some opioid agonists that are also NMDA receptors antagonists, such as methadone and tramadol (Compton & Gebhart, 1998).

The excitatory neurotransmitter glutamate and its receptors, particularly NMDA, substance P and its receptor NK-1, and opioids are each involved in ascending pain facilitation, or “wind up” (Mao, Price & Mayer, 1995). An explanation of this mechanism is critical to understand how patients respond to injury on the one hand and to opioid pharmacologic treatment on the other (Rodríguez-Muñoz, Sánchez-Blázquez, Vicente-Sánchez, Berrocoso & Garzón, 2012; Gu, Wu, Liu, Cui & Ma, 2009; Mao et al., 1995). The following is a more detailed description of those processes in animals.

**OIH in Animals**

When mu-opioid receptors are activated by their agonists (e.g., morphine),
there is a simultaneous triggering of the NMDAR. Opioid receptor binding to its receptor on a nerve initiates the phosphorylation of the NMDAR on that same nerve. This phosphorylation removes the tonic magnesium blockage of the NMDAR receptor. Once the magnesium is removed from the NMDAR, glutamate, having been released from the primary afferent can bind to it, rapidly increasing intracellular calcium concentrations and activating cellular depolarization (Gu et al., 2009). Gu and colleagues (2009) demonstrated in rats that postoperative hyperalgesia induced by the mu-agonist remifentanil induced this phosphorylation which was, in turn, attenuated by the administration of ketamine (Gu et al., 2009). Rodríguez-Muñoz and colleagues (2012) recently reported that a specific subtype of NMDAR (NR1) and mu opioid receptors coexist on the same neurons within the PAG. At these locations morphine initiates phosphorylation of the specific NR1 and therefore potentiates the action of the NMDAR pathway. This potentiation would allow glutamate activity to become more efficient, resulting in enhanced nociceptive transmission (Rodríguez-Muñoz et al., 2012). Finally, Kissin and colleagues (2000) and others (Devillers et al., 1995; Marek, Page, Ben-Eliyahu, & Liebeskind; 1991; Marek, Ben-Eliyahu, Gold & Liebeskind, 1990) showed in animals that opioid administration activates NMDARs, lowering pain thresholds, and that the NMDAR antagonists such as ketamine can inhibit this process. In addition to animal research, research in humans has shown that the NMDAR antagonist ketamine increases the effectiveness of opioids by 20-30% and allows opioid dose reductions by 25-50% (Fitzgibbon & Viola, 2005; Lossignol, Obiols-Portis & Body, 2005).
In addition to the important role of the NMDAR in OIH, it is known that substance P and its NK-1 receptor are also involved in the process. It is well known that substance P is involved in dorsal horn nociceptive transmission. In support of this, Vera-Portocarrero and colleagues (2007) demonstrated that destruction of NK-1 receptors in the dorsal horn of rats attenuated or reversed many important pain facilitory mechanisms, all of which contribute to ongoing pain. Specifically, NK-1 destruction had four important effects on pain facilitation, two of which were specific to chronic opioid exposure (Vera-Portocarrero et al., 2007). First, NK-1 destruction diminished the level of spinal FOS, a protein known to be elevated from pain and opioid related neuronal excitability. Second, NK-1 destruction blocked the up-regulation of pro-nociceptive spinal dynorphin, also known to be increased in the setting of injury and opioid exposure. Third, NK-1 destruction inhibited the development of opioid tolerance. And finally, NK-1 destruction inhibited OIH, measured by both thermal and tactile noxious stimuli (Vera-Portocarrero et al., 2007). This last finding was the most impressive and direct evidence for a relationship between OIH and NK-1 receptors. Despite the fact that these processes happens at the dorsal horn, all of the findings associated with the destruction of spinal NK-1 cells were replicated by spinal administration of ondansetron, a 5HT3 (serotonin) receptor antagonist. When the 5HT3 receptor was blocked (inhibiting the inhibitor) the NK-1 cells continue to fire normally. Because these serotonergic neurons descend from the RVM, this last finding indicates involvement of the descending modulatory system in OIH. In summary, the pain facilitory mechanism of substance P and its NK-1 receptors,
as well as glutamate and its NMDARs, are controlled by ongoing primary afferent-fiber activation. However, it is now known that they are also independently activated by opioid exposure in the absence of injury. This final point, therefore, also links the serotonergic descending pain system to OIH (Vera-Portocarrero et al., 2007).

**OIH in Humans**

A common approach in the evaluation of pain in humans has been use of the “cold pressor” test, which induces ischemic type pain by ice water immersion, usually of a hand and forearm. Using this test, Compton and colleagues evaluated withdrawal latency (WL), that is the time an individual can maintain their hand in the ice water bath, in methadone (a mu opioid agonist) and buprenorphine (a partial mu opioid agonist) maintained but detoxified ex-opioid addicts and normal volunteers (Compton, Charuvastra & Ling, 2001). They found that withdrawal latency was significantly shorter (i.e., the subjects could tolerate less pain) in the methadone-maintained group compared to normal volunteers. The same group (Compton, 1998) also measured cold pressor WL in opioid addicts who were maintained on the opioid antagonist naltrexone. They revealed that 8 of the 10 subjects had a longer WL on naltrexone than off. Both of these findings support the conclusion that opioids are involved in pain facilitation which could be related to OIH. The authors suggest some important limitations of the above findings: (1) these samples may have had pre-existing changes in their response to opioids, and (2) these samples may have exhibited an up-regulation of µ-receptors in response to chronic naltrexone exposure, making them
paradoxically more sensitive to endogenous opioids. However, because it is known that opioids independently activate NMDARs (Rodríguez-Muñoz et al., 2012; Gu et al., 2009; Devillers et al., 1995; Mao et al., 1995; Marek et al., 1991; Marek et al., 1990), it is possible that opioid antagonism in the naltrexone group significantly inhibited the activation of NMDARs, thereby diminishing glutaminergic nociceptive transmission in response to pain.

Angst and colleagues (2003) attempted to determine the clinical relevance of NMDAR blockade on OIH in an experiment that included 10 normal volunteers. They infused opioid naïve subjects with the µ-agonist remifentanil alone and in conjunction with the NMDAR antagonist ketamine, for 90 minutes. They found that opioids alone extended the size of the skin area manifesting mechanical hyperalgesia (OIH) within 30 minutes of stopping the opioid infusion, and that the extended hyperalgesia was eliminated by the simultaneous infusion of ketamine and remifentanil (Angst, Koppert, Pahl, Clark & Schmelz, 2003).

Hay and colleagues (2009) determined that patients taking methadone (n=10) or morphine (n=10) for chronic non-cancer pain and those taking methadone for drug dependence (n=10) were significantly less tolerant of experimentally induced pain, tested just prior to their next scheduled dose, than a control group of opioid naïve subjects (n=10) (Hay, White, Blochner, Somogyi, Semple & Rounsefell, 2009). This finding indicated that two unique subsets of opioid exposed people, those who are addicted/dependent and those being treated for pain alone, have indistinguishable but diminished abilities to tolerate pain (Hay et al., 2009), at least when their normal opioid levels were at low
(trough) levels (Hay et al., 2009). While this study did not directly implicate the role of NMDARs, it does indicate some change in the pain system of these patients. Given the experimental and theoretical evidence cited above, OIH is a possible contributor to these findings.

Despite the fact that the administration of NMDAR antagonist agents have been shown to diminish or reverse experimentally induced OIH (Rodríguez-Muñoz et al., 2012; Gu et al., 2009; Devillers et al., 1995; Mao et al., 1995; Marek et al., 1991; Marek et al., 1990), these promising findings regarding the role of the NMDAR in OIH were less impressive in a more recent experiment. Compton and colleagues (2008) experimentally evaluated the pain tolerance and threshold (the sensitivity to pain) in a sample of forty methadone maintained subjects who were given the NMDAR blocker dextromethorphan (DEX) but found no diminished pain reports (Compton, Ling & Torrington, 2008). One possible cause for the conflicting findings may be related to the fact that in the first study by Hay et al., (2009), pain was measured at the lowest drug level, which could have contributed to withdrawal pain in that arm of the sample. Therefore, the heightened pain reports in that study (Hay et al, 2009) may not be related to OIH.

Work on opioid tolerance and OIH in humans is not complete, with conflicting information still being demonstrated. Some of the conflict is due to research study limitations and some to an incomplete picture of who is being studied, i.e. subject/control issues. Most authors agree that more research is needed of broad samples of opioid naïve persons in addition to current and past opioid dependent persons who are well controlled for current drug use (Hay L., et
al, 2009; Compton et al., 2008; Angst et al., 2003). Despite the limitations and disagreements, there is now a greater understanding of at least three components that relate OIH and the NMDA receptor. First, the mechanisms by which NMDA receptors are involved in the process of tolerance and OIH have been identified. Second, it has been shown that even the short term administration of opioids to opioid naïve people extends mechanical hyperalgesia immediately after administration (96). Most important is that fact that the NMDAR antagonist ketamine blocks this extended hyperalgesia. Finally, although not formally linked to the NMDA receptor, the findings by Hay and colleagues (2009) that both MMTP and opioid exposed chronic pain patients have lower pain tolerance than opioid naïve patients tends to implicate the opioid system with worse pain. While it is seems that NMDARs are an important area of inquiry for the understanding of OIH, they are not the only contributor OIH. The next section examines the role of cholecystokinin in the current understanding of OIH in animal studies.

**Opioid Tolerance, Dependence, OIH and the role of Cholecystokinin (CCK)**

In a 2001 study, Vanderah and colleagues (2001) established that injection of lidocaine (chemical lesioning) into the RVM or DLF pathway (figure 2.) abolished opioid-induced hyperalgesia. This finding strongly implicated a role for the descending opioid system in nociceptive facilitation (Vanderah, Ossipov, Lai & Malan, 2001). Heinricher et al., (2001) then extended this finding by identifying the role of cholecystokinin (CCK), a pronociceptive peptide, in descending nociceptive facilitation from the RVM during continuous opioid administration in
rats. Using opioid naïve rats, CCK injected into the RVM produced hyperalgesia that was blocked by a CCK antagonist and by lesions to the DLF. They also found that by injecting CCK into rat RVM, opioid tolerance was induced and that three days of continuous systemic morphine infusion worsened this hyperalgesia. Both opioid-induced hyperalgesia and opioid tolerance were reversed by CCK antagonist injection into the RVM. Rats that received morphine were found to have five times the levels of CCK in their RVM when compared with controls. From these data it was posited that enhanced endogenous CCK activity in the RVM during sustained morphine exposure may diminish spinal morphine antinociceptive potency. It was theorized that this is accomplished by activation of descending pain facilitory mechanisms which exacerbate spinal nociceptive sensitivity. In other words, brainstem CCK inhibits opioid dependent descending inhibitory modulation. Thus, CCK activity can be thought of as an off switch component for descending inhibition; it inhibits the inhibition of pain. This conception is important because the pro-nociceptive impact of CCK seems to be driven by opioid exposure itself (Heinricher, McGaraughty, & Tortorici, 2001).

The literature examined here indicates that a great deal has been learned about the role of opioids in pain facilitation, or OIH. Clearly some of the likely physiologic mechanisms by which opioid dependent people might demonstrate heightened pain experiences have been identified. Still, there remains much to be elucidated and clarified. Importantly, the research has yet to distinguish among multiple factors which may contribute to the findings. High among these are the co-existence of ongoing injury-induced versus opioid-induced
hyperalgesia. Put another way, because some in the opioid using population may be chronically ill or injured (hence their use of the drug in the first place), it is difficult to say whether the injury or opioid exposure, or both cause their clinical pain.

This paper has identified some of the contributing factors related to the altered pain physiology of opioid exposed people. However, there are other likely contributions to their alterations which were not discussed. For example, some people have underlying and pre-existing vulnerabilities to pain that may be unrelated to opioid exposure. As a case in point, it is known that pain perception is increased in the setting of co-morbid psychiatric disorders such as anxiety and depression (Bair, Wu, Damush, Sutherland, & Kroenke, 2008; Bair et al, 2004; Bair, Robinson, Katon & Kroenke, 2003). Therefore, people living with these disorders, whether situationally acquired or related to inherited vulnerability, may be vulnerable to the development of a pain syndrome. This development may address the diathesis-stress model, which is associated with a combination of physical, social, and psychological stresses that themselves are associated with pain syndromes (Turk, 2002). Another possible contributor to worse pain is the exposure to fetal and childhood trauma. According to the theory of epigenetic modulation of gene expression, many medically unexplained symptoms such as pain could be related to maternal/fetal hormone transfer, predisposing or inclining fetal physiology toward the hypersensitivity of environmental stimuli (Buffington, 2009). It is possible that people who become opioid dependent and addicted were also exposed to fetal and childhood trauma, making epigenetic modulation
a possible contributor of their future pain experience. Because of this, rigorous experimental science will be required to further articulate and clarify the phenomena of pain and OIH in the chronic opioid using population.

**SUMMARY**

The pain physiology of opioid dependent patients is a complex and multifactorial phenomenon. It is not clear at this time whether their heightened pain experience is related to underlying tissue injury and inflammation, to nerve injury, to a specific opioid-driven process (OIH), or to some combination of all three. Yet, as demonstrated in this paper, the modulation of pain involves multiple parts of the central nervous system. The many pathways within the CNS define what can be conceived as a whole body system response to pain. In addition to articulating the nervous system connections related to pain modulation, this paper demonstrates that the type of pain, both in nature (i.e., inflammatory or neuropathic), duration (acute versus chronic) and proximity to injury, (primary versus secondary pool), has a great deal to do with the manner in which the body responds to and adapts to it. Finally, it has been shown that opioid exposure has a direct relationship to the experience of pain and is highly related to the NK-1 receptor, NMDARs, as well as to CCK.

Future research is warranted on pain and OIH in chronic opioid users. First, research is needed to clarify that opioid users have a heightened pain system because of opioid exposure and not because of other pre-existing states or traits. Second, research is needed to investigate whether opioid users have characteristics or life experiences which make them more vulnerable to pain,
opioid use and OIH. Third, research is needed to identify the best approach to decrease the pain and OIH of opioid exposed patients. While the pain of opioid exposed people is likely a complex and multifactorial problem, all patients who are chronically exposed to opioids appear vulnerable to having worse pain, and this can be in part related to their opioid exposure.
The PAG is involved in descending modulation of pain transmission from the dorsal horn of the spinal cord using primarily serotonin system via the RVM. The locus coeruleus (LC) is involved in descending pain modulation and in opioid physical dependance.
Figure 2.
The descending pain pathways of the brain. Higher order areas of emotion and cognitive processing, the anterior cingulated cortex (ACC), the prefrontal cortex (PFC), Insular Cortex (Insula), Hypothalamus (HT) each communicate with the brainstem peri-aqueductal grey area (PAG), either directly or via the amygdala. The PAG is then involved in descending modulation of pain transmission to the nucleus raphe magnus (NRM) of the rostral ventral medulla (RVM) via the Dorsolateral Funiculus (DLF) to the dorsal horn of the spinal cord.
References


Kissin I, Bright C & Bradley D. (2000). The effect of ketamine on opioid-Induced acute tolerance: Can it explain reduction of opioid consumption with
ketamine-Opioid Analgesic Combinations? *Anesthesia and Analgesia*, 91(6), 1483-1488


inflamed hindpaw of the rat. *Brain Research, 545*(1-2), 17-23.


Schaible HG, Neugebauer V, Cervero F & Schmidt RF. (1991). Changes in tonic descending inhibition of spinal neurons with articular input during the
development of acute arthritis in the cat. *Journal of Neurophysiology*,
Sep;66(3):1021-32.

Schmelz M & Petersen LJ (2001). Neurogenic Inflammation in Human and

practices and the patient's perspective. *Journal of Emergency Nursing,*
25(3), 171-177.

Thompson AR & Ray JB. (2003). The importance of opioid tolerance: a
therapeutic paradox. *Journal of the American College of Surgeons,* 196(2),
321-324.

Todd A. (2002). Anatomy of primary afferents and projection neurones in the rat
spinal dorsal horn with particular emphasis on substance P and neurokinin
1 receptor. *Experimental Physiology,* 87(2), 245-249.

Todd KH, Samaroo N & Hoffman JR. (1993). Ethnicity as a risk factor for
inadequate emergency department analgesia. *The Journal of the
American Medical Association,* 269(12), 1537-1539.

Tsuruoka M & Willis JWD. (1996). Bilateral lesions in the area of the nucleus
locus coeruleus affect the development of hyperalgesia during

Turk DC. (2002). Chronic non-malignant pain patients and health economic


Vera-Portocarrero LP et al. (2007). Spinal NK-1 receptor expressing neurons
mediate opioid-induced hyperalgesia and antinociceptive tolerance via activation of descending pathways. *Pain, May;129(1-2):35-45*


CHAPTER 3

A Comparison of Brain Regions Associated with Chronic Pain and Addiction: Implications for Potential Overlap

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A Comparison of Brain Regions Associated with Chronic Pain and Addiction: Implications for Potential Overlap

Introduction

Acute and chronic pain are common complaints among hospitalized and community dwelling populations (Nation Centers of Health Statistics, 2006). While definitions vary, the most common definition of chronic pain is ongoing pain that persists beyond the expected period of tissue healing (Turk & Ojifuji, 2001). The definition of “ongoing” varies, but most researchers define it as between 3 and 12 months of pain (Bogduk & Merskey, 1994). The prevalence of chronic pain within the general population is unclear, but over the last decade rates have been estimated to range from 2% to 40% of the adult population (Verhaak, Kersssens, Dekker, Sorbi & Bensing, 1998). As many as 76 million Americans live with chronic pain (Nation Centers of Health Statistics, 2006). One study with over 10,000 subjects reported that 11.0% of respondents lived with chronic pain, with back pain being the most common type (Hardt, Jacobsen, Goldberg et al., 2008). A multinational survey of 25,916 primary care patients recorded an overall pain prevalence (chronic and acute) of 22% (Gureje, Von Korff, Simon & Gater, 1998), with the overall United States chronic pain rate being 17%. The authors of that study posited that some of the variation in chronic pain rates is related to differences in definitions, measurement techniques, and sample type. In addition to being highly prevalent, pain is the most common form of long term disability (Stewart, Ricci & Chee et al., 2003), with the vast majority
(75%) of those living with chronic pain also reporting some pain-related disruption of their daily life and relationships (Vo, Marx & Penles, 2008). Acute or chronic pain accounts for 20% of healthcare visits, 12% of prescription medications, and has been estimated to cost over $100 billion dollars a year in direct and indirect costs (Alford, Liebschutz & Chen, 2008). Because of the enormity of personal and social cost, coupled with the disparate findings related to prevalence rates, research continues to investigate detailed and specific explanations of pain within unique populations. Amongst those living with very high rates of chronic pain, and the focus of this paper, are the opioid addicted and dependent (Barry et al. 2009; Sheu et al., 2008; Rosenblum et al., 2003; Jamison et al., 2000; Kauffman & Katz, 2000). The relevant pain literature above does not clearly define what is meant by chronic opioid use, dependence or addiction. Therefore, for the purposes of this paper, people are defined as addicted and dependent chronic opioid users if they are receiving methadone maintenance for opioid addiction replacement therapy or are active illicit opioid users who experience withdrawal when abstaining from opioids.

The mechanisms and relationships among pain and opioid addiction exist at the biological, psychological, behavioral and social levels (Engel, 1980). However, the scope of this paper is limited to a discussion of the brain systems related to those problems. To date there is no research that specifically evaluates changes within the central pain systems of opioid addicted patients. Therefore, before more specific examinations such as those can take place, the central brain mechanism of pain will be detailed here. This detail will then overlay
relevant findings related to the central processes of opioid addiction and dependence. This, in turn, will lay important groundwork for future study of pain in this population. To that end, the paper has three primary sections. The first section is an explanation regarding the uniqueness of pain reports within opioid addicted and dependent populations. This provides the logical rationale and imperative for this inquiry. The second section provides an overview of the brain mechanism related to opioid addiction, with a focus on areas known to be related to pain processing. The third section describes the brain mechanisms related to pain processing, with an eye toward how these mechanisms overlap with those related to addiction.

**Pain and Opioid Addiction**

Chronic Pain is reported by up to 61% of people participating in methadone maintenance treatment programs (MMTP) for opioid addiction (Barry et al., 2009; Sheu et al., 2008; Rosenblum et al., 2003; Jamison et al., 2000; Kauffman & Katz, 2000). These rates far exceed the general population reports cited above and are consistent with findings from very vulnerable populations, such as those living with cancer and AIDS (Breitbart, Rosenfeld & Passik, 1996; Cleeland, Gonin & Hatfield et al., 1994). Given those high pain rates, many people who are addicted to or dependent on opioids will likely require opioid pain management at some time. In fact, the inherent relationship between pain and opioids is enhanced in the setting of opioid dependence and addiction. While the majority of patients encounter opioids with no ill effects, the same is not true for the opioid addicted or dependent, who are by definition in a conflicted
relationship with the drugs. Finally, MMTP patients living with chronic pain experience higher levels of psychiatric and physical co-morbidities than similar MMTP's without chronic pain (Rosenblum et al., 2003), increasing the imperative to understand their chronic pain.

A growing literature describes some potential physiologic processes that may underlie pain in this population (Compton, Athanasos & Elashoff, 2003; Compton, Charuvastra & Ling, 2001; Compton, Charuvastra, Kintaudi & Ling, 2000; Devillers, Boisserie, Laulin, Larcher & Simonette, 1995; Kissin, Bright, & Bradley, 2000a & 2000b). Many of these are discussed in Chapter 2. Still, there are likely many contributors to the increased pain in opioid dependent people yet to be explored. Of those, the role of the central pain systems in the pain experience of this population should be considered. The following section is an overview of important brain mechanisms related to opioid addiction, with a focus on the systems that are likely to be involved in the pain experience. For a more general review of opioid addiction, see Koob et al., (2004).

**Opioid Addiction: Central Mechanisms**

A reward is defined by Wise (2002) as an incentive that an animal returns to after having an original positive contact. A critical component of this reward system in opioid (and other) addiction(s) is the mesolimbic dopamine system (see Figure 1). Dopamine neurons within this system, especially in the ventral tegmental area (VTA), are known to communicate with specific regions in response to many rewards. Specifically, opioid drugs (rewards) bind to and inhibit GABA neurons, which are themselves inhibitors of VTA dopamine neurons. The
outcome of opioid administration then is increased dopamine neuron transmission through an inhibition of the (GABA) inhibitors. The dopamine neurons then communicate with many regions, some of which are known to be related to the experience of pain. These include the nucleus accumbens (NA), the amygdala and the pre-frontal cortex (PFC). (See Figure 1) Generally, it is thought that the increase in dopamine transmission within this system due to opioid drug exposure is the underlying and shared action of many drugs of abuse (Girault & Greengard, 2004; Lingford-Hughes & Nutt, 2003). Although other parts of the brain are involved in addiction, the mesolimbic system of connected pathways is the most robust regarding reward seeking and drug addiction (Wise, 1998). Also, although the focus of this paper is on opioid drugs, a literature review of the dopamine system finds it is associated with many pleasurable (rewards) activities (Aragona, Liu, Curtis, Stephan, & Wang, 2003; Blood & Zatorre, 2001; Carr, 2002; Fibiger, Phillips, & Brown, 1992; Hansen, Bergvall, & Nyiredi, 1993; Hernandez, Lopez, & Vanegas, 1989; Ikegami & Duvauchelle, 2004; Kampe, Fritht, Dolant, & Frith, 2001; Kiyatkin, 2002; Knutson, Fong, Adams, Varner, & Hommer, 2001; Marinelli et al., 1998; Melis & Argiolas, 1995; Mobbs, Greicius, Abdel-Azim, Menon, & Reiss, 2003; Pfaus, Damsma, Wenkstern, & Fibiger, 1995; Vanderschuren, Niesink, & Van Pee, 1997; Zubieta et al., 2001). Three important components of this system that are also known to be involved in pain modulation are the NA, the amygdala and the Pre-Frontal Cortex (PFC) (See Figure 1).
Addiction, Dopamine and the NA

The NA is a limbic structure located in the base of the forebrain (see Figure 1), and divided into two major subdivisions, the shell and the core. It is involved in many functions of motivation and reward, ranging from feeding to drug addiction. The NA is the specific region within the mesolimbic system in which changing dopamine levels are known to play a critical role in mediating the rewarding effects of drugs of misuse, including heroin (Koob & Le Moal, 2000; Matthews & German, 1984).

A rat study by Alderson, Robbins & Everitt (2001), found that destruction of the core of the NA but not the shell diminished heroin self-administration down to control levels. However, Gerrits et al., (2002), reported that falling extracellular dopamine levels within the NA shell were positively associated with drug withdrawal and reward seeking. In other words, less dopamine within the NA shell drove the organism toward drugs. Martinez et al., (2012) used PET scans to show that heroin users have diminished pre and post-synaptic dopamine receptor levels within their NA. However, those low levels were not found to correlate with the clinical desire to self-administer, as other studies would suggest (Martinez at al., 2012).

Kiyatkin (2002) presented more contradicting evidence regarding dopamine, the NA, and opioid addiction. A review of five methodologically similar studies (single unit neuron recording) clarified the relationship between heroin self-injection and the activation of dopamine neurons in the NA. In these reviews, heroin self-administration caused dopamine levels within the NA to lower. As
heroin levels fell (between doses) dopamine levels rose (see Figure 2). This phasic depression-arousal pattern of the NA neurons after heroin self-injection was also correlated with depressed (during heroin peak) then aroused (during dopamine peak) behavior and blood pressure (Kiyatkin, 2002). These findings support the idea that rising dopamine levels between opioid dosing (during withdrawal) drive the organism (i.e., generates want) toward reward. This is supported by the fact that after opioid administration NA dopamine levels fell off, with a simultaneous lowering of sympathetic activity. The findings by Kiyatkin, 2002) indicate that craving as opposed to pleasurable satisfaction is associated with rising NA dopamine levels, which is relieved (along with lowered dopamine levels) by opioid drug taking (Cannon & Bseikri, 2004; Berridge & Robinson, 1998). The above findings support the importance of NA dopamine in rewarding processes, but indicate a specific role in the withdrawal and craving (Cannon and Bseikri (2004), as opposed to the pleasurable (Koob & Le Moal, 2001) phase of the reward process. An anecdote from a self-described heroin addict reported by Abbott (2002) is an interesting corollary. According to the author, the addict described that “when you’re addicted, there is no euphoria when you shoot up, you only want heroin.” The addict goes on to say that heroin had become his “only want,” but that it “gave him no pleasure.” It is possible that the heroin addict experienced a deficit in the pleasure/liking component of opioid use and was left with only a heightened or overactive dopamine driven craving and “wanting.”

**Addiction and the Amygdala**

In addition to its role in altered mood states (Davis, 1998) and pain
modulation (Neugebaur, 2004; Davis, 1998), the central nucleus of the amygdala (CeA) (see Figures 1 & 3 for amygdala location and nuclei) has been shown to produce reward in response to amphetamines (O’Dell, 1999) and heroin (Alderson, 2000) injection. However, this has not been true with injection into the basal nucleus (BLA) (Alderson, 2000; O’Dell, 1999). However, inactivation of the BLA has been shown to abolish both conditioned reward seeking and heroin induced reinstatement of drug seeking, following previously extinguished heroin-seeking behavior (Fuchs & See, 2002). Taken together, this is evidence that the BLA is involved in re-initiation of reward while the CeA is involved in reward behaviors themselves.

**Addiction and the PFC/Insular Cortex**

Imaging studies have found that opioid dependent people have diminished grey matter density in their bilateral prefrontal (PFC) and insular cortices (IC), areas involved in both emotional and cognitive control (Lyoo et al., 2006). (See Figure 4 for PFC and IC location). Also, current or previous opioid users demonstrate greater activation (measured as cerebral blood flow using PET) of their left orbitofrontal cortex during risky decision making compared to non-drug using controls, who showed greater activation in the right dorsolateral PFC (Earsche et al., 2005). As will be made clear in the pain section of this paper, the dorsolateral pre-frontal cortex DLPFC might be important to a person’s ability to contextualize and modulate their pain experience (Apkarian, 2009). (See Figure 5 for PFC subregions)
Opioid Addiction Summary

Opioid addiction is related to the dopaminergic reward system with important structures being the NA, the amygdala, the insular and prefrontal cortices. Specific mechanisms continue to be elucidated, with the role of dopamine within the NA remaining of particular interest and debate. The amygdala, while involved in reward, appears important to the memory of wanting, as evidenced by its role in the reinstatement of drug self-administration. The PFC, especially the DLPFC and its role in behavioral oversight of emotions (Price & Drevets, 2010) might have an especially important crossover influence between pain and addiction.

In order to adequately discuss pain anatomy and its role in unique types of pain and addiction, the language of pain must first be articulated. The next section will describe the pain concepts and language being discussed throughout the paper.

Chronic Pain

Chronic pain is most often defined as that which has no obvious biologic value and has persisted beyond the expected time for tissue to heal (Turk & Okifuji, 2001). Still, studies do not clearly define their operational definitions of chronic pain, which should be considered when interpreting any results. Also, there is a great deal of complexity regarding the multidimensional nature of pain.

Pain Multi-dimensionality

The multi-dimensionality of pain is most commonly separated into three categories; the sensory-discriminative, motivational-affective, and cognitive
evaluative dimensions (Melzack 1975, 1982). The sensory-discriminative
dimension (Melzack, 1975) is related to the intensity and location of the pain
sensation. The motivational-affective dimension is related to an individual’s
feelings and emotions and behaviors related to the sensation. The cognitive-
evaluative dimension is related to the applied meaning or appraisal that the
individual applies to the experience of their pain.

The sensory-discriminative dimension independently measures the
intensity component of pain. An individual may experience (and report) a mild or
intense sensation, but that sensation may or may not be strongly related to their
global interpretation of the “badness” of their pain. This “badness” or suffering is
the second important component of the pain experience, and is usually referred
to as the motivational-affective dimension.

The motivational-affective dimension independently measures the moment
to moment aversion, or desire to escape the experience, in spite of any particular
level of intensity. An example of an experience that might influence the
motivational-affective dimension follows.

An early study by Price, Harkins & Baker (1987) found that pregnant
laboring women demonstrated higher sensory and lower affective scores, using
visual analog (VAS) intensity and unpleasantness scales, than patients with
cancer and other chronic life-threatening pain conditions. When the women
focused on their labor rather than their pain, they reported lower affective
(unpleasantness) but not sensory scores (Price et al., 1987). This finding
supported the theory that unpleasantness (their place holder for the
motivational/affective domain) is a unique component of pain and can be independent of intensity. It also may indicate that manipulation of the cognitive component (attention) may influence the affective more than sensory component.

The third domain, the cognitive-evaluative dimension is related to an individual’s attention to and interpretation of the meaning that pain may have in their life. For example, a person who has continually had pain that has been ignored, untreated or undertreated might experience that pain with a unique sense of dread, expectation and undue attention. When actual or potential pain sensations arise in their body, their interpretation of its meaning could be influenced by their previous experiences.

Based upon the recognition of pain’s multidimensionality, Price (2000) advocated research methods that separated pain into distinct components, representing unpleasantness on the one hand and the severity of the pain sensation on the other. According to Price (2000), unpleasantness is defined as the moment to moment emotional feelings, such as distress or fear, which pertain to the present or short term future. From that definition it follows that unpleasantness would likely contain components of the affective and cognitive dimensions, and could be influenced by sensory dimension.

The importance of pain multi-dimensionality is demonstrated in a study by Rainville, Duncan & Price (1999). It was found that hypnotic suggestion (in subjects previously trained) directed at altering unpleasantness was effective at modifying reports of unpleasantness (using VAS) while it had no impact on intensity ratings. Conversely, hypnotic suggestion to alter intensity changed both
intensity and unpleasantness scores, indicating the possibility that intensity is in
the causal path of unpleasantness but not vice-versa. These findings become
especially significant surrounding in detailed discussion of the prefrontal cortex
which follows. The multidimensionality of pain, validated by the above studies,
directed researchers toward the goal of more clearly elucidating the possible
involvement of discreet neuroanatomical regions relating to each unique pain
dimension. The following is a description of some of those studies and their
findings.

**Pain and the Brain**

Pain is highly complex and involves physiologic processes with
mechanisms reaching from the furthest peripheral sensory nerves to high order
sensory, emotional and evaluative components of the brain. Given the
importance of pain's dimensionality described above, an understanding of the
anatomy and physiology that determines it is required in order to best understand
patients' pain experiences. This is especially true for opioid addicts, who
experience alterations in important pain modulating brain systems, as was
discussed in the *pain and opioid addiction* section of this paper and more
extensively in chapter 2. Overall, most studies agree with Melzack (1978), Price
(2000) and others' assertions that pain intensity, unpleasantness and cognition
are unique but overlapping dimensions of the pain experience. Also, it is now
known that each dimension is modulated within discreet but communicating brain
regions. (See Figure 4 for pain related brain regions)

Two reviews (Hudson, 2000; Schnitzler and Ploner, 2000), in addition to a
meta-analysis of 26 studies of functional imaging of brain responses to pain (Peyron, Laurent & Garcia-Larrea, 2000) identified the brain regions that are most frequently and consistently associated with distinct types of experimental and clinical pain. The areas of the brain implicated in the *sensory-discriminative* dimension include the lateral thalamus, the insular cortex and the S1 cortex. The brain areas most implicated in the motivational-affective dimension (usually measured as unpleasantness) include the medial aspect of the anterior cingulate cortex (ACC), the S2 cortex as it is related to learning and memory associated with pain, and the insular cortex (IC), as it is involved in autonomic reactions (e.g., heart rate, blood pressure). The latter is thought to be part of a positive feedback loop, where aversion increases as one senses an increased autonomic response to the original pain stimuli. The activation of neurons in the posterior parietal as well as the pre-frontal cortices showed the greatest correlation with the *cognitive/evaluative* dimension of pain (Peyron et al., 2000). From those studies, and others (Bruce, Poobalan, Smith & Chambers, 2004; Lua, Salek, Finlay, & Lloyd-Richards, 2005; Melzack, 1982, 2001a, 2001b) it is now known that the brain regions associated with pain dimensionality include: the prefrontal and insular cortices, the amygdala, the anterior-cingulate cortex, the hypothalamus and the nucleus accumbens. The following is a description of these regions, including their functions and roles in pain.

**Function-Prefrontal Cortex (PFC)**

The prefrontal cortex (PFC) is the anterior part of the frontal lobes of the brain. The components known to be related to pain are the dorsolateral prefrontal
cortex (DLPFC), which is involved in executive functions and control, and the medial prefrontal cortex (mPFC), which is related to emotionality and affective learning (Baliki et al., 2006). Activity in both regions is also known to positively correlate with pain reports (Maletic & Raison, 2009; Davidson, 2003; Drevets, 1998). (see Figure 5). Additionally, Price and Drevets (2010) described a prefrontal network conceived as three communicating regions. The first is the ventral medial PFC (VMPFC), which is involved in the mediation of pain, aggression, sexual function, and eating. The second is the lateral occipital PFC (LOPFC), which is involved in the modulation of risk, maladaptive behaviors and some perseverative affective states, such as depression, anxiety and anger (Davidson, 2003; Drevets, 1998). The VMPFC and the LOPFC are then each independently connected to a third region, the dorso-lateral PFC (DLPFC), which is mostly involved in executive function, effortful attention, and working memory. Changes in any of these systems can influence pain (Price and Drevets, 2010; Davidson, 2003).

**Function- Insular Cortex**

The insular cortex lies deep in the brain's lateral surface bilaterally (See Figure 4.) The insula is known to be involved with body awareness including negative affect and the emotional importance of concepts such as pain and depression (Craig, 2002). This structure is connected to other limbic regions and to paralimbic cortical areas (ACC and LOPFC) and is thought to be involved in integration and modulation of the sensory and affective systems (Craig, 2004; Wang, 2008).
Pain-Prefrontal and Insular Cortices

A meta-analysis by Apkarian et al., (2005) examined the relationship between many discrete brain regions and a variety of pain states. Sixty-eight studies covering a broad range of pain conditions were included, with the aim of distinguishing the brain regions activated on PET scan during acute experimental pain versus ongoing unpleasant clinical pain conditions. Clinical pain was positively correlated to the PFC, while experimental pain was positively correlated with the ACC, S1, S2, IC, and thalamus. The findings support the idea that there are multiple pain networks, including a predominantly somatosensory (S1, S2, IC), a limbic (IC, ACC) and what the authors called an associative (PFC) region.

Baliki et al., (2006) also found that higher intensity ratings of clinical back pain were positively correlated with greater activation in the medial PFC (mPFC), while rapidly rising (changing) pain ratings were correlated with activation of the insula and ACC. More than 80% of the variance in the patients’ back pain intensity ratings was accounted for by activation in the mPFC. These findings indicate that the mPFC is highly involved in the intensity of ongoing back pain, while the insula and ACC were related to changes in that pain.

Apkarian et al., (2009), formulated a model of chronic back pain related to unique and specific brain differences seen in chronic pain patients. They found that back pain patients with combined high sensory and unpleasantness pain ratings demonstrated diminished grey matter in their dorsolateral PFC (DLPFC), and postulated that the changes within the DLPFC itself might be the actual
mechanism of chronic pain.

Chronic pain is highly associated with grey matter loss within the DLPFC (an area known to be involved in cognitive control and decision making). This loss could lead to uninhibited mPFC activation. Therefore, chronic pain appears related to emotional learning circuits, such as those in the mPFC, and its cause or persistence is related to un-antagonized activation of brain regions such as the mPFC due to the destruction of modulatory DLPFC neurons. This loss of modulation might allow what would otherwise be noted, interpreted and contextualized as a strong or intense sensation to be experienced and described as painful and unpleasant (Apkarian et al., 2009).

The above work also demonstrates the possibility of two important clinical findings. First, because of the loss of DLPFC neurons in the setting of chronic pain, as described by Apkarian et al., (2009), the intensity of pain sensations may be perceived with a greater sense of unpleasantness than might otherwise be expected. This is because, according to those authors, the normally functioning DLPFC is known to provide control over the mPFC. Therefore, when DLPFC neurons are lost, the mPFC (and it attendant influence over affective experience) becomes hyperactive. Because opioid addiction alone has been found to manifest with diminished IC and PFC grey matter (Lyoo et al., 2006), opioid addicts with pain might be especially vulnerable to this process influencing their pain. From this, patients with identical injuries might experience different levels of acute pain, based entirely upon existing chronic pain and opioid use. Second, changes in chronic pain (exacerbations) activate the insula, an area known to be
involved in affective interpretation. This could mean that even small changes in chronic pain intensity might invoke more pronounced negative affective experiences. This has important clinical implications for those chronic opioid users who have chronic pain.

**Pain and the Anterior Cingulate Cortex**

The ACC sits on top of the brainstem and between the hemispheres (see Figure 4) where it is connected to a number of cortical and sub-cortical areas involved in both higher thought processes and emotions. Activity within the ACC is known to influence the subjective experience of pain unpleasantness (Rainville, 2002; Maletic & Raison, 2009).

A rat study by Johansen, Fields & Manning (2001) found the rostral ACC to be uniquely linked to the affective pain dimension. When neurons originating from the rostral ACC were destroyed, the animals did not avoid previously established fear (conditioned place avoidance) related to pain, but they continued to demonstrate acute pain behaviors related to actual injury. Therefore, it was argued that the rostral ACC is necessary for memory based aversion behaviors related to pain, but not to the actual pain experience.

Hofbauer, Rainville, Duncan, & Bushnell (2001) and Rainville, (1999) implicated the ACC in the unpleasantness (affective) dimension of the pain experience in humans. Positron emission tomography (PET) demonstrated that cerebral blood flow (CBF) was altered in the setting of pain related conditions and could be manipulated through hypnosis. Specifically, verbal reports of increasing pain intensity were correlated with S1 and ACC activation and
increases in the report of unpleasantness. Alternately, changes in unpleasantness scores alone were only correlated with ACC activation and had no effect on intensity scores. These data indicate that intensity is in the causal line of unpleasantness, but not the inverse. These findings were consistent with the earlier ones by Price and colleagues (1987) showing that women could alter the unpleasantness, but not the intensity score of labor pain, through changes in their attention.

Zubieta and colleagues (2001) showed that the ACC was related to the endogenous opioid system of subjects undergoing experimentally induced pain using PET imaging. Systemic administration of the µ-opioid agonist fentanyl increased CBF to the ACC while at the same time producing a reduction of pain intensity and unpleasantness scores. In the same report, another experiment found that induced pain correlated with the activation of the endogenous µ-opioid system in the ACC. This activation was also followed by decreases in affective and sensory components of the pain experience, which were measured using the McGill Pain Questionnaire (Melzack, 1975). The study demonstrates that pain and the endogenous opioid system (and its role in pain relief) are all related to ACC activation (Gebhart, 2004). The ACC is also activated during the anticipation of pain (Critchley and colleagues (2001), with less activations as the pain becomes more predictable. This has been argued to be related to the emotional (anxiety) response of anticipation.

Overall, the ACC seems to be related to changes in the sensory component of the pain experience. It is also strongly linked to the affective
dimension, is influenced by the opioid system, and may be responsive to anticipation of aversive stimuli, including pain. Because chronic pain can be anticipated, the ACC might be an important brain region related to patients with chronic pain, including some opioid dependent addicts.

**Pain and the Amygdala**

The amygdala, described above for its role in addiction, is known to be involved in the emotional evaluation of sensory stimuli, including pain (Neugebauer et al., 2004). Important amygdala sub-regions related to pain include its central (CeA) and Basal (BA) nuclei (Neugebauer et al., 2004; Gauriau & Bernard, 2002; LeDoux, 2000; Shi & Davis, 1999) (See Figure 3). There are multiple emotional, sensory and autonomic pain-related inputs to the amygdala, including those coming from the insular cortex, the ACC and the hypothalamus. There are also pain-related outputs projecting to the brainstem and the descending pain modulatory system from the amygdala (see Figure 6) (LeDoux, 2000). This complex circuitry defines an area that is known to be involved in many affective processes, but especially those related to fear and attention, both of which are related to pain. (Neugebauer et al., 2004; Rhudy & Meagher, 2003; Bourgeais, Gauriau & Bernard, 2001; Fields, 2000; LeDoux, 2000; Davis, 1998).

Morphine injection into the amygdala’s CeA (Manning et al., 2003), and BLA (Fields, 2000; Helmsstetter, Tershner, Poore, & Bellgowan, 1998), has been shown to inhibit pain behaviors in rats and primates experiencing pain. In both cases their anti-nociceptive effects were inhibited by inactivation of both the peri-
aqueductal grey (PAG) and rostral ventral medulla (RVM), both of which are known to be important components of the descending pain modulatory system, described in chapter 1 (See Figure 4). Therefore, the pain modulation stemming from opioid activation within the CeA and BLA both operate via the descending pain pathways (PAG and RVM), and when they are inactivated, the amygdala has no modulatory effect.

However, it has also been shown that certain types of formalin induced inflammatory pain (Manning et al., 2003) became worse with opioid injection into the CeA. It is thought that this induced inflammatory pain either inhibits “Off” or induces “On” cells in the RVM, both of which would then facilitate pain transmission (See chapter 2 for a more complete description of “On” and “Off” Cells within the descending pain modulatory system.) These conflicting findings indicate that different types of inflammatory pain influence the descending system in unique ways and that the CeA is involved in these distinctions. (Manning, Martin, & Meng, 2003)

In line with these findings, Li & Neugebauer (2004, 2006) reported that some neurons within the CeA undergo sensitization in response to induced inflammatory arthritis pain in both rats and mice. The sensitization was found to be related to the activation of specific glutamate receptors and to be inhibited by both antagonists to N-methyl-D-aspartate (NMDA) and non-NMDA receptors. Because the amygdala is highly related to both negative affect and to pain, changes within these nuclei could be influential in correlating negative affect with chronic pain, at least as it relates to arthritis (Li & Neugebauer, 2004, 2006).
In summary, the amygdala is involved in pain processing, with the most important nuclei being the CeA and BLA. Generally, activation of the amygdala contributes to pain inhibition via the descending modulatory system. However, in the setting of formalin induced inflammatory pain, which appears to increase pain through activation of the excitatory glutamine pain system, the CeA is involved in a pain facilitory process. Also, given its multiple connections to emotional centers such as the ACC and IC, the amygdala’s role in the descending pain modulatory system should be considered to be important.

**Pain and the Hypothalamus**

Kingery and colleagues (2001) demonstrated that the glucocorticoid methylprednisolone, an analogue of the stress hormone cortisol which is released as part of the hypothalamic-pituitary-adrenal system, reversed neuropathic hyperalgesia in rats. Corticotrophin releasing factor (CRF), a critical hormone released from the hypothalamus under stress conditions, is analgesic when injected both peripherally and centrally (Lariviere & Melzack, 2000). Some, but not all, of the analgesia derived from centrally administered CRF can be attributed to its activation of endogenous opioids. There is also evidence that CRF is analgesic only in the setting of ongoing inflammation pain.

The hypothalamus is also involved in descending pain facilitation and inhibition (Lumb, 2004). Specifically, it was reported that escapable and in-escapable pain are each correlated to unique hypothalamic regions. According to Lumb (2004), projections from the hypothalamus to the PAG demonstrate a high degree of functional organization (see Figure 7), with different projections
corresponding to A-delta (first and fast) versus C-fibers (slow and second).
Specifically, those A-delta fibers which carry brief, escapable somatic stimuli such
as pinch, target the dorsolateral and lateral sectors of the rostral hypothalamus.
Those stimuli carried by more visceral noxious C-fibers, which the authors
describe as being related to more inescapable and persistent pain, project more
to the ventro-lateral sector of the rostral hypothalamus. It was hypothesized that
the representation of escapable versus inescapable pain is manifested in the
organization of projections between discreet parts of the rostral hypothalamus
and the PAG. Thus, the hypothalamus is involved in stress-induced anti-
ociception through the influence of the endogenous opioid system and CRF.
Also, hypothalamic modulation depends upon the type and character of pain,
with unique circuits being activated contingent upon the type and chronicity of the
pain. All of this indicates that the stress analgesia response is not a single
phenomenon and varies depending upon the type and length of pain
experienced.

**The Brain and Pain-Summary**

Numerous higher order brain regions are involved in the experience and
modulation of pain. These include regions which are mostly involved in
interpretation and evaluation of acute sensation on the one hand (i.e., sensory
cortex, PAG) and emotional and evaluative interpretation (ACC, NA and Insular
cortex) on the other. Intertwined with these structures are brain regions which
have multiple roles or are in the service of other systems as relays or modulators.
These include the amygdala, hypothalamus, the DLPFC and the mPFC. Not
discussed formally in this paper, but critically important to the control of pain is the brainstem descending modulating system, which includes the PAG, LC and RVM. For a more detailed description, see Chapter 2.

There are overlapping neuro-anatomical regions linking pain with opioid addiction. As has been discussed, both processes are highly related to the function of the amygdala, nucleus accumbens, the IC and the PFC. Of particular importance are the similar findings of grey matter atrophy within DLPFC in both chronic pain as well as chronic opioid addiction. Future attempts to locate and articulate relationships between addiction and pain will likely benefit from an understanding of these shared neuroanatomical systems described here.

**Conclusion and Implications for Opioid Addicts with Chronic Pain**

This review supports the well-established notion that pain is a complex multi-dimensional phenomenon related to multiple body domains, including higher order brain structures. The specific dimensions of pain, such as sensation intensity, unpleasantness, and evaluation, also appear to be related to unique brain structures.

The results and theories reported in this paper have implications for research and clinical care. First, the use of pain dimensionality in research is required in order to accurately identify important and specific brain regions related to unique pain experiences. The current literature provides the scientific support for the recognition of pain as something that while fundamentally subjective, does objectively exists in the brain of those who are experiencing it. From this, it may be that the newest and most predictive models of chronic pain
will one day be based upon the findings of neuroimaging, as opposed to a variety of self-reports.

The above literature also suggests possible avenues for improved care and future research related to opioid dependent and addicted people and their pain. Opioid users are vulnerable to having chronic pain (Barry, Beitel, Joshi & Schottenfeld 2009; Sheu et al., 2008; Rosenblum et al., 2003; Jamison, Kauffman & Katz, 2000). People living with chronic pain appear to at risk for experiencing all pain in an altered and heightened manner. As Apkarian et al., (2009) theorized, this may be related to deficits within parts of the PFC, particularly the DLPFC, and to its role as a modulator of mPFC driven emotionality. That chronic pain amounts to a disease of the brain, whereby the brain itself is more sensitive to nociceptive sensations such as acute pain, has major implications for all people with chronic pain. This coupled with the woefully inadequate chronic pain management (British Pain Society, 2006; Carroll, Angst & Clark, 2004; Jage (2000a, 2000b, 2004; McCreadie & Davison, 2002; McCaffery & Pasero, 2001), indicates the need for further research into vulnerable populations, including opioid addicts. Further research is needed to determine if opioid addicts with and without chronic pain demonstrate unique brain response patterns and injury, especially as they relate to unique regions of the PFC.
Figure 1.
Location of some of the regions in the human brain that are affected by opioids, including the mesolimbic dopamine system (which includes the ventral tegmental area [VTA], nucleus accumbens (NA), and prefrontal cortex), amygdala, the thalamus and hippocampus. Important brain regions involved in the reward system. Each region communicates in a network using either glutamate, dopamine or GABAergic neurons. Areas involved include the amygdala, nucleus accumbens (NA), medial pre-frontal cortex (mPFC), ventral tegmental area (VTA) and ventral pallidum (VP).

Figure 2.
Dopamine levels within the nucleus accumbens have been shown to rise with withdrawal and craving symptoms during abstinence and then to fall off after drug ingestion and intoxication.

Figure 3. Lobes of the amygdala and directions of communication. Input generally comes into the lateral nucleus (LA), or the lateral portion of the basal nucleus (BLA). The primary output region is the central nucleus (CeA).

Adapted with (pending) permission from “The Amygdala and Its Allies.” The Brain from Top to Bottom http://thebrain.mcgill.ca/flash/i/i_04/i_04_cr/i_04_cr_peu/i_04_cr_peu_1a.jpg
Figure 4.
The descending pain pathways of the brain. Higher order areas of emotion and cognitive processing, the anterior cingulated cortex (ACC), the prefrontal cortex (PFC), Insular Cortex (Insula), each communicate with the brainstem peri-aquaductal grey area (PAG), either directly or via the amygdala. The PAG is then involved in descending modulation of pain transmission from the dorsal horn of the spinal cord.
Figure 5. The prefrontal cortex and its subregions involved in both pain and depression. Lateral View: Dorsal lateral Pre-Frontal Cortex (DLPFC), Rostral Pre-Frontal Cortex (RPFC), Ventral lateral Pre-Frontal cortex (VLPFC), Lateral Occipital Pre-Frontal Cortex (LOPFC). Medial View: Ventral Medial Pre-Frontal Cortex (VMPFC).
Figure 6. The amygdala and communication pathways with important structures of the affective and pain systems. Anterior Cingulate Cortex (ACC) and Insular Cortex (INS) Adapted with (pending) permission from “The Amygdala and its Allies.” The Brain from Top to Bottom http://thebrain.mcgill.ca/flash/i/i_04/i_04_cr/i_04_cr_peu/i_04_cr_peu_1a.jpg
Figure 7. The hypothalamus and its sub-regions Areas known to be involved in pain modulation differ depending upon the type of pain. Sharp acute pain is modulated by the dorsal lateral and lateral regions. More ongoing “inescappable” pain is modulated by the ventral lateral sections. Hypothalamic neurons activated by brief, escapable, somatic stimuli (such as pinch) target the dorsolateral/lateral sector, while neurons driven by cutaneous C-fibers or by inescapable noxious visceral stimuli project more heavily to the ventrolateral sector. Together, these data support the notion that the central representation of escapable vs. inescapable pain is seen in the organization of projections from the rostral hypothalamus to the PAG.


References Chapter 3


Proceedings of the National Academy of Sciences of the United States of America, 98(20), 11818-11823.


Chung KF, Tso KC, Yeung WF & Li WH. (2011) Quality of life in major depressive disorder: the role of pain and pain catastrophizing cognition.


Davis LL, Rush JA, Wisniewski SR, Rice K, Cassano P, Jewell ME, Biggs MM,


Ersche KD, Fletcher PC & Lewis SJG, et al. Abnormal frontal activation related to decision-making in current and former amphetamine and opioid dependent individuals. *Psychopharmacology* 2005; 180;621-623


Decrease in basal dopamine levels in the nucleus accumbens shell during daily drug-seeking behaviour in rats. Brain Research. Jan 11;924(2):141-50


HelmstetterFJ, Tershner SA, Poore LH. & Bellgowan PSF. (1998). Antinociception following opioid stimulation of the basolateral amygdala is expressed through the periaqueductal gray and rostral ventromedial medulla. Brain


Kiyatkin EA. (2002). Dopamine in the nucleus accumbens: cellular actions, drug-


Maletic V & Raison CL. (2009). Neurobiology of depression, fibromyalgia and


and medial prefrontal cortex; a substrate for emotional behavior.


Pritchard TC, Nedderman EN, Edwards EM, Petticoffer AC, Schwartz GJ & Scott
TR. (2008). Satiety-responsive neurons in the medial orbitofrontal cortex

experimental pain perception and autonomic responses. *Pain*. Dec
5;118(3):306-18.

Opinion in Neurobiology*, 12(2), 195-204.


Rhudy JL & Meagher MW. (2003). Negative affect: effects on an evaluative

Mar;10(3):284-94.

Prevalence and characteristics of chronic pain among chemically
dependent patients in methadone maintenance and residential treatment


CHAPTER 4

The Pain and Health Characteristics of Skin Injecting Opioid Users

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The Pain and Health Characteristics of Skin Injecting Opioid Users

ABSTRACT

Some opioid users are known to have a high prevalence of chronic pain as well as other physical and mental health problems. However, data remain limited on the pain experience of active skin injecting opioid users. The aims of this descriptive study were twofold: (1) to examine the overall prevalence of moderate to severe chronic pain (MSCP) as well as other health and pain characteristics of skin injecting opioid users who seek hospital care for treatment of a painful skin abscess related to injecting drugs, and; (2) to identify potential predictors of MSCP, including demographics, acute pain intensity, physical and mental health, and pain treatment characteristics. An urban sample of 91 adult English speaking patients was interviewed in an abscess treatment clinic at a large medical university. MSCP was defined as pain that was experienced within the last week, had persisted for more than 6 months, and was of moderate to severe intensity or interference. Any chronic pain within the last week was reported by 73% of patients and MSCP by 67%. Fifty-percent of all patients reported psychiatric diseases, including depression, anxiety and bipolar disorder.
There were no characteristics under study that significantly predicted MSCP in this sample. However, this sample of skin-injecting opioid users was found to report extremely high rates of moderate to severe chronic pain as well as high levels of physical and psychiatric disease. Future research is warranted to investigate approaches aimed at achieving optimal, safe pain relief for this very vulnerable population.
INTRODUCTION

Introduction and Background

Chronic pain is a frequent and distressful experience, with adult rates ranging from 2% to 40% of the population (Verhaak, Kerssens & Dekker, 1998), and as many as 40% of primary care patients reporting chronic pain (Breivik, Collett, Ventafridda et al., 2006; Moulin et al., 2002; Hensler et al., 2009). Some populations defined by ethnicity such as African Americans and Latinos, (Bonham, 2001; Breitbart et al., 1996; Cleeland et al., 1994; Edwards, Fillingim, & Keefe, 2001; Edwards et al., 2001; Faucett et al., 1994), socio-economic status such as the poor or disenfranchised (Portenoy, Ugarte, Fuller & Haas, 2004), and those with certain disease states such as cancer (Cleeland et al., 1997; Cleeland & Ryan, 1994; Portenoy, Kornblith & Wong et al., 1994) or AIDS (Breitbart et al., 1996; Hewitt, McDonald, Portenoy et al., 1997; Rosenfeld, Breitbart, McDonald, et al., 1996; Vogl, Rosenfeld, Breitbart, et al., 1999), have very high rates of chronic pain. In addition, patients in methadone maintenance treatment programs (MMTP) have reported chronic pain rates ranging from 30-61% (Rosenblum et al., 2003; Jamison, Kauffman & Katz, 2000; Sheu et al., 2008; Barry et al., 2009). Those MMTP patients with high levels of chronic pain have been shown to require significantly more methadone than those without pain (Peles et al., 2005) and to demonstrate higher levels of psychiatric, emotional, and medical co-morbidities (Barry et al., 2009; Rosenblum et al., 2003). Pain in opioid addicted patients could contribute to a variety of negative outcomes, including poor pain control and increased illicit drug use (Rosenblum et al., 2003). Increased self-
management of pain via drug injection could be a contributing factor to the physical harm, abuse, and poverty associated with drug using lifestyles (Barry et al., 2011; Marther et al., 2010; Barry et al., 2009; Salmon et al., 2007; Aceijas & Rhodes., 2007). Additionally, chronic pain alone is harmful to the individual (O’Connor, 2009; McCarberg & Billington, 2006; Liebschutz et al., 1997) and to society (Van Huet, Innes & Whiteford, 2009; Pankratz, Hickman & Toth, 1989). To date, information about opioid users and pain has been largely limited to MMTP patients, and little is known about the prevalence of chronic pain in active skin injecting opioid users.

To understand more about chronic pain in active skin injecting opioid users, the two primary aims of this study were: (1) to examine the overall prevalence of moderate to severe chronic pain (MSCP) as well as other health and pain characteristics of skin injecting opioid users who seek hospital care for treatment of a painful skin abscess related to injecting drugs, and; (2) to identify potential predictors of MSCP, including demographics, acute pain intensity, physical and mental health, and pain treatment characteristics.

CONCEPTUAL FRAMEWORK

Chronic pain is a complex phenomenon with many possible contributing factors, and the reasons for its high prevalence in the opioid dependent population are still emerging. The current literature addressing their pain suggests that some individual characteristics such as being older, having a chronic physical or psychiatric illness, drug use patterns, pain treatment variables, level of drug craving, and time in methadone treatment, help to predict
their chronic pain experience (Rosenblum et al., 2003). In addition, other issues, including having a low socio-economic status (SES) (Poleshuck et al., 2009; Saastamoinen et al., 2005; Portenoy, 2004; Eachus et al., 1999; Lock et al., 1999; Badley & Ibañez, 1994; Andersson et al., 1993), being a member of an ethnic minority (Portenoy et al., 2004; Edwards, Fillingim & Keefe, 2001; Edwards et al., 2001; Cleeland et al., 1998; Faucett, Gordon & Levine, 1994), living with mental illness (Barry et al., 2009; Demyttenaere et al., 2004; Bair et al., 2003) and physical health problems such as HIV (Vogl et al., 1999; Hewitt et al., 1997; Rosenfeld et al., 1996; Breitbart et al., 1996), AIDS (Vogl et al., 1999; Breitbart, Rosenfeld, & Passik et al., 1996) and cancer (Lesage & Portenoy, 1999; Portenoy et al., 1994; Portenoy & Thaller et al., 1994; Gonin & Hatfield, 1994) have been found to worsen the chronic pain experiences of even non-opioid dependent people. Taken together, these variables make up a conceptual framework (see Figure 1) for the investigation of chronic pain in active skin injecting opioid users. The operational definitions of important concepts that could influence an illicit opioid user’s chronic pain follow.

Demographic characteristics that could influence pain include age, sex, ethnicity and SES (operationally defined by type of health insurance) were collected by self-report.

For this study, chronic pain was defined as any pain that had persisted for more than six months. In order to determine if the chronic pain was clinically relevant (Rosenblum et al., 2003), a strict “moderate to severe” definition of chronic pain (MSCP) was operationalized. MSCP was defined as that which had
been experienced in the past week, had persisted for at least six months, and had reached a moderate level of intensity (≥ 4 on a 0 – 10 NRS) or interference on the Brief Pain Inventory (BPI) (Cleeland & Ryan, 1994).

*Acute pain* was defined as current skin abscess pain which had not persisted for longer than two weeks. Acute pain and chronic pain are important independent variables and can influence each other.

*Pain treatment characteristics* which could influence pain included the relief received from prescription, over the counter (OTC) and street drugs that were used over the last two weeks. Street drugs were defined as any illegal drug, alcohol, or medication received from a source other than a prescriber and used to treat pain.

*Mental health characteristics* which could influence pain included the presence of a previous professionally diagnosed *psychiatric illness*, defined by self-report. The level of *psychological distress* experienced over the last week, defined as the recent mood state distinct from physical illness (such as pain and opioid withdrawal). The level of *opioid addiction* was defined by the patients’ self-report of the impact of their drug use on their life. *Methadone maintenance* (MMTP) was defined by current enrollment for opioid replacement (i.e. addiction) therapy. Additional information regarding methadone use included the number of months enrolled in MMTP (if any) and current methadone dose (if any).

*Physical health characteristics* which could influence pain included the presence of a previously professionally *diagnosed illness* defined by self-report, *opioid physical dependence*, defined as the severity of the withdrawal symptoms
experienced when abstaining from opioids for more than one day, and drug craving, defined as the current urge to use drugs

METHODS

Design

This descriptive, prospective, cross sectional study was based on the conceptual framework described above. The inclusion of variables within the study was guided by literature or theoretical relationships. Some of these were included because they are important descriptors of the sample, and others because previous studies found them to be predictive of chronic pain in MMTP patients. The design allowed for the collection of acute and chronic pain, demographic, health, and pain treatment variables, and the testing of those variables as predictors of MSCP.

MEASURES

The brief questionnaire developed for this study was adapted from one used by previous researchers and was shown in that study to take approximately 20 minutes to complete (Rosenblum et al., 2003). Content validity of the original questionnaire was tested in an inpatient drug treatment program and at a needle injection clinic (Rosenblum et al., 2003). Individual instruments incorporated in the questionnaire for this study were selected for validity and reliability. Specific items captured on the questionnaire were divided into five categories; (1) demographic information, (2) pain experience, (3) pain treatment, (4) physical and mental health characteristics, and (5) drug use.

Instruments Incorporated in Questionnaire
Please see Appendix A for the study questionnaire.

*Measures of demographic information* were captured by checklist on the questionnaire.

*Measures of acute and chronic pain*: A 0-10 numeric rating scale (NRS), where 0=no pain and 10= pain as bad as you can imagine, was used to measure the severity of acute abscess pain (Gagliese, Theizblit, Ellis & Chan, 2005). The Brief Pain Inventory (BPI) was used to define MSCP. The BPI consists of two subscales: pain severity and pain-related interference with function. The severity dimension is measured as the average pain over the last week using an NRS 0-10 scale. The interference scale of the BPI also uses NRS 0-10 scales, where 0=does not interfere and 10=completely interferes. The BPI was used to measure pain's interference with the function of seven specific areas, including: general activity, mood, walking, work, relationships with others, sleep, and enjoyment of life. Both scales of the BPI have been extensively validated across a variety of populations (Gagliese, Theizblit, Ellis & Chan, 2005; Willanson & Hoggart, 2005; Tan et al., 2004; Serlin et al., 1995; Daut, Cleeland & Flanery, 1983). Using both BPI scales, MSCP was operationalized as chronic pain experienced within the last week with an average intensity of at least four on the Brief Pain Inventory (Cleeland & Ryan, 1994) intensity scale or a score of at least four on the BPI interference scale.

*Measures of Pain Treatment*: A checklist was used to record the three categories of medications taken for management of pain over the last two weeks: prescribed, over the counter (OTC), and street drugs. The relief obtained from
the medications or street drugs was measured using a 0-10 NRS, where 0=no relief and 10=complete relief.

Measures of physical health characteristics: Questions regarding physical health included whether the patient had been diagnosed with any health care problems. There was a checklist or “fill in” area for those problems. The Short Opiate Withdrawal Scale (SOWS) (Gossop, 1990) was used to measure opioid physical dependency. The SOWS is a shortened 9-item version of the 32-item Opiate Withdrawal Scale (Bradley et al., 1987). It consists of nine categories scored 0-3 (0=none, 1=mild, 2=moderate, 3=severe), for a possible range of scores between 0 and 27. The SOWS allows a parsimonious but valid and reliable evaluation of opioid physical dependence (Gossop, 1990). Level of drug craving was measured using an NRS 0-10 scale where 0=no urge to use and 10=uncontrollable urge to use drugs.

Measures of mental health: A previous professionally diagnosed psychiatric illness was self-reported as yes/no. The level of recent (within the last week) psychological distress was measured using a validated short version of the Symptom Checklist-90 (Derogatis, 1983), which is a well validated measure of general psychological distress. See instrument in appendix A for specific items within the instrument.

The six-item instrument was scored based upon how many days a particular symptom was felt over the last week. A score of 0=less than 1 day; 1=1-2 days; 2=3-4 days; 3=5-7 days; for a possible range of scores between 0 and 18. The short form is able to distinguish psychological from physical distress,
which is especially important when studying people who are potentially experiencing physical symptoms related to illness and drug withdrawal. The level of self-perceived opioid addiction was measured as the score on the Severity of Dependence Scale (SDS). The SDS is composed of five items related to how often one believes they have a particular drug related problem. Each item is scored 0=never; 1=sometimes; 2=often; 3=always/nearly always, for a possible score of 0-15. The SDS has been validated for the evaluation of addiction (i.e, psychological dependence) experienced by users of a broad range of drugs, including opioids. The SDS was previously validated on five separate samples of English and Australian urban drug users (Gossop et al., 1995). Methadone maintenance (MMTP) was measured by current enrollment for opioid replacement (i.e., addiction) therapy, the number of months enrolled in MMTP (if any) and current methadone dose (if any).

SAMPLE

A total of ninety-one subjects participated in the study. Data were collected from adult patients receiving treatment for an acute painful abscess related to skin injecting opioids. The site was a large university hospital-based clinic in San Francisco, CA. Incarcerated subjects were not recruited for the study.

Power Analysis

The two primary aims of this descriptive study were: (1) to examine the overall prevalence of MSCP, as well as other health and pain characteristics, of skin injecting opioid users who seek hospital care for treatment of a painful skin abscess related to injecting drugs, and; (2) to identify potential predictors of
MSCP, including demographics, acute pain intensity, physical and mental health, and pain treatment characteristics. The results from previous work by Rosenblum et al., (2003) were used to estimate the effect sizes of each variable and to aid in determining sample size. To achieve this, odds ratios from Rosenblum et al. were transformed into probabilities using an alpha of 0.05 and a power of 80%. The required number of subjects was determined by the variable “drug craving” which had the smallest effect size to predict chronic pain in that study. This power analysis demonstrated the need for 156 subjects. The study was stopped after inclusion of 91 patients, prior to a multivariate logistic regression because interim univariate logistic regression and t-test analyses did not indicate any statistically significant predictors of MSCP. The interim analysis indicated that a sample of 267 patients would have been required to achieve a power of 80%.

PROCEDURES

The institutional review boards of the University of California San Francisco and San Francisco General Hospital approved the research protocol. All patients who presented to the clinic with an abscess were screened by an intake RN staff member for inclusion criteria. Those who met these criteria were referred, with their permission, to the study researcher (CS). Prospective study candidates were provided time to review the informed consent and to ask questions about the study. Consenting participants were then interviewed in a private room by the study researcher using the study questionnaire. In all but two cases, the study researcher read the questionnaire aloud to the subject.

Statistical Analyses
The prevalence of MSCP was calculated, along with the frequencies of covariates of interest (i.e., those thought to be related to or predictive of chronic pain in previous studies). The Chi Square test was used to examine the relationships between respondent characteristics, drug use, treatment behaviors, and chronic pain. T-test analysis was used to compare those with MSCP to those without MSCP on continuous variables. A logistic regression model was used to identify the characteristics uniquely predictive of chronic moderate to severe pain.

RESULTS

Patient Characteristics

Of the qualified patients approached by the intake nurse to participate in the study, 91 of 120 (76%) agreed to participate. Three patients agreed to participate but were excluded: one because of incarceration and two due to having skin abscesses related to the injection of amphetamines rather than opioids. The mean (SD) age of the patients was 45 (11.4) years, and 24% were women. Fifty-nine percent were White, and 26% were African American. There were 4% each of Hispanics and Native Americans and 6% from other ethnicities. Fifty-seven percent of all patients reported being uninsured; one subject held private insurance; and 41% were covered by either Medicare or medical/SSI.

Pain Prevalence, Characteristics, and Functional Interference

The presence of any chronic pain was reported by 73% and MSCP by 67%. For those patients with chronic pain over the last week, the “average intensity” of their chronic pain over the last week was 5.97(2.3) on the 0-10 NRS
scale (See Table 1). The average (SD) intensity of acute abscess pain reported by all patients was 6.58 (2.8). The mean BPI interference score for all chronic pain patients over the last week was 6.43 (2.3), with sleep receiving the highest degree of interference 6.96 (3.4) (See Table 2).

Pain Treatment

Sixty-one patients had taken some form of prescription pain medication within the last two weeks. See Table 3. The mean (SD) pain relief received from drugs prescribed to them by a physician was 5.9 (3.0) on a scale of 0-10. The greatest relief for all drugs was reported by 11 patients who took oxycontin [8.0 (1.6)]. Only 24 patients took an over the counter (OTC) pain medication within the last 2 weeks. Of the OTC drugs, the most commonly used and most potent pain reliever [4.4 (2.2)] was ibuprofen. The mean pain relief from all OTC drugs was 3.7 (3.1). Ninety-five percent (n = 86) of all patients reported taking a street drug to treat their pain within the last two weeks, 71% of which was heroin. The mean (SD) pain relief achieved by the street drugs was 7.3 (2.6).

Physical and Mental Health Characteristics

Physical Health. Of the health problems reported, Hepatitis C was the most common, with 73% reporting infection, followed by HIV (15%) and arthritis (7%). The mean opioid withdrawal score was 18.7(6.9), on a 0-27 scale, indicating a severe level of physical dependence (Bradley et al.,1987; Gossop et al.,1990). The current drug craving was 5.1(3.7) on a 0-10 NRS scale. (See Table 4).

Mental Health: Fifty-one percent reported a previous diagnosis of a mental
health or psychiatric problem. Of those, the most common diagnosis was depression (26%). Those with a psychiatric diagnosis were more likely to experience MSCP, although neither statistic reached significance. (See tables 5 & 6 for non-significant predictors of MSCP). Patients reported moderate 9.4 (6.2) levels of recent psychological distress (Derogatis, 1983). The self-assessed level of addiction score was 8.9 (3.6) on a scale of 0-15, indicating a moderate level of self-perceived addiction (Gossop et al., 1995). Sixty-two percent (n = 56) of patients reported currently receiving methadone maintenance for opioid dependence treatment, for a median duration of 12 months and a mean (SD) dose of 79 (37.0)mg/day. (See Table 4)

**Lack of MSCP Predictors**

In a bivariate logistic regression, no demographic, pain, physical or mental health, or pain treatment variables were found to be statistically predictive ($P<.10$) of chronic moderate to severe pain. Because of this, no multivariate analyses were performed. As can be seen from tables 5 & 6, many variables did demonstrate high t-statistics and odds ratios, despite remaining statistically insignificant.

**Discussion**

The pain experience of active heroin users who are seeking hospital care for abscess related pain has not yet been explored. In this sample, those patients demonstrated a very high prevalence of MSCP. Up to now there has been a limited amount of research about the pain experience of community dwelling opioid users (mostly methadone), and these reports indicate that they have high
prevalence rates of severe, life interfering pain (Barry et al., 2009; Sheu et al., 2008; Rosenblum et al., 2003; Jamison et al., 2000). Using similar measures as those in this study, previous investigators (Rosenblum et al., 2003) found that being older, having a diagnosis of a medical or psychiatric illness, having a greater level of psychiatric distress, pain being amongst the reasons for first using opioids, and having participated in MMTP for more time, each contributed to a greater likelihood of MMTP patients having severe chronic pain. The current study, on the other hand, did not find any measured variables to be significantly predictive of MSCP. Some possible explanations for the findings in the current study follow.

Lack of Significant Predictors

Given the above literature, the lack of any significant predictors of MSCP in this study must be examined. First, the study did not reach its post-hoc interim power analysis sample size of 267. After 91 patients were enrolled, it was found that the study was not adequately powered to identify statistically significant demographic and health predictors of MSCP. Thus, even the strong relationships seen between some predictor variables and MSCP were not statistically significant (see tables 5 & 6).

Demographics

Socio-Economic Status: The majority of patients in the current study live under deprived socio-economic conditions, defined here as a lack of health insurance (57%). A previous study (Rosenblum et al., 2003) did not report any findings regarding the relationship between low SES and severe chronic pain.
However, many studies have reported that low SES is highly related to chronic pain (Portenoy et al., 2004; Edwards, Fillingim & Keefe, 2001; Edwards et al., 2001; Cleeland et al., 1998; Faucett, Gordon & Levine, 1994). Also, the prevalence of low SES seen in this sample has important physical (Mathers et al., 2010; Liebschultz, Mulvey & Samet, 1997) and mental (Barry et al., 2009; Demyttenaere et al., 2004; Bair et al., 2003) health implications for this population. Because of their known relationship, the possibility that low SES alone is related to the mental and physical illness seen here cannot be dismissed (Saatamoinen et al., 2005; Eachus et al., 1999; Lock et al., 1999; Badley & Ibañez, 1994; Anderson et al., 1993). However, because this study did not aim to determine the relationship between low SES and mental and physical health problems, their relationship in this population remains an untested but important one for future research. Also, because the sample was somewhat under-representative of ethnic minorities and women, their presence was an unlikely contributor to the high prevalence of MSCP in this sample.

**Chronic Pain Prevalence**

The few studies that have specifically addressed the chronic pain rates of community dwelling methadone maintained people, or those first seeking methadone maintenance (MMT), reported chronic pain prevalence to be as high as 66% (Barry et al., 2009; Sheu et al., 2008; Rosenblum et al., 2003; Jamison et al., 2000). However, when more narrowly defined by intensity, interference and time in a manner similar to the current study, those rates fell to a maximum of 37%. Still, it now seems that a range of opioid users have chronic pain
prevalence similar to that reported in terminally ill patients living with cancer and AIDS (Lesage & Portenoy, 1999; Vogl et al., 1999; Breitbart, Rosenfeld, & Passik et al., 1996; Portenoy et al., 1994; Portenoy & Thaller et al., 1994; Gonin & Hatfield, 1994). The very high levels of pain interference scores reported here were similar to those reported by Rosenblum et al., (2003). Pain interference with mood is especially important considering the corresponding high levels of psychological distress reported here.

Rosenblum and colleagues (2003) and Barry et al., (2011) also found higher rates of chronic severe pain among MMTP patients than other drug users (primarily alcohol and cocaine) seeking rehabilitation (37% versus 24%), indicating the possibility that opioids have a unique role in the pain experience. Sheu and colleagues (2008) investigated the prevalence and severity of pain in a sample of mostly employed, educated alcoholic patients, and reported a 30% rate of any chronic pain (Sheu, Lussier & Rosenblum, 2008). While there may be other unmeasured differences between the above samples, opioid use versus “other” drug use should be considered for its contribution to the high pain rates seen in this study.

Pain Treatment

Only half of the patients reported taking a prescription pain medication within the last two weeks, indicating the possibility of an unwillingness of providers to treat pain, limited access to health care, or a lack of desire for care on the patients’ part. Those prescription pain medications which were taken were reported as moderately effective. However, patients reported moderate to severe
6.58 (2.8) acute abscess pain upon arrival to the clinic, indicating the persistence of moderate to severe pain. A minority of patients reported taking OTC drugs, which were the least effective for pain relief. On the other hand, over 70% of patients admitted to using heroin for pain control, which was rated as highly effective. Finally, while very few patients received it, (n=11), oxycontin was reported as the most effective analgesic. While this study did not formally distinguish between the times a patient injected for pain control versus opioid craving, a large percentage of patients were injecting a harmful drug for the purpose of pain relief. Given the harm induced by injecting drugs, these findings indicate that alternate modes of pain management for this population should be pursued.

To that end, a study by Blinderman and colleagues (2009) investigated the effectiveness of managing the pain of a group of MMTP patients with chronic pain related to AIDS, using methadone. They reported that, on average, a group of opioid dependent chronic pain patients being treated with methadone, dosed explicitly for pain, experienced very significant improvement over 12 months. Overall, pain rates fell from an initial rating of 9.4 to 4.2 on a NRS (0-10) scale, with the dose of methadone increasing by 200% over the study period. There were few adverse impacts upon the patients over the study period, suggesting that specifically addressing pain in opioid exposed patients can lead to improved outcomes without causing harm (Blinderman, Sekine, Zhang, Nilsson & Shaiova, 2009)

*Physical and Mental Health Characteristics*
**Physical Illness:** HIV infection was reported by 15% of this sample, which is 30 times that of the general population (CDC, 2008). Hepatitis C was reported at a rate of 70% versus 1% normally found in the general population, although both the Hepatitis C (CDC, 2005) and HIV (Mathers, 2008) rates are consistent with those previously reported among skin injecting drug users. In populations of skin injecting drug users, literature suggests that both of these infections are likely to be highly related to injecting drugs (CDC, 2008; CDC, 2005), although this was not explicitly tested in the current study. Still, all means of diminishing the acquisition of infectious disease should be pursued, and that includes decreasing the use of illicit pain relieving drugs through skin injection.

Finally, the high chronic pain rates found in this study are consistent with those found in very ill populations, including those living with HIV (Breitbart et al., 1996; Hewitt, McDonald, Portenoy et al., 1997; Rosenfeld, et al., 1996; Vogl et al., 1999), AIDS (Vogl et al., 1999; Breitbart et al., 1996), and cancer (Lesage & Portenoy, 1999; Portenoy et al., 1994; Portenoy & Thaller et al., 1994; Gonin & Hatfield, 1994). However, it is unlikely that the rates of these diseases within the sample are responsible for the high rates of MSCP, and they were non-significant contributors to MSCP.

**Mental Illness:** It is a commonly reported finding that chronic pain and mental illness are highly related (Bair et al., 2003). A diagnosed mental health disorder, not including chemical dependency, was present in 53% of one sample of 390 patients (Rosenblum et al., 2003), which is almost twice the rate within the of the general U.S. population (Demyttenaere, Bruffaerts, Posada-Villa, Gasquet,
Additionally, fifty-three percent of the MMTP patients with mental illness reported living with severe chronic pain (Rosenblum et al., 2003). Barry and colleagues (2009) also found a strong relationship between severe chronic pain and psychiatric disturbance in a sample of MMTP's. Both findings indicate that the presence of psychiatric illness and distress could also be related to the pain of skin injecting opioid users. We did not find a significant relationship between the presence of chronic pain and mental illness, although given the high odds ratios relating mental illness and MSCP in this study (see table 6), lack of significance might be related to insufficient statistical power.

Also, given the study design and inclusion criteria, opioid use itself was not explicitly tested as a predictor in this study. However, previous work by Rosenblum et al., (2003) did find much higher severe chronic pain rates in a sample of MMTP (37%) versus a sample of inpatient poly-substance users. Therefore, the high overall prevalence of MSCP and the lack of significant predictors indicate that skin injecting opioid use itself should considered as an important, yet untested, predictor of MSCP.

Finally, it is possible that the differences between this sample and those in previous studies contributed to the lack of significant predictors of MSCP. Possible distinctions include the fact that this sample was composed of active heroin users seeking care for acute injury, as opposed to being community dwelling people reporting upon their chronic condition. There is evidence that opioids alter the pain system of exposed patients, generating the phenomenon of opioid induced hyperalgesia (Compton, Athanasos et al., 2003; Compton,
Charuvastra & Ling, 2001; Compton, Charuvastra & Kintaudi, 2000; Kissin, Bright & Bradley, 2000; Devillers et al., 1995). This is thought to be especially true of opioids, such as heroin, that do not contain any N-Methyl-D-Aspartate (NMDA) receptor antagonistic qualities versus methadone, which does demonstrate some NMDAR antagonism. Therefore, opioid induced hyperalgesia might be a more potent predictor of the pain experience of active heroin users than it is to those also taking methadone (Lee et al., 2011). The study did not examine the role of opioid physiology on the characteristics of those who become chronic opioid users.

**Limitations**

The study was limited to skin injecting illicit opioid users who had an acute painful abscess. This sample was found to have very high levels of physical dependence and moderate levels of self-perceived addiction. This makes generalizing the findings of high MSCP prevalence to a broader population of opioid exposed patients impossible. All data collection depended upon face to face and self-report interviews, both of which provide limitations. Despite the fact that it was made explicitly clear to subjects that the study researcher was not part of the clinical team, there remains the possibility that the subjects were performing/inflating and or withholding information for reasons unknown to the researchers.

**Implications**

The high rates of chronic pain and illness seen in this sample should be considered through the lens of both individual and social costs, and research
should continue to pursue the relationship between each and active skin injecting opioid use. This study did not test the relationship between pain treatment through injection and the possible harm induced by that self-treatment. However, it did identify a great deal of harm likely related to injection drug use (HIV, Hep C, acute abscess), and a high rate of pain self-management with heroin, which was reported to be a highly effective analgesic. Therefore, the high prevalence of MSCP identified in the current study, and the continued harm and costs associated with injecting drugs, indicate there is now an imperative upon clinicians and researchers to investigate approaches, such as that by Blinderman et al., (2009) aimed at achieving optimal, safe, pain relief for this very vulnerable population. Also, while illnesses such as Hepatitis C and HIV are very likely to be related to skin injection of drugs, the high rates of psychological burden require further investigation. It is not clear if the psychological distress and disease reported here are related to chronic pain, drug use, illness, or are entirely independent variables.

Conclusions

Previous research has suggested that low SES, in addition to higher rates of physical and mental disease burden, are positively associated with chronic pain prevalence and severity. Those variables were not predictive of MSCP in this study. However, the findings in this study and others (Rosenblum, et al., 2003; Jamison et al., 2000; Sheu et al., 2008; Barry et al., 2009) suggest that opioid exposed people have higher than expected rates of clinically relevant chronic pain. The findings in this study extend that knowledge from community dwelling
methadone maintained subjects to include active heroin users who are seeking hospital care for acute injury. Also, very high rates of mental and physical illness were found in this sample, each consistent with previous reports. Therefore, skin injecting opioid users seeking hospital care for acute abscess related injuries, have a very high burden of co-morbid pain and disease.
Figure 1
Conceptual Framework: Chronic Moderate to Severe Pain in Injecting Opioid Users

Physical Health and Illness Characteristics such as:
- HIV
- Hepatitis C
- Opioid Physical Dependence
- Drug Craving

Mental Health Characteristics:
- Psychiatric Diagnosis
- Current Psychological Distress
- Opioid Addiction
- Methadone Maintenance

Acute Pain Intensity

Chronic Pain
Defined as pain for at least 6 months

Any

Moderate to severe MSCP
Defined as:
average => 4 NRS 0-10 over the past week OR
average Interference => 4 on BPI 0-10 interference scale

Demographics:
- Age
- Sex
- Ethnicity
- SES (Health Insurance)

Pain Treatment/Relief:
- Prescription
- Over-the-Counter
- Street Drugs
Table 1:
Patients with Acute or Chronic Pain *
Mean Intensity Scores (0-10 NRS)

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
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<tbody>
<tr>
<td>Acute Pain (All Patients)</td>
<td>6.58</td>
<td>2.8</td>
</tr>
<tr>
<td>Chronic Pain Least (past 7 days)</td>
<td>3.26</td>
<td>2.6</td>
</tr>
<tr>
<td>Chronic Pain Aver (past 7 days)</td>
<td>5.97</td>
<td>2.3</td>
</tr>
<tr>
<td>Chronic Pain Worst (past 7 days)</td>
<td>8.34</td>
<td>2.0</td>
</tr>
</tbody>
</table>

* Calculated for those reporting any chronic pain (present for at least 6 months) within 7 days (N=66).

Table 2:
Patients with Chronic Pain
Mean Interference Scores (0-10 NRS) *

<table>
<thead>
<tr>
<th>Pain interference with:</th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Activity</td>
<td>6.50</td>
<td>2.9</td>
</tr>
<tr>
<td>Mood</td>
<td>6.69</td>
<td>2.8</td>
</tr>
<tr>
<td>Walking</td>
<td>6.73</td>
<td>3.2</td>
</tr>
<tr>
<td>Activities of Daily Living</td>
<td>6.19</td>
<td>2.7</td>
</tr>
<tr>
<td>Relationships</td>
<td>5.29</td>
<td>3.5</td>
</tr>
<tr>
<td>Sleep</td>
<td>6.96</td>
<td>3.4</td>
</tr>
<tr>
<td>Enjoyment</td>
<td>6.63</td>
<td>3.2</td>
</tr>
<tr>
<td>BPI** Mean Interference Score</td>
<td>6.43</td>
<td>2.3</td>
</tr>
</tbody>
</table>

* Calculated for those reporting any chronic pain (present for at least 6 months) within 7 days (N=66).
* Brief Pain Inventory

Table 3
Drug Use and Pain Treatment Variables

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Min.</th>
<th>Max.</th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTC Drug Pain Relief</td>
<td>24</td>
<td>3.7</td>
<td>3.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescription Drug Pain Relief</td>
<td>61</td>
<td>5.9</td>
<td>3.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Street Drug Pain Relief</td>
<td>86</td>
<td>7.3</td>
<td>2.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pain relief from drugs rated on NRS (0-10) with 0=no relief and 10=complete relief

Table 4
Physical and Psychological Symptoms

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Min.</th>
<th>Max.</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>Median</th>
</tr>
</thead>
</table>

130
<table>
<thead>
<tr>
<th>Current opioid Addiction Score</th>
<th>91</th>
<th>0</th>
<th>15</th>
<th>8.9</th>
<th>3.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current urge to use drugs</td>
<td>91</td>
<td>0</td>
<td>10</td>
<td>5.1</td>
<td>3.7</td>
</tr>
<tr>
<td>Current psychological distress</td>
<td>91</td>
<td>0</td>
<td>18</td>
<td>9.4</td>
<td>6.2</td>
</tr>
<tr>
<td>Current Months on Methadone</td>
<td>56</td>
<td>0</td>
<td>456</td>
<td>41.5</td>
<td>79.9</td>
</tr>
<tr>
<td>Current Methadone Dose</td>
<td>56</td>
<td>0</td>
<td>190</td>
<td>78.8</td>
<td>37.0</td>
</tr>
</tbody>
</table>

### Table 5
Non-significant predictors of MSCP (continuous)

<table>
<thead>
<tr>
<th></th>
<th>t</th>
<th>df</th>
<th>Sig. (two-tailed)</th>
<th>Mean Difference</th>
<th>Std. Error Difference</th>
<th>95% Confidence Interval of the Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>.888</td>
<td>64.545</td>
<td>.378</td>
<td>2.16833</td>
<td>2.44136</td>
<td>-2.7081 7.0447</td>
</tr>
<tr>
<td>Acute pain</td>
<td>.208</td>
<td>66.126</td>
<td>.836</td>
<td>.122</td>
<td>.589</td>
<td>-1.053 1.298</td>
</tr>
<tr>
<td>Physical Dependence</td>
<td>-.574</td>
<td>70.775</td>
<td>.568</td>
<td>-.824</td>
<td>1.436</td>
<td>-3.688 2.040</td>
</tr>
<tr>
<td>Opioid Addiction</td>
<td>-.803</td>
<td>61.567</td>
<td>.425</td>
<td>-.628</td>
<td>.783</td>
<td>-2.194 .937</td>
</tr>
<tr>
<td>Current Drug Craving</td>
<td>1.009</td>
<td>89</td>
<td>.316</td>
<td>.847</td>
<td>.844</td>
<td>-.842 2.536</td>
</tr>
<tr>
<td>Recent Psychological Distress</td>
<td>1.207</td>
<td>89</td>
<td>.231</td>
<td>1.664</td>
<td>1.378</td>
<td>-1.075 4.403</td>
</tr>
<tr>
<td>Methadone dose</td>
<td>-1.71</td>
<td>35.135</td>
<td>.121</td>
<td>-17.529</td>
<td>10.224</td>
<td>-38.283 3.225</td>
</tr>
<tr>
<td>Months Methadone Relief from prescriptions</td>
<td>-1.45</td>
<td>54</td>
<td>.286</td>
<td>-24.67</td>
<td>22.84</td>
<td>-70.4 21.16</td>
</tr>
<tr>
<td>Relief from street drugs</td>
<td>-.159</td>
<td>48.164</td>
<td>.874</td>
<td>-.09744</td>
<td>.61317</td>
<td>-1.3302 1.13532</td>
</tr>
<tr>
<td>Relief from OTC drugs</td>
<td>1.020</td>
<td>6.977</td>
<td>.342</td>
<td>1.722</td>
<td>1.688</td>
<td>-2.272 5.717</td>
</tr>
<tr>
<td>Variable</td>
<td>No of Respondents</td>
<td>OR (95%CI)</td>
<td>P Value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------------</td>
<td>----------------</td>
<td>---------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female Sex</td>
<td>22</td>
<td>.918 (.385-2.19)</td>
<td>.848</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Diagnosed Mental Illness</td>
<td>47</td>
<td>2.019 (.830-4.914)</td>
<td>.121</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White Ethnicity</td>
<td>54</td>
<td>1.714 (.431-6.826)</td>
<td>.445</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>24</td>
<td>2.036 (.591-7.014)</td>
<td>.260</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>13</td>
<td>1.00</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current Methadone</td>
<td>54</td>
<td>1.342 (.548-3.290)</td>
<td>.520</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Own Apartment</td>
<td>28</td>
<td>2.217 (.768-6.404)</td>
<td>.141</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRO</td>
<td>23</td>
<td>2.094 (.682-6.432)</td>
<td>.197</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homeless</td>
<td>40</td>
<td>1.00</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>66</td>
<td>.727 (.256-1.995)</td>
<td>.536</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>14</td>
<td>1.275 (.364-4.458)</td>
<td>.704</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Covered by Health Insurance</td>
<td>39</td>
<td>1.812 (.729-4.504)</td>
<td>.200</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix A-Questionnaire

Opioid User Health and Pain Questionnaire

ID#: ___ ___ ___ ___
Date__/__/____

PLEASE ANSWER ALL QUESTIONS. This survey is confidential. Do not put your name on this survey. Please answer each question by circling the correct number or filling in the blank.

General Questions (Circle that which applies)

1) Circle One
   1. Male
   2. Female
   3. Other

2) Date of birth
   ___ / ___ / ___

3) Racial/ethnic background? (CIRCLE ONE):
   1. African-Amer
   2. White
   3. Hispanic, Latino/a
   4. Asian
   5. Native Amer/Alaskan
   6. Biracial (mixed)
   7. Other

4) Health Insurance? Yes; type _______ No

5) What is your current employment status (include “off-the-books” jobs)? [CIRCLE ONE]
   1. Full-time
   2. Part-time
   3. Unemployed
   4. Homemaker
   5. “Off the Books” describe __________________________

6) What has been your usual sleeping place in the past 30 days? Please check One of the following:

   A. My own home/apartment
   B. Hotel (SRO)
   C. Jail or prison
   D. Shelter/Crisis Center
   E. On the street, park, subway or other place not designed for sleeping
   F. Other __________________________
The following section addresses issues related to your pain

7) What is the severity of your abscess pain **Now**?

<p>| | | | | | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>No Pain</td>
<td>Pain as bad as you can imagine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

8) In addition to the abscess pain you are experiencing today, have you had other pain that has persisted for more than six months (i.e., chronic pain)?
   - Yes
   - No

9) Have you experienced that (non abscess) pain in the last 7 days?
   - Yes
   - No

10a) Where in your body has that pain (non abscess) been? (Circle all that apply)

<table>
<thead>
<tr>
<th>Location</th>
<th>Cause/Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Face</td>
<td>______________________________</td>
</tr>
<tr>
<td>B. Head</td>
<td>______________________________</td>
</tr>
<tr>
<td>C. Neck</td>
<td>______________________________</td>
</tr>
<tr>
<td>D. Shoulder</td>
<td>______________________________</td>
</tr>
<tr>
<td>E. Back</td>
<td>______________________________</td>
</tr>
<tr>
<td>F. Chest</td>
<td>______________________________</td>
</tr>
<tr>
<td>G. Stomach</td>
<td>______________________________</td>
</tr>
<tr>
<td>H. Pelvic Region</td>
<td>______________________________</td>
</tr>
<tr>
<td>I. Knee</td>
<td>______________________________</td>
</tr>
<tr>
<td>J. Foot</td>
<td>______________________________</td>
</tr>
<tr>
<td>K. Skin</td>
<td>______________________________</td>
</tr>
<tr>
<td>L. Tooth/Mouth</td>
<td>______________________________</td>
</tr>
<tr>
<td>M. Other</td>
<td>______________________________</td>
</tr>
</tbody>
</table>

10b) If other body area please describe;

________________________________________________________________________
________________________________________________________________________

10c) **SKIP TO Q11 IF YOU HAVE only one non-abscess pain**

Which of the above pain is the most severe?
(Write name or letter code for example “E” for back pain) __________________
11) What best describes your chronic pain? (Circle one)

1. It comes and goes
2. It has always been there
3. Both (Always there, but also gets worse and better)

12) What effect does going through heroin withdrawal have on your pain? (Circle one)

0 1 2 3 4 5 6 7 8 9 10
Makes it no worse Makes it extremely worse

13) How many times in the last six months did you see a doctor for your chronic (not abscess) pain? (If no chronic pain skip to question 18)

Enter number _______

Circle the number that best applies to your chronic pain (not abscess pain). If No Chronic Pain In Past 7 days skip to question number 16

14) Considering the chronic pain problem (not abscess) that bothers you the most, what number best describes:

a) The severity of your pain AT ITS WORST during the past week?

0 1 2 3 4 5 6 7 8 9 10
No Pain Pain as bad as you can imagine

b) The severity of your pain ON AVERAGE during the past week?

0 1 2 3 4 5 6 7 8 9 10
No Pain Pain as bad as you can imagine

c) The severity of your pain AT ITS LEAST during the past week?

0 1 2 3 4 5 6 7 8 9 10
No Pain Pain as bad as you can imagine
The next section addresses issues related to all your chronic pain taken together

15) Considering ALL the areas of chronic (not abscess) pain together that you have experienced during the past week, what number best describes how much it has interfered with the following:

a) General Activity
   0  1  2  3  4  5  6  7  8  9  10
   Does Not Interfere  Completely Interferes

b) Mood
   0  1  2  3  4  5  6  7  8  9  10
   Does Not Interfere  Completely Interferes

c) Walking Ability
   0  1  2  3  4  5  6  7  8  9  10
   Does Not Interfere  Completely Interferes

d) Normal Daily Activities (including work and housework)
   0  1  2  3  4  5  6  7  8  9  10
   Does Not Interfere  Completely Interferes

e) Relationships with Other People
   0  1  2  3  4  5  6  7  8  9  10
   Does Not Interfere  Completely Interferes

f) Sleep
   0  1  2  3  4  5  6  7  8  9  10
   Does Not Interfere  Completely Interferes

g) Enjoyment of Life
   0  1  2  3  4  5  6  7  8  9  10
   Does Not Interfere  Completely Interferes
16) At the time when you started using opioids, was your chronic pain:
   1. worse          2. better          3. the same as now          4. I had no pain at that time
   5. N/A (no chronic pain now)
17) Was pain one of the reasons why you started using opioids? No Yes

The next section addresses issues about the treatment of your pain

18) When did you last take pain medications prescribed to you by a doctor? (Circle one)
   1. Within the past week  4. 4 to 6 months ago
   2. 2 to 3 weeks ago      5. More than 6 months ago
   3. 1 to 3 months ago     6. N/A

19) In the past two weeks what type of prescribed pain medications did you take? (Leave blank if none)

20) How much did these prescribed medications relieve your chronic pain? (Skip to question 21 if none taken)
   0 1 2 3 4 5 6 7 8 9 10
   No Relief of Pain Complete Relief of Pain

21) In the past two weeks what type of over-the-counter pain medications did you take? (skip to Q23 if none)

22) How much did these over-the-counter medications relieve your chronic pain?
   0 1 2 3 4 5 6 7 8 9 10
   No Relief of Pain Complete Relief of Pain

23) When did you last use a friend’s drugs or street drugs to treat your pain? (Circle one)
   1. Past week          4. 4 to 6 months ago
   2. 2 to 4 weeks ago   5. More than 6 months ago
   3. 1 to 3 months ago  6. Never (Skip to number 24)

23a) At that time (when you were treating your pain), what type of "street" drugs did you take for the purpose of treating pain?

23b) How much did these street drugs relieve your chronic pain? (N/A)
   0 1 2 3 4 5 6 7 8 9 10
   No Relief of Pain Complete Relief of Pain
24) When did you last use, sell or barter your pain medications prescribed to you for the purpose of pain control. (Circle one)
   1. Past week
   2. 2 to 3 weeks ago
   3. 1 to 3 months ago
   4. 4 to 6 months ago
   5. More than 6 months ago
   6. Never
   7. N/A; (I have never had prescribed pain meds)

25) What drug(s) prescribed to you did you use in this way? (leave blank if none)

___________________________________________________________________________
___________________________________________________________________________

The next section addresses questions relating to your drug use

26) How old were you when you first began to use drugs or drink heavily?
   Age _____ Drug or Alcohol Type(s)____________________

27) Which is your substance of choice?____________________

28) Which is your substance of 2nd choice? _________________

29) What street drugs did you last use?______________________ When______

30) What number best describes your urge to use drugs over the past week:

   0 1 2 3 4 5 6 7 8 9 10
   No urge to use Uncontrollable Urge to Use

31) What number best describes your urge to use alcohol over the past week:

   0 1 2 3 4 5 6 7 8 9 10
   No urge to use Uncontrollable Urge to Use

32) In the past 30 days did you ever inject drugs
   Yes   No

33) Are you currently:

   0 1 2 3 4 5 6 7 8 9 10
   High from Drugs Withdrawning
34) If not withdrawing now, when did you last experience opioid withdrawal? (Circle one)
   1. Past week          4. 4 to 6 months ago
   2. 2 to 3 weeks ago   5. 7 months to 1 year ago
   3. 1 to 3 months ago  6. More than 1 year ago
35) Check the box below that corresponds with each symptom when you stop using opioids for more than a day.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>None-0</th>
<th>Mild-1</th>
<th>Moderate-2</th>
<th>Severe-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeling Sick</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach Cramps</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle Spasms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeling of Coldness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Pounding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscular Tension</td>
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<td></td>
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<tr>
<td>Aches and Pains</td>
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</tr>
<tr>
<td>Yawning</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Runny eyes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

36) The following questions address your drug use

<table>
<thead>
<tr>
<th>Question</th>
<th>Never/Almost</th>
<th>Sometimes</th>
<th>Often</th>
<th>Always/Nearly</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Do you think your use of drugs is out of control?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>B. Does the prospect of missing a fix (or dose) make you anxious or worried?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>C. Do you worry about your use of drugs?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>D. Do you wish you could stop using?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>E. How difficult do you find it to stop or go without drugs</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

37) How long have you been in methadone treatment? _______ (N/A)

38) What is your current methadone dose? ____ ____ ____ Mg (N/A)
The following section addresses issues related to your health

39) Prior to today, when did you last see a doctor for any medical problem? (Circle one)

1. Past week  
2. 2 to 3 weeks ago  
3. 1 to 3 months ago  
4. 4 to 6 months ago  
5. More than 6 months ago  
6. More than 1 year ago

40) Do you currently have any of the following health problems? (Circle those that apply)

A. Diabetes  
B. Arthritis  
C. Cirrhosis (Liver disease)  
D. Hepatitis C  
E. Emphysema  
F. Cancer  
G. HIV  
H. AIDS  
I. Seizures  
J. Sickle Cell Disease  
K. Asthma  
L. Other serious diseases?

(IF OTHER diseases, what are they?)

41) Have you ever been diagnosed with a mental health or psychiatric disorder? No  Yes

42) (IF YES) What was the psychiatric disorder(s)?
43) In the past 7 days, how often have you experienced the following:

Key: less than 1 day=0; 1-2 days=1; 3-4 days=2; 5-7 days=3

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
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<tbody>
<tr>
<td>A. Felt hopeless about the future</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>B. Felt blue</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>C. Felt alone even when with others</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>D Felt something was wrong with your mind</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>E Felt tense or keyed up</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>F Felt fearful</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>G Felt pain due to drug or alcohol withdrawal or drug/alcohol hunger</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

44) Please add any comments you have about this questionnaire or your experiences with drugs and pain.

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
References


May 24, 2005


Hewitt D, McDonald MDS patients. *Pain*, 70, pp. 117–123


Van Huet H, Innes E & Whiteford G. (2009). Living and doing with chronic pain:
narratives of pain program participants. *Disability Rehabilitation*, 1(24):2031-40


CHAPTER 5

Dissertation Summary: The pain and Health Characteristics of Skin Injecting Opioid Users

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Dissertation Summary: The Pain and Health Characteristics of Skin Injecting Opioid Users

The review of the literature surrounding pain and health in opioid-addicted and dependent people identified an emerging but incomplete understanding of the relationship between ongoing opioid use and chronic pain. Some of the gaps in the literature included the pain experience of skin-injecting opioid users as opposed to pain in patients receiving methadone maintenance for opioid detoxification. In addition, the existing literature did not describe the chronic pain experience of patients actively seeking care for an acute injury or illness but focused instead on the experience of community dwelling opioid users. It was felt that, in order to understand the pain and health characteristics of active skin injecting opioid users with acute pain, research should be done in the hospital setting. For this reason, data were collected on skin injecting opioid users with active acute pain who were simultaneously seeking hospital care for that injury (i.e., an abscess). The study did use previous research that had identified high rates of chronic pain and mental and physical illness within a population of methadone maintained subjects (Barry, Beitel, Joshi & Schottenfeld, 2009; Jamison, Kauffman, & Katz, 2000; Rosenblum, Herman & Chunki et al., 2003; Sheu, Lussie & Rosenblum et al., 2008). The current study was an extension of that work to current opioid users. The data collected on 91 patients seeking hospital care for acute pain related to skin abscesses were used to better understand the pain and health characteristics of this population and to validate the findings of previous work on similar populations.
The sample was a highly defined group of active skin injecting opioid users, all of whom had the same complaint of acute pain related to a skin abscess. Because of this, we were able to ask important questions relating to their pain and health experiences without the confounding issues related to variations of pain induced by differences in injury or illness. The questionnaire for the current study was adapted in consultation with the authors from a previous study (Rosenblum et al., 2003) which had examined a similar sample, giving us confidence in the validity and usability of our instrument. Approval for this study was obtained from the University of California, San Francisco’s Committee on Human Research (CHR#H10-03203).

The study results demonstrated that skin-injecting opioid users seeking care for the pain and injury related to acute abscess were often uninsured Caucasian men in their 40’s who had been using opioids for an average of 20 years and were currently severely physically dependent. In addition to their intense acute abscess pain [6.58 (2.8) on NRS 0-10 scale], 73% reported suffering with chronic pain, and 67% had experienced highly interfering moderate to severe chronic pain within the last week. They also had exceptionally high rates of physical and mental illness, including Hepatitis C (73%), diagnosed depression (26%), and HIV (15%). Logistic regression models did not find any demographic, health, or pain treatment variables to be predictive of a person being more likely to report moderate to severe chronic pain.

Although all subjects had recently injected opioids into their skin, 59% reported active participation in methadone maintenance, with a strong trend
toward significantly worse chronic pain in those using more methadone for a longer period of time. Given the physiologic literature linking a heightened pain experience to chronic opioid exposure, as described in chapter 2, further research is needed to understand the unique role methadone may play in chronic pain prevalence. Also, it remains unclear why subjects chose to use illicit opioids to treat their chronic pain when they report that legal prescription drugs such as oxycontin to be at least as effective, and, theoretically, do not induce the same order of physical harm as skin injecting. Finally, given the high prevalence of chronic pain in this sample, additional research is needed to identify the barriers to adequate pain assessment and management within the population of skin injecting opioid users.

Overall, this research demonstrated that skin injecting opioid users seeking hospital care for painful acute abscesses have very high rates of moderate to severe chronic pain, as well as high rates of mental and physical illness. Many questions remain as to why this is true, and there are implications for practice and further research.

First, skin-injecting opioid users, such as those reported on here, should be assessed for the presence of chronic pain. Second, further research is needed to determine if chronic pain is an influence on these patients’ continued skin-injecting drug use. Finally, because ongoing opioid injecting is associated with high personal and social costs, future research should determine if the implementation of effective evidenced-based pain management protocols within this population could decrease pain and simultaneously decrease the harm
related to skin injecting opioid users.
References


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