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RESEARCH ARTICLE

The Antidepressant Effects of Vaporized *N,N*-Dimethyltryptamine: An Open-Label Pilot Trial in Treatment-Resistant Depression

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Abstract

Introduction: *N,N*-Dimethyltryptamine (DMT), a naturally occurring psychedelic tryptamine contained in the indigenous ayahuasca brew, has shown antidepressant effects. This open-label clinical trial investigates for the first time the efficacy of vaporized DMT in treatment-resistant depression (TRD).

Methods: Six TRD patients participated in an open-label, fixed-order, dose-escalation study, receiving a lower (15 mg) and then a higher (60 mg) dose of vaporized DMT in a single-day session. Depression severity was assessed using the Montgomery–Asberg depression rating scale (MADRS) and the Patient Health Questionnaire-9 (PHQ-9) up to one month post-dosing.

Results: Significant reductions in MADRS and PHQ-9 scores were noted from Day 1 to Month 1 (M1). The mean MADRS score variation from baseline to Day 7 (D7) was −22 points and −17 points at M1. PHQ-9 scores also showed significant decreases, mirroring the MADRS results. By D7, 83.33% of patients responded to treatment, with 66.67% achieving remission. At M1, 66.67% maintained response, and 50% maintained remission.

Discussion: The rapid onset and sustained antidepressant effects of vaporized DMT align with the paradigm of rapid-acting antidepressants to be used in the scope of interventional psychiatry. The noninvasive route and short-acting nature of DMT offer practical advantages, potentially enhancing accessibility to psychedelic treatments.

Clinical Trial Registration: Clinicaltrials.gov NCT06094907

Keywords: *N,N*-Dimethyltryptamine, DMT, psychedelic, depression, treatment-resistant depression

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Introduction

N,*N*-Dimethyltryptamine (DMT) is a naturally occurring psychedelic tryptamine, endogenous in small amounts in humans.[1] When administered parenterally it induces profound changes in consciousness, including altered visual and auditory perceptions, frequently accompanied by deep emotional meaning, insights, significant shifts in thought processes, and mystical experiences, all condensed into an intensely powerful yet brief psychedelic experience.[2,3] Despite its potent psychedelic properties, the function and regulation of endogenous DMT within the human body is still a mystery.[1] Although DMT is orally inactive due to the presence of monoamine oxidase (MAO) in the gut, South American Indigenous populations have long harnessed the psychoactive properties of DMT through ayahuasca. This brew ingeniously incorporates MAO inhibitors to prevent DMT's rapid deamination by MAO, thus enabling its psychotropic effects. In this case, the effects last a few hours, commonly including nausea and vomiting, besides the psychedelic effects.[4]

Recent clinical evidence has suggested the therapeutic effects of ayahuasca, particularly in the context of mood disorders.[4,5] The results from our Phase 2a and Phase 2b clinical trials with ayahuasca in treatment-resistant depression (TRD) have been remarkable, suggesting rapid and sustained antidepressant effects in individuals with TRD,[6–8] a condition notoriously challenging to manage.

Following a comprehensive Phase 1 dose-escalation study, vaporized DMT proved safe and well tolerated among healthy participants within the dosage range explored.[9] Encouraged by these findings, we have embarked on the first open-label clinical trial to investigate the efficacy of vaporized DMT in treatment-resistant depression. By exploring this alternative route of administration, we aim to untangle the intricate relationship between DMT's rapid psychedelic effects and its impact on depressive symptoms, contributing to the expanding horizon of psychedelic-assisted therapies.

Methods

Study design

This is an open-label, fixed-order, dose-escalation clinical trial in patients with TRD. The study was approved by the Ethics Committee of the University Hospital Onofre Lopes (#45532421.0.0000.5292), registered at clinicaltrials.gov (NCT06094907).

Participants

Candidates were recruited by physician referrals and were screened by a trained psychiatrist using the Mini International Neuropsychiatric Interview (MINI 5.0.0, Brazilian version). A subsequent in-depth psychiatric evaluation, in line with DSM-5 criteria and averaging 90 min, meticulously verified each candidate's eligibility. In addition, all selections were thoroughly reviewed with a supervising psychiatrist to agree on each participant's suitability for the study. Inclusion criteria: patients in a moderate/severe depressive episode according to MADRS (MADRS ≥ 20) during at least four weeks and who have previously used at least two antidepressant medications but without successful results (treatment-resistant, TRD). Participants were excluded if they had a psychotic disorder, unstable medical conditions, a history of (hypo)mania, current/recent drug dependency, or pregnancy. For exclusion criteria details, see Supplemental Methods in Supplementary Data S1. Patients signed an informed consent before participation, maintained their pharmacological treatment, and abstained from psychedelics 14 days before dosing.

Substance

DMT-free base[1] was vaporized using a device used for medical purposes in similar studies[9,10] (for details, see Supplemental Methods in Supplementary Data S1).

Procedures and measurements

The study was conducted in the university hospital. After the screening, patients underwent psychological preparation. The preparation session was standardized, lasted 90 min, and was conducted in person by an experienced psychologist to establish rapport; inform about the DMT effects, safety, and support; provide strategies for difficult experiences; and answer specific questions about the study protocol. On dosing day (D0), they first received a lower DMT dose (15 mg), followed by a higher DMT dose (60 mg), 90 min after[2]. During the 15-min acute effects, patients remained lying down on a recliner with eyeshades and listened to music (see Supplemental Procedures in Supplementary Data S1).

Patients underwent an immediate psychological integration after the end of each dosing (first session: 30 min, second session: 60 min). The second integration session included drawing a mandala with crayons to express and elaborate the experience. Integrations were standardized and aimed to (1) provide psychological support, (2) facilitate the expression and interpretation of the experiences, and (3) integrate these experiences and everyday life. After the second integration, patients completed questionnaires about the intensity, valence, and altered consciousness[11] (ASC; see Supplemental Measurements in Supplementary Data S1). Two hours after the second dosing, patients were evaluated by a psychiatrist and discharged with a family member or friend. One (D1) and seven (D7) days after the session, patients participated in follow-up integration sessions.

At D0, D1, D7, day 14 (D14), and one month (M1), depressive symptoms were evaluated by psychiatrists using the Montgomery–Asberg depression rating scale (MADRS)[12] and self-reports on the Patient Health

[1]Purity by gas chromatography–mass spectrometry (GC-MS) analysis > 96%.
[2]The definition of these doses was based on our Phase I trial, which investigated 10 different doses across 5 schemes, ranging from 5 to 60mg[9].

Questionnaire-9 (PHQ-9).[13] Medical assessments to identify adverse events were conducted after each dosing session on D0, along with clinical and psychiatric evaluations. Additionally, physiological safety data were gathered both before the sessions (baseline) and afterward.

Outcomes

The primary outcome measure was the mean change in depression severity assessed by the MADRS scale, comparing baseline with seven days after the dosing session. Secondary outcomes included the mean change in MADRS scores from baseline to D1, D14, and M1 after the dosing session; the response rate, defined as the proportion of patients meeting a reduction of 50% or more in baseline MADRS scores, and remission rates (MADRS $\leqslant$10); the mean change in PHQ-9 scores from baseline to D1, D7, D14, and M1 after the dosing session; and changes in the ASC during the acute effects of DMT.

Statistical analyses

Depression scores (D0 to M1) were analyzed in repeated measures General Linear Models [GLM; within-subjects factor = time; significance level = 0.05 (two-tailed)]. Post hoc Dunnett's multiple comparison test was used to compare each time point with the baseline values and effect sizes calculated by Hedge's g. Analyses were performed with GraphPad Prism 7. The psychedelic experience measured by visual analogue scale (VAS) and ASC scores [means (±SD) of dosing 2] are shown descriptively.

Results

In this preliminary report, we included data from the first six patients who completed all assessments until M1, with no participant dropout (the CONSORT flow diagram is depicted in Supplementary Figure S1). Patients' sociodemographic, medication, and drug use are depicted in Table 1. Only one out of the six patients had previous experience with psychedelics (8 times in life, last time in 2022). For individual data, see Supplementary Table S1. No participant showed critical physiological changes (Supplementary Table S2). On the dosing day, ten types of single medical concepts were identified and classified into six-system organ classes according to MedDRA standardized international medical terminology (v. 25.1) (Reston, n.d.) for both sessions. All adverse events were mild; the most common were throat clearing (n = 6) and headache (n = 4), and no serious adverse event was found; for details, see Supplementary Table S3. Suicide ideation was assessed by the Beck Scale for Suicide Ideation, and no increase was observed throughout the study (Supplementary Table S4). Psychedelic experiences were subjectively intense (84.15 ± 28.47), positive (30.40 ± 19.02), and elicited mild effects in ASC total scores (35.17 ± 14.38).

Table 1. Demographics and Clinical Characteristics

Age, mean (SD), *y*	31.33 (13.25)
Female sex (%)	50.00
Estimated illness duration, mean (SD), *y*	7.92 (6.07)
Number of previous treatments, mean (SD)	3.50 (1.22)
Baseline MADRS, mean (SD)	32.50 (2.59)
Baseline PHQ-9, mean (SD)	18.50 (3.73)
Patients under antidepressant treatment (%)	66.67
Psychedelic use in lifetime, mean (SD)	1.33 (3.27)

MADRS, Montgomery–Asberg depression rating scale; PHQ-9, Patient Health Questionnaire-9; SD, Standard deviation; *y*, years.

Effects in each 5-ASC dimension are described in Supplementary Table S5.

For MADRS scores, there was a main effect of time [$F(4,20) = 10.41$, $p = 0.0001$, $\eta_p = 0.67$]. Pairwise comparisons revealed a significant reduction of depressive symptoms at D1 ($\mu = 8.17 \pm 6.85$; $p < 0.0001$; Hedge's g = 4.70), D7 ($\mu = 10.50 \pm 10.46$; $p = 0.0002$; Hedge's g = 2.89), D14 ($\mu = 10.5 \pm 8.96$; $p = 0.0002$; Hedge's g = 3.34), and M1 ($\mu = 15.5 \pm 13.07$; $p = 0.003$; Hedge's g = 1.80); Figure 1A). Figure 1B shows the proportion of patients who responded at D1: 5/6 (83.33%), at D7: 5/6 (83.33%), at D14: 5/6 (83.33%), and at M1: 4/6 (66,67%); and the remission rate at D1: 4/6 (66.67%), at D7: 4/6 (66.67%), at D14: 4/6 (66.67%), and at M1: 3/6 (50%). Individual % of change from baseline of MADRS scores at each time point are depicted in Supplementary Figure S2.

For PHQ-9 scores, we also observed a main effect of time [$F(4,20) = 6.27$, $p = 0.006$, $\eta_p = 0.68$]. Pairwise comparisons revealed decreases, compared with D0, at D1 ($\mu = 7.83 \pm 5.71$; $p = 0.0008$; Hedge's g = 2.21), D7 ($\mu = 8.67 \pm 7.31$; $p = 0.002$; Hedge's g = 1.69), D14 ($\mu = 9.33 \pm 5.89$; $p = 0.003$; Hedge's g = 1.86), and M1 ($\mu = 10.83 \pm 8.09$; $p = 0.014$; Hedge's g = 1.22); Supplementary Figure S3.

Discussion

This is the first clinical trial on the antidepressant effects of vaporized DMT in TRD. All patients showed improvement in their scores at different time points (D1, D7, D14, and M1) compared with the baseline. The rapid onset of antidepressant effects observed in our study, with significant reductions in MADRS and PHQ-9 scores as early as D1, aligns with the emerging paradigm of rapid-acting antidepressants.

No serious adverse events were observed during or after dosing. This is in line with what we observed in the Phase 1 study.[9] During both sessions involving DMT, there was a rapid yet temporary increase in blood pressure and heart rate. DMT caused an acute rise in peripheral oxygen saturation. Overall, the findings suggest that our intervention with DMT is safe and tolerable for patients with depression.

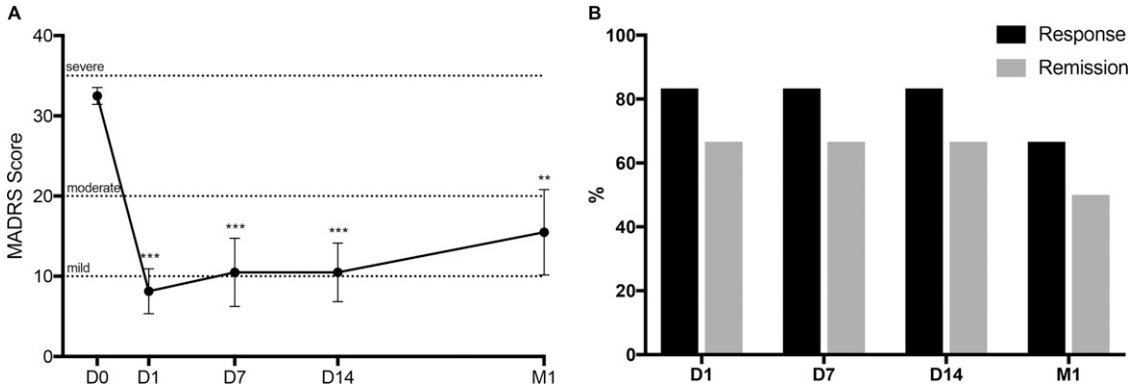

Fig. 1. **(A)** MADRS scores significantly decrease from one day, remaining significantly low until one month after the dosing session. **(B)** The bars indicate the proportion of patients meeting the response criteria (reduction ≥50% in baseline MADRS Score, in *black*) and the proportion of patients meeting the remission criteria (MADRS Score ⩽10, in *gray*). $^{**}p < 0.001$; $^{***}p < 0.0001$. MADRS, Montgomery–Asberg depression rating scale.

A recent exploratory study on the antidepressant effects of intravenous DMT in seven patients with Major Depressive Disorder reported a moderate effect size (Hedge's g = 0.75) with a mean reduction of 4.5 points in the Hamilton depression rating scale at D1.[14] In contrast, our study achieved a substantially higher effect size (Hedge's g = 4.70) in the MADRS score at D1, which was sustained for one month. Multiple factors may help to explain this difference, including the administration routes, dosages, patient profiles, a specialized therapeutic environment, and psychological support.

Another recent study investigated the safety and efficacy of vaporized 5-methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT) in 16 patients with TRD.[15] They found a mean MADRS reduction at D7 versus baseline of −24.4 points, whereas we found a mean reduction of −22 points (D7 vs. baseline). Both studies highlight the rapid antidepressant effects of short-acting psychedelic tryptamines using the same vaporizer device. However, our study differs in its use of DMT versus 5-MeO-DMT and a single ascending fixed-dose approach, as opposed to an individualized dosing regimen. The positive outcomes in both studies reinforce the viability of using vaporized psychedelics as a promising therapeutic approach.

Furthermore, our data suggest the use of a short-acting psychedelic, such as DMT, over longer-lasting oral psychedelics (e.g., psilocybin, ayahuasca) offers practical advantages in terms of cost and operationalization. The noninvasive inhalation route, contrasting to the intravenous methods, lowers the level of health care complexity required (secondary vs. tertiary or in-hospital care). Those aspects could be crucial in enhancing accessibility to psychedelic treatments and becoming suitable for public health systems, such as the Brazilian SUS (Unified Health System).

The open-label design and reduced number of patients in this study is a limitation, as it does not allow for the disentanglement of placebo effects from the results observed. Future directions include increasing the number of patients, assessing the need for repeated doses over time, and employing a more controlled experimental design (randomized and placebo-controlled). Another potential limitation is associated with administering the psychiatric scales (MADRS, PHQ-9, and BSI) at short intervals, such as one day after dosing. Decreases at this time point should be taken with caution. As we continue to understand the therapeutic potential of DMT, this preliminary study is poised to offer novel insights into the antidepressant capabilities of DMT, potentially transforming our understanding of its role in treating mood disorders.

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Authors' Contributions

M.F.C., I.W., N.G.C., D.B.A., and F.P.F. designed the study; E.A., D.B.A., and F.P.F. acquired the authorizations; S.R.B.S., J.V.C.M., and E.J.P. extracted and purified the substance; M.F.C. and F.P.F. selected the participants; M.F.C. led the session, administered the substance, and served as head of psychiatry for the study; H.B., R.B., and S.L. provided psychological support; D.M., E.T., and R.F.V. served as psychiatrists to medical

follow-up; R.A., R.K.A.M., and F.A. provided nursing support; M.F.C., H.B., R.B., S.L., D.M., E.T., R.F.V., R.A., R.K.A.M., and F.A. acquired the data; I.W., N.C.G., D.B.A., and F.P.F. provided research assistance; I.W. and F.P.F. analyzed the data; M.F.C., I.W., D.B.A., and F.P.F. wrote the article; and all authors reviewed the article and approved the final version.

Author Disclosure Statement

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Supplementary Material

Supplementary Data S1
Supplementary Figure S1
Supplementary Figure S2
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Supplementary Table S1
Supplementary Table S2
Supplementary Table S3
Supplementary Table S4
Supplementary Table S5

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