Is ibogaine treatment durable? 12-month follow-up of magnesium–ibogaine therapy (MISTIC) in Special Operations Veterans with traumatic brain injuries

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Is ibogaine treatment durable? 12-month follow-up of magnesium–ibogaine therapy (MISTIC) in Special Operations Veterans with traumatic brain injuries

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ABSTRACT

Traumatic brain injury (TBI) can result in chronic functional disability and is associated with persistent psychiatric symptoms, including posttraumatic stress disorder (PTSD), depression, and anxiety. Ibogaine, an oneirogenic alkaloid with unique pharmacological properties, has shown initial promise as a potential treatment for TBI-related sequelae. We previously observed large improvements in functional and psychiatric outcomes up to one month after a single treatment with magnesium-ibogaine in male U.S. Special Operations Veterans with a history of TBI. However, further evidence on the durability of these effects is needed. In this prospective long-term follow-up study, we evaluated the persistence of these clinical improvements over the subsequent year. Participants underwent comprehensive baseline and post-treatment assessments, with follow-up evaluations conducted at 3, 6, 9, and 12 months. Of 30 participants treated with magnesium-ibogaine, 25 completed the 12-month follow-up assessments. Outcome measures included a self-report measure of functional disability and clinician-administered assessments of psychiatric symptoms. Results demonstrated robust and sustained reductions in disability, PTSD, depression, and anxiety symptoms through 12 months post-treatment, with large effect sizes (Cohen's $d \geq 2.18$ at 12 months). Survival analyses estimated the probability of sustained remission at 12 months as 84% for PTSD, 66% for depression, and 61% for anxiety. These findings suggest that ibogaine treatment may lead to durable, clinically meaningful improvements in TBI-related symptoms. Further investigation through randomized controlled trials is warranted to validate these promising preliminary results.

Traumatic brain injury (TBI) is a significant and growing health problem that can be associated with lasting emotional, behavioral, and cognitive deficits with large public health costs (1–3) and is among the greatest contributors of all trauma-related injuries to death and disability globally (4). A substantial proportion of individuals who suffer a mild or moderate TBI develop a constellation of symptoms that can last for months or years, with long-term impacts on functioning across many domains of life, including work, relationships, cognition, emotion, and overall quality of life (5). Despite ongoing clinical management of chronic symptoms (2), psychiatric and functional limitations may persist (3), highlighting the need for new treatments.

Psychedelic medicine is transforming our understanding of rapid-acting treatment options in psychiatry, although investigations into the long-term outcomes of psychedelic treatments are needed (6–8). Ibogaine in particular is an oneirogenic alkaloid that shows promise as a rapid-acting treatment, and preliminary studies have shed light on the potential durability of its therapeutic effects. For example, patients with opioid use disorder reported reductions in problematic drug use one year after ibogaine treatment (9,10), with secondary findings of sustained reductions in self-reported depression (10). Similarly, a clinical chart review study in veterans found reductions in self-reported PTSD, depression, and anxiety symptoms for up to six months after ibogaine treatment paired with 5-MeO-DMT (11).

Recently, Cherian et al. (12) found that a single treatment with MISTIC (Magnesium-Ibogaine: the Stanford Traumatic Injury to the CNS) led to significant improvements in disability severity, as well as clinician-rated measures of post-traumatic stress disorder (PTSD), depression, and anxiety symptoms in Special Operations Veterans (SOVs) with a history of TBI, with benefits sustained at 1-month follow-up. Additionally, there was no evidence of negative effects of MISTIC on cognitive functions. Whether these therapeutic benefits endure beyond the first month, however, remains unknown. In the current prospective long-term follow-up study, participants from Cherian et al. (12) were reassessed by clinicians at approximately 3, 6, 9, and 12 months posttreatment to evaluate the durability of MISTIC effects.

Methods

Participants. Thirty male SOVs underwent baseline and posttreatment assessments. Inclusion criteria were age between 18 and 70 years, history of combat or blast exposure, history of TBI (based on Department of Defense TBI classification (13)), no contraindication to magnetic resonance imaging (MRI), ability to travel to Stanford, and ability to provide written informed consent. Exclusion criteria included a history of neurological disorders (except TBI), psychotic symptoms or disorders, risk for suicidal behavior, cardiovascular problems, liver or kidney problems, pregnancy, clinical abnormalities on screening physical exam that could impact safety or study integrity, and participation in a recent/ongoing relevant study. See Cherian et al. (12) for CONSORT and further details. All participants provided written informed consent, and research procedures were approved by the Stanford University Institutional Review Board.

At baseline, 15 participants met the criteria for major depressive disorder, 14 for anxiety disorder, and 23 for posttraumatic stress disorder. Nineteen participants reported prior use of psychedelic drugs; however, the nature of use differed notably, from a single use in younger ages to periods of regular use. Additionally, 21 participants had received formal mental health treatment before the ibogaine trial, and 19 participants reported a history of treatment with psychotropic medication in particular. The average (± standard deviation) number of prior TBIs reported was

38.6 ± 52.4. TBIs were mostly mild (n=28), with two participants reporting a history of moderate (n=1) or moderately severe TBI (n=1). Participants enrolled in the study an average of 7.7 ± 4.8 years after military discharge and 15.2 ± 5.9 years after their most severe TBI (range: 8 - 28 years).

Treatment. Participants independently elected to undergo ibogaine treatment at Ambio Life Sciences in Mexico, facilitated by Veterans Exploring Treatment Solutions (VETS), Inc., a nonprofit organization. VETS, Inc. informed potential participants about the study and referred interested individuals to the Stanford research team. All psychiatric and neuroimaging assessments, both pre- and post-treatment, were conducted by the Stanford team - either in-person at Stanford University or virtually. All aspects of ibogaine treatment took place at Ambio Life Sciences, as ibogaine use is restricted in the United States. VETS, Inc. funded treatment, travel, and accommodation expenses.

As part of Ambio's internal application process, medical screenings were conducted to rule out contraindicated medical conditions and avoid drug-drug interactions. To mitigate risks of Q-T interval prolongation (12,14), magnesium sulfate (1g) was administered intravenously while participants were in a fasting state 1-2 hours before ibogaine dosing. Ibogaine was administered orally, starting with an initial test dose of 2-3 mg/kg. Depending on response, treatment doses of up to a total of <14 mg/kg of oral ibogaine were administered in 3 or 4 doses across a 2-hour period beginning approximately 40 minutes after the initial test dose. An additional dose of magnesium sulfate was delivered intravenously approximately 12 hours after ibogaine dosing. One participant received an additional 4mg/kg dose of ibogaine 12 hours after the first ibogaine dose due to insufficient treatment effects. Participants were monitored for 72 hours after dosing, as the effects of ibogaine can last 24-72 hours (15). For further information and a detailed description of the full MISTIC protocol, see Cherian et al. (12).

As part of Ambio's program, ibogaine is typically followed a few days later by 5-MeO-DMT, but participants in the current study refrained from using 5-MeO-DMT until after the 1-month measures had been collected. Also as part of Ambio's program, participants were partnered with a coach for intention setting, practicing navigation techniques for the psychedelic experience, managing expectations, exploring relationship dynamics, implementing supportive change in the home, and physical preparation. Additionally, participants received a workbook recommended to use before and after the retreat. After treatment, coaches assist with processing emotions, helping to define meaning, and integrating insights from the treatment experience into participants' everyday lives. Coaching does not involve diagnosing, delving into past traumas, or medication-based approaches to healing. Both coaching and workbook use were voluntary and varied substantially across participants (mean preparation hours = 2.7 ± 0.8, range: 1-4.3; mean integration hours = 4.1 ± 3.0, range: 0-13.5).

Structured Assessments. The initial in-person assessments were performed at baseline (2-3 days pre-MISTIC), immediately (4-5 days) post-MISTIC, and 1-month post-MISTIC. Follow-up assessments were performed approximately 3-, 6-, 9-, and 12-months post-MISTIC via teleconferencing. Self-report and clinician-administered measurements included the World Health Organization Disability Assessment Schedule, 2nd Edition (WHODAS-2.0 (16); functional disability), Clinician-Administered PTSD Scale for DSM-5 (CAPS-5 (17); posttraumatic stress

symptom severity), Montgomery–Åsberg Depression Rating Scale (MADRS (18); depression symptom severity), and Hamilton Anxiety Rating Scale (HAM-A (19); anxiety symptom severity). TBI severity was assessed using the Ohio State University Screening for TBI exposure (20), and the lifetime incidence of TBIs was assessed using the Boston Assessment of Traumatic Brain Injury–Lifetime (BAT-L) (13). For further details about the measures used, see Cherian et al. (12).

Data Analysis. Analysis followed the approach used by Cherian et al. (12); Linear mixed-effects models were performed for each outcome measure (WHODAS, CAPS-5, MADRS, and HAM-A), with outcome measure scores as the dependent variable and time point (baseline, immediate post-MISTIC, 1-, 3-, 6-, 9-, and 12-months post-MISTIC) as a categorical independent variable, with a fixed slope and random intercept, and age, Combat Exposure Scale, and total number of reported TBIs included as fixed effects. Contrasts between baseline and 12-month follow-up (primary outcome, registered at osf.io: https://osf.io/uxjsp/) and each additional post-MISTIC follow-up (secondary outcomes) were performed using the MATLAB hypothesis test on fixed-effect coefficients of LME models. False discovery rate (FDR) correction was applied for multiple comparisons. A secondary Kaplan-Meier survival analysis was performed to assess the time to relapse across PTSD, depression, and anxiety diagnoses for participants meeting MINI diagnostic criteria at baseline, who also met remission criteria immediately post-MISTIC. Relapse was defined as the first recorded departure from remission criteria for a respective diagnosis (12), and cases that were lost to follow-up or never experienced a relapse were censored at their last recorded observation. See Supplement for further details and analyses of associations between baseline characteristics and long-term outcomes. All descriptive statistics are shown as mean ± standard deviation, unless noted otherwise.

Results

Of the 30 participants treated with MISTIC, 27 completed at least one long-term follow-up assessment (age = 44.8 ± 7.1 years). At the 12-month post-MISTIC follow-up (primary outcome), 25 of the 30 participants completed self-report and clinician-administered assessments. Of them, 23 used at least one psychedelic substance (either via microdosing, full dose, or both) between the 1-month and 12-month follow-ups (Table S1). This included 19 participants who reported 5-MeO-DMT use after the 1-month visit, 18 of them in the context of a retreat. In addition, 12 participants engaged in some form of therapy or counselling during the 12-month follow-up period, while only 3 participants reported any psychotropic medication use (Table S1).

Functional disability, PTSD, depression, and anxiety scores were all significantly lower 12 months post-MISTIC compared to pre-MISTIC (all p_{FDR} <0.001) with large effect sizes (all Cohen's d >2.17). Post-MISTIC scores were also significantly lower than pre-MISTIC scores at 3-, 6-, and 9-month follow-ups (all p_{FDR} <0.001) with large effect sizes (all Cohen's d >1.81). See Figure 1 for individual score trajectories and Table 1 for linear mixed-effects model results.

Long-term outcomes were similar in participants who did and did not pursue additional interventions during the follow-up period (including structured mental health treatment, psychotropic medication, 5-MeO-DMT, psilocybin, ibogaine, or ayahuasca; Table S1). Significant long-term outcomes were also observed in sensitivity analyses, including only participants who met diagnostic criteria for PTSD, depression, or anxiety disorder at baseline (Table S2). Additionally, sensitivity analyses confirmed that the results were not driven by participants with

moderate to moderately severe TBI: when analyses were restricted to participants with a history of mild TBI, all effects remained significant (all Cohen's d > 1.7; Table S3).

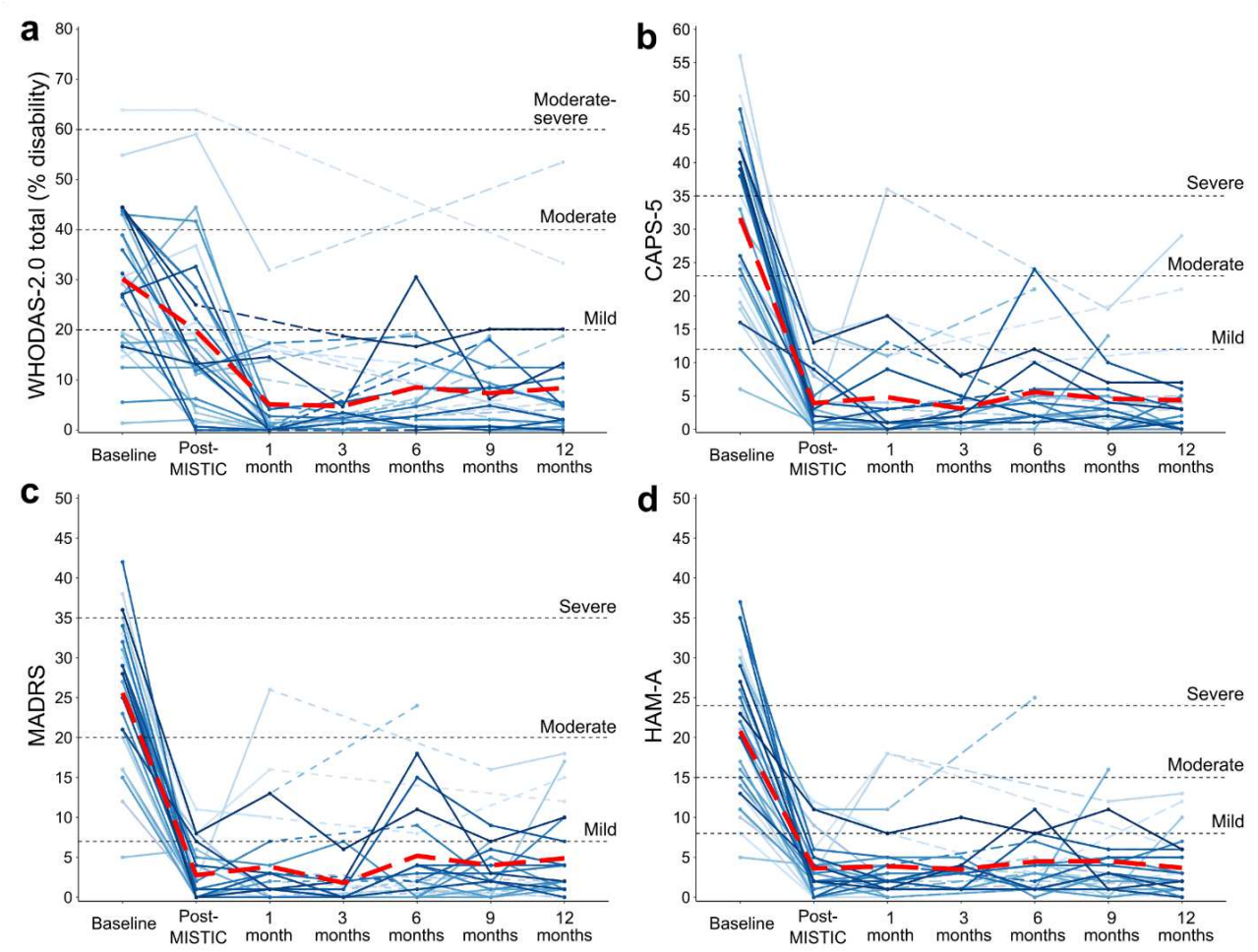


Figure 1. Individual score trajectories for (a) WHODAS-2.0 (percentage disability), (b) CAPS-5 (posttraumatic stress), (c) MADRS (depression), and (d) HAM-A (anxiety). Clinical interpretation thresholds were added for each measure. Dashed blue lines reflect missing data at some time points in between follow-up assessments. The dashed red line represents the mean score at each time point. *Abbreviations:* CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; HAM-A = Hamilton Anxiety Rating Scale; MADRS = Montgomery–Åsberg Depression Rating Scale; WHODAS-2.0 = WHO Disability Assessment Schedule, 2nd Edition.

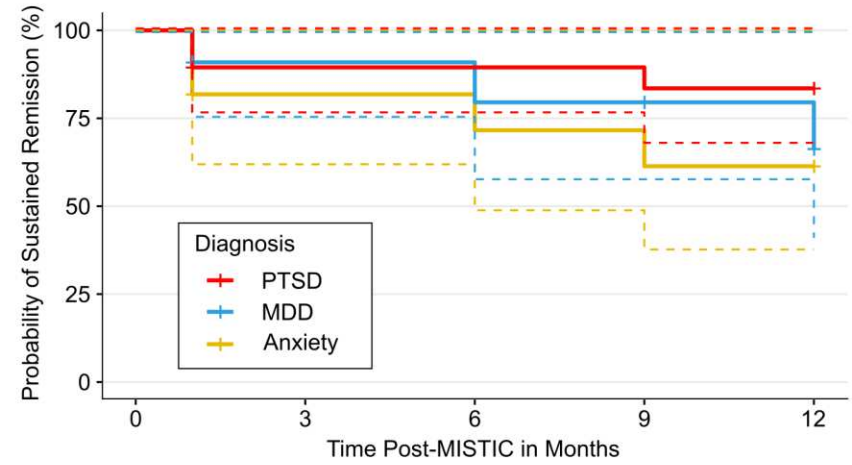
Table 1. Linear mixed-effects model results showing long-term improvements in functional disability, PTSD, depression, and anxiety after a single treatment with Magnesium-Ibogaine: the Stanford Traumatic Injury to the CNS (MISTIC).

		WHODAS-2.0	CAPS-5	MADRS	HAM-A
Baseline	N	30	30	30	30
	M (SD)	30.2 (14.7)	31.7 (12.5)	25.6 (8.7)	20.8 (8.5)
Immediate-Post	N	30	30	30	30
	M (SD)	19.9 (16.3)	3.9 (4.8)	2.8 (3.3)	3.6 (3.4)
	F	29.19	319.97	358.30	230.62
	p_{FDR}	<.001	<.001	<.001	<.001
	d	0.74	2.30	2.65	2.06
1 Month	N	26	30	30	30
	M (SD)	5.1 (8.1)	4.8 (7.9)	3.8 (6.0)	3.9 (4.6)
	F	123.02	297.67	328.97	230.62
	p_{FDR}	<.001	<.001	<.001	<.001
	d	2.20	2.54	2.80	2.13
3 Months	N	8	10	10	10
	M (SD)	4.8 (5.9)	3.1 (2.4)	1.8 (2.6)	3.5 (2.7)
	F	55.54	173.46	201.51	121.40
	p_{FDR}	<.001	<.001	<.001	<.001
	d	2.26	3.46	4.45	2.58
6 Months	N	17	21	21	21
	M (SD)	8.5 (8.8)	5.6 (6.5)	5.2 (6.7)	4.5 (5.5)
	F	69.97	221.28	229.74	166.54
	p_{FDR}	<.001	<.001	<.001	<.001
	d	2.05	2.17	2.83	2.10
9 Months	N	15	17	17	17
	M (SD)	7.3 (7.2)	4.6 (5.2)	4 (4.1)	4.5 (4.5)
	F	69.49	234.91	250.64	160.88
	p_{FDR}	<.001	<.001	<.001	<.001
	d	1.81	2.94	4.08	2.06
12 Months	N	25	25	25	25
	M (SD)	8.4 (12.3)	4.4 (6.9)	4.9 (5.5)	3.7 (3.6)
	F	90.68	284.83	265.90	203.34
	p_{FDR}	<.001	<.001	<.001	<.001
	d	2.27	2.72	3.35	2.18

Results are presented as raw mean (M) and standard deviation (SD). Degrees of freedom: (1, 129) for WHODAS; (1, 139) for CAPS-5, MADRS, and HAM-A. Cohen's d reflects the effect size for the contrast between each post-treatment time point and baseline.

Abbreviations: CAPS-5 = Clinician Administered PTSD Scale for DSM-5; HAM-A = Hamilton Anxiety Rating Scale; MADRS = Montgomery–Åsberg Depression Rating Scale; WHODAS-2.0 = World Health Organization Disability Assessment Schedule, 2nd Edition

Secondary Kaplan-Meier survival analyses were completed for participants who achieved remission from PTSD (N=19 of 23), depression (N=11 of 15), or anxiety (N=11 of 14) immediately post-MISTIC (Figure 2, Table S4). Mean times to relapse were 10.7 (SE=0.8), 10.3 (SE=1.1), and 9.1 (SE=1.3) months for PTSD, depression, and anxiety, respectively, with no significant differences in time to relapse by diagnosis (χ^2= 1.7, df= 2, p= 0.43). KM-estimated probabilities of maintained remission 12 months following acute remission to MISTIC were 84%, 66%, and 61%, for PTSD, depression, and anxiety, respectively. See Supplement for Kaplan-Meier estimates of the duration of response for PTSD, depression, and anxiety.



Number at Risk					
PTSD	19	15	15	15	14
MDD	11	8	8	7	6
Anxiety	11	8	8	7	6
Cumulative Number Censored					
PTSD	0	2	2	2	16
MDD	0	2	2	3	8
Anxiety	0	1	1	1	7

Figure 2. Kaplan-Meier curves of the duration of remission for post-traumatic stress disorder (PTSD; red), major depressive disorder (MDD; blue), and anxiety (yellow) diagnoses as a function of time (months) following MISTIC. Solid lines represent the overall survival estimate, hatched marks indicate censored participants, and dashed lines represent 95% confidence intervals. Number at risk and cumulative number censored tables provide accompanying information. Remission criteria for PTSD: CAPS-5 <12, MDD: MADRS <8, anxiety: HAM-A <8, and a loss of diagnosis.

Discussion

This prospective, long-term follow-up study found clinically meaningful reductions in disability, PTSD, depression, and anxiety symptom severity that persisted 12 months after a single session of MISTIC. Throughout the 12 months, of those who achieved remission immediately after MISTIC treatment, we observed a probability of sustained remission of over 80% for PTSD and over 60% for depression and anxiety. As this study was an open-label

observational study with a modest sample size, larger randomized controlled trials are needed to replicate these effects.

Considering that participants continued to suffer from substantial psychiatric and cognitive symptoms years after sustaining their TBIs, the durability of the clinical effects observed here is encouraging. Although we did not control for participants' specific engagement in activities and treatments or significant life events between the 1-month and 12-month follow-ups, we included participant-specific random intercepts in our models, which accounted to some extent for individual variability. Exploratory subgroup analyses further suggested that long-term symptom improvements after ibogaine treatment were evident regardless of whether participants pursued additional interventions (Table S1). Nevertheless, in addition to ibogaine, a variety of factors likely contributed to the durability of improvements in disability, posttraumatic stress, depression, and anxiety. Among such factors, participants sought treatment through psychotherapy or psychiatric medication, attended self-help seminars and workshops, used other psychedelics, and experienced significant life events. Future studies are needed to identify specific factors that may interact with MISTIC durability.

Of note, most participants endorsed some psychedelic use between 1 and 12 months after the initial retreat (Table S1). While naturalistic psychedelic use for some substances (e.g., LSD) may be associated with increased odds of substance abuse, findings are inconsistent (21), other substances may be associated with lower odds (e.g., peyote) (22), and psychedelic drugs are of the lowest likelihood of dependence or abuse (23). Nevertheless, clinical trials or treatment-focused retreat settings are not equivalent to naturalistic or recreational use, and further evidence is needed to evaluate the specific risks for such settings.

Given the open-label design of this initial study, expectancy effects may have contributed to the observed clinical outcomes. However, we previously found that symptom improvements were accompanied by improvements in objective neuropsychological test scores that are less sensitive to placebo effects (12,24). Additionally, placebo responses tend to be less durable than true drug responses (25,26). In prior work, we also observed neural correlates of ibogaine-related symptom improvements that differed from those associated with placebo responses (27). As such, it is unlikely that the large, persisting symptom improvements observed in this study are caused by expectancy effects alone.

Growing evidence indicates that psychedelic and psychedelic-assisted treatments may be effective for a variety of psychiatric conditions (28). Existing evidence suggests that psychedelic and psychedelic-assisted treatment effects may also persist long-term, but only a few studies have prospectively explored long-term outcomes beyond 6 months (29–31). It is imperative for the field to investigate the long-term durability of such treatments. Although regulatory restrictions for ibogaine currently limit access and impose a high travel and financial burden, the present findings suggest that ibogaine treatment may confer lasting therapeutic benefits for veterans with TBI.

Data availability. Owing to the sensitivity of psychiatric patient data, our IRB requires individualized review before data sharing. We have produced anonymized data related to the present findings for sharing with all scientists with research and data safeguarding plans that comport with Stanford University guidelines. Please contact C. Rolle at crolle@stanford.edu with data-sharing requests.

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Conflicts of interest. N.R. Williams is a named inventor on Stanford-owned intellectual property relating to magnesium-ibogaine; he has served on scientific advisory boards for Otsuka, NeuraWell, Magnus Medical, Soneira, and Nooma as a paid advisor, and he has equity/stock options in NeuraWell, Soneira, and Nooma. I.H. Kratter is a named inventor on Stanford-owned intellectual property relating to magnesium-ibogaine; he currently receives a salary from Soneira and consulting fees from Neuralink and Salma Health, and he has equity/stock options in Soneira and Salma Health. A.D. Geoly and J.P. Coetzee are named inventors on Stanford-owned intellectual property relating to magnesium-ibogaine. The remaining authors declare no competing interests.

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