Pain Medicine

Pain Medicine 2010; 11: 1092–1098
Wiley Periodicals, Inc.

Review Article

Opioids, Pain, the Brain, and Hyperkatifeia: A Framework for the Rational Use of Opioids for Pain

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Abstract

Objective. Opioids have relieved more human suffering than any other medication, but their use is still fraught with significant concerns of misuse, abuse, and addiction. This theoretical article explores the hypothesis that opioid misuse in the context of pain management produces a hypersensitivity to emotional distress, termed *hyperkatifeia*.

Results. In the misuse of opioids, neural substrates that mediate positive emotional states (brain reward systems) are compromised, and substrates mediating negative emotional states (brain stress systems) are enhanced. A reflection and early marker of such a nonhomeostatic state may be the development of opioid-induced hyperkatifeia, defined as the increased intensity of the constellation of negative emotional/motivational symptoms and signs observed during withdrawal from drugs of abuse (derived from the Greek "katifeia" for dejection or negative emotional state) and is most likely to occur in subjects in whom the opioid produces a break with homeostasis and less likely to occur when the opioid is restoring homeostasis, such as in effective pain treatment. When the opioid appropriately relieves pain, opponent processes are not engaged. However, if the opioid is administered in excess of need because of overdose, pharmacokinetic variables, or treating an individual without pain, then the body will react to that perturbation by engaging opponent processes in the domains of both pain (hyperalgesia) and negative emotional states (hyperkatifeia).

Conclusions. Repeated engagement of opponent processes without time for the brain's emotional systems to reestablish homeostasis will further drive changes in emotional processes that may produce opioid abuse or addiction, particularly in individuals with genetic or environmental vulnerability.

Key Words. Opioids; Pain; Addiction; Hyperalgesia; Hyperkatifeia; Emotion

Introduction

Over the past 100 years, the legitimate medical use of opioids to relieve pain and suffering has been strongly affected by political forces and prevailing opinions. A century ago, opioid use was not restricted. In fact, opioids were included in many nonprescription remedies. Subsequently, opioid use was greatly curtailed, both legally and by changes in medical practice. This was partly driven by the realization that opioids were potent drugs with life-threatening side effects and the potential for recreational abuse and addiction. Widespread misconceptions, such as the fear that prolonged opioid use would turn pain patients into drug addicts, also evolved because of confusion between the phenomena of tolerance, dependence, and addiction to drugs. Tolerance (i.e., decreased effect with prolonged dosing) and dependence (i.e., withdrawal syndrome occurring when chronic drug administration is stopped) are very different conditions than addiction (i.e., compulsive and uncontrollable use of a drug).

Over the past 20 years, the clinical use of opioids has become widespread. High-potency, extended-release,

and immediate-release opioid formulations were proven effective for the treatment of a variety of chronic pain conditions in addition to long-standing roles in the treatment of severe acute pain and cancer pain. Despite the obvious benefits of opioid administration and widespread rational guidelines for their appropriate use, these formulations were often inappropriately marketed and prescribed, thus partially precipitating the current epidemic of recreational opioid use and addiction. This led to a major concern about the addiction liability resulting from overdosing (or underdosing) pain patients and gross overreaction by regulatory agencies. In the United States, physicians prescribing opioids for pain relief and, in particular, nonmalignant pain, are being sued in alarming numbers for pain undertreatment, overtreatment, or even murder [1]. These factors threaten to deter physicians from the many legitimate and compassionate uses of opioids.

The scientific literature on abuse liability during opioid therapy for pain treatment is limited, and definitions of medication abuse, dependence, and addiction have been confusing (e.g., the constant misconception that the presence of physical withdrawal symptoms [dependence] constitutes a state of addiction). Estimates of nontherapeutic opioid use by pain patients ranged from 3.2% to 18.9%, similar to the prevalence of alcohol and drug addiction in the general population [2]. Nevertheless, a certain percentage of chronic pain patients, and definitely patients with a substance abuse history, will remain vulnerable to addiction [3]. The identification of environmental and physiological factors that convey this vulnerability is critical. A theoretical framework of exactly what constitutes addiction may provide insights into these factors.

Drug addiction is a chronic relapsing disorder characterized by: 1) compulsion to seek and take the drug; 2) loss of control in limiting intake; and 3) the emergence of a negative emotional state (e.g., dysphoria, anxiety, irritability) when access to the drug is prevented (also defined as dependence) [4]. Drug addiction can be conceptualized as a disorder that progresses from impulsive drug use to uncontrollable, compulsive drug use in a cycle comprising three stages: *preoccupation/anticipation*, *binge/intoxication*, and *withdrawal/negative affect* [5]. As opioid addiction develops, a compulsive pattern of drug taking evolves, characterized by intoxication via the intravenous or inhaled routes for heroin and oral or intravenous routes for opioid analgesics, and the development of tolerance to this intoxication, with a resulting escalation in drug intake. Escalated drug use enhances the negative emotional symptoms of abstinence, resulting in profound dysphoria, irritability, sleep disturbances, anxiety, emotional pain, and an intense preoccupation with obtaining opioids (i.e., craving). These symptoms, in contrast to the somatic symptoms of withdrawal, are hypothesized to be a key motivational component of addiction [4]. Craving often precedes somatic signs of withdrawal and is associated not only with obtaining the drug and anticipation of its rewarding effects, but also with anticipation of the aversive effects of withdrawal. In this case, the drug must be taken to avoid the severe dysphoria, discomfort, and psychic stress experienced during withdrawal and abstinence. The framework proposed here encompasses the classic "4 Cs" of addiction: compulsive use, loss of control, craving, and continued use despite harm.

Dependence has multiple meanings. Particularly confusing has been the use of the term "physical dependence," referring to physiological adaptations that occur with repeated drug exposure. Upon discontinuation of drug use, these adaptations result in withdrawal symptoms that can be mild (such as fatigue with cocaine) or severe (such as a flu-like state with opioids or hyperthermia and seizures with alcohol). These changes are distinct from adaptations in brain reward systems that result in addiction. Thus, an individual can become physically dependent on a drug without being addicted and, conversely, can be addicted without suffering from physical dependence. Unfortunately, emphasizing the distinction between physical dependence and addiction has diminished attention on the role that motivational aspects of opioid withdrawal play in the genesis of the addicted state. Clearly, the negative emotional effects of drug withdrawal (sometimes incorrectly, in the authors' opinion, described as "psychological dependence") are a key element of addiction and may be the key to understanding the current conundrum associated with the use, misuse, and underuse of therapeutic opioid drugs.

One homeostatic hypothesis to explain the emotional dysregulation that develops during withdrawal from drugs of abuse is the "opponent process" theory of changes caused by pleasurable or aversive stimuli [6]. Opponent process theory posits that a positive emotional stimulus (*a-process*) is followed by a subsequent negative emotional state (*b-process*). Over time, the *b-process* gets larger and larger, contributing to the reduction in the outward manifestations of the *a-process*. Indeed, with chronic drug administration, negative emotional states during abstinence worsen over time. The worsening of the negative emotional states exceeds the capacity of the reward system to maintain homeostasis and leads to changes in the reward system which has been termed *allostasis*.

The concept of allostasis proposes that an individual maintains functional stability by defending a set point outside the homeostatic range. These adjustments lead to an *allostatic state*, or a chronic deviation of compensatory systems to a range outside of normal (homeostatic) parameters (in this case, ever-increasing emotional distress leading to escalation in dysphoria and aberrant behavior). The ultimate cost to the individual of this instability is known as *allostatic load* (physiological changes that lead to pathology such as addiction) [7]. How could this theory be applied to the concept of opioid-induced changes leading to excessive or uncontrolled drug use in chronic pain patients, and what are the appropriate markers for allostatic-like changes? One formulation based on the opponent process construct could be that opioid-induced hyperalgesia represents a homeostatic

resetting of analgesic systems. The administration of an opioid under conditions in which no need for pain relief exists would then be followed by the opposing response of hyperalgesia during drug withdrawal. Such hyperalgesia involves key elements of neuroadaptation within the brain *N*-methyl-D-aspartate receptor systems [8].

Before carrying this analysis further, one must consider whether opioid-induced hyperalgesia is a clinically relevant phenomenon. There has been a resurgence of interest in the concept, first described over 100 years ago [9], that opioid use can induce a hyperalgesic state [10,11]. Hyperalgesia after opioid administration has also been postulated to be an acute sign of opioid withdrawal [9,12], a hypothesis compatible with the opponent process theory. A review of opioid-induced hyperalgesia summarized findings from 180 studies [12]. Animal studies showed that the administration of opioids may increase the sensitivity to pain and potentially aggravate preexisting pain. From human studies, the authors concluded that opioid-induced hyperalgesia could occur when patients received high doses of opioids for surgical procedures or in patients with a history of high-dose opioid treatment or a prior history of addiction [12]. These findings suggest that chronic or high-dose opioid treatment might be an important contributing factor to the perception of pain in the clinical setting. Yet hyperalgesia is unlikely per se to drive the "switch" to addiction in the small percentage of opioid-treated patients who are vulnerable to addiction.

One hypothesis to explain the vulnerability to addiction in opioid-treated patients is that chronic pain is well known to cause both emotional distress and negative emotional states. An allostatic emotional formulation of the concept of opioid-induced hyperalgesia suggests that a potential *escalating* emotional distress ("emotional pain") can parallel opioid hyperalgesia during opioid withdrawal that is much different in character and extends far beyond the physical pain that initiated treatment. This emotional distress is what we define as hyperkatifeia. *Hyperkatifeia* (derived from the Greek word *katifeia* for dejection, sadness, or negative emotional state) is defined as the increased intensity of negative emotional/motivational symptoms and signs observed during withdrawal from abused drugs. The term "hyperkatifeia" refers to the increases in emotional distress and emotional pain experienced by addicts during abstinence. Hyperkatifeia reflects a pathological change in the emotional "set point" of addicted individuals and is analogous to the term *hyperalgesia*. Although severe negative emotional states, including athymia, anhedonia, and anergy, characterize a variety of psychiatric disorders, including major depressive episodes and schizophrenia, hyperkatifeia is hypothesized to represent more elements such as dysphoria, irritability, alexithymia, or simply symptoms often described as ill at ease, uncomfortable within one's own skin, or simply not hedonically normal, symptoms historically difficult to define. In short, hyperkatifeia is hypothesized to reflect a hypersensitivity to emotional distress, similar to how hyperalgesia is a hypersensitivity to pain.

The neural substrates underlying allostatic emotional changes seen in addiction include decreases in reward function mediated by neurochemical changes in the ventral striatum (loss of function of dopamine and opioid peptide systems) and increases in brain stress system function meditated by neurochemical changes in the extended amygdala (recruitment of corticotropin-releasing factor, dynorphin, and norepinephrine) [4,13]. Could a link exist between the neural mechanisms responsible for hyperkatifeia and opioid-induced hyperalgesia? Strong evidence suggests that the neural substrates of stress system neuroadaptations associated with addiction may overlap with substrates of emotional aspects of pain processing in areas such as the amygdala [13] (Figure 1). For example, the spino (trigemino)-ponto-amygdaloid pathway, which projects from the dorsal horn of the spinal cord to the mesencephalic parabrachial area and then to the central nucleus of the amygdala, has been implicated in processing emotional components of pain perception [14,15]. Pain-responsive neurons are also abundant in the lateral part of the central nucleus of the amygdala [16], an area that may also be responsible for negative emotional responses to abused drugs [17,18].

What might predispose these patients to hyperkatifeia? An allostatic view would suggest that opioid-induced hyperkatifeia would be much less likely to occur when the opioid is restoring homeostasis by relieving pain. In this framework, the presence of pain would minimize activation of the opponent process (hyperalgesia and, concomitantly, hyperkatifeia), and long-term pain control could be achieved with stable doses of analgesics. In a recent open label study of 231 chronic, nonmalignant pain patients followed prospectively for up to 3 years, pain intensity ratings decreased significantly after opioid treatment and remained stable or improved throughout the study. After an appropriate opioid dose was established, dose escalation was minimal and gradual [19]. Although few studies have evaluated long-term chronic opioid treatment in patients with nonmalignant pain, this example demonstrates that with the determination of proper opioid doses, stable, long-term pain relief can be obtained by using opioids in chronic pain patients.

Based on this conceptual framework, we propose the following hypothesis. A negative emotional state or hyperkatifeia to opioids is most likely to occur when the opioid produces a break with homeostasis. Hyperalgesia, in fact, is then just a physical pain-related phenomenon that may precede or parallel the more emotional state of hyperkatifeia. Hyperalgesia/hyperkatifeia is much less likely to occur when the opioid is restoring homeostasis, such as during pain treatment. However, if excessive opioids are administered, either because of overdosing, rapid escalation (overshooting), pharmacokinetic variables, or genetic sensitivity, then the body will react to that perturbation with the engagement of opponent processes. Repeated engagement of opponent processes without time for the system to reestablish homeostasis will engage the allostatic mechanisms described previously. Thus,

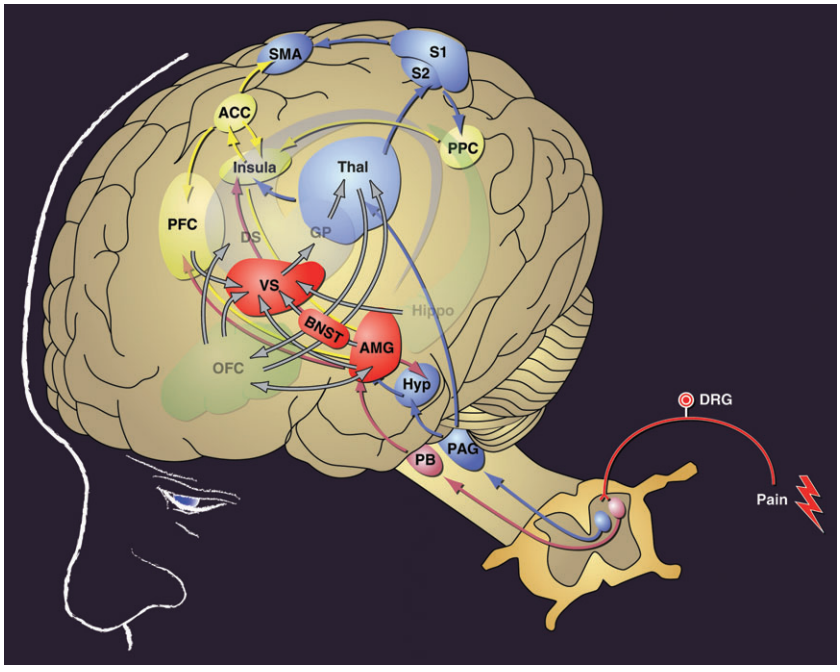

Figure 1 Pathways for the supraspinal processing of pain superimposed on key elements of addiction circuitry implicated in negative emotional states. Blue structures are involved in the "fast" processing of pain via the spinothalamic tract and arrive indirectly at the amygdala. Pink structures are involved in the "fast" processing of pain via the spinal-parabrachial-amygdala pathway and arrive directly at the amygdala. Yellow structures are involved in the "slower" cognitive processing of pain. Addiction circuitry is composed of structures involved in the three stages of the addiction cycle: *binge/intoxication* (ventral striatum, dorsal striatum, thalamus), *withdrawal/negative affect* (ventral striatum, bed nucleus of the stria terminalis, central nucleus of the amygdala; red structures), *preoccupation/anticipation* (prefrontal cortex, orbitofrontal cortex, hippocampus). Notice significant overlap of the supraspinal processing of pain and addiction in the amygdala. Modified with permission from [25] and [26]. ACC = anterior cingulate cortex; AMG = amygdala; BNST = bed nucleus of the stria terminalis; DRG = dorsal root ganglion; DS = dorsal striatum; GP = globus pallidus; Hippo = hippocampus; Hyp = hypothalamus; Insula = insular cortex; OFC = orbitofrontal cortex; PAG = periaqueductal grey; PB = parabrachial nucleus; PFC = prefrontal cortex; PPC = posterior parietal cortex; S1, S2 = somatosensory cortex; SMA = supplementary motor area; Thal = thalamus; VS = ventral striatum.

opioid-induced hyperalgesia could serve as an indicator that allostatic processes (hyperkatifeia) have occurred.

In summary, excessive opioid use is hypothesized to disrupt the homeostatic regulation of emotional behavior, compromising neural substrates mediating positive emotional (reward) states and augmenting neural substrates mediating negative emotional states. Such a framework suggests that any indications of opioid-induced hyperalgesia has two extremely important clinical implications: 1) the opioid has exceeded the amount that is effective for pain control; and 2) susceptible individuals are at risk for developing hyperkatifeia, the unstable emotional and behavioral state underlying addiction. This hypothesis is presented schematically in Figure 2.

From the previous discussion, either over- or undertreatment of pain with opioids could theoretically be problematic. Most recent attention has focused on overmedication with potent, long-lasting opioids and the perceived risks of addiction and hyperalgesia. However, excesses of other opioid actions can have equally deleterious, if not more serious, consequences. For example, respiratory depression can be life-threatening, and tolerance to this effect may not develop at the same rate as analgesic tolerance. These actions have been comprehensively reviewed elsewhere [20]. Undertreatment of pain can also have severe detrimental consequences. *Pseudoaddiction* is a term used to describe a syndrome of addiction-like behaviors related to undertreated pain [21]. These behaviors represent an attempt on the part of the patient to obtain

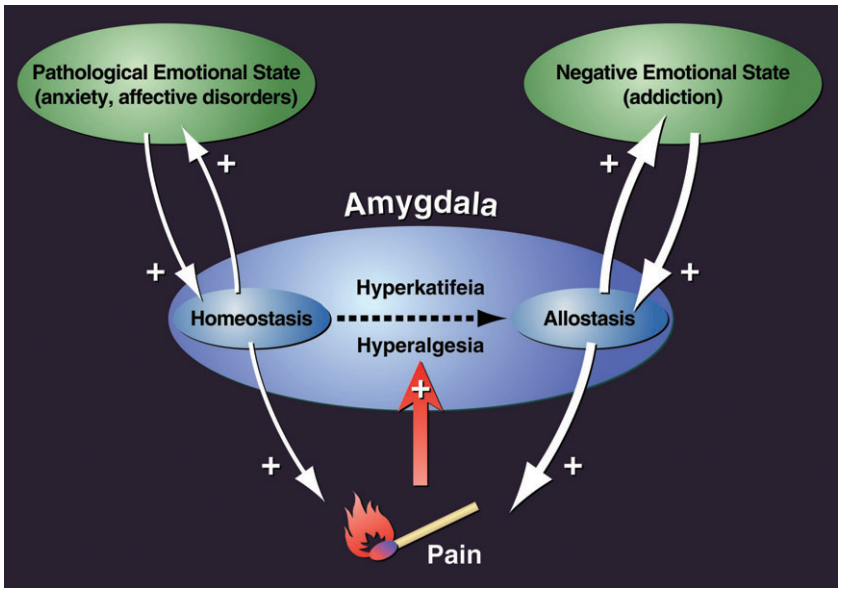

Figure 2 Schematic diagram summarizing the hypothesized relationship between addiction and pain. Pathological emotional states are known to exacerbate pain. We hypothesize that, in parallel, the negative emotional state of drug withdrawal and protracted abstinence can also exacerbate pain; conversely, pain can exacerbate both pathological emotional states and addiction. Hyperalgesia, an increased sensitivity to pain, caused by opioid treatment could indicate the parallel development of hyperkatifeia, or increased sensitivity to negative emotions. Hypothetically, the converse could occur in addiction (hyperkatifeia reflecting underlying hyperalgesia). The conceptual framework for such changes involves a break from emotional homeostasis termed allostasis (stability through change) in neurobiological mechanisms in the extended amygdala.

adequate pain relief. Patients may seem inappropriately anxious for medication because of inadequate analgesia rather than from a craving for nonanalgesic effects. Once pain is controlled, the symptoms of pseudoaddiction resolve [21]. However, when confronted with this behavior, physicians tend to threaten termination of treatment instead of querying the patient about the effectiveness of the medication. Undertreated pain could also have severe physiological consequences, including depression, anxiety, sleep disturbances, hypertension, immune suppression, and more rapid disease progression [20].

Given the facts that chronic pain is epidemic and opioids are still a frontline treatment, severe restrictions imposed on opioid use will lead to unnecessary pain and suffering for millions of patients. Until new classes of analgesic compounds that effectively treat severe, chronic pain without undesirable side effects are developed, a rational approach to opioid use is needed to avoid the extremes of opioid underuse and overuse that have characterized recent trends in medical practice. The theoretical foundation we have outlined here suggests several obvious procedures for minimizing the risks of hyperalgesia, abuse, and other undesirable complications of chronic opioid use. First and foremost is careful patient evaluation. Individuals with a history of drug abuse require specialized treatment plans, optimally with monitoring (urine toxicology screening) and guidance by addiction medicine specialists. Individuals with a history of severe emotional disorders would also likely benefit from psychiatric/psychologic input.

Second, pharmacokinetic and pharmacodynamic variables must match the condition being treated. Theoretically, the development of long-acting preparations and new deterrents (e.g., tamper-resistant packaging and formulations) that permit steady-state pharmacokinetics to be achieved should attenuate the development of neuroadaptive mechanisms that ultimately go awry, and as a result attenuate the potential for abuse. Carefully controlled studies investigating pharmacokinetic and pharmacodynamic properties of long-acting opioid preparations in appropriate patient populations are needed to confirm this hypothesis. Indeed, support for this hypothesis can be found from the observation that long-acting opioids are well tolerated if titration is performed gradually (thus avoiding hyperkatifeia) [22].

The use of opioid-sparing adjuvants has also been recommended to minimize opioid use and, concomitantly, undesirable side effects. The use of a stepwise approach to analgesic administration, beginning with less potent,

non-opioid analgesics and progressing to strong opioids (the "analgesic ladder") [23] has been advocated as a general approach to pain treatment. This makes good theoretical sense, but currently available adjuvant drugs are not very potent. Thus, in patients presenting with severe persistent pain, strict adherence to these guidelines could lead to undertreatment and prolonged suffering. We propose that adjuvants should be used as the name implies—coadministered with an adequate dose of opioids or another first-line analgesic drug. Although adjuvants are generally inadequate as primary analgesics, they could possibly reduce dose escalation, the development of tolerance, and hyperalgesia due to tolerance, withdrawal, or allostatic changes. Supporting this hypothesis, the anticonvulsant gabapentin can reduce hyperalgesia induced by short-term use of fentanyl in rats [24].

In conclusion, chronic pain is an enormous, ever-increasing clinical problem with a dramatic impact on both individuals and society. Opioids remain a first-line drug for the treatment of severe, chronic pain. Opioid-induced hyperalgesia is likely to be a consequence of opioid use in excess of the amount required for pain treatment and may reflect underlying neuroadaptive processes (hyperkatifeia) in brain reward systems that indicate a parallel transition to addiction vulnerability. The guidelines presented previously may reduce the potential risk of hyperkatifeia and the increased vulnerability to addiction. Substantial evidence suggests that opioids can indeed be used rationally and effectively to treat select patients with severe chronic pain. If the use of opioids is eliminated or greatly restricted, then many patients will once again suffer needlessly.

Acknowledgments

We thank Stephen P. Koob for suggesting the word "katifeia" to describe a negative emotional state. The authors also wish to thank Michael Arends for his assistance with manuscript preparation. GFK and HBG were supported by National Institutes of Health grants DA04043 and DA15146 from the National Institute on Drug Abuse and AA16157 from the National Institute on Alcohol Abuse and Alcoholism. GFK was also supported by the Pearson Center for Alcoholism and Addiction Research. GFK and JS are current consultants for Casa Palmera.

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