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Rapid and sustained antidepressant effects of vaporized *N,N*-dimethyltryptamine: a phase 2a clinical trial in treatment-resistant depression

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Depression affects over 185 million people worldwide, with approximately one-third classified as treatment-resistant depression (TRD). Current treatments, such as oral antidepressants, often take around 3 weeks to become effective, with no immediate anti-suicidal benefits. The field urgently needs innovative therapies that provide rapid relief. Psychedelics like psilocybin and ayahuasca have shown promising antidepressant effects; however, their long duration (several hours) makes them costly and impractical for public health systems. *N,N*-Dimethyltryptamine (DMT), an endogenous psychedelic also found in ayahuasca, offers a viable alternative with a short duration of action (10–20 min) and non-invasive inhalation administration. Unlike ayahuasca, which contains monoamine oxidase inhibitors, vaporized DMT acts quickly and poses fewer pharmacological interaction risks. This open-label trial evaluated inhaled DMT for TRD for the first time, within the framework of interventional psychiatry. Fourteen patients ($N_{\text{female}} = 6$) participated in a fixed-order, dose-escalation study (15 mg and 60 mg). The treatment was safe, well-tolerated, and produced manageable psychedelic effects with no serious adverse events. A subpopulation using antidepressants showed similar safety outcomes. Results showed rapid and sustained antidepressant effects, with an average reduction of 21.14 points on the Montgomery-Asberg Depression Rating Scale by day 7 ($p < 0.001$). The response rate was 85.71%, and the remission rate was 57.14% 7 days post-administration, lasting up to 3 months. Suicidal ideation significantly decreased, with no severe ideation the day after dosing. Vaporized DMT offers a non-invasive, time-efficient, and cost-effective alternative to other psychedelics and traditional antidepressants, supporting its role in interventional psychiatry and public health. Clinicaltrials.gov NCT06094907.

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INTRODUCTION

Major Depressive Disorder (MDD) is a prevalent mental health condition globally affecting over 185 million people [1]. Traditional antidepressants often take over 3 weeks to exert their effects [2], which leaves patients vulnerable to persistent depressive symptoms and an increased risk of suicide during this latency period [3]. Approximately one-third of patients with depression are classified as Treatment-resistant depression (TRD) [4], with only 50% responding to the first antidepressant, response rates dropping to 30% with a second treatment and just 10% for subsequent therapies [5]. The high prevalence and the limitations of current treatments underscore the urgent need for novel, effective, and scalable therapeutic approaches that can be integrated into public health systems [6, 7].

Serotonergic psychedelics such as psilocybin, ayahuasca, and *N,N*-dimethyltryptamine (DMT) have shown promising evidence of rapid antidepressant effects in patients with MDD [8–13]. Our research group has conducted clinical trials for TRD using ayahuasca [8, 14, 15], a DMT-containing brew traditionally used by Amerindians for medicinal and spiritual purposes for centuries [16, 17]. Evidence from our open-label and randomized, placebo-controlled trials indicate that ayahuasca can produce rapid antidepressant effects, with improvements starting one day after a single session and lasting at least seven days [8, 14, 15].

However, the long-lasting psychedelic effects of ayahuasca, psilocybin, mescaline, and lysergic acid diethylamide (LSD) typically last several hours [18–21], posing practical and economic

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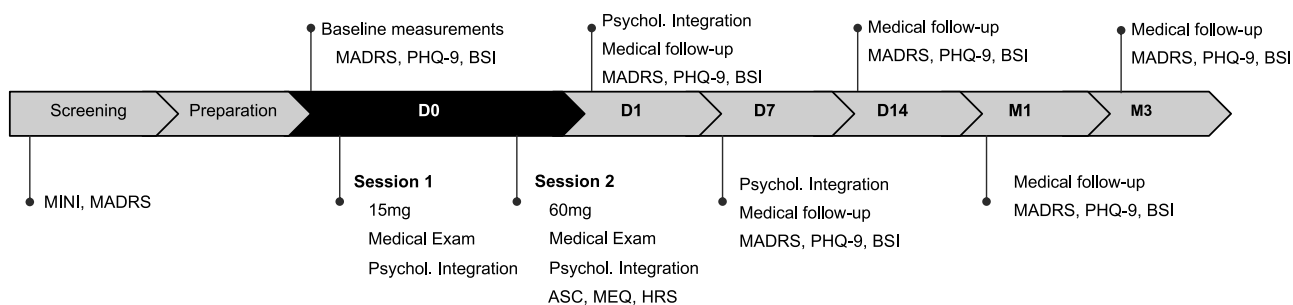


Fig. 1 The study procedures. After medical screening, the patients underwent a preparation. The dosing day (D0) comprised a first, lower DMT dose (15 mg) for safety check (session 1), followed by the second, higher dose (60 mg) (session 2). Questionnaires and physiological and biochemical measurements were gathered on D0. One (D1) and seven (D7) days after dosing, patients underwent a psychological integration. On D1, D7, fourteen days (D14), 1 month (M1), and 3 months (M3) after dosing, a medical follow-up was provided to ensure safety, collect clinical data, and verify for adverse events. MINI Mini International Neuropsychiatric Interview, MADRS Montgomery-Åsberg Depression Rating Scale, PHQ-9 Patient Health Questionnaire-9, BSI Beck Scale for Suicide Ideation, Psychol. psychological, ASC Altered States of Consciousness, MEQ Mystical Experiences Questionnaire, HRS Hallucinogen Rating Scale.

challenges for their widespread clinical use. This context highlights the need for rapid-acting and short-lasting alternatives, such as parenteral DMT [22, 23].

DMT, an indole alkaloid, occurs naturally across various species, including plants, fungi, animals, and humans [24]. The compound was first synthesized by Manske in 1931 and subsequently isolated from *Mimosa tenuiflora* roots by Gonçalves-Lima in 1946 [25]. Although its biosynthesis, metabolism, and biological roles remain partly elusive, DMT is understood to interact with multiple neuroreceptors, notably serotonin 2A, 2C, and 1A receptors, as well as sigma-1 and Trace Amine-Associated Receptors (TAAR) [24–26]. When ingested orally, DMT is rapidly metabolized by monoamine oxidase (MAO), rendering it inactive unless paired with an MAO inhibitor (MAOI), as seen in the traditional brew ayahuasca. This combination induces potent psychedelic effects but also increases the risk of serotonergic syndrome when used alongside conventional antidepressants, making oral administration less ideal for clinical settings. Hence, a parenteral route for DMT administration might offer a more controlled and safer application in therapeutic contexts.

The first explorations into the human effects of isolated DMT date back to the 1950s, with intramuscular administration [27], followed by intravenous studies in the 1990s [28, 29]. These investigations revealed that while DMT induces experiences similar to other psychedelics, such as visual and sensory alterations, its effects have a much quicker onset (2–5 min) and shorter duration (10–60 min) when administered intramuscularly or intravenously [27, 30]. Moreover, a recent study explored its potential antidepressant properties following intravenous administration [11].

However, a non-invasive route might be safer and would simplify the clinical use of DMT; therefore, we first conducted an open-label, single-ascending, fixed-order, dose-response study to assess the feasibility of inhaled DMT in healthy volunteers [31]. Our findings indicated that vaporized DMT mildly and transiently increased blood pressure and heart rate without serious adverse events (SAEs). The effects were dose-dependent, provoking an altered state of consciousness, vivid imagery, body distortions, changes in auditory perception, cognition, mood, arousal, and positive valence, lasting less than 20 min.

The present study aimed to investigate vaporized DMT's efficacy, safety, and tolerability in patients with TRD. We hypothesized that DMT would provide rapid and sustained antidepressant effects. This could offer a novel therapeutic approach that could be integrated into clinical practice, with significant advantages over traditional antidepressant treatments and better cost-effectiveness compared to other long-lasting psychedelics.

MATERIALS AND METHODS

Study design

This is a phase 2a clinical trial on patients with TRD using an open-label, single-ascending, fixed-order, dose-escalation design. The study was approved by the Ethics Committee of the University Hospital Onofre Lopes (HUOL) of the Federal University of Rio Grande do Norte (UFRN) (#45532421.0.0000.5292) and registered at clinicaltrials.gov (NCT06094907). It was conducted according to the safety guidelines for human psychedelic research [32], the principles of good clinical practice, and the declaration of Helsinki.

Participants

Participants were recruited through online advertisements, word-of-mouth, and physician referrals via clinical groups, with online platforms primarily targeting younger individuals through university channels and the social media networks of our research group. The sample size was estimated based on previous studies investigating the antidepressant effects of DMT and 5-Methoxy-*N,N*-Dimethyltryptamine (5-MeO-DMT) [11, 33]. Eligible participants were adults aged 18–60 years who met the criteria for unipolar TRD, as diagnosed by a psychiatrist evaluation supported by the Mini International Neuropsychiatric Interview (MINI 5.0.0, Brazilian version) [34]. They had to be experiencing a current moderate to severe depressive episode, indicated by a Montgomery-Åsberg Depression Rating Scale (MADRS) score ≥ 20 for at least 4 weeks [35] and had failed to achieve remission with at least two different antidepressant medications during their current episode. While participants referred by healthcare providers had detailed histories confirming TRD criteria, the adequacy of dosage and duration for self-referred individuals was based on self-reported data, which may lack precision.

Participants also were required to have no unstable clinical conditions and no history or current symptoms of bipolar or psychotic disorders. All patients signed informed consent before participation. The complete eligibility criteria, including detailed inclusion and exclusion criteria, are provided in the Supplementary Materials and Methods.

Substance

DMT freebase was isolated and purified from *M. tenuiflora* root barks (purity > 96% by gas chromatography-mass spectrometry analysis). The DMT was dissolved in 99% ethanol and distributed on a metallic mesh for vaporization in a medical-grade vaporizer (Volcano® “Medic 2”, Storz & Bickel GmbH & Co, Tübingen, Germany). The DMT isolation and administration followed the procedures of our previous phase 1 [31] (see Supplementary Materials and Methods).

Procedures

The study was conducted in the university hospital's Clinical Psychedelic Research Unit. The study room was furnished in a modern living room style in warm colors with paintings, dimmed lighting, smoothly changing LED lights, and medical devices. The complete protocol is depicted in Fig. 1.

After the screening, 8 days before dosing (D-8), the patients filled in several online questionnaires, which will be reported elsewhere. The day afterward (D-7), a preparation was conducted in person by an experienced psychologist to inform about the DMT effects, establish rapport, realistic and positive expectations regarding safety and limits, and provide strategies for challenging experiences.

On the dosing day (D0), patients underwent two sessions. The first session comprised a lower DMT dose (15 mg) for safety checks, including critical physiological measurements and medical examination. This approach minimizes the risk of adverse events during the more intense psychedelic experience induced by the second dose. Additionally, the lower dose allows participants to acclimate to the study environment and inhalation procedure, reducing situational anxiety and enhancing comfort for the subsequent session. Participants were allowed to proceed to the second session if they wished and showed no critical changes in physiological measurements during the first session. The second session, 90 min after the first dose, comprised a higher DMT dose (60 mg). Throughout the sessions, at least one experienced clinical professional (psychiatrist, psychologist, nurse) remained in the room with the patient.

During the acute effects (+0 min to +22 min), the psychiatrist and psychologist ensured the patient's safety and provided support when needed. The patients remained lying on a recliner using eyeshades and, for the first 15 min, listening to music (see Supplementary Materials and Methods), followed by 7 min in silence.

At the end of acute effects, adverse reactions were examined by the psychiatrist. Afterward, patients underwent an integration to report their experience, led by the psychologist and accompanied by the psychiatrist (first session: 30 min, second session: 60 min). The second session's integration included drawing a mandala with crayons to express and elaborate the experience [36]. Afterward, the subjective experience was evaluated by self-report questionnaires.

In both sessions, physiological measurements were assessed at baseline (+0 min), during the acute effects (+2 to +22 min in 2-min intervals), and sub-acutely (+30 min); session 2 comprised an additional measurement (+120 min). Blood samples were taken before the first session (-20 min) and after the second session (+120 min). Two hours after the second session, the psychiatrist ensured that the patients were physically and psychologically stable before discharging them under the care of a family member or friend.

One (D1) and 7 days (D7) after dosing, preceding the MADRS collection as the primary outcome, psychological support was conducted online with the psychologist to integrate the psychedelic experience into the patient's life. These sessions aimed to foster meaning-making, address emotional or cognitive challenges from the acute phase, and promote insights to sustain therapeutic benefits [37]. At D0, D1, D7, 14 days (D14), 1 month (M1), and 3 months (M3) after dosing, medical, psychiatric measurements, and other questionnaires were applied online, part of which will be reported elsewhere. For Measurements, see Supplementary Materials and Methods.

Outcomes

The primary outcome was the mean change in depression severity assessed by the MADRS scale, comparing the baseline with D7. Secondary outcomes included the mean MADRS change from D0 to D1, D14, M1, and M3, the response rate, defined as the proportion of patients meeting a reduction of 50% or more in baseline MADRS scores, and remission rates (MADRS ≤ 10), the mean change in MADRS-SI, PHQ-9 and BSI from D0 to D1, D7, D14, M1 and M3, and changes in physiological measurements, biochemical markers, and psychedelic scales during the acute DMT effects.

Statistical analysis

The psychiatric scale scores (D0, D1, D7, D14, M1, M3) and physiological measurements for session 2 (+0, +2 to +22, +30, +120 min), were analyzed using a repeated measures General Linear Model with "time" as within-subjects factor. *Post hoc* Dunnett's multiple comparison test was used to compare each time point with baseline. Effect sizes were calculated by Hedge's *g*. Differences in depressive symptoms between the group of patients taking antidepressants (AD) and those not taking them at D7 were analyzed using the Mann-Whitney test. The biochemistry measurements (-20 min vs. +120 min after session 2) were analyzed with a paired samples *t*-test. The subjective experience measured by VAS, ASC, MEQ, and HRS items scores (means \pm SD) is shown descriptively.

The relationship between the primary outcome and acute psychedelic effects was calculated using Spearman's rank coefficients (*r*) between MADRS deltas (D0-D7) and ASC and MEQ scores. Significant *p*-values were

Bonferroni-corrected *post hoc* for multiple comparisons by the number of factors (ASC = 11, MEQ = 5). The association between changes in suicidality and depressive symptoms at D7 was investigated by correlating the scores in suicidality (MADRS-SI and BSI) with scores in non-suicide-related depressive symptoms (MADRS-nonSI). The significance level was $\alpha = 0.05$ (two-tailed). Analyses were performed with GraphPad Prism 7 and IBM SPSS Statistics (v. 22).

RESULTS

Participants

We assessed 23 patients for eligibility, and 14 were allocated for treatment. The study was conducted between October 9, 2023, and March 30, 2024. The CONSORT flow diagram is shown in Figure. S1. The patients' sociodemographic and clinical characteristics are depicted in Table 1 (for details, see Table S2 and Table S3). No participant showed critical physiological changes, and all participants voluntarily chose to proceed to the higher dose (60 mg) session after the initial dose, highlighting the tolerability and perceived benefit of the dose-escalation protocol.

Psychiatric

For MADRS, there was a main effect of time ($F(5,65) = 13.04$, $p < 0.0001$, $\eta_p^2 = 0.50$). Pairwise comparisons revealed a significant reduction of depressive symptoms at D1 ($\mu = 8.93 \pm SD = 10.45$; $p < 0.001$; $g = 2.76$), D7 ($\mu = 11.07 \pm 12.33$; $p < 0.001$; $g = 2.20$), D14 ($\mu = 11 \pm 10.68$; $p < 0.001$; $g = 2.47$), M1 ($\mu = 14.21 \pm 12.08$; $p < 0.001$; $g = 1.90$), and M3 ($\mu = 18.79 \pm 13.07$; $p < 0.001$; $g = 1.33$) (Fig. 2A). Figure 2B shows the proportion of patients who responded at D1: 11/14 (78.57%), at D7: 12/14 (85.71%), at D14: 12/14 (85.71%), M1: 9/14 (64.29%) and at M3: 8/14 (57.14%); and the remission rate at D1: 10/14 (71.43%), at D7: 8/14 (57.14%), at D14: 8/14 (57.14%), M1: 8/14 (57.14%) and at M3: 5/14 (35.71%). Table S4 shows the detailed results. Figure. S2 shows individual MADRS scores and responses at each time point. Additionally, we explored the difference between the patients who were under antidepressants and those without antidepressants at D7. Decreases in MADRS scores were marginally significantly larger in the AD group ($U = 7.5$; $p = 0.07$). The response and remission rates at D7 were 100% and 70% for the AD group, while for the patients without AD were 50% and 25%, respectively (Fig. S3).

For PHQ-9 scores, we also observed a main effect of time ($F(5,65) = 10.78$, $p < 0.001$, $\eta_p^2 = 0.45$). Pairwise comparisons revealed a significant reduction in PHQ-9 scores, compared to D0, at D1, D7, D14, M1, and M3 (all $p < 0.001$). Figure. S4 and Table S5 show detailed results.

MADRS-SI changes assessed suicidality. Figure 2C shows mean MADRS-SI scores over time. We observed a significant main effect of time ($F(5,65) = 9.97$, $p < 0.001$, $\eta_p^2 = 0.43$). Pairwise comparisons revealed a significant reduction of suicidality, compared to D0, at D1 ($\mu = 0.36 \pm 0.63$; $p < 0.001$; $g = 2.61$), D7 ($\mu = 1.07 \pm 1.64$; $p < 0.001$; $g = 1.34$), D14 ($\mu = 0.57 \pm 1.16$; $p < 0.001$; $g = 2.00$), M1 ($\mu = 0.93 \pm 1.54$; $p < 0.001$; $g = 1.49$), and M3 ($\mu = 1.21 \pm 1.42$; $p < 0.001$; $g = 1.35$) (Table S6). Figure 2D shows the percentage of patients stratified in three groups according to the suicidality severity: (i) severe SI (MADRS-SI ≥ 4); (ii) suicidal ideation ($2 \leq$ MADRS-SI < 4); (iii) no suicidal ideation (MADRS-SI < 2) over time. Before dosing, at D0, 43% of patients showed severe risk, 43% had suicidal ideation, and only 14% showed no sign of suicidality. At D1, no patient demonstrated severe suicidal ideation. The number of patients with suicidal risk remained low until M3, where 21% of patients showed some suicidal ideation, compared to 86% at the beginning. Additionally, we measured the self-reported suicidal ideation using BSI. We observed a significant main effect of time ($F(5,65) = 3.70$, $p = 0.005$, $\eta_p^2 = 0.22$). Pairwise comparisons revealed a significant reduction of suicidality compared to D0, at D1, D7, D14, M1 (all $p < 0.01$), and M3 ($p < 0.05$). See Fig. S5 and Table S7 for a complete description.

Table 1. Sociodemographics and Clinical Characteristics.

Characteristic	Measure	Value
Age	mean years (SD), range	35.2 (12.15), 21–59
Sex	Female	6 (42.8%)
	Male	8 (57.2%)
Ethnicity	White	7 (50%)
	Mixed race	5 (35.7%)
	Black	2 (14.3%)
Education	<12 years	1 (7.1%)
	12–16 years	7 (50%)
	>16 years	6 (42.8%)
Marital status	Single	9 (64.3%)
	Married	2 (14.3%)
	Separated	3 (21.4%)
Household income ^a	1 minimum wage	1 (7.1%)
	1–2 minimum wages	1 (7.1%)
	2–5 minimum wages	5 (35.7%)
	5–10 minimum wages	5 (35.7%)
	>10 minimum wages	2 (14.3%)
Employment status	Employed	4 (28.6%)
	Occasionally employed/freelancer	2 (14.3%)
	Unemployed	4 (28.6%)
	Student	4 (28.6%)
	Religion	No religion
	Catholic	2 (14.3%)
	Protestant or Evangelical	2 (14.3%)
	Buddhism	1 (7.1%)
	Spiritist	1 (7.1%)
	Spiritualist	1 (7.1%)
	Umbanda or Candomblé	1 (7.1%)
Estimated illness duration	mean years (SD)	11.1 (9.64)
Previous treatments	mean number (SD)	4.1 (1.99)
Baseline MADRS	mean score (SD)	32.2 (5.79)
Baseline PHQ-9	mean score (SD)	18.5 (4.97)
Patients under antidepressant treatment		10 (71.4%)
Psychedelic use in lifetime	mean number (SD)	1.5 (3.30)

SD standard deviation, MADRS Montgomery-Åsberg Depression Rating Scale, PHQ-9 Patient Health Questionnaire-9.

^aThe minimum wage was 1.320 Brazilian Reals (~266 USD) at the time of study conduction.

Subjective experience

Subjective experiences for the high dose seemed intense ($\mu = 84.37 \pm 21.49$), positive ($\mu = 24.71 \pm 25.81$) as measured by VAS, and elicited mild effects as measured by ASC total scores ($\mu = 31.64 \pm 14.55$) and MEQ total scores ($\mu = 2.41 \pm 1.13$). Figure 3 shows average scores for each ASC dimension and MEQ factor. HRS items are displayed in Fig. S6. Additionally, no difference was observed in the intensity of the experience between the patients who were under antidepressants and those without

antidepressants ($\mu_{AD} = 86.35 \pm 15.85$; $\mu_{none} = 79.42 \pm 34.66$; $p = 0.98$). Subjective experiences for the low dose are detailed in Fig. S7.

Correlations

A positive marginal correlation was observed between improvements on D7 in MADRS scores with the ASC factor Complex Imagery ($r = 0.72$, $p = 0.057$). No other correlations survived correction for multiple tests. See Table S8 (ASC factors) and Table S9 (MEQ factors) for detailed correlations. We also investigated the relationship between decreased suicidality and non-suicide-related items of MADRS at D7. We found a positive correlation between MADRS-SI reductions and MADRS-nonSI ($r = 0.84$, $p = 0.0004$), as well as for BSI reductions and MADRS-nonSI ($r = 0.75$, $p = 0.004$).

Physiological

Vital signs increased significantly after the second administration of DMT, but in a limited manner over time. We observed a main effect of time on SBP ($F(13,169) = 12.12$, $p < 0.0001$, $\eta_p^2 = 0.48$), DBP ($F(13,169) = 12.49$, $p < 0.0001$, $\eta_p^2 = 0.49$), and HR ($F(13,169) = 4.80$, $p < 0.001$, $\eta_p^2 = 0.27$). For SBP, there were higher means, compared to baseline, from +2 min to +8 min (all $p < 0.02$). There were higher means for DBP, compared to baseline, from +2 min to +6 min (all $p < 0.001$). There were higher means for HR, compared to baseline, from +2 min to +4 min (all $p < 0.001$). For SpO2 and RR, one subject was not assessed during session 2; therefore, was excluded from the analysis. No significant change was observed for SpO2 ($F(13,156) = 1.62$, $p = 0.08$) nor for RR ($F(13,156) = 0.93$, $p = 0.52$).

Figure 4 shows the significant physiological changes over time. For SpO2 and RR measurements, see Fig. S8. Measurements during session 1 are detailed in Fig. S9.

Biochemical

Blood could not be collected in two subjects due to difficulty locating suitable veins; therefore, both were excluded from blood analyses. Significant increases were observed in ALT ($t(11) = 3.12$, $p = 0.01$), AST ($t(11) = 2.43$, $p = 0.03$), cholesterol total ($t(11) = 3.19$, $p = 0.009$), HDL ($t(11) = 2.73$, $p = 0.02$), LDL ($t(11) = 5.31$, $p = 0.0002$) and GFR ($t = 2.564$, $p = 0.03$). A significant decrease was observed in triglycerides ($t(11) = 3.67$, $p = 0.004$). No significant changes were observed for glucose and Na^+ , Ca^{2+} , and K^+ electrolytes. Mean (\pm SD) values for both time points were within the population references (Table S10).

Adverse events

Descriptive analysis revealed that a total of 77 distinct single medical concepts (SMC) were identified across 11 system organ classes over the six time points (D0 - including session 1 and session 2 -, D1, D7, D14, M1, and M3). The majority of adverse events (AEs) were mild, with 27 SMCs having an incidence of over 10% in the sample (Table S11). Notably, the most frequently observed AEs included pharyngeal discomfort ($n = 16$ on D0), cough ($n = 12$ on D0), and headache ($n = 9$ on D1). Additionally, 50 other terms presented with less than 10% incidence, which are detailed in Table S12. AEs were mild and transient, predominantly occurring during the acute dosing phase.

DISCUSSION

This study aimed to investigate the antidepressant effects, safety, and tolerability of vaporized DMT in patients with TRD, based on the optimized dosing regimen identified in our phase 1 clinical trial [31].

The antidepressant effects of inhaled DMT were rapid. Significant improvements were observed as early as one day post-administration (D1), with a marked reduction in depression

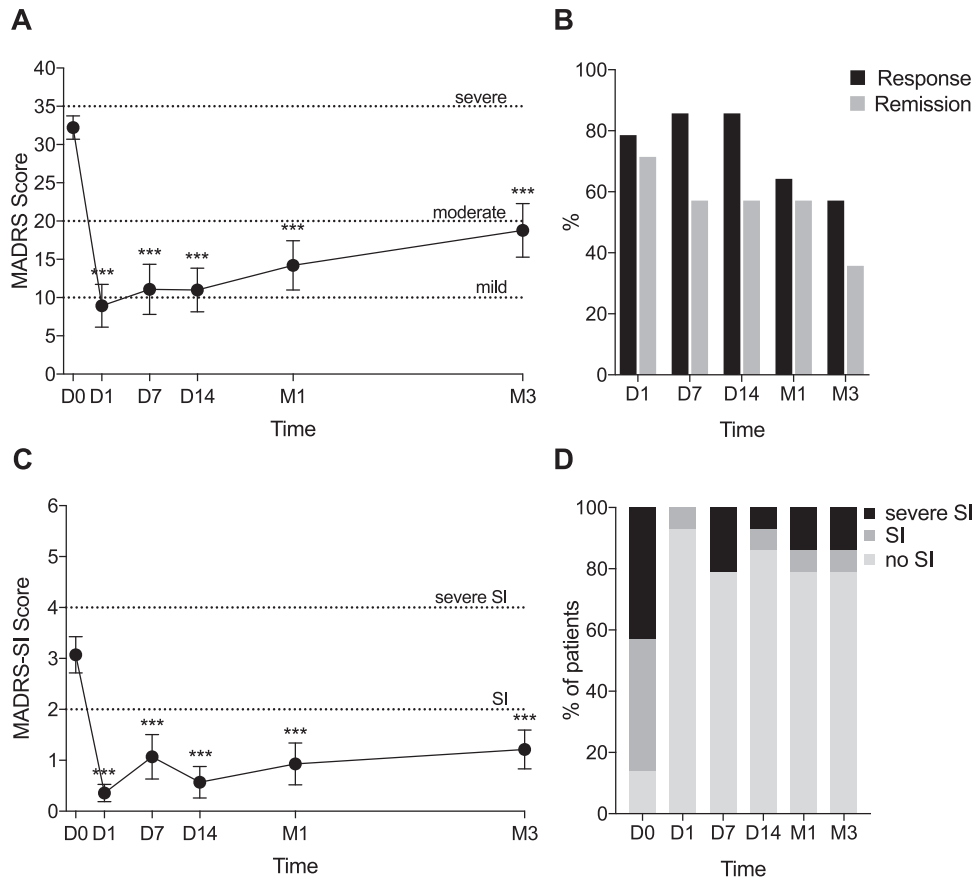


Fig. 2 Changes in depression and suicidality over time. **A** MADRS scores significantly decreased from D1 until M3 compared to D0. The data are expressed as the mean \pm SEM. **B** The bars indicate the proportion of patients meeting the response criteria (reduction \geq 50% in baseline MADRS score, in black) and the proportion of patients meeting the remission criteria (MADRS score \leq 10, in gray). **C** MADRS-SI scores significantly decreased from D1 until M3 compared to D0. The data are expressed as the mean \pm SEM. **D** Percentage of patients per suicidality severity. In black, those with severe SI (MADRS-SI \geq 4); in dark gray, those with suicidal ideation ($2 \leq$ MADRS-SI $<$ 4) and light gray patients with no suicidal ideation (MADRS-SI $<$ 2). D0 baseline, D1, D7 and D14 one, seven, and 14 days after the dosing session, M1, M3, one and three months after the dosing session, SI Suicidal ideation. *** $p < 0.001$.

severity. The MADRS scores showed a substantial decrease from moderate to severe depression to no clinically relevant symptoms on average by D1. These antidepressant effects were not only immediate but also sustained, with significantly lower depression scores persisting for up to three months post-intervention (M3), the final follow-up period.

On average, patients experienced a reduction of 23.28 points on MADRS by the 1st day after dosing, reflecting a clinical response rate of 78.57% and a remission rate of 71.43%; at D7, the response rate peaked (85.71%). In the 3rd month, there still was a significant reduction, with 57.14% of patients remaining in the response range and 35.71% in the remission range. Notably, over the three months of MADRS evaluations by psychiatrists, the results consistently matched the self-reported PHQ-9 scores. The rapid onset of antidepressant effects observed in our study, with significant reductions in MADRS and PHQ-9 as early as D1, aligns with the emerging paradigm of psychedelic treatments [38] and rapid-acting antidepressants [39]. For comparison, the SYNAPSE study [40] with esketamine (plus oral antidepressants) achieved a 32% remission rate after 74 days of multiple dosages, whereas our study reached 35% remission after 84 days (M3) with a single-day intervention.

An exploratory study on the antidepressant effects of intravenous (I.V.) DMT in seven patients with MDD reported a moderate effect size (Hedge's $g = 0.75$) with a mean reduction of 4.5 points on the Hamilton Depression Rating Scale (ranging from 0 to 52) one day after dosage [11]. In contrast, our study achieved a higher

effect size (Hedge's $g = 2.76$) on the MADRS score at D1, which was partially sustained for three months.

Beyond the administration route (I.V. vs. vaporized), notably, D'Souza et al. [11] utilized a lower dose of DMT (~21 mg), which may account for the more modest antidepressant response observed. However, it is challenging to draw definitive conclusions about the impact of dosage due to the absence of pharmacokinetic (PK) data in both studies. The intravenous route likely provides full bioavailability, while the inhaled route may be influenced by factors such as pulmonary capacity and losses associated with the vaporization device. Both studies assessed subjective experience intensity using a Visual Analog Scale (VAS). D'Souza et al. reported a mean VAS score of 94.3 with 0.3 mg/kg I.V. DMT, whereas we observed a mean score of 84.3 with 60 mg inhaled DMT. Despite these differences, the subjective intensity of the experience was comparable, highlighting the complexity of dose-response relationships in psychedelic treatments. Additionally, our study provided a structured setting with preparation and psychological support, potentially contributing to the stronger effects observed.

A recent study investigated the safety and efficacy of vaporized 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT) in 16 patients with TRD. At D7 vs. baseline, they found a MADRS reduction of 24.4 points; similarly, we found a reduction of 21.14 points [33]. Both studies highlight the rapid antidepressant effects of short-acting psychedelic tryptamines using the same vaporizer device. However, our study used a single ascending fixed-dose approach

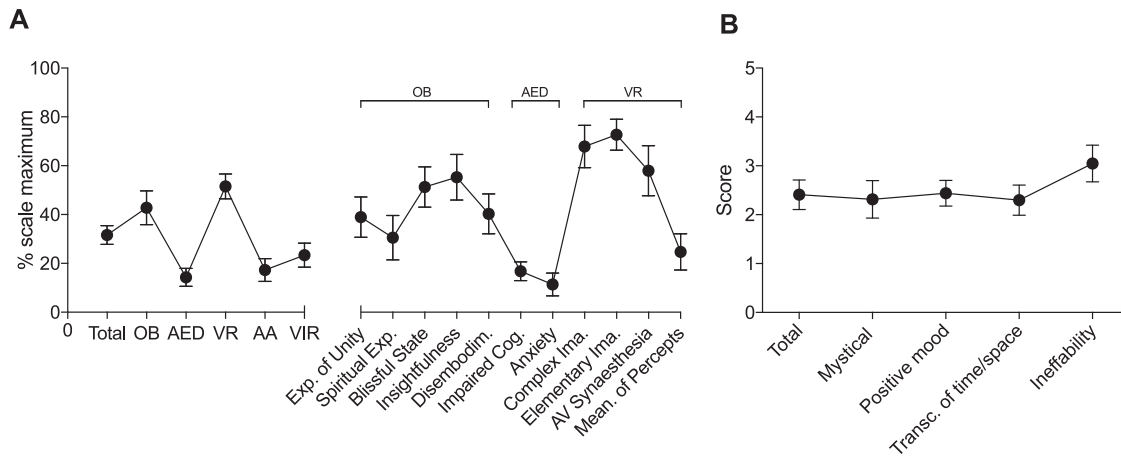


Fig. 3 Acute subjective experience during the dosing session 2. **A** Alterations of consciousness on the 5 and 11 Dimensions of Altered States of Consciousness (ASC) scale. **B** Mystical-type experiences on the Mystical Experiences Questionnaire (MEQ). The data are expressed as the mean \pm SEM. Total includes all 94 items of the ASC. OB Oceanic Boundlessness, AED Anxious Ego Dissolution, VR Visionary Restructuralization, AA Auditory Alterations, VIR Vigilance Reduction, Exp. Experience, Disembodim. Disembodiment, Cog Cognition, Ima Imagery, AV Audio-Visual, Mean. Changed Meaning, Transc. Transcendence, SEM Standard Errors of Measurement.

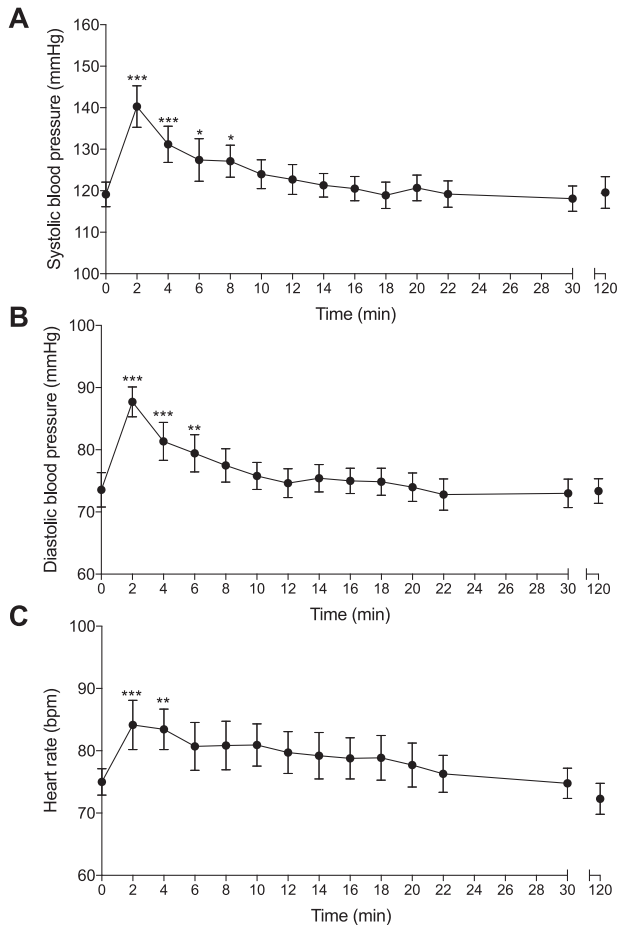


Fig. 4 The effects of DMT on physiological measurements in session 2. **A** Systolic blood pressure; **B** Diastolic blood pressure; **C** Heart rate. Displayed are means (points) and Standard Errors of Measurement (SEM; bars) over the time course of the acute and subacute effects (+0 min to +120 min). * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ (each time point compared to +0 min).

as opposed to an individualized dosing regimen used by Reckweg et al. [33]. The positive outcomes in both studies reinforce the viability of using vaporized short-lasting psychedelics as a promising therapeutic approach.

Ayahuasca, a DMT-containing brew, has also demonstrated rapid and significant antidepressant effects in TRD, with response rates reaching up to 77% and reductions in suicidality observed within 24 h post-administration [8, 41]. These effects have been linked to changes in neural networks involved in emotional regulation and a decrease in inflammatory and stress biomarkers [42–44]. Compared to ayahuasca, vaporized DMT provides a shorter duration of action, avoids the need for MAOi coadministration, and offers advantages in scalability, cost, and clinical applicability while maintaining promising antidepressant potential.

Furthermore, we also observed a positive impact on severe outcomes associated with depression, such as the risk of suicide. In this regard, the results of MADRS-SI and BSI are particularly noteworthy. At baseline, 86% of patients exhibited suicidal ideation, with 43% assessed as being at severe risk. Remarkably, by the day after dosing, no patient demonstrated severe suicidal ideation. This rapid improvement was largely sustained, with only 21% of patients showing any signs of suicidal ideation at the 3-month follow-up. While most participants showed reductions in suicidality, one (P12) worsened to severe SI (from D7 to M1), and others (P6 and P13 at M3, and P14 at D7 and M1) experienced transient changes, with SI returning to baseline by follow-up. Notably, no participants developed severe SI beyond baseline levels.

Additionally, a significant correlation was found between the reduction in depression scores (MADRS-nonSI) and the BSI and MADRS-SI scales at D7, suggesting that the improvement in suicidality was likely mood-dependent rather than an independent effect. Ketamine has been well-established for its rapid antisuicidal effects [45]. Lopes et al. reported a Hedge's g of 0.5 in suicidality reduction one day after the first ketamine dose, measured by the BSI [46]. Our study found a comparable effect size of 0.67 on D1. For MADRS-SI, Lopes reported a Hedge's g of 0.5 on D7, while our study observed a stronger effect of 1.34 with DMT. These findings indicate that DMT may have potential as a candidate for further exploration in antisuicidal treatments.

Regarding the psychedelic effects, the onset seemed rapid, emerging within a few seconds, peaking around 2 min, and lasting for 10–20 min; the effects appeared intense and well tolerated, as

measured subjectively by the VAS. Participants rated the experience as overall pleasant, with high satisfaction (HRS item 46) and positive valence, while there was a desire to repeat within a week (HRS item 48) and have regular sessions (HRS item 49). The relatively low frequency suggests minimal addiction risk. However, this evaluation is indirect and does not fully address addiction potential. As psychedelics have a low potential for misuse [47], this finding probably points to good tolerability rather than addiction concerns.

Our results on the ASC scale highlighted substantial effects in Complex Imagery and Elementary Imagery, which are hallmarks of DMT experiences [48, 49]. High scores were also observed in Blissful State and Insightfulness, grouped under Oceanic Boundlessness. Scores for Anxiety and Impaired Cognition were low, indicating good tolerability. Spiritual Experience did not show high scores, aligning with MEQ results, where only two individuals rated >60% [50, 51].

In our study, we observed a marginal positive correlation between reductions in MADRS scores with Complex Imagery but no association with MEQ scores. These marginal correlations may reflect variability in absorbed DMT doses due to incomplete inhalation, coughing, or vaporizer deposition. Mystical experiences are associated with sustained therapeutic outcomes in psilocybin treatments [52, 53]. On the other hand, Palhano-Fontes et al. found perceptual (visual) changes, not MEQ scores, to correlate with decreased depressive symptoms after ayahuasca treatment, pointing to a potential variable impact of different psychedelics [8]. These intriguing trends likely lack significance due to the small sample size. PK studies are needed to clarify dose-response relationships and optimize delivery methods.

Regarding visual phenomena, it may confer an ontological sense to the psychedelic experience [54, 55]. Another possible explanation is that these aspects could enhance the psychotherapeutic integration process by providing rich narrative content. The saying “seeing is believing” underscores the significance of vision in affirming reality. Interestingly, closed-eye visuals induced by ayahuasca activate brain regions to a similar extent as regular open-eye vision in ordinary states of consciousness [43], which may enhance therapeutic benefits by amplifying expectancy effects: patients who experience vivid imagery might perceive the treatment as more effective, potentially enhancing the broad therapeutic impact. The efficacy of psychedelic therapies in treating depression is influenced by a combination of factors that underscore their complexity, including the direct pharmacological effects of the substances, patient expectations, and the psychotherapeutic integration of the experiences during session [56].

The physiological findings confirmed that DMT was safe with respect to vital signs. During the acute phase (+0 to +22 min), there were mild, temporary, and self-limiting increases in both blood pressure and heart rate without any clinical consequences. These alterations were similar to those typically seen during moderate-to-vigorous exercise in healthy individuals without cardiac issues [57]. All patients returned to baseline values in sub-acute effects (+30 and +120 min). Regarding biochemical parameters, while some significant changes were noted following DMT administration, none were clinically relevant.

Regarding AEs, no serious AE was reported. The most commonly reported AEs fell into three categories: Respiratory, Thoracic, and Mediastinal Disorders, Nervous System Disorders, and Gastrointestinal Disorders across all time points. Most AEs occurred during the acute phase, encompassing both dosing sessions (1 and 2), which accounted for most of the complaints. The most frequently reported single medical concept was pharyngeal discomfort, followed by cough on D0 and headache on D1. Pharyngeal discomfort included symptoms such as burning throat, throat clearing, throat discomfort, and scratchy throat. This effect was reported in 57.1% of sessions on D0 (16 out of 28 sessions) but resolved for all but one participant by D1 and D7.

These results align with our phase 1 trial [31], where pharyngeal discomfort occurred in 48.1% of sessions (26 out of 54 sessions) but did not persist beyond D14, the next medical evaluation. These findings suggest an irritative effect of inhaled DMT vapor, primarily restricted to the acute phase and rarely persisting [31].

This trial has some limitations. The open-label design and small sample size present a major caveat, as it does not allow for the disentangling of placebo effects from DMT effects. The need for repeated doses over time was not assessed, and longer follow-up periods are desirable. Also, the absence of PK data hinders understanding of dose-blood concentration relationships. The characterization of TRD relied partly on self-reported treatment histories, which may lack precision, particularly for self-referred participants. The sample's homogeneity in ethnicity, educational, and socioeconomic status limits generalizability. Furthermore, the lack of comprehensive cardiac assessments, such as QT interval monitoring using a 12-lead ECG, represents another limitation. Similarly, while implemented to minimize risks, the upper age limit of 60 years restricts the generalizability of findings to older populations with potentially higher cardiovascular risk. While most participants experienced therapeutic benefits, individual variability in response was observed. One participant (P12) showed symptom worsening at D7, closer to the intervention, suggesting a possible temporal association with the treatment. Conversely, another participant (P13) exhibited worsening only at M3, likely influenced by external life events rather than the intervention itself. These findings emphasize the importance of contextualizing individual outcomes and considering extra-pharmacological factors in the evaluation of psychedelic treatments. Future studies should aim to identify predictors of both positive and negative responses, integrating life circumstances into their analyses to improve patient selection and ensure safety.

Future directions include increasing participant numbers, a more diverse population, and employing randomized, placebo-controlled designs for more robustness. Future studies will also evaluate the impact of cumulative dosing regimens as a strategy to sustain and potentially enhance antidepressant responses over longer periods and should focus on identifying predictors of both positive and negative responses to improve patient selection and safety monitoring. Additionally, extending psychological integration sessions may help reinforce therapeutic gains. Enhanced cardiac safety monitoring, including QT interval assessments and validated addiction risk assessments, will provide a more comprehensive understanding of the risks, along with PK evaluations to clarify the relationship between administered and absorbed DMT doses, enabling optimization of inhalation procedures and dose standardization. To further refine the DMT administration protocol to optimize session duration, evaluations of tachyphylaxis should test repeated DMT administrations at shorter intervals (e.g., less than 30 min apart), allowing for a condensed procedure of 1–2 h.

The integration sessions on D1 and D7 were designed to support meaning-making, sustain benefits, and reinforce positive patterns to prevent relapse. While we hypothesize that these sessions contribute significantly to the therapeutic response, our study design does not isolate their effects from those of the DMT session itself. Future research will aim to disentangle these contributions, further refining the balance between pharmacological and psychological components in interventional psychiatry.

Our findings suggest that inhaled DMT has a rapid antidepressant and antisuicidal effect, is safe and well-tolerated. Vaporized DMT offers a noninvasive alternative suitable for outpatient care, with advantages over longer-acting psychedelics like psilocybin and LSD, such as shorter sessions and lower healthcare costs. Notably, DMT can potentially be used without the need to discontinue traditional antidepressants, which enhances its practicality by avoiding the need for tapering. These features make it a practical and scalable option for treating mood disorders

within public health systems, addressing the high prevalence of depression and the ongoing need for more accessible treatments.

DATA AVAILABILITY

The data that support the findings of this study are available on request from the corresponding authors, PPF and DBA.

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AUTHOR CONTRIBUTIONS

MFC, FPF, IW, NGC and DBA designed the study; EA, FPF and DBA acquired the authorizations; SRBS, EJP, and JVCN extracted and purified the substance; MFC, FPF and DCB selected the participants; MFC led the session, administered the substance and served as head of psychiatry for the study; HB, RB, and SL provided psychological support; DM, ET, and RFV served as psychiatrists to medical follow-up; RA, RKAM, and FA provided nursing support; MFC, HB, RB, SL, DM, ET, RFV, RA, RKAM, and FA acquired the data; FPF, IW, NCG, and DBA provided research assistance; JACN, LAACN,

LFNF, LDC, RBCB preprocessed the data; FPF analyzed the data; MFC, FPF, IW and DBA wrote the article; all authors reviewed the manuscript and approved the final version.

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COMPETING INTERESTS

DBA has served as a scientific and clinical advisor for Biomind Labs from June 2021 to December 2022. MFC has served as the Head of the Psychiatric Research Unit at Biomind Labs Inc. from January 2022 to May 2023; both positions concluded before the start of the study on October 9, 2023, and no other relationships or activities could appear to have influenced the submitted work. The remaining authors have nothing to disclose.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41386-025-02091-6>.

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