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Psychedelic Therapy: A Primer for Primary Care Clinicians—*N,N*-Dimethyltryptamine and Ayahuasca

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Background: *N,N*-dimethyltryptamine (DMT) is a naturally occurring serotonergic psychedelic found in natural plants around the globe. As the main psychoactive component in ayahuasca, which also contains monoamine oxidase inhibitors, DMT has been consumed as plant-based brew by indigenous peoples for centuries. Further research is required to delineate the therapeutic utility of DMT.

Areas of Uncertainty: Although previous research has shown that DMT is synthesized endogenously, it may not be produced at physiologically relevant concentrations. Additionally, the phenomenological similarities between the DMT-induced state and near-death experiences led to the popular hypothesis that endogenous DMT is released during the dying process. However, this hypothesis continues to be debated. Generally, DMT and ayahuasca seem to be physiologically and psychiatrically safe, although ayahuasca is known to cause transient vomiting.

Therapeutic Advances: A double-blind, randomized controlled trial showed that, within 1 week, ayahuasca causes remission in 36% of patients with treatment-resistant depression. According to topline results from a recent phase IIa trial, 57% of patients with major depressive disorder experienced remission 12 weeks after receiving a single intravenous dose of DMT.

Limitations: There has only been a single published double-blind randomized controlled trial on ayahuasca and 2 on DMT. All clinical trials have had small sample sizes (≤34 participants). DMT requires further research to understand its therapeutic and clinical potential as a psychedelic.

Conclusions: Preliminary evidence indicates that ayahuasca and DMT may be more effective than existing antidepressants for treating major depressive disorder and treatment-resistant depression.

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CLINICAL CASE

A 44-year-old man has been referred to psychiatry by his primary care physician for further options in the management of his recurrent depression. He had not responded to treatment in the primary care setting. He describes 3 previous episodes of major depression with pervasive sadness, difficulties sleeping, decreased appetite and subsequent weight loss, and loss of interest in "hanging out with his family and friends." He describes wanting to "just disappear into thin air." He clarifies this is true only if his family or friends would be spared ("I would never want to do that to them") and denies any active suicidality. He has tried multiple antidepressants with no benefit, including citalopram titrated to 40 mg/d for 10 weeks and sertraline titrated to 100 mg/d for 12 weeks. His vital signs are unremarkable, and his physical examination is noncontributory. On mental status examination, he was calm, cooperative, and engaged with the interviewer. No psychomotor issues were noted, and eye contact was appropriate. Speech was at a normal rate but low in volume. He described his mood as "obviously sad." Affect seemed to be fatigued and intermittently dysphoric. His thought process was linear, goal-directed, and future-oriented. He denied active suicidal ideation, and he denied any homicidal ideation or hallucinations. No delusions were elicited. He was cognitively intact and well oriented, with a Mini Mental State Examination of 30/30. His insight was good, as he recognized his depressive symptoms, in keeping with his Patient Health Questionnaire-9 (PHQ-9) score of 22. His judgment was good, as he requested help for treatment options to consider.

BACKGROUND

N,N-dimethyltryptamine (DMT) is a serotonergic psychedelic found in plants around the globe. It is the primary psychoactive component in ayahuasca, a South American brew that typically consists of 2 plants: *Psychotria viridis*, which contains DMT, and *Banisteriopsis caapi*, which consists of harmala alkaloids that make the DMT orally ingestible.[1] Ayahuasca has been consumed by indigenous peoples for centuries in traditional and religious ceremonies.[2,3] In the context of Western society, however, DMT was first synthesized in 1931 by Canadian chemist Richard Manske.[4] In 1946, Brazilian microbiologist Oswaldo Gonçalves de Lima documented DMT's natural occurrence in plants.[5] In 1956, Hungarian chemist and psychiatrist Stephen Szára administered DMT intramuscularly to himself.[6] He was emboldened by the discovery of DMT in a snuff used in South American religious ceremonies. This consequently helped to establish the study of DMT in modern Western science.[7]

Although this review will primarily focus on *N,N*-DMT, it is worth calling attention to its structural analog 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT). It is secreted as a venom by the Sonoran Desert toad (*Bufo alvarius*), and it also occurs naturally in the seeds, bark, and leaves of some plants in the Amazonian rainforest.[8] As we shall review in the "Therapeutic Advances" section, preliminary evidence suggests that 5-MeO-DMT may be effective for treating depression.

Chemistry and Mechanism of Action

Like the other classical psychedelic psilocybin, DMT is a tryptamine. In DMT, the 2 hydrogen atoms on the ethylamine side chain of tryptamine are substituted with 2 methyl groups, hence its name dimethyltryptamine.[9]

When administered orally, DMT is inactivated by monoamine oxidase (MAO) through first-pass metabolism, which is facilitated by the human cytochrome P450 isozymes 2D6 and 2C19.[10] Thus, oral DMT must be coadministered with a MAO inhibitor to allow enough of the compound to reach the CNS in a bioavailable form.[11] In ayahuasca, DMT is consumed together with naturally plant-occurring harmala alkaloids that inhibit MAO. Intravenous or smoked DMT is very short-acting, with an elimination half-life of 9–12 minutes, because of its rapid metabolism through oxidase deamination into the primary metabolite indole-3-acetic acid.[10–14] Up to 50% of DMT is recovered as indole-3-acetic acid, whereas less than 1% of DMT is excreted unchanged in human urine.[15,16]

As with other classical psychedelics, the hallucinogenic effect of DMT is mainly achieved by stimulating the 5-HT_{2A} receptor.[17,18] However, researchers have identified other targets of DMT as well, including various 5-HT receptors, the sigma-1 receptor, and the trace amine-associated receptor.[19–21] The detection of DMT in the blood and urine of normal human subjects without being sourced from diet or gut bacteria implicates an endogenous production of DMT.[22–24] However, the specific role of DMT in human physiology or pathology has yet to be determined.

DMT can be ingested, inhaled, insufflated, injected intravenously, or inflamed. Depending on the dose and route of administration, subjective effects of DMT may vary. These include changes in auditory, visual, and time perception, emotional experiences, and memory impairment.[25,26] However, at higher doses, the DMT "trip" rapidly progresses into a deep, immersive state that has been compared with a near-death experience.[6,27,28] Users describe leaving their

body, "breaking through" to other hypervivid and intricate worlds, and interacting with other sentient, independent, and familiar beings.[28,29]

In addition, researchers have debated DMT's significance and relevance in mammalian physiology since the early 1960s.[30] Some researchers have proposed that DMT is a neurotransmitter, neuromodulator, and neurohormone[3,31] that serves a protective function in peripheral tissues by regulating systemic inflammation and stimulating neuroplasticity.[30,32,33] Proper measurement of endogenous DMT is difficult because of the small concentration of DMT in the human body,[23] DMT's rapid breakdown by MAO,[34] and the traditional use of whole-brain homogenate samples in experiments that may dilute local peaks in DMT concentration.[30,35] Other researchers believe that DMT is neither produced nor accumulated at physiologically relevant concentrations.[36] Additionally, there is conflicting evidence as to whether elevated endogenous DMT levels are implicated in psychotic disorders.[37] Ultimately, more research is needed to investigate the endogenous role of DMT.

Evidence from a recent double-blind, placebo-controlled randomized controlled trial (RCT) on ayahuasca[38] indicates that the drug blunts the awakening salivary cortisol response, both in patients with treatment-resistant depression (TRD) and in healthy controls, although this effect only lasts for 48 hours after the treatment.[39] Ayahuasca also elevates brain-derived neurotrophic factor, which correlated negatively with depression symptoms.[40] This finding aligns with previous literature that has firmly established the role of brain-derived neurotrophic factor in mediating depression by downregulating neural plasticity.[41] Finally, ayahuasca also decreases a biomarker of neural inflammation, C-reactive protein; this effect correlates with reductions in depression symptoms.[42] This result is consistent with rat studies that observed declines in other inflammatory cytokines, namely tumor necrosis factor-α, interleukin (IL)-1β, and IL-6, and increases in anti-inflammatory biomarker IL-10.[43] Taken together, these studies suggest an abundance of mechanisms by which ayahuasca may exert its antidepressant effects.

AREAS OF UNCERTAINTY

Safety

Historically, since the 1950s, one of the most prominent concerns regarding the use of hallucinogens was the potential of inducing prolonged psychotic reactions or disorders.[44–49] However, the incidence of such cases in controlled clinical and experimental settings was reported as rare in both healthy volunteers and psychiatric patients.[44–49] In the case of DMT, the existence of global religious societies revolving around the ritualistic consumption of ayahuasca affords a unique opportunity to study the impact of this drug on mental health. One such society, the União de Vegetal, found only 29 incidences of psychosis among 1.56 million servings of ayahuasca over a 13-year period.[50] Adolescents consuming ayahuasca in a religious context have lower anxiety levels, as measured with the Beck Anxiety Inventory and the State-Trait Anxiety Inventory, than age-, sex-, and education-matched controls; however, these comparisons failed to reach statistical significance.[51] Chronic users of ayahuasca in religious settings tend not to exhibit any psychiatric symptoms, and some of them self-report that they achieved remission from the past psychiatric disorders through their participation in ritualistic use.[52,53] However, these observational studies were not controlled. In a recent review of 6 case reports of psychotic episodes after either ayahuasca or DMT use, 5 were abusing other drugs, had a family history of schizophrenia or mania, or were personally diagnosed with mental illness in the past.[54]

In controlled therapeutic and clinical settings where participants are meticulously screened for risk factors, both DMT and ayahuasca seem to be psychologically and physiologically safe, and they are not considered drugs of dependence.[38,55,56] In the only RCT on ayahuasca to date, ayahuasca did not induce any significant increases in manic symptoms, as measured by the Young Mania Rating Scale, nor did it have a significant effect on responses to the Brief Psychiatric Rating Scale, which captures symptoms of psychosis, or the Clinician-Administered Dissociative States Scale.[38] Another open-label trial of ayahuasca did not report any adverse effects other than vomiting.[56]

Indeed, vomiting is the most common adverse effect that is unique to ayahuasca. In total, 47%–57% of participants vomited in clinical trials of ayahuasca for depression.[38,56] The recent Global Ayahuasca Survey of 10,836 ayahuasca users reported that 62% of respondents vomited at least once during past sessions.[57] The MAO inhibitors in ayahuasca cause high levels of unmetabolized serotonin to accumulate in the gut.[58] Consequently, an excess concentration of serotonin may bind to vagal sensory neurons in the gut, which overstimulates the vagus nerve and triggers vomiting.[59] Neurobiological studies of ayahuasca have enrolled experienced, rather than naive, users of ayahuasca to mitigate the risk of vomiting.[60] However, this strategy is, of course, not viable for clinical trials on ayahuasca, where many of the patients who stand to benefit the most are those who have not taken ayahuasca before. It is also worth noting that vomiting is not considered an "adverse effect" in ritualistic use of

ayahuasca but rather an essential component of the emotional catharsis that ayahuasca engenders; the psychological release of toxic thoughts and feelings entails a physical release of toxins.[61]

The excess accumulation of serotonin arising from MAO inhibition may also induce serotonin syndrome, a condition characterized by shivering and muscle rigidity that can, in rare instances, cause death if untreated.[62,63] No instances of serotonin syndrome have been reported in clinical trials of ayahuasca.[38,56] However, the use of MAOIs together with selective serotonin reuptake inhibitors or serotonin and norepinephrine reuptake inhibitors (SNRIs) is considered to be the most dangerous combination of drugs for triggering serotonin syndrome.[62] Therefore, people who are using selective serotonin reuptake inhibitors or SNRIs for depression may be advised to withdraw from their medication before taking ayahuasca.[64]

Because MAO inhibitors are part of ayahuasca but not DMT, DMT on its own does not typically cause vomiting; instead, more common adverse effects are headache and anxiety, which are usually transient.[65] DMT may also induce cardiac stress. An intravenously administered 0.4 mg/kg dose of DMT raises heart rate by 26 beats per minute, systolic pressure by 35 mm Hg, and diastolic pressure by 30 mm Hg,[66] although apparently these effects are less hazardous than those of other popular psychoactive substances.[63] A recent phase IIa trial of intravenous DMT did not report any serious adverse events.[67] Side effects were generally mild; the most common ones were catheter site reactions (41%), sleep disorder (16%), and headache (13%).

The Putative Role of DMT in Near-Death Experiences

The DMT experience has been specifically noted to include reflections on death, dying, and the afterlife.[68–70] Ayahuasca directly translates to "the vine of the dead" or "vine of the soul" in the traditional Quechua language.[71] Furthermore, users of DMT experience a state of consciousness that has striking similarities to near-death experiences,[28,72] giving rise to the popular hypothesis that endogenous DMT may be released in large concentrations during the dying process.[70] Endogenously, the pineal gland is proposed to excrete large quantities of DMT during extremely stressful life episodes, notably in the events of birth and death, in ways that may affect the "lingering consciousness" of the human mind.[70] However, this hypothesis has been refuted, with some researchers arguing that the minute concentrations of DMT in the mammalian brain are not sufficient to produce psychoactive effects.[36] Although a recent experiment intriguingly demonstrated a slight increase in DMT in the visual cortices of rats as they were undergoing cardiac arrest,[24] critics felt that the study did not sufficiently control for the "brainstorm" of neurotransmitters that are released during death, including serotonin, which binds to the 5-HT_{2A} receptor with much higher affinity than DMT.[36,73,74]

THERAPEUTIC ADVANCES

In clinical research over the last decade, ayahuasca and DMT have primarily been investigated as treatments for depression. There are at least 2 studies on ayahuasca for major depressive disorder (MDD), and 1 long-term follow-up and 1 secondary analysis; one on ayahuasca for TRD and one secondary analysis; and 1 on DMT for TRD. The first clinical ayahuasca study, an open-label trial, reported that ayahuasca significantly reduced ratings of depression symptoms by 82% on the Montgomery-Åsberg Depression Rating Scale (MADRS) and 72% on the Hamilton Rating Scale for Depression (HAM-D) 1 week after administration, in a group of just 6 participants.[75] Although the study did not explicitly report remission rates, the mean HAM-D and MADRS scores seem to meet the criteria for remission (HAM-D $\leq$7, MADRS $\leq$9). In an apparent extension of this study, which had a larger sample size of 17 participants, depression symptoms dropped significantly, by 61% on the HAM-D scale 3 weeks after the treatment. The mean HAM-D score (7.56) at this timepoint was just above the threshold for remission.[56] However, in a 5-year follow-up, the mean HAM-D score decreased even further to 6.75, which is below the threshold for remission. It is worth noting that the authors were unable to contact about half the participants in the initial sample.[76] A secondary analysis of the initial study demonstrated that ayahuasca significantly reduced suicidality by 86%, 3 weeks after the treatment, as assessed by the suicidal ideation subscale of the MADRS.[77] Finally, in a recent observational study of clinically depressed participants who attended an ayahuasca ceremony, 13 of 19 (68%) were in remission (Beck Depression Inventory score $<$13) after 1 month.[78]

To our knowledge, there is only placebo-controlled, double-blind RCT on ayahuasca for depression, which enrolled 29 participants with TRD.[38] The study reported a remission rate of 36%, 7 days after the treatment, although this was insignificant. However, reductions in depression symptoms, as measured by the MADRS scale, were highly significant after 7 days; mean MADRS scores were 57% lower in the ayahuasca group than in the placebo group. A secondary analysis revealed that ayahuasca caused an insignificant 66% reduction in symptoms of suicidality, which were

Table 1. Contemporary (21st-century) clinical trials on *N,N*-DMT, 5-MeO-DMT, and ayahuasca.

Study	Type	Dose	Sample	Findings
56,75–77	Open-label	2.2 mL/kg ayahuasca	17 patients with MDD	Mean HAM-D scores dropped significantly by 61% and suicidal ideation declined significantly by 86%, 3 weeks after treatment; mean HAM-D score decreased even further in 5-year follow-up
38,79	Double-blind, placebo-controlled RCT	Ayahuasca with 0.36 mg/kg *N,N*-DMT	29 patients with TRD	Mean MADRS scores significantly declined by 57%, 7 days after treatment; remission rate of 36% at same timepoint was insignificant; suicidal ideation reduced insignificantly by 66%
65	Open-label (phase I)	0.1 mg/kg IV DMT +0.3 mg/kg IV DMT 2 d later	7 patients with MDD and 3 healthy controls	Mean HAMD-17 scores decreased significantly by 15% at 1d
80–82	Double-blind, placebo-controlled RCT (phase IIa; top-line results)	21.5 mg IV DMT	34 patients with MDD	Mean change in MADRS scores was significantly greater in the DMT group than placebo group (difference: −10.8 points), 7 days after treatment; remission rate was 57% 12 wk after
83,84	Open-label, dose-escalation (phase IIa; preprint)	15 mg vaporized DMT + 60 mg vaporized DMT in the same day	6 patients with TRD	Mean MADRS scores decreased significantly by 17 points 1 mo after treatment; remission rate was 50% at 1 mo
85	Open-label (phase I and II)	Phase I: fixed doses of 12, 18 mg 5-MeO-DMT; phase II: individualized dosing regimen of up to 3 increasing doses (6, 12, and 18 mg)	Phase I: 8 TRD participants; phase II: 8 TRD participants	Phase I: 50% remission rate (MADRS scores) in 12 mg group; 50% remission rate in 18 mg group, 7 days after treatment Phase II: 87.5% remission rate, 7 days after treatment Across phases, 6 out of 10 remissions were observed after 2 hours

Note that this does not include observational studies.
HAM-D (HAMD-17), Hamilton Depression Rating Scale (17-item); IV, intravenous; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; TRD, treatment-resistant depression.

measured with MADRS-SI. However, mean baseline MADRS-SI scores in the placebo group were already 58% lower than those of the ayahuasca group which likely confounded the results.[79]

There is only a single published study on DMT for depression, which was an open-label, phase I study that administered DMT intravenously to 7 patients with TRD and 3 healthy controls.[65] The primary aims of the study were to establish safety and tolerability in both groups, but the study also demonstrated that mean HAMD-17 scores significantly decreased by 15%, 1 day after the second dosing session. (The first

dosing session administered 0.1 mg/kg of DMT, and the second gave 0.3 mg/kg 2 days later.) However, the mean HAMD-17 score after the second dosing session (20.20) was far above the threshold for remission. There are several active trials on DMT that are registered on clinicaltrials.gov and 2 completed phase IIa trials that have yet to be published.[80,81] Top-line results from these 2 trials, which had a sample size of 34 patients with major depressive disorder, showed that 57% of participants experienced remission 12 weeks after receiving a single intravenous dose of DMT.[82] The decrease in MADRS scores was significantly greater in the DMT group than in the placebo group (difference: −10.8 points). Another phase IIa trial that is still recruiting participants[83] recently produced a preprint of preliminary results.[84] Using an open-label study design, it administered vaporized DMT (15 mg followed by 60 mg, in a single day) to 6 patients with TRD. One month after treatment, MADRS scores significantly decreased by 17 points, and half of participants were in remission.

Finally, in a recent phase II study, 7 of 8 patients with TRD experienced remission within 7 days of receiving 5-MeO-DMT, a structural analog of DMT.[85] Startlingly, most remissions were observed after 2 hours. Observational studies found that 5-MeO-DMT use in naturalistic settings reduced self-reported ratings of depression, anxiety, and stress; however, these studies were not controlled.[86–88]

Although the published open-label data on DMT did not indicate remission in any participants, its primary endpoint was measured only 1 day after the dosing session, which may have been too soon to capture the full antidepressant effects of DMT. The top-line results from the phase IIa trials, which were collected 12 weeks after the DMT treatment, are more promising; the remission rate is much higher than that of antidepressants, which is around 30%.[89] The remission rate of ayahuasca, according to the double-blind RCT on patients with TRD, is much lower at 36%. Nevertheless, this is higher than the remission rate of second-line (31%), third-line (14%), and fourth-line (13%) antidepressants, suggesting that ayahuasca is superior to alternative antidepressants for TRD.[90] Although the remission rate associated with 5-MeO-DMT is very promising, experiments with larger sample sizes need to be conducted to verify the results (Table 1).

CONCLUSION

The study of DMT has traversed multidisciplinary boundaries, revealing its intricate pharmacological mechanisms, profound impact on human consciousness, and benefits for treating depression. This review consolidates a spectrum of research, elucidating DMT's pharmacology, safety, therapeutic efficacy, and its role as an endogenous compound. DMT's agonism at the 5-HT_{2A} receptor mediates its psychoactive properties. Contemporary clinical research suggests that ayahuasca and DMT are not only physiologically and psychologically safe, but they may also be effective for treating depression. The profound and transformative experiences reported by individuals in controlled settings invite further investigation into harnessing DMT's psychoactive properties for therapeutic interventions.

However, the number of published double-blind RCTs is very low. There are zero on DMT and only 2 on ayahuasca, which had small sample sizes of 17 and 29 participants.[38,56] The role of DMT's endogenous production in brain function and consciousness warrants continued exploration as well.

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