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DSM-5 Psychiatric Diagnoses and Opioid Use Disorder

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Abstract

The treatment of pain with opioid medications is a nowadays frequently discussed and concerning topic. Opioid medications have been prescribed since ancient years even though they are known to cause severe adverse reactions and co-morbid reactions. Depression and anxiety are the most common co-morbid psychiatric conditions observed in patients receiving opioid treatment. In the majority of cases, the provider for the pain medicine and the provider for the mood disturbance are not the same, which complicates diagnosis and treatment.

The presenting symptoms of depression and anxiety are frequently not contributed to the opioid medication. Opioids cause anxiety through development of dependence and withdrawal as evidenced by the need to dose opioids frequently throughout a 24 h period. To treat opioid induced anxiety and depression associated with chronic use of opioid medications, physicians frequently concomitantly prescribe anxiolytics like benzodiazepines. Benzodiazepines significantly exacerbate both substance induced depression and anxiety.

The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) clearly requires the exclusion of the influence of a substance in order to diagnose major depressive disorder or generalized anxiety disorder but those are frequently given even though the patient is receiving treatment with opioid medications. Ultimately the correct diagnosis is crucial for the right treatment.

This article is a review of literature discussing the correlation of opioid treatment and co-morbid psychiatric diagnoses including the differentiation as well as diagnostic criteria.

Keywords: Mental health; Epidemiology; Anxiety; Addiction; Psychoactive substances

Introduction

The use and prescribing of opioids has been increasing over the last 3 decades. Opioids are acting centrally and peripherally by binding to specific opioid receptors. The best-described receptor is the mu-receptor, which plays a major role in analgesia as well as addiction and euphoria. The Mu-receptor is responsible for the rush or the thrill and the urge to acquire more opioids [1,2].

The inordinate and massive prescribing and use of opioid drugs in the United States reflects addictive use and does not correlate to the magnitude of pain conditions. The United States constitutes only 4.6% of the world population; however, it consumes 80% of the world's opioid supply and 99% of the world's hydrocodone supply [3].

Preoccupation with acquiring the drug, such as seeking drugs from a physician and seeking medical care. Patients frequently seek medical care to obtain drugs and have an extensive and elaborate rationalization for pain medications. Opioid addiction is perfect compliance in opioid treatment because of compulsive use. Compulsive use is continued opioid use despite adverse consequences. These adverse consequences range from mild to significant and can be medical, legal, and occupational [4].

This article summarizes the inherent addictive pharmacologic properties that are the impetus and basis for America's current opioid epidemic and shows the co-morbidities resulting from the treatment with opioid medications. The article used mainly PubMed as a source as well as web and national databases. Words used for literature research where addiction, opioids, benazodiazepines, withdrawal and physical dependence

High rates of depression and anxiety in populations prescribed opioid medications DSM-5 exclusionary criteria for depressive and anxiety disorders

Clinicians are commonly faced with patients prescribed opioid medications who have high levels of depression and anxiety. Unfortunately, studies do not account for the substance induced depression and anxiety and intoxication and withdrawal from opioid medications. Further complicating the care of these patients is that the psychiatrist assessing the depression and anxiety is not prescribing the opioid medications. Ultimately, the proper diagnosis of the sources of the depression and anxiety is crucial to their treatment.

Most studies diagnose depression and anxiety in cross sectional observations that do not account for the depressive and anxiety inducing effects of opioid medications. Pharmacologically, opioid medications are classified as depressants, and predictably depress mood and cause symptoms that mimic criteria for a depressive

episode. Opioids cause anxiety through development of dependence and withdrawal as evidenced by the need to dose opioids frequently throughout a 24 h period [2].

Unless studies observe the participants in the absence of opioids, a definitive diagnosis of major depressive disorder or generalized anxiety disorder cannot be made per the exclusionary criteria in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) that requires the depressive symptoms are not better accounted for by a medication, such as opioids. All that can be diagnosed otherwise is a depressive or anxiety episode induced by opioid medications per DSM-5 criteria [4]. There are a few prospective studies that show patients who are prescribed opioid medications become depressed and anxious with increasing duration and doses of opioid prescribing and use.

Studies of opioid medication associated with depression and anxiety

Nonetheless, in a 2005 study by Sullivan, respondents with common mental disorders in the past year such as major depression, generalized anxiety disorder and panic disorder, were more likely to report regular prescription opioid use than those without any of these disorders [3]. Patients with mental health disorders are often excluded from trials that assess effectiveness of opioids for chronic pain. However, results from observational studies suggest associations between mental disorders and increased opioid use for chronic non cancer pain. [5].

Another study published by Sullivan in 2006 indicates that respondents with major depression, dysthymia, generalized anxiety disorder, or panic disorder have higher rates of prescription opioid use than those without. Each individual disorder was significantly associated with opioid use. In this study, patients receiving opioids were 2 to 3 times more likely to report a perceived need for mental health treatment. Among 237 users of prescribed opioids that were studied, 8 of the 21 (38.1%) reported having physical or psychological problems because of misusing drugs. Individuals on chronic opioid therapy reported greater need for mental health care [2].

Grattan et al. found that compared with patients who were not depressed; patients with moderate depression and severe depression were 1.8 and 2.4 times more likely, respectively, to misuse their opioid medications for non-pain symptoms [6]. Patients with mild, moderate, and severe depression were 1.9, 2.9 and 3.1 times more likely, respectively, to misuse their opioid medications by self-increasing their dose. This study concluded that depression is significantly associated with 2 forms of self-reported prescription opioid misuse: using opioids for sleep and using more opioids than prescribed. Misuse of opioids is likely addictive use of opioid medications in therapeutic and non-therapeutic settings, prescribed and not prescribed. A dose-response relationship was evident, with high rates of misuse among those with more severe depression [5]. The self-increasing doses of opioid medications reflect addictive use e.g. continued use despite increasing depression.

A study by Braden et al. found that long term opioid use rates were three times higher in those with depression [7]. Those with depression were more likely to receive a higher daily dose, greater days' supply and schedule II drugs relative to non-depressed patients. They were also more likely to have a concurrent sedative-hypnotic use with 180 days or greater supply. Braden and colleagues studied patients enrolled in two health plans from 1997 to 2005. Within that time long term opioid use per 1,000 patients with a history of depression increased from 69.8 to 125.9 at Group Health and 84.3 to 117.5 at Kaiser Permanente of Northern California [6].

A study by Edlund studied two different clinical populations (Healthcore insurance and Arkansas Medicaid) and found that in both groups, among individuals with chronic non-cancer pain, the proportion of individuals with chronic opioid use (defined as greater than 90 days supply) was higher in those with a mental health diagnosis (adjustment disorders, anxiety disorders, mood disorders, personality disorders, eating disorders, etc.) [8]. In the 2005 Healthcore insurance population, individuals with a mood disorder diagnosis were three times more likely to have greater than 90 days of opioid use compared to those with no mood disorder diagnosis.

Among those who received any opioids, individuals without a mental health diagnosis received an average of 44 days of opioids while those with any mental health diagnosis received an average of 89.6 days. In the other insurance population studied, Arkansas Medicaid, in 2005 those without a mental health diagnosis received an average of 102.6 days of opioid therapy while those with a mental health diagnosis received 136.3 days. Chronic opioid use was found in nearly one third (31%) of Arkansas Medicaid enrollees with a mental health diagnosis. This study concludes that opioid use for chronic non cancer pain was more common, prolonged, and potent and increased more rapidly from 2000 to 2005 among enrollees with mental health disorders in both populations [7].

In 2011, Schepis and Hakes found evidence between prescription opioid use and incident bipolar disorder among respondents with past psychopathology [9]. Among those with no history of past psychopathology, they also found association between lifetime depression and anxiety." There is no evidence for self-medication because opioid users improve when they discontinue opioid medications. Thus, there is no lasting positive medicinal/medication effect for depression or anxiety. Opioid users continue to use despite induced depression and anxiety while taking opioids and predictably have less depression and anxiety prescription opioid use and incident depressive, bipolar and anxiety disorder.

Becker et al. performed a cross sectional survey from 2002-2004 to find correlations between psychiatric, medical and substance use characteristics [10]. On multivariate analysis, they found that opioid use within the past year was associated with panic, depressive and social phobic/agoraphobic symptoms. Additionally, those using opioids were more likely to self-report poor health, misuse of another class of prescription medications and initiation of substance use before the age of 13.

Reid and her colleagues studied the use of opioids in two primary care populations: a Virginia primary care clinic (VA) and an urban hospital based primary care center in the north-eastern US (PCC) [4]. In their study populations of chronic non-cancer pain patients they found rates of individual psychiatric comorbidities were a staggering 44% and 54% for depressive disorder and 20% and 21% for anxiety disorder among VA and PCC patients, respectively. The prevalence of psychiatric comorbidities in these study populations is substantial.

Substance induced disorders: Depression and anxiety

Intoxication and withdrawal

In DSM-5, the essential feature of opioid intoxication is significant problematic behavioral or psychological changes that develop during or shortly after opioid administration. For example, initial euphoria

followed by symptoms of depression and anxiety such apathy, dysphoria, psychomotor agitation or retardation and impaired judgment. Additionally, intoxication is often accompanied by pupillary constriction, drowsiness, slurred speech, and signs of anxiety such as impairment in attention or memory and inattention to the environment even to the point of ignoring potentially harmful events [11].

Opioid withdrawal is characterized by either cessation of opioid use that has been h/days/weeks or longer or administration of an opioid antagonist after a period of opioid use. Additionally, three or more of those following criterion must develop during withdrawal: dysphoric mood, nausea or vomiting, muscle aches, lacrimation or rhinorrhea, pupillary dilation, piloerection or sweating, diarrhea, yawning, fever or insomnia. These symptoms must cause clinically significant distress in social, occupational or other important areas of functioning and not be attributable to another mental disorder or withdrawal or intoxication from another substance.

Substance/medication induced depressive disorder

The diagnostic feature of substance/medication-induced depressive disorder include the symptoms of a depressive disorder, however, the depressive symptoms are associated with the administration of a substance and the depressive symptoms persist beyond the expected length of physiological effects, intoxication or withdrawal period. The depressive disorder associated with opioid medication use must cause clinically significant distress or impairment in social, occupational or other important areas of functioning and clinical history, physical examination, or laboratory findings must evidence that the relevant depressive disorder developed during or within one month after use of a substance that is capable of producing depressive disorder. As there is a high comorbidity of depression in opioid users; depression is caused by opioids until otherwise as per DSM-5 exclusionary criteria. This is a major error that confounds all the studies.

Substance/medication induced anxiety disorder

Similarly, the high comorbidity of anxiety among opioid users is caused in part by opioids. The essential feature of substance/medication-induced anxiety disorder are prominent symptoms of panic or anxiety that are attributed to the effects of a substance as evidenced by clinical history, physical examination or laboratory findings [12]. Opioid medications are capable of producing the anxiety symptoms which develop during or soon after opioid use, intoxication, withdrawal or exposure. Opioid withdrawal occurs within hours of use and is frequently associated with anxiety as a withdrawal symptom [13].

Psychiatric disorders are associated with increased physical symptoms such as pain and may be associated with opioid use, but no studies have addressed this issue. Self-medication is often rationalization for addictive use, e.g. "opioids help pain after discontinuing opioids."

Prior opioid use induces depression and anxiety

Martins et al. estimated the adjusted relative hazard of psychiatric disorders in relation to pre-existing opioid use [14]. Demographics and prior illegal drug use (marijuana, cocaine, heroin, hallucinogens, inhalants and use of stimulants, sedatives and tranquilizers) were adjusted for and a time dependent covariate was created. They found that pre-existing opioid use was significantly associated with an increased likelihood of subsequent mood disorders, bipolar I disorder, major depressive disorder, anxiety disorders, panic disorder and generalized anxiety disorder in both adjusted and unadjusted models [4].

An important study illustrated the critical psychopathology of opioid use by Hah et al. explored underlying factors associated with decreased rate of opioid cessation after surgery [15]. They found preoperative opioid use was significant risk for continued prescribed opioid use and depressive symptoms. Preoperative prescribing of opioid medication use was associated with self-loathing symptoms including past failure, guilty feelings, self-dislike, self-criticalness, suicidal thoughts and worthlessness independently predicted a significant decrease in opioid cessation rate after surgery [16]. These data shows connections between emotional state and patterns of opioid use by defining self-loathing symptoms as the most reliable predicting factor of lack of opioid cessation after surgery. This finding clearly defines depressive symptoms that are most strongly related to prolong and unnecessary opioid use before and after surgery. Delayed prescription opioid cessation after surgery sustains prescription opioid misuse and addiction.

Regular opioid use and its intoxicating effects induce depression, e.g. by increasing apathy, depressed mood and lethargy. Depressed patients perceive their pain as more severe, which prompts additional misuse and addictive use [17]. A study of elderly adults indicates that patients with depression were more likely to continue opioid therapy than those who were not depressed.

Opioids produce short-term mood elevation that typically requires increasing dose to maintain this effect and cause dysphoria during withdrawal when they are discontinued [18]. This problematic relationship causes patients to seek higher and higher doses of opioids and become resistant to cessation of use.

In a study by Marins, the risk of incident anxiety disorders was increased among respondents with baseline opioid use after controlling for all covariates [19]. This concurs with previous findings by Schepis and Hakes that the risk of incident anxiety disorder was increased among respondents with baseline opioid use without prior psychopathology [20]. Thus, the intoxicating effects and withdrawal from opioids, likely precipitates anxiety disorders. This suggests that opioid users are particularly vulnerable to the development of medication induced anxiety disorders and should be monitored closely for development of comorbid psychiatric symptoms.

Studies do not confirm major depressive disorder or generalized anxiety disorder in opioid users because they fail to exclude effects of opioids in causing depression and anxiety.

Depression, anxiety and drug use disorders are associated with increased use of opioid medications in the general population. Depressive and anxiety disorders are more common and more strongly associated with prescribed opioids than other drug use disorders [21]. In DSM-5, one of the exclusionary criterions to diagnose major depressive disorder is "depressive symptom manifestation in the absence of any substance and/or any other medical condition." This is a substantial limitation in accurately diagnosing major depressive disorder in the presence of opioid medications [10]. If a patient is receiving opioids, the DSM-5 exclusionary criterion requires depressive symptoms induced by opioids be considered. The observed depression from the opioids must be accounted for [22].

A major error in most of the studies of comorbid depression and anxiety is that patients on opioid medications have symptoms that mimic major depressive disorder and generalized anxiety disorder that are likely induced by the medications. Limitations imposed by DSM-5 require that you must exclude the effects of all involved drugs and substances before making a diagnosis of another psychiatric disorder. Thus, until that distinction is made the diagnosis of major depressive disorder or generalized anxiety disorder cannot be established.

Exemplary studies reveal the antecedent and causative role of opioid medications in the development of depression and anxiety. In 2013, a study analyzed the medical records for 50,000 veterans with no use of opioid use or depression [23]. Patients who started and remained on opioids for 180 days or longer were at a 53 percent increased risk of developing depression and those who used opioids for 90-180 days were at a 25 percent increased risk relative to patients who took opioids for up to 89 days. The results of this study depict that the duration one is exposed to opioids is positively correlated with development of depression.

In a study by Dyer et al. in comparison with controls, methadone patients showed increased anger, depression, tension, confusion and fatigue as well as decreased vigor [24]. Mood changes from methadone such as depression, anger and anxiety increased the perceived severity of opioid withdrawal and induce craving for additional opioids, thus is associated with a poorer clinical outcome [25].

Associated benzodiazepine use/addiction

To treat opioid induced anxiety and depression associated with chronic use of opioid medications, physicians often concomitantly prescribe anxiolytics like benzodiazepines. Benzodiazepines significantly exacerbate both substance induced depression and anxiety. DSV-V classifies major depressive disorder as a prominent and persistent depressed mood causing clinically significant distress or impairment in social, occupational or other important areas of functioning that is not attributable to the psychological effects of a substance or another medical condition. Studies clearly document that chronic use of benzodiazepines cause depression and anxiety. Thus, it is impossible to independently diagnose major depressive disorder and/or generalized anxiety disorder in a patient that is using or in withdrawal of benzodiazepines. In cases such as these substance/medication-induced depressive disorder is a more appropriate diagnosis in which the symptoms of a prominent and persistent disturbance in mood characterized by depressed mood or markedly diminished interest or pleasure in activities developed during or soon after benzodiazepine intoxication or withdrawal or after exposure to the medication [4,26].

DSM-5 defines generalized anxiety disorder as a condition where panic attacks of anxiety are predominant in the clinical picture and these disturbances cannot be attributable to the physiological effects of a substance or another medical condition. Benzodiazepines cause and exacerbate anxiety symptoms; thus, it is not possible to independently diagnose an individual on opioids and or benzodiazepines with generalized anxiety disorder. Substance/medication-induced anxiety disorder would be the appropriate diagnosis in which panic attacks or anxiety is predominant in the clinical picture but these symptoms developed during or soon after benzodiazepine intoxication or withdrawal or exposure to medication and where the involved substance is capable of producing the relevant symptoms, which opioids and benzodiazepines both are [4,27].

Benzodiazepine associated overdoses

Aside from medication induced depression and anxiety disorders, Benzodiazepines are substantially involved in opioid deaths. A study by Chen et al. followed opioid overdose deaths by involvement of Benzodiazepines. In 1999, 13% or 527 opioid overdose deaths involved benzodiazepines. By 2011, 31% or 5,188 opioid overdose deaths involved Benzodiazepines [28]. The total number of opioid poisoning deaths involving benzodiazepines increased, on average by 14% each year from 1999-2011. Notably, in that same time frame (1999-2011) the number of opioid deaths not involving benzodiazepines was relatively steady [29]. Another study by Christopher Jones showed that in 2013, opioids were involved in 77.2% of Benzodiazepine over dose deaths. It appears the concomitant prescribing of benzodiazepines with opioids be responsible for the opioid overdose epidemic [30].

Mechanisms of overdose deaths

Opioids depress central nervous system activity including decreased respirations, lowered heart rate and loss of consciousness potentially preceding coma or death [31]. When opioids are taken together with other drugs that depress central nervous system activity, such as benzodiazepines there is often serious, even life threatening problems. A report by Rockville found that combining benzodiazepines with opioid analgesics was associated with a 24-25 percent increase in the predicted risk of a more serious outcome compared with benzodiazepines alone. These findings held true when no other drugs were involved and across all age groups. This highlights that the co-prescribing of opioids and benzodiazepines is especially dangerous and often times lethal [32].

Opioids are most often prescribed by primary care physicians and opioid induced anxiety compels patients to seek out benzodiazepines, often from a psychiatrist. Seeking out prescriptions from multiple doctors, or pharmacies, is a warning sign for addiction. It is imperative that better coordination between primary care physicians and psychiatrists be implemented and required to protect patients from this potentially morbid co-prescribing. The rise in prescribing of opioids is directly related to the increased prescribing of benzodiazepines [33,34].

Medical vs. nonmedical with chronic opioid prescribing/use: Useless distinctions

Opioid psychoactive effects

Whether opioids are prescribed in a medical setting or taken outside of a medical setting, they have the same psychoactive effects. A prescription from a physician does not change the pharmacological properties of opioid medication or their classification as controlled substance as a dangerous drug. Just as prescribing for pain or taking for pain without a prescription does not change the addiction potential of opioid drugs nor their inherent pharmacological effects.

A study by Lin finds that severe chronic pain, treated with opioid medications makes depression more treatment resistant. Depressed patients on chronic opioid therapy are at a higher risk for overdose, whether it be accidental or intentional. High rates of depression and anxiety occur in medical and nonmedical populations. There is little rationale to distinguish between medical and nonmedical opioid use and most studies do no attempt to do so. However, they tend to label and designate use as nonmedical if there are adverse effects and complications from use of and prescribing of opioid medications.

The self-medication pathway is defined by the assumptions that the individual starts using a drug and becomes dependent on it to alleviate pain and psychiatric symptoms. However, there is correspondence between the neurobiological effects of the drug used and the specific symptomology of the pain and psychiatric disorder. More commonly, those with pre-existing pain and psychiatric conditions use the self-medication pathways as a rationalization for their eventual addictive opioid use. There is no evidence for this practice of self-medication of pain and depression because when they discontinue the opioids, most of the aversive symptoms of pain and depression are alleviated and quality and functionality of life improve and increase. Individuals consciously and unconsciously rationalize their addictive use as self-medication as reason to continue administering the drug although they are in pain and depressed despite decreasing efficacy and adverse consequences [35]. The DSM-V exclusionary criterion of substance/medication induced disorders does not support the self-medication pathway and it remains a mere hypothesis [36].

It is generally recognized that recreational drug use often is detrimental to a person's mental and physical health. It is problematic that such effects are rarely considered when psychiatric medications are prescribed. The mind numbing effects of psychoactive drugs, like opioids, stop users from addressing underlying personal and psychological issues, environmental adversity, forming positive social relationships all of which improve chances of long term recovery. Similar to the approach of substance addiction services, it would be beneficial for psychiatric services to assist patients in identifying alternative ways of coping with emotional distress rather than prescribing addicting medications [37].

Opioid drugs do not have a disease-specific action independent of their demonstrable psychoactive effects. Patients prescribed these medications should be informed on the behavioral pharmacology including all mental, behavioral and physical effects they induce in the acute phase and long term, during consumption and withdrawal. Radical change is needed to view opioids as psychoactive substances that cause the same effects across the board to all patients, regardless of diagnosis, medical or nonmedical use. When opioids are appreciated as psychoactive substances with predictably negative effects with chronic use, prescribers and consumers would be better able to use these medications effectively and lower morbidity and mortality.

Medical and non-medical use

Many studies attempt to differentially and arbitrarily categorize the medical and nonmedical use of opioids. This is extremely problematic. If opioids are prescribed "medically," patients and clinicians mistakenly view them as a safe modality of treatment [38]. Yet, since opioids are psychoactive substances that are not diagnosis specific, their demonstrable psychoactive effects are induced in all users regardless if they are prescribed inside a medical setting for pain or outside a medical setting. Also, incorrectly adverse outcomes from prescribing opioid medications are seen as nonmedical even if occurring in medical use, e.g. addiction, increased doses, uncontrolled use, or overdose [39].

A woman prescribed opioids by her doctor for low back pain experiences the exact same pharmacologic effects as a woman buying them off the street. Tolerance to opioids develops quickly in both cases. For instance, say patient A and patient B is administered the same dose by their physicians. After a certain amount of time, they both visit their physicians requesting an increased dose due to tolerance and/or opioid induced hyperalgesia [11]. Say the physician of patient A willingly increased the opioid dose but patient B's physician declined the request. Patient B takes to the streets procuring the same dose patient A got from his physician. Both became addicted to the opioid medications [40].

Although patient A's usage is seen as "medical" and patient B's usage is seen as non-medical, there is no differentiation in using. Both patients experience the same pharmacological, physical, mental and emotional effects. Additionally noteworthy is that "nonmedical use" is often preceded by medical use through the predictable development of tolerance, dependence and addiction to opioids. Often, patients become addicted to opioid medications upon being prescribed by a medical doctor. Due to tolerance, inherent opioid addictive properties, and opioid induced hyperalgesia "medical" patients often engage in non-medical use by using over the recommended dose or continuing opioid use for longer than prescribed with or without the cooperation of the physicians [41]. A common scenario is if their physicians truncate opioid therapy, they often turn to the streets to find more dangerous opioids, such as heroin to satisfy their dangerous addiction. And the transition to heroin by previously "medical patients" is dreadfully high. As many 50% of those addicted to heroin previously were prescribed and/or used prescription opioid medications [42].

What is clear is the physician is the physician is the source of opioid medications whether used in medical or nonmedical settings. Most opioid medications can be traced to a physician prescription [42]. Little imagination is necessary to attribute the eventual escalation of opioid medications availability to their highly addicting pharmacological properties. Not much progress in improving psychiatric care of patients with opioid induced disorders and opioid addiction will result until opioid medications are limited in their prescribing and use [42]. There is scant evidence for the efficacy beyond short term prescribing of opioid medications, and abundant illustrations for their morbidity and mortality.

Conclusion and recommendations for treatment of opioid use disorders and opioid induced disorders

1. Opioid medications are associated with high rates of depression and anxiety.

2. Opioid medications induce treatment resistant depression, anxiety and pain.

3. Apply DSM-5 Exclusionary Criteria to account for opioid induced depressive and anxiety effects.

4 Opioid medications induce depression and anxiety disorders predicated on their pharmacological properties to induced depression and anxiety.

5. Opioid medications induce depression and anxiety predicated on their intoxicating and dependent withdrawal producing properties.

6. Discontinue opioid medications to treat depression, anxiety, and suicidal overdose risks.

7. Refer and treat opioid addiction if resistant to opioid discontinuation or relapse to opioid medications despite adverse effects.

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