European Neuropsychopharmacology 80 (2024) 27–35

Contents lists available at ScienceDirect

European Neuropsychopharmacology

journal homepage: www.sciencedirect.com/journal/european-neuropsychopharmacology

Safety and tolerability of inhaled N,N-Dimethyltryptamine (BMND01 candidate): A phase I clinical trial

Marcelo Falchi-Carvalho [a,b,1], Isabel Wießner [c,1], Sérgio Ruschi B. Silva [c], Lucas O . Maia [c], Handersson Barros [d], Sophie Laborde [d], Flávia Arichelle [c], Sam Tullman [c], Natan Silva-Costa [c], Aline Assunção [c], Raissa Almeida [e], Érica J. Pantrigo [c], Raynara Bolcont [c], José Victor Costa-Macedo [c], Emerson Arcoverde [f], Nicole Galvão-Coelho [e], Draulio B. Araujo [c,d,*], Fernanda Palhano-Fontes [c,*]

[a] Biomind Labs, Brookfield Place, 181 Bay Street, Suite 1800, Toronto, ON M5J 2T9, Canada
[b] Department of Clinical Medicine, Health Science Center, Federal University of Rio Grande do Norte, Natal, Rio Grande do Norte, Brazil
[c] Brain Institute, Federal University of Rio Grande do Norte, Natal, Rio Grande do Norte, Brazil
[d] Graduate Program in Health Sciences, Federal University of Rio Grande do Norte, Natal, Rio Grande do Norte, Brazil
[e] Department of Physiology and Behavior, Federal University of Rio Grande do Norte, Natal, Rio Grande do Norte, Brazil
[f] University Hospital Onofre Lopes, Federal University of Rio Grande do Norte, Natal, Rio Grande do Norte, Brazil

ARTICLE INFO

Keywords:
N,N-Dimethyltryptamine
DMT
Psychedelics
Dose-response study
Clinical trial
Mood disorders

ABSTRACT

Psychedelics are being increasingly examined for their therapeutic potential in mood disorders. While the acute effects of ayahuasca, psilocybin, and lysergic acid diethylamide (LSD) last over several hours, inhaled N,N-Dimethyltryptamine (DMT) effects last around 10 min, which might provide a cost- and time-effective alternative to the clinical application of oral psychedelics. We aimed at investigating the safety and tolerability of inhaled DMT (BMND01 candidate). We recruited 27 healthy volunteers to receive a first, lower dose and a second, higher dose (5/20 mg, 7.5/30 mg, 10/40 mg, 12.5/50 mg, or 15/60 mg) of inhaled DMT in an open-label, single-ascending, fixed-order, dose-response study design. We investigated subjective experiences (intensity, valence, and phenomenology), physiological effects (blood pressure, heart rate, respiratory rate, blood oxygen saturation, body temperature), biochemical markers (liver, kidney, and metabolic functions), and adverse events during the acute and post-acute effects of DMT. DMT dose-dependently increased intensity, valence and perceptual ratings. There was a mild, transient, and self-limited increase in blood pressure and heart rate. There were no changes in safety blood biomarkers and no serious adverse events. DMT dose-dependently enhanced subjective experiences and positive valence. Inhaled DMT might be an efficient, non-invasive, safe route of administration, which might simplify the clinical use of this substance. This is the first clinical trial to test the effects of inhaled DMT (BMND01 candidate).

1. Introduction

Classic psychedelics such as ayahuasca, N,N-dimethyltryptamine (DMT), and psilocybin are among the few new compounds with promising evidence of rapid antidepressant effects in patients with Treatment-Resistant Depression (TRD) (Palhano-Fontes et al., 2019; Vollenweider and Preller, 2020; Carhart-Harris et al., 2021; D'Souza et al., 2022; Goodwin et al., 2022). We have conducted two clinical trials for TRD with ayahuasca (Osório et al., 2015; Sanches et al., 2016; Palhano-Fontes et al., 2019), a DMT-containing brew discovered by Amerindians and used for medicinal purposes for hundreds of years (Luna, 2011; Miller et al., 2019). Evidence from our open-label and randomized placebo-controlled trials suggests a rapid antidepressant effect of ayahuasca in TRD, starting one day after a single dosing session, which persisted for at least seven days (Osório et al., 2015; Sanches et al., 2016; Palhano-Fontes et al., 2019).

The acute psychedelic effects of ayahuasca, psilocybin, mescaline, and lysergic acid diethylamide (LSD) last over several hours (Riba et al.,

* Corresponding authors at: Instituto do Cérebro (ICe)/UFRN, Av. Senador Salgado Filho, 3.000, 59078-900, Natal/RN, Brazil.
E-mail addresses: draulio@neuro.ufrn.br (D.B. Araujo), fernandapalhano@neuro.ufrn.br (F. Palhano-Fontes).
[1] Equal contribution.

https://doi.org/10.1016/j.euroneuro.2023.12.006
Received 11 August 2023; Received in revised form 11 December 2023; Accepted 14 December 2023
Available online 22 December 2023

2001; Holze et al., 2022; Ley et al., 2023; Maia et al., 2023). Current research suggests that dosing sessions with these substances should be attended by two therapists (Johnson et al., 2008) and recent Psychedelic-Assisted Psychotherapy (PAP) protocols include multiple dosing sessions with these substances (Mitchell et al., 2021). This imposes an important practical and economic limitation on the wide clinical use of psychedelics and encourages the investigation of short-acting alternatives, such as DMT in parenteral routes.

DMT is an indole alkaloid endogenously found in different plants, fungi, and animals, including humans (Carbonaro and Gatch, 2016). It was first synthesized by Manske (1931) and first isolated by Gonçalvez-Lima (1946) from the roots of the *Mimosa tenuiflora* (Barker, 2018). DMT's biosynthesis, metabolism, function, and mode of action are barely understood, but it seems to be involved in several biological processes (Carbonaro and Gatch, 2016; Barker, 2018). DMT is an agonist of diverse neuroreceptors, particularly serotonin 2A, 2C, and 1A, sigma-1, and Trace Amine-Associated Receptors (TAAR) (Fontanilla et al., 2009; Carbonaro and Gatch, 2016).

The first DMT study in humans was conducted in 1956 using intramuscular (IM) administration (Szára, 2007), followed by later studies with intravenous (IV) administration (Strassman and Qualls, 1994; Strassman et al., 1994). The results showed that DMT induces transient changes in blood pressure and heart rate (Strassman and Qualls, 1994; D'Souza et al., 2022). Regarding the subjective experience, low doses induce deep relaxation and comfort, while high doses induce intense psychedelic experiences with changes of consciousness, imagery, body distortions, changed auditory perception, cognition, mood, arousal, and entity encounters (Strassman et al., 1994; Szára, 2007; Pallavicini et al., 2021; Lawrence et al., 2022; D'Souza et al., 2022; Vogt et al., 2023).

The psychological effects of DMT are similar to those of other psychedelics (visions, body distortions, mood changes) but have a faster onset (2–5 min) and shorter duration (10–60 min) for IM administration (Szara, 1956; Szára, 2007). The fastest action is evoked by IV or inhaled administration (onset: seconds to minutes, duration: 10–30 min) with similarly intense subjective effects (Strassman and Qualls, 1994; Timmermann et al., 2019; Lawrence et al., 2022; Vogt et al., 2023).

Previous research investigated inhaled 5-Methoxy-N,N-Dimethyltryptamine (5-MeO-DMT) (Reckweg et al., 2021). However, 5-MeO-DMT and DMT show a distinct stability *in vivo*, transport via blood-brain barrier, and receptor affinity. 5-MeO-DMT has a high binding affinity for 5-HT1A auto-receptors that produce sympathoinhibition, whereas DMT is sympathomimetic through 5-HT2A receptors (Reckweg et al., 2022). Moreover, the subjective experience induced by these substances seems different, DMT usually leads to more vivid and complex visual images, while 5-MeO-DMT produces a marked ego-dissolution (Barker, 2018). Thus far, only IM and IV DMT administration have been explored in controlled studies (Strassman et al., 1994; Szára, 2007; Timmermann et al., 2019; D'Souza et al., 2022; Vogt et al., 2023). However, inhaled administration might be a safer, non-invasive route, which would simplify the clinical use of DMT. Therefore, in this first in-lab study, we aimed to investigate the safety, tolerability, subjective experiences and optimized dosing regimen of inhaled DMT (BMND01 candidate) in healthy subjects.

2. Experimental procedures

2.1. Study design

This is an open-label, single-ascending, fixed order, dose-response study to assess the feasibility of inhaled DMT (BMND01 candidate) in healthy volunteers in preparation for a phase II clinical trial with TRD patients. 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) (#45.532.421.0.0000.5292). The study was registered at clinicaltrials.gov (NCT05573568) and conducted in accordance with the declaration of Helsinki.

2.2. Participants

We recruited 27 healthy subjects through online advertisements and word-of-mouth. The sample size was estimated based on our previous studies with ayahuasca (Palhano-Fontes et al., 2019). Candidates for participation underwent a medical, clinical, and psychiatric screening, including an evaluation of self-reports, medical records, complementary exams (if necessary), collection of demographic data, and check for eligibility criteria (as listed in the **Supplemental Methods**). Each subject signed an informed consent before participation. Participants were asked to abstain from psychedelics (DMT, ayahuasca, psilocybin, LSD, mescaline, ketamine, 3,4-Methylenedioxymethamphetamine (MDMA), and other phenylethylamines and tryptamines) 14 days prior to dosing until 28 days afterward.

2.3. Substance

The DMT free base was isolated and purified from *M. tenuiflora* root barks. The gas chromatography-mass spectrometry (GC–MS) analyses indicated an average purity of 99.0 ± 0.4 % (range: 98.4–99.5). The drug was then dissolved in 99 % ethanol, a solution denominated as BMND01. The solution was distributed on a metallic mesh for vaporization in a medical-grade vaporizer (Volcano® Medic 2, Storz & Bickel GmbH & Co, Tübingen, Germany) previously used in similar clinical trials (Hazekamp et al., 2006; Reckweg et al., 2021). The advantage of a DMT solution compared to solid forms is the more equal distribution on the mesh allowing for more even DMT vaporization over the device's ventilation period.

For the inhalation, the participants were informed about the inhalation procedures while heating the vaporizer to 200 °C. Then, subjects underwent three training runs inhaling the air of a 2-l balloon. Afterwards, the DMT solution was vaporized for 10 s into the balloon for inhalation. For each inhalation (training and DMT), participants sat upright in an armchair, emptied completely the lungs and were instructed to inhale the entire balloon content in one continuous, slow flow to prevent the vapor from swirling in the initial airway passages, which seems to contribute to irritation and coughing. The balloon content was retained in the lungs for 3 s and exhaled upon the psychiatrist's signal (for further details, see **Supplemental Methods**; for a classification of inhalation quality, see **Table S1**).

2.4. Procedures

All procedures followed the safety guidelines for human psychedelic research (Johnson et al., 2008) and the principles of Good Clinical Practice (GCP). The study was conducted in the clinical psychedelic research unit of the HUOL. The study room was adorned with art and homey furnishings in a modern boho-like living room style, painted in warm colors, lit with dim lighting, color changing LEDs, and medical devices integrated into the ambiance.

The study protocol is depicted in Fig. 1. After screening, a preparation session was conducted by an experienced psychologist to 1) establish rapport with the participant, 2) inform about the DMT effects and establish realistic and positive expectations regarding safety, limits, and support, 3) provide strategies for managing challenging experiences, and 4) answer questions about the study.

On the day of DMT administration (D0), participants underwent two dosing sessions. The first session with a lower DMT dose was intended for safety check. The second session with a higher dose was administered 120 min after the first dose. If participants presented critical changes in physiological measurements during the first session, they would not undergo the second session. To explore an optimized dosing regimen, each participant received one of five dose schemes (5/20 mg, 7.5/30 mg, 10/40 mg, 12.5/50 mg, or 15/60 mg).

Throughout the day, at least one trained clinical professional (psychiatrist, psychologist, and nurse) remained in the room with the

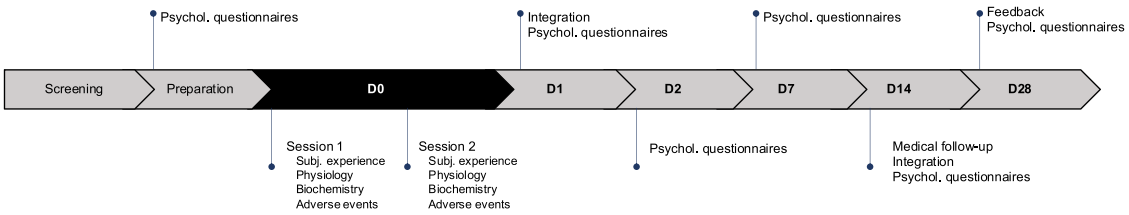

Fig. 1. Study protocol. After screening and preparation of the participants, on the day of DMT administration (D0), a first, lower dose was applied, followed by a second, higher dose +120 min afterwards. From one (D1) to 28 days after dosing (D28), repeated questionnaires, integrations, and a medical follow-up were applied.

subject. During the acute effects of each dose (+0 min to +10 min), all three professionals provided clinical, organizational, and emotional support to ensure the participant's safety and comfort. Meanwhile, the participant remained comfortably lying on a recliner and listened to music specifically composed and produced for the study.[2]

In each session, physiological measurements were measured around the acute effects (-5 min to +40 min in 2-min intervals) and sub-acutely (+60 min and +120 min). Peak expiratory flow rate (PEFR) was evaluated before (-15 min) and afterward (+60 min). Blood samples were collected before, during, and after the effects (-10 min, +2 min, +5 min, +10 min, +23 min, +120 min). Saliva was collected before and afterward (-11 min, +23 min, +120 min). Brain activity was recorded by electroencephalography (EEG) before (-40 min), during (+0 min to +20 min), and after the effects (+25 min). Results from acute blood samples (+2 min to +23 min), saliva samples, and EEG will be reported elsewhere.

In each session, the subjective experience was scored regarding intensity, valence, and the Hallucinogen Rating Scale (HRS). Additionally, intensity and valence of the first dose were re-rated after the second dose. After the first dose, participants underwent a 15-min integration with the psychologist and psychiatrist to report their experience. After the second dose, they underwent a 60-min integration (Zeifman and Maia, 2023), including drawing a mandala with colored crayons for expression and elaboration of the experience (Aixalà, 2022). At the end of each session, adverse reactions were examined by the psychiatrist. Two hours after the second dosing, the team ensured that the participants were physically and psychologically stable and released them into the custody of a family member or friend.

Follow-up assessments occurred from day 1 to day 28 after dosing (D1, D2, D7, D14, D28; **Supplemental Methods**). This included, at D14, spontaneous reports within clinical and psychiatric assessments to characterize adverse events, a systematic review of systems, and mental and physical exams.

2.5. Measurements

Perceptual measurements included subjective intensity (Visual Analogue Scale (VAS) from 0 = no effect to 100 = extremely intense effect), valence (VAS from -50 = extremely unpleasant effect to +50 = extremely pleasant effect) (Wießner et al., 2021), and the HRS. The HRS consists of 100 items, mostly rated on a 5-point Likert scale (from 0 = not at all to 4 = extremely) (Strassman et al., 1994; Mizumoto et al., 2011) and comprises six validated factors (sensitive distortion, cognitive distortion, affect, security/control, visual distortion, quality of experience) (Bouso et al., 2016). Moreover, we analyzed the six original factors for comparison purposes (intensity, somaesthesia, affect, perception, cognition, volition) (Strassman et al., 1994; Mizumoto et al., 2011). Lastly, in an exploratory analysis, we examined several HRS single items related to safety and tolerability (**Table S2**).

[2] The music was composed by the musician Raphael Egel and comprised elements of electronic, harmonic, ambient and chill out tunes to guide the experience and create a climate of safety and relaxation (www.raphael-egel.com).

Physiological measurements included systolic (SBP) and diastolic blood pressure (DBP), heart rate (HR), respiratory rate (RR), peripheral blood oxygen saturation (SpO2), and axillary temperature (AT), which were continuously monitored using a C80 multiparameter monitor (Shenzhen Comen Medical Instruments Co. Ltd., China). PEFR was evaluated with a high-precision portable Peak Respiratory Flow meter (Philips Respironics, EN 13,826, LocMed Hospitalar, Brazil).

Biochemical measurements included aspartate aminotransferase (AST), alanine aminotransferase (ALT), glomerular filtration rate (GRF) (using creatinine level within the Cockcroft & Gault formula), cholesterol (total, LDL, and HDL), triglycerides, and glucose in blood samples collected by venipuncture using *jelco* catheters (**Supplemental Methods**).

Adverse events were classified according to the preferred terms of the single medical concepts within the MedDRA standardized international medical terminology (vers. 25.1) (Reston, n.d.).

2.6. Statistical analysis

For each perceptual measurement, a General Linear Model for repeated measures (GLMrep) with 'session' (1, 2) as within-subjects factor and 'dose' (5/20 mg, 7.5/30 mg, 10/40 mg, 12.5/50 mg, 15/60 mg) as between-subjects factor was performed. For each physiological measurement, the GLMrep was complemented by the within-subjects factor 'time point' (2 for peak flow, 21 for the others). For each biochemical measurement, a GLMrep with time point (-10 min, +120 min after session 1, +120 min after session 2) as within-subjects factor and 'dose' as between-subjects factor was performed. For glucose and lipidogram measurements, BMI was included as covariate. Main effects of session, time point, and dose and interaction effects were examined, followed by pairwise comparisons. For physiological measurements, baseline was compared to each time point. For biochemical measurements, we compared: a) baseline to +120 min after session 1, and b) +120 min after session 1 to +120 min after session 2.

Pearson correlations were calculated between doses (5 mg to 60 mg) and measurements yielding significant differences between sessions.

All *p*-values were Bonferroni-corrected *post hoc* for multiple comparisons by the number of comparisons for doses ($n = 10$) or time points ($n = 20$ for physiology and $n = 2$ for biochemistry) for pairwise comparisons and by the number of measurements yielding significant effects (VAS = 2, HRS factors = 5, HRS items = 5, physiology = 2) for correlations. The significance level was set to α=0.05, two-tailed. All analyses were performed using IBM SPSS Statistics (vers. 22).

3. Results

3.1. Participants

The CONSORT flow diagram is depicted in **Fig. S1**. The participants' sociodemographic and drug use characteristics are shown in Table 1. No participant showed critical changes in physiological measurements, and all chose to undergo session 2 after completing session 1. Two subjects (both 10/40 mg) showed unsatisfactory inhalation quality (**Table S1**) in at least one session and were therefore excluded from the analyses.

Table 1
Sociodemographic and drug use characteristics of the participants.

Characteristic[a]	Measure	Value
Participants		25 (100 %)
Age	years (mean ± SD; range)	30.3 ± 6.5; 21–51
Sex	female	12 (48 %)
	male	13 (52 %)
Body Mass Index	kg/m^2 (mean ± SD; range)	23.7 ± 4.2; 17.3–34.7
Ethnicity	White	14 (56 %)
	Pardo	7 (28 %)
	Black	2 (8 %)
	Indigenous	1 (4 %)
	not declared	1 (4 %)
Marital status	single	18 (72 %)
	married/cohabitation	7 (28 %)
Living arrangements	alone	10 (40 %)
	with parents/siblings	8 (32 %)
	with partner/children	7 (28 %)
Education	12–16 years	14 (56 %)
	>16 years	11 (44 %)
Employment status	employed	21 (84 %)
	occasionally employed/ freelancer	4 (16 %)
Household income[b]	1–3 minimum wage	8 (32 %)
	3–5 minimum wages	8 (32 %)
	5–10 minimum wages	4 (16 %)
	>10 minimum wages	5 (20 %)
Religion	none	14 (56 %)
	Spiritualism	3 (12 %)
	Spiritism	3 (12 %)
	multiple	2 (8 %)
	Candomblé	1 (4 %)
	Santo Daime	1 (4 %)
	indigenous traditions	1 (4 %)
Spirituality	yes	19 (76 %)
	no	3 (12 %)
	unsure	3 (12 %)
Tobacco use	never	11 (44 %)
	<1 time/month	6 (24 %)
	1–10 times/month	4 (16 %)
	11–30 times/month	2 (8 %)
	>30 times/month	2 (8 %)
Cannabis use	never	5 (20 %)
	<1 time/month	1 (4 %)
	1–10 times/month	8 (32 %)
	11–30 times/month	5 (20 %)
	>30 times/month	6 (24 %)
Coffee use	cups/day (mean ± SD; range)	1.6 ± 1.8; 0–6
Alcohol use	units/month (mean ± SD; range)	8.8 ± 10.5; 0–40
MDMA	lifetime (mean ± SD; range)	8.5 ± 10.6; 0–40
Stimulants	lifetime (mean ± SD; range)	6.2 ± 12.4; 0–50
Opioids	lifetime (mean ± SD; range)	0.0 ± 0.0; 0–0
Sedatives	lifetime (mean ± SD; range)	2.1 ± 6.2; 0–30
DMT free base (INH)	lifetime (mean ± SD; range)	1.2 ± 2.8; 0–10
DMT changa (INH)	lifetime (mean ± SD; range)	1.5 ± 4.1; 0–20
DMT jurema (PO)	lifetime (mean ± SD; range)	0.9 ± 3.0; 0–15
DMT yopo (NAS)	lifetime (mean ± SD; range)	0.2 ± 0.7; 0–3
DMT ayahuasca (PO)	lifetime (mean ± SD; range)	5.5 ± 9.1; 0–40
5-MeO DMT (INH)	lifetime (mean ± SD; range)	0.1 ± 0.4; 0–2
LSD	lifetime (mean ± SD; range)	13.3 ± 24.0; 0–100
Psilocybin	lifetime (mean ± SD; range)	2.5 ± 3.7; 0–15
Mescaline	lifetime (mean ± SD; range)	0.2 ± 0.5; 0–2

[a] Data is based on self-reported information, including drug use experience and frequency.
[b] Brazilian minimum wage is 1,212.00 BRL (=229.93 USD; exchange rate from 30 November 2022).
SD, standard deviation; INH, inhaled; PO, per oral; NAS, intranasal.

Blood could not be collected in one subject +120 min after session 1 and in another subject at all time points; therefore, both subjects were excluded from blood analyses.

3.2. Subjective experience

For intensity, there was a main effect of session ($F(1,20) = 153.9$, $p < 0.001$, $\eta_p^2 = 0.89$) with higher means in session 2 than session 1 (Fig. 2**A**). There was a main effect of dose ($F(4,20) = 3.96$, $p = 0.016$, $\eta_p^2 = 0.44$) with higher means for 12.5/50 mg compared to 10/40 mg ($p = 0.012$). No interaction effect was observed. For valence, there was a main effect of session ($F(1,20) = 5.17$, $p = 0.034$, $\eta_p^2 = 0.21$) with higher means in session 2 (Fig. 2**A**). No main effect of dose and interaction effect was observed.

For the HRS, there were main effects of session for the factors visual distortion ($F(1,20) = 36.79$, $p < 0.001$, $\eta_p^2 = 0.65$), cognitive distortion ($F(1,20) = 40.30$, $p < 0.001$, $\eta_p^2 = 0.67$), sensitive distortion ($F(1,20) = 19.45$, $p < 0.001$, $\eta_p^2 = 0.49$), security/control ($F(1,20) = 12.40$, $p = 0.002$, $\eta_p^2 = 0.38$) and quality of experience ($F(1,20) = 24.34$, $p < 0.001$, $\eta_p^2 = 0.55$), with higher means in session 2 (Fig. 2**B**). There was a main effect of dose for agitation ($F(4,20) = 3.28$, $p = 0.032$, $\eta_p^2 = 0.40$) and an interaction session * dose for security/control ($F(4,20) = 3.38$, $p = 0.029$, $\eta_p^2 = 0.40$), but no pairwise comparison survived correction for multiple comparisons. No other session, dose, and interaction effect was observed.

The HRS non-factor items related to safety and tolerability included items on body perception, emotion, control and the desire to repeat the experience (**Table S2**). Regarding body perception, there was an effect of dose for breathing ($F(1,20) = 3.73$, $p = 0.020$, $\eta_p^2 = 0.43$), but no pairwise comparison survived correction for multiple comparisons (**Fig. S2**). Regarding emotion, there was an effect of session for excited ($F(1,20) = 14.17$, $p = 0.001$, $\eta_p^2 = 0.42$), with higher excitement in session 2. Regarding control, there was an effect of session for ease ($F(1,20) = 5.36$, $p = 0.031$, $\eta_p^2 = 0.21$) and sanity ($F(1,20) = 4.54$, $p = 0.046$, $\eta_p^2 = 0.19$), with higher ease and sanity in session 2 (**Fig. S2, S3**). There was also an effect of dose for sanity ($F(1,20) = 4.73$, $p = 0.008$, $\eta_p^2 = 0.49$), but no pairwise comparison survived correction for multiple comparisons. Regarding the desire to repeat the experience, there were effects of session for satisfaction ($F(1,20) = 8.66$, $p = 0.008$, $\eta_p^2 = 0.30$) and regular ($F(1,20) = 8.72$, $p = 0.008$, $\eta_p^2 = 0.30$), with higher satisfaction and desire for regular experiences in session 2 (**Fig. S2**).

For the original HRS factors, see **Supplemental Results** and **Fig. S4**. For all non-significant effects, see **Table S3**.

3.3. Physiology

For SBP, there was a main effect of time point ($F(20,400) = 57.5$, $p < 0.001$, $\eta_p^2 = 0.74$), with higher means, compared to baseline, from +2 min to +26 min in both sessions (all $p \leq 0.02$).

For DBP, there was a main effect of time point ($F(20,400) = 53.0$, $p < 0.001$, $\eta_p^2 = 0.73$) and interaction session * time point ($F(20,400) = 1.63$, $p = 0.042$, $\eta_p^2 = 0.08$). There were higher means, compared to baseline, from +2 min to +18 min in session 1 and from +2 min to +24 min in session 2 (all $p \leq 0.02$). Moreover, a main effect of dose ($F(4,20) = 3.55$, $p = 0.024$, $\eta_p^2 = 0.42$) was found, but no pairwise comparison survived correction for multiple comparisons.

For HR, there was a main effect of session ($F(1,20) = 20.8$, $p < 0.001$, $\eta_p^2 = 0.51$), with higher means in session 2. Moreover, there was a main effect of time point ($F(20,400) = 34.2$, $p < 0.001$, $\eta_p^2 = 0.63$) and interaction session * time point ($F(20,400) = 3.34$, $p < 0.001$, $\eta_p^2 = 0.14$), with higher means, compared to baseline, from +2 min to +6 min in session 1 (all $p \leq 0.02$) and from +2 min to +10 min in session 2 (all $p \leq 0.04$).

For RR, there was a main effect of time point ($F(20,400) = 2.71$, $p < 0.001$, $\eta_p^2 = 0.12$), but no pairwise comparisons survived correction for multiple testing.

For SpO2, there was a main effect of time point ($F(20,400) = 7.74$, $p < 0.001$, $\eta_p^2 = 0.28$), with higher means, compared to baseline, from +2 min to +6 min in both sessions (all $p \leq 0.04$).

For AT, there was a main effect of session ($F(1,20) = 8.17$, $p = 0.010$, $\eta_p^2 = 0.30$), with higher means in session 2, and for time point ($F(20,400) = 6.74$, $p < 0.001$, $\eta_p^2 = 0.26$), with higher means, compared to baseline, from +24 min to +36 min in both sessions (all $p \leq 0.04$).

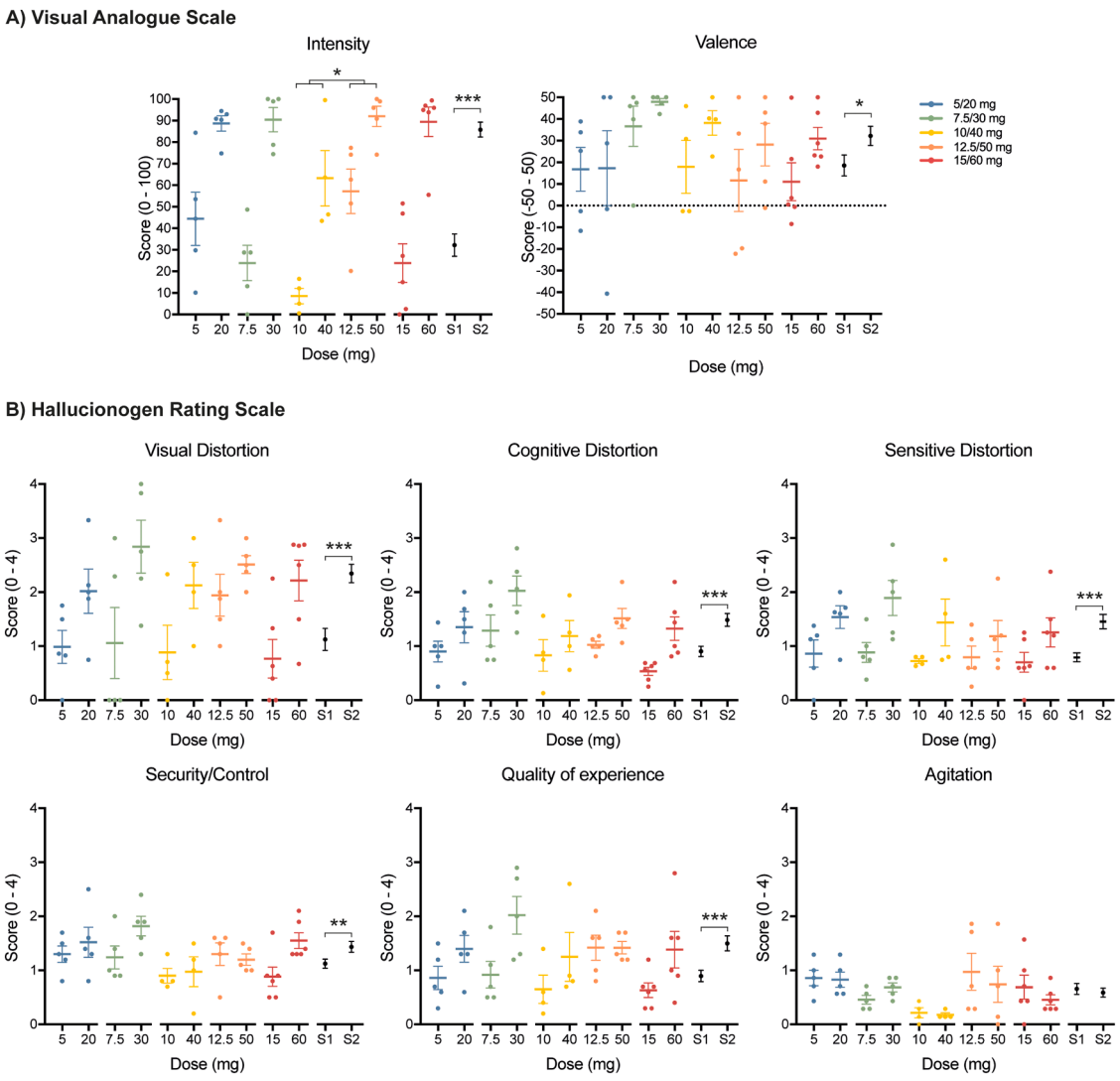

Fig. 2. The effects of DMT on subjective experiences, as measured with a first, lower dose (session 1) and a second, higher dose (session 2) regarding (A) intensity and valence visual analogue scales (VAS) and (B) Hallucinogenic Rating Scale (HRS) factors. Displayed are single subject data (points), means (bold bars) and Standard Errors of Measurement (SEM; narrow bars). *$p \leqslant 0.05$, **$p \leqslant 0.01$, ***$p \leqslant 0.001$. S1, all doses in session 1; S2, all doses in session 2.

For PEFR, no main effects of session, time point, dose or interaction effects were observed.

No other main effects of session, time point, dose and interaction effects were observed.

Fig. 3 shows the physiological changes over time. Results of the non-significant effects are shown in **Table S4**. Means ± SEM of the physiological measurements at +60 min and +120 min are described in **Table S5**.

3.4. Biochemistry

No effect of time point, dose or interaction was observed for glucose, cholesterol, HDL, LDL, triglycerides, AST, and ALT. For GFR, there was a main effect of time point with slight increases over time ($F(2,36) = 3.78$, $p = 0.032$, $\eta_p^2 = 0.17$), but no pairwise comparison survived correction for multiple testing. Results of the non-significant effects are shown in **Table S6**. Mean values for all time points were within population norms (**Table S7**).

3.5. Adverse events

At D0, 54 types of single medical concepts were identified and classified into ten system organ classes. All of them were mild, and 21 of them had an incidence above 10 % in the sample (table 2). Adverse events below an incidence of 10 % were mainly mild ($n = 29$) and occasionally moderate ($n = 3$) (**Table S8**). At D14, only five participants had some mild ($n = 4$) to moderate ($n = 1$) adverse events (**Table S9**). There were no considerable differences in the number of adverse events between sessions or doses.

3.6. Correlations

For subjective experiences, there were positive correlations of dose with intensity ($r = 0.584$, $p < 0.001$, $n = 54$), the HRS factor visual distortion ($r = 0.437$, $p = 0.005$, $n = 54$), and the original HRS factors intensity ($r = 0.415$, $p = 0.009$, $n = 54$) and perception ($r = 0.439$, $p = 0.005$, $n = 54$) (**Fig. S5**). Dose did not correlate with other perceptual, physiological or biochemical measurements.

4. Discussion

This study aimed to assess the safety and tolerability of inhaled DMT (BMND01 candidate) in a phase I clinical trial. We also aimed at identifying an optimized dosing regimen (5/20 mg, 7.5/30 mg, 10/40 mg,

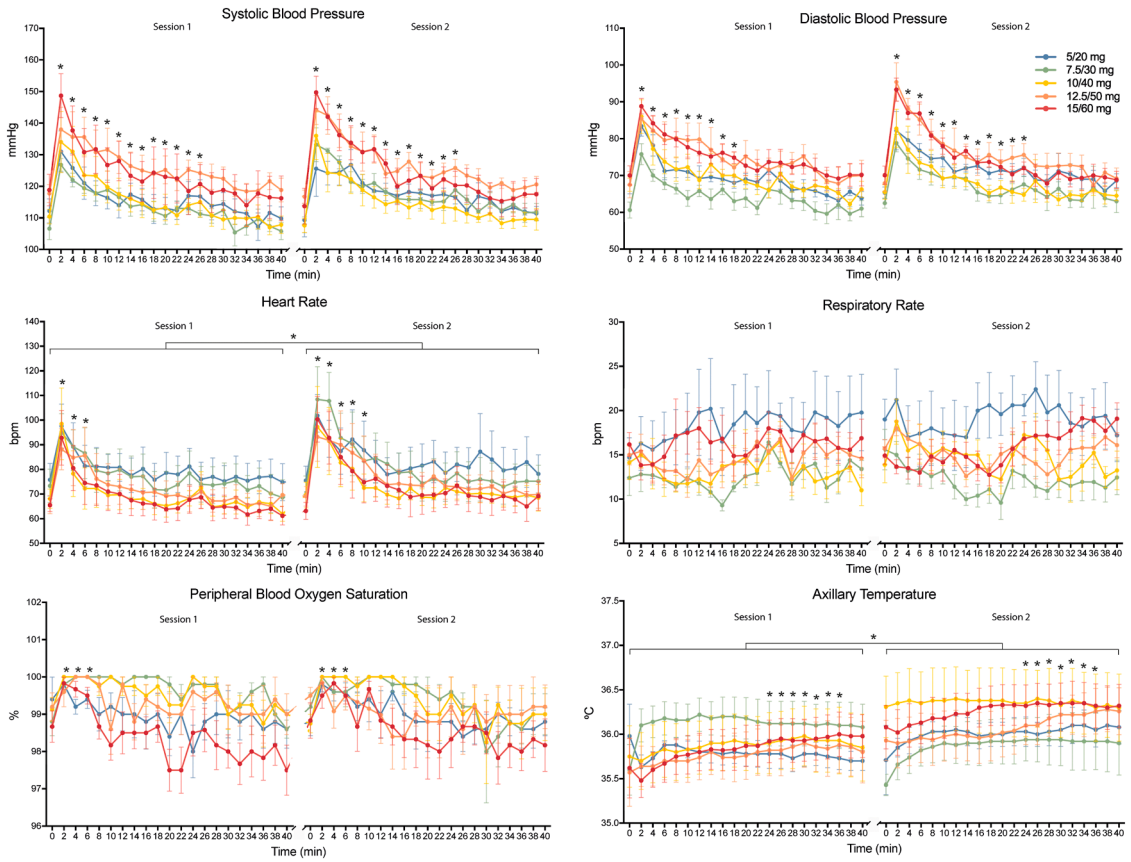

Fig. 3. The effects of DMT on physiological measurements as measured with a first, lower dose (session 1) and a second, higher dose (session 2). Displayed are means (points) and Standard Errors of Measurement (SEM; bars) over the time course of the acute and subacute effects (+0 min to +40 min). *$p \leqslant 0.05$ (each time point compared to baseline).

Table 2
Adverse events during the acute effects with an incidence above 10 %, coded by MedDRA system organ class and preferred term.

Severity	System organ class	Preferred term	5 mg	7.5 mg	10 mg	12.5 mg	15 mg	20 mg	30 mg	40 mg	50 mg	60 mg
Mild	Cardiac disorders	Palpitation	0	0	0	1	0	0	1	0	1	0
	Eye disorders	Lacrimation	2	0	0	0	1	0	0	0	0	1
	Gastrointestinal disorders	Nausea	1	0	0	1	2	0	0	0	1	1
		Sialorrhea	0	0	0	2	1	0	0	0	2	0
		Xerostomia	2	1	0	2	0	0	1	0	1	0
	General disorders and administration site conditions	Feeling cold	4	3	0	1	0	2	1	1	0	1
		Feeling hot	2	0	1	0	0	2	0	0	1	0
		Feeling of "internal" tremor [a]	2	0	0	0	2	1	1	0	1	1
		Tight chest	2	0	1	0	0	0	1	2	0	2
	Musculoskeletal and connective tissue disorders	Shivering	2	1	1	0	1	2	1	0	0	0
		Twitching	2	0	0	0	1	1	0	0	0	1
	Nervous system disorders	Dizziness and giddiness	1	0	0	1	1	0	0	1	1	1
		Headache	1	0	1	0	0	3	1	0	1	2
		Muscle fasciculation	0	0	0	1	0	0	1	0	1	0
		Paraesthesia	0	0	0	0	1	1	1	0	0	2
		Tremor	0	0	0	1	1	1	1	0	0	0
	Psychiatric disorders	Laughter	1	2	1	0	1	3	2	2	0	2
	Respiratory, thoracic and mediastinal disorders	Cough	1	1	1	2	2	2	0	0	2	2
		Hoarseness	1	0	0	0	1	1	0	0	0	1
		Throat clearing	3	2	3	2	4	1	3	2	4	2
		Yawn	1	2	1	1	3	1	1	1	0	2
	Skin and subcutaneous tissue disorders	Sudoresis	0	1	0	0	1	1	2	0	1	0

[a] This item is not a MedDRA term but was maintained due to the high prevalence in the sample.

12.5/50 mg, or 15/60 mg) in a first safety session and a second effective session. Regarding the subjective experience, session 2 compared to session 1 elicited higher intensity, positive emotionality, comfort, control, and psychedelic experiences. In both sessions, the cardiovascular system exhibited a rapid onset of transiently increased blood pressure and heart rate. DMT increased peripheral oxygen saturation acutely and body temperature sub-acutely. DMT did not change biomarkers for acute hepatotoxicity or renal failure. Only mild to moderate but no

serious adverse events were found, mostly classified as presumably adverse drug reactions (ADR). Overall, the results indicate that inhaled DMT is safe and well tolerated by healthy individuals and that first lower doses might aid to enhance security and comfort in second, higher doses. Therefore, we propose a single-ascending fixed-order dose escalation procedure within the scope of interventional psychiatry (Brunoni et al., 2022) at the outpatient care level, in contrast to the psychedelic-assisted psychotherapy model (Carhart-Harris et al., 2018) and in line with previous recommendations of dose escalation schemes for 5-MeO-DMT (Reckweg et al., 2021) or IV DMT (D'Souza et al. 2022). Yet, in contrast to D'Souza et al. (2022), we propose a prepared setting and no tertiary care level. We believe this model is cost- and time-effective and scalable.

4.1. Subjective experience

The effects emerged within a few seconds, peaked around 1 min, lasted for a few minutes, and subsided after 10–20 min. This combines with previous reports of rapid intensity onset (<1 min), peak (2–3 min) and end (17–30 min) for IV administration (Strassman and Qualls, 1994; Timmermann et al., 2019; Vogt et al., 2023). Compared to the first, lower dose, the second higher dose elicited higher intensity, positive emotionality (valence, excitement, affect, laughter), comfort (quality of experience, satisfaction, regular), control (security, ease, sanity), somatosensory (somaesthesia) and psychedelic experiences (visual, cognitive, and sensitive distortion), indicating stronger perceptual effects and comfort for higher doses. In a similar line are the correlations of dose with intensity and visual distortions, pointing to a close relationship between DMT dose and (visual) psychedelic experiences.

Yet, higher comfort and control in the second session might be influenced by order effects, since lower doses always preceded higher doses. Together with the lack of correlations between doses and security, this suggests that a first session promotes the tolerability of the second session, increasing familiarity with the setting. This is supported by corresponding feedback during the integration (**Supplemental Results**) and in line with a previous 5-MeO-DMT study recommending escalating doses over single doses (Reckweg et al., 2021). Therefore, our design of a first, lower safety dose followed by a higher "psychedelic" dose seems suitable for future clinical trials with patients.

Main effects of dose for intensity, agitation, breathing and sanity indicate influences of the dosing group on perceptual and somatosensory effects. However, this might be explained by the overall lower ratings in the 10/40 mg group (Fig. 1**, S2**), containing two subjects with unsatisfactory inhalation, and highlights the need to carefully interpret dosing group effects due to the small sample size within groups. Similarly, note that valence and HRS ratings were overall in a similar range in both sessions, despite a four times higher dose. This includes even intensity ratings which showed less than three times the difference. Overall these findings indicate a higher importance of the successive sessions (lower followed by higher doses) than specific dosing schemes (5/20 mg to 15/60 mg) and reinforce the crucial importance of external/situational factors (e.g. administration protocol, repetition of sessions), compared to less influential mg-dosages, on the overall experience. Moreover, an explanation might lie in the limitations of our drug inhalation method, which is prone to variability depending on lung capacity and previous experience in inhaling drugs.

Similarly to our findings, online reports on inhaled DMT reflected somaesthetic experiences, visualizations, entity encounters, unusual places, altered consciousness, and positive emotions (Kagan, 2022; Lawrence et al., 2022). IV DMT studies (7 to 30 mg) reported intense visual, bodily and emotional experiences (Strassman et al., 1994; Timmermann et al., 2019). Contrastingly, another IV DMT study reported dose-related changes for cognition (HRS), but not for other HRS factors (intensity, somaesthesia, affect, perception) (Gouzoulis-Mayfrank et al., 2005). This might be due to differences in administration route (IV), dose (low ≈ 12 mg, high ≈ 18 mg), or design (initial dose followed by continuous infusion of around 1 mg/min over 84 min) and remains to be better explored in future studies.

All doses were well tolerated, i.e., effects were considered overall as pleasant (positive valence, low agitation, high satisfaction). Participants rarely reported panic or despair (HRS items 27, 38) and mostly desired to repeat the experience within one week or month (HRS item 48), indicating an acceptable profile for subjective tolerability. The low agitation may indicate that DMT has low risks of triggering the psychomotor agitation syndrome, a psychiatric urgency which, in fact, was not observed in any volunteer. This encourages the DMT use for mental disorders at greater risk of psychomotor agitation, such as personality disorder, anxiety disorder, and agitated depression (Garriga et al., 2016).

Notably, the higher desire for regular experiences in the second session might point to higher potential of drug addiction for higher doses. However, this seems improbable, considering that the desired frequency was less than "within a week", that another DMT study did not find higher risks (D'Souza et al., 2022), and that the general misuse potential for psychedelics is low (Nutt et al., 2007).

4.2. Physiology

Overall, all doses were safe regarding vital signs and no participant reached hypertensive crisis levels.[3] During the acute effects, there were only mild, transient, and self-limited increases in blood pressure and heart rate of up to 30 % compared to baseline, with no clinical implications. This is comparable to moderate-to-vigorous physical activity in healthy individuals (Burger et al., 2009). Moreover, post-acute safety measurements after each session (+60 and +120 min) indicate that physiology returned to baseline in all subjects (**Table S5**).

Similarly to the subjective effects, physiological effects (Fig. 3), compared to baseline, peaked in the first minutes (+2 min) for systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and peripheral oxygen saturation (SpO2) and subsided between +6 min to +26 min. Axillary temperature (AT) exhibited delayed increases from +24 min to +36 min. Consistent with literature (Vogt et al., 2023; D'Souza et al. 2022; Strassman et al., 1994), DMT produced rapid onsets and acute, transient increases in the cardiovascular system, including SBP, DBP, and HR. SpO2 increased from +2 min to +6 min. DMT did not induce respiratory depression and alter respiratory rate (RR) or peak expiratory flow rate (PEFR).

Compared to the first, lower dose, the second, higher dose elicited higher SBP and DBP and longer increases in DBP and HR (Fig. 3), indicating that DMT dose-dependently affects the cardiovascular system. Contrastingly, previous findings on IV DMT found higher HR, but not SBP, for higher doses and overall weaker cardiovascular effects (D'Souza et al. 2022). These differences may be explained by various factors, including assessment timing, dose, route, salt (fumarate in IV, free base in inhaled), and duration of psychedelic effects. Therefore, a direct comparison between both routes is necessary to determine differences and similarities.

4.3. Biochemistry

This is the first study to investigate safety biomarkers after non-oral DMT. Safety blood biomarkers were unchanged 120 min after DMT dosing. Therefore, DMT seems not to induce strong changes in glycemia and free lipids or acute hepatotoxicity and renal failure. In line with our findings, a long-term study with ayahuasca reported unchanged liver and kidney blood biomarkers after multiple ayahuasca sessions over one year, pointing to its safety regarding hepatic and renal functions (Mello et al., 2019). Beyond that, a rodent study showed that DMT induces

[3] Defined by an increase in SBP > 180mmHg and DBP > 120mmHg (Satheeshkumar et al. 2022).

potential renal protective actions after kidney injury (Nemes et al., 2019).

4.4. Adverse events

There was no serious adverse event during acute, sub-acute (D0), or post-acute effects (D14) due to DMT administration and all participants chose to undergo both dosing sessions. Adverse events were cautiously considered adverse drug reactions (ADR) and mainly mild. The three most common adverse events were related to respiratory, thoracic, and mediastinal disorders (n = 56), followed by general disorders and administration site conditions (n = 35) and nervous system disorders (n = 27) (Table 2).

The respiratory, thoracic, and mediastinal disorders resulted from the irritating DMT vapor, causing coughing during inhalation (**Table S1**), which rarely persisted until the subacute effects. Mild hoarseness was observed sub-acutely but resolved after a few minutes. Throat clearing was observed during psychological integration but resolved by the sessions' end. The general disorders and administration site conditions included reports of feeling cold (n = 13), mostly in lower doses (5/20 mg, 7.5/30 mg); this has implications for the setting, which should provide thermal comfort and blankets. Notably, feeling cold was not related to objective measurements of body temperature. Similarly, some volunteers reported "internal" tremors (n = 8), but only a few had visible tremors (n = 4) (table 2). The nervous system disorders could be attributed, on the one hand, to neuromuscular hyperactivity (tremor and muscle fasciculation), and on the other hand, dilation-vasoconstriction in blood vessels affecting nociceptive receptors (headache) as a physiological response to the DMT-induced 5-HT agonism (Thor et al., 2007; Aggarwal et al., 2012; Francescangeli et al., 2019). Individual case reports are described in the **Supplemental Material**.

Beyond that, DMT as an endogenous substance (Carbonaro and Gatch, 2016) elicits no risks of anaphylaxis. Overall, we consider the main risks to be related to the sympathomimetic effects on the cardiovascular system and the airways' hyperresponsiveness due to inhalation route and vaporized formulation. Moreover, given the cardiovascular effects of DMT, previous screening for cardiovascular risk factors and real-time cardiovascular monitoring is critical.

4.5. Limitations

The fixed-order design, intended for safety check by administering a first, lower dose before a second, higher dose, does not allow to disentangle dose effects from order effects. This is particularly relevant for subjective experiences and highlights the need for placebo-controlled, randomized designs. Moreover, we did not quantify the time course of subjective effects, but focused on overall experiences. Furthermore, the lack of pharmacokinetic data impedes examining the correlation between doses and blood concentration, which is a vital aspect to be investigated for future therapeutic applications. The sample was ethnically and socioeconomically homogenous, highly experienced with psychedelics, and had a small sample size per dosing scheme. The inhalation technique's variability and the occasionally unsatisfactory quality underscore the need to refine the administration procedures and measure serum DMT concentrations to quantify the absorbed doses. Future research should incorporate ECG morphology evaluations, specifically the QT interval and QRS complex, and investigate the potential for tachyphylaxis effects to optimize dosing regimens for patient populations.

4.6. Conclusions

This study provides the first in-lab results on inhaled DMT in healthy individuals, which we found to be safe and well tolerated. Isolated DMT seems to have several advantages compared to oral psychedelics, including shorter duration and lower and better manageable risk of interaction with antidepressants. Additionally, compared to IV administration, inhaled DMT offers a non-invasive administration route that may be of advantage for a wider application in outpatient health facilities with simpler clinical protocols. If phase II clinical trials indicate antidepressant properties of inhaled DMT, this paradigm might prompt an economic and safe alternative to resource-intensive oral psychedelic treatments, potentially enabling broader accessibility and ease of use in more diverse therapeutic contexts.

Contributors

MFC, IW, LOM, NGC, DBA, and FPF designed the study; EA, DBA, and FPF acquired the authorizations; SRBS and EJP extracted the substance; MFC selected the participants, lead the session, administered the substance and served as psychiatric head of the study; HB and SL provided psychological support; FA and AA provided nursing support; MFC, IW, HB, SL, FA, ST, NSC, AA, RA, and LOM acquired the data; NSC, RA, RB, and JVCM provided research assistance; MFC, IW, and FPF analyzed the data; MFC, IW, DBA, and FPF wrote the article; all authors reviewed the manuscript and approved the final version.

Role of funding source

This study was jointly funded by Biomind Labs Inc. and the Federal University of Rio Grande do Norte (UFRN). Additionally, the Hospital Universitário Onofre Lopes (HUOL), the CAPES Foundation, and the Fulbright Foundation provided support for this work. These funding sources had no further roles in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decisions to submit the paper for publication.

Conflict of Interest

Marcelo Falchi was the Head of the Psychiatric Research Unit at Biomind Labs Inc during the course of the study. Draulio Barros de Araujo was the Scientific and Clinical Advisor of Biomind during the course of the study. The remaining authors declare that the research was conducted in the absence of any commercial relationships that could be construed as a potential conflict of interest.

Acknowledgements

We thank Geissy Araujo for her help in the design of the protocol for psychological support, Stela Antas Urbano, Rubens Gustavo, and José Ednágelo (Edson) Silva for handling the *M. tenuiflora* specimens, Dayanne Lopes Porto for her support in the chemical analysis, Raphael Egel for the composition of the music used in the study, Hítalo Breno de Oliveira Souza for helping with the blood sample collection, Iago Morais Barreto, Paulo Ricardo Reis Scarin, and Elisabete Castelon Konkiewitz for their medical advice, Kaike Thiê da Costa Gonçalves and Scarlett O'Hara Gabriela Medeiros Gonçalves Pereira for their help with the clinical and psychiatric follow-up, Dimitri Daldegan-Bueno for his advice in the statistical models, and Gabriel Kazuo Masuko Hotta for layout advice.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2023.12.006.

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