

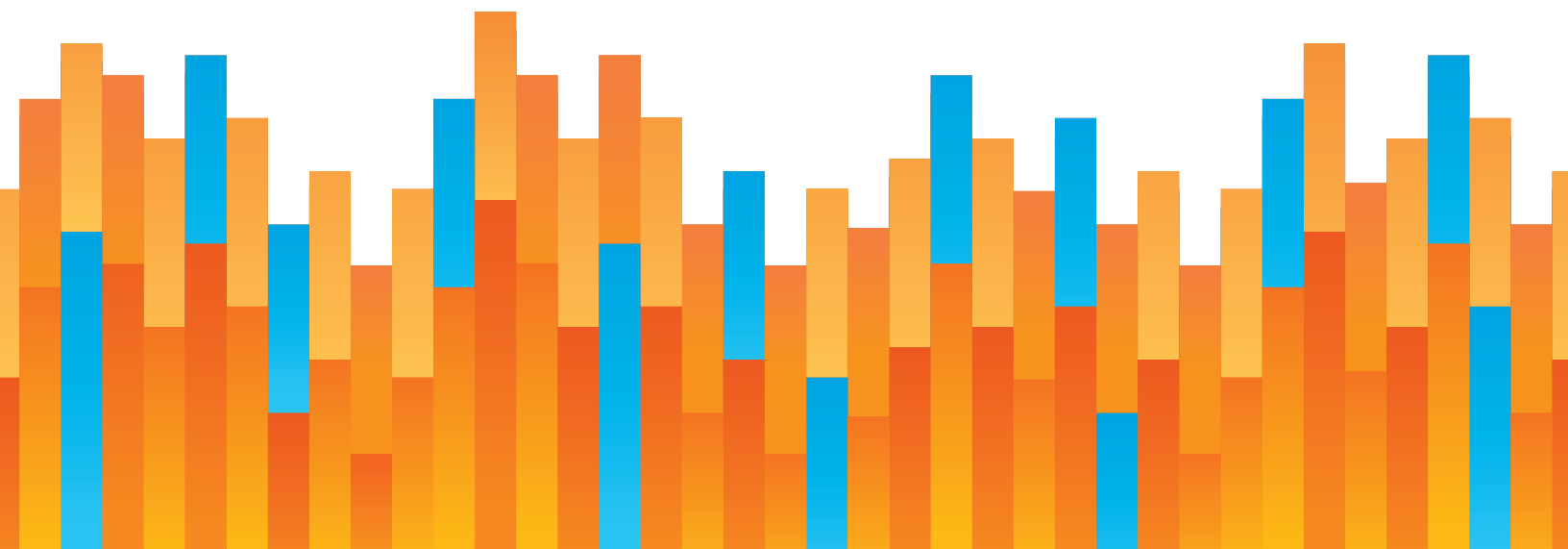


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IBOGAINE TREATMENT FOR OPIOID USE DISORDER

by Madison Carlino
Project Director: Geoffrey Lawrence

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EXECUTIVE SUMMARY

The last decade has seen an explosion of opioid addiction and overdose deaths, a public health crisis fueling a demand for medical and governmental intervention. This brief is a comprehensive overview of the reported results of studies investigating the potential of ibogaine, a psychoactive compound derived from the Tabernanthe iboga plant, in treating opioid addiction.

Existing Medication-Assisted Treatments (MATs), also referred to as Medications for Opioid Use Disorder (MOUD), are examined as a frame of reference. Outcome measures examined include withdrawals and craving, retention, relapse, abstinence duration, mortality, adverse events, risk of diversion, short-term abstinence, long-term abstinence, program costs, and depression.

A consistent theme emerges from the research conducted to date into ibogaine as a prospective treatment for opioid use disorder (OUD): Ibogaine and ibogaine analogues are the only known treatments that consistently and immediately reduce both physical withdrawal symptoms from opioid addiction and psychological dependence without the need for ongoing medication. However, there are no large-scale studies of ibogaine and more research is needed to understand if it could satisfy patients' medical needs.

Existing challenges of MATs include increased mortality rates following treatment cessation, high relapse rates, low retention rates, adverse events that include respiratory

depression and QT prolongation, risk of diversion, and limited access. Some studies suggest ibogaine treatment is more effective than MATs in combating these existing challenges.

Based on existing research, ibogaine therapy shows potential to be an effective alternative treatment method for OUD. Its ability to reduce and eliminate opioid withdrawal and craving symptoms plays a key role in the reduction and abstinence of illicit opioid use. Hence, ibogaine can help users achieve lasting anti-addictive effects at fewer doses, whereas traditional MATs just abate dependence. Policymakers should consider ibogaine as a potential alternative treatment for OUD.



... traditional abatement mechanisms present many challenges for recovering addicts and have demonstrated only limited success in helping opioid-addicted persons overcome their addiction.



Nonetheless, it is still important to acknowledge the existence of potential safety risks associated with ibogaine treatment. More serious risks include cardiotoxicity and death. However, mitigation strategies have proven successful when administered in clinical settings. For example, Deborah Mash's ibogaine clinic in St. Kitts, West Indies, conducted 257 treatments from 1996 to 2004 without any related deaths or serious adverse events. Hence, professional oversight and proper clinical procedures are necessary conditions.

Several states participated in lawsuits against manufacturers and distributors of prescription opioids and received large settlement funds that are largely restricted for programs intended to abate the impact of opioid addiction. One potential avenue for doing this is to advance the development of a therapy that may allow individuals to overcome opioid addiction in as little as one treatment. Based on the clinical and academic studies reviewed here, traditional abatement mechanisms present many challenges for recovering addicts and have demonstrated only limited success in helping opioid-addicted persons overcome their addiction. By contrast, early research shows ibogaine treatment may be a far more promising approach that enables rapid and sustained recovery from addiction.

The State of Kentucky was the first to consider this possibility. Kentucky received \$842 million in settlement proceeds from its participation in a multistate lawsuit. Former

Attorney General Daniel Cameron then established a Kentucky Opioid Abatement Advisory Commission to direct the allocation of these funds toward abatement programs. Throughout a series of public hearings in 2023, the commission considered allocating \$42 million—roughly 5% of Kentucky’s share of opioid settlement proceeds—toward FDA-supervised clinical trials that could lead to approval of ibogaine or its derivatives as a treatment for opioid use disorder. In December 2023, Russell Coleman succeeded Daniel Cameron as Kentucky Attorney General and pressed the commission for a change in direction. Chair Bryan Hubbard said he was asked to resign due to his support for funding ibogaine trials, and he was replaced with a former agent of the federal Drug Enforcement Administration.

However, the initiative first launched in Kentucky now continues elsewhere. In February 2024, Hubbard was retained by the Reaching Everyone in Distress (REID) Foundation, an Ohio-based nonprofit to advance FDA-supervised clinical trials for ibogaine. The REID Foundation will engage in broad based statewide advocacy for the creation of a public-private partnership to advance ibogaine or an ibogaine therapeutic through the FDA. ResultsOHIO has also retained Hubbard to explore projects related to the research, development, and delivery of novel therapeutics like ibogaine for treatment of traumatic brain injury and post-traumatic stress disorder. Despite the change of venue, Ohio is poised to capitalize on the materials accumulated by and on behalf of the Kentucky Opioid Abatement Advisory Commission, including the compilation of research presented here.



Based on existing research, ibogaine therapy shows potential to be an effective alternative treatment method for OUD.



Based on the existing evidence, Reason Foundation concludes that development of ibogaine as a pharmaceutical treatment for opioid use disorder may be the most cost-effective use of funds earmarked for mitigating the harms of the opioid epidemic.

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PART 1

INTRODUCTION

1.1

BACKGROUND

The opioid crisis is a significant public health issue in the United States, affecting communities across the nation. Opioids, including prescription painkillers and illicit substances like heroin and fentanyl, have been associated with a rising number of overdoses, addiction, and deaths. The crisis has had far-reaching social, economic, and healthcare consequences.

In Ohio, like many other states, the opioid crisis has had a profound impact. Ohio has faced high rates of opioid-related deaths, addiction, and associated challenges like strained healthcare systems and increased social and economic burdens. In 2020, Ohio had the fourth-highest age-adjusted drug overdose fatality rate in the United States, at 47.2 deaths per 100,000 people. The total age-adjusted drug overdose fatality rate for the United States was 28.3 in 2020. Approximately 81% of Ohio resident overdose deaths in 2020 involved opioids.¹ Ohio was a party to multistate litigation against pharmaceutical companies, alleging the companies' marketing and distribution practices contributed to the opioid epidemic.

¹ "Drug overdose prevention," kiprc.uky.edu, KIPRC, n.d. <https://kiprc.uky.edu/injury-focus-areas/drug-overdose-prevention> (accessed 1 Dec. 2023).

This legal action resulted with a \$26 billion settlement paid by opioid manufacturers and distributors over 18 years. These funds are intended to address the harms caused by the crisis and support various initiatives, including addiction treatment, prevention, education, and recovery programs. Each state's share of this settlement was determined by agreement among the participating states using a formula that considered a state's number of overdose deaths, number of residents with substance use disorder, the overall quantity of opioids delivered within the state, and the state's population. Ohio's proportionate share of the settlement under this formula was \$680 million.²

“

The total age-adjusted drug overdose fatality rate for the U.S. was 28.3 deaths per 100,000 people in 2020.

”

State lawmakers in Ohio approved legislation to distribute 15% of these funds toward the bulk purchase of prevention, treatment and support services, 30% to local governments for community recovery programs, and the remaining 55% to a state-chartered nonprofit called the OneOhio Recovery Foundation. The OneOhio Recovery Foundation is charged with funding immediate and long-term projects that will help combat the opioid crisis.³ Ohio separately boasts a framework for public-private partnerships called ResultsOHIO that requires private financiers to pay upfront costs of a promising new project but allows for subsequent public reimbursement after the project yields verifiable results. A third entity, the REID Foundation—a private nonprofit—has pledged to financially support development of ibogaine as pharmaceutical and later seek reimbursement from the OneOhio Recovery Foundation through ResultsOHIO.⁴

² Ohio Attorney General's Office, "AG Yost Secures \$679.6 Million for Opioid Recovery from Settlement with 2 Drug Makers, 2 Pharmacies," June 9, 2023 Press Release, [https://www.ohioattorneygeneral.gov/Media/News-Releases/June-2023/AG-Yost-Secures-\\$679-6-Million-for-Opioid-Recovery](https://www.ohioattorneygeneral.gov/Media/News-Releases/June-2023/AG-Yost-Secures-$679-6-Million-for-Opioid-Recovery).

³ Dylan Armstrong, "OneOhio Recovery Foundation: How'd We Get Here and What's Been Done?" The Center for Community Solutions, October 9, 2023, <https://www.communitysolutions.com/oneohio-recovery-foundation-howd-we-get-here-and-whats-been-done/>

⁴ Gregory Ferenstein and Leonard Gilroy, "Nonprofit Announces New Partnership with Ohio to Tackle Opioid Addiction with Ibogaine," Reason Foundation commentary, February 28, 2024, <https://reason.org/commentary/nonprofit-announces-new-partnership-with-ohio-to-tackle-opioid-addiction-with-ibogaine/>.

The research provided here should inform both public and private partners about the potential of ibogaine as a prospective treatment for opioid use disorder.

1.2

OVERVIEW

Many proposed treatments for opioid use disorder (OUD) target addiction neural circuitry. Treatments that interrupt these neural circuitries are theorized to reduce craving and substance use, aiming to help individuals beat their opioid addiction.

Medication Assisted Treatments (MATs) are traditionally considered the gold standard for treatment of opioid use disorder. However, the persistence of the opioid crisis suggests that MATs may not be as effective as previously believed. Clinical data reveals that MATs tend to maintain opioid dependence and carry high risks of relapse. Poor retention rates, limited access, and the immediate withdrawal and craving symptoms associated with treatment cessation are leading causes of opioid relapse. Relapse after successful detoxification presents a high risk of overdose-related death as individuals overestimate their tolerance and revert to doses of nonmedical opioids similar to what they were previously accustomed to.

Unlike current MATs, ibogaine therapy may offer lasting anti-addictive effects at fewer doses, offering greater potential relief than simple abatement of opioid dependence. Early research suggests that ibogaine treatment has the potential to diminish or eliminate both physical withdrawal symptoms and psychological drug cravings. As a result, individuals often achieve longer periods of opioid abstinence. In some cases, individuals have achieved total abstinence after a single ibogaine treatment.



Early research suggests that ibogaine treatment has the potential to diminish or eliminate both physical withdrawal symptoms and psychological drug cravings. As a result, individuals often achieve longer periods of opioid abstinence.



A major advantage of ibogaine treatment is that treatment usually occurs in a single session. By contrast, traditional MATs require individuals to engage in multiple treatments at a regulated facility for treatment to remain opioid free. Another major advantage is that ibogaine is not addictive, and individuals rarely identify the treatment itself as a pleasurable experience. For that reason, there is little incentive to consume ibogaine recreationally, and therefore it is less likely to be diverted than other OUD treatments.

KEY TERMINOLOGY

- **Relapse Rates:** The rate of participants who engaged in illicit opioid use within 30 days post-treatment.
- **Retention:** The rate of participants who self-reported enrollment in MAT for two consecutive follow-up periods (an approximately six-month retention interval). Because ibogaine treatment is typically or usually administered in a single session, retention is not considered an outcome measure relevant to ibogaine treatment.
- **Short-term abstinence:** The rate of participants who abstained from illicit opioid use for at least three months (≥ 90 days) but less than one year (< 365 days) following treatment cessation.
- **Long-term abstinence:** The rate of participants who abstained from illicit opioid use for at least one year (≥ 365 days) following treatment cessation.
- **Abstinence Duration:** The length of time participants abstained from illicit opioid use following treatment cessation.
- **Adverse Event:** An event in which treatment resulted in an undesirable clinical outcome not caused by underlying disease or resulting in fatality that prolonged the patient stay, caused permanent patient harm, or required life-saving intervention.
- **Mortality Risk:** Risk of mortality in people with opioid dependence as a result of treatment or cessation of treatment.
- **Risk of Diversion:** The rate of illegal abuse of treatment opioids or their use for purposes not intended by the prescriber.
- **Depression:** The rate of participants who self-reported a change in depression symptoms.

PART 2

THE STATE OF OPIOID ADDICTION IN THE UNITED STATES

Opioids are highly potent pain-relieving medications derived from the opium poppy. They have the capacity to induce relaxation and euphoria, making them susceptible to abuse and addiction.⁵ In the United States, the escalating issue of opioid addiction has been officially recognized as a crisis, leading to the passage of the Opioid Crisis Accountability Act of 2019 by the 116th Congress.⁶ The number of people who died from a drug overdose in 2021 was more than six times greater than those who died in 1999. Drug overdose deaths increased more than 16% from 2020 to 2021 alone. More than 75% of the nearly 107,000 drug overdose deaths in 2021 involved an opioid.⁷

This crisis encompasses two interrelated problems: first, the misuse and addiction to prescription opioids, and second, the addiction to illicit opioids such as heroin and synthetic

⁵ Jennifer Veilleux et al, “A review of opioid dependence treatment: Pharmacological and psychosocial interventions to treat opioid addiction.” *Clinical Psychology Review* 30 (2010). 155–166.

⁶ “H.R. 2917 (IH) - Opioid Crisis Accountability Act of 2019,” www.govinfo.gov, GovInfo, n.d. www.govinfo.gov/app/details/BILLS-116hr2917ih (accessed 12 Sep. 2023).

⁷ “Understanding the Opioid Overdose Epidemic,” www.cdc.gov, Centers for Disease Control and Prevention, 7 Oct. 2022. www.cdc.gov/opioids/basics/epidemic.html (accessed 28 Sep. 2023).

opioids like fentanyl.⁸ The definition of misuse includes taking opioids in a manner or dose other than prescribed; taking someone else's prescription, even for a legitimate medical complaint such as pain; and/or consuming opioids to feel euphoria.



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One particularity regarding prescription opioids is that individuals use these products for both medical and non-medical purposes. In other words, some users have been prescribed opioids for the treatment of pain, while other users hold no prescription and illicitly purchase prescription opioids through medically unsanctioned means. Data suggests that few medical users become nonmedical users who later transition to other types of opioids. Instead, nonmedical users of prescription opioids appear to transition to other opioids as the supply of prescription opioids available through illicit markets contracts.⁹

The National Survey on Drug Use and Health reveals staggering figures: Approximately 9.8 million individuals misused pain relievers and/or heroin, while roughly 5.6 million individuals grappled with opioid use disorder (OUD) in 2021. Among people aged 12 or older in 2020, 3.4 percent (or 9.5 million people) misused opioids (heroin or prescription pain relievers) in the past year. Among the 9.5 million people who misused opioids in the past year, 9.3 million people misused prescription pain relievers compared to 902,000 people who used heroin. An estimated 667,000 people both misused prescription pain relievers and used heroin in 2020.¹⁰

⁸ Wilson Compton and Christopher Jones, "Epidemiology of the U.S. opioid crisis: The importance of the vector," *Annals of the New York Academy of Sciences* 1451 (2019). 130–143.

⁹ Jeffrey Singer, Jacob Sullum and Michael Schatman, "Today's Nonmedical Opioid Users Are Not Yesterday's Patients; Implications of Data Indicating Stable Rates of Nonmedical Use and Pain Reliever Use Disorder," *Journal of Pain Research* 12 (2019). 617-620.

¹⁰ Douglas Richesson and Jennifer M. Hoenig, "Key substance use and mental health indicators in the United States: Results from the 2020 National Survey on Drug Use and Health," samhsa.gov, Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, Oct. 2021. www.samhsa.gov/data/sites/default/files/reports/rpt35325/NSDUHFFR1PDFWHTMLFiles2020/2020NSDUHFFR1PDFW102121.pdf (accessed 2 Sep. 2023).



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The rise in overdoses began with a modest increase in deaths from prescription opioids in the late 1990s through 2010, transitioning into a wave of heroin use in the following decade, and more recently, a consistent influx of fentanyl and other synthetic opioids. According to the National Institute on Drug Abuse, 70% of drug overdoses can be attributed to illicit or prescription opioids.¹¹ Opioid-involved overdose deaths (prescription and illicit) rose from 21,089 in 2010 to 47,600 in 2017 and remained steady through 2019. This was followed by a significant increase in 2020 with 68,630 reported deaths and again in 2021 with 80,411 reported overdose deaths.

Drug overdose deaths involving prescription opioids rose from 3,442 in 1999 to 17,029 in 2017. From 2017 to 2019, the number of deaths declined to 14,139. This was followed by a slight increase in 2020, with 16,416 reported deaths. In 2021, the number of reported deaths involving prescription opioids totaled 16,706.

Among the 7.7 million American adults struggling with severe mental illnesses, a staggering 6.4 million individuals contend with comorbid substance use disorders (SUD), with 10.3% involving the misuse of opioids.

¹¹ “Drug Overdose Death Rates,” nida.nih.gov, National Institute on Drug Abuse; National Institutes of Health, 30 June 2023. nida.nih.gov/research-topics/trends-statistics/overdose-death-rates (accessed 25 Sep. 2023).



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According to the National Institute on Drug Abuse, 78% of people suffering from OUD did not receive MAT in 2021. Similarly, in 2017, 80% of people with OUD did not receive MAT.¹²

2.1

CAUSES

The use of pain medications, particularly opioids, is undeniably a necessary approach in managing chronic pain that is unresponsive to alternative treatments. However, the widespread availability and use of exogenous opioids has not been without repercussions. Substance use disorder, as defined, encompasses a range of symptoms characterized by recurrent cycles of tolerance and withdrawal.¹³

In the context of opioids, individuals often encounter these medications due to severe acute pain, chronic pain, or recreational use, driven by a desire to experience euphoria or alleviate pain.

Two prevailing theories attempt to explain the underlying mechanisms of addiction. The first theory suggests that patients are drawn to opioids in pursuit of pleasure, seeking the rewarding sensations they provide. The second theory posits that individuals turn to opioids to evade the distressing symptoms of withdrawal after initiating opioid use for various reasons, including medically prescribed treatments that were abruptly discontinued.

¹² “Opioid Use Disorder Treatment,” [nida.nih.gov](https://nida.nih.gov/nidamed-medical-health-professionals/treatment/opioid-use-disorder-treatment), National Institute on Drug Abuse, 17 March 2023. nida.nih.gov/nidamed-medical-health-professionals/treatment/opioid-use-disorder-treatment (accessed 23 Sep. 2023).

¹³ Amber Edinoff 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* 10 (2022). 2-3.

These abrupt cessations can inadvertently trigger unwanted withdrawal experiences. Notably, one study reported that fear of withdrawal discomfort was the most frequent concern among individuals (68%, n=187) considering MAT cessation.¹⁴

¹⁴ Adam Winstock et al., “Should I stay or should I go? Coming off methadone and buprenorphine treatment,” *International Journal of Drug Policy* 22 (2011): 78.

PART 3

THE COSTS OF OPIOID ADDICTION

The economic burden of opioid use disorder and fatal opioid overdose is presented in Table 1. The overall economic burden totaled approximately \$1 trillion nationally in 2017.¹⁵ Slightly less than half of these costs were attributable to opioid use disorder. Almost \$35 billion of the costs were associated with health care (\$31.3 billion) and opioid use disorder treatment (\$3.5 billion). Approximately \$23 billion are related to criminal justice spending (\$14.8 billion) and lost productivity of incarcerated individuals (\$7.8 billion). Lost productivity for individuals with opioid use disorder (\$23.5 billion) and individuals who have died to a fatal opioid overdose (\$68.7 billion) together accounts for over \$92 billion.

The greatest components of the overall economic burden, however, are the actuarial values of reduced quality of life from opioid use disorder (\$390.0 billion) and life lost to opioid overdose (\$480.7 billion). These two cost components account for over 85% of the total economic burden, according to scholars affiliated with the Centers for Disease Control and Prevention.¹⁶

¹⁵ Curtis Florence et al., “The economic burden of opioid use disorder and fatal opioid overdose in the United States, 2017,” *Drug and Alcohol Dependence* 218, (2020). 1-6.

¹⁶ Florence et al., “The economic burden of opioid use disorder and fatal opioid overdose in the United States, 2017.” 6.

TABLE 1: ESTIMATED COSTS OF OPIOID USE DISORDER AND FATAL OVERDOSE, UNITED STATES 2017 (MILLIONS OF 2017\$)

| | Nonfatal Costs | Nonfatal Aggregate Costs % of Aggregate Costs |
|--|--------------------|--|
| Health care | | |
| • Private insurance | \$12,902 | 1.3% |
| • Medicare | \$3,170 | 0.3% |
| • Medicaid | \$11,142 | 1.1% |
| • Champus/VA | \$1,124 | 0.1% |
| • Other | \$820 | 0.1% |
| • Uninsured | \$2,151 | 0.2% |
| Total | \$31,309 | 3.1% |
| Substance Abuse Treatment | | |
| • Federal | \$844 | 0.1% |
| • State and local | \$2,326 | 0.2% |
| • Private | \$365 | 0.0% |
| Total | \$3,535 | 0.3% |
| Criminal Justice | | |
| • Police protection | \$6,209 | 0.6% |
| • Legal and adjudication | \$2,819 | 0.3% |
| • Correctional facilities | \$5,445 | 0.5% |
| • Property loss due to crime | \$347 | 0.0% |
| Total Criminal Justice costs | \$14,820 | 1.5% |
| Lost Productivity | | |
| • Reduced productive time/increased disability | \$23,479 | 2.3% |
| • Production lost for incarcerated individuals | \$7,832 | 0.8% |
| Subtotal: Lost Productivity | \$31,311 | 3.1% |
| Value of Reduced Quality of Life | \$390,003 | 38.2% |
| Total Nonfatal Costs | \$452,625 | 46.1% |
| | Fatal Costs | Fatal Aggregate Costs % of Aggregate Costs |
| Lost Productivity | \$68,694 | 6.7% |
| Health Care | \$260 | 0.0% |
| Value of Statistical Life Lost | \$480,737 | 47.1% |
| Subtotal: Fatal Costs | \$549,691 | 53.9% |
| Total of Fatal and Nonfatal | \$1,020,666 | 100.0% |

Source: Curtis Florence et al., "The economic burden of opioid use disorder and fatal opioid overdose in the United States, 2017," *Drug and Alcohol Dependence* 218, (2020). 4.

PART 4

TRADITIONAL TREATMENTS FOR OPIOID USE DISORDER (MATS)

Three medications are currently registered in the United States for use in Medication Assisted Treatment (MAT) of opioid use disorder (OUD): methadone, buprenorphine (including Suboxone and Subutex), and naltrexone (including Vivitrol).¹⁷ These medications aim to prevent withdrawals and reduce cravings for opioid drugs by providing controlled doses of medications without inducing a “high.”¹⁸

Methadone, which triggers opioid receptors in the nervous system (an “opioid agonist”), is recognized by the U.S. Food and Drug Administration (FDA) as an effective treatment for opioid addiction.¹⁹ It operates as a replacement therapy, aiming to help individuals manage

¹⁷ “Information about Medication-Assisted Treatment,” fda.gov, U.S. Food and Drug Administration, 14 Feb. 2019. www.fda.gov/drugs/information-drug-class/information-about-medication-assisted-treatment-mat (accessed 17 Sep. 2023).

¹⁸ Amber Edinoff 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* 10 (2022). 3.

¹⁹ “Information about Medication-Assisted Treatment,” fda.gov, U.S. Food and Drug Administration. 14.

cravings and withdrawal symptoms.”²⁰ However, replacement therapies require long-term treatment and pose unique challenges and complications. Methadone itself is addictive, leading to illicit opioid use and fatal overdoses. For reference, 4.2% of monthly overdose deaths reported in 2019 involved solely methadone.²¹ In terms of illicit opioid use, one study examining methadone maintenance treatment programs found that about 38% of participants enrolled in such programs continued to use heroin, and about 10% continued to use other opioids while receiving their methadone.²²

“
...replacement therapies require long-term treatment and pose unique challenges and complications.
”

Methadone treatment faces additional challenges, including patient compliance and dosing. Patients may initially need frequent clinic visits for dose titration, posing a compliance barrier. Moreover, adverse events, such as QT prolongation and respiratory depression due to overdose, have been linked to methadone treatment.

Buprenorphine is a semisynthetic opioid derivative that functions as a partial opioid agonist. Unlike full opioid agonists, buprenorphine has limited effects on pain control and does not induce a feeling of being high or euphoric. Buprenorphine imposes comparatively fewer withdrawal symptoms, contributing to a lower risk of lethal overdose. However, similar to methadone, it has the additional risk of diversion and misuse of medication. As a result, it is often combined with naloxone to deter misuse by injection.²³

²⁰ “Medications for Substance Use Disorders,” [samhsa.gov](https://www.samhsa.gov), Substance Abuse and Mental Health Services Administration, 3 Oct. 2023. www.samhsa.gov/medications-substance-use-disorders (accessed 2 Sep. 2023).

²¹ Christopher Jones, “Methadone-Involved Overdose Deaths in the US Before and After Federal Policy Changes Expanding Take-Home Methadone Doses From Opioid Treatment Programs,” *JAMA Psychiatry* (2022). 933.

²² Alexander Walley et al, “Opioid overdose prevention with intranasal naloxone among people who take methadone,” *Journal of Substance Abuse Treatment* 44 (2013). 241–247.

²³ Rachna Kumar, Omar Viswanath, & Abdolreza Saadabadi, “Buprenorphine,” [nih.gov](https://www.ncbi.nlm.nih.gov/books/NBK459126), National Library of Medicine, 29 April 2023. www.ncbi.nlm.nih.gov/books/NBK459126 (accessed 4 Oct. 2023).

Naltrexone, an MOR antagonist and partial kappa-opioid receptor (KOR) agonist, presents its own challenges, including causing withdrawal symptoms in opioid-tolerant individuals. Patients must achieve abstinence from opioid agonists for typically 7-10 days before receiving naltrexone, a feat often requiring medical intervention.²⁴ Furthermore, orally administered naltrexone has not been proven to significantly reduce opioid use, primarily due to poor treatment retention.

4.1

CHALLENGES OF MATS

RELAPSE RATES

While MATs are widely accepted as OUD treatment, they exhibit an alarmingly high relapse rate. A review of buprenorphine maintenance therapy (BMT) studies revealed that most patients relapsed to illicit opioid use within one month following BMT cessation. Mean relapse to illicit opioid use exceeded 50% in all the studies examined, while the amount of people who remained abstinent ranged from 9.6% to 50%.²⁵ Notably, high relapse rates were observed in young adults, as well as primary prescription opioid abusers.^{26,27}

“

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”

Similarly, a comparison of buprenorphine/naloxone vs. methadone results revealed that 50.9% and 41.1% of patients, respectively, had used heroin or opiates throughout the 60-

²⁴ Stacey Sigmon et al, “Opioid Detoxification and Naltrexone Induction Strategies: Recommendations for Clinical Practice,” *The American Journal of Drug and Alcohol Abuse* 38 (2012). 187–199.

²⁵ Brandon Bentzley et al, “Discontinuation of Buprenorphine Maintenance Therapy: Perspectives and Outcomes,” *Journal of Substance Abuse Treatment* 52 (2015). 48–57.

²⁶ George Woody et al, “Extended vs Short-term Buprenorphine-Naloxone for Treatment of Opioid-Addicted Youth,” *JAMA*, 300 (2008).

²⁷ Roger Weiss et al, “A multi-site, two-phase, Prescription Opioid Addiction Treatment Study (POATS): Rationale, design, and methodology,” *Contemporary Clinical Trials* 31 (2010).

month follow-up.²⁸ Although extending maintenance and tapering phases of treatment has been shown to increase initial success rates, added opioid drug counseling did not significantly improve outcomes either immediately post-treatment (46.7% vs. 51.7%) or after an 8-week follow-up (7.2% vs. 10%).²⁹

TABLE 2: OUTCOMES FOLLOWING BMT CESSATION

| Study | Sample size at taper start | Prior heroin use | Maintenance period | Mean dose | Abstinent maintenance | Taper duration | Follow-up time | Naltrexone | Abstinent post-taper |
|---------------|----------------------------|------------------|------------------------------|-----------|-----------------------|----------------|----------------|---|----------------------|
| Sigmon (2013) | 70 | ~50% | 2 weeks | 11.5mg | 82% | 1 week | 9 weeks | 50mg (p.o.) daily | 5/24 (21%) |
| | | | | | | 2 weeks | 8 weeks | 50mg (p.o.) daily | 4/24 (17%) |
| | | | | | | 4 weeks | 6 weeks | 50mg (p.o.) daily | 11/22 (50%) |
| Weiss (2011) | 323 | 26% | 12 weeks | 20.8mg | 177/323 (54%) | 4 weeks | 8 weeks | None | 31/323 (9.6%) |
| Ling (2009) | 516 | 83% | 4 weeks | 20.3mg | 191/516 (37%) | 1 week | 4 weeks | None | 45/255 (18%) |
| | | | | | | 4 weeks | 4 weeks | None | 46/261 (18%) |
| Woody (2008) | 55 | 76% | 8 weeks | 15.1mg | 54% | 4 weeks | 6 months | None | 34% |
| Breen (2003) | 50 | 100% | 2weeks (>6 months methadone) | 8.6mg | Not reported | 11 weeks | 4 weeks | Optional (p.o.) 5 participants received | 22/50 (44%) |

Non-opioid compounds attempt to mitigate acute withdrawal symptoms along with traditional detoxification therapy, but generally have high rates of relapse. In one multi-site study in the United States, patients given Naltrexone, which can temporarily reduce opioid cravings, still had a high failure rate—between 59–93% of participants used opioids within 26 weeks.³⁰

²⁸ Yih-Ing Hser et al, “Long-term outcomes after randomization to buprenorphine/naloxone versus methadone in a multi-site trial,” *Addiction* 111 (2015). 695–705.

²⁹ Roger et al, “Adjunctive Counseling During Brief and Extended Buprenorphine-Naloxone Treatment for Prescription Opioid Dependence,” *Archives of General Psychiatry* 68 (2011). 1238.

³⁰ Edward Nunes et al, “Relapse to opioid use disorder after inpatient treatment: Protective effect of injection naltrexone,” *Journal of Substance Abuse Treatment* 85 (2018). 49–55.

RETENTION RATES

Medication for Opioid Use Disorder (MOUD) programs serve as a critical protective factor against a return to opioid use. Furthermore, the risks of death and other adverse consequences significantly increase upon discontinuation of treatment.

Although MOUD is initially intended as a long-term treatment, the reality is that treatment retention often faces challenges, resulting in drop-outs or program discharges. As a result, the duration of MOUD treatment tends to be shorter than ideal. For instance, average stays in methadone-maintained treatment frequently last less than one year, while for buprenorphine, they typically extend less than three months in observational studies. Most studies have reported retention rates of less than 50% at the six-month mark.

A 2018 report on the use of naltrexone and buprenorphine in a large U.S. commercially insured population reported that 52% of individuals treated with extended-release naltrexone and 31% of individuals treated with sublingual buprenorphine discontinued treatment after only one month.³¹ Abstinence from opioids after the cessation of treatments varies greatly by treatment condition and geography. Among comparable approaches that are the size of state-level programs, continuous abstinence of one year is generally no greater than 51%.³²



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³¹ Jake Morgan et al, J. R., “Injectable naltrexone, 2 oral naltrexone, and buprenorphine utilization and discontinuation among individuals treated for opioid use disorder in a United States commercially insured population,” *Journal of Substance Abuse Treatment* 85 (2017). 90–96.

³² Laura Lander et al, “Long-term treatment retention in West Virginia’s comprehensive opioid addiction treatment (COAT) program,” *Journal of the Neurological Sciences* 411 (2020).

LONG-TERM ABSTINENCE

Slowly tapering doses of methadone or buprenorphine have been used in medically managed withdrawal from opioids (“detoxification”). However, short-term abstinence is not predictive of long-term remission. Longitudinal studies have provided valuable insights into the experiences of individuals with Opioid Use Disorder (OUD) as they navigate through various phases of their addiction or treatment journey. These studies suggest that the share of individuals who achieve abstinence through treatment also rises with duration of treatment episodes. Moreover, the longer an individual maintains abstinence, the higher the probability of continued abstinence.

“
... *short-term abstinence is not predictive of long-term remission.*
”

It is essential to acknowledge the sobering reality that some longitudinal studies have reported alarmingly high death rates, reaching up to 50%. Additionally, the probability of individuals remaining engaged in treatment and maintaining abstinence from illicit opioid use is relatively low, typically ranging from 10% to 20% of those who enroll in a treatment program after 20 to 30 years.

AVAILABILITY AND COST

MAT options are also limited in their availability. The National Institute on Drug Abuse reported that “less than half of privately-funded substance use disorder treatment programs offer MAT and only 1/3 of patients with opioid dependence at these programs actually receive it.”³³ NIDA reports that “nearly all” of the U.S. states are unable to adequately provide MAT to people with OUDs.

When MAT therapies are available, they are frequently expensive. According to NIDA, the average cost of methadone therapy is \$126 per week, or \$6,552 a year. Treatment with buprenorphine typically costs \$115 per week, or \$5,980 annually. The most expensive

³³ “Effective Treatments for Opioid Addiction,” [nida.nih.gov](https://nida.nih.gov/publications/effective-treatments-opioid-addiction), National Institute on Drug Abuse, Nov. 2016. nida.nih.gov/publications/effective-treatments-opioid-addiction (accessed 17 Oct. 2023).

medication is naltrexone, which runs a monthly average of \$1,176.50 (about \$289 per week), or an annual average of \$14,112.³⁴

In addition to the medication, all the prices for MAT treatments listed include costs for medical assistance and outpatient treatment programs. To put these costs into perspective, individuals with diabetes mellitus pay about \$3,560 a year, while those with kidney disease pay about \$5,624 annually.

TABLE 3: MAT AVAILABILITY AND COSTS

| MAT Treatment Option | Availability in Privately-Funded Programs | Average Cost Per Week | Average Cost Per Year |
|-----------------------------|--|------------------------------|------------------------------|
| Methadone | Less than 50% | \$126 | \$6,652 |
| Buprenorphine | Less than 50% | \$115 | \$5,980 |
| Naltrexone | Less than 50% | \$289 | \$14,112 |

Source: “How much does opioid treatment cost?” nida.nih.gov, National Institute on Drug Abuse, Dec. 2021. nida.nih.gov/publications/research-reports/medications-to-treat-opioid-addiction/how-much-does-opioid-treatment-cost

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Moreover, individuals receiving MOUD treatment with buprenorphine or methadone often struggle to maintain continuous commercial health insurance.

”

Moreover, individuals receiving MOUD treatment with buprenorphine or methadone often struggle to maintain continuous commercial health insurance. A cohort study revealed that individuals receiving MOUD treatment with buprenorphine or methadone and MOUD treatment with naltrexone had the highest disenrollment rates. For individuals receiving buprenorphine or methadone treatment (n=5123), 53.8% (or 2755) of individuals were

³⁴ “How much does opioid treatment cost?” nida.nih.gov, National Institute on Drug Abuse, Dec. 2021. nida.nih.gov/publications/research-reports/medications-to-treat-opioid-addiction/how-much-does-opioid-treatment-cost (accessed 13 Oct. 2023).

disenrolled. Similarly, individuals receiving naltrexone treatment (n=963), 54% (or 520) of individuals were disenrolled.³⁵

4.2

SAFETY OF MAT

The most severe adverse effect from methadone is the potential for apnea, respiratory failure, and hypoxia, leading to coma, seizures, hypotension, and death.³⁶

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MORTALITY

Mortality rates increase significantly following cessation of MOUD treatment. One large-scale review of patients (n=122,885) found that pooled all-cause mortality rates were 11.3 per 1,000 person-years receiving inpatient methadone treatment and 36.1 per 1,000 person-years receiving outpatient methadone treatment. Those figures were 4.3 and 9.5 per 1,000 person-years for patients receiving inpatient and outpatient buprenorphine treatment, respectively. Pooled mortality rates specifically due to overdose were 2.6 and 12.7 per 1,000 person-years for patients receiving inpatient and outpatient methadone treatment, and 1.4 and 4.6 per 1,000 person-years for patients receiving inpatient and outpatient buprenorphine treatment, respectively.³⁷ These numbers suggest that both methadone and buprenorphine treatments are associated with higher all-cause mortality and overdose mortality rates for individuals who receive treatment and return home the same day.

³⁵ Sarah Wakeman et al, "Comparative Effectiveness of Different Treatment Pathways for Opioid Use Disorder," *JAMA Netw Open* 3 (2020). 4.

³⁶ Ilene Anderson & Thomas Kearney, "Use of methadone," *Western Journal of Medicine* 172 (2000). 43–46.

³⁷ Luis Sordo et al, "Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies," *BMJ* 357 (2017). 4.

RESPIRATORY DEPRESSION AND OVERDOSE

Methadone can lead to respiratory depression if given to individuals who are less tolerant to opioids than others.³⁸ Methadone treatment aims to build a lower level of tolerance than what's typically experienced with illicit drugs. However, raising the dose too quickly can result in potentially fatal respiratory depression. During the initial induction phase, the blood level achieved by a stable dose gradually increases over the first week due to tissue binding and methadone's long half-life. Surprisingly, a dose that was well-tolerated on day one can potentially trigger fatal respiratory depression in non-tolerant patients on days two or three.

Buprenorphine presents a different profile. Increasing doses of buprenorphine produce minimal or no increase in opioid effects due to what's known as a "ceiling effect."³⁹ This phenomenon reduces the risk of respiratory depression in cases of overdose. Induction onto buprenorphine is linked to a significantly lower risk of overdose compared to methadone.

While patients actively receiving MAT are at a reduced risk of overdose, there is an increased risk of fatal overdose in the month following discontinuation of MAT.⁴⁰ Additionally, Benzodiazepine usage is prevalent among individuals with OUD, and when combined with methadone, it is associated with an elevated risk of fatal overdose and emergency room visits.⁴¹

QT INTERVAL PROLONGATION

Methadone has been found to prolong the QTc interval, and in cases of high-dose methadone, it has been linked to ventricular tachycardia known as "torsades de pointes." QTc prolongation is when the time it takes for an individual's heart to beat in a regular rhythm becomes longer than normal. When the heart's rhythm is prolonged, it may increase the risk of developing a dangerous heart rhythm problem. Ventricular tachycardia (VT) is a rapid heartbeat in the heart's lower chambers, and torsades de pointes is a specific, twisting

³⁸ Ilene Anderson & Thomas Kearney, "Use of methadone," 43–46.

³⁹ Paul Whelan & Kimberly Remski, "Buprenorphine vs methadone treatment: A review of evidence in both developed and developing worlds," *Journal of Neurosciences in Rural Practice*, 3 (2012). 45.

⁴⁰ "The Effectiveness of Medication-Based Treatment for Opioid Use Disorder," nih.gov, National Academies Press (US), 2019. www.ncbi.nlm.nih.gov/books/NBK541393/ (accessed 4 Nov. 2023).

⁴¹ "Trends in Opioid Use, Harms, and Treatment," nih.gov, National Academies Press (US), 13 July 2019. www.ncbi.nlm.nih.gov/books/NBK458661/ (accessed 14 Sep. 2023).

type. This rhythm, especially with a prolonged QT interval (often due to medications or imbalances), can lead to serious complications, including death. Doctors closely monitor and manage this to prevent such complications. While this complication is rare, there is not a clear consensus on its implications for treatment programs. Unlike methadone, buprenorphine appears to have a minimal impact on the QTc interval.

DIVERSION

As the prescribing of methadone or buprenorphine increases in a given jurisdiction, there is a corresponding rise in overdose deaths from these drugs among individuals not undergoing treatment. Some level of diversion is almost inevitable when prescribing agonist medications. A substantial portion of diverted medication ends up in the hands of individuals with OUD who are not in treatment.



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Due to its “ceiling effect,” as previously mentioned, the diversion of buprenorphine is associated with significantly less risk of fatal overdose compared to diverted methadone.⁴² However, it still carries the risk of diversion. An extreme example is the diversion of buprenorphine from France, which led to a black market in the Republic of Georgia where injected buprenorphine became the primary drug of abuse.⁴³

To address this risk, a combination of buprenorphine and naloxone has been introduced to minimize intravenous misuse. The rationale is that when taken orally or sublingually, naloxone has low bioavailability. However, if the medication is crushed and injected, naloxone attenuates the opioid agonist effect, potentially precipitating withdrawal in

⁴² Paul Whelan & Kimberly Remski, “Buprenorphine vs methadone treatment: A review of evidence in both developed and developing worlds,” 45.

⁴³ Paul Rimple, Refugees, “Georgia fighting losing battle against designer drug,” refworld.org, Refworld, 26 Oct. 2023. www.refworld.org/docid/46a484df1e.html (accessed 22 Oct. 2023).

individuals dependent on opioids. There is conflicting evidence regarding the effectiveness of this combination in deterring intravenous misuse. The added naloxone appears to reduce, though not eliminate, intravenous misuse.⁴⁴

⁴⁴ Christopher Blazes & Jonathan Morrow, "Reconsidering the Usefulness of Adding Naloxone to Buprenorphine," *Frontiers in Psychiatry* 11 (2020). 3.

PART 5

WHAT IS IBOGAINE AND WHERE IS IT USED?

Ibogaine, a psychoactive substance with ancient roots in Central African rituals, has emerged as an unconventional yet promising option for opioid addiction treatment. The discovery of ibogaine's potential in mitigating opioid dependence did not originate within a clinical framework but rather emerged from recreational experimentation—a recurring narrative within the context of hallucinogenic substances during the 1960s. Howard Lotsof and a cohort of 19 individuals, among whom seven grappled with heroin dependence, embarked on an endeavor to attain a psychoactive experience by ingesting substantial quantities of ibogaine.⁴⁵ Strikingly, their collective observations yielded a notable absence of heroin withdrawal symptoms and cravings both during and immediately following the ibogaine experience. This phenomenon culminated in a sustained abstinence from opioid use spanning at least six months for five of the seven heroin-dependent subjects, suggesting that ibogaine had “anti-addictive” properties.⁴⁶

⁴⁵ Kenneth Alper, “Ibogaine: A review,” *Academic Press* 56 (2001). 1-38.

⁴⁶ Lindsay Mader, “Howard Lotsof,” herbalgram.org, HerbalGram, n.d. /www.herbalgram.org/resources/herbalgram/issues/87/table-of-contents/article3572/ (accessed 26 Oct. 2023).

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Strikingly, their collective observations yielded a notable absence of heroin withdrawal symptoms and cravings both during and immediately following the ibogaine experience.

In 1967, the U.S. government made ibogaine possession and consumption illegal due to its hallucinogenic properties.⁴⁷ Ibogaine was classified as a controlled substance in the United States in 1970 when it was assigned to schedule I under the Controlled Substances Act, implying a high potential for abuse with no recognized medical use.⁴⁸ Despite its schedule I status in the U.S., ibogaine has not been widely abused or associated with addiction.

Outside of the U.S., ibogaine remains unscheduled in most parts of the world, with the exceptions of New Zealand, Brazil, and South Africa, where it is classified as a pharmaceutical substance and used by licensed practitioners.⁴⁹ Substance use treatment centers that offer ibogaine have been found in New Zealand, Mexico, Canada, Costa Rica, Brazil, South Africa, Spain, Greece, the Netherlands, Panama, St. Kitts, and elsewhere.

An array of published reports, inclusive of clinical trials, suggests ibogaine exhibits the capacity to ameliorate withdrawal symptoms and cravings while facilitating sustained opioid abstinence for a prolonged duration following a single therapeutic intervention.

5.1

TREATMENT PROCESS

Ibogaine treatment for opioid addiction typically involves several steps. First, a comprehensive assessment evaluates the patient's medical history, current substance use,

⁴⁷ Jessica Meisner, Susan Wilcox, & Jeremy Richards, “Ibogaine-associated cardiac arrest and death: case report and review of the literature,” *Therapeutic Advances in Psychopharmacology*, 6 (2016). 95–98.

⁴⁸ Mandy Oaklander, “Inside Ibogaine, One of the Most Promising and Perilous Psychedelics for Addiction,” *time.com*, *Time*, 5 April 2021. time.com/5951772/ibogaine-drug-treatment-addiction/ (accessed 25 Sep. 2023).

⁴⁹ Thomas Brown & Kenneth Alper, “Treatment of opioid use disorder with ibogaine: Detoxification and drug use outcomes,” *The American Journal of Drug and Alcohol Abuse* 44 (2018). 24–36.

and overall health to determine their suitability for ibogaine treatment.⁵⁰ The second step involves preparation, which includes psychological counseling and education about the ibogaine experience, its potential risks, and benefits. Eventually, the actual ibogaine session takes place, often lasting around 12-36 hours. Patients who are in the early stages of opioid withdrawal are administered ibogaine orally. Following ingestion, the treatment typically follows a structured process with three distinct phases: the acute phase, the evaluative phase, and the residual stimulation phase.⁵¹

The acute phase is characterized by the onset of ibogaine's psychedelic effects, often referred to as the "waking dream." This phase is marked by intense visual and sensory experiences that are most pronounced when the patient's eyes are closed. During the "waking dream," individuals often report a profound sense of being within a vividly imagined internal landscape.⁵² The acute phase typically spans a duration of four to eight hours, during which patients delve into deep introspection and may gain valuable insights into their addiction and life experiences.

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During the "waking dream," individuals often report a profound sense of being within a vividly imagined internal landscape.

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Following the acute phase, the evaluative stage unfolds. In this phase, patients transition from the intense visionary experiences of the first phase to a state of contemplation and self-reflection.⁵³ Lasting anywhere from eight to 20 hours, the evaluative stage offers individuals the opportunity to review and explore the insights they gained during the "waking dream." It is a period of deep introspection and emotional processing, often accompanied by difficulty sleeping. During this phase, patients confront their addiction and

⁵⁰ Kenneth Alper et al, "Treatment of acute opioid withdrawal with ibogaine," *The American Journal of Drug and Alcohol Abuse* 38 (2012). 493-502.

⁵¹ Alan Davis et al, "Subjective effectiveness of ibogaine treatment for problematic opioid consumption: Short- and long-term outcomes and current psychological functioning," *Journal of Psychedelic Studies* 1 (2017). 65–73.

⁵² Kenneth Alper, Howard Lotsof, & Charles Kaplan, "The ibogaine medical subculture," *Journal of Ethnopharmacology* 115 (2008). 11. <https://doi.org/10.1016/j.jep.2007.08.034>

⁵³ Alan Davis et al, "Subjective effectiveness of ibogaine treatment for problematic opioid consumption: Short- and long-term outcomes and current psychological functioning," 65–73.

personal histories in a meaningful way, setting the stage for potential healing and transformation.

The residual stimulation phase is the final phase of ibogaine treatment. During this stage, which occurs as patients return to a more ordinary state of functioning, individuals often describe themselves as feeling "open" or "vulnerable."⁵⁴ This phase represents the integration of the therapeutic insights acquired during the previous stages into the individual's everyday life and recovery journey. While some residual effects may linger, the intense visionary and introspective experiences tend to subside, allowing patients to gradually return to their normal level of functioning. The residual stimulation phase is instrumental in helping individuals apply the lessons learned during treatment to their ongoing pursuit of sobriety and personal growth.⁵⁵

Ibogaine treatment should only be administered by trained healthcare professionals in a controlled and medically supervised environment due to the potential risks associated with its use, including its intense psychological effects and cardiac considerations.⁵⁶

5.2

ADDICTION NEUROLOGY AND PHARMACOLOGY OF IBOGAINE

Addiction as a complex neurobiological phenomenon hinges on specific regions, neural circuits, and neurotransmitters within the brain. Central to this understanding is the nucleus accumbens, often referred to as the brain's reward center, which orchestrates reward and motivational systems. These systems involve intricate interactions between various brain areas, including the anterior cingulate cortex, orbital prefrontal cortex (PFC), the ventral striatum, and the dopamine neurons in the midbrain.⁵⁷

⁵⁴ Jennifer Donnelly, "The Need for Ibogaine in Drug and Alcohol Addiction Treatment," *Journal of Legal Medicine*, 32 (2011). 7.

⁵⁵ Thomas Brown, "Ibogaine in the treatment of substance dependence," *Current Drug Abuse Reviews*, 6 (2013). 1–14.

⁵⁶ Kenneth Alper, Marina Stajić, James Gill, "Fatalities Temporally Associated with the Ingestion of Ibogaine," *Journal of Forensic Sciences* 57 (2011). 398.

⁵⁷ Francesca Filbey, *The Neuroscience of Addiction*, (Cambridge University Press, 2019).



When a behavior or substance triggers a rewarding response, such as drug use, there is an accompanying surge in dopamine levels within the nucleus accumbens, reinforcing the connection between the stimulus and the pleasurable experience.



The nucleus accumbens functions as a key player in encoding the learned associations between stimuli and rewarding responses. When a behavior or substance triggers a rewarding response, such as drug use, there is an accompanying surge in dopamine levels within the nucleus accumbens, reinforcing the connection between the stimulus and the pleasurable experience.⁵⁸

This reinforcement fuels the selection of drug-seeking behaviors and adaptive learning processes. However, when drugs are introduced into these regions and neural pathways, they can disrupt this delicate balance, leading to dysregulation. This dysregulation extends to areas like the anterior cingulate cortex and orbitofrontal cortex, which are crucial for cue-induced motivation and decision-making in drug-seeking behaviors.

Understanding the pharmacology of ibogaine sheds light on its potential role in mitigating addiction. While the exact pharmacological mechanisms of ibogaine and its active metabolite, noribogaine, are multifaceted and not yet fully elucidated, certain key aspects have been identified. Noribogaine has been found to inhibit the reuptake of serotonin type 2A, primarily within the nucleus accumbens, a region that plays a significant role in addictions and cravings.⁵⁹

Ibogaine exhibits a broader impact than noribogaine, primarily increasing serotonin levels across the brain. Moreover, both ibogaine and noribogaine interact with various receptor

⁵⁸ M.D. Scofield et al, “The Nucleus Accumbens: Mechanisms of Addiction across Drug Classes Reflect the Importance of Glutamate Homeostasis,” *Pharmacological Reviews* 68 (2016). 816–871.

⁵⁹ Francesca Filbey, *The Neuroscience of Addiction*, (Cambridge University Press, 2019).

systems, including opioid receptors.⁶⁰ This interaction is one of the factors contributing to the pharmacological effects of ibogaine, as it may reduce the perception of opioid withdrawal symptoms and cravings. Ibogaine's unique ability to modulate dopamine levels in the nucleus accumbens further underscores its relevance to addiction treatment. It is widely accepted that the nucleus accumbens' dopamine system significantly mediates the addictive properties of various drugs.⁶¹



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These neurobiological and pharmacological insights contribute to mitigating addiction. Ibogaine's potential to reset serotonin levels in the nucleus accumbens presents a promising avenue for reducing drug cravings and disrupting established addiction patterns. By effectively rewiring the reward system and offering a fresh start, ibogaine may serve as a valuable tool in addiction treatment. One 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.⁶²

However, it is necessary to emphasize that ibogaine is not without risks, including cardiotoxicity and other adverse effects, underscoring the necessity for rigorous research, medical supervision, and regulatory oversight to maximize its therapeutic potential while ensuring patient safety.

⁶⁰ Kenneth Alper, Howard Lotsof, & Charles Kaplan, "The ibogaine medical subculture," *Journal of Ethnopharmacology* 115 (2008). 9-24.

⁶¹ Stanley Glick & Isabelle Maisonneuve, "Mechanisms of Antiaddictive Actions of Ibogaine," *Annals of the New York Academy of Sciences*, 844 (1998). 214–226.

⁶² Deborah Mash et al, "Oral noribogaine shows high brain uptake and anti-withdrawal effects not associated with place preference in rodents," *Journal of Psychopharmacology* 30 (2016). 688–697.

This comprehensive understanding of the neurobiological foundations of addiction and the pharmacological actions of ibogaine highlights the potential role of ibogaine in addiction treatment.⁶³

⁶³ Stanley Glick & Isabelle Maisonneuve, "Mechanisms of Antiaddictive Actions of Ibogaine," 214–226.

PART 6

EFFECTIVENESS OF IBOGAINE FOR OUD

6.1

WITHDRAWAL SYMPTOMS AND CRAVINGS

Withdrawal symptoms are challenging and often detrimental to recovery from opioid addiction. Individuals often experience intense discomfort, cravings, emotional distress, risk of overdose, and psychological impact (depression, anxiety, irritability, insomnia, and difficulty concentrating), all of which can easily lead to relapse.

Existing clinical data reveals ibogaine treatment resolves opioid withdrawal symptoms in 75-100% of patients. Ibogaine treatment appears to offer sufficient evidence of its ability to reduce opioid withdrawals and cravings.

In one study, 33 participants received ibogaine at doses ranging from 6 to 29 mg/kg.⁶⁴ Within 72 hours, 76% (25) of the participants reported the resolution of opioid withdrawal symptoms without drug-seeking behavior. Relief from these withdrawal symptoms was said to have been obtained within one to three hours of ibogaine ingestion. One patient experienced sweating at 24 hours, but not at 48 hours post-treatment, while another patient experienced chills at both 24 and 48 hours. Four patients had fully resolved

⁶⁴ Kenneth Alper et al, "Treatment of acute opioid withdrawal with ibogaine," *The American Journal on Addictions* 8 (2010). 234–242.

withdrawal symptoms, but did engage in drug-seeking during the 72 hours following ibogaine treatment.

Only one patient in this study had clear signs and subjective complaints of opioid withdrawal after ibogaine ingestion, including chills, muscle aches, nausea, sweating, and was observed as having dilated pupils. This patient, a 27-year-old female, left treatment eight hours after being administered ibogaine. Researchers theorized that this failure was due to the inadequate dose size of ibogaine the patient received.

Deborah Mash followed this study with a clinical trial of 27 subjects receiving ibogaine at doses between 8 to 12 mg/kg. Her findings indicated decreased cravings over 14 days to one month.⁶⁵ Similar to prior studies, Alan Davis found a large proportion (80%) of participants ($n=88$) in his study reported that ibogaine greatly reduced or ameliorated withdrawal symptoms during treatment.⁶⁶ Also consistent with prior research, 50% of the study's sample experienced a reduction in craving lasting for one week, and 25% for at least three months following treatment. Craving outcomes were measured 48 hours and 24 hours pre-ibogaine dose and at 24-hour and 48-hour post-ibogaine dose in the sole study examining ibogaine therapy for opioid dependency using the Brief Substance Craving Scale (BSCS).

The BSCS demonstrated significant reduction in craving scores following ibogaine administration, but no follow-up data were reported. Craving was measured at baseline, discharge following ibogaine treatment, and at one-month follow-up using the Heroin Craving Questionnaire (HCQ) for opioid-dependent participants. Both measures showed significant reductions in all subscales, sustained at one-month follow up.

A later study by Mash, which examined both opioid and cocaine dependencies, reported a reduction in withdrawal symptoms as measured by the Objective Opioid Withdrawal Scale. Scores decreased significantly, from a range of 3–13 before the ibogaine dose to 0–2 approximately 24 hours after treatment.⁶⁷

⁶⁵ Deborah Mash et al, "Ibogaine: Complex Pharmacokinetics, Concerns for Safety, and Preliminary Efficacy Measures," *Annals of the New York Academy of Sciences* 914 (2000). 394–401.

⁶⁶ Alan Davis et al, "Subjective effectiveness of ibogaine treatment for problematic opioid consumption: Short- and long-term outcomes and current psychological functioning," *Journal of Psychedelic Studies* 1 (2017). 8.

⁶⁷ Deborah Mash et al, "Ibogaine Detoxification Transitions Opioid and Cocaine Abusers Between Dependence and Abstinence: Clinical Observations and Treatment Outcomes," *Frontiers in Pharmacology* 9 (2018). 5.



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Similarly, two 2018 studies focused solely on ibogaine intervention for opioid dependency also reported decreases in withdrawal scores. Both studies used validated outcome measures. In Brown and Alper’s study, the Subjective Opioid Withdrawal Scale (SOWS) was administered one hour before the first dose and at varying intervals thereafter, with an average reduction of 17 points (from 31 to 14) recorded over an average of 76.5 hours between baseline and the second SOWS assessment.⁶⁸

In the other study, both SOWS and the Clinician Opioid Withdrawal Scale (COWS) were employed. SOWS scores averaged 20.51 ± 13.66 and 17.09 ± 12.95 before the ibogaine dose, decreasing to 12.63 ± 11.95 and 10.04 ± 11.65 after the dose. COWS scores averaged 8.2 ± 5.21 and 7.64 ± 5.27 before the ibogaine dose, followed by a decrease to 5.26 ± 4.31 and 3.30 ± 3.13 post-ibogaine dose.⁶⁹

Comparing SOWS scores in both studies, Brown and Alper’s study reported a greater reduction in withdrawal symptoms compared to Malcolm’s. (an average reduction of 17 vs. 10.47 points). This difference may be attributed to variations in study design and measurements. The Brown and Alper study tailored the initial test dose to the participant’s weight (3 mg/kg), while Malcolm used a total dose of 18-20 mg/kg with a standard 100 mg dose for all participants, followed by additional dosing within two hours.

⁶⁸ Thomas Brown & Kenneth Alper, “Treatment of opioid use disorder with ibogaine: Detoxification and drug use outcomes.” 28.

⁶⁹ Benjamin Malcolm et al, “Changes in Withdrawal and Craving Scores in Participants Undergoing Opioid Detoxification Utilizing Ibogaine,” *Journal of Psychoactive Drugs* 50 (2018). 256–265.

Additionally, the timing of flood and booster doses differed between the studies, with the Brown and Alper study providing flood doses (12 mg/kg) 2–12 hours after the initial dose and booster doses (3–5 mg) 1–16 hours post-flood dose. In contrast, the Malcolm et al. study administered the flood dose within two hours of the test dose and only provided booster doses (1–5 mg/kg) if withdrawal symptoms persisted.

Furthermore, the time intervals between SOWS assessments varied, with Brown and Alper conducting follow-up assessments on average 28.5 hours later than Malcolm. These differences in dosing protocols and timing likely contributed to variations in reported outcomes between the two studies.

A 12-month observational follow-up study conducted in New Zealand, which included 15 enrolled participants seeking ibogaine treatment for methadone dependence, demonstrated sustained reductions in drug cravings and use. Participants experienced an 80% reduction in the drug use subscale of the Addiction Severity Index Lite (ASIL), indicating substantial progress.⁷⁰

A retrospective study conducted by Malcolm et al. (2018) with 50 participants who received ibogaine dosages ranging from 18 to 20 mg/kg, assessed participants within 48 hours.⁷¹ At 48 hours following ibogaine administration, withdrawal and craving scores were significantly lowered in comparison to baseline: 78% of patients did not exhibit objective clinical signs of opioid withdrawal, 79% self-reported minimal cravings for opioids, and 68% self-reported subjective withdrawal symptoms in the mild range.

6.2

ABSTINENCE

Laurie Cloutier-Gill Wood presented a single-case report involving an individual administered with ibogaine at a dosage of 2.5 to 20 mg/kg (32 mg/kg total). The case documented a 37-year-old female with a 19-year history of severe OUD achieving an ongoing 18-month period of abstinence following a four-day ibogaine treatment.⁷² Her previous longest period of continuous abstinence from opioids was two months while on

⁷⁰ Geoffrey Noller et al, “Ibogaine treatment outcomes for opioid dependence from a twelve-month follow-up observational study,” *The American Journal of Drug and Alcohol Abuse* 44 (2017). 7.

⁷¹ Benjamin Malcolm et al, “Changes in Withdrawal and Craving Scores in Participants Undergoing Opioid Detoxification Utilizing Ibogaine.” 256–265.

⁷² Laurie Cloutier-Gill, “Remission of Severe Opioid Use Disorder with Ibogaine: A Case Report,” *Journal of Psychoactive Drugs*, 48 (2016). 215.

methadone. This individual reported sustained abstinence attributed to what they described as a "spiritual awakening" lasting 18 months.



Of the population in this study, Brown and Alper found that the subset that received the most distinctive benefit from the ibogaine treatment was a subset of 12 individuals who had histories of resistance to traditional methods.



Observational studies have provided more extensive data. Brown and Alper (2018) observed individuals who underwent ibogaine treatment for opioid detoxification reported various degrees of reduction in opioid use over time. For instance, during the one-month follow-up, 50% reported no opioid use in the previous 30 days. These percentages fluctuated at subsequent follow-ups in which participants reported on opioid use within the preceding 30 days. At three months, 33% reported complete abstinence over the prior 30 days, 20% did so at six months, 37% at nine months, and 23% at 12 months.⁷³ Of the population in this study, Brown and Alper found that the subset that received the most distinctive benefit from the ibogaine treatment was a subset of 12 individuals who had histories of resistance to traditional methods.

In the study performed by Geoffrey Noller, ibogaine was administered at dosages ranging from 25 to 55 mg/kg, and the assessment period extended for 12 months. Participants (n=14) achieved sustained abstinence rates of 87.5% at 3 months, 85.7% at 6 months, and 75% at 12 months.⁷⁴ Abstinence was determined by opioid urine tests. At one month post-treatment, six participants (43%) reported benzodiazepine use (five prescribed), while at 12 months, only one of the remaining 11 participants reported this.⁷⁵

⁷³ Thomas Brown & Kenneth Alper, "Treatment of opioid use disorder with ibogaine: Detoxification and drug use outcomes." 28.

⁷⁴ Geoffrey Noller et al, "Ibogaine treatment outcomes for opioid dependence from a twelve-month follow-up observational study," *The American Journal of Drug and Alcohol Abuse*, 44 (2017). 8.

⁷⁵ Geoffrey Noller et al, "Ibogaine treatment outcomes for opioid dependence from a twelve-month follow-up observational study." 9.

A retrospective study by Davis et al. (2018) involving 73 participants who received an ibogaine dosage of 15 ± 5 mg/kg, with an assessment period of at least one year, showed promising results.⁷⁶ Thirty percent of participants reported never using opioids again following ibogaine treatment. And over one half (54%) of these abstainers had been abstinent for at least one year, with 31% abstinent for at least two years. At the time of survey, 41% of all participants reported sustained abstinence (>six months) and another 45% reported a substantial decrease in opioid use.

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Thirty percent of participants reported never using opioids again following ibogaine treatment.
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In a case study series, two participants received ibogaine dosages of 25.5 mg/kg and 13–34 mg/kg, with respective assessment periods of 24 months and 36 months. One patient achieved total opioid abstinence for three years, and the other achieved total abstinence for two years.⁷⁷

In a retrospective self-report questionnaire study, data revealed that 76% (n=21) of participants had ceased their primary and secondary drug use within the first 1.5 years post-ibogaine treatment. 24% remained completely abstinent from all illicit substances for 3.5 years after treatment. The average drug free period of this group of people was 41.2 months—almost 3.5 years.⁷⁸

⁷⁶ Alan Davis et al, “Subjective effectiveness of ibogaine treatment for problematic opioid consumption: Short- and long-term outcomes and current psychological functioning,” *Journal of Psychedelic Studies* 1 (2017). 65–73.

⁷⁷ Claire Wilson, Trevor Millar, & Zac Matieschyn, Z, “Novel treatment of opioid use disorder using ibogaine and iboga in two adults,” *Journal of Psychedelic Studies* 4 (2018). 152.

⁷⁸ Annamarie et al, “Examination of the Phenomenology of the Ibogaine Treatment Experience: Role of Altered States of Consciousness and Psychedelic Experiences,” *Journal of Psychoactive Drugs* 49 (2017). 201–208.

PART 7

IS IBOGAINE SAFE?

Ibogaïne treatment for opioid addiction presents several risks, with one of the primary concerns being its potential for cardiotoxicity. The risk with ibogaïne comes from its ability to influence certain channels in the heart, specifically those responsible for the electrical recovery process. This can cause a delay in the heart's electrical reset, potentially leading to a serious and life-threatening disruption in its rhythm.⁷⁹ While lower doses of ibogaïne may stimulate the cardiovascular system, higher doses have been observed to decrease heart rate, thus establishing a complex relationship between ibogaïne and cardiac function.⁸⁰

Notably, individuals with a history of chronic use of sympathomimetic agents, such as crack cocaine and methamphetamine, are particularly susceptible to cardiovascular complications during potential ibogaïne treatment.⁸¹ Nonetheless, in-depth research is crucial to fully comprehend the intricate connection between ibogaïne and heart arrhythmias.⁸²

⁷⁹ Geoffrey Noller et al, "Ibogaïne treatment outcomes for opioid dependence from a twelve-month follow-up observational study," *The American Journal of Drug and Alcohol Abuse* 44 (2017). 3.

⁸⁰ Kenneth Alper, Marina Stajić, James Gill, "Fatalities Temporally Associated with the Ingestion of Ibogaïne." 398-412.

⁸¹ Eduardo Schenberg et al, "Treating drug dependence with the aid of ibogaïne: A retrospective study," *Journal of Psychopharmacology* 28 (2014). 993–1000.

⁸² Xaver Koenig & Karlheinz Hilber, "The Anti-Addiction Drug Ibogaïne and the Heart: A Delicate Relation," *Molecules* 20 (2015). 2208–2228.

Furthermore, the administration of high doses of ibogaine orally in humans has been linked to various side effects, including nausea, vomiting, tremors, and ataxia, often resolving without enduring consequences.⁸³ However, more severe side effects have been documented, such as comas, seizures, respiratory difficulties, and pulmonary aspiration. Some cases have suggested a potential link between ibogaine use and the onset of manic episodes, although these cases were complex, involving individuals with multifaceted medical histories and concurrent substance use. Consequently, additional research is warranted to establish any conclusive connections and causations in this context.



...some individuals have overdosed and died because they used heroin simultaneously with ibogaine, underscoring the critical importance of stringent safety protocols.



A significant risk associated with ibogaine treatment is its potential to amplify the lethality of opioids due to its augmentation of opioid signaling. There were 19 reported deaths linked to ibogaine in the 18-year period between 1990 and 2008.⁸⁴ Tragically, some individuals have overdosed and died because they used heroin simultaneously with ibogaine, underscoring the critical importance of stringent safety protocols. To mitigate these risks effectively, a comprehensive assessment of medical history and pre-existing conditions is imperative before considering ibogaine treatment.

For instance, a retrospective study revealed that individuals with medical comorbidities, such as liver disease, cardiovascular conditions, and obesity, were more vulnerable to complications. Cardiac disease, pulmonary thromboembolism, and seizures were identified as contributing factors in some of the reported fatalities.⁸⁵ Thus, meticulous candidate screening, continuous monitoring throughout the treatment process, and the provision of treatment in regulated facilities are essential safety measures.

⁸³ L Schep et al, "Ibogaine for treating drug dependence. What is a safe dose," *Drug and Alcohol Dependence* 166 (2016). 3.

⁸⁴ Kenneth Alper, Marina Stajić, James Gill, "Fatalities Temporally Associated with the Ingestion of Ibogaine." 398-412.

⁸⁵ Kenneth Alper, Marina Stajić, James Gill, "Fatalities Temporally Associated with the Ingestion of Ibogaine." 398-412.

While unregulated ibogaine treatment clinics have been associated with unknown numbers of deaths, those that adhere to strict safety measures and are staffed with medical professionals have significantly lower risk profiles. For example, Mash's ibogaine clinic in St. Kitts, West Indies, conducted 257 treatments from 1996 to 2004 without any related deaths. Mash's clinic in Cancun, Mexico, reported conducting 1,200 treatments without any associated or related deaths, demonstrating the significance of adherence to safety protocols in a controlled and supervised treatment environment with professional oversight.⁸⁶



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Despite these risks, the most recent clinical trial, a 2023 open-label study, reported no fatalities.⁸⁷ The study consisted of consecutive ibogaine and 5-MeO-DMT assisted-therapy for 86 trauma-exposed male Special Operations Forces Veterans (SOFV). Participants were referred to the clinical program via word of mouth and were required to complete a comprehensive medical and psychological screening before enrolling to ensure safety and appropriateness for participation. The program consisted of a three-day retreat in Mexico.

On the first day, a program therapist conducted a group preparation session, explaining the potential effects of ibogaine, guiding participants to set their intentions, and providing mindfulness techniques. Attendees underwent urine toxicology and alcohol tests to confirm the absence of contraindicated substances. Those who passed these tests were administered a single oral dose of ibogaine hydrochloride (10 mg/kg) in a group setting

⁸⁶ Deborah Mash, "Breaking the cycle of opioid use disorder with Ibogaine," *The American Journal of Drug and Alcohol Abuse* 44 (2017). 2.

⁸⁷ Alan Davis, Yitong Xin, Nathan Sepeda & Lynnette, "Open-label study of consecutive ibogaine and 5-MEO-DMT assisted-therapy for trauma-exposed male special operations forces veterans: Prospective Data from a clinical program in Mexico," *The American Journal of Drug and Alcohol Abuse* 49 (2023). 1–10.

with cardiac and blood pressure monitoring. Participants were instructed to lie on a bed in a supine position and received intravenous saline and electrolytes during the ibogaine session, aimed at ensuring safety and comfort throughout the experience. This program aimed to provide a therapeutic and controlled environment for individuals undergoing ibogaine treatment. As a result, no fatalities occurred.

7.1

ABUSE POTENTIAL

Ibogaine's psychedelic properties have stirred debate over its potential for abuse, a consideration that factors into discussions about its legalization. Opponents argue that these psychedelic qualities might make ibogaine addictive, increasing the risk of abuse.⁸⁸ However, it's important to note that ibogaine's hallucinogenic characteristics differ from those of traditional psychedelics. Individuals who have experienced ibogaine therapy often describe it as a mentally, emotionally, and physically demanding ordeal, which diminishes its appeal for recreational use.⁸⁹

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Historically, ibogaine did surface on the black market for recreational consumption, albeit briefly, during the 1960s, particularly in California and New York. However, its popularity waned, likely because it had no appeal for illicit drug dealers. Counterintuitively, its anti-addictive effects reduced the dealers' customer bases.⁹⁰

Studies involving animals have provided further insights into the risk of ibogaine abuse. Animals do not exhibit self-administration behavior with 18-methoxycoronaridine, a

⁸⁸ Jennifer Donnelly, “The Need for Ibogaine in Drug and Alcohol Addiction Treatment.” 14.

⁸⁹ Jennifer Donnelly, “The Need for Ibogaine in Drug and Alcohol Addiction Treatment.” 19.

⁹⁰ Jennifer Donnelly, “The Need for Ibogaine in Drug and Alcohol Addiction Treatment.” 8.

synthesized compound closely related to ibogaine, suggesting a similar pattern might be expected with ibogaine.⁹¹

Removing the hallucinogenic and psychedelic components of ibogaine, which some argue contribute to its therapeutic efficacy by fostering insight and spiritual growth, could substantially reduce its potential for addiction treatment.⁹²

7.2

CRIME

There have been only a few arrests related to ibogaine that are currently known to the public. In one notable 2005 case, a couple in Wyoming was arrested after the Drug Enforcement Agency (DEA) became aware of their intentions to import ibogaine from Switzerland.⁹³ This couple, reportedly struggling with addiction themselves, sought ibogaine as a potential treatment for their substance use issues.

In 2011, Dimitri Mugianis, an individual who had previously provided ibogaine treatment to heroin addicts in the United States, faced arrest by federal agents in Seattle for possession. His charges were reduced to a misdemeanor, and he served 45 days' house arrest. According to a report from *The New York Times*, he had planned to administer ibogaine treatment to an individual struggling with addiction, who, as it turned out, was working as an informant for the authorities.⁹⁴

⁹¹ Kenneth Alper, Marina Stajić, James Gill, "Fatalities Temporally Associated with the Ingestion of Ibogaine," (2011). 398.

⁹² Borja Rodríguez-Cano et al, "Underground ibogaine use for the treatment of substance use disorders: A qualitative analysis of subjective experiences," *Drug and Alcohol Review* 42 (2022).

⁹³ Jennifer Donnelly, "The Need for Ibogaine in Drug and Alcohol Addiction Treatment." 93–114.

⁹⁴ Corey Kilgannon, "A shaman, coaxing sobriety," *nytimes.com*, *The New York Times*, 5 April 2013. <https://www.nytimes.com/2013/04/07/nyregion/dimitri-mugianis-helps-addicts-with-an-african-spiritual-practice.html> (accessed 17 Nov. 2023).

PART 8

EFFECTIVENESS OF IBOGAINE RELATIVE TO EXISTING THERAPIES

Compare the risks associated with ibogaine treatment with the reality of opioid overdose deaths. While some have genuine concerns about the safety of ibogaine, these concerns are relatively modest and manageable compared to the alarming statistics surrounding methadone-related deaths. Unintentional methadone-related deaths increased significantly from 790 deaths to more than 5,400 deaths between 1990 and 2006, marking the fastest increase among all drug-related deaths during that period.⁹⁵

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In the mid-to-late 2000s, methadone-related overdose deaths accounted for an average of 30% of all opioid-related overdose deaths....

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⁹⁵ R Lev et al, “Methadone related deaths compared to all prescription related deaths,” *Forensic Science International* 257 (2015). 347–352. <https://doi.org/10.1016/j.forsciint.2015.09.021>

In the mid-to-late 2000s, methadone-related overdose deaths accounted for an average of 30% of all opioid-related overdose deaths, despite representing only 2% of opioid prescriptions.⁹⁶ While it's worth noting that methadone-related deaths decreased to approximately 6.7% of opioid-related deaths in 2017, partly due to a reduction in methadone prescriptions for pain management, the Centers for Disease Control still attributed an average of 5,000 deaths per year to methadone overdose in 2012.⁹⁷

The issue of methadone abuse and misuse is equally concerning. Lifetime nonmedical use of methadone in the United States increased significantly from around 928,000 in 2002 to approximately 1.8 million in 2008.⁹⁸ The estimated number of emergency room visits for nonmedical use of prescription opioids increased 111% during 2004-2008 (from 144,600 to 305,900 visits) and increased 29% from 2007 to 2008 alone.⁹⁹ In 2007, there were 69,506 emergency department visits that mentioned methadone, compared to 48,864 visits in 2004. Of these cases in 2007, a substantial 78% involved nonmedical use of methadone.¹⁰⁰

Traditional MATs also struggle to retain patients. A systematic review of retention rates in programs that deploy an opioid substitute, such as methadone or buprenorphine, are around 57% at 12 months, with 3-year rates at 38%. Ibogaine's treatment may offer an advantage in regards to retention rates, as its treatment process often does not require repeated treatments to be effective.

These statistics underscore the pressing need for comprehensive strategies to address opioid addiction and overdose deaths. While ibogaine treatment has associated risks, it is essential to consider these risks within the broader context of the opioid epidemic and explore evidence-based alternatives to improve addiction treatment and reduce harm.

⁹⁶ Wilson Compton & Christopher Jones, "Epidemiology of the U.S. opioid crisis: The importance of the vector." 130–143.

⁹⁷ "CDC Telebriefing on Vital Signs Report: Risk for Overdose from Methadone Used for Pain Relief – United states, 1999–2010," *cdc.gov*, Centers for Disease Control and Prevention Online Classroom, 3 July 2012. www.cdc.gov/media/releases/2012/t0703_methadone.html (accessed 11 Oct. 2023).

⁹⁸ Jane Maxwell & Elinore McCance-Katz, "Indicators of buprenorphine and methadone use and abuse: What do we know," *The American Journal on Addictions* 19 (2010). 73–88.

⁹⁹ Centers for Disease Control and Prevention (CDC). (2010). Emergency department visits involving nonmedical use of selected prescription drugs - United States, 2004-2008. *MMWR. Morbidity and Mortality Weekly Report*, 59(23), 705–709. <https://pubmed.ncbi.nlm.nih.gov/20559200/>

¹⁰⁰ Jane Maxwell & Elinore McCance-Katz, "Indicators of buprenorphine and methadone use and abuse: What do we know." 73–88.

TABLE 4: OVERVIEW OF INTENTIONS, SUBSTANCES AND DOSING, MAIN FINDINGS, AND ADVERSE EVENTS.

| Study information | N | Intention | Substance (s) | Dose | Main results | serious AE |
|--|----|--------------------|-------------------------------|--|--|---------------------------|
| Case reports/case series | | | | | | |
| Sheppard, 1994; CR | 7 | Tx OUD | ibogaine HCl | 11.7–25 mg/kg, p.o. | Reduct. of WS for all; 3 subj. remained drug-free for >14 wk | None reported |
| Luciano, 1998; CS | 3 | Tx CUD/SUD | ibogaine HCl domperidon | 20–25 mg/kg, p.o. 10 mg, p.o. | No subj./obj. signs of WS or craving; neurological exams normal | None reported |
| Alper et al., 1999; CS | 33 | Tx OUD | ibogaine*** | 19.3 ± 6.9 mg/kg, p.o. | Absence or reduct. of OWS; 76% abstinence for at least 3 days | 1 fatality |
| Cloutier-Gill et al., 2016; CR | 1 | Tx OUD | ibogaine HCl hydromorphone | To 32 mg/kg, p.o., multi-dose in 4 d; 30/45 mg (d1/d2), p.o. | Opioid abstinence for 18 mo | None reported |
| Wilkins et al., 2017; CS | 1 | Tx OUD, MMT-detox. | ibogaine HCl methadone | Max. 600 mg/d, p.o. decreasing doses, p.o. | No relapse in 12 mo post-Tx; no OAT | None reported |
| Wilson et al., 2020; CS | 2 | Tx OUD/SUD | ibogaine HCl | To 30.6 mg/kg, p.o. multi-dose | >2 yrs total opioid abstinence | QTc 512 ms, 53 bpm – >ICU |
| Retrospective/observational studies | | | | | | |
| Schenberg et al., 2014; RA | 75 | Tx SUD | ibogaine HCl domperidone | 7.5–20 mg/kg p.o., multi-dose 20 mg | Median of abstinence 5.5 mo (1 Tx); and 8.4 mo (multiple Tx) | None reported |
| Davis et al., 2017; RA | 88 | Tx OUD | ibogaine HCl | 15 mg ± 5 mg/kg, p.o. | 80% reduct. of WS; 50% reduct. of craving for 1 wk.; 25% reduct. of craving for 3 mo; 68 | None reported |

| Study information | N | Intention | Substance (s) | Dose | Main results | serious AE |
|------------------------------------|----|------------------------------|--|---|--|---------------|
| | | | | | responders/ 20 non-responders | |
| Malcolm et al., 2018; RA | 40 | Tx OUD | ibogaine HCl | 18–20 mg/kg p.o. | Sign. reduct. in COWS, SOWS, and BSCS | None reported |
| Davis et al., 2020; RA | 51 | Tx PTSD/depr./anx. | ibogaine HCl 5-MeO-DMT | 10 mg/kg, p.o. (d1) ~ 7.5 mg, inh. (d3) | Sign. reduct. of symptoms of PTSD, depr. and anx. | Not assessed |
| Brown et al., 2018; OS | 30 | Tx OUD | ibogaine HCl | 1540 ± 920 mg, p.o. | SOWS decrease (post 76 h) in >50% of subjects; in 50% of subjects no OU for 1 mo; in 12 subjects reduct. of drug use 75% | none reported |
| Noller et al., 2018; OS | 14 | Tx OUD | ibogaine HCl diazepam, zopiclone, ondansetron | 25–55 mg/kg p.o. (some received usual clinical doses, p.o.) | Sign. reduct. in SOWS; sign. Reduct. ASI-Lite Subscale “Drug” and BDI; 8 subj. Opioid-negative after 12 mo | 1 fatality |
| Brown et al., 2019*; OS | 0* | Tx OUD | ibogaine HCl | 31.4 ± 7.6 mg/kg, p.o. | Sign. reduct. BDI; ~ 75% report “transformational experience” | None reported |
| Heink et al., 2017; RA | 27 | 92% psych. Tx, 78% Tx SUD | ibogaine*** | Not stated | 96% reduct. of WS; 68% “dramatically” reduct. of WS; 41% report “important hallucinations” | Not assessed |
| Open-label clinical trials | | | | | | |
| Mash et al., 2000; OL, CT | 27 | Tx OUD | ibogaine HCl | To 800 mg, p.o. | Sign. reduct. in BDI, HCQN-29; diminished craving 1 mo post-Tx | None reported |
| Mash et al., 2001; OL, CT | 32 | Tx OUD | ibogaine HCl | 800 mg, p.o. | Sign. reduct. in OOWS, HCQN-29, OP-SCL | None reported |
| Glue, Winter, et al., 2015; OL, CT | 21 | Pharm./safety assessment | ibogaine | 20 mg, p.o. | Safe and well-tolerated; AUC and <i>C_{max}</i> incr. with | None reported |

| Study information | N | Intention | Substance (s) | Dose | Main results | serious AE |
|------------------------------|-----|-----------|-------------------------------|---------------------|--|------------------|
| | | | 11 subj. pre-Tx paroxetine | 10–20 mg/d, p.o. | paroxetine pre-Tx due to CYP2D6 inhibition | |
| Mash et al., 2018; OL, CT | 191 | Tx OUD | ibogaine HCl | 8–12 mg/kg, p.o. | Sign. Reduct. in HCQ, BDI | None reported |

Tx = treatment, CR = case report, CS = case series, RA = retrospective analysis, OS = observational study, OL = open-label, CT = clinical trial, HCl = hydrochloride, OAT = Opioid Agonist Treatment, MMT = Methadone Maintenance Treatment, OUD = Opioid Use/Disorder, CUD = Cocaine Use Disorder, SUD = Substance Use Disorder, depr. = depressive disorder, anx. = anxiety disorder, p.o. = per os, HCl = hydrochloride, mo = month(s), wk. = week(s), sign. = significant, reduct. = reduction, C/O/S/OWS = clinical/objective/subjective/opioid withdrawal symptoms, WS = withdrawal symptoms, subj. = subjective, obj. = objective, ICU = intensive care unit, incr. = increase, pharm. = pharmacological, AUC = area under the curve, Cmax = maximum concentration, psych. = psychological, CYP2D6 = Cytochrome P450 2D6, PTSD = post-traumatic-stress-disorder, sympt. = symptoms, QTc = corrected QT interval, QTcF = corrected QT interval by Fredericia formula, bpm = beats per minute, ASI-Lite = Addiction Severity Index Lite, BSCS = Brief-Substance-Craving-Scale, BDI = Beck Depression Inventory, HCQN = Heroin Craving Questionnaire, OP-SCL = Opiate Symptom

PART 9

CONSIDERATIONS FOR STATE-BASED CLINICAL TRIALS

The State of Ohio is considering funding clinical trials of ibogaine for opioid use disorder from opioid abatement settlement funds. This section details the challenges and opportunities for clinical trials overseen by state agencies.

9.1

SAFETY

As previously detailed, there are serious concerns around the safety of ibogaine treatment, especially from cardiotoxicity-related fatalities.

There are three potential strategies to mitigate safety risks:

- 1) Medical oversight: Fatalities are largely due to poor medical oversight and contraindicated substance use. Ibogaine, in rare instances, can cause irregular heartbeats, but this kind of arrhythmia is a commonly solved problem within emergency room medicine; there are a variety of known protocols to regain heartbeat regularity. For the last five years, when patients had medical oversight, there have been no recorded deaths in clinical trials.

- 2) Screening: Ibogaine facilities ban opioid use since concurrent ibogaine and heroin use can be fatal. However, addicts may defy rules and secretly consume opioids despite the risks. Additionally, undiscovered heart infections from previous contaminated intravenous drug paraphernalia can increase susceptibility to heart problems during ibogaine treatment.
- 3) Low-dose protocol: There is an ongoing trial in Spain that uses ascending low-dose ibogaine to help titrate addicted patients off of substance addiction.¹⁰¹ The approach can include higher-risk populations because patients do not need to go “cold turkey.” It also avoids the dangers of higher dose ibogaine protocols.

9.2

ACCESS AND COMPASSIONATE USE

Ibogaine is one of the most difficult psychedelics to access safely in the United States. Within the last three years, two states have legalized personal possession of botanical psychedelics, and more are considering similar decriminalization efforts.

In Colorado and Oregon, there has been a proliferation of service providers, offering psilocybin-assisted mental health services. To a lesser extent, dimethyltryptamine (DMT) is also offered.

But, given ibogaine’s risk profile, there are no publicly available ibogaine service centers in the United States as of this writing.

¹⁰¹ “First Ever Clinical Trial with Ibogaine for Opioid Dependency,” [iceers.org](https://www.iceers.org), ICEERS, 14 April 2022. www.iceers.org/first-ever-clinical-trial-with-ibogaine-for-opioid-dependency/ (accessed 25 Sep. 2023).

PART 10

CONCLUSION

In the realm of treating OUD, medical experts have established several evidence-based pharmacotherapies that include methadone and buprenorphine. However, it's crucial to recognize that MAT necessitates long-term adherence, which can be a challenging commitment for many individuals. Consequently, there's a pressing need for innovative therapies, especially for patients who do not respond to MAT or are hesitant to engage in lengthy MAT programs.

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One potential alternative treatment that has shown promise for OUD is ibogaine. Several reasons support its consideration. First, studies have suggested that ibogaine is effective in alleviating opioid withdrawal symptoms and reducing cravings. Although the precise pharmacological mechanisms behind ibogaine's anti-addictive properties are not fully elucidated, the simultaneous action of ibogaine and its primary metabolite, noribogaine, on

various neurotransmitter transporters and receptors provides a biologically plausible explanation for its anti-addictive effects.¹⁰²

Second, ibogaine is typically administered in a single session, obviating the need for ongoing, continuous administration. This single-session approach can be advantageous for individuals with OUD, facilitating a smoother transition back to daily life, including employment, and thereby reducing both direct and indirect societal costs.

Third, it has been postulated that the mystical experiences often associated with ibogaine and other traditional psychedelic substances might lead to a resetting of psychological processes or neuroadaptations underlying substance use disorders. This resetting effect could potentially contribute to long-term abstinence. One patient herself mentioned that such a transformative experience was pivotal to her success.¹⁰³

Finally, ibogaine has exhibited a low potential for abuse due to its anti-addictive properties shown in animal models, where ibogaine did not induce a desire for the substance or aversion to it.¹⁰⁴ In addition, the limited number of arrests linked to ibogaine further reveals the low probability of diversion.



... ibogaine has exhibited a low potential for abuse due to its anti-addictive properties shown in animal models, where ibogaine did not induce a desire for the substance or aversion to it.



Despite these encouraging attributes of ibogaine, its potential for the treatment of substance use disorders has been hampered by safety concerns. The lack of clinical research on ibogaine has resulted in a dearth of evidence-based clinical and pharmaceutical standards for its safe administration, exacerbating its potential risks.

¹⁰² Xaver Koenig & Karlheinz Hilber, “The Anti-Addiction Drug Ibogaine and the Heart: A Delicate Relation,” *Molecules* 20 (2015). 2208–2228.

¹⁰³ Laurie Cloutier-Gill et al, “Remission of Severe Opioid Use Disorder with Ibogaine: A Case Report,” *Journal of Psychoactive Drugs*, 48 (2016). 214-217.

¹⁰⁴ L Schep et al, “Ibogaine for treating drug dependence. What is a safe dose,” *Drug and Alcohol Dependence* 166 (2016). 3.

Reports indicate 22 deaths were temporally related to ibogaine use between 1991 and 2014, with most linked to pre-existing medical comorbidities (particularly cardiovascular disease), inadequate dosing, concurrent use of other substances, and electrolyte imbalances (e.g., hypokalemia).¹⁰⁵ Only three of the 22 fatalities occurred after 2008.

Clinical observations and animal studies suggest that many of these deaths may have been due to cardiac arrhythmias induced by ibogaine's propensity to prolong the QT interval.¹⁰⁶ Therefore, the safe administration of ibogaine would necessitate precautions such as screening for electrolyte imbalances and conducting ECG screenings before treatment. Additionally, patients with cardiovascular disease should be excluded from ibogaine treatment, and individuals should abstain from any other substances that might potentially prolong the QTc interval.

In summary, the presented literature review highlights the complexities of treating refractory OUD and underscores the urgent need for expanding treatment options, not only for OUD but also for other substances like cocaine, where pharmacotherapies are currently lacking. While ibogaine holds promise as a potential treatment, its use in individual patients should be guided by a thorough risk-benefit analysis, considering factors like potential cardiotoxicity versus untreated substance use disorder. Furthermore, the selection of eligible candidates and the administration of ibogaine should occur in appropriately safe settings.

¹⁰⁵ Xaver Koenig & Karlheinz Hilber, "The Anti-Addiction Drug Ibogaine and the Heart: A Delicate Relation." 2208–2228.

¹⁰⁶ Kenneth Alper, "Ibogaine: A review." 1–38.

ABOUT THE AUTHOR

Madison S. Carlino is a policy analyst and researcher at the Reason Foundation. Her work primarily focuses on drug policy in the United States, including psychedelic medicine and marijuana laws.

Before joining Reason, Carlino worked as a research intern and grant writer with the James Madison Institute (JMI) in Tallahassee, Florida. At JMI, she focused on education policies that empower Florida parents to choose schools, courses, resources, and programs that fit their child's unique needs, interests, and learning styles. Her research at JMI also emphasized the role of constitutional rights in promoting democracy and freedom. As a grant writer, she was responsible for drafting JMI proposals.

As an undergraduate, Carlino worked as a policy analyst at the DeVoe L. Moore Center. During her tenure there, she developed and conducted a research project examining the relationship between Cuban enclaves and Cuban wages in Miami, Florida. One of her favorite projects included a business plan she created to increase high school graduation rates via alternative teaching methods and education programs. Through these experiences, she gained a greater understanding and appreciation of policy and hopes to use it to advocate for greater economic and social support of disadvantaged Americans.

Carlino recently graduated summa cum laude with a B.S. in economics from Florida State University, where she double-majored in economics and media/communication studies with

a minor in business. Her plans include continuing her work in research and policy. She intends to eventually pursue a Ph.D. in either public economics or econometrics.

