

Ibogaine for Opioid Use Disorder: Can We Root Out Addiction at Its Source?

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Shuang Ouyang, Pharm.D., BCPS

Advanced Addiction Treatment Fellow
South Texas Veterans Health Care System, San Antonio, Texas
Division of Pharmacotherapy, the University of Texas at Austin College of Pharmacy
Pharmacotherapy Education and Research Center
The University of Texas Health Science Center at San Antonio

Learning Objectives:

1. Discuss the stages of addiction progression alongside pertinent neurobiological changes
2. Review opioid use disorder (OUD) and the current treatment modalities broadly accepted by the medical community
3. Introduce ibogaine as a single source, multifaceted treatment for substance and opioid use disorder
4. Evaluate available evidence on ibogaine

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PART I. BACKGROUND

Table 1. Common Substance Use Terms¹

Term	Definition
Misuse	Usage of a substance for a purpose that is inconsistent with legal or medical guidelines
Abuse	Maladaptive pattern of use despite knowledge of psychological or physical problems directly exacerbated by continued drug use
Aberrant Behavior	Type of behavior a drug misuser or abuser may engage in, such as recurrent requests for early prescription refills
Pseudo-Addiction	Pattern of drug-seeking behavior in pain patients receiving inadequate pain management and mistaken for addiction, portraying an unfortunate interstice of warped emotional salience and undertreated pain in the setting of iatrogenic dependence to opioid analgesics
Tolerance	Decrease in response to a drug dose that occurs with continued use, with both physiological and psychological factors contributing to its development
Withdrawal	Cluster of symptoms with varying degrees of severity that occur upon cessation or reduction of a psychoactive substance
Physical Dependence	Adaptation manifested by production of a withdrawal syndrome inducible upon abrupt cessation, rapid dose reduction, decreasing drug serum concentration, and/or administration of an antagonist
Psychological Dependence	Constellation of emotional reliance for a substance beyond its physical effects, often amplified in the drug's absence

I. Neurobiology of Addiction

a. What is “addiction?”

- i. Addiction can be conceptualized as the most severe stages of a disease severity spectrum from drug misuse/abuse to chronic relapsing and remitting pattern^{2,3}
- ii. Represented by the 3-stage cycle of 1) binge/intoxication, 2) withdrawal/negative affect, and 3) preoccupation/anticipation

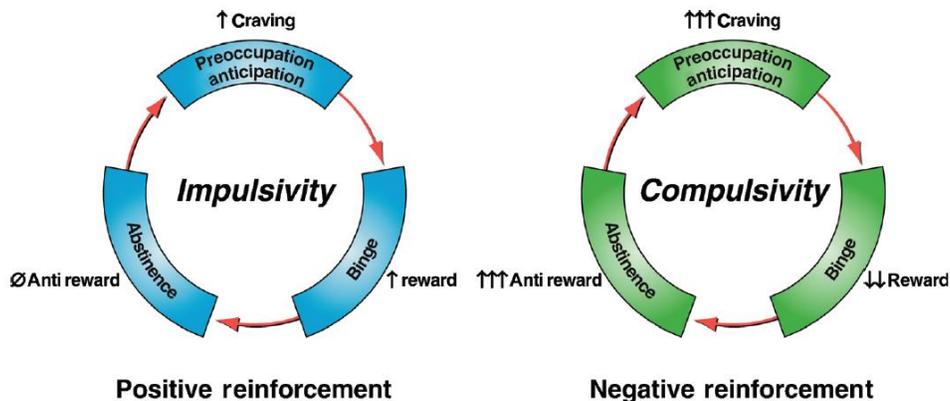


Figure 1. Cycles of Addiction³

b. Binge/intoxication: positive reinforcement

- i. Mesocorticolimbic dopamine (DA) system
- ii. Limbic system contains structures integral to processing memory and emotional information
 - 1. Cues generated via experiences with food, drinks, sex, and social interaction⁴
 - 2. Drug euphoria represents a perverse hijacking of natural reward centers evolved to ensure survival
- iii. Several mechanisms account for increased DA in the limbic system (Appendix 1)
 - 1. Direct DA release in the ventral tegmental area (VTA) and its projections into the nucleus accumbens (NAc) (also called the ventral striatum) and the limbic forebrain such as the prefrontal cortex (PFC)
 - 2. Activation of endogenous opioid pathways innervating the VTA and NAc by opioids, nicotine, ethanol, and other drugs

3. Direct action on the NAc by other drugs of abuse

Table 2. Neurobiological substrates for the acute reinforcing effects of drugs of abuse⁴

Drug of abuse	Neurotransmitters involved	Site
Nicotine	Nicotinic acetylcholine (N-Ach), dopamine (DA), γ -aminobutyric acid (GABA)	<i>Nucleus accumbens</i> , amygdala, ventral tegmental area
Δ^9 -Tetrahydrocannabinol (THC)	Endocannabinoids, DA, opioid peptides	<i>Nucleus accumbens</i> , ventral tegmental area
Alcohol (EtOH)	DA, opioid peptides, GABA, endocannabinoids	<i>Nucleus accumbens</i> , amygdala, ventral tegmental area
Cocaine and amphetamines	DA, GABA	<i>Nucleus accumbens</i> , amygdala
Opiates	Opioid peptides, DA, endocannabinoids	<i>Nucleus accumbens</i> , ventral tegmental area

- c. Withdrawal/negative affect: negative reinforcement
 - i. Acute withdrawal produces elevated brain reward thresholds
 1. Decreased activity in mesocorticolimbic DA system
 2. Decreased opioid peptide, GABA, and glutamate activity in the NAc and amygdala
 - ii. Chronic usage produces different neurochemical adaptations
 1. DA receptor density decreases, resulting in hypofrontality (reduced baseline metabolism in the PFC)
 2. Brain stress systems like the hypothalamic-pituitary-adrenal (HPA) axis and other corticotrophin-releasing factor (CRF) systems are activated to counter the constant fluctuations induced by substance use
 3. Resultant increase in adrenocorticotrophic hormone (ACTH), corticosterone, and extended amygdala (Ex-AMG) CRF levels is common for all major drugs of abuse
 - iii. A key component to emotional pain processing, the Ex-AMG represents regions of the forebrain with similar circuitry, including the central nucleus of the amygdala (CeA) and bed nucleus of the stria terminalis (BNST)
 1. Anti-reward systems like CRF, norepinephrine, and dynorphin are highly suspected of mediating negative affective states during withdrawal in order to deter future exogenous drug intake

Table 3. Neurotransmitters Implicated During Acute Withdrawal from Drugs of Abuse⁴

Neurotransmitter	Functional effect
↓ Dopamine	dysphoria
↓ Serotonin	dysphoria
↓ γ -Aminobutyric acid	Anxiety, panic attacks
↓ Neuropeptide Y	Reduction in antistress
↑ Dynorphin (κ -opioid receptor agonist)	dysphoria
↑ Corticotropin-releasing factor	Stress
↑ Norepinephrine	Stress

- d. Preoccupation/anticipation: craving, protracted abstinence, and relapse
 - i. Opposite spectrum outcome from drug misuse/abuse and represents classic addiction symptomatology
 - ii. Craving can be defined as “the memory of the rewarding effects of a drug, superimposed upon a negative motivational state”
 1. Type 1: state induced by drugs or stimuli, such as environmental cues, that have been paired with drug self-administration
 2. Type 2: motivational state change characterized by anxiety, dysphoria, or other negative emotional state that leads to relapse to drug seeking, often in combination with type 1 craving

- iii. Negative affective changes of chronic use and hypofrontality may facilitate activation of drug-, cue-, and stress-induced reinstatement neurocircuits to form the hallmark vulnerability of a return to compulsive drug use among substance abusers³
 1. Drug-induced reinstatement is likely mediated via the dopaminergic medial PFC-NAC-glutamatergic circuit
 2. Cue-induced reinstatement likely involves a glutamatergic projection from the basolateral amygdala to the NAc, which is modulated by dopamine in the amygdala
 3. Stress-induced reinstatement involves anti-reward system activation of CRF and NE in areas of the extended amygdala (CeA and BNST)
- iv. As drug addiction progresses, homeostatic brain regulatory mechanisms integral to emotional maintenance dynamically shift to new setpoints via allostasis
 1. Allostasis is defined as “stability through change”
 2. Allostasis primarily relies on feed-forward mechanisms in contrast to the feed-back mechanisms of homeostasis, and can react more readily to changes as it represents a continual readjustment of parameters to new setpoints
 3. Prolonged deviation from homeostasis results in an allostatic load that leads to pathological development of a disorder
- v. The process of allostasis may contribute to development of hyperkatifeia⁵—describing:
 1. Increased intensity of negative affective or motivational symptoms during withdrawal and abstinence
 2. Hypersensitivity to negative emotional states associated with addiction
 3. Analogous to hyperalgesia induced after long-term analgesic therapy

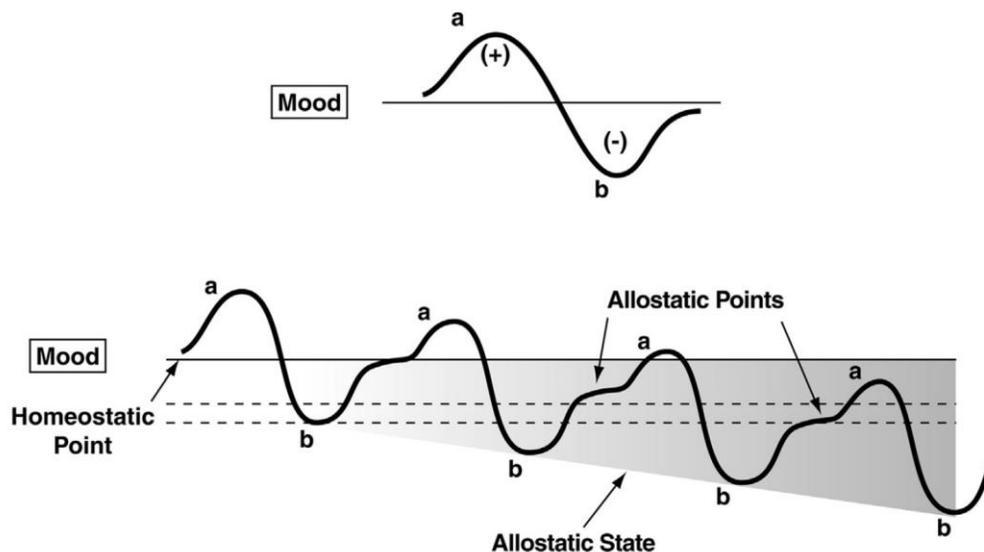


Figure 2. Allostasis Load Shifting Allostatic Points⁵

KEY POINTS

- Process and progression of addiction hijack natural brain pathways meant for survival
- Unmitigated use results in long-term neuroadaptations
- Neuroadaptations predispose patients to affective and motivational vulnerabilities
 - Makes the experience of sobriety miserable
 - Makes it nearly impossible to “just quit”
 - Contributes to chronic relapsing-remitting pattern of disease

PART II. REVIEW OF OPIOID USE DISORDER

I. Epidemiology and Health Consequences

a. 2014 National Survey on Drug Use and Health⁶

- i. Use of heroin among individuals aged ≥ 12 years:
 1. 4.8 million lifetime; 914,000 past-year; 435,000 past-month
 2. As percentage of population: 1.8%; 0.3%; 0.2% (respectively as stated above)
- ii. Non-medical use of prescription pain relievers among individuals aged ≥ 12 years:
 1. 36 million lifetime; 10.3 million past-year; 4.3 million past-month
 2. As percentage of population: 13.6%; 3.9%; 1.6% (respectively as stated above)

b. Shifting patterns of opioid and heroin in the US⁷

- i. Prescription pain relievers only
 1. Stable from 2008-2010, at 70%
 2. Decreased to less than 50% in 2014
- ii. Concurrent heroin and prescription opioid use
 1. Annual increase of 10.3% (Fig. 3)
 2. Overall increase 23.6% to 41.8% from 2008-2014
- iii. Heroin only doubled from 4.3% to 9.0% from 2008-2014

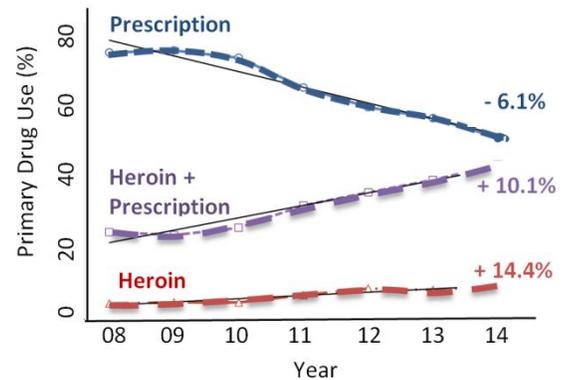


Figure 3. Drug Use Rates by Year

c. Clinical course

- i. May begin at any age, but typically problems present during late teens or early 20s
- ii. Relapse after abstinence is common, and only 20%-30% of patients achieve long term abstinence with treatment

d. Health consequences

- i. Mortality
 1. Primarily due to overdose or trauma
 2. Untreated heroin patients have a mortality rate 63 times higher than similarly aged comparators; those in methadone maintenance (MMT) reported a rate 8 times higher
 3. Opioid related overdose is now the leading cause of injury-related death in the U.S.
- ii. Morbidity
 1. Nonsterile injection conditions and drug supplies can lead to both local and systemic infections (cellulitis or endocarditis) in addition to transmission of bloodborne pathogens like hepatitis B, hepatitis C, and human immunodeficiency virus
 2. Chronic opioid use may result in hyperalgesia, narcotic bowel syndrome, and increased likelihood of motor vehicle accidents

II. Diagnosis

- a. American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)⁸ updated substance use disorder (SUD) definitions in 2013 by replacing abuse and dependence with the modifiers mild, moderate, and severe
- b. Prior assessment criteria for abuse and dependence were combined and craving was added
- c. See Appendix 2 for details

III. Maintenance Treatment after Detoxification^{10,13}

- a. Pharmacotherapy with three FDA-approved medications
 - i. Two available agonist medications with the full agonist methadone and partial agonist buprenorphine
 1. Rationale for use include suppression of cravings and withdrawal symptoms via stabilization of neuronal systems, in addition to blocking the acute effects of other opioids in the case of relapse
 2. Appropriate use allows patients to return to a productive lifestyle and address the negative consequences that often arise due to OUD

- ii. One available antagonist medication with naltrexone
 1. Intended for reinforcement of abstinence (via prevention of opioid intoxication)
 2. Does not directly affect the neuronal systems of OUD and reduce craving
- iii. Comparative pharmacology and evidence listed in Appendix 3
- b. Psychotherapy^{22,23}
 - i. Mandatory for some modalities (methadone) while heavily recommended for others
 - ii. Available in three general formats: large groups/therapeutic communities, small groups, and individual treatment (Appendix 4-6)
 - iii. Focus on contingency management (CM) due to its large effect size Cohen $d > 0.6$ ²²⁻²⁴
 1. Uses principles of operant conditioning to modify frequency and pattern of voluntary behavior through positive and negative reinforcers
 - a. Positive reinforcement generally involves rewards that escalate in value directly proportional to continued abstinence
 - b. Negative reinforcement involves non-aversive punishments, e.g. resetting of monetary vouchers to a previous low point or denial of previously agreed upon rewards
 2. CM uses *contrived* reinforcements that exist solely due to treatment involvement
 3. Common CM criticisms include high cost (vouchers) and difficult sustainability (frequent urine testing and funding) so non-monetary contingencies have been investigated, all to positive effect as described in Appendix 7
 4. Groß et al., 2006²⁹ compared abstinence results from urine drug screens of opioids and cocaine for 12 weeks among 3 cohorts: (1) low-magnitude vouchers, (2) buprenorphine medication contingencies, and (3) usual care (details in Appendix 8)
 - a. The voucher cohort was given positive reinforcers while the BUP contingency cohort was punished upon a positive urine drug screen with denial of one day's BUP dose
 - b. Although there were no overall differences, the BUP contingency group did show the largest period of continuous abstinence
 - c. If threatening the removal of an addiction medication generates more favorable results than rewarding good behavior, does that imply a newfound psychological dependence or shift in emotional salience
- c. Goals of treatment: re-defining or refining "recovery"
 - i. Consensus panels of policy, clinical, research, and recovery advocacy leaders identified 3 essential elements: sobriety, global health improvement, citizenship¹⁷
 1. Sobriety can be defined as total abstinence or diagnostic remission
 2. Global health improvement encompasses physical, emotional, relational, and spiritual health
 3. Citizenship denotes positive community integration, such as social functioning and improved quality of personal and family life
 - ii. Traditional recovery oriented peer support organizations such Narcotics Anonymous approach "recovery from addiction through abstinence" and still have not embraced individuals who are on agonist/partial-agonist medications as "being in recovery," often curtailing their presence at meetings but not shunning them entirely¹⁸
 - iii. Ongoing debate¹⁹ persists between the divergence or convergence of "recovery" and "remission"
 1. Remission typically refers to the subtraction of a pathology from a patient's life or no longer meeting diagnostic criteria
 2. Recovery implies additions and further enrichment of the patient's life
 - iv. Do the neurochemical and psychological impact of agonist/partial-agonist treatments erode patients' abilities to achieve true recovery?
 1. A metaphor analysis²⁰ of patients' sensemaking of medication assisted treatment with methadone revealed:

- a. Negativity toward methadone treatment as an unnecessary “crutch,” “shortcut,” or “liquid handcuffs” preventing true freedom from substances
- b. However, many participants also credited methadone treatment with preventing their recidivism to the criminal justice system
- 2. Similarly, 21 former inmates with opioid use disorder were interviewed in addiction treatment settings regarding their views on buprenorphine maintenance treatment (BMT) and 4 themes emerged²¹:
 - a. Reliance on willpower—most patients felt that sufficient willpower can overcome addiction and represents the mantle of responsibility
 - b. Fear of dependency—buprenorphine and methadone are still opioids, and patients want to live an *opioid-free* life; utilization of agonist treatments could also set patients up for withdrawal symptoms upon abrupt discontinuation
 - c. Variable exposure to buprenorphine—illicitly obtained buprenorphine utilized without medical direction can produce negative experiences that diminish patient acceptability of future buprenorphine
 - d. Acceptability of BMT following relapse—overall patients recognized the ability of buprenorphine to reduce likelihood of recidivism, but many wanted to reserve it for after another failed attempt at abstinence
- d. Negative aspects of agonist/partial-agonist treatment
 - i. Time commitment from the patient
 - 1. Methadone dispensing and direct administration take place at Opioid Treatment Programs (OTPs) certified by the Substance Abuse and Mental Health Services Administration (SAMHSA)
 - a. The OTP medical director considers 8 federal regulatory criteria prior to modifying a patient’s maximum take-home dose limits
 - b. In addition, patients must also concurrently meet time in treatment requirements
 - 2. Buprenorphine and buprenorphine/naloxone (BUP) have less stringent regulations than methadone, but time burden remains problematic
 - a. SAMHSA no longer requires that OTPs follow time-in-treatment frequencies for BUP prescribing
 - b. Take home scheduling for South Texas VA HCS is listed in Table 4 for comparison

Table 4. Maximum Take-Home Dose Limits for OTPs¹⁰ and South Texas VA Health Care System

Minimum Time in Treatment (days)	Maximum OTP Methadone Take-Home Dose Limits	Maximum STVHCS Buprenorphine Take-Home Limits	Expected STVHCS Buprenorphine Group Attendance
1-90	1 daily dose per week	7 daily doses	2 meetings per week
91-180	2 daily doses per week	14 daily doses	1 meeting per week
181-270	3 daily doses per week	21 daily doses	2 meetings per month
271-365	6 daily doses per week		1 meeting per month
366-730	14 daily doses per visit	28 daily doses	
730+	1 month’s supply per visit		

- 3. Impressions of methadone-maintained patients in Malvini Redden²⁰ note that, “most...seemed resigned to daily clinic visits, living on government aid, and achieving rudimentary aspects of ‘the good life’...fulfilling basic needs such as food, shelter, and safety...the image of recovery seemed bleak, lonely, difficult, and boring”
- ii. Medical consequences of agonist/partial-agonist pharmacotherapies³⁰
 - 1. For methadone, general overdose warnings are amplified due to its highly variable metabolism, potential for tissue sequestration, long half-life, and QTc prolongation risk
 - 2. Buprenorphine carries the same risks as methadone, but to a lesser degree

3. Maintenance medications may have other negative long term effects, such as increased pain sensitivity³⁵ and reduced emotional reactivity³⁶, while being unable to fully address the neurochemical effects of opioid use³⁷
 4. Ultimately, methadone and buprenorphine are not curative agents
 - a. Blum et al., 2013³¹ and O'Brien 2005³² highlighted the inability of MAT to prevent relapse post medical detoxification after long-term use
 - b. Similarly, forced detoxification of patients stabilized on MAT negatively affects treatment retention^{33,34}
- iii. Misuse and abuse of methadone and buprenorphine
1. Concurrent illicit drug use
 - a. Non-adherence to MAT may increase relapse probability by 10-fold³⁸
 - b. At any given time in treatment, 15% of methadone maintenance patients will have ongoing illicit opioid use³⁹
 - c. A single site retrospective study⁴⁰ reviewed methadone maintenance patients in the Washington, D.C. area
 - i. Concurrent illicit drug use during MAT have a 3-fold greater chance of attrition
 - ii. Concurrent illicit opioid use results in greater than a 4-fold chance of attrition
 2. Misuse and diversion
 - a. Most studies originate from surveys⁴¹⁻⁴⁵ with 15% to 100% reporting misuse and past 30-day misuse reported at 20% to 41%
 - b. The act of diversion has criminal elements which may expose a patient to environments detrimental to maintenance of recovery
 3. Discovery of diversion may preclude future treatment services
 4. Self-treatment without professional guidance may result in unforeseen and deadly consequences, such as opioid overdose

KEY POINTS

- Recovery can go beyond remission to describe how much normalcy an individual has reclaimed
- Agonist/partial-agonist treatments are corrective, not curative
- Short-term concerns include time burden and overdose risk
- Long-term effects are not benign and potentially detrimental to pain management and emotional reactivity
- Diversion more likely occurs for non-euphoric reasons, but may have serious treatment and health consequences

PART III. IBOGAINE FOR SUBSTANCE USE DISORDER(S)

I. History and Background^{15,16}

- a. Ibogaine is one of many naturally occurring psychoactive compounds in the rainforest shrub *Tabernanthe iboga* that grows in West Central Africa
 - i. Scrapings from the root bark have various traditional uses with low doses demonstrating stimulant effects and higher doses psychoactivity for religious ceremonies
- b. The shrub was brought to France from Gabon in 1864 with ibogaine specifically crystallized from *T. iboga* root bark extracts in 1901
- c. Initial medical uses
 - i. From 1939 to 1970 it was marketed in France as “Lambarene” tablets for its neuromuscular stimulant properties to treat fatigue, depression, and infectious disease
 - ii. In 1957, ibogaine was patented for its use in enhancing the analgesic effects of opiates
 - iii. In the 1950s and 1960s, ibogaine was used in psychiatric treatments to enhance retrieval of personal subjective memories to aid in the closure of unresolved conflicts
- d. Classified Schedule I by the FDA in 1970, ibogaine is presently largely unregulated in most nations, but illegal in the U.S., Australia, Belgium, Denmark, France, Sweden, and Switzerland

- i. From 1989 to 1993, treatment in non-medical settings in the Netherlands paved the way for preclinical evidence and case series of efficacy that led to the U.S. National Institute on Drug Abuse (NIDA) to fund phase I pharmacokinetics and safety trials
- ii. The 1993 death of a female patient in the Netherlands halted ongoing treatment and soured funding decisions with NIDA, even though ibogaine's suspected role was officially ruled out
- iii. Ibogaine access is now relegated to alternative treatment settings
- e. An ethnographic study¹⁶ of the "ibogaine medical subculture" identified four distinct "scenes" where ibogaine was utilized with 68% of respondents using it to treat a substance use disorder (53% for opioid dependence) and a "sizable minority" for personal psycho-spiritual growth
 - i. "Medical model" where the provider is a licensed physician and setting is a medical hospital or clinic or a clinical research facility with associated governmental jurisdiction credentials
 - ii. "Lay provider/treatment guide" where the provider lacks official medical credentials and setting is a private residence or hotel
 - iii. "Activist/self-help" where the provider has an activist or evangelical mindset with the explicit goal of gaining wider acceptance for the use of ibogaine and treating a stigmatized population
 - iv. "Religious/spiritual" with a lay provider and a setting intended for a spiritual or ceremonial experience with the goal of psycho-spiritual growth rather than substance abuse treatment

II. Typical User Experience of Ibogaine

- a. When used for substance abuse treatment, ibogaine is commonly ingested as a single-dose at 15 to 20 mg/kg, which is roughly twice the dosage used for psycho-spiritual purposes¹⁶
- b. After ingestion, the patient stays in a quiet, darkened room for the duration of treatment with reports of ataxia and sudden vomiting common during the first few hours
- c. Three distinct experiential stages have been subjectively reported:
 - i. Acute phase occurs within 1-2 hours of ingestion and lasts for 4-8 hours, characterized by emotional intensity and the oneiric experience
 - ii. Evaluative phase occurs 4-8 hours after ingestion and lasts for 8-20 hours, characterized by diminishing emotional tone, extinction of panoramic recall, and continued introspection
 - iii. Residual stimulation phase occurs 12-24 hours after ingestion and lasts for 24-72 hours or even longer; emotional intensity subsides but there is often a lingering state of arousal and patients sometimes report a decreased need for sleep that lasts for days or weeks
- d. The oneiric experience^{15,16,63}
 - i. Differs from typical hallucinogenic experiences (LSD or psilocybin) where keeping the eyes open intensifies experiences in the form of alterations in colors, textures, and patterns
 - ii. Ibogaine experiences, in contrast, are described to be more intense with the eyes closed and likened to a "waking dream with interrogatory exchanges involving ancestral beings, archetypal entities, and panoramic memory recall"
 - iii. Anecdotal evidence support ibogaine's apparent lack of appeal for recreational use with the subjective experiences noted as "unpleasant, harrowing, and brutal"
 - iv. Such oneiric experiences may impart psychological benefits with patients reporting "insight into destructive behaviors, feeling a need to be abstinent, a sense of having been cleansed and healed, and having been granted a second chance at life"

III. Biochemistry and Pharmacology

- a. Ibogaine is often studied with two other closely related compounds (active metabolite noribogaine and synthetic congener 18-methoxycoronaridine (18-MC)) for their anti-addictive properties, so all three compounds will be included for review
- b. Pharmacological activity on receptor systems as well as significance is summarized in Table 5, while comparative pharmacokinetic data is listed in Table 6

Table 5. Ibogaine and Ibogaine Derivatives' Comparative Receptor Bindings⁴⁷⁻⁵⁷

System	Ibogaine	Noribogaine	18-MC	Significance
Serotonin	Antagonist at serotonin transporter, produces presynaptic release of 5HT, agonism at 5HT2a and 5HT3 receptors	Similar to ibogaine, but more potent (10 times) at elevating extracellular 5HT, however has marginal affinity to 5HT2a	No activity at serotonin transporter	<ul style="list-style-type: none"> • Agonism at 5HT2a receptors are thought to be the primary driver of hallucinogenic experiences • Oneiric experience likely exclusive to ibogaine
Dopamine	Conflicting results of extracellular dopamine level change in the nucleus accumbens	Conflicting results of extracellular dopamine level change in the nucleus accumbens	No direct action on dopamine	<ul style="list-style-type: none"> • More likely that any change seen in the mesolimbic dopaminergic system is a result of downstream effects by other receptor systems
N-Methyl-D-Aspartate (NMDA)	Noncompetitive antagonism that is greater than noribogaine	Noncompetitive antagonism that is lesser than ibogaine resulting in marginal affinity overall	Negligible activity	<ul style="list-style-type: none"> • More likely that NMDA antagonism (via opioid potentiation) is the mechanism of action for ibogaine's role in treating opioid withdrawal rather than the basis for its anti-addictive properties
Opioid	Weaker μ -receptor affinity than noribogaine	Greater affinity at μ -receptors than ibogaine; unique κ -agonism biased toward G-protein and antagonizes β -arrestin	Modest μ -opioid antagonism	<ul style="list-style-type: none"> • Mounting evidence suggests no intrinsic activity for iboga compounds at μ-receptors • Opioid potentiation likely due to NMDA binding • Noribogaine uniquely demonstrates biased κ-receptor affinity with agonism toward G-protein and antagonism toward β-arrestin • May account for the lack of dysphoric effects typically generated by κ-agonists • Could represent another anti-addictive mechanism
Acetylcholine	Muscarinic agonist and nicotinic antagonist, including the $A_3\beta_4$ receptor	Non-competitive nicotinic antagonist	Most selective $\alpha_3\beta_4$ nicotinic antagonism	<ul style="list-style-type: none"> • Present in all three, but 18-MC's mechanism may be wholly attributed to this receptor system • $\alpha_3\beta_4$ nicotinic receptors are predominantly located in the medial habenula (MHb) and interpeduncular nucleus (IPN) and may affect mesolimbic DA • The MHb has afferents from the NAc and efferents to the VTA; the IPN connects to the brainstem raphe nuclei and medial dorsal thalamic nucleus
Glial-cell Derived Neurotrophic Factor (GDNF)	Increase GDNF mRNA levels in the ventral tegmental area (VTA)	Increase GDNF mRNA levels in the ventral tegmental area (VTA)	Negligible activity	<ul style="list-style-type: none"> • Increased GDNF expression may contribute to neuronal survival, especially that of midbrain dopaminergic neurons • It may contribute to synaptic plasticity processes, learning and memory, and as a negative regulator of neuroadaptations to drugs of abuse • Infusions of GDNF into the VTA of rats blocked or reversed cocaine induced neuronal changes in NMDA receptors and behavioral effects • GDNF may function via a positive feedback mechanism • Ibogaine and noribogaine triggered long-lasting GDNF expression in VTA

Table 6. Ibogaine and Ibogaine Derivatives' Comparative Pharmacokinetics^{15,57-59}

	Ibogaine	Noribogaine	18-MC
Absorption	Rat studies showed gender-dependent bioavailability with plasma levels in females 3 times higher than in males and dose-dependent bioavailability with larger doses demonstrating greater absorption	From Phase I study, rapid absorption with time to peak at 2-3 hours post oral dosing; in contrast to ibogaine, C _{max} and AUC increased linearly with dose	Phase I study completed but unpublished
Distribution	Highly lipophilic with 100 times greater concentration in adipose tissue than plasma 1 hour after administration; sequestering may occur	Very high; has roughly 9 times higher AUC in whole blood than ibogaine, but only 2 times higher in the brain	Phase I study completed but unpublished
Metabolism	Metabolized by CYP2D6 into the active metabolite noribogaine; half-life in rats was 1-3 hours, but given possible sequestering, plasma levels can remain high beyond expected half-life calculations	Phase II metabolism to noribogaine glucuronide with mean half-lives of 28-49 hours	Metabolized by 2C19 into the major metabolite 18-hydroxycoronaridine (18-HC)
Elimination	In rats, 60-70% is excreted in the first 24 hours via the renal and gastrointestinal tract	Between 1.4% to 3.9% excreted as unchanged drug in the urine	Phase I study completed but unpublished

PART IV. EVIDENCE OF IBOGAINE FOR SUBSTANCE USE DISORDER(S)

I. Animal Models¹⁵

- a. In rat models of addiction, ibogaine has demonstrated efficacy in reducing self-administration of morphine or heroin, cocaine, and alcohol, with persistent effects from even a single dose regimen
- b. A more optimal dosing scheme for persistent reductions in self-administration appears to be multiple doses given over a period of time rather than a single dose
- c. Other studies have also looked at noribogaine and 18-MC for reduction in self-administration
 - i. Noribogaine effective for cocaine, morphine, and alcohol^{49,56}
 - ii. 18-MC effective for cocaine, morphine, methamphetamine, nicotine, and alcohol^{50,53}
- d. All three compounds have demonstrated an ability to attenuate opioid withdrawal symptoms precipitated by naloxone, with positive results in 13 of 14 independent replications across two rodent and two primate species¹⁵

II. Human Studies

- a. Due to its originally experimental role transitioning to that of a Schedule I substance, only low-quality ibogaine studies exist, with the most common form coming as case reports or case series

Table 7. Three Howard Lotsof Case Series^{15,60}

	Outcome	Population Characteristics	Results
n=33	Abstinence	<ul style="list-style-type: none"> • Young Caucasian males (late teens to early 20s) in NYC exploring psychotherapeutic substances • All heroin dependent • Dose used was 0.14 to 19 mg/kg 	<ul style="list-style-type: none"> • 5 remained abstinent for ≥ 6 months • 2 validated ibogaine's efficacy but identified as heroin users and returned to use
	Attenuation of opioid withdrawal	<ul style="list-style-type: none"> • Adds 26 heroin dependent cases from Netherlands • 26 primarily used intravenous route, 4 intranasal, and 3 by inhalation; average daily heroin use was 0.64 grams • Dose used was 6 to 29 mg/kg • 72 hour opioid withdrawal period 	<ul style="list-style-type: none"> • 25 (76%) completers without drug-seeking behavior • 4 (12%) completers who chose to relapse • 2 (6%) non-completers who did not relapse • 1 non-completer who relapsed
n=41	Abstinence	<ul style="list-style-type: none"> • 31 cases of single session ibogaine use • 9 cases of two session use • 1 case of triple session use 	<ul style="list-style-type: none"> • 15 were abstinent < 2 months • 15 were abstinent 2-6 months • 7 were abstinent 6-12 months • 10 were abstinent >12 months • 5 unknown cases

- b. A separate team headed by Dr. Deborah Mash treated more than 150 patients at a freestanding clinic in St. Kitts, West Indies in a 12-14 day inpatient setting¹⁵
 - i. Twenty-seven heroin or cocaine dependent individuals participated in a dose escalation study with open label randomization to 500mg, 600mg, or 800mg of ibogaine and 1-month follow-up
 - 1. Both heroin and cocaine groups had decreases in self-reported depression and drug craving
 - ii. Thirty-two opioid (heroin or methadone) users were given 800mg of ibogaine for its effect on opioid withdrawal symptoms
 - 1. Heroin craving scores were decreased at time of discharge roughly seven days after dosing
 - 2. Beck Depression Inventory averages were decreased at discharge and 1-month follow-up
- c. An unpublished Dutch doctorandus thesis⁶¹ by Ehud Bastiaans described 21 responses to an online questionnaire based on the European Addiction Severity Index
 - i. On average, 21.8 months had elapsed between answering the questionnaire and dosing of ibogaine for treatment of a substance use disorder with 18 affirming primary use of opioids
 - ii. Eight received single session ibogaine; ten were treated twice; and three were treated thrice
 - iii. Nineteen patients reported abstinence of at least seven days following ibogaine, but overall the 21 patients could be divided into three distinct groups
 - 1. Five quit all substances with average abstinence lasting 3.5 years with a median of 2 years
 - 2. Nine quit their primary and secondary drugs of abuse for an average of 18 months and median of 4.5 months, but either started new drugs of abuse or continued their tertiary or quaternary substances (typically cannabis and/or alcohol)
 - 3. Seven returned to their primary and secondary drugs of abuse shortly after treatment, but six of those seven reported a reduction in quantities of use
- d. The most recent published case report⁶² of ibogaine for opioid use disorder documented a 37-year-old Caucasian woman's follow-up visit after 18 months of sobriety subsequent to a 4-day residential ibogaine treatment in Canada
 - i. Prior to ibogaine treatment, the patient reported a 19-year history of severe OUD (heroin) and multiple treatment failures including 12-step programs, detoxification centers, support groups, sponsors, recovery houses, and methadone maintenance treatment (MMT)
 - ii. Her previous longest period of continuous abstinence was two months while on MMT
 - iii. Of note, the patient volunteered that the key to ibogaine's success was its transformative, mystical experience
- e. Anecdotally, oneiric and other hallucinogenic experiences can provide a necessary boost at the outset to recovery, as paralleled by case reports of LSD's efficacy in ethanol dependence^{15,63}
 - i. This attribute supports Howard Lotsof's characterization of ibogaine as an "addiction interrupter" which allows the drug user to return to an original setpoint of freedom of choice regarding continued drug use, instead of an cure or vaccine against addiction
 - ii. The oneirophrenic properties of ibogaine have not been consistently documented in its active metabolite noribogaine and is proposed to be abstinent from its congener 18-MC
 - iii. This represents an interesting treatment conundrum as ibogaine holds the most safety disadvantages among the three compounds yet is the most readily available

III. Safety Concerns

- a. Ibogaine toxicities are broadly divided into neurotoxic and cardiovascular risks with most data concerning fatalities existing in the form of case reports or case series
 - i. One extensive case series⁶⁴ followed up on available autopsy, toxicological, and investigative reports for 19 known fatalities outside of West Central Africa from 1990 to 2008 that occurred within 1.5 to 76 hours of taking ibogaine (average of 24.6 hours)
 - 1. There were fifteen men and four women aged 24 to 54 years old (average age of 39.1)
 - 2. Fifteen cases used it to treat opioid withdrawal (four of those were dependent on alcohol, three on cocaine, and one on methamphetamine); two cases involved spiritual or psychological use; two cases did not have an identifiable use, but had a history of SUD

3. Fourteen cases involved ibogaine HCL (in the twelve cases with reported doses, dose ranged from 4.5 to 29 mg/kg, average of 14.3 mg/kg); the alkaloid extract was used in two cases; root bark in two cases; a brown powder (either alkaloid or root) used in the final case
4. Eleven decedents had a post-mortem toxicology analysis performed with 8 cases positive for commonly abused drugs (benzodiazepines, cocaine, opiates, and methadone)
5. Cardiac disease was a contributing or proximate cause in six cases; pulmonary thromboembolism was the cause in three cases (all in Mexico, with possibly inadequate autopsy confirmation); heart failure was identified as the cause of death in two cases
6. There were two cases of combinatory use of ibogaine, opioids, and benzodiazepines, one case of ibogaine, opioids, and cocaine, and two cases of unknown combinatory use
- ii. The most recent case report⁶⁵ of death involved a 40-year-old man with a history of heroin abuse who purchased ibogaine and a “booster” online for the purpose of opioid detoxification
 1. His family stated that the victim’s last use of heroin was four days prior to ibogaine usage
 2. After ingesting 4g of ibogaine and 2g of the booster, the victim was discovered eight hours later unresponsive and covered in emesis
 3. Despite cardiopulmonary resuscitation producing spontaneous circulation en route to the hospital, there was severe anoxic brain damage and brain death was later confirmed
- b. Ibogaine’s neurotoxicity^{15,66} has been observed primarily in rat studies at high doses (100 mg/kg)
 - i. This toxicity has not been confirmed in mice and primate studies
 - ii. The proposed mechanism involves the degeneration of cerebellar Purkinje cells
 - iii. A commonly observed neurological side effect of ibogaine is reversible ataxia and tremors, whereas the metabolite noribogaine and congener 18-MC do not produce them
 - iv. While there are case reports of seizures with concurrent ibogaine use, the mechanism is not yet fully elucidated, especially given ibogaine’s antagonistic action at NMDA receptors
- c. The most scrutinized of ibogaine’s toxicities is its effect on the cardiovascular system^{15,65-67}, with QT interval prolongation suspected as the main culprit in sudden death after ibogaine use
 - i. Ibogaine, noribogaine, and 18-MC have all shown inhibitory activity at the human ether-a-go-go related gene (hERG), although 18-MC’s effect is four times weaker than ibogaine
 1. hERG channels are intimately involved in one of the mechanisms by which the QT interval becomes prolonged, and addiction treatment doses of ibogaine will sufficiently inhibit these channels
 2. Furthermore, ibogaine can also inhibit human sodium and calcium currents in ventricular cardiomyocytes, which may also prolong the QT interval
 3. QT interval prolongation is a known risk factor for development of ventricular tachyarrhythmias like torsades de pointes and sudden cardiac death
 - ii. Additionally, ibogaine tends to reliably produce bradycardia in humans, which can precipitate acute heart failure

Table 8. Comparative Differences between Mechanisms of Action and Side Effects of Iboga Compounds

	Ibogaine	Noribogaine	18-methoxycoronaridine
Proposed Mechanism(s) of Action	<ul style="list-style-type: none"> • $\alpha_3\beta_4$ nicotinic receptor antagonism • GDNF stimulation • Oneiric experience 	<ul style="list-style-type: none"> • $\alpha_3\beta_4$ nicotinic receptor antagonism • GDNF stimulation 	<ul style="list-style-type: none"> • $\alpha_3\beta_4$ nicotinic receptor antagonism
Side Effects	<ul style="list-style-type: none"> • QTc prolongation • Bradycardia • Tremors and ataxia • Potentiation of opioids • Nausea/vomiting • Oneiric experience 	<ul style="list-style-type: none"> • QTc prolongation (equal) 	<ul style="list-style-type: none"> • QTc prolongation (four times weaker)

- d. To mitigate the aforementioned risks as well as account for the potentiation of opioid induced analgesia and toxicities, it appears ibogaine programs have adapted stringent monitoring protocols
 - i. In the case report of the Canadian woman who used ibogaine to successfully treat her OUD⁶²
 1. Last use of opioids was 12 hours prior to admission with day 1 doses limited to test doses of 2.5 mg/kg; day 2 doses were up to 20 mg/kg with booster doses on days 3 and 4 (5 mg/kg)
 2. There was continuous nursing monitoring with hourly heart rate and blood pressure checks
 3. Pre-treatment screening included liver and cardiovascular work-ups, including ECG
 - ii. In a retrospective study on 75 individuals treated at a residential clinic in Brazil⁶⁸
 1. A mandatory 60-day period of abstinence prior to ibogaine administration
 2. Only individuals considered in “good health” via clinical exam were admitted (normal electrolyte levels, liver function, etc.) including absence of psychiatric comorbidities
 3. Exclusionary criteria included pregnancy, surgery within the last 6 months, uncontrolled high blood pressure, uncontrolled diabetes, cardiac arrhythmias, renal or hepatic insufficiency, Alzheimer’s disease, and Parkinson’s disease
 4. Typical dose was 17 mg/kg, with flexible dosing not to exceed 20 mg/kg
 5. After ingestion, the patient was visited by the administering physician every 25 or 30 minutes during the acute phase lasting approximately 10 hours and blood pressure, cardiac frequency, and oxygen saturation was measured each time

KEY POINTS

- Ibogaine’s anti-addictive properties may involve 2 novel mechanisms via antagonism of $\alpha_3\beta_4$ nicotinic receptors and stimulation of GDNF in the limbic midbrain
- While these properties have been replicated in animal models by less toxic agents like noribogaine and 18-methoxycoronaridine (18-MC), case reports of patients who achieve sustained abstinence after ibogaine administration credit its unique oneiric abilities as instrumental in facilitating the first steps toward recovery
- Despite its popular use for opioid withdrawal, ibogaine’s potentiating effects on opioid signaling may contribute to its toxicity alongside the more commonly assessed risk of QTc prolongation
- Many ibogaine treatment programs have protocols to monitor cardiotoxicity during treatment

PART V. OVERALL SUMMARY AND RECOMMENDATIONS

I. Addiction Represents a Hijacking of Survival Neurocircuitry with Subsequent Behavioral Changes That Sabotage an Individual’s Efforts to Cease Drug Use

- a. There has been increased attention paid to opioid use disorder given the opioid epidemic fueled in recent years by increased prescribing of opioid analgesics, but the shifting patterns of use suggest that as medical sources of opioids have become scarcer, heroin has been taking its place
- b. Despite literature evidence supporting medication assisted treatment for opioid use disorder, overall treatment attrition rates remain high alongside the ever-present risk of misuse or diversion
- c. Furthermore, methadone and buprenorphine are not benign drugs, but instead possess notable physiological and psychological disadvantages in addition to the risk of fatal overdose
- d. Although the extended release formulation of naltrexone appears to have addressed the non-adherence dilemma with oral naltrexone, long-term studies are still lacking

II. Two Novel Pathways Mediate Ibogaine’s Anti-Addictive Properties and May Produce Persistent Treatment Effects with Only Periodic Dosing

- a. Status as a Schedule I drug has been detrimental to the development of high quality published evidence for ibogaine with mostly case reports and case series available for review
- b. Many non-U.S. ibogaine treatment centers have rigorous safety protocols to mitigate known ibogaine’s toxicities of QTc prolongation, bradycardia, potentiation of opioid effects, nausea/vomiting, and tremors/ataxia

- c. Despite ongoing research with safer ibogaine derivatives like noribogaine and 18-MC, ibogaine's unique oneiric experiences have anecdotally played an instrumental initiatory role in recovery

III. Future Directions

- a. Unfortunately, a rescheduling of ibogaine does not appear to be imminent and neither does higher quality human subject research, as a non-patentable natural product does not hold many commercial incentives for investment
- b. A phase I trial of noribogaine was completed in 2015 (published), but currently zero studies registered at clinicaltrials.gov
- c. A phase I trial of 18-MC was completed in 2014 (unpublished), but currently zero studies registered at clinicaltrials.gov

IV. OUD Patients Should Still Be First Treated with Evidence Based Combinations of Pharmacotherapy and Psychotherapy

- a. For individuals who struggle with the motivational aspect of recovery and demonstrate repeated treatment failures, a trial of ibogaine may be reasonable
- b. Patients who suffer from a prolonged QTc interval, whether congenital or medication-induced, should not be considered for ibogaine treatment
- c. Despite anecdotal reports of positive outcomes, patients who suffer from severe psychiatric comorbidities should avoid ibogaine due to the unknown nature of their oneiric experience
- d. Any patient who indicates an interest in ibogaine should be warned against self-administration and counseled on the available systematic evidence, or lack thereof

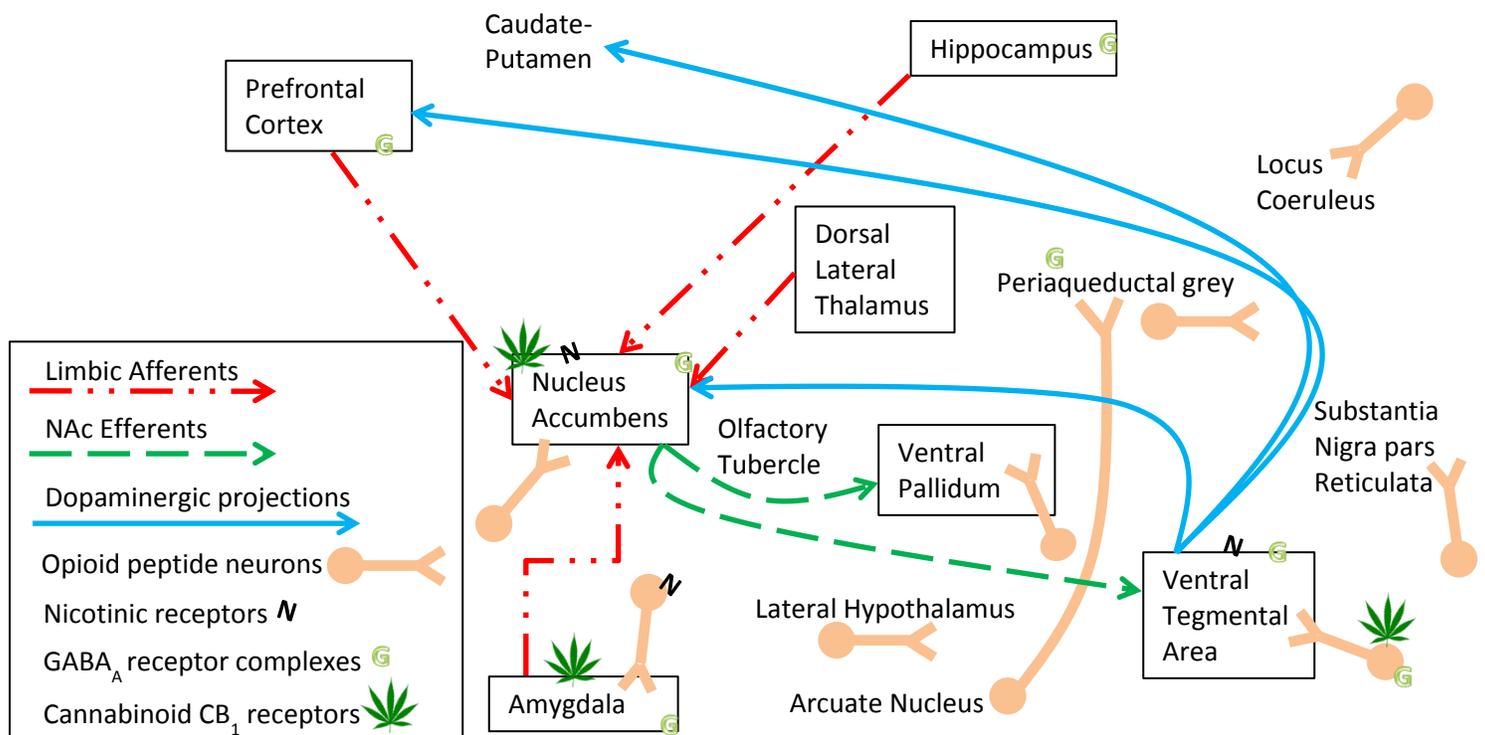
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Appendix 1. Pathways and Receptor Systems Implicated in Acute Reinforcing Actions of Drugs of Abuse^{2,4}



Appendix 2. Substance Use Disorder Diagnosis Differences Between DSM-IV and DSM-5⁸

DSM-IV substance abuse:	DSM-5 substance use disorder:	Notes:
<p>Maladaptive pattern of substance use manifested by one of the following within 12 months:</p> <ol style="list-style-type: none"> 1. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home 2. Recurrent substance use in situations in which it is physically hazardous 3. Continued use despite persistent or recurrent social or interpersonal problems caused/exacerbated by effects of substance use 	<p>Problematic pattern of substance use leading to clinically significant impairment or distress, manifested by at least two of the following within 12 months:</p> <ol style="list-style-type: none"> 1. The substance is often taken in larger amounts or over a longer period than was intended 2. Persistent desire or unsuccessful efforts to cut down or control substance use 3. Great deal of time spent in activities necessary to obtain the substance, use the substance, or recover from its effects 4. Craving, or a strong desire or urge to use the substance 5. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home 6. Continued substance use despite having persistent or recurrent social or interpersonal problems caused/exacerbated by substance use 7. Important social, occupational, or recreational activities are given up or reduced because of substance use 8. Recurrent substance use in situations in which it is physically hazardous 9. Substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by substance use 10. Tolerance, as defined by either (a) need for markedly increased amounts of the substance to achieve intoxication or desired effect; or (b) markedly diminished effect with continued use of same amount of the substance 11. Withdrawal, as manifested by either (a) characteristic substance withdrawal syndrome; or (b) needing to use more of the substance to avoid withdrawal symptoms 	<p>Correlations between DSM-5 criteria and DSM-IV criteria for abuse (A) and dependence (D):</p> <ol style="list-style-type: none"> 1. 5(1) = D(3) 2. 5(2) = D(4) 3. 5(3) = D(6) 4. 5(4) = NEW 5. 5(5) = A(1) 6. 5(6) = A(3) 7. 5(7) = D(5) 8. 5(8) = A(2) 9. 5(9) = D(7) 10. 5(10) = D(1) 11. 5(11) = D(2) <p>For DSM 5, mild = 2-3 symptoms; moderate = 4-5; severe = ≥6</p> <p>Very loose analogy of mild modifier approximating substance abuse & moderate or severe approximating substance dependence</p>
<p>DSM-IV substance dependence:</p>		
<p>Maladaptive pattern of substance use manifested by three of the following within 12 months:</p> <ol style="list-style-type: none"> 1. Need for markedly increased amounts of substances to achieve intoxication or desired effect; or markedly diminished effect with continued use of same amount of the substance 2. Experiencing substance withdrawal syndromes or needing to use to avoid withdrawal symptoms 3. Using larger amounts or over a longer period than intended 4. Persistent desire or one or more unsuccessful efforts to cut down or control substance use 5. Important social, occupational, or recreational activities given up or reduced because of substance use 6. A great deal of time spent in activities necessary to obtain, to use, or to recover from the effects of substance use 7. Continued substance despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to be caused or exacerbated by substance use 		

Appendix 3. Pharmacotherapies for OUD¹⁰⁻¹⁴

	Methadone (MET)	Buprenorphine and Buprenorphine/Naloxone (BUP)	Naltrexone Oral (NTX) and Extended-Release Injection (XR-NTX)
Route of Administration	Oral liquid consumption that is usually witnessed at an Opioid Treatment Program (OTP). Take-home doses allowed after meeting regulatory criteria	Sublingual film or tablets that can be taken at home or in a physician's office	Oral tablets to be taken at home or an intramuscular injection to be administered by a healthcare professional
Prescribing Restrictions	For treating OUD, can only be purchased and dispensed by certified OTPs or hospitals	For treating OUD, prescribers must complete limited special training and qualify for a DEA prescribing waiver; does not have dispensary restrictions	None; can be filled at any pharmacy
Evidence in OUD	MET has been the gold-standard treatment since FDA approval in 1960s; Cochrane reviews have demonstrated MET's favorable treatment retention rate compared to placebo treatments and reduced rates of opioid positive urine drug screens	Since passing of Drug Abuse Treatment Act in 2000, BUP has been used for office based management of OUD resulting in greater access and less stigmatized treatment; Cochrane reviews have noted BUP's inferiority to MET for treatment retention, but BUP performs equally well in reduction of opioid positive urine drug screen rates	NTX is best reserved for highly motivated OUD patients (e.g. mandated treatment by a professional licensing board), as Cochrane reviews confirm the poor clinical utility of NTX due to poor adherence and low treatment retention; XR-NTX was approved in 2010 and has more encouraging data
Mechanism of Action	Full mu-opioid receptor agonist; also exhibits NMDA antagonism	Partial mu opioid receptor agonist and kappa opioid receptor antagonist	Full antagonist at mu, delta, and kappa opioid receptors
Absorption	36% to 100% bioavailability	Sublingual tablet has lower bioavailability (29%) than buccal film (46% to 65%)	Variable bioavailability (5% to 40%)
Distribution	Lipophilic; 85% to 90% protein binding	~95% protein binding; CSF concentrations are ~15% to 25% of plasma concentrations	21% protein binding; large volume of distribution
Metabolism	Hepatic, primarily via CYP3A4, 2B6, 2C19; half-life 9 to 87 hours	Hepatic; primarily by CYP3A4 to active metabolite; half-life 37 hours for sublingual vs 27 hours for buccal	Metabolized via non CYP-mediated dehydrogenase to an active metabolite
Excretion	Urine with <10% as unchanged drug; drug may sequester in tissues and prolong pharmacological effect despite low serum levels	70% Feces and 30% urine with ~33% total unchanged	Primarily via urine with small amounts of unchanged drug
Interactions	Inhibits CYP2D6 moderately; major substrate of CYP3A4 and 2B6	Weak inhibitor for CYP1A2, 2A6, 2C19, and 2D6; major substrate of CYP3A4	None known enzymatic interactions, but will induce opioid withdrawal if administered in an opioid-using individual
Safety Concerns	Respiratory depression with overdose risk, especially with concomitant CNS depressants; increased risk of QTc prolongation	Lower risk of respiratory depression with overdose relative to methadone is largely negated in the presence of concomitant CNS depressants; risk of QTc prolongation is lower than methadone but not null	XR-NTX has a REMS program focused on prevention of severe injection site reactions, but also for provider counseling against precipitated opioid withdrawal and hepatotoxicity

Appendix 4. Large Groups and Therapeutic Communities for OUD^{22,23}

Types	Description	Rating of Available Evidence in OUD
Network therapy	<ul style="list-style-type: none"> Useful for frequent relapsers Identify and address relapse triggers Generate and maintain support of patient's natural social network 	Positive, <i>limited</i>
Therapeutic communities	<ul style="list-style-type: none"> Evolved out of Alcoholic Anonymous with heavy emphasis on personal willpower 12 to 18 month treatment duration in a long-term residential setting 	Positive, <i>limited</i>
Aversion therapies	<ul style="list-style-type: none"> Counterconditions the body by developing an avoidant response to substance use Uses nausea, faradic, and covert sensitization 	Positive, <i>limited</i> ; strongest evidence in daily drinkers

Appendix 5. Small Groups for OUD^{22,23}

Types	Description
Milieu	<ul style="list-style-type: none"> Common in residential programs Provide patients an opportunity to reflect on their experiences and insights from that day's activities
Psychoeducational	<ul style="list-style-type: none"> Provide specific information regarding a variety of topics related to addiction and recovery May include written assignments in addition to lectures or group discussions
Coping Skills	<ul style="list-style-type: none"> Teach problem-solving methods, stress management, and relapse prevention strategies to improve patients' intrapersonal and interpersonal skills
Therapy groups	<ul style="list-style-type: none"> Less structured and likely solicit patient discussion and sharing of problems, conflicts, and struggles Not intended to be didactic in contrast to psychoeducational groups
Evidence	<ul style="list-style-type: none"> Controlled trials are limited, but those available show reductions in drug use, improved health, and reduced social pathology
Barriers	<ul style="list-style-type: none"> Early termination often involved time commitment problems, desire for individual treatment, or general unwillingness to participate Within group barriers include low motivation to change, over-emphasis on external issues, proselytizing and hiding behind AA/NA, and playing co-therapist Higher dropout rates reported in group therapy vs. individual therapy

Appendix 6. Individual Psychotherapy for OUD²²⁻²⁴

Notable Types	Elements of Focus	Rating of Available Evidence in OUD
Motivational interviewing and motivational enhancement therapy	Enhancing motivation; fostering treatment alliance	Mixed; strongest for nicotine and alcohol use disorders
Brief advice	Enhancing motivation; fostering treatment alliance	Unavailable
Supportive-expressive therapy	Development of coping skills	Positive, limited
Individual drug counseling	Direct focus on substance abuse; enhancing motivation	Unavailable; literature available for cocaine users
Relapse prevention and coping skills	Development of coping skills; managing contingencies	Mixed
12-step facilitation	Direct focus on substance abuse; enhancing motivation	Mixed; strongest evidence for alcohol use disorder
Contingency management and community reinforcement approach	Managing contingencies; development of coping skills; direct focus on substance abuse	Positive, robust (Cohen d > 0.6), (Dutra et al., 2008)

Appendix 7. Studies of Non-Monetary Contingencies²⁵⁻²⁸

Study Authors	Contingencies	Study Design	Results
Tuten et al., 2012 ²⁵	Housing/Groups	<ul style="list-style-type: none"> Randomization to 3 groups: usual care (UC), recovery housing alone (RH), or recovery housing + reinforcement based intensive outpatient (RH+RBT) Positive urine drug screens resulted in time out from paid housing (RH) and group activities (RBT) Assessed abstinence by urine drug screen (UDS) 	<ul style="list-style-type: none"> Overall abstinence: 50% vs 37% vs 13%, p<.001 for RH+RBT vs RH vs UC At 6 months, % abstinent for RH+RBT vs UC was 37% vs 20%
Dunn et al., 2013 ²⁶	Employment	<ul style="list-style-type: none"> After PO naltrexone induction, randomization to 2 arms: Contingency (CM) and prescription (Rx) CM patients underwent staff-observed ingestion of naltrexone to gain access to a therapeutic workplace Rx patients received take-home doses of naltrexone & had free access to the therapeutic workplace Assessed % urine positive screens for naltrexone and negative screens for opiates & cocaine at 30 days 	<ul style="list-style-type: none"> %UDS+ for naltrexone: CM > Rx; 72% vs 21%, p<0.01 %UDS- for opiates and cocaine did not separate; opiate positive samples were more likely to occur in cocaine positive samples
Holtyn et al., 2014 ²⁷	Employment	<ul style="list-style-type: none"> After methadone induction, patients were employed at a therapeutic workplace and randomized into 3 arms: work reinforcement (WR), WR + methadone maintenance (MM), WR + MM + abstinence (AB) WR patients had 0 restrictions WR + MM and WR + MM + AB patients had their methadone enrollment double checked WR + MM + AB patients needed negative urine drug screens to work Assessed % retention in methadone treatment and % urine drug screens positive for opiates and cocaine 	<ul style="list-style-type: none"> Methadone retention rate did not differ between arms WR + MM + AB group had significantly less positive urine drug screens for opiates, cocaine, and the combination of the two than WR group Secondary analysis showed sequential administration of abstinence contingent employment increases abstinence rates
Petry & Carroll 2013 ²⁸	Fishbowl prizes	<ul style="list-style-type: none"> Retrospective review of Petry 2011 data (n=239) Examined contingency management (CM) vs usual care (UC) in intensive outpatient treatment (IOP) n=33 for OUD patients <i>not</i> receiving MAT n=47 for OUD patients receiving methadone or buprenorphine Assessed longest duration of abstinence achieved and % negative urine drug screens at 12 months 	<ul style="list-style-type: none"> Absence at 12-month follow up was imputed as a positive urine drug screen 54.7% (87/159) non-OUD, 60.6% (20/33) OUD w/o MAT, and 46.8% (22/47) OUD w/ MAT pts tested negative for cocaine, methamphetamine, opioids, and EtOH

Appendix 8. Overview of Groß et al., 2006²⁹

Arm	Received Buprenorphine	Received Behavioral Drug Counseling	Effect of Negative Urine Drug Screen	Effect of Positive Urine Drug Screen
Low-Magnitude Voucher, (n=20)	Yes	Yes	Voucher's redemption value increases (max total of \$269)	Resets redemption value to baseline
Medication Contingency (n=20)	Yes	Yes	None	1 day's buprenorphine dose withheld
Usual Care (n=20)	Yes	Yes	None	None
Outcomes	Mean duration of continuous abstinence; total number of weeks abstinent			
Results & Authors' Conclusions	<ul style="list-style-type: none"> Medication contingency group achieved greater weeks of <i>continuous</i> abstinence than voucher group (M = 5.9, SD = 4.6 vs M = 2.9, SD = 3.3, p < .05), but did not separate from usual care No difference observed in weeks of <i>total</i> abstinence (voucher (M = 3.9, SD = 3.7); contingency (M = 6.9, SD = 4.7); usual care (M = 5.8, SD = 3.8)) Patients in contingency group received on average 5.5 less doses Lack of statistical difference between usual care and low-magnitude voucher group could have been due to small sample size and short duration, as a previous 23-week trial have demonstrated efficacy of low-magnitude voucher design There was a trend toward higher attrition rate for negative contingency management group 			