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A Clinical Correlation Made Between Opioid-induced Hyperalgesia and Hyperkatifeia with Brain Alterations Induced by Long-term Prescription Opioid Use

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ABSTRACT

The goal of this article is to establish a correlation between the clinical manifestations of opioid-induced hyperalgesia and hyperkatifeia with the morphological and functional connectivity changes seen in the human brain that can be caused by long-term prescription opioid use. This will be accomplished by reviewing the imaging results found in a small but unique study that demonstrated morphological and functional connectivity changes in long-term prescription opioid users. The primary regions that were affected were the amygdala and the white matter tracts connected to it. Therefore, by reviewing the known functions of the amygdala and the white matter tracts- uncinate fasciculus, stria terminalis, and ventral amygdalofugal- and then doing a comparative analysis between the signs and symptoms of the clinical syndromes of opioid-induced hyperalgesia and hyperkatifeia a very obvious correlation has been recognized.

Keywords: *amygdala, POATS, opioid-induced neuron atrophy, intracellular messenger phosphokinase C, and NMDA receptors.*

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1. INTRODUCTION

There has been an enormous increase in the long-term use of prescription opioids over the past decade and a half. The use of opioids for pain management can cause several problematic scenarios to the medical provider, particularly in the primary and urgent care setting. For example, there has been a significant rise in the number of physicians being sued for pain under-treatment, overtreatment, and in some cases charged for murder [1]. Despite all of this, studies involving the long-term health consequences that are incurred by patients who are long-term users of prescription opioids are deficient in the medical literature. Although it has been known for some time that the use of short-acting and long-acting opioids alter physiological and behavioral functions [2], the majority of existing studies have been done on heroin and methadone users.

The most frequently prescribed opioids are hydrocodone [3] and oxycodone [4]. As previously mentioned only a handful of studies have been completed on the long-term use of those two prescription opioids. This article will discuss a recent study done on patients who have used long-term prescription opioids and their effects on the brain morphology and functional connectivity. Then a correlation to clinical phenomenon e.g. opioid-induced hyperalgesia and hyperkatifeia will be made. The goal will be to provide the clinician with more knowledge about the potential long-term harm caused by prescription opioids.

2. UNDERSTANDING OPIOID TOLERANCE AND DEPENDENCE

Opioids have been extremely effective in managing pain for hundreds of years. This is primarily due to their potent ability to alter pain perception. However, opioids can have potential life-threatening side effects and can eventually decrease a patient's quality of life. Thus identifying dependence is of the upmost importance when participating in the treatment of this patient population. The DSM IV-TR criteria for tolerance and dependence is listed on Table I.

Table I: *The DSM IV-TR Definition of Tolerance and Dependence.*

- **Tolerance- is the decrease in effectiveness of a drug with repeated administration. Due to the physiological process of tolerance the patient usually requires a larger dose to obtain the desired effect.**
- **Dependence- is a central nervous system disorder with physical and psychological components that are characterized by neurobiological changes that lead to the compulsive consumption of the drug despite harmful outcomes. The key component of opioid dependence is the occurrence of withdrawal symptoms when the opioid dose is decreased or discontinued.**

3. UNDERSTANDING OPIOID WITHDRAWAL

The diagnosis of opioid withdrawal (based on the DSM IV-TR criteria) is made when there are at least three or more of the nine symptoms listed on Table II. In addition to the nine symptoms listed, the patient may exhibit elevated blood pressure, respirations, and pulse while going through the process of withdrawal. Psychiatric symptoms can include agitation and emotional liability. These withdrawal symptoms must cause significant distress or impairment in occupational, social, or other important areas of functioning. Finally, these symptoms must not be due to any underlying medical condition or psychiatric disorder.

Hyperalgesia is a clinical symptom in where there is an increased sensitivity to pain or the presence of pain levels that are not proportionate to the injury or stage of recovery. This can be defined medically as a state of paradoxical increase in nociceptive sensitivity after opioid treatment is initiated. This condition was first reported with the use of opioids in the medical literature in 1880 [5]. Currently, there are a large number of studies that confirm opioid-induced hyperalgesia (OIH) as a clinical syndrome in opiate users [6].

Table II: *Symptoms of Opioid Withdrawal.*

• **dysphoric mood**	• **mydriasis, piloerection, or sweating**	• **yawning**
• **nausea or vomiting**	• **diarrhea**	• **fever**
• **myalgias**	• **lacrimation or rhinorrhea**	• **insomnia**
These symptoms must develop after either one of the following:		
• **Cessation or reduction of opioid use that has been heavy and prolonged- typically several weeks or longer**		
• **Administration of an opioid antagonist (e.g. naloxone) after a prolonged period of opioid use**		

4. OIH

Prolonged levels of administered opioids cause the cells in the body that produce endogenous opioid peptides to decrease the production of those peptides. Endogenous opioid peptides are endorphins, enkephalins, and dynorphins. They act as neurotransmitters in the CNS and are produced by the pituitary gland and hypothalamus. These endogenous opioid peptides are released during exercise, excitement, pain, and orgasm. It is believed that because the endogenous opioids are involved in pain perception, that when their production is decreased (in this case due to the presence of a synthetic opioids), then the patient becomes more sensitive to pain.

There are other physiological mechanisms by which OIH takes place [7]. Initially opioids stimulate mu-opioid receptors (as well as others e.g. kappa) which hyperpolarize neurons by activating inward rectifying potassium channels (this is represented electrochemically by the inward flow of a positive charge into a neuron). These molecular actions manifest the analgesic effect by providing a decrease in anticipatory anxiety associated with emotional or physical pain. Consequently, there is an alteration of pain perception. However, the ongoing stimulation of the mu-opioid receptors can cause hyperalgesic effects by two pathways. The first pathway is the prolonged mu-opioid receptor activation causes the upregulation of intracellular messenger phosphokinase C, which enhances neuron excitability- this is the clinical equivalent to the hyperalgesic effect. The second pathway causes the neuroadaptation of the N-methyl-D-aspartate (NMDA) receptor system.

NMDA receptors are activated during pain that involves peripheral tissues (peripheral

NMDA receptors) and nerve injury (central NMDA receptors). Current research suggests that hyperalgesia perception is perpetuated by the central NMDA receptor systems [8]. This takes place in the following four phases. First, initial changes take place at the peripheral NMDA receptors after there is trauma and secondary inflammation, which leads to sensitization of these receptors, which is known as *peripheral sensitization*. Second, the central NMDA receptors begin to receive an increase in dorsal horn excitability in response to the facilitated sensory input from the sensitized peripheral NMDA receptors. Third, it is during this increased stimulation that the central NMDA receptors enter into a state of low-threshold afferent for pain perception known as *central sensitization*. Fourth, it is in this sensitized state that low-intensity stimulus will generate an action potential that is augmented in amplitude and duration for pain perception. This results in the manifestation of hyperalgesia.

These two pathways contribute to enhanced neuronal excitability which results in the hyperalgesic effect. At this point we have addressed the effect of opioids on three physiological pathways involved in OIH: 1) alterations in the endogenous opioids, 2) mu-receptor dependent increases in intracellular messenger phosphokinase C and 3) abnormal functioning of NMDA receptors. Therefore, in OIH three potential results take place [9]:

- Increased sensitivity to pain
- An aggravation of preexisting pain
- The expression of novel pain symptoms

5. HYPERKATIFEIA

Hyperkatifeia (*katifeia* is Greek for dejection or sadness) is condition in where a patient using opioids displays hypersensitivity to negative emotional states and/or increased intensity of emotional distress[10]. Symptoms of a negative emotional state are listed on Table III. It is believed that a potential escalating state of emotional distress in hyperkatifeia can parallel OIH during withdrawal. The symptoms of hyperkatifeia are listed on Table IV.

Hyperkatifeia is now recognized as a clinical syndrome that can be manifested during the process of opioid withdrawal. The hypersensitivity to emotional distress that is seen in hyperkatifeia is similar to hypersensitivity to pain that is seen in hyperalgesia. Therefore, there is a change in the "set point" of these patients' threshold related to the response to pain and emotional distress.

At this point it is apparent that OIH and hyperkatifeia are related somehow to the long-term use of opioids. Are there neurobiological mechanisms that can account for this? In the next section we will examine changes in the human brain that were caused by the long-term use of prescribed opioids and then identify any clinical correlation to OIH and hyperkatifeia.

Table III: *Symptoms of the Negative Emotional State.*

• **Athymia- this is the absence of feeling and emotion.**
• **Anhedonia- this is the absence of pleasure or happiness as well as the withdrawal from experiences that would normally elicit these responses. This is often associated with depression.**
• **Anergy- this is the absence of energy or activity with no underlying metabolic explanation.**

Table IV: *Symptoms of Hyperkatifeia*

• **Dysphoria- this is expressing feelings characterized by depression and anguish.**
• **Irritability- this is the display of abnormal excitability or sensitivity.**
• **Alexithymia- this is the inability to recognize or explain emotions.**
• **The sensation of being uncomfortable in one's skin.**

6. NEURAL ATROPHY AND BRAIN ABNORMALITIES INDUCED BY LONG-TERM PRESCRIPTION OPIOID USE

A recent multi-site study, called the *Prescription Opioid Addiction Treatment Study* (POATS), which was headed by the P.A.I.N. Group at Harvard Medical School McLean Hospital found several structural and functional connectivity abnormalities in patients in a controlled cohort taking prescription opioids [11]. These results were analyzed using structural magnetic resonance imaging, diffusion tensor imaging, and resting-state functional magnetic resonance imaging.

In this study 133 individuals in the original group of subject patients met the criteria for prescription opioid dependence. This group was screened for alcohol and other drug dependence, comorbid psychiatric conditions, neurological diseases, and chronic pain diagnosis. The screening implemented yielded 85 patients that were enrolled into the POATS. From these patients 10 non-smokers were selected that met the DSM (4-TR) criteria for opioid dependence and were enrolled for the imaging phase of the study.

The patient age range was 18-48 years old, 7 males and 3 females, and 9 white and 1 Hispanic. Most of the patients were taking a combination of oxycodone and hydrocodone/morphine/tramadol/methylmorphine/buprenorphine, with only 3 of the patients taking solely oxycodone. The individuals in this final group had been using prescribed opioids for a period ranging from 9 months to 8 years.

The imaging results showed:

- Bilateral volumetric loss in the amygdala

- Decreased anisotropy (this means being directionally dependent as opposed to isotropic) in axonal pathways specific to the subdivisions of the amygdala- stria terminalis, ventral amygdalofugal pathway, and uncinate fasciculus.
- Decrease in functional connectivity in the anterior insula, nucleus accumbens, and amygdala subdivisions.

The imaging results illustrated a decrease in functional anisotropy in these patients, which was demonstrated in three specific white matter tracts. The subject specific functional anisotropy values were most notable in the uncinate fasciculus, which connects the amygdala to the prefrontal cortex. However, there was no relationship to the decrease in functional anisotropy to the duration of opioid dependence.

Significant decreases in resting-state functional connectivity in the centromedial, superficial and basolateral subdivisions of the amygdala were seen in these patients. More specifically the basolateral amygdala showed a loss of functional connectivity to certain brain regions e.g. the nucleus accumbens. There is also a convincing relationship between the decreased functional connectivity of the basolateral amygdala to the duration of years of prescription opioid use.

There are some obvious weaknesses in the POATS. Obviously the very small number of subjects who qualified for the study is one element that stands out, but as mentioned in the introduction there are not many studies that focus on solely prescription opioid dependence, thus the POATS is one of the first studies of its kind. Secondly, there was an inability to distinguish pre-existing versus the acquired nature of the observed alterations as baseline imaging was not available prior to the study. Despite these two limitations these findings are still significant and necessitate further research as well as more caution when prescribing opioids for prolonged periods of time.

7. THE FUNCTIONS OF THE AMYGDALA AND THE THREE CONNECTING WHITE MATTER TRACTS

The main neurologic changes seen in the POATS were in the amygdala and the three connecting white matter tracts. Therefore, in order to establish a correlation to the symptoms of OIH and hyperkatifeia a survey of the known functions of these brain regions must be conducted. The amygdala is part of the limbic system and has eight known functions [12]:

1) **Autonomic effects:** specifically involved in heart rate, respiration, blood pressure, and gastric motility. Please note that heart rate, respiration, and blood pressure can be abnormally elevated during opioid withdrawal.

2) **Orienting process:** involvement in the responsiveness to novel events and visual environment related to reward response.
3) **Emotional behavior:** lesions in the corticomedial nuclear group produce fear, sadness, anxiety, aphagia, and a decrease in emotional tone. Stimulation of this same region produces defensive and aggressive reactions. The basolateral nuclear group of the amygdala is associated with fear and flight response when stimulated. However, lesions in this area produce hyperphagia, happiness, and pleasure reactions.
4) **Facial expression:** the amygdala integrates other brain regions (extrastriate visual cortex, fusiform and temporal gyri) to construct the representation of faces and the perception of the face to the retrieval of knowledge about its emotional and social meaning with significance to negatively valenced emotions- anger, fear, and sadness.
5) **Arousal response:** stimulation of basolateral nuclear group produces an arousal response, which is separate from the reticular activating system. Reciprocally, the stimulation of corticomedial nuclear group of the amygdala causes decrease in arousal and result in sleepiness. In addition, ablation of the amygdala in general results in hypoactivity, sluggishness, avoidance of social interactions, and a tendency toward social isolation.
6) **Sexual activity:** the amygdala is associated with sexual behavior, erection, ejaculation, copulatory movements, and ovulation.
7) **Motor activity related to eating:** stimulation of the corticomedial nuclear group produces complex rhythmic movements that are involved with chewing, licking, swallowing, and lip smacking.
8) **Pain perception:** pain-related neural activity changes have been detected in the amygdala during the modulation of pain perception. Extracellular signal-regulated kinase (ERK) in the central nucleus of the amygdala has been shown to act as an endogenous modulator of pain [13].

I have already reviewed the general functions of the amygdala. Next I will briefly outline what is known about the three white matter tracts that were affected in the POATS:

1) **Stria terminalis:** this is the main outflow tract (efferent) of the amygdala to the brain stem. This region has been shown to contribute to longer anxiety-like states that respond to environmental responses and dangerous stimuli, which often persist long after the removal of the threat [14].
2) **Ventral amygdalofugal:** is a ventral outflow tract (also efferent) [12]. This

region is well known to influence limbic response for motivation and drive. It also involved in associative learning.

3) **Uncinate fasciculus:** this region connects the basolateral nuclear group of the amygdala reciprocally with the prefrontal cortex. Surgical removal of this region is associated with an impairment of naming famous faces and objects [15].

I have surveyed the functions of the white matter tracts that integrate the amygdala to other regions of the brain which are also illustrated in diagram one. Next, I will now extrapolate clinical correlations related to OIH and hyperkatifeia based on these morphological changes in the brain that were induced by long-term prescription opioid use.

8. THE CLINICAL CORRELATION BETWEEN NEUROLOGICAL CHANGES DUE TO LONG-TERM PRESCRIPTION OPIOID USE WITH OIH AND HYPERKATIFEIA

In the POATS bilateral volumetric loss and functional connectivity changes were noted in the amygdala and the white matter tracts, respectively. Of significance was the decrease found in the functional connectivity of the amygdala to the nucleus accumbens via ventral amygdalofugal white matter tract. This decrease in functional connectivity was strongly correlated with the bilateral decrease seen in the volume of the amygdala. The link between the nucleus accumbens and the amygdala is important clinically as the relationship between these two regions play a role in mediating reward, motivation, and addictive behavior. In fact, a new study shows that the basolateral portion of the amygdala can specifically control the processing of opiate reward information and that this is directly related to the function of an opiate exposure state involving dopamine one and dopamine two receptor transmission to the nucleus accumbens [16].

The corticomedial nuclear group and basolateral nuclear group are known to be involved in emotions e.g. fear, sadness, anxiety, and emotional tone; as is the stria terminalis white matter tract associated with the brain stem. The basolateral nuclear group is also involved in arousal responses and damage in this particular region is associated with hypoactivity, sluggishness, and social avoidance/isolation. Two of the white matter tracts that are integrated with the amygdala-the stria terminalis and ventral amygdalofugal are associated with exaggerated states of anxiety and motivation, respectively. Taking this all into account, collectively, we can see a clear correlation between atrophy and loss of functional connectivity in these brain regions and the manifestation of the clinical symptoms of hyperkatifeia e.g., dysphoria, irritability, and alexithymia.

The amygdala is known to function in pain perception by acting as an endogenous modulator of pain. With this in mind we can see how decreases in amygdala volume and functional connectivity can contribute to OIH, which is the brain's misinterpretation of pain response secondary to a gross loss of properly functioning pain perception pathways. In addition, abnormal neuromodulation of NMDA receptors, mu-receptor dependent increases in intracellular messenger phosphokinase C, and decreases in endogenous opioids also contribute to OIH. Therefore, there is a collective multi-pathway system at work.

Therefore, an important association between changes in the structure and functional connectivity in the amygdala can be made with the long-term use of prescription opioids. Based on these changes in the amygdala a reasonable correlation can also be made to the clinical manifestation of OIH and hyperkatifeia.

9. CONCLUSION

It is clearly evident that opioid overuse and dependence has three main consequences. First, there is a decrease in the production of endogenous opioids, the central sensitization of the NMDA receptor response to pain, and mu-receptor dependent increases in intracellular messenger phosphokinase C, which all contribute to the clinical condition of OIH. Second, the disruption of homeostatic regulation of emotional behavior that is proposed to happen due to the compromise of neural substrates that mediate positive emotions and augment neural substrates that mediate negative emotional states. Third, in a small but one of a kind study, alterations in brain morphology, connectivity, and functioning has been discovered, which are related to long-term prescription opioid use. Obviously larger studies are needed on the long-term use of prescription opioids as their use is becoming more frequent in the general population. The regions of the brain affected by the opioid-induced neuron atrophy in the POATS appear to correlate well with some withdrawal symptoms, OIH, and hyperkatifeia that are seen in the patient population that use long-term prescription opioids.

Recent genetic studies have illustrated that FosB/delta-FosB genes, which are involved in neuron plasticity, are adversely affected by opioid administration [17]. The downstream effects due to neuron plasticity by these genes have been demonstrated in the prefrontal cortex, striatal regions, and the amygdala. However, there are no current studies that focus on the effect of prescription opioids on these genes and their contribution to opioid-induced neuron atrophy.

The proposal that the FosB/delta-FosB genes may be involved in the brain changes illustrated in the POATS study was implemented in Diagram one. Could opioids cause abnormal expression patterns in these

genes which adversely affect the neuron plasticity of the neurons located in the amygdala, prefrontal cortex, and striatum? This would be analogous to gene mutations in the APP, PSEN1, and PSEN2 genes which ultimately result in Alzheimer disease (AD) [18]. One of the distinguishing characteristics of AD is the manifestation of cortical atrophy. Thus, in both cases- AD and long-term opioid use, we see decreases in brain mass that is connected to genes. Future neurogenetic studies may ultimately discover a clear connection between the FosB genes and the morphologic brain changes seen in the POATS.

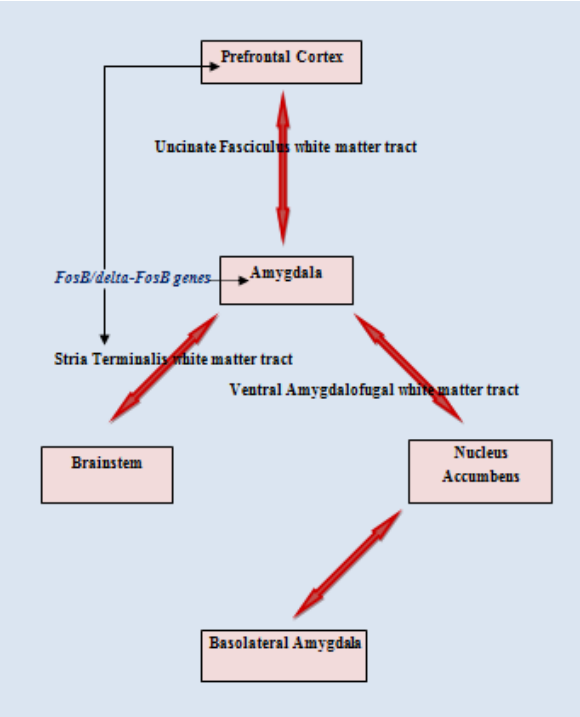

Diagram one: *This is a representation of the amygdala, the three white matter tracts, and the other brain regions that are innervated. In general, the amygdala processes information involving the emotional response to the external environment and the memory of emotional reactions. ERK in the central nucleus of the amygdala acts as an endogenous modulator of pain. The uncinate fasciculus tract innervates the amygdala to the prefrontal cortex, which is involved in planning and executive functions. The stria terminalis tract innervates the amygdala to the brainstem, which is involved in fear and anxiety. The ventral amygdalofugal tract innervates the nucleus accumbens, which is involved in motivation, drive, and addictive behaviors. In addition, the basolateral subdivision of the amygdala is connected to the nucleus accumbens and is involved in the fear and flight response, as well as the arousal response, which is decreased by stimulation from the corticomedial amygdala (not shown). The FosB/delta-FosB genes were added with reference to the three brain regions that showed abnormal mRNA expression in opioid users- these genes may contribute to bilateral volumetric loss and decrease in functional connectivity.*

The findings and clinical correlations discussed in this article should force clinicians to exert more caution when prescribing opioids and to provide more education to the patient who is a potential candidate to take opioids for long-term management. It is extremely important for the patient to be aware of OIH, hyperkatifeia, changes in the brain, and even newer findings that show changes in the endocrine system that can potentially result from opioid use [19]. This information collectively will serve to augment the patient-provider relationship when treating pain long-term with prescription opioids.

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