1-1-2022

Historical Pathways for Opioid Addiction, Withdrawal with Traditional and Alternative Treatment Options with Ketamine, Cannabinoids, and Noribogaine: A Narrative Review

Amber N. Edinoff
Department of Psychiatry, Harvard Medical School, Massachusetts General Hospital; Department of Psychiatry and Behavioral Medicine, Louisiana State University Health Shreveport; Louisiana Addiction Research Center.

Natalie W. Wu
Department of Psychiatry and Behavioral Medicine, Louisiana State University Health Shreveport.

Catherine A. Nix
Department of Psychiatry and Behavioral Medicine, Louisiana State University Health Shreveport; Louisiana Addiction Research Center.

Bryce Bonin
School of Medicine, Louisiana State University Health Shreveport.

Rama Mouhaffel
School of Medicine, Louisiana State University Health Shreveport.

Recommended Citation

Edinoff, A. N., Wu, N. W., Nix, C. A., Bonin, B., Mouhaffel, R., Vining, S., Gibson, W., Cornett, E. M., Murnane, K. S., Kaye, A. M., & Kaye, A. D. (2022). Historical Pathways for Opioid Addiction, Withdrawal with Traditional and Alternative Treatment Options with Ketamine, Cannabinoids, and Noribogaine: A Narrative Review. *Health Psychology Research, 10*(4), 38672. DOI: 10.52965/001c.38672
https://scholarlycommons.pacific.edu/phs-facarticles/646

Edinoff AN, Wu NW, Nix CA, et al. Historical Pathways for Opioid Addiction, Withdrawal with Traditional and Alternative Treatment Options with Ketamine, Cannabinoids, and Noribogaine: A Narrative Review. *Health Psychology Research*. 2022;10(4). doi:10.52965/001c.38672

General

Historical Pathways for Opioid Addiction, Withdrawal with Traditional and Alternative Treatment Options with Ketamine, Cannabinoids, and Noribogaine: A Narrative Review

Amber N. Edinoff[1] [a], Natalie W. Wu[2], Catherine A. Nix[3], Bryce Bonin[4], Rama Mouhaffel[4], Stephen Vining[4], William Gibson[5], Elyse M. Cornett[6], Kevin S. Murnane[7], Adam M. Kaye[8], Alan D. Kaye[9]

[1] Department of Psychiatry, Harvard Medical School, Massachusetts General Hospital; Department of Psychiatry and Behavioral Medicine, Louisiana State University Health Shreveport; Louisiana Addiction Research Center, [2] Department of Psychiatry and Behavioral Medicine, Louisiana State University Health Shreveport, [3] Department of Psychiatry and Behavioral Medicine, Louisiana State University Health Shreveport; Louisiana Addiction Research Center, [4] School of Medicine, Louisiana State University Health Shreveport, [5] School of Medicine, Louisiana State University New Orleans, [6] Department of Anesthesiology, Louisiana State University Shreveport, [7] Department of Psychiatry and Behavioral Medicine, Louisiana State University Health Shreveport; Louisiana Addiction Research Center; Department of Pharmacology, Toxicology & Neuroscience, Louisiana State University Health Shreveport, [8] Department of Pharmacy Practice, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, [9] Louisiana Addiction Research Center, Shreveport; Department of Anesthesiology, Louisiana State University Shreveport

Keywords: Noribogaine, Ketamine, Cannabinoids, Dronabinol, Opiates, Opioid Use Disorder, Withdrawal

https://doi.org/10.52965/001c.38672

Health Psychology Research

Vol. 10, Issue 4, 2022

Even as prescription opioid dispensing rates have begun to decrease, the use of illicit opioids such as heroin and fentanyl has increased. Thus, the end of the opioid epidemic is not in sight, and treating patients that are addicted to opioids remains of utmost importance. Currently, the primary pharmacotherapies used to treat opioid addiction over the long term are the opioid antagonist naltrexone, the partial-agonist buprenorphine, and the full agonist methadone. Naloxone is an antagonist used to rapidly reverse opioid overdose. While these treatments are well-established and used regularly, the gravity of the opioid epidemic necessitates that all possible avenues of treatment be explored. Therefore, in this narrative review, we analyze current literature regarding use of the alternative medications ketamine, noribogaine, and cannabinoids in treating patients suffering from opioid use disorder. Beyond its use as an anesthetic, ketamine has been shown to have many applications in several medical specialties. Of particular interest to the subject at hand, ketamine is promising in treating individuals addicted to opioids, alcohol, and cocaine. Therapeutically administered cannabinoids have been proposed for the treatment of multiple illnesses. These include, but are not limited to epilepsy, Parkinson's disease, multiple sclerosis, chronic pain conditions, anxiety disorders, and addiction. The cannabinoid dronabinol has been seen to have varying effects. High doses appear to reduce withdrawal symptoms but this comes at the expense of increased adverse side effects such as sedation and tachycardia. Noribogaine is a weak MOR antagonist and relatively potent KOR agonist, which may explain the clinical anti-addictive effects. More research should be done to assess the viability of these medications for the treatment of OUD and withdrawal.

INTRODUCTION

Since the mid-1990s, the use of opioid agents in the United States has grown at a rapid and unprecedented rate. For reference, between 1997 and 2007 the amount of milligram of morphine per person in circulation increased by nearly 600% from 96 to 700 mg.[1] Between 1999 and 2011, opioid overdose deaths nearly quadrupled from 1.4 to 5.4 deaths

a **Corresponding author:**
Dr. Amber Edinoff, MD
Massachusetts General Hospital
Department of Psychiatry
55 Fruit St
Boston, MA, 02114
Phone: (617) 726-2000
aedinoff@mgh.harvard.edu

per 100,000 people.[2] In 2020 alone, over 68,000 people died from opioid overdoses.[3] Beyond the toll on human life, the opioid crisis also presents a tremendous financial burden on society. A Council of Economic Advisers report estimated the annual cost of the opioid crisis in 2015 to be a staggering $504 billion (2.8% of that year's GDP).[4] Addiction to opiates, technically termed opioid use disorder (OUD), is estimated to affect three million Americans at present.[5]

The acute increase in opioid prescription, misuse, and addiction has been described as the most severe public health crisis in the history of the United States.[6] The problem has become the subject of much public discourse, analysis, and state and federal policy.[7] Even as the prescription opioid dispensing rate has begun to decrease, the use of illicit opioids such as heroin and fentanyl has increased.[6,8] Thus, the end of the opioid epidemic is not in sight, and treating patients that are addicted to opioids is of utmost importance at present. Currently, the primary pharmacotherapies used to treat opioid addiction over the long term are the opioid antagonist naltrexone, the partial-agonist buprenorphine, and the full agonist methadone. Naloxone is an antagonist used to rapidly reverse opioid overdose.[9] While these treatments are well-established and used regularly, the gravity of the opioid epidemic necessitates that all possible avenues of treatment be explored. Therefore, in this narrative review, we analyze current literature regarding the use of the alternative medications of ketamine, noribogaine, and cannabinoids in treating patients suffering from OUD.

OPIOID USE DISORDER OVERVIEW

The origin of the opioid crisis is multifaceted. Following the production of OxyContin in 1995, Purdue Pharma began a prolonged campaign to encourage the use of opioids in treating chronic, non-cancer pain.[9] Purdue Pharma encouraged the prescribing of opioids by providing free coupons and promotional products for patients starting on these products. For healthcare providers, on the other hand, the company organized over 20,000 educational programs and 40 free-of-charge conferences.[6] Ultimately, Purdue Pharma was fined billions of dollars for misconduct in the marketing and sale of opioids and the company is to be dissolved into a public benefit corporation.[10] Concurrent with the promotion of opioids by pharmaceutical manufacturers, medical societies in the United States began campaigning for the increased utilization of opioids and for pain to be classified as the "fifth vital sign." For instance, the American Pain Society introduced this phrase in 1995 at the group's annual meeting.[9] Following this, the Veteran Affairs system and Joint Commission also adopted pain measurement as the fifth vital sign.[11]

OPIOID USE DISORDER DEFINITION

The Diagnosis and Statistical Manual 5 (DSM-5) defines OUD as the following: 1) taken in larger amounts or over a longer period of time than intended, 2) persistent desire or unsuccessful efforts to cut down or control use, 3) spends a great deal of time in activities necessary to obtain the opioid, 4) crabbing or a strong desire to use opioids, 5)use resulting in a failure to fulfill major role obligations at work, school or home, 6) continue use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the drug's effects, 7) social, occupational or recreational activities are given up or reduced because of use, 8) recurrent use in situations where it is physically hazardous, 9) continued use despite the knowledge of having a persistent or recurrent physical or psychological problem that is probably to have been caused by or exacerbated by opioids, 10) tolerance and 11) withdrawal.[12]

Tolerance is defined as experiencing one or more of the following: 1) the need for markedly increased amounts of opioids to either achieve intoxication or the desired effect and/or a markedly diminished effect with continued use of the same amount of opioid.[12] Withdrawal is defined as manifesting as one or more of the following: 1) the characteristic opioid withdrawal syndrome and/or the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms.[12]

According to the DSM 5, the symptoms of opioid withdrawal include excessive lacrimation, rhinorrhea, piloerection, diarrhea, nausea, vomiting, mydriasis, insomnia, and autonomic hyperactivity. With chronic short-acting opioids, withdrawal symptoms can present in as little as 4-12 hours. In contrast, long-acting opioid abuse typically presents withdrawal symptoms within 24-48 hours.[13] The severity of OUD is based on the number of criteria that are met. Mild is defined as having 2 or 3 of the criteria listed above. Moderate is when 4 to 5 of the above criteria is met. Severe is when 6 or more of the above criteria are present.[12]

CAUSES

It has become evident that pain medications, specifically opioids, are both necessary and justifiable in chronic pain resistant to other treatment forms. However, the widespread introduction of exogenous opioids has not come without consequences. Substance use disorder, by definition, involves a constellation of symptoms that equate to repeated periods of tolerance and withdrawal.[14] Concerning opioids, patients are typically introduced to these medications as a result of severe acute pain, chronic pain, or by recreational use to achieve a sensation of euphoria or to alleviate pain states. Currently, there are a few theories that hypothesize the driving force behind addiction: one involves the patient seeking pleasure, and the other consists of the patient trying to avoid undesirable withdrawal symptoms after starting the use of opioids for any variety of reasons. One of these reasons could be that the medications were prescribed but then were stopped suddenly by a provider, precipitating an unwanted withdrawal.

There are a few theories in the literature that highlight where a person's use which can result in addiction. The first theory describes three phases that could lead to addiction. These phases are the following: A) recreational, sporadic use in which intake is mild to moderate, and the user still enjoys other activities, B) sustained use in which

drug intake is the main recreational activity, but the behavior is still primarily controlled, and C) full addiction characterized by structural changes in reward-related areas of the brain.[15] Phase three involves drug use being the sole reward-based activity along with avoiding severe withdrawal symptoms upon cessation of drug use.[15] This phase also highlights the overriding of the brain's salient system where all attention is focused on the acquisition of the drug as well as the drug's use. The second theory explains that withdrawal's physical and psychological symptoms are so immense that they outweigh the adverse effects of continued drug use.[16] It is important to note that as a person progresses from healthy use to addiction the use starts to become out of their control. That is why abstinence may be an option for many people and further highlights the importance of medical treatment and treatment options in general.

PRESENTATION

A patient with OUD can present with a wide range of physical and psychiatric manifestations largely dependent on the chronicity of use. When accurate history is unknown, attention must also be paid to the possibility of opioid withdrawal, which can be confused with other forms of intoxication.[17] An acutely intoxicated patient classically presents signs of CNS depression such as miotic pupils, yawning and sedation, slurred speech, and decreased respiratory rate in severe cases. It is important to note that a normal pupil examination does not rule out opioid overdose; many patients have ingested other substances that can mask this presentation.[18,19] A patient with more severe CNS symptoms is likely a relatively new user who has not developed tolerance or a chronic user who has taken a larger dose than usual.

In contrast, a chronic user who has developed tolerance may show no apparent signs of use or intoxication. OUD in this subset of patients is typically discovered by urine drug screen, careful interview, or in the case of withdrawal after admission to the hospital. These patients frequently also have socioeconomic compromises as well. This is particularly true for chronic users who often have trouble maintaining jobs and social relationships. In severe cases, lifestyle may be affected to the point of illegal behavior centered around obtaining money to purchase additional drugs. As a healthcare professional evaluating a patient who may be impacted by OUD, considering and evaluating all avenues of downstream effects is paramount.

PATHOPHYSIOLOGY

Opioids bind to and activate three specific G-protein coupled receptors: mu, kappa, and delta, which are spread throughout the CNS, skin, and gastrointestinal tract. While each of these receptors has a similar physiologic effect on the CNS, it has been observed that each subtype has unique products and a specific distribution within the brain.[20] Delta opioid receptors (DORs) are located in the basal ganglia and activation is associated with anxiolytic effects. Kappa opioid receptors (KORs) are typically localized to the hypothalamus, periaqueductal gray. They are known to cause dysphoria but also cause sedation, which has been suggested as a possible cause of individuals using opioids to resolve negative psychological feelings.[21,22] Mu opioid receptors (MORs) were the first subtype to be discovered and play a significant role in the reward system and development of addiction. MORs are located in several parts of the brain, such as the cerebral cortex, thalamus, and periaqueductal gray, and are primarily responsible for the euphoria associated with opioids. Upon binding of an opioid agonist to the MOR, there is a subsequent decrease in cAMP and decreased activation of protein kinase A (PKA). This results in decreased norepinephrine release and autonomic hypoactivity, which manifests as hypotension, reduced respiratory rate, and sedation. When a habituated system is suddenly deprived of an agonist, there is a relative increase in cAMP and PKA, resulting in an increased release of norepinephrine, which materializes as lacrimation, diaphoresis, tachycardia, and mydriasis – classic symptoms of opioid withdrawal.[13,23] Additionally, recent studies have shown that many clinical manifestations of opioid withdrawal and tolerance are potentiated by endothelin-A (ET_A) and thus relieved by ET_A antagonists.[24]

MORs localized to the ventral tegmental area (VTA) play an essential role in the mesolimbic dopaminergic reward system and the development of addiction. Upon binding of opioids to MORs in the VTA, there is an increase in dopamine release in the nucleus accumbens (NAc) and basolateral amygdala, which is associated with pleasure and a sense of contentment. The mesolimbic pathway is affected by both endogenous and exogenous opioids.[25] When an individual participates in activities such as eating, exercise, or sexual activity, the brain releases endogenous opioids that activate this pathway and associate the behavior with a reward. This pathway is hacked by exogenous opioids, which generally results in increased dopamine concentration relative to what is seen with a natural response. This release is supraphysiologic. Over time, neuronal structure and signaling adaptations occur, and tolerance develops, which manifests clinically as an increased craving for exogenous opioids and less reliance on natural rewards to achieve satisfaction. In OUD, the normal inhibitory function of the prefrontal cortex is compromised, and mesolimbic pathway homeostasis is lost.[26,27] This was what was induced as the high jacking of the salient system in a prior section of his manuscript.

OPIOID USE DISORDER CURRENT TREATMENT

Before the 1960s the treatment of addiction, and opioid addiction, in particular, was largely inadequate for meaningful pharmacological therapy. At the time, the mainstay of treatment was federally funded "farms" in which patients were given morphine followed by six months of abstinence from working on the farm. This was largely ineffective as many patients relapsed soon after returning home. This therapy was replaced in 1965 with the introduction of highly regulated administration of long-acting opioid agonists that were expected to decrease feelings of euphoria while concurrently avoiding the effects of withdrawal.[28]

Recently, partial opioid agonists such as buprenorphine and opioid antagonists such as naltrexone have also been approved for the treatment of OUD. This section will discuss the various currently accepted forms of OUD treatment.

WITHDRAWAL

Medically supervised withdrawal is the first step in complete opioid cessation. However, relapse usually follows this if the patient does not subsequently begin maintenance therapy. First-line treatment is typically with buprenorphine which is preferred over methadone due to the lower risk of lethal overdose. However, buprenorphine must be given after the first signs of withdrawal occur. In contrast, methadone can be given before withdrawal but carries a higher side effect burden.[29] Alpha-2 agonists such as clonidine and lofexidine are also used to treat opioid withdrawal. Rather than being used as primary therapy, these medications are typically used in addition to buprenorphine or methadone to alleviate autonomic side effects.[30]

METHADONE

The answer to the worsening opioid epidemic came with the introduction of the long-acting opioid agonist known as methadone which the FDA approved in 1972. Initial studies began trials with methadone under the hypothesis that a long-acting opioid administered in a scheduled fashion would occupy the opioid receptor, thus decreasing euphoria and eliminating the dreaded withdrawal effects; the so-called "narcotic hunger" would be diminished. When coupled with a rehabilitation program, methadone maintenance therapy programs (MMTPs) decreased opioid dependence and remain an effective opioid addiction therapy today.[20]

Although effective and widely used, there are several challenges with the use of methadone. One of the most significant barriers is patient compliance and dosing. With most classic MMTPs, dosing must start at around 30 mg/day and slowly be titrated up to 80-150 mg/day, which is considerably higher than what is used to treat chronic pain. Gradually increasing the daily dose at a rate of 10-20 mg/week allows the patient to develop a sufficient "blockade" against short-acting opioids and prevent withdrawal effects. However, this comes at the cost of patients having to visit clinics 6-7 times/week initially, which creates a barrier to compliance.[22] In addition to barriers to compliance, side effects are also a concern. QT prolongation with subsequent Torsade de Points and respiratory depression secondary to overdose are both significant concerns with methadone treatment.[31,32]

Despite the obstacles involved in methadone therapy, the treatment has proven to improve several outcomes in compliant patients. Decreased death rates, intravenous drug use, reduction in crime, and even reductions in HIV have been noted since the early stages of MMTPs.[20]

BUPRENORPHINE

Buprenorphine is a synthetic, partial opioid agonist that has become increasingly popular in recent years. In theory, buprenorphine has several advantages over methadone largely due to its unique pharmacologic characteristics. Buprenorphine has a relatively weak activity but a high affinity for the MOR, which results in decreased "euphoria" and mitigation of withdrawal symptoms while retaining a receptor blocking effect. To deter OUD patients from injecting buprenorphine, buprenorphine can be prescribed as a combination with naloxone, a potent MOR antagonist, to mitigate the euphoric effects of the buprenorphine when injected. When considering two of the significant measures of effectiveness, retention in treatment and reduction of opioid use, buprenorphine was superior to placebo in retention in treatment in all dose categories but only superior concerning the reduction of service in the high dose treatment category.[32] Buprenorphine is effective in treatment retention at all doses and suppressing opioid use at high doses.

NALTREXONE

Naltrexone is a MOR antagonist and partial KOR agonist that has been FDA approved for use in OUD. Initially, naltrexone was administered as a tablet, but a sustained-release depot injection has also been approved. As an opioid receptor antagonist, one of the main concerns is eliciting adverse withdrawal symptoms in opioid-tolerant patients. Before administration, patients must be abstinent from opioid agonists for a minimum of 5-7 days which is difficult for many patients to achieve without medical intervention. While the naltrexone depot injection is relatively new, preliminary studies have not shown a significant improvement in retention in treatment or opioid use compared to agonists.[33] It has been hypothesized that naltrexone may be a promising treatment option for patients with a milder form of OUD.

ALTERNATIVE MEDICATIONS

KETAMINE

Beginning in the 1950s, the drug phencyclidine (PCP) was widely synthesized and utilized as a dissociative anesthetic.[34] Because of its severe psychodysleptic side effects (delusions, hallucinations, and "out-of-body" experiences) and a high potential for abuse, PCP was pulled from the market in 1978. Beginning in the 1970s, PCP's derivative ketamine gradually took its place as a clinical anesthetic.[35] Like PCP, ketamine produces dissociative and psychodysleptic effects, but it does so to a far lesser extent and has the advantage of maintaining hemodynamic stability.[36] Even so, the unique side effects of ketamine have led to it being used primarily as a veterinary anesthetic. Presently, its use in humans is typically relegated to specialized anesthetic cases such as pediatrics, burn victims, and hemodynamically compromised patients.[37,38] However, far less potent and shorter-acting than its parent drug PCP,

ketamine is still abused recreationally. Its recreational effects are commonly described as a sensation of "melting" into the environment, weightlessness, out-of-body experiences, and visions.[39]

Upon intravascular administration, ketamine quickly reaches target receptors in less than a minute. When administered intramuscularly, ketamine retains a high bioavailability of 93%.[34] Ketamine is metabolized by the liver enzymes CYP2B6 and CYP3A4, mainly to the active metabolite norketamine, before being excreted in the feces and urine.[34,40] Ketamine's primary dissociative anesthetic and analgesic effects are thought to be mediated via the non-competitive antagonism of open NMDA receptors.[41,42] It decreases the duration and frequency of ion conduction by occupying the site either inside the Ca^{2+} pore itself or within the hydrophobic portion of the receptor.[34] Apart from NMDA receptors, ketamine has also been characterized as interacting to a lesser extent with monoaminergic, cholinergic, and opioid receptors. The uptake of serotonin, norepinephrine, and dopamine is inhibited to some extent by ketamine, though what role this plays in its clinical effects is still under discussion.[43] While ketamine blocks nicotinic receptors, this is thought to play little part in sedating or immobilizing effects. However, it may be connected to analgesic effects.[44] Ketamine's action at μ-, δ-, and κ-opioid receptors are thought to play a part in analgesia.[45] Besides anesthetic and analgesic effects, ketamine raises blood pressure and heart rate, very mildly depresses respiration, and produces psychodysleptic's effects in a dose-dependent fashion.[34,46]

Beyond its use as an anesthetic, ketamine has been shown to have many applications in several medical specialties. For example, ketamine is commonly used as an analgesic. For acute pain management, adding ketamine to opioids has been shown to lessen respiratory depression and prevent hyperalgesia.[19] It has also been influential in treating chronic pain, though its use as a stand-alone drug in non-treatment resistant patients is controversial.[18] Several studies have indicated that ketamine is a rapid-acting and effective treatment in the management of treatment-resistant depression and suicidal ideation.[47–49] Studies have even shown that ketamine may be a promising drug for the treatment of certain forms of cancer.[50,51] Of particular interest to the subject at hand, ketamine is promising in treating individuals addicted to opioids, alcohol, and cocaine.[52–54]

CANNABINOIDS

Cannabis sativa has been utilized for medicinal, religious, and recreational purposes for over three millennia. It was initially introduced to Western medicine in the 19th century, but its use stagnated due to difficulties obtaining consistent dosages of medical preparations.[55] In the 20th century, cannabis became the most popular recreational drug in the Western world.[56] Recreational use of cannabis products is associated with psychotropic effects, such as relaxation, euphoria, tiredness, and time distortion.[57] Less desirable results can include paranoia, increased risk of psychotic disorders, and cardiovascular disease.[57,58]

Since the 1990s, interest in the medicinal use of cannabis has been reignited. This is partly due to the isolation and study of a group of compounds within cannabis, called cannabinoids. The most important of these are Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD).[59] Notably, the human body has been found to have two cannabinoid receptors distributed throughout it: the primarily CNS and PNS-located CB_1 receptors and the immune principally tissue-located CB_2 receptors.[60] Therapeutically administered cannabinoids have been proposed for the treatment of multiple illnesses. These include, but are not limited to epilepsy, Parkinson's disease, multiple sclerosis, chronic pain conditions, anxiety disorders, and addiction.[56,59,61–63]

Recreational cannabis is commonly smoked. However, due to the undesirable respiratory side-effects associated with smoking, vaporization may be used as an alternative with minimal pharmacokinetic differences.[64] The bioavailability of inhaled THC ranges from 10-35%, and that of CBD is 31%.[65] Cannabinoids may also be given via oromucosal, oral, rectal, and transdermal administration with various levels of bioavailability and distribution.[66] Highly lipophilic cannabinoids tend to distribute rapidly to the adipose tissue, brain, and other organs.[67] Their predominant mode of metabolism is through hepatic CYP 450 isozymes, followed by fecal and urinary excretion.[68,69] The primary effects of cannabinoids are thought to be mediated through a cascade of events stimulated by interactions with CB_1 receptors and CB_2 receptors.[66,70]

NORIBOGAINE

Noribogaine is the primary metabolite of ibogaine, a psychoactive alkaloid isolated from *Tabernathe iboga*. Ibogaine undergoes extensive first-pass metabolism in the liver and gastrointestinal tract and is primarily metabolized via O-demethylation by CYP2D6. Although never approved for the use of addiction treatment in the United States, early trials of ibogaine showed promising results in the treatment of opioid abuse. It was discovered that ibogaine had a relatively short half-life of about 140 minutes but displayed anti-addictive properties for almost 24 hours. It was later found that the extended effects were due to noribogaine.[71] The resulting metabolite has a longer half-life, excellent blood-brain permeability, and complex effects on many neurotransmitter systems. Additionally, compared to ibogaine in preclinical rodent trials, noribogaine showed many of the same anti-addictive results but lacked the tremors and side effects seen with ibogaine.[72] Collectively, these features make noribogaine a good candidate for clinical development.

Noribogaine is a potent serotonin reuptake inhibitor, a relatively weak NMDA antagonist, and has activity at the MOR and KOR. Notably, noribogaine binds to opioid receptors with greater affinity than ibogaine. Regarding use in opioid addiction, noribogaine has a unique and potentially helpful interaction with opioid receptors. Noribogaine is a weak MOR antagonist and relatively potent KOR agonist, which may explain the clinical anti-addictive effects. Recent studies have taken this a step further and focused on

the little interaction of noribogaine with other modulators such as β-arrestin. In a normal state, arrestins interact with GPCRs in a regulatory manner and function to negatively regulate signal transduction. The previously mentioned studies have established that noribogaine activates the KOR GPCR signaling pathway with slightly less efficacy than dynorphin A, an endogenous KOR agonist.

In contrast, noribogaine activates the KOR β-arrestin with significantly less efficacy than dynorphin A; in this case, noribogaine is effectively acting as an agonist of the GPRC pathway and antagonist of the β-arrestin pathway.[71] The typical adverse effects such as dysphoria and anhedonia have been thought to result from the β-arrestin pathway.[73] It is hypothesized that this unique, biased KOR agonist/antagonist pharmacology coupled with weak MOR antagonism may allow noribogaine to have analgesic and anti-addictive properties without the side-effect profile typical to other KOR agonists.

CLINICAL STUDIES

KETAMINE

Despite the promising effects of LSD, the illegality of the drug has led researchers to favor other potential psychedelic therapies since Savage and McCabe's paper was published in 1973. Another potential therapy is ketamine, a general anesthetic that can elicit a psychedelic experience in smaller doses. A 2002 study in Russia compared the effects of a high, psychedelic dose of ketamine with a low, non-psychedelic amount.[74] In this double-blind, randomized controlled trial, 70 detoxified heroin-addicted patients were randomly assigned to either the treatment, high-dose group (2.0 mg/kg) or the control, low-dose group (0.2 mg/kg). Patients and clinical evaluators were unaware of the dose assigned to each participant. In addition, the control group was given an amount that would not bring about a whole psychedelic experience. Still, it would induce some pharmacological effects, thus serving as an "active placebo" and preserving the double-blind nature of the study.[74] Each patient received ten hours of psychotherapy to prepare them for their psychedelic experience. Patients then underwent one ketamine session, lasting from 1.5 to 2 hours. Psychotherapy was also provided during the session. Patients received further psychotherapy after their ketamine session to help integrate the experience into their lives and allow them to use the occasion to confront their drug use. Psychiatrists collected follow-up data monthly for 24 months after the ketamine-assisted psychotherapy (KPT) session. Participants in the high-dose group showed statistically significantly higher rates of abstinence and lower rates of relapse than those in the low-dose group from the first month and the subsequent 23 months. Both high and low dose groups had statistically significant decreases in craving for heroin, anhedonia, anxiety, and depression. Both groups also displayed a high internal locus of control and an increased understanding of the meaning and purpose of one's life. Of note, none of the participants experienced psychiatric complications or became addicted to ketamine following the session. While both high and low-dose treatments were associated with decreases in craving for heroin, the high-dose treatment proved significantly more effective in maintaining abstinence. The high-dose treatment also achieved a higher rate of abstinence than conventional treatment programs for heroin addiction in Russia.

As a follow-up to the previous study, the same research team conducted a similar study focusing on the effect of repeated treatments of ketamine-assisted psychotherapy (KPT).[52] This study compared a three-session KPT regimen with a single session in people with heroin addiction. Fifty-nine participants were randomly assigned to either a three KPT session group or a control, single KPT session group. Both groups received a psychedelic high-dose administration of ketamine (2.0 mg/kg). Both groups also received psychotherapy before, during, and after ketamine administration. Before the first administration, all patients received five hours of psychotherapy. All patients received monthly one-hour sessions of addiction counseling one and two months following the first KPT session. Participants in the multiple KPT group also received one hour of psychotherapy following their second and third sessions. Follow-up was conducted with all patients one month after their final treatment and then at three-month intervals for the remainder of the year. Kaplan-Meier survival analysis was used to evaluate abstinence rates between the two groups. This revealed that the multiple KPT group had a statistically higher rate of abstinence throughout the year of follow-up, with 13 of 26 participants (50%) remaining abstinent as compared to 6 of 27 participants (22.2%) in the single KPT group. Craving for heroin, anxiety, and depression were significantly reduced in both groups; there was no significant difference between the multiple and single KPT groups. The results of this study suggest that various treatments with ketamine-assisted psychotherapy are more beneficial in preventing opioid relapse than a single session.[52]

IBOGAINE

A 1999 paper by Alper et al. recounts 33 cases from 1962-1993 of patients with heroin-dependence treated with ibogaine who were experiencing withdrawal.[75] These patients were instructed to ingest their last food, liquids, heroin, or other substances 8-10 hours before ibogaine administration. Treatments were then provided in an informal setting in a hotel room or apartment with one or more co-authors present for at least the first 48 hours post-treatment. Withdrawal symptoms were monitored by the co-authors, who had extensive experience observing opioid withdrawal reactions. 25 of the 33 participants (76%) had no signs or symptoms of opioid withdrawal at 24 and 48 hours and did not seek to obtain opioids for at least 72 hours following ibogaine administration.[75] Many of the patients were already experiencing mild withdrawal symptoms at the time of the first ibogaine dosage. Relief of withdrawal symptoms typically occurred within 1-3 hours of ibogaine administration. Only one of the 33 subjects had clear signs and symptoms of opioid withdrawal. It was suspected that the ibogaine dosage administered in this case

was not sufficient. One patient also suffered a fatal outcome, dying of respiratory arrest approximately 19 hours after ibogaine treatment. The forensic pathological examination could not determine a definitive cause of death, but the patient may have used opioids following ibogaine administration. There is evidence that ibogaine strengthens the effects of opioids, which could have led to the patient's respiratory arrest. While the informal setting of these observations and the lack of an objective rating system for opioid withdrawal symptoms limits the conclusiveness of this study, it can be assumed that ibogaine administration did attenuate the symptoms of opioid withdrawal.[75]

An observational study published in 2018 further validated the potential of ibogaine in treating opioid use disorder.[76] This study followed up with patients treated with ibogaine at two private clinics in Baja, California, Mexico. Thirty patients were initially enrolled in the study; these patients averaged 29.0 ± 3.2 days of opioid use over the previous 30 days and used at least one opioid for an average of 5.2 ± 3.0 consecutive years. Patients were stabilized on a short-acting opioid for two to three days before receiving ibogaine. Subjects were instructed to abstain from opioid use overnight before administration of ibogaine. A "test" dose of ibogaine (3 mg/kg) was given when participants began to exhibit three or more signs of opioid withdrawal. A larger, "flood" dose of ibogaine was administered 2 to 12 hours after the test dose. "Booster" doses were also occasionally given if withdrawal symptoms re-emerged. Evaluation of response to ibogaine was conducted using the Subjective Opioid Withdrawal Scale (SOWS) and the Addiction Severity Index (ASI), Lite Version. SOWS is used to quantify subjective feelings of opioid withdrawal. SOWS data was recorded pre-treatment and within the first few days post-treatment. The average time between baseline and repeat SOWS evaluation was 76.5 ± 30 hours. The average SOWS score pre-treatment was 31.0 ± 11.6 compared to 14.0 ± 9.8 post-treatment, a mean reduction of 17.0 ± 12.5 points ($t = 7.07$, $df = 26$, $p < .001$).[76]

This effect is similar to that seen in methadone treatment of opioid withdrawal.[77] ASI evaluation was done pre-treatment and at 1, 3, 6, 9, and 12 months post-treatment. This assessment records values in seven distinct areas: drug use, alcohol use, family/social, employment, legal, medical, and psychiatric status.[78] The scores in each area can be combined into an ASI Composite score (ASIC). Statistically significant decreases in ASIC scores, indicating improvement from baseline, were seen at all post-treatment time points in the drug use, family/social status, and legal status categories. 50% of subjects reported no opioid use in the previous 30 days at one-month post-treatment and 33% reported complete abstinence over the previous 30 days at three months post-treatment. This is compared to 18% abstinence at four weeks following treatment with buprenorphine and 26% abstinence at six weeks following methadone, according to systematic reviews conducted in 2015 and 2013, respectively.[79,80]

Participants in the study frequently stated that they found the psychedelic experience associated with ibogaine beneficial in addition to the cessation of opioid withdrawal symptoms.[76] A common theme was visions of past life experiences accompanied by a feeling of remorse about prior drug use. Some participants also experienced an interval of decreased drug-craving following ibogaine treatment in which they felt that they were able to achieve stability in their lives that helped them from relapsing.

Another study further reinforced the anti-addictive properties and blood-brain permeability of noribogaine while also evaluating the liability burden in rodents. The study showed that administration of noribogaine improved symptoms of naloxone-induced withdrawal in opioid-dependent mice. Measured objectively, there was an 88% decrease in the global opiate withdrawal score. Other portions of the study sought to test the blood-brain permeability further and evaluate for abuse liability. Results of the study indicated a high blood-brain penetration with a brain/blood ratio of 7. Abuse liability was assessed using a place paradigm; rats treated with noribogaine did not show a place preference, suggesting any reward-based stimulus associated with administration.[81]

DRONABINOL

It has been noted as far back as 1976 that cannabinoids may reduce the severity of opioid withdrawal and several other preclinical studies have supported this finding.[82–85] Dronabinol, a synthetic form of THC, has become a popular potential therapy for opioid use disorder in recent years. A 2015 double-blind, placebo-controlled trial examined the effect of dronabinol administration on naltrexone-assisted opioid cessation.[86] Naltrexone is one of the traditional treatments for OUD, but its use may be associated with significant withdrawal symptoms, as it is an opioid receptor antagonist. It was hypothesized that using dronabinol would reduce withdrawal symptoms during the initial stage of naltrexone treatment.

Study participants were admitted to an inpatient research unit for an eight-day stay consisting of opioid detoxification and XR-naltrexone induction. Subjects were stabilized on buprenorphine on Day 2 before undergoing opioid washout on days 3 and 4. Increasing doses of naltrexone were given on Days 5-7, followed by an injection of XR-naltrexone on Day 8. Patients were discharged on Day 9. Participants were randomized to receive either dronabinol or placebo in addition to other medications.[86] Forty patients were given 30 mg dronabinol, while 20 were given a placebo. After discharge, patients received an additional eight weeks of outpatient treatment, attending the clinic thrice weekly. Dronabinol or placebo was continued outpatient for five weeks. A further injection of XR-naltrexone was given at four weeks. The severity of opioid withdrawal was assessed using the SOWS. Patients presented on Day 1 with low to moderate levels of withdrawal severity with no significant difference between treatment groups.[86]

Overall, observed withdrawal scores were higher in the placebo group (26.5) than in the dronabinol group (16.7) ($p = 0.005$).[86] This difference appeared to be mainly attributable to differential effects in the pre-naltrexone stage of treatment. On Days 2-4, before the induction of naltrexone therapy, a significant difference in observed with-

drawal symptoms was observed, with a difference of 11.34 ($p = 0.003$). Withdrawal scores for the two groups became more similar after the start of naltrexone therapy, with a difference of 6.69 and no statistical significance seen ($p = 0.13$).[86] Despite this apparent difference between Days 2-4 and Days 5-8, no difference was noted when the SOWS scores of these two time periods were compared.

While the effect of dronabinol on withdrawal symptoms was the primary objective of this study, a secondary goal was to determine if dronabinol would increase patient retention in treatment. Analysis showed no significant difference in the completion of 8 weeks of naltrexone treatment between the two groups (66% in the dronabinol group, 55% in the placebo group; $p = 0.23$).[86] The most common adverse effects seen in the study were insomnia, nausea/vomiting, diarrhea, mood changes, and fatigue/drowsiness. These effects were likely due to naltrexone-related prolonged withdrawal, and no difference was seen between treatment groups. This suggests that dronabinol may only be effective at relieving acute opioid withdrawal and not protracted withdrawal or naltrexone-induced withdrawal. Dronabinol was well-tolerated, as indicated by the similar number of adverse effects among treatment groups. Additionally, there were identical requests to decrease dosage in control and treatment groups.

Another study examined the effects of dronabinol alone on opioid withdrawal compared to oxycodone and placebo.[87] Subject participants were self-reported users of short-acting opiates on ⩾ 21 of the past 30 days. The study was conducted at a residential research facility at the University of Kentucky. After admission to the research facility, patients were stabilized on oral oxycodone. After at least five days of stabilization, seven double-blind experimental sessions were conducted, each separated by at least 72 hours. Patients were given placebo, oxycodone (30 or 60 mg), or dronabinol (5, 10, 20, or 40 mg). After the first two subjects to receive dronabinol 40 mg developed tachycardia and anxiety, this dose was lowered to 30 mg. Results of this study showed a reliable attenuation of opioid withdrawal symptoms by oxycodone. Higher doses (20 and 30 mg) of dronabinol showed some efficacy in attenuating withdrawal symptoms; however, it was much less effective than oxycodone.[87] High-dose dronabinol was associated with withdrawal scores 34-48% lower than placebo, compared with a 62-70% decrease on oxycodone.[87] Lower doses (5 and 10 mg) of dronabinol showed minimal efficacy in suppressing withdrawal. Higher doses of dronabinol were associated with tachycardia (107.6 bpm with 20 mg, 112.6 bpm with 30 mg) and psychoactive effects. Dronabinol also increased subjective "drug effect," "high," "sedation," and "bad effects" as compared to placebo. Dronabinol 20 mg did, however, reduce the "desire for opiates."[87] Limitations of this study include a small sample size, with only 12 participants involved. The author of this study concluded that dronabinol is not a very effective treatment for opioid withdrawal due to its modest effect and association with significant tachycardia.[87] These adjuvant agents are summarized in Table 1.

Table 1. Adjuvant agents, efficacy and disadvantages in opioid abuse patients.

Agent	Efficacy	Disadvantages
Ketamine	Increased rates of abstinence; decreased opioid craving, anxiety	Possible negative psychedelic experience
Ibogaine	Decreased opioid withdrawal symptoms; increased rates of abstinence	Illegal, QT prolongation
Dronabinol	Variable effects, with high doses resulting in moderate decreases in withdrawal symptoms	Tachycardia, sedation

CONCLUSION

The opioid epidemic is one of the most pressing public health crises the United States has ever faced. The crisis presents a multifaceted burden on human lives, relationships, and the economy. Preventing the development of opioid addiction via primary prevention measures such as provider education and more cautious prescription is desirable. However, even since the magnitude of the crisis has been recognized and actions such as these have begun to be implemented, the use of illicit street drugs such as fentanyl and heroin has continued to rise. Overdose deaths continue to increase every year. It is thus imperative that tertiary treatment measures for patients suffering from OUD continue to be explored and refined.

Current tertiary treatment typically revolves around using a variety of opioid receptor agonists, partial-agonists, and antagonists. Beyond these standard medications used for OUD, alternative medications can be effective in some instances. Ketamine has effectively decreased opioid cravings both by itself and when used in conjunction with psychotherapy. The primary negatives of ketamine as a therapy revolve around potential psychodysleptic experiences. Ibogaine has been shown to decrease withdrawal symptoms and increase abstinence rates. The primary downsides of ibogaine are visual disturbances and QT prolongation, which would necessitate routine cardiac monitoring. Finally, the cannabinoid dronabinol has been seen to have varying effects. High doses appear to reduce withdrawal symptoms. This high dosing comes at the expense of increased adverse side effects such as sedation and tachycardia. As is apparent, there are potentially both benefits and risks of using these alternative medications in treating OUD. Further research certainly needs to be performed to determine how to maximize the efficacy and minimize unwanted side effects of these medications in treating patients suffering from opioid addiction.

REFERENCES

1. Centers for Disease Control and Prevention (CDC). CDC grand rounds: prescription drug overdoses - a U.S. epidemic. *MMWR Morb Mortal Wkly Rep*. 2012;61(1):10-13.

2. Chen LH, Hedegaard H, Warner M. Drug-poisoning Deaths Involving Opioid Analgesics: United States, 1999-2011. *NCHS Data Brief*. 2014;(166):1-8.

3. Hedegaard H, Miniño AM, Spencer MR, Warner M. Drug Overdose Deaths in the United States, 1999–2020. *NCHS Data Brief*. 2021;(426):1-8. doi:10.15620/cdc:112340

4. Advisors WHC of E. The underestimated cost of the opioid crisis. Published online 2017.

5. Azadfard M, Huecker MR, Leaming JM. Opioid Addiction. In: *StatPearls*. StatPearls Publishing; 2022. Accessed June 24, 2022. http://www.ncbi.nlm.nih.gov/books/NBK448203/

6. Vadivelu N, Kai AM, Kodumudi V, Sramcik J, Kaye AD. The Opioid Crisis: a Comprehensive Overview. *Curr Pain Headache Rep*. 2018;22(3):16. doi:10.1007/s11916-018-0670-z

7. Hagemeier NE. Introduction to the opioid epidemic: the economic burden on the healthcare system and impact on quality of life. *Am J Manag Care*. 2018;24(10 Suppl):S200-S206.

8. U.S. Opioid Dispensing Rate Maps | Drug Overdose | CDC Injury Center. Published March 18, 2022. Accessed June 21, 2022. https://www.cdc.gov/drugoverdose/rxrate-maps/index.html

9. Kolodny A, Courtwright DT, Hwang CS, et al. The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction. *Annu Rev Public Health*. 2015;36:559-574. doi:10.1146/annurev-publhealth-031914-122957

10. Dyer O. Opioid lawsuits: Sackler family agree final $6bn civil settlement with US states. *BMJ*. 2022;376:o616. doi:10.1136/bmj.o616

11. Mularski RA, White-Chu F, Overbay D, Miller L, Asch SM, Ganzini L. Measuring Pain as the 5th Vital Sign Does Not Improve Quality of Pain Management. *J Gen Intern Med*. 2006;21(6):607-612. doi:10.1111/j.1525-1497.2006.00415.x

12. DSM 5 criteria for Opioid Use Disorder. DSM 5 criteria for Opioid Use Disorder. Accessed July 3, 2022. https://www.asam.org/docs/default-source/education-docs/dsm-5-dx-oud-8-28-2017.pdf

13. Pergolizzi JV Jr, Raffa RB, Rosenblatt MH. Opioid withdrawal symptoms, a consequence of chronic opioid use and opioid use disorder: Current understanding and approaches to management. *J Clin Pharm Ther*. 2020;45(5):892-903. doi:10.1111/jcpt.13114

14. Wang SC, Chen YC, Lee CH, Cheng CM. Opioid Addiction, Genetic Susceptibility, and Medical Treatments: A Review. *Int J Mol Sci*. 2019;20(17):4294. doi:10.3390/ijms20174294

15. Piazza PV, Deroche-Gamonet V. A multistep general theory of transition to addiction. *Psychopharmacology (Berl)*. 2013;229(3):387-413. doi:10.1007/s00213-013-3224-4

16. Koob GF. Negative reinforcement in drug addiction: the darkness within. *Curr Opin Neurobiol*. 2013;23(4):559-563. doi:10.1016/j.conb.2013.03.011

17. Schwartz RP, Kelly SM, O'Grady KE, et al. In-treatment vs. out-of-treatment opioid dependent adults: drug use and criminal history. *Am J Drug Alcohol Abuse*. 2008;34(1):17-28. doi:10.1080/00952990701653826

18. Tsuang MT, Lyons MJ, Meyer JM, et al. Co-occurrence of abuse of different drugs in men: the role of drug-specific and shared vulnerabilities. *Arch Gen Psychiatry*. 1998;55(11):967-972. doi:10.1001/archpsyc.55.11.967

19. Chawarski MC, Hawk K, Edelman EJ, et al. Use of Amphetamine-Type Stimulants Among Emergency Department Patients With Untreated Opioid Use Disorder. *Ann Emerg Med*. 2020;76(6):782-787. doi:10.1016/j.annemergmed.2020.06.046

20. Salsitz E, Wiegand T. Pharmacotherapy of Opioid Addiction: "Putting a Real Face on a False Demon." *J Med Toxicol*. 2016;12(1):58-63. doi:10.1007/s13181-015-0517-5

21. Wang S. Historical Review: Opiate Addiction and Opioid Receptors. *Cell Transplant*. 2019;28(3):233-238. doi:10.1177/0963689718811060

22. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev*. 2014;(2):CD002207. doi:10.1002/14651858.cd002207.pub4

23. Sharma B, Bruner A, Barnett G, Fishman M. Opioid Use Disorders. *Child Adolesc Psychiatr Clin N Am*. 2016;25(3):473-487. doi:10.1016/j.chc.2016.03.002

24. Bhalla S, Andurkar SV, Gulati A. Neurobiology of opioid withdrawal: Role of the endothelin system. *Life Sci*. 2016;159:34-42. doi:10.1016/j.lfs.2016.01.016

25. McElrath K, Joseph H. Medication-Assisted Treatment (MAT) for Opioid Addiction: Introduction to the Special Issue. *Substance Use & Misuse*. 2017;53(2):177-180. doi:10.1080/10826084.2017.1404106

26. Kreek MJ, Levran O, Reed B, Schlussman SD, Zhou Y, Butelman ER. Opiate addiction and cocaine addiction: underlying molecular neurobiology and genetics. *J Clin Invest*. 2012;122(10):3387-3393. doi:10.1172/jci60390

27. Webster LR. Risk Factors for Opioid-Use Disorder and Overdose. *Anesth Analg*. 2017;125(5):1741-1748. doi:10.1213/ane.0000000000002496

28. Kreek MJ, Reed B, Butelman ER. Current status of opioid addiction treatment and related preclinical research. *Sci Adv*. 2019;5(10):eaax9140. doi:10.1126/sciadv.aax9140

29. Kosten TR, Baxter LE. Review article: Effective management of opioid withdrawal symptoms: A gateway to opioid dependence treatment. *Am J Addict*. 2019;28(2):55-62. doi:10.1111/ajad.12862

30. Srivastava AB, Mariani JJ, Levin FR. New directions in the treatment of opioid withdrawal. *Lancet*. 2020;395(10241):1938-1948. doi:10.1016/s0140-6736(20)30852-7

31. Tisdale JE, Chung MK, Campbell KB, et al. Drug-Induced Arrhythmias: A Scientific Statement From the American Heart Association. *Circulation*. 2020;142(15):e214-e233. doi:10.1161/cir.0000000000000905

32. Whelan PJ, Remski K. Buprenorphine vs methadone treatment: A review of evidence in both developed and developing worlds. *J Neurosci Rural Pract*. 2012;3(1):45-50. doi:10.4103/0976-3147.91934

33. Sigmon SC, Bisaga A, Nunes EV, O'Connor PG, Kosten T, Woody G. Opioid detoxification and naltrexone induction strategies: recommendations for clinical practice. *Am J Drug Alcohol Abuse*. 2012;38(3):187-199. doi:10.3109/00952990.2011.653426

34. Mion G, Villevieille T. Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). *CNS Neurosci Ther*. 2013;19(6):370-380. doi:10.1111/cns.12099

35. Dundee JW, Bovill J, Knox JWD, et al. Ketamine as an induction agent in anaesthetics. *Lancet*. 1970;295(7661):1370-1371. doi:10.1016/s0140-6736(70)91273-0

36. Zanos P, Moaddel R, Morris PJ, et al. Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms. *Pharmacol Rev*. 2018;70(3):621-660. doi:10.1124/pr.117.015198

37. Morgan CJA, Curran HV, Independent Scientific Committee on Drugs. Ketamine use: a review. *Addict Abingdon Engl*. 2012;107(1):27-38. doi:10.1111/j.1360-0443.2011.03576.x

38. Nowacka A, Borczyk M. Ketamine applications beyond anesthesia – A literature review. *Eur J Pharmacol*. 2019;860:172547. doi:10.1016/j.ejphar.2019.172547

39. Curran HV, Morgan C. Cognitive, dissociative and psychotogenic effects of ketamine in recreational users on the night of drug use and 3 days later. *Addict Abingdon Engl*. 2000;95(4):575-590. doi:10.1046/j.1360-0443.2000.9545759.x

40. Rao LK, Flaker AM, Friedel CC, Kharasch ED. Role of Cytochrome P4502B6 Polymorphisms in Ketamine Metabolism and Clearance. *Anesthesiology*. 2016;125(6):1103-1112. doi:10.1097/aln.0000000000001392

41. Franks NP, Lieb WR. Molecular and cellular mechanisms of general anaesthesia. *Nature*. 1994;367(6464):607-614. doi:10.1038/367607a0

42. Dilmore JG, Johnson JW. Open channel block and alteration of N-methyl-D-aspartic acid receptor gating by an analog of phencyclidine. *Biophys J*. 1998;75(4):1801-1816. doi:10.1016/s0006-3495(98)77622-2

43. Kohrs R, Durieux ME. Ketamine: teaching an old drug new tricks. *Anesth Analg*. 1998;87(5):1186-1193. doi:10.1097/00000539-199811000-00039

44. Udesky JO, Spence NZ, Achiel R, Lee C, Flood P. The role of nicotinic inhibition in ketamine-induced behavior. *Anesth Analg*. 2005;101(2):407-411. doi:10.1213/01.ane.0000155291.81338.90

45. Pacheco D da F, Romero TRL, Duarte IDG. Central antinociception induced by ketamine is mediated by endogenous opioids and μ- and δ-opioid receptors. *Brain Res*. 2014;1562:69-75. doi:10.1016/j.brainres.2014.03.026

46. Domino EF, Chodoff P, Corssen G. Pharmacologic effects of CI-581, a new dissociative anesthetic, in man. *Clin Pharmacol Ther*. 1965;6(3):279-291. doi:10.1002/cpt196563279

47. Serafini G, Howland R, Rovedi F, Girardi P, Amore M. The Role of Ketamine in Treatment-Resistant Depression: A Systematic Review. *Curr Neuropharmacol*. 2014;12(5):444-461. doi:10.2174/1570159x12666140619204251

48. Loo CK, Gálvez V, O'Keefe E, et al. Placebo-controlled pilot trial testing dose titration and intravenous, intramuscular and subcutaneous routes for ketamine in depression. *Acta Psychiatr Scand*. 2016;134(1):48-56. doi:10.1111/acps.12572

49. Reinstatler L, Youssef NA. Ketamine as a potential treatment for suicidal ideation: a systematic review of the literature. *Drugs R D*. 2015;15(1):37-43. doi:10.1007/s40268-015-0081-0

50. Zhou X, Zhang P, Luo W, et al. Ketamine induces apoptosis in lung adenocarcinoma cells by regulating the expression of CD69. *Cancer Med*. 2018;7(3):788-795. doi:10.1002/cam4.1288

51. Malsy M, Gebhardt K, Gruber M, Wiese C, Graf B, Bundscherer A. Effects of ketamine, s-ketamine, and MK 801 on proliferation, apoptosis, and necrosis in pancreatic cancer cells. *BMC Anesthesiol*. 2015;15:111. doi:10.1186/s12871-015-0076-y

52. Krupitsky EM, Burakov AM, Dunaevsky IV, Romanova TN, Slavina TY, Grinenko AY. Single versus repeated sessions of ketamine-assisted psychotherapy for people with heroin dependence. *J Psychoactive Drugs*. 2007;39(1):13-19. doi:10.1080/02791072.2007.10399860

53. Krupitsky EM, Grinenko AY. Ketamine psychedelic therapy (KPT): a review of the results of ten years of research. *J Psychoactive Drugs*. 1997;29(2):165-183. doi:10.1080/02791072.1997.10400185

54. Dakwar E, Levin F, Foltin RW, Nunes EV, Hart CL. The effects of subanesthetic ketamine infusions on motivation to quit and cue-induced craving in cocaine-dependent research volunteers. *Biol Psychiatry*. 2014;76(1):40-46. doi:10.1016/j.biopsych.2013.08.009

55. Zuardi AW. History of cannabis as a medicine: a review. *Rev Bras Psiquiatr Sao Paulo Braz 1999*. 2006;28(2):153-157. doi:10.1590/s1516-44462006000200015

56. Cohen K, Weizman A, Weinstein A. Positive and Negative Effects of Cannabis and Cannabinoids on Health. *Clin Pharmacol Ther*. 2019;105(5):1139-1147. doi:10.1002/cpt.1381

57. D'Souza DC, Perry E, MacDougall L, et al. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol*. 2004;29(8):1558-1572. doi:10.1038/sj.npp.1300496

58. Thomas G, Kloner RA, Rezkalla S. Adverse cardiovascular, cerebrovascular, and peripheral vascular effects of marijuana inhalation: what cardiologists need to know. *Am J Cardiol*. 2014;113(1):187-190. doi:10.1016/j.amjcard.2013.09.042

59. Fraguas-Sánchez AI, Torres-Suárez AI. Medical Use of Cannabinoids. *Drugs*. 2018;78(16):1665-1703. doi:10.1007/s40265-018-0996-1

60. Console-Bram L, Marcu J, Abood ME. Cannabinoid receptors: nomenclature and pharmacological principles. *Prog Neuropsychopharmacol Biol Psychiatry*. 2012;38(1):4-15. doi:10.1016/j.pnpbp.2012.02.009

61. Porter BE, Jacobson C. Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. *Epilepsy Behav EB*. 2013;29(3):574-577. doi:10.1016/j.yebeh.2013.08.037

62. Chagas MHN, Zuardi AW, Tumas V, et al. Effects of cannabidiol in the treatment of patients with Parkinson's disease: an exploratory double-blind trial. *J Psychopharmacol Oxf Engl*. 2014;28(11):1088-1098. doi:10.1177/0269881114550355

63. Müller-Vahl KR, Schneider U, Koblenz A, et al. Treatment of Tourette's syndrome with Delta 9-tetrahydrocannabinol (THC): a randomized crossover trial. *Pharmacopsychiatry*. 2002;35(2):57-61. doi:10.1055/s-2002-25028

64. Newmeyer MN, Swortwood MJ, Barnes AJ, Abulseoud OA, Scheidweiler KB, Huestis MA. Free and Glucuronide Whole Blood Cannabinoids' Pharmacokinetics after Controlled Smoked, Vaporized, and Oral Cannabis Administration in Frequent and Occasional Cannabis Users: Identification of Recent Cannabis Intake. *Clin Chem*. 2016;62(12):1579-1592. doi:10.1373/clinchem.2016.263475

65. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet*. 2003;42(4):327-360. doi:10.2165/00003088-200342040-00003

66. Lucas CJ, Galettis P, Schneider J. The pharmacokinetics and the pharmacodynamics of cannabinoids. *Br J Clin Pharmacol*. 2018;84(11):2477-2482. doi:10.1111/bcp.13710

67. Devinsky O, Cilio MR, Cross H, et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia*. 2014;55(6):791-802. doi:10.1111/epi.12631

68. Schwope DM, Karschner EL, Gorelick DA, Huestis MA. Identification of recent cannabis use: whole-blood and plasma free and glucuronidated cannabinoid pharmacokinetics following controlled smoked cannabis administration. *Clin Chem*. 2011;57(10):1406-1414. doi:10.1373/clinchem.2011.171777

69. Gaston TE, Friedman D. Pharmacology of cannabinoids in the treatment of epilepsy. *Epilepsy Behav EB*. 2017;70(Pt B):313-318. doi:10.1016/j.yebeh.2016.11.016

70. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. *Br J Pharmacol*. 2008;153(2):199-215. doi:10.1038/sj.bjp.0707442

71. Maillet EL, Milon N, Heghinian MD, et al. Noribogaine is a G-protein biased κ-opioid receptor agonist. *Neuropharmacology*. 2015;99:675-688. doi:10.1016/j.neuropharm.2015.08.032

72. Corkery JM. Chapter 8 - Ibogaine as a treatment for substance misuse: Potential benefits and practical dangers. In: Calvey T, ed. *Progress in Brain Research*. Vol 242. Psychedelic Neuroscience. Elsevier; 2018:217-257. doi:10.1016/bs.pbr.2018.08.005

73. Ehrich JM, Messinger DI, Knakal CR, et al. Kappa Opioid Receptor-Induced Aversion Requires p38 MAPK Activation in VTA Dopamine Neurons. *J Neurosci*. 2015;35(37):12917-12931. doi:10.1523/jneurosci.2444-15.2015

74. Krupitsky E, Burakov A, Romanova T, Dunaevsky I, Strassman R, Grinenko A. Ketamine psychotherapy for heroin addiction: immediate effects and two-year follow-up. *J Subst Abuse Treat*. 2002;23(4):273-283. doi:10.1016/s0740-5472(02)00275-1

75. Alper KR, Lotsof HS, Frenken GM, Luciano DJ, Bastiaans J. Treatment of acute opioid withdrawal with ibogaine. *Am J Addict*. 1999;8(3):234-242. doi:10.1080/105504999305848

76. Brown TK, Alper K. Treatment of opioid use disorder with ibogaine: detoxification and drug use outcomes. *Am J Drug Alcohol Abuse*. 2018;44(1):24-36. doi:10.1080/00952990.2017.1320802

77. Handelsman L, Cochrane KJ, Aronson MJ, Ness R, Rubinstein KJ, Kanof PD. Two new rating scales for opiate withdrawal. *Am J Drug Alcohol Abuse*. 1987;13(3):293-308. doi:10.3109/00952998709001515

78. Cacciola JS, Alterman AI, McLellan AT, Lin YT, Lynch KG. Initial evidence for the reliability and validity of a "Lite" version of the Addiction Severity Index. *Drug Alcohol Depend*. 2007;87(2-3):297-302. doi:10.1016/j.drugalcdep.2006.09.002

79. Discontinuation of Buprenorphine Maintenance Therapy: Perspectives and Outcomes - PMC. Accessed July 3, 2022. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4382404/

80. Amato L, Davoli M, Minozzi S, Ferroni E, Ali R, Ferri M. Methadone at tapered doses for the management of opioid withdrawal. *Cochrane Database Syst Rev*. 2013;(2):CD003409. doi:10.1002/14651858.cd003409.pub4

81. Mash DC, Ameer B, Prou D, Howes JF, Maillet EL. Oral noribogaine shows high brain uptake and anti-withdrawal effects not associated with place preference in rodents. *J Psychopharmacol Oxf Engl*. 2016;30(7):688-697. doi:10.1177/0269881116641331

82. Yamaguchi T, Hagiwara Y, Tanaka H, et al. Endogenous cannabinoid, 2-arachidonoylglycerol, attenuates naloxone-precipitated withdrawal signs in morphine-dependent mice. *Mol Brain Res*. 2001;909(1-2):121-126. doi:10.1016/s0006-8993(01)02655-5

83. Vela G, Ruiz-Gayo M, Fuentes JA. Anandamide decreases naloxone-precipitated withdrawal signs in mice chronically treated with morphine. *Neuropharmacology*. 1995;34(6):665-668. doi:10.1016/0028-3908(95)00032-2

84. Opioid and Cannabinoid Modulation of Precipitated Withdrawal in Δ9-Tetrahydrocannabinol and Morphine-Dependent Mice | Journal of Pharmacology and Experimental Therapeutics. Accessed July 3, 2022. https://jpet.aspetjournals.org/content/298/3/1007/tab-article-info

85. Wills KL, Parker LA. Effect of Pharmacological Modulation of the Endocannabinoid System on Opiate Withdrawal: A Review of the Preclinical Animal Literature. *Front Pharmacol*. 2016;7:187. doi:10.3389/fphar.2016.00187

86. Bisaga A, Sullivan MA, Glass A, et al. THE EFFECTS OF DRONABINOL DURING DETOXIFICATION AND THE INITIATION OF TREATMENT WITH EXTENDED RELEASE NALTREXONE. *Drug Alcohol Depend*. 2015;154:38-45. doi:10.1016/j.drugalcdep.2015.05.013

87. Lofwall MR, Babalonis S, Nuzzo PA, Elayi SC, Walsh SL. Opioid withdrawal suppression efficacy of oral dronabinol in opioid dependent humans. *Drug Alcohol Depend*. 2016;164:143-150. doi:10.1016/j.drugalcdep.2016.05.002