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- Ibogaine in Psychiatry: Neuropharmacology, Emerging Therapeutic Applications, and Psychiatric Safety
- DEA's Renewed Push to Schedule Five Tryptamines: What Researchers Need to Know



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Ibogaine in Psychiatry: Neuropharmacology, Emerging Therapeutic Applications, and Psychiatric Safety

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Abstract:

Ibogaine is an atypical psychedelic indole alkaloid historically investigated for its potential to reduce substance withdrawal, craving, and subsequent drug use. It is primarily metabolized in the liver to form the active compound, noribogaine. Its complex neuropharmacology, effects on neuroplasticity and reward circuitry, and emerging clinical data suggest potential neuropsychiatric effects extending beyond substance use disorders (SUDs). This narrative review examines the pharmacology and pharmacokinetics of ibogaine relevant to psychiatric treatment and evaluates preclinical and human evidence for its potential effects on depression, anxiety, post-traumatic stress disorder (PTSD), trauma-related symptoms, and cognitive dysfunction. We additionally examine the phenomenology of the ibogaine experience and emerging evidence regarding the relationship between subjective psychedelic effects and clinical outcomes, as well as the development of non-hallucinogenic iboga-inspired compounds.

Preclinical studies demonstrate effects on neurotrophic signaling, reward-related circuitry, and antidepressant- and anxiolytic-like behaviors. Clinical evidence remains preliminary but includes improvements in depressive and anxiety symptoms among individuals treated for SUDs and reductions in PTSD, depression, anxiety, disability, and cognitive impairment in trauma-exposed Special Operations Forces veterans. Interpretation of these findings is limited by small samples, uncontrolled and observational study designs, concurrent substance cessation, highly selected populations, and multimodal interventions including psychotherapy and additional psychedelic administration. Emerging evidence also suggests an association between the intensity of ibogaine-induced mystical experiences and subsequent improvement in PTSD symptoms.

Despite these signals, no controlled clinical trial has established ibogaine as a treatment for a primary mood, anxiety, or trauma-related disorder. Significant cardiovascular, neurologic, and psychiatric risks pose constraints in its clinical application. Future studies should evaluate ibogaine in well-characterized psychiatric populations independent of active SUD, clarify the contributions of noribogaine and subjective psychedelic effects, establish standardized safety protocols, and determine whether safer iboga-inspired compounds can preserve therapeutic mechanisms while reducing toxicity. Collectively, current evidence supports further investigation of ibogaine and related compounds as potential neuropsychiatric therapeutics but remains insufficient to establish efficacy for primary psychiatric disorders.

Keywords: ibogaine; noribogaine; psychedelic psychiatry; substance use disorders; posttraumatic stress disorder; neuroplasticity; psychoplastogens

INTRODUCTION

Psychiatric disorders, including major depressive disorder (MDD), posttraumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), and substance use disorders (SUDs), contribute substantially to morbidity and remain difficult to treat in a

considerable proportion of patients. Although established pharmacotherapies, including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and other antidepressant agents, are effective for many patients, treatment resistance, incomplete response, and relapse remain important clinical challenges. These

limitations have contributed to renewed interest in psychedelic therapies as potential treatments for psychiatric disorders [1,2]. Emerging evidence involving psilocybin, 3,4-methylenedioxymethamphetamine (MDMA), and other psychedelic compounds has demonstrated promising effects across several psychiatric conditions, particularly treatment-resistant depression and PTSD [1,2]. However, less is known about the potential psychiatric applications of ibogaine.

Ibogaine is a naturally occurring psychoactive indole alkaloid derived principally from the root bark of *Tabernanthe iboga*, a shrub native to West-Central Africa with a longstanding history of ceremonial and spiritual use [3]. Pharmacologically, ibogaine is considered an atypical psychedelic and differs from classic serotonergic psychedelics in both its subjective effects and pharmacologic profile [3,4]. Its prolonged psychoactive state is frequently described as oneirogenic, characterized by vivid, dream-like imagery, autobiographical recollection, and introspection [3]. Unlike classic psychedelics whose effects are predominantly associated with serotonin 2A (5-HT_{2A}) receptor agonism, ibogaine interacts with multiple neurotransmitter systems, including serotonergic, glutamatergic, opioid, dopaminergic, and nicotinic pathways [3,4]. The liver metabolizes ibogaine primarily via CYP2D6 to the active metabolite noribogaine. Noribogaine has a distinct pharmacologic profile and more prolonged exposure that may contribute to sustained neurobehavioral effects following the acute ibogaine experience [5,6].

Modern interest in ibogaine has centered on its potential anti-addictive properties, particularly its reported ability to attenuate opioid withdrawal and craving and reduce subsequent substance use [3,6,7]. More recently, preclinical and clinical findings have suggested potential effects on depression, anxiety, trauma-related symptoms, reward processing, neuroplasticity, and broader

psychological functioning [8–10]. In a prospective observational study of 30 male Special Operations Forces veterans with mild traumatic brain injury (TBI), magnesium and ibogaine treatment was associated with significant improvements in disability, PTSD, depression, and anxiety 1 month following treatment. However, controlled trials are needed to establish efficacy [10].

At the same time, ibogaine presents substantial safety concerns. Ibogaine and noribogaine inhibit cardiac human ether-à-go-go-related gene (hERG) potassium channels, resulting in delayed cardiac repolarization and QT interval prolongation, with ventricular arrhythmias and fatalities reported following administration [11–13]. Psychiatric adverse effects have also been reported, including cases of mania following ibogaine exposure [14]. These risks are particularly relevant when considering the potential expansion of ibogaine from addiction-focused settings into populations with primary psychiatric disorders.

Interest in the therapeutic development of ibogaine has accelerated alongside the broader resurgence of psychedelic medicine. In June 2025, Texas enacted Senate Bill 2308, authorizing a state-supported framework and \$50 million in matching funds for FDA-regulated clinical development of ibogaine for opioid use disorder, co-occurring substance use disorders, and other neurological or mental health conditions [15]. This policy development reflects growing institutional interest, but it does not itself establish clinical efficacy. Despite this growing interest, the existing ibogaine literature remains disproportionately focused on SUDs, while its potential applications across other psychiatric disorders have received comparatively limited synthesis. Important questions remain regarding whether observed psychiatric improvements are independent of reductions in substance use, whether the acute psychedelic experience contributes meaningfully to

therapeutic outcomes, and whether sustained effects may instead, or additionally, reflect the pharmacologic activity of noribogaine and ibogaine-induced neuroplasticity.

This narrative review examines the neuropharmacology and pharmacokinetics of ibogaine relevant to psychiatric treatment; evaluates preclinical and human evidence for its effects on depression, anxiety, PTSD, and trauma-related symptoms; and examines reported psychiatric adverse effects, including mania and psychosis. We additionally consider the relationship between subjective psychedelic experiences and clinical outcomes, the psychiatric and medical safety limitations of ibogaine, the emerging development of non-hallucinogenic iboga-inspired compounds, and key priorities for future clinical investigation.

HISTORICAL CONTEXT

Tabernanthe iboga has long been used in ceremonial and spiritual contexts in Gabon and neighboring regions of West-Central Africa, particularly within Bwiti traditions, where root bark preparations have been used in initiation rites and practices involving ancestral communication [16]. European descriptions of iboga emerged during the colonial period, and iboga alkaloid preparations were later marketed in France, including the low-dose stimulant preparation Lambarène, before the French market removed ibogaine in the 1960s [17–19]. In the United States, ibogaine was placed in Schedule I in 1970 [17].

Modern interest in ibogaine as a potential treatment for addiction was stimulated by Howard Lotsof's reports that a single psychedelic-dose exposure was followed by reduced opioid withdrawal and craving. Lotsof subsequently obtained a series of U.S. patents describing the use of ibogaine for opioid, stimulant, alcohol, and nicotine dependence [20]. These observations helped motivate

subsequent preclinical and clinical investigation of ibogaine's anti-addictive effects.

PHARMACOLOGY AND PHARMACOKINETICS OF IBOGAINE

Ibogaine and Noribogaine

Ibogaine (10-methoxyibogamine) is a naturally occurring indole alkaloid with a complex pharmacologic profile that distinguishes it from classic serotonergic psychedelics [3,4]. After oral administration, ibogaine undergoes first-pass hepatic metabolism, primarily through demethylation by cytochrome P450 2D6 (CYP2D6), producing its active metabolite, noribogaine (12-hydroxyibogamine) [3–6]. CYP2D6 phenotype strongly influences the pharmacokinetics of both ibogaine and noribogaine, with poor metabolizers showing greater ibogaine exposure and reduced noribogaine formation than extensive metabolizers [5].

Ibogaine is cleared more rapidly than noribogaine, and CYP2D6 activity substantially alters ibogaine exposure; noribogaine persists after the parent compound has declined and may contribute to delayed pharmacologic effects [3,5,6]. Noribogaine has pharmacologic properties distinct from its parent compound, including potent inhibition of the serotonin transporter (SERT) and activity at opioid receptors [3,4]. The prolonged systemic exposure and distinct pharmacology of noribogaine raise the possibility that some of the sustained behavioral and psychiatric effects following a single administration of ibogaine may reflect ongoing noribogaine activity rather than, or in addition to, the acute psychoactive effects of ibogaine itself. This distinction may be particularly important when considering the potential mechanisms underlying persistent changes in mood, anxiety, craving, and behavior following the resolution of the acute psychedelic experience.

Receptor and Transporter Pharmacology

Unlike classic psychedelics, whose psychoactive effects are primarily associated with serotonin 2A receptor (5-HT_{2A}) agonism, ibogaine does not appear to exert its effect through a single dominant receptor system. Ibogaine and noribogaine interact with multiple molecular targets implicated in mood, reward, cognition, and addictive behavior, including serotonergic, glutamatergic, opioid, dopaminergic, and nicotinic systems [3,4].

Ibogaine and noribogaine both interact with the serotonergic system, although their effects differ substantially. Ibogaine demonstrates relatively weak activity at 5-HT_{2A} receptors compared with classic serotonergic psychedelics, suggesting that 5-HT_{2A} agonism alone is unlikely to explain its distinctive psychoactive state [3,4]. Noribogaine, by contrast, is a potent SERT inhibitor [3,4]. Structural studies of SERT have demonstrated that ibogaine binds within the central SERT site and stabilizes conformations along the transport cycle, including an inward-open state, through a mechanism distinct from conventional competitive serotonin reuptake inhibitors [21]. These serotonergic effects provide one potential mechanism through which ibogaine and noribogaine may influence mood and anxiety, although their contribution to sustained psychiatric outcomes remains uncertain.

Dopaminergic signaling represents another potentially important mechanism. Ibogaine interacts with dopaminergic signaling, including modulation of the dopamine transporter (DAT) and mesolimbic dopamine transmission [3,4]. Unlike psychostimulants such as cocaine, ibogaine does not produce the same pattern of competitive DAT inhibition or robust elevations in extracellular dopamine associated with euphoria and reinforcement [3,4]. Instead, its effects on dopaminergic transmission appear complex and

may contribute to reductions in drug-seeking behavior and altered reward processing.

Ibogaine and noribogaine also interact with the endogenous opioid system. Ibogaine has affinity for μ - and κ -opioid receptors, while noribogaine demonstrates greater activity at opioid receptors, including partial agonist activity at the μ -opioid receptor [3,4]. These effects are particularly relevant to ibogaine's ability to attenuate opioid withdrawal, but opioid signaling may also influence mood, stress responses, and reward processing. Importantly, noribogaine's pharmacologic profile differs from ibogaine's, suggesting that the parent compound and its metabolite may contribute differently to acute and sustained effects.

Effects on nicotinic acetylcholine receptors may additionally contribute to ibogaine's influence on reward circuitry and addictive behavior. Ibogaine acts as a noncompetitive antagonist at several nicotinic acetylcholine receptor subtypes, with particular interest in $\alpha 3\beta 4$ -containing receptors because they are involved in mesolimbic reward pathways [3,4,22]. Antagonism of $\alpha 3\beta 4$ nicotinic receptors subsequently became an important target for developing iboga-inspired compounds designed to preserve anti-addictive effects while reducing the toxicity and psychoactive properties of ibogaine [17].

Lastly, ibogaine acts as a noncompetitive antagonist at N-methyl-D-aspartate (NMDA) receptors [3,4,23]. NMDA receptor modulation has been implicated in neuroplasticity, mood regulation, and the rapid antidepressant effects of other pharmacologic agents, making this activity potentially relevant to ibogaine's psychiatric effects [3,4]. However, the extent to which NMDA antagonism contributes to ibogaine's acute subjective effects or longer-term behavioral changes remains unclear.

The broad receptor and transporter activity of ibogaine makes it difficult to attribute its potential psychiatric effects to any single

molecular target. Its clinical effects may instead arise from interactions among multiple neurotransmitter systems and from pharmacologic differences between ibogaine and its longer-lasting metabolite, noribogaine.

Ibogaine as a Psychoplastogen

Beyond its acute receptor-level effects, growing interest has focused on the ability of psychedelics and related compounds to promote neuroplasticity. Psychoplastogens are compounds capable of rapidly inducing structural and functional neural plasticity, effects that have been proposed as a potential mechanism underlying sustained improvements in psychiatric symptoms following relatively brief drug exposure [24]. This may be particularly relevant to ibogaine because reported behavioral and psychological changes can persist well beyond the period during which the parent compound is present at substantial concentrations.

Preclinical research involving ibogaine-related compounds provides evidence that the iboga alkaloid scaffold may promote structural neural plasticity. Cameron and colleagues developed tabernanthalog (TBG), a water-soluble, non-hallucinogenic analog of ibogaine designed to retain its psychoplastogenic and therapeutic properties while reducing its adverse-effect profile [24]. In rodents, TBG promoted structural neural plasticity and produced antidepressant-like effects as well as reductions in alcohol- and heroin-seeking behavior [24]. Notably, these behavioral effects occurred without the head-twitch response commonly used as a behavioral proxy for 5-HT_{2A}-mediated psychedelic effects in rodents [24]. These findings suggest that at least some of the neuroplastic and behavioral effects associated with the iboga alkaloid scaffold may occur independently of a classic psychedelic-like state.

Overall, ibogaine is best conceptualized as a multimodal neuropharmacologic agent

whose parent compound, active metabolite, and downstream effects on neural plasticity may each contribute to its behavioral and psychiatric effects. The relative contributions of these pharmacologic effects and the acute subjective experience remain uncertain.

PRECLINICAL EVIDENCE FOR NEUROPSYCHIATRIC EFFECTS

Glick and colleagues [25,26] showed that ibogaine (40 mg/kg) demonstrated long-lasting reductions in morphine and cocaine self-administration in rats, with effects persisting for several days after systemic clearance of the parent compound. The persistence of these behavioral effects raised the possibility that noribogaine or downstream neurobiological changes contribute to sustained effects. More recent animal studies have extended ibogaine's preclinical profile beyond anti-addictive effects and into therapeutic potential for mood and anxiolytic effects. Kalueff et al. [27] exposed adult zebrafish to noribogaine (1, 5, and 10 mg/L) for 20 minutes and tested them in the novel tank test. Fish given noribogaine spent more time near the surface and froze less often. These behavioral patterns were interpreted as primarily anxiolytic rather than sedative, as the fish did not show locomotor changes when experiencing acute effects of noribogaine.

Marton and colleagues more recently explored these mood-related effects [28], administering ibogaine (20 or 40 mg/kg, intraperitoneally) to rats and measuring neurotrophic factor expression across the mesocorticolimbic and nigral dopaminergic circuits. Both doses produced a large increase in brain-derived neurotrophic factor (BDNF) mRNA in the prefrontal cortex, nucleus accumbens, and substantia nigra; the 40 mg/kg dose also upregulated glial cell line-derived neurotrophic factor (GDNF) in the ventral tegmental area and substantia nigra, and NGF across all four regions studied.

These findings led Rodríguez and colleagues [8] to test whether the effect translated into antidepressant-like behavior. Using the forced swim test, they administered ibogaine and noribogaine (20 or 40 mg/kg, intraperitoneally). They found dose- and time-dependent antidepressant-like effects in both compounds, without changes in locomotor activity. Noribogaine's effect was brief, lasting about 30 minutes and correlating with high brain concentrations, while ibogaine's effect appeared later and persisted for 3 hours. Neither compound alone reached brain concentrations at that time point sufficient to explain the behavioral effect, pointing to a combined, polypharmacological mechanism between ibogaine and its metabolite.

HUMAN CLINICAL EVIDENCE AND PSYCHIATRIC APPLICATIONS

Substance Use Disorders

The largest body of human evidence for ibogaine comes from its use in SUDs, particularly opioid and cocaine use disorders. In an open-label case series of 191 individuals undergoing medically supervised inpatient detoxification for opioid or cocaine dependence, Mash and colleagues [29] reported reductions in opioid withdrawal symptoms and significant reductions in opioid and cocaine craving following ibogaine administration. Craving reductions persisted at one-month follow-up among participants with available follow-up data. Although these findings support a potential role for ibogaine in facilitating detoxification and reducing craving, the uncontrolled design limits conclusions regarding efficacy and longer-term substance use outcomes.

Davis and colleagues [7] retrospectively surveyed 88 individuals who had received ibogaine treatment for problematic opioid use in Mexico between 2012 and 2015. Eighty percent reported that ibogaine eliminated or

substantially reduced opioid withdrawal symptoms, and 50% reported reduced opioid craving, with 25% reporting craving reductions lasting at least three months. Thirty percent reported no opioid use following ibogaine treatment, while 41% of the overall sample reported sustained abstinence for more than six months at the time of the survey. Although 70% reported relapsing at some point after treatment, 48% subsequently reported reduced opioid use relative to pretreatment levels and an additional 11% eventually achieved abstinence. These findings suggest potentially persistent effects on opioid use in some individuals, although the retrospective, self-reported design precludes causal conclusions. The study also identified associations between favorable opioid-use outcomes and improved psychological functioning, which are discussed in the following section.

Controlled human evidence remains considerably more limited. Prior and Prior [30] conducted a small double-blind, placebo-controlled study in 20 men with cocaine dependence who received either a capsule containing 1,800 mg of dried ibogaine extract at 75% purity or placebo. Participants receiving ibogaine demonstrated significant reductions in cocaine craving compared with placebo at 72 hours and 24 weeks, as well as fewer cocaine-positive urine tests at 24 weeks. Although the small sample substantially limits interpretation, the study provides preliminary controlled evidence supporting an effect of ibogaine on cocaine craving and use.

Collectively, the SUD literature provides the primary human foundation for ibogaine's potential therapeutic effects and has motivated investigation of its effects on reward processing, neuroplasticity, and psychiatric symptoms. However, the predominance of uncontrolled and retrospective studies, heterogeneous treatment settings, and reliance on self-reported outcomes limit conclusions regarding efficacy and durability. Importantly

for the present review, improvements in depression, anxiety, and psychological well-being observed within these populations cannot establish direct psychiatric effects independent of changes in substance use and are therefore considered separately below.

Depression

An open-label clinical case series of 191 individuals undergoing medically supervised ibogaine detoxification for opioid or cocaine dependence showed changes in depressive symptoms following ibogaine treatment [29]. Participants were prospectively assessed for depressive symptoms using the Beck Depression Inventory-II (BDI-II), Profile of Mood States (POMS), and SCL-90-R. Both the opioid and cocaine groups showed a substantial reduction in depressive symptoms, with improvements persisting at one month, long after acute ibogaine exposure. However, the participants were undergoing detoxification from opioids/cocaine, which introduces a major confounding variable given that resolution of withdrawal, decreased craving and substance use, the residential treatment environment, and associated psychosocial changes could all improve mood.

An online survey of 88 individuals who had undergone ibogaine treatment for problematic opioid use at a treatment center in Mexico between 2012–2015 similarly showed that participants who had better opioid-use outcomes also had lower current depressive and anxiety symptoms and greater subjective well-being [7]. In addition, 43% reported an improvement in mood or psychological well-being lasting at least one month, and 10% reported improvement lasting more than five months. These findings suggest psychological changes extending beyond the period of acute withdrawal. However, the association between treatment response and lower depression does not tell us whether ibogaine improved depression directly. Overall, it

remains unclear whether mood improvement exceeds what would be expected from resolution of withdrawal or reduced substance use.

A case report described a 47-year-old woman with a 20-year history of bipolar II disorder who presented during a depressive episode and improved during ibogaine microdosing [31]. She took 4-mg capsules twice daily, which the authors described as approximately 1% of a conventional full dose; thus, the scheduled daily exposure was about 2% by that estimate, although the report also describes dose adjustments during treatment. Depression, anxiety, and hopelessness were followed using the BDI, BAI, and BHS. During the treatment period, the patient self-tapered her mood stabilizers and escitalopram, while alprazolam was continued, creating substantial medication confounding. Clinically, she reported increased mental clarity and more organized thinking by day 15, followed by improvements in appetite, occupational initiative, routines, and social relationships. Improvements remained evident at the 90-day assessment after ibogaine treatment had ended. No manic switch was reported during follow-up; however, the uncontrolled medication changes and single-case design preclude attribution of improvement to ibogaine, and mania temporally associated with unregulated ibogaine use has been described in a three-patient case series [14].

No controlled trial has established ibogaine as an antidepressant treatment for primary depressive disorders. The strongest human depression signals come largely from SUD populations, making it impossible to separate a direct antidepressant effect from withdrawal resolution, reduced substance use, expectancy, psychosocial treatment, or other factors.

PTSD, Trauma-Related Symptoms, and TBI

Preliminary evidence for the effects of ibogaine-containing interventions on trauma-related psychiatric symptoms was reported in a retrospective survey of 51 U.S. Special Operations Forces veterans who attended a psychedelic treatment program in Mexico between 2017 and 2019 [9]. Participants reported significant reductions in PTSD symptoms, depression, anxiety, cognitive impairment, and suicidal ideation following treatment. Importantly, participants did not receive ibogaine alone; treatment consisted of a single dose of ibogaine followed by three to five doses of 5-MeO-DMT over approximately three days. The authors also assessed psychiatric and cognitive functioning during the 30 days before and after treatment retrospectively. Despite these limitations, the study provided an early human signal that an ibogaine-containing intervention might have effects extending beyond substance use and withdrawal to trauma-related psychiatric and cognitive symptoms.

This treatment paradigm was subsequently prospectively studied in 86 trauma-exposed male Special Operations Forces veterans [32]. Outcomes were assessed at baseline and 1, 3, and 6 months following treatment and included PTSD, depression, anxiety, insomnia, post-concussive symptoms, cognitive functioning, disability, psychological flexibility, life satisfaction, anger, and suicidality. Significant improvements were observed across multiple psychiatric and neurobehavioral outcomes, including PTSD, depression, anxiety, insomnia, post-concussive symptoms, and cognitive functioning, with improvements persisting during follow-up. Although the prospective design strengthened the earlier findings, participants again received sequential ibogaine and 5-MeO-DMT, preventing attribution of the observed psychiatric improvements to ibogaine alone.

More direct evidence comes from the Magnesium–Ibogaine: the Stanford Traumatic Injury to the CNS (MISTIC) study, a

prospective observational study of 30 male Special Operations Forces veterans with predominantly mild TBI and histories of repeated blast or combat exposure [10]. At baseline, 23 participants met criteria for PTSD, 15 for major depressive disorder, 14 for an anxiety disorder, and 15 for alcohol use disorder, underscoring substantial psychiatric and substance-use comorbidity in the cohort. Participants received a single oral dose of ibogaine averaging 12.1 ± 1.2 mg/kg, coadministered with magnesium. They were assessed at baseline, immediately after treatment, and one month later using validated clinician-rated psychiatric measures and neuropsychological testing.

The prespecified primary outcome was change in disability immediately after treatment; one-month outcomes were secondary. At one month, large improvements were observed in PTSD (Cohen's $d = 2.54$), depression ($d = 2.80$), anxiety ($d = 2.13$), and disability ($d = 2.20$) [10]. Neuropsychological testing also showed improvements in processing speed, executive functioning, sustained attention, and aspects of memory, with no evidence of deterioration across cognitive domains. These findings are particularly relevant to the potential neuropsychiatric applications of ibogaine because they suggest improvements in both psychiatric symptoms and objectively assessed cognitive functioning in individuals with histories of TBI, while the uncontrolled design and high baseline comorbidity limit causal attribution.

MISTIC provides a more direct signal for ibogaine's potential effects on trauma-related psychiatric and cognitive symptoms than earlier studies involving sequential ibogaine and 5-MeO-DMT. Nevertheless, the evidence remains preliminary. MISTIC's limitations include its small, open-label, uncontrolled design. Additionally, it involved a highly selected population of male Special Operations Forces veterans, and incorporated complementary non-pharmacological treatment

modalities. Across the available studies, the concentration of evidence within military populations also limits generalizability to civilian patients with primary PTSD or TBI. Randomized controlled trials of ibogaine, without additional psychedelic administration, are therefore needed to determine whether these findings represent a specific therapeutic effect of ibogaine and whether they generalize to broader trauma-exposed populations.

Anxiety

More encouraging anxiety signals have emerged as secondary outcomes in studies of trauma-exposed populations. As described above, both retrospective and prospective studies of Special Operations Forces veterans receiving sequential ibogaine and 5-MeO-DMT reported significant reductions in anxiety symptoms following treatment [9,32]. However, these findings cannot establish an anxiolytic effect of ibogaine specifically because of the subsequent administration of 5-MeO-DMT and the absence of controlled comparison groups.

The MISTIC study provides a more direct human signal, with anxiety assessed using the clinician-rated Hamilton Anxiety Rating Scale (HAM-A). Following magnesium-ibogaine treatment, anxiety symptoms decreased significantly, with a large effect at one month (Cohen's $d = 2.13$) [10]. Nevertheless, anxiety was a secondary outcome in a small, uncontrolled study of Special Operations Forces veterans with mild TBI rather than a primary endpoint in patients recruited for an anxiety disorder.

Taken together, available human studies suggest that anxiety symptoms may improve following ibogaine-containing interventions, particularly in trauma-exposed populations. However, there are currently no controlled clinical trials establishing ibogaine as a treatment for a primary anxiety disorder. Whether

observed improvements reflect a direct anxiolytic effect of ibogaine, improvement in co-occurring PTSD or other psychiatric symptoms, or broader psychological changes following treatment remains unclear.

THE PSYCHEDELIC EXPERIENCE AS A POTENTIAL THERAPEUTIC MECHANISM

Phenomenology of the Ibogaine Experience

The acute psychoactive effects of ibogaine differ substantially from those of classic serotonergic psychedelics. They are frequently characterized as prolonged and oneirogenic, with dream-like imagery, altered sensory perception, autobiographical recollection, and introspection. Descriptions of the ibogaine experience commonly identify three overlapping phases involving both psychological and physical effects [33]. During the initial phase, individuals may experience vivid, dream-like imagery and altered perceptions of light, sound, space, and time. Visual phenomena have been described as rapid sequences resembling a slideshow or high-speed movie. The second phase is characterized by greater introspection and evaluation of the imagery and experiences that emerged during the initial phase. Participants have described their visions as containing narratives or symbolism related to past and current life experiences, relationships, and broader existential themes. During the third phase, the intensity of the psychoactive effects diminishes and awareness of the external environment increases, although residual psychological effects may persist beyond the acute experience [34]. The prolonged duration of this altered state is another feature distinguishing ibogaine from many other psychedelic compounds [34].

Qualitative studies suggest that autobiographical recollection, emotional processing, and changes in self-perception may be

particularly salient features of the ibogaine experience. In a qualitative study of individuals who received ibogaine for problematic opioid use, Camlin et al. reported themes of decreased self-critical thinking, increased self-acceptance, and renewed hope and self-confidence following treatment [35]. Participants also described spiritual or transpersonal experiences characterized by feelings of connection to others and the broader world.

Schenberg and colleagues [36] similarly examined the subjective experiences of individuals receiving ibogaine in a treatment program incorporating cognitive behavioral therapy for substance use. Participants described increased awareness of problematic interpersonal dynamics and the consequences of their substance use. Participants reported that autobiographical imagery and imagined future scenarios facilitated introspection, emotional processing, and reconsideration of maladaptive behavioral patterns. Participants also reported improvements in secondary psychosocial outcomes, including self-efficacy, quality of life, and family and social relationships. Because ibogaine was administered within a broader therapeutic program, however, these changes cannot be attributed solely to the psychedelic experience itself.

The acute experience also includes prominent somatic effects that may shape its overall phenomenology. Reported effects include dizziness or lightheadedness, impaired coordination, sensations of physical heaviness or warmth, auditory phenomena such as buzzing, emotional distress, nausea, vomiting, and gastrointestinal symptoms. Thus, the ibogaine experience encompasses not only perceptual and introspective phenomena but also substantial physical effects, distinguishing it from the phenomenology typically described with classic serotonergic psychedelics.

Relationship Between Subjective Experience and Clinical Outcomes

The prominent introspective and autobiographical features of the ibogaine experience raise the question of whether the nature or intensity of the acute subjective experience contributes to subsequent therapeutic outcomes. Qualitative studies suggest that individuals often attribute behavioral and psychological changes to insights, emotional processing, autobiographical recollection, and changes in self-perception during or after the ibogaine experience [33,35,36]. However, retrospective attribution of therapeutic benefit to a meaningful psychedelic experience does not establish that the experience itself is responsible for subsequent clinical improvement.

More direct evidence comes from a secondary analysis of the MISTIC study [37]. Researchers quantified mystical-type experiences during magnesium-ibogaine treatment using the 30-item Mystical Experience Questionnaire (MEQ30). Greater mystical-experience intensity was associated with larger reductions in PTSD severity both immediately and one month after treatment. It was also associated with a persisting decrease in EEG peak alpha frequency at one month. These findings provide preliminary evidence that the subjective experience accompanying ibogaine administration may be related to subsequent PTSD improvement. Still, the analysis did not establish corresponding associations with depression or anxiety outcomes.

However, the observational nature of these associations precludes causal inference. A more intense mystical experience may contribute to therapeutic improvement. Still, it may also reflect greater pharmacologic exposure, individual psychological characteristics, expectancy, treatment context, or other factors associated independently with clinical response. The relationship between subjective experience and outcome therefore does not establish that a mystical or psychedelic experience is necessary for ibogaine's therapeutic effects.

Is the Psychedelic Experience Necessary?

Whether ibogaine's acute psychedelic experience is necessary for sustained therapeutic benefit remains unresolved. One possibility is an experience-dependent model in which autobiographical recollection, psychological insight, emotional processing, reappraisal of maladaptive behaviors, mystical-type experiences, and subsequent meaning-making contribute directly to clinical improvement. The qualitative findings described above and the association between mystical-experience intensity and psychiatric outcomes in the MIS-TIC secondary analysis are consistent with this possibility.

An alternative, although not mutually exclusive, model proposes that sustained effects may arise primarily from pharmacologic and neurobiological mechanisms that do not require conscious psychedelic experience. Ibogaine and its active metabolite, noribogaine, modulate multiple neurotransmitter systems involved in mood, stress, and reward processing. In contrast, the substantially longer persistence of noribogaine provides a potential mechanism for biological effects extending beyond the acute ibogaine experience. Neuroplasticity and modulation of maladaptive reward circuitry may further contribute to sustained behavioral and psychiatric changes.

The development of non-hallucinogenic iboga-inspired compounds provides an important experimental test of this distinction. Tabernanthalog (TBG), for example, produces structural neural plasticity and antidepressant-like and anti-addictive behavioral effects in animal models without producing the head-twitch response commonly used as a behavioral proxy for psychedelic-like 5-HT_{2A} activity [24]. These findings suggest that at least some therapeutic properties associated with the iboga alkaloid scaffold may

be separable from the classic psychedelic-like state.

Current evidence therefore supports neither a purely experience-dependent nor a purely pharmacologic explanation for ibogaine's sustained effects. Psychological processes during the acute experience and subsequent neurobiological changes may instead interact, with ibogaine potentially creating a period of enhanced plasticity during which autobiographical, emotional, and behavioral processing becomes particularly consequential. Determining whether subjective experience is necessary, contributory, or incidental to therapeutic response will require studies directly comparing ibogaine with noribogaine and non-hallucinogenic analogs, while prospectively measuring both subjective experiences and clinical outcomes.

SAFETY AND PSYCHIATRIC RISKS

Cardiovascular Toxicity

A significant barrier to clinical development of ibogaine is its safety profile [38]. Early U.S. development efforts in the 1990s did not progress to completed efficacy trials, and subsequent clinical research has largely occurred outside the United States. Because the detailed regulatory history is not necessary to the present safety analysis, the discussion below focuses on the experimentally and clinically documented cardiac, neurologic, and psychiatric risks.

The most concerning adverse effect is cardiac arrhythmia. Koenig and colleagues [11] demonstrated a plausible mechanism through inhibition of human ether-à-go-go-related gene (hERG) potassium channels, which are essential for cardiac repolarization. Ibogaine reduced hERG current in a concentration-dependent and reversible manner, providing a mechanistic basis for QT prolongation and increased risk of ventricular tachyarrhythmias and torsades de pointes.

A subsequent study by Rubi and colleagues [12] extended these findings to noribogaine, ibogaine's long-lived active metabolite. Using human induced pluripotent stem cell-derived cardiomyocytes, the authors found that both ibogaine and noribogaine significantly delayed action-potential repolarization. Given noribogaine's longer persistence, these *in vitro* findings provide a plausible mechanistic basis for cardiac risk extending beyond the acute ibogaine exposure. Still, they do not by themselves establish the timing or magnitude of delayed clinical risk.

Clinical safety reports support these mechanistic findings. A 2012 forensic review identified 19 known deaths occurring 1.5–76 hours after ibogaine ingestion outside West-Central Africa between 1990 and 2008; advanced medical comorbidity and/or co-ingested substances contributed to many cases with adequate postmortem data [13]. An updated systematic review of reports published from 2015 through 2020 identified additional serious adverse events and fatalities associated with ibogaine or noribogaine, while emphasizing substantial heterogeneity in products, doses, settings, and the ability to establish causation [39]. Case reports also document combined neurologic and cardiac toxicity; Grogan and colleagues [40] described seizure-like episodes with QTc prolongation and captured dysrhythmias after ibogaine ingestion.

Rocha and colleagues [38] systematically reviewed 12 clinical sources examining setting factors associated with ibogaine safety. The included literature was heterogeneous in design and should not be characterized as 12 controlled trials. The review supports the importance of structured medical screening, cardiac monitoring, trained personnel, and controlled treatment settings. Still, it does not establish that clinically important adverse effects are uniformly mild or self-limited.

Prospective clinical data illustrate the magnitude of the cardiac signal even under

monitoring. In Knuijver and colleagues' open-label study of 14 patients with opioid use disorder receiving 10 mg/kg ibogaine-HCl, the median maximum QTc increase was 102 ms; 7 of 14 participants exceeded a QTc of 500 ms, 6 of 14 remained above 450 ms at 24 hours, and 8 of 14 received magnesium infusions according to protocol [41]. No torsades de pointes occurred. Noribogaine itself also prolongs repolarization: in an ascending-dose study, QTc increased in a concentration-dependent manner by approximately 0.17 ms/ng/mL, with mean effects of approximately 16, 28, and 42 ms at 60, 120, and 180 mg, respectively [42]. Taken together, these findings establish clinically meaningful, exposure-related QT prolongation and support intensive pretreatment screening and cardiac monitoring rather than reassurance based solely on treatment setting.

Neurologic Toxicity

Beyond its cardiac risk profile, ibogaine carries a distinct set of neurologic concerns spanning mild, self-limited effects to rare but serious events. At the mechanistic level, several of ibogaine's neurologic effects trace back to its action at the NMDA receptor: ibogaine binds the same site targeted by the non-competitive antagonist MK-801, with an IC₅₀ of approximately 5.2 micromolar in human caudate and 9.8 micromolar in human cerebellum, a profile thought to underlie the dissociative, ketamine-like quality of the ibogaine experience [3].

Preclinical work has also identified dose-dependent cerebellar toxicity in some animal models. In rats, high-dose ibogaine can produce Purkinje-cell injury in the cerebellar vermis, whereas this finding has not been consistently reproduced across species [3]. These animal data establish a preclinical neurotoxicity signal but do not define a reliable human dose threshold or safety margin.

Neurologic effects also occur at clinically studied doses. Knuijver and colleagues [41] reported severe, transient ataxia with inability to walk without support in all 14 opioid-dependent patients who received a single 10 mg/kg dose under monitored inpatient conditions. The finding demonstrates that clinically significant motor impairment can occur even in a structured medical setting and warrants fall precautions and direct observation during the acute period.

Seizures are a rare but serious reported neurologic complication, particularly after high or poorly characterized exposures. Breuer and colleagues [43] described a 22-year-old man who developed generalized tonic-clonic seizures after ingesting a cumulative 38 g of dried iboga root bark in two closely spaced doses; the seizures required treatment with midazolam and levetiracetam, and subsequent diagnostic evaluation was unrevealing. Grogan and colleagues [40] documented seizure-like episodes occurring alongside QTc prolongation and cardiac dysrhythmias in a toxicology-confirmed case. These reports support caution but do not establish a precise dose-response relationship for seizure risk in humans.

Taken together, ibogaine's neurologic risk profile ranges from a transient ataxia that has been common in some clinically studied cohorts, to a rare but serious seizure risk concentrated at very high or poorly characterized doses. As with the cardiac findings, the clearest common thread across these reports is that the most severe outcomes cluster in uncontrolled settings, reinforcing the same conclusion reached in the cardiovascular section: dose control and clinical monitoring appear to be the primary levers available for reducing ibogaine's neurologic risk.

Psychiatric Adverse Events

Case-level reports also document the risk of serious psychiatric adverse events. Houenou

and colleagues [44] described a 26-year-old man's first psychotic episode, with persecutory and mystic delusions and hallucinations, occurring after ibogaine ingestion during a shamanic ritual context in Gabon; the authors describe this as ibogaine "revealing" an underlying, previously undiagnosed schizophrenia, with two further psychotic episodes following. The authors call for the need for careful screening and exclusion criteria for those with risk of, or current, psychotic disorder such as schizophrenia. However, this risk extends to even those without a prior history of psychiatric concerns in Marta and colleagues' [14] work. There, they described a case series of three patients aged 35 to 40, none with a prior diagnosis of bipolar illness, who developed manic episodes, including grandiosity, impulsivity, and pressured speech lasting one to two weeks after ibogaine use. These cases were confounded by one of the cases also being associated temporally with recent psilocybin experimentation and heavy chronic cannabis use, as well as all the cases using ibogaine in an unstructured, non-clinical setting. Taken together, these reports underscore that ibogaine's psychiatric risk profile extends beyond its well-documented cardiac toxicity.

Clinical Implications

Across the cardiac, neurologic, and psychiatric risks described above, structured clinical settings permit more systematic screening, detection, and management of adverse effects than uncontrolled use. Rocha and colleagues' systematic review [38] of 12 heterogeneous clinical sources identified recurring safety practices including pretreatment medical and psychiatric assessment, laboratory testing, baseline ECG, and access to trained personnel. Knuijver and colleagues [41] provide a concrete example of intensive cardiac surveillance: they obtained ECGs frequently for at least 24 hours, used a prespecified

magnesium protocol, and escalated monitoring when QTc exceeded 500 ms. These practices should be understood as risk-mitigation measures rather than evidence that monitored ibogaine administration is intrinsically low risk.

These same protective factors are relevant to the psychiatric risks described above. Houenou and colleagues [44] called for screening and exclusion of individuals with current psychotic disorders or elevated psychosis risk. Marta and colleagues' case series [14], however, illustrates the limits of screening: none of the three patients had a prior bipolar diagnosis before developing manic episodes temporally associated with ibogaine use. Pretreatment assessment may identify some vulnerable individuals, but psychiatric monitoring during and after dosing remains important because risk cannot be eliminated by intake screening alone.

Rocha and colleagues [38] also identify a gap across these risk domains: physical and cardiac monitoring was described more consistently than psychological or therapeutic support. Few reports clearly characterized structured psychotherapy accompanying dosing. Given the intense and prolonged subjective effects of ibogaine and the case-level psychiatric adverse events described above, psychological support and post-treatment follow-up warrant explicit attention alongside cardiac and neurologic monitoring.

Drug Interactions and Patient Selection

Conversion of ibogaine to its active metabolite noribogaine is mediated primarily by CYP2D6, creating clinically relevant pharmacokinetic variability. In a crossover study of 21 healthy volunteers given a single 20 mg ibogaine dose after placebo or the CYP2D6 inhibitor paroxetine, reduced CYP2D6 activity markedly altered ibogaine disposition: ibogaine remained detectable longer, its elimination half-life was 10.2 hours under

CYP2D6 inhibition, and combined exposure to ibogaine plus noribogaine was approximately doubled [5]. CYP2D6 phenotype correlated strongly with ibogaine AUC and Cmax. The authors therefore suggested CYP2D6 genotyping and consideration of at least halving the intended dose in poor metabolizers. Importantly, these pharmacokinetic data were obtained with a 20 mg experimental dose, substantially below doses used in many therapeutic settings.

This finding has direct clinical implications beyond genetics alone, because CYP2D6 activity can be pharmacologically inhibited, not just genetically reduced. Paroxetine, the drug used to model this effect in the Glue study, is itself a commonly prescribed SSRI, meaning that a patient already taking one of several common antidepressants could be phenocopied into a poor metabolizer state at the moment of ibogaine dosing, without any pre-existing genetic vulnerability. This is not a hypothetical concern for the population most likely to seek ibogaine treatment: Glue and colleagues [42] found that in their sample of patients on methadone maintenance, 55 percent were taking one or more concurrent medications, including antidepressants (22 percent), antipsychotics (11 percent), and psychostimulants (4 percent), and 78 percent had at least one diagnosed medical illness, most commonly chronic hepatitis C or chronic obstructive pulmonary disease. Ibogaine's target population, patients with longstanding substance use disorders, is therefore also a population with substantial rates of polypharmacy and medical comorbidity, both of which compound the pharmacokinetic risk described above.

This pharmacokinetic vulnerability compounds directly with the cardiac risk already described. Because prolonged ibogaine and noribogaine exposure raises the concentration-dependent risk of hERG channel inhibition and QT prolongation, any factor that increases plasma concentration, whether a

CYP2D6 poor metabolizer genotype, a concurrent CYP2D6-inhibiting medication, or impaired hepatic clearance from comorbid liver disease, effectively increases cardiac risk as well. Electrolyte abnormalities, particularly hypokalemia and hypomagnesemia, are well-established independent risk factors for QT prolongation and would be expected to compound ibogaine's effect on cardiac repolarization, which supports the magnesium bolus protocols described in the Clinical Implications section above. Concurrent use of other QT-prolonging medications, common in patients with the kind of medical comorbidity described above, represents an additional, additive risk that pretreatment screening should specifically account for.

A more speculative but pharmacologically plausible interaction concerns serotonergic medications. Ibogaine and its metabolites interact with multiple serotonin receptor subtypes. While no confirmed cases of serotonin syndrome from ibogaine have been established in the literature reviewed here, the combination of ibogaine with SSRIs, SNRIs, or MAOIs remains a theoretical concern that has not been systematically studied and is worth flagging as a gap rather than a settled risk.

Taken together, these findings support careful patient selection and medication review before ibogaine exposure: assessing for CYP2D6-inhibiting medications and other potential pharmacokinetic interactions; identifying concurrent QT-prolonging drugs and relevant polypharmacy; assessing baseline hepatic and renal function; and correcting electrolyte abnormalities. Existing studies vary considerably in exclusion criteria and medication washout procedures, so frame these considerations as risk-mitigation priorities rather than a standardized, evidence-based protocol.

NON-HALLUCINOGENIC IBOGAINE ANALOGUES

There has been promising investigative work into iboga alkaloid derivatives that aim to preserve ibogaine's therapeutic potential without its classical psychedelic effects or safety liabilities. Glick and colleagues [45] demonstrated the potential of 18-methoxycoronaridine (18-MC), a novel synthetic analog that mimicked ibogaine's effects on decreasing rodent self-administration of cocaine and morphine, without the acute effects associated with ibogaine, namely tremors and generally decreased motivated behavior, and without evidence of neurotoxic damage to the cerebellum (Purkinje cell loss in the cerebellar vermis) [45].

Preclinical studies of 18-MC suggest that it may retain anti-addictive behavioral effects while reducing some liabilities associated with ibogaine. In rodent work, 18-MC reduced morphine and cocaine self-administration without evidence of the Purkinje-cell degeneration reported with high-dose ibogaine [45]. These findings support continued investigation of 18-MC as a potentially safer analog, although animal data do not establish comparative safety in humans.

Pharmacologic comparisons indicate that 18-MC has a narrower receptor-binding profile than ibogaine and lacks measurable affinity at several targets implicated in ibogaine's broader effects [46]. 18-MC also antagonizes $\alpha 3\beta 4$ nicotinic receptors, a mechanism investigated in preclinical models of nicotine self-administration [23]. These findings provide mechanistic support for anti-addictive activity, but the relative contribution of individual circuits and receptors remains incompletely defined.

A structurally distinct approach came from Cameron and colleagues, who developed the non-hallucinogenic iboga analog tabernanthalog (TBG) [24]. TBG promoted structural neural plasticity, produced antidepressant-like effects in rodents, and reduced alcohol- and heroin-seeking behavior without

producing the head-twitch response used as a proxy for psychedelic-like 5-HT_{2A} activity [24]. It also showed substantially less hERG-channel inhibition than ibogaine in preclinical testing. These findings make TBG an important experimental tool for testing whether psychoplastogenic and anti-addictive effects can be separated from ibogaine's hallucinogenic and cardiotoxic properties. At the same time, its therapeutic relevance in humans remains unknown.

Among the best-studied analogs, 18-MC (zolunicant/MM-110) completed a Phase 1 study in healthy volunteers in 2021. MindMed subsequently reported suspending further development in 2022, with additional development contingent on non-dilutive funding or collaboration [47]. TBG remains preclinical [24].

Ultimately, if non-hallucinogenic analogs like 18-MC and TBG can reproduce ibogaine's sustained psychiatric and anti-addictive effects in humans, this would challenge the hypothesis that the subjective psychedelic experience itself is necessary for therapeutic benefit. Conversely, the association observed between mystical experience intensity and clinical improvement in the MISTIC cohort [37] suggests that psychological and biological mechanisms may not be mutually exclusive. Both could contribute independently to outcomes.

CURRENT LIMITATIONS

Methodological Limitations

The existing ibogaine literature is limited by small sample sizes and a predominance of observational and retrospective studies, case reports, and case series, with relatively few randomized controlled trials. Common methodological limitations include selection bias, reliance on self-reported outcomes, heterogeneous treatment settings, variable ibogaine preparations and dosing protocols, and

limited long-term follow-up. The absence of adequate control groups in many studies also makes it difficult to distinguish treatment effects from expectancy, placebo effects, regression to the mean, or the natural course of symptoms. Collectively, these limitations restrict causal inference and make the magnitude and durability of ibogaine's potential psychiatric effects difficult to determine.

Confounding

Interpretation of psychiatric outcomes is further complicated by substantial confounding. Much of the human literature involves individuals undergoing treatment for SUDs, in whom ibogaine administration frequently coincides with substance cessation and resolution of acute withdrawal. Improvements in depression, anxiety, sleep, and overall psychological functioning may therefore reflect, at least in part, reduced substance use or withdrawal resolution rather than a direct psychiatric effect of ibogaine. Several treatment protocols also incorporate psychotherapy, supportive interventions, or other components that may independently contribute to improvements in both self-reported and clinician-rated outcomes. Additionally, several studies involving Special Operations Forces veterans used sequential administration of ibogaine followed by 5-MeO-DMT, preventing attribution of subsequent psychiatric improvements specifically to ibogaine.

Generalizability

The populations represented in the existing literature also limit generalizability. Human studies have predominantly involved individuals with severe SUDs or highly selected military and Special Operations Forces cohorts. Findings from these populations may not generalize to broader civilian psychiatric populations, particularly women and individuals with different medical, psychiatric, or

trauma histories. Evidence remains especially limited in patients with primary mood, anxiety, or trauma-related disorders without co-occurring SUD or TBI. Consequently, the efficacy and safety of ibogaine for primary psychiatric disorders remain largely undetermined.

Regulatory and Treatment-Setting Limitations

The unusual legal and regulatory environment surrounding ibogaine creates additional challenges for evaluating the literature. Because ibogaine remains restricted in several countries, including the United States, much of the available human evidence has emerged from treatment programs and research conducted in jurisdictions where ibogaine administration is permitted or less restricted. Treatment settings vary considerably in patient selection, dosing, product standardization, medical screening, monitoring, and availability of emergency care. Adverse events associated with informal or unregulated ibogaine use may also be incompletely captured in the published literature. These factors complicate comparisons across studies and limit the ability to characterize both therapeutic effects and the true incidence of adverse outcomes.

FUTURE DIRECTIONS

The path forward for ibogaine research runs along two parallel tracks: broadening what it might treat and making it safer to test and use. Nicolas [48] presents a Hypothesis and Theory framework proposing that ibogaine's effects on GDNF, glutamatergic and dopaminergic signaling, and neuroplasticity could influence dysfunctional reward processing across diagnostic categories, including addiction, PTSD, and OCD. This remains a theoretical model rather than clinical evidence. Broader reviews of psychedelic

neuroplasticity, including Palhas and colleagues [49], describe overlapping but not necessarily identical plasticity-related pathways across compounds; ibogaine may engage growth-factor mechanisms that differ from those emphasized for classic serotonergic psychedelics and ketamine. Vorobyeva and Kozlova [50] likewise identify ibogaine as a naturally occurring psychedelic warranting dedicated mental health research. Wong and colleagues [2] further illustrate how limited the ibogaine-specific clinical literature remains relative to the broader psychedelic field.

Translating this potential into practice will require trials designed to answer questions the current literature cannot. Priority should go to dedicated psychiatric trials in PTSD, treatment-resistant depression, and SUD-associated anhedonia, recruiting populations without active substance use disorder so that psychiatric improvement can be disentangled from improvement driven by reduced substance use. A second open question is mechanistic: whether noribogaine, ibogaine's long-lived active metabolite, could be developed as a therapeutic, and whether its pharmacokinetics track directly with symptom improvement. A third, and perhaps the most conceptually important, is whether the subjective psychedelic experience itself is necessary for benefit, a question that comparisons between ibogaine, noribogaine, and non-hallucinogenic analogs such as TBG are uniquely positioned to answer, alongside direct tests of whether the intensity of that subjective experience mediates outcome.

Regarding safety, Swieczkowski and colleagues' [51] cross-sectional review of the ibogaine clinical trials landscape describes continued clinical-trial activity. It highlights the need for future trials to standardize what the studies reviewed in this paper's safety section did inconsistently: routine ECG and QTc monitoring, electrolyte assessment and correction, systematic screening for drug

interactions and CYP2D6 status, structured screening for bipolar and psychotic vulnerability, and standardized adverse event reporting extending into longer-term psychiatric follow-up. Parallel to this, continued development of safer iboga-inspired therapeutics, including TBG, 18-MC, and future compounds, remains the most direct route toward separating ibogaine's therapeutic mechanism from its cardiotoxicity and hallucinogenic liability altogether.

CONCLUSION

Ibogaine occupies an unusual position within the emerging field of psychedelic psychiatry. Although historically investigated primarily for its anti-addictive effects, its complex neuropharmacology, active metabolite noribogaine, effects on neuroplasticity and reward-related circuitry, and emerging clinical findings suggest potential neuropsychiatric relevance extending beyond SUDs. Preliminary human studies have reported improvements in depression, anxiety, trauma-related symptoms, and cognitive functioning. At the same time, preclinical findings provide biologically plausible mechanisms through which sustained effects might occur after the acute psychoactive experience has resolved.

However, the strength of this evidence remains behind the therapeutic promise it suggests. No controlled clinical trial has established ibogaine as an effective treatment for a primary mood, anxiety, or trauma-related disorder. Much of the existing human evidence derives from individuals undergoing treatment for SUDs or highly selected military populations, and interpretation is complicated by substance cessation, concurrent psychotherapy or supportive interventions, additional psychedelic exposure, expectancy effects, and uncontrolled study designs. Cardiovascular toxicity, neurologic adverse effects, and reported cases of mania and psychosis further distinguish ibogaine from

psychedelic compounds with more advanced clinical development and underscore the importance of careful patient selection, standardized dosing, medical monitoring, and psychiatric screening in future research.

Several fundamental questions therefore remain unresolved. It is not yet known whether the psychiatric improvements observed following ibogaine represent direct effects on mood and trauma-related pathology or are secondary to improvements in substance use and broader psychosocial functioning. Similarly, the relative contributions of ibogaine, sustained noribogaine exposure, neuroplasticity, and the acute subjective experience remain uncertain. Associations between mystical-type experiences and subsequent psychiatric improvement suggest that psychological processes may contribute to therapeutic outcomes. In contrast, preclinical findings with non-hallucinogenic iboga-inspired compounds demonstrate that at least some neuroplastic and behavioral effects may occur without a classic psychedelic-like state.

Rather than supporting the clinical use of ibogaine for established psychiatric indications, the current literature supports its continued investigation as both a potential neuropsychiatric therapeutic and a platform for understanding mechanisms that may inform the development of safer treatments. Dedicated controlled trials in well-characterized psychiatric populations, coupled with mechanistic studies of noribogaine and continued development of safer iboga-inspired compounds, will be necessary to determine whether the promising signals identified to date translate into clinically meaningful psychiatric treatments

AUTHOR INFORMATION

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DEA's Renewed Push to Schedule Five Tryptamines: What Researchers Need to Know

Tyler Kjorvestad, MD

Major scheduling actions rarely go unnoticed. On September 22, 2026, Psychedelic Alpha reported that the DEA is once again moving to put five tryptamine psychedelics on Schedule I. The next day, the official notice appeared in the Federal Register. If you want your voice heard, you have until October 23—no extensions.

Don't rely on secondary reports suggesting a longer window—the Federal Register date is the one that counts.

I am not arguing these five compounds are safe, effective, or medically accepted. The NPRM says DEA finds no accepted medical use in the United States and that Health and Human Services recommended Schedule I ^[1]. This piece's point is narrower: reconstruct what the agencies put on the record, recall that this proposal came and went in 2022, and mark what finalization would mean for research and handling without inventing trial pipelines or therapeutic claims.

What the September Notice Actually Does

The September 23 filing is a proposed rule, not a final one ^[2]. If adopted, the five tryptamines would fall under Schedule I controls on manufacture, distribution, reverse distribution, import and export, research, instructional activities, chemical analysis, and possession ^[2]. That list covers the whole chain. Once a molecule is in Schedule I, every link becomes a controlled activity under the Act's most restrictive tier.

Under 21 U.S.C. 812, Schedule I requires three findings: high potential for abuse; no currently accepted medical use in treatment in the United States; and a lack of accepted safety for use under medical supervision ^[3]. The NPRM tracks that statutory

framework ^[2]. Agency findings on this docket are not the same thing as FDA approval, and they are not clinical conclusions of this journal.

The Eight-Factor Record, Without the Fog

Scheduling under 21 U.S.C. 811 depends on eight factors. The 2026 NPRM states that HHS, in an April 2, 2026 scientific and medical evaluation, recommended Schedule I after considering those factors. DEA completed its own eight-factor analysis in August 2021 and updated it in May 2026 ^[2]. The published notice summarizes each factor. The full HHS and DEA analyses, with supporting data and citations, are flagged as Supporting Documents in Docket DEA1715 on regulations.gov ^[2]. Commenters seeking substance should read those filings, not just the news cycle.

A few agency points from that summary are worth knowing before filing. DEA cites cumulative National Forensic Laboratory Information System drug encounters of these tryptamines, and HHS's review of America's Poison Centers National Poison Data System cases involving one or more of the five ^[2]. The NPRM states the substances are not FDA-approved drugs and are not immediate precursors of substances already controlled under the CSA ^[2]. DEA's proposed determination is that they meet the three Schedule I findings ^[2]. These propositions belong to the administrative record. I do not adopt them as clinical truth, nor manufacture a counter-efficacy literature that does not appear here.

How much depth sits behind the summary? Enough that serious commenters should open the Supporting Documents tab rather than argue with a press paraphrase. The

NPRM's eight-factor write-up covers abuse potential, scientific knowledge, history and pattern of abuse, scope and significance of abuse, public-health risk, dependence liability, and precursor status as framed by the agencies ^[2]. Quoting every assay here would turn an editorial into a reprint. Pointing readers to the docket is the honest move.

One more procedural beat matters for the timeline. After withdrawing the 2022 proposal, DEA requested the updated HHS evaluation on November 16, 2023 ^[2]. The September 2026 NPRM is the visible end of that restart.

2022: Proposal, Hearing Requests, Withdrawal

This is a rematch, not a debut. On January 14, 2022, DEA published an earlier NPRM at 87 FR 2376 seeking the same placement ^[4]. DEA followed with a hearing notice on July 6, 2022 (87 FR 40167) ^[7]. On July 27, 2022, DEA withdrew both the proposed rule and the hearing notice (87 FR 45076), saying it needed a fresh HHS scientific and medical evaluation ^[5]. The withdrawal text is blunt: numerous comments, four hearing requests, a public hearing set for August 22, 2022, then canceled when the proposal died ^[5]. Contemporary secondary reporting covered that fight for the same five compounds ^[6]. Chronology still belongs to the Federal Register.

So what changed between then and now? So what changed between then and now? An updated HHS evaluation dated April 2, 2026, and DEA's decision to republish ^[2]. The scheduling theory did not change. The process stalled, then restarted. For psychiatrists and investigators, that recurrence is the news: withdrawn proposals can return when HHS refreshes its evaluation, and DEA chooses to try again. Pathways get used when parties contest the science or the procedure ^[5]. Whether similar requests appear before October 23, 2026 is an open question. The

calendar is not.

What Finalization Would Mean, and What It Would Not

Schedule I is the CSA's tightest box ^[3]. Placement does not require a new Act of Congress for each molecule. It proceeds through administrative rulemaking informed by HHS evaluation and DEA's authority under the statute [2,3]. The machinery is bureaucratic, but the consequences are concrete for anyone who needs to possess, analyze, teach about, or study these compounds under federal law.

If this proposal becomes final, the operational consequences named in the NPRM are clear. Manufacture, distribution, reverse distribution, import and export, research, instructional activities, chemical analysis, and possession would all fall under Schedule I controls ^[2]. Research and possession usually hit academic and clinical communities hardest. Investigators who work with other Schedule I psychedelics know the registration burden, regulatory context, protocols, secure storage, quota and inventory rules, and the friction of getting work approved. Specific registration tallies or grant-impact numbers for these five tryptamines are not claimed here ^[2,3].

What does that mean in practice for a psychiatry department or controlled-substance research program? A molecule that might today sit in a gray or lightly watched space, if not already controlled under another theory, would after finalization require the full Schedule I apparatus before legitimate work proceeds ^[2]. Instructional and analytical uses, not only clinical trials, fall inside the control list the NPRM enumerates ^[2]. That breadth is easy to miss when headlines focus only on banning psychedelics.

What the NPRM does not do is also plain. It does not approve a medicine. It does not create a treatment protocol. It does not open a state access pathway. It proposes federal

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controls grounded in a finding of no currently accepted medical use in the United States ^[2]. Scheduling is not FDA therapeutic evaluation. This piece advances no claim that these five compounds are safe or effective for any indication.

One further boundary: I do not assert whether any of the five are already treated as controlled under temporary orders or Federal Analog Act theories. That status was not verified from primary sources for this draft, and it is not part of the argument. If a lab or counsel needs that answer, they should pull primary DEA and CSA materials, not infer it from this editorial.

Why Psychiatry Should Care About the Comment Window

This move isn't happening in a vacuum—it comes as the conversation around psychedelics is heating up. Some compounds are under intense study, while others, like these five, are barely touched by researchers. Debate alone isn't evidence, and there are no robust clinical trials or safety data to lean on for these substances. Still, how Schedule I is used affects the whole field, not just the drugs at issue. The comment period is your shot to shape the process; miss it, and the discussion shifts to red tape and legal battles instead of real input.

Commenting is not the same as cheering medicalization or opposing it. Useful comments can press procedural completeness, the adequacy of the updated HHS eight-factor evaluation as summarized in the NPRM and filed in the docket, the clarity of isomer and salt definitions, or the practical drag of Schedule I research controls on legitimate science [2,3]. Unpublished efficacy stories do not help the record. Engagement with the actual NPRM text does. Hearing requests, where appropriate under the CSA and DEA's hearing rules, remain a separate procedural tool. The 2022 cycle shows they get used ^[5,7].

I approach scheduling questions as earlier Journal of Psychedelic Psychiatry policy pieces have: tie claims to primary sources, separate agency findings from clinical conclusions, and treat administrative deadlines as part of the science-policy interface [2,3]. Debates over medicalization, decriminalization, and legalization still matter as context for how Schedule I shapes research paths. They do not license therapeutic claims about these five tryptamines on the present record ^[3].

Institutions that run or oversee Schedule I research may want a quiet internal check: would planned chemical analysis, instructional use, or comparative pharmacology involving these molecules change if the rule finalizes as proposed ^[2]? Most clinicians will never see these substances in approved practice. The nearer stake is the integrity of the administrative record and whether research regulation stays predictable enough for serious investigators to plan work without guessing which tryptamine will next jump from news alert to Federal Register.

Conclusion

DEA's September 23, 2026 NPRM brings back a Schedule I proposal for five tryptamines that was withdrawn in July 2022 after hearing requests and pending updated HHS review [2,5]. The substances, 4-OH-DiPT, 5-MeO-AMT, 5-MeO-MiPT, 5-MeO-DET, and DiPT, would, if finalized, face full Schedule I controls on handling, research, and possession ^[2]. Comments and hearing requests are due on or before October 23, 2026 ^[2]. HHS recommended Schedule I after its April 2, 2026 eight-factor evaluation; DEA's own eight-factor analysis was updated in May 2026 ^[2]. Those findings sit inside the statutory Schedule I criteria of high abuse potential, no currently accepted medical use in

treatment in the United States, and lack of accepted safety under medical supervision [3].

This editorial does not settle whether Schedule I is the right long-term home for each molecule. It does argue that psychiatrists, investigators, and institutional stewards of controlled-substance research have a concrete, time-bounded interest in reading the NPRM and the docket, supporting documents, checking dates against the Federal Register rather than secondary summaries, and deciding whether to comment [2]. A 2022 withdrawal did not end the story. An updated HHS evaluation brought it back [2,5]. Careful engagement with the administrative record, not invented clinical narratives, best serves patients, science, and the law. dementia, the altered sensorium risks compounding disorientation and precipitating delirium-like states [34]. A systematic review noted serious adverse events in approximately 4% of participants with preexisting neuropsychiatric conditions [35].

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