Original paper

Beyond symptom reduction: DMT improves anxiety, life satisfaction, and quality of life in healthy volunteers and patients with depression

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Abstract

Background: Recent studies have demonstrated rapid antidepressant effects of inhaled *N,N*-dimethyltryptamine (DMT); however, long-term effects, including broader well-being dimensions, are sparsely explored across populations.

Aims: Investigating whether DMT produces sustained improvements in anxiety, life satisfaction, and quality of life, in both healthy individuals and patients with treatment-resistant depression (TRD).

Methods: In 2 open-label clinical trials, 27 healthy individuals and 14 patients with TRD, respectively, received inhaled DMT in a supportive clinical setting. Repeated assessments were conducted from baseline up to 12 months (only patients), including state anxiety (State-Trait Anxiety Inventory State, STAI-S), life satisfaction (Satisfaction with Life Scale, SWL), and quality of life (World Health Organization Quality of Life Instrument – Abbreviated Version, WHOQOL-BREF, and Spirituality, Religion and Personal Beliefs Module, WHOQOL-SRPB).

Results: All volunteers showed reduced state anxiety after inhalation up to 1 day afterward. Healthy volunteers reported increased life satisfaction up to 14 days post-administration. Beyond symptom reduction, patients reported increased life satisfaction after 12 months and sustained improvements in quality of life over that period, including Physical Health, Psychological Health, Social Relationships, and Environment (WHOQOL-BREF), and partially Inner Peace and Hope & Optimism (WHOQOL-SRPB).

Conclusion: These findings suggest that inhaled DMT, combined with psychological support, is associated with recovery of daily functioning and health domains in patients with depression. Although limited by open-label design, lacking placebo control, and modest sample size, this exploratory study highlights the value of incorporating multidimensional outcomes in psychedelic research and DMT's potential relevance in both clinical and public health contexts.

Keywords

N, *N*-dimethyltryptamine, anxiety, life satisfaction, quality of life, depression, treatment-resistant depression

Introduction

Recent studies have demonstrated that inhaled *N,N*-dimethyltryptamine (DMT) produces rapid and robust antidepressant effects, positioning this molecule as a promising candidate within the field of psychedelic-assisted interventions (D'Souza et al., 2022; Falchi-Carvalho et al., 2025). These findings are notable given the enduring challenge of treatment-resistant depression (TRD), a condition associated with limited response to conventional therapies, high recurrence rates, and significant functional impairment (Baig-Ward et al., 2023; Sforzini et al., 2022). Yet, while symptom remission remains a critical outcome, contemporary frameworks of recovery increasingly emphasize the importance of broader dimensions of well-being, such as anxiety relief, life satisfaction, and quality of life that more fully capture the lived experience of patients with depression (Schrank et al., 2012; Yang et al., 2022).

The potential for psychedelics to influence these outcomes has been increasingly documented. For example, studies with

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psilocybin and ayahuasca, an indigenous natural preparation containing DMT, have consistently reported enhancements in psychological flexibility, meaning in life, social connectedness, and existential well-being (Griffiths et al., 2016; Jiménez-Garrido et al., 2020; Palhano-Fontes et al., 2018; Thomson and Thomacos, 2025). Improvements in life satisfaction and quality of life are of particular interest, as they extend the therapeutic focus from symptom reduction to encompassing physical, psychological, social, and environmental domains of functioning. Such outcomes are critical to reintegration, resilience, and long-term health, yet remain underexplored in the literature on DMT.

Among classic psychedelics, DMT is unique for its pharmacokinetic profile: when inhaled, it induces immersive but short-lived experiences lasting 5–20 minutes (Strassman and Qualls, 1994; Wießner et al., 2025). This brevity contrasts with the prolonged durations of psilocybin and ayahuasca (4–8 hours). It carries implications for scalability and accessibility, reducing the infrastructure demands and costs associated with psychedelic-assisted therapy (Marseille and Mitchell, 2025). Beyond practical considerations, the subjective effects of DMT are often described as particularly intense, emotionally charged, and personally meaningful, suggesting its potential as a catalyst for psychological and existential transformation (Lawrence et al., 2022; Pallavicini et al., 2021; Rodrigues et al., 2025; Timmermann et al., 2019).

Despite these advantages, evidence linking inhaled DMT to improvements in domains such as anxiety, quality of life, and life satisfaction remains limited. Observational studies with ayahuasca have reported reductions in state anxiety and increases in quality of life across physical, psychological, and social domains (Jiménez-Garrido et al., 2020; Lowe et al., 2024; Van Oorsouw et al., 2022). Clinical studies on psilocybin in patients with life-threatening illness have also demonstrated enduring benefits in life satisfaction and existential peace alongside reductions in anxiety (Griffiths et al., 2016; Ross et al., 2016). Together, these data suggest that psychedelics may facilitate recovery processes that extend beyond the alleviation of core affective symptoms, addressing dimensions often overlooked by standard pharmacological or psychotherapeutic approaches.

The present exploratory study builds on these insights by investigating whether inhaled DMT, administered in a supportive clinical setting, produces sustained improvements in anxiety, life satisfaction, and quality of life. We evaluated these outcomes in both healthy volunteers and patients with TRD, using validated measures across follow-up periods up to 12 months. By this, we sought to determine whether DMT supports durable changes in broader domains of well-being, thereby expanding the therapeutic relevance of its effects. This multidimensional perspective is particularly important for patients with TRD, where reductions in depressive symptoms may be necessary but not sufficient for recovery, and where gains in these other domains can signify a fuller restoration of functioning and existential health.

Methods

Study design

This article presents an exploratory, secondary analysis of data from two previously published clinical trials. The trials had distinct objectives, aiming to investigate the effects of inhaled DMT, combined with psychological support, on healthy individuals—phase I (Falchi-Carvalho et al., 2023) and on patients with depression—phase IIa (Falchi-Carvalho et al., 2025). The first was a phase I trial to evaluate the safety, tolerability, and dose optimization of DMT. It employed an open-label, single-ascending, fixed-order dose–response design with five dosing schemes. Each scheme consisted of two administrations on the same day: a lower dose in session 1 (S1), followed by a higher dose in session 2 (S2). Accordingly, the five dosing schemes were as follows (S1/S2): 5/20 mg, 7.5/30 mg, 10/40 mg, 12.5/50 mg, and 15/60 mg. The second was a phase IIa trial in TRD patients to investigate antidepressant effects. It followed an open-label design with a fixed dosing scheme of 15/60 mg.

Both studies were approved by the Ethics Committee of the University Hospital Onofre Lopes (HUOL) of the Federal University of Rio Grande do Norte (approval number 45532421.0.0000.5292), registered at clinicaltrials.gov (NCT05573568, NCT06094907), and conducted following the Declaration of Helsinki. The analyses of anxiety, life satisfaction, and quality of life were pre-registered for healthy individuals, but not for patients.

Participants

Recruitment in both studies occurred through online advertisements, word of mouth, and, for patients, physicians' referrals via professional social media networks. For details on the candidate selection and participant requirements, see Supplemental Methods.

In short, healthy individuals had to be aged 21–60 years. They underwent a comprehensive screening, including a medical and psychiatric interview, review of self-reports and medical records, complementary examinations when necessary, and a check of the eligibility criteria. Overall, 27 healthy volunteers were recruited.

Patients with TRD had to be aged 18–60 years. They were required to meet the diagnostic criteria for experiencing a moderate to severe depressive episode for at least 4 weeks and without achieving remission with at least two antidepressant medications. Diagnoses were confirmed during screening by psychiatric evaluation, supported by the Mini International Neuropsychiatric Interview (MINI 5.0.0, Brazilian version) (Amorim, 2000). Patients also had to score at least 20 points on the Montgomery Åsberg Depression Rating Scale (MADRS; Carneiro et al., 2015). Exclusion criteria included a history of bipolar or psychotic disorders or other relevant medical conditions. Altogether, 14 patients were selected.

All participants signed informed consent before enrollment and agreed to abstain from psychedelics. Healthy volunteers abstained from 14 days before to 28 days after dosing, and patients with depression abstained from 14 days before to 3 months after dosing. Patients were instructed to maintain their usual pharmacological treatment, including psychotropic medications, in order to avoid clinical destabilization in this treatment-resistant population. No systematic medication washout was required, except for lithium and monoamine oxidase inhibitors, which were discontinued at least 5 and 14 days before dosing, respectively.

Drug

Both samples received purified DMT freebase, isolated from the root bark of regionally and organically growing *jurema* trees

(*Mimosa tenuiflora*). Chromatography-mass spectrometry analyses indicated a purity >99% (healthy) and >96% (patients). The freebase was dissolved in 99% ethanol to ensure more uniform distribution on a metallic mesh, which was used for vaporization in a vaporizer (Volcano Medic 2, Storz & Bickel GmbH & Co, Tübingen, Germany).

Measurements

Psychological outcomes in both samples included self-reported anxiety, life satisfaction, and quality of life. State anxiety was assessed using the State-Trait Anxiety Inventory – State Version (STAI-S), consisting of 20 items answered on a 4-point Likert scale (1 = not at all; 4 = very much; Fioravanti-Bastosa et al., 2011). Life satisfaction was measured using the Satisfaction with Life Scale (SWL), consisting of five items answered on a 7-point Likert scale (1 = strongly disagree; 7 = strongly agree; Gouveia et al., 2009). Quality of life was assessed using two instruments, including the World Health Organization Quality of Life Instrument – Abbreviated Version (WHOQOL-BREF), which consists of 26 items answered on a 5-point Likert scale (1 = not at all; 5 = completely). The WHOQOL-BREF comprises four domains: Physical, Psychological, Social Relationships, and Environment (Fleck et al., 2000). In addition, we used the WHOQOL – Spirituality, Religion and Personal Beliefs Module (WHOQOL-SRPB), which consists of 32 items answered on a 5-point Likert scale (1 = not at all; 5 = completely). The WHOQOL-SRPB evaluates the eight domains: Spiritual Connection, Meaning & Purpose in Life, Experiences of Awe & Wonder, Wholeness & Integration, Spiritual Strength, Inner Peace, Hope & Optimism, and Faith (Panzini et al., 2011).

Psychedelic experiences were reported in previous publications (Falchi-Carvalho et al., 2023, 2025) and reemployed in this work for their correlations with the psychological outcomes. Details on the psychedelic scales are described in the Supplemental Methods. Briefly, both samples received a Visual Analog Scale (VAS) on Intensity and Valence (Wießner et al., 2023). For healthy individuals, we also used the Hallucinogen Rating Scale (HRS; Mizumoto et al., 2011). For patients, we used the Five Dimensions of Altered States of Consciousness Scale (5D-ASC; Rodrigues et al., 2025) and Mystical Experience Questionnaire (MEQ; Schenberg et al., 2017).

In patients, we also used previously reported psychiatric outcomes (Falchi-Carvalho et al., 2025) for correlations with the psychological outcomes. These included clinician-rated depression by the MADRS (Carneiro et al., 2015), self-rated depression by the Patient Health Questionnaire – 9 Item Version (PHQ-9; Nunes and Faro, 2022), and suicidal ideation by the Beck Scale for Suicide Ideation (BSI; Cunha, 2001; Supplemental Methods).

Procedures

Both trials were conducted in the Psychedelic Research Unit of the HUOL, in a research room designed to combine clinical safety with a comfortable environment, consistent with the extrapharmacological safety standards recommended for psychedelic clinical trials (Pronovost-Morgan et al., 2025). After screening, participants attended a preparation meeting with a psychologist. This preparation was designed to build rapport, clarify questions, explain the effects of DMT, cultivate intentions, align expectations, and provide strategies for managing challenging experiences. Baseline measurements (D0) of SWL, WHOQOL-BREF, and WHOQOL-SRPB were completed during preparation (healthy individuals) and online (patients).

On the dosing day, all participants arrived in the morning and underwent baseline measurements, including the STAI-S (D0). In the first session (S1), participants underwent preparation with the psychologist shortly beforehand, at 9:30 AM (healthy)/8:45 AM (patients), receiving the lower DMT dose, intended primarily to verify safety and prepare for the higher dose. Afterward, they underwent a short psychological integration, reporting their experience (healthy: 15 minutes; patients: 30 minutes), and filled in the STAI-S (only healthy) and psychedelic experience questionnaires. In the second session (S2), at 11:40 AM (healthy)/10:30 AM (patients), they received the higher DMT dose. Subsequently, they went through a 60-minute integration, including drawing a mandala as a non-verbal expression of the experience (Barros et al., 2025) and filled in the psychedelic experience questionnaires and the STAI-S. During the acute DMT effects in both sessions, participants lay in a recliner with their eyes closed and listened to music composed for the study (freely available at egel.bandcamp.com/album/music-for-dmt-trials). The sessions were accompanied by a psychiatrist and a psychologist, ensuring safety and providing support when needed. At the end of S2, participants were evaluated psychiatrically and medically and discharged into the care of a family member or trusted companion.

Follow-up online meetings with a psychologist were conducted to promote the integration of the psychedelic experience into daily life. For healthy participants, these integrations occurred on day 1 (D1) and 14 days after dosing (D14), while for patients, they occurred on D1 and 7 days after dosing (D7). Each integration lasted a maximum of 1 hour. Here, the psychologist adopted an empathic and supportive stance and encouraged the participant to verbally process the experience through guiding questions to foster its emotional integration beyond the conceptual level. Questions included, for example, "How are you feeling today?" and "Did the experience have any impact on how you see yourself?" The questions were aimed at the emotional elaboration of the experience by the individual in their life, with an emphasis on their perception of themselves in the post-experience period.

Follow-up online assessments were also collected at several time points from D1, 2 days post-administration (D2), up to 3 months (M3), and 12 months post-administration (M12). However, assessment time points were not completely identical between trials. Specifically, these included the STAI-S at D1, D2 (only healthy), D7, D14, M1, and M12 (only patients); the SWL at D1 (only healthy), D7, D14, M1, M3 (only patients), and M12 (only patients); and the WHOQOL-BREF and WHOQOL-SRPB at D14, M1, M3 (only patients), and M12 (only patients).

Statistical analyses

Given the methodological differences between the trials, analyses were conducted separately using a linear mixed model with a Toeplitz covariance structure, and no formal pooled analysis was performed. Missing data were estimated using restricted maximum-likelihood estimation. Time (D0 to M12) and domain (only for WHOQOLs) were included as within-subject factors. For

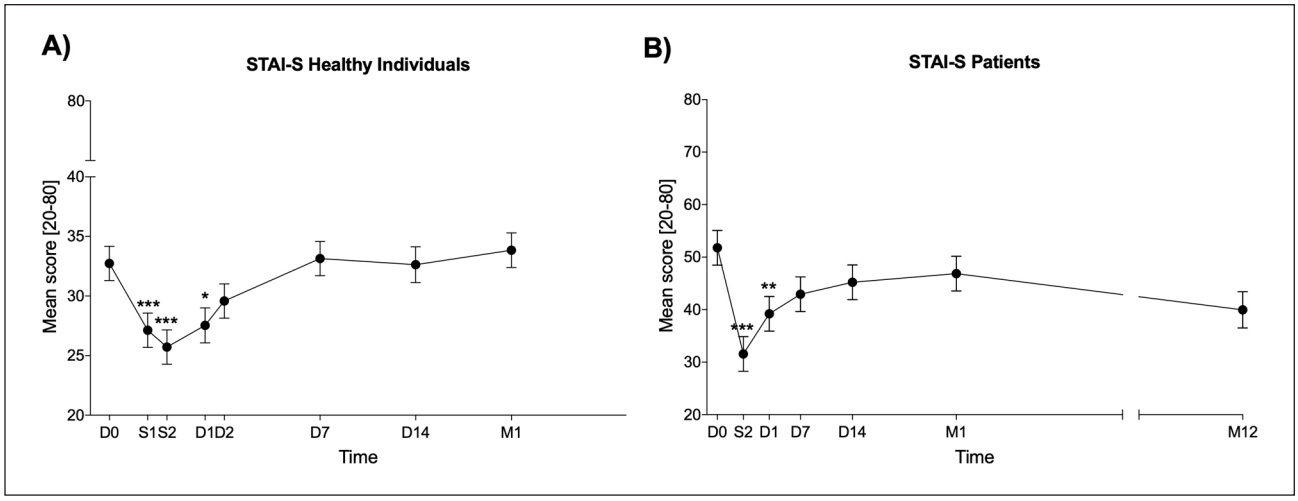

Figure 1. DMT post-acutely reduced anxiety in healthy individuals and patients with depression. (a) Healthy individuals reported decreased anxiety, compared to baseline, after the first, lower DMT dose, which persisted until 1 day after dosing. (b) Similarly, TRD patients reported decreased anxiety, compared to baseline, after DMT administration until the next day. Data represent mean ± SEM scores on the STAI-S.
$^{*}p < 0.05$. $^{**}p < 0.01$. $^{***}p \leqslant 0.001$ (Bonferroni-corrected post hoc pairwise comparisons).
D0, baseline; S1, after the first dosing session; S2, after the second dosing session; D1, 1 day post-administration; D2, 2 days post-administration; D7, 7 days post-administration; D14, 14 days post-administration; M1, 1 month post-administration; M12, 12 months post-administration; DMT, N,N-dimethyltryptamine; TRD, treatment-resistant depression; SEM, standard error of the mean; STAI-S, State-Trait Anxiety Inventory – State Version.

healthy individuals, dose (5/20 mg, 7.5/30 mg, 10/40 mg, 12.5/50 mg, 15/60 mg) was included as a between-subject factor. The main effect of time and dose, and the interactions time × dose and time × domain were evaluated. Post hoc pairwise comparisons were performed between D0 and the corresponding follow-up measurement. Cohen's *d* effect sizes were calculated as the difference between means divided by the pooled standard deviation, using the baseline and the timepoints at which statistically significant differences were observed.

Spearman's correlations were computed to examine associations between changes in psychological outcomes (STAI-S, SWL, WHOQOL-BREF, WHOQOL-SRPB) and the previously reported psychedelic experiences (VAS, HRS, 5D-ASC, MEQ) at time points with significant effects. For patients, we also correlated psychological outcomes with the previously reported psychiatric outcomes (MADRS, PHQ-9, BSI). For details on the correlation analyses, see Supplemental Methods.

All *p*-values were Bonferroni corrected for multiple comparisons, and the significance level was defined at $\alpha = 0.05$ (two-tailed). All analyses were performed using IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA).

Results

Participants

All participants completed both dosing sessions (low and high DMT dose). In the phase I trial, two individuals were excluded from the analyses due to unsatisfactory inhalation, resulting in a final sample of $n = 25$. One participant did not complete the questionnaires at D14, and another at M1. In both cases, responses could not be obtained within the data collection period despite repeated attempts by the research team to establish contact. In addition, one participant did not complete the STAI-S at D1 and another at D14, possibly reflecting minor procedural limitations in verifying response completeness during data collection. The healthy group had a mean age of 30.3 years (±6.5), with 12 women and 13 men, and several previous experiences with psychedelics (mean 26.8 ± 30.2). In the phase IIa trial, all participants completed assessments at all time points, except for two patients (one male, 48 years old, and one female, 33 years old) who did not complete the M12 assessment. It was not possible to contact these participants at follow-up, as they did not respond to the research team's attempts. The patient group had a mean age of 35.2 years (±12.2), with six women and eight men, and substantially less previous experience with psychedelics (mean 1.5 ± 3.3). Both samples were predominantly White or of mixed ethnicity, highly educated, single, and unaffiliated with any religion. While the healthy participants were mostly employed and had a household income of 1–5 minimum wages, the patients were mostly unemployed and had a household income of 3–10 minimum wages. Detailed sociodemographic data of both samples are shown in Table S1. Table S2 describes the medication regimen for the patients.

Anxiety

Among healthy participants, self-reported STAI-S scores showed a main effect of time ($F(7, 40.47) = 5.32$, $p < 0.001$). Pairwise comparisons revealed decreases from D0 to S1 ($p < 0.001$, $d = 0.89$; 95% CI: 0.31, 1.47), S2 ($p < 0.001$, $d = 1.11$; 95% CI: 0.51, 1.70), and D1 ($p = 0.040$, $d = 0.58$; 95% CI: −0.003, 1.15; Figure 1(a)). No main effects of dose or interaction time × dose were detected (Table S3), overall indicating post-acute, dose-independent reductions in anxiety up to 1 day after dosing. For all fixed effects estimates and Cronbach's α, see Table S4.

In patients, a similar time effect emerged on the self-reported STAI-S ($F(6, 31.02) = 7.18$, $p < 0.001$, Table S4). Post hoc

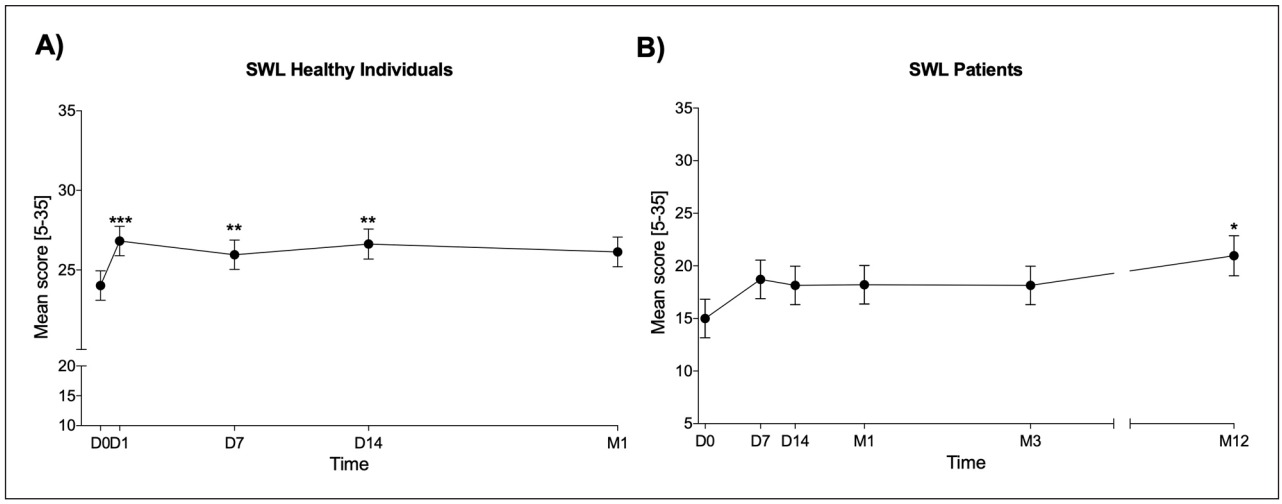

Figure 2. DMT enhanced long-term life satisfaction in healthy individuals and patients with depression. (a) Healthy individuals reported greater life satisfaction than at baseline, from day 1–14 days after dosing. (b) TRD patients reported increased life satisfaction after 12 months, compared to baseline. Data represent mean ± SEM scores on the SWL.

*$p < 0.05$. **$p < 0.01$. ***$p \leq 0.001$ (Bonferroni-corrected post hoc pairwise comparisons).

D0, baseline; D1, 1 day post-administration; D7, 7 days post-administration; D14, 14 days post-administration; M1, 1 month post-administration; M3, 3 months post-administration; M12, 12 months post-administration; DMT, N,N-dimethyltryptamine; TRD, treatment-resistant depression; SEM, standard error of the mean; SWL, Satisfaction with Life Scale.

analyses revealed decreases from D0 to S2 ($p < 0.001$, $d = 2.38$; 95% CI: 1.41, 3.34) and D1 ($p = 0.006$, $d = 0.96$; 95% CI: 0.18, 1.74; Figure 1(b)), indicating post-acute anxiety decreases in TRD patients up to 1 day after DMT administration. Although mean STAI-S scores at M12 appeared lower than baseline, this difference did not reach statistical significance ($p = 0.239$) and was therefore not marked as significant in Figure 1(b).

Life satisfaction

In healthy volunteers, we observed self-reported changes in SWL over time ($F(4, 28.73) = 5.22$, $p = 0.003$, Table S4). Pairwise comparisons showed increases from D0 to D1 ($p = 0.001$, $d = -0.50$; 95% CI: −1.06, 0.07), D7 ($p = 0.014$, $d = -0.33$; 95% CI: −0.89, 0.23), and D14 ($p = 0.006$, $d = -0.43$; 95% CI: −1.00, 0.14; Figure 2(a)). No main effects of dose or interaction time × dose were detected (Table S3), altogether indicating dose-independent enhancements of life satisfaction up to 14 days after DMT administration.

For patients, the self-reported SWL showed a main effect of time ($F(5, 24.27) = 3.03$, $p = 0.030$), with increases from D0 to M12 ($p = 0.050$, $d = -0.92$; 95% CI: −1.73, −0.11; Figure 2(b)), suggesting long-term improvements in life satisfaction among TRD patients.

Quality of life

In healthy individuals, we did not find any self-reported WHOQOL-BREF effects for time, dose, and interactions time × dose and time × domain (Figure 3(a); Tables S3 and S4).

In contrast, self-reported patient WHOQOL-BREF scores exhibited a pronounced main effect of time ($F(4, 31.31) = 9.15$, $p < 0.001$, Table S4), with pairwise comparisons showing increases from D0 to D14 ($p < 0.001$), M1 ($p < 0.001$), M3 ($p < 0.001$), and M12 ($p = 0.007$; Figure 3(b)). There was no interaction time × domain (Table S3), overall suggesting sustained long-term improvements in quality of life across all domains, including physical health, psychological health, social relationships, and environment.

Beyond that, healthy individuals showed no effects on the self-reported WHOQOL-SRPB for time, dose, or the time × dose and time × domain interactions (Figure 4(a); Tables S3 and S4).

For patients, the self-reported WHOQOL-SRPB demonstrated a main effect of time ($F(4, 478.71) = 5.65$, $p < 0.001$, Table S4), with overall increases from D0 to D14 ($p = 0.003$) and M12 ($p = 0.041$; Figure 4(b)). Moreover, there was an interaction time × domain ($F(28, 450.13) = 1.50$, $p = 0.050$), with increased Inner Peace from D0 to D14 ($p = 0.003$, $d = -0.94$; 95% CI: −1.72, −0.16]; Figure 4(c)) and increased Hope & Optimism from D0 to D14 ($p < 0.001$, $d = -0.93$; 95% CI: −1.71, −0.15]) and to M12 ($p = 0.002$, $d = -1.33$; 95% CI: −2.19, −0.49; Figure 4(d)). Altogether, this indicates long-term improvements, particularly in peace, hope, and optimism in TRD patients after DMT administration.

Correlations

For healthy volunteers, no correlations of self-reported improved anxiety (STAI-S) and life satisfaction (SWL) with psychedelic experiences survived correction for multiple comparisons (Table S5).

For patients, no correlations of anxiety (STAI-S), life satisfaction (SWL), and quality of life (WHOQOL-SRPB) with psychedelic experience ratings survived correction for multiple

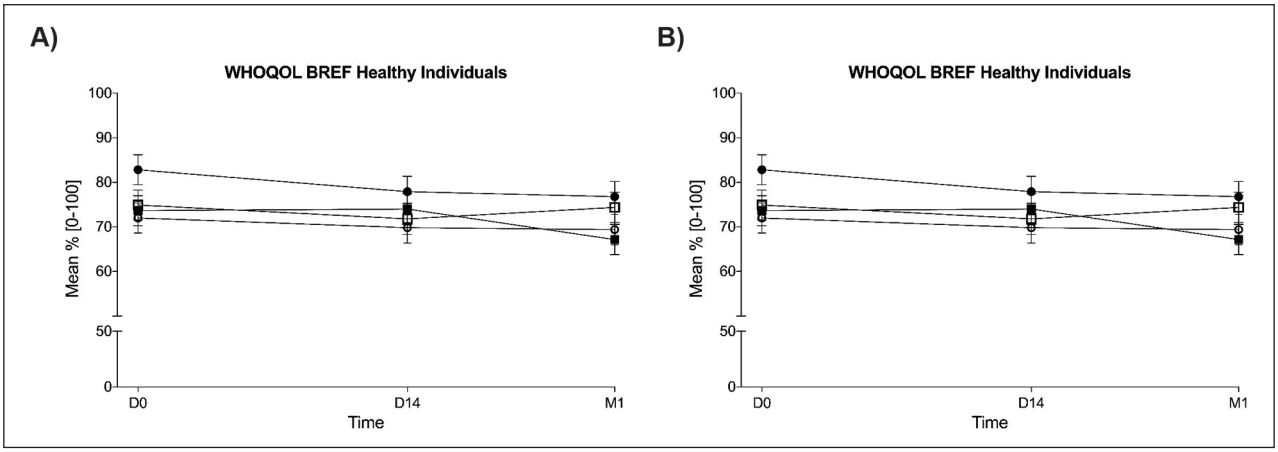

Figure 3. DMT enhanced long-term physical, psychological, social, and environmental quality of life in patients with depression. (a) Healthy individuals showed no changes in quality of life. (b) TRD patients demonstrated a sustained increase in quality of life from 14 days to 12 months, compared to baseline, as reflected across physical, psychological, social relationships, and environment domains. Data represent mean ± SEM scores on the WHOQOL-BREF.

$^{**}p < 0.01$. $^{***}p \leq 0.001$ (Bonferroni-corrected post hoc pairwise comparisons).

D0, baseline; D14, 14 days post-administration; M1, 1 month post-administration; M3, 3 months post-administration; M12, 12 months post-administration; DMT, N,N-dimethyltryptamine; TRD, treatment-resistant depression; SEM, standard error of the mean; WHOQOL-BREF, World Health Organization Quality of Life Instrument – Abbreviated Version.

comparisons (Table S6). Throughout the analyses, only one positive correlation was observed between self-reported reduced anxiety (STAI-S) and reduced depression (PHQ-9) from D0 to D1 ($r = 0.57$, $p = 0.040$, $n = 14$; Figure 5). This suggests that early improvements in anxiety may be linked to concurrent decreases in depressive symptoms.

Discussion

This study contributed exploratory evidence on the therapeutic potential of inhaled DMT combined with psychological support in patients with TRD, expanding the scope of psychedelic research beyond symptom remission. Building on our previous findings of its rapid antidepressant effects (Falchi-Carvalho et al., 2025), the present analysis suggests that the intervention was associated with post-acute reductions in state anxiety up to 1 day post-administration, beyond enhanced life satisfaction for up to 14 days in healthy individuals and at 12 months in patients, while quality of life was only sustainably improved for up to 12 months in patients. Importantly, these multidimensional outcomes indicate that DMT may act not only as a fast-acting antidepressant but also be related to broader psychological and existential recovery, engaging domains often overlooked by conventional treatments.

Accumulating evidence suggests that ayahuasca and DMT share comparable therapeutic profiles (Falchi-Carvalho et al., 2025; Palhano-Fontes et al., 2018). Studies with ayahuasca have shown rapid antidepressant and anxiolytic effects, alongside improvements in quality of life, often after a single administration (Barbosa et al., 2012; Palhano-Fontes et al., 2018; Ruffell et al., 2023; Sanches et al., 2016). Psilocybin trials have consistently reported sustained improvements in depression, anxiety, and well-being (Schimmers et al., 2022; Thomson and Thomacos, 2025). Our findings extend this evidence by suggesting that inhaled DMT combined with psychological support is associated with similar short-term anxiolytic effects and enduring improvements in quality of life, despite DMT's shorter duration of action. This challenges the assumption that session length or intensity necessarily determines therapeutic efficacy and instead highlights the importance of subjective meaning-making and integration processes (Earleywine et al., 2022; Roseman et al., 2017; Wießner et al., 2022a).

Anxiety is highly comorbid with depression and frequently exacerbates functional disability, undermining treatment outcomes (Kessler et al., 2003). In the present study, reduced state anxiety was observed in both patients with depression and healthy individuals during the acute and immediate post-acute period. These findings align with prior observational studies on ayahuasca, which have reported reductions in both state and trait anxiety in clinical and non-clinical populations (Dos Santos et al., 2016; Sarris et al., 2021). This also resonates with controlled trials of psilocybin for patients with depression and existential distress related to life-threatening illnesses, where reductions in anxiety co-occurred with increases in life satisfaction, meaning in life, and psychological flexibility (Goodwin et al., 2023; Griffiths et al., 2016; Raison et al., 2023; Sloshower et al., 2024).

From a mechanistic standpoint, reductions in self-reported short-term anxiety may reflect processes related to emotional distress modulation. Even brief changes in anxiety may not only relieve immediate distress but also facilitate re-engagement with meaningful life activities, including social interactions, occupational functioning, and the pursuit of valued goals (Kessler et al., 2003; Rush et al., 2008). Such outcomes are consistent with frameworks that describe psychedelics as enhancers of psychological flexibility, enabling patients to confront avoided material and restructure maladaptive patterns

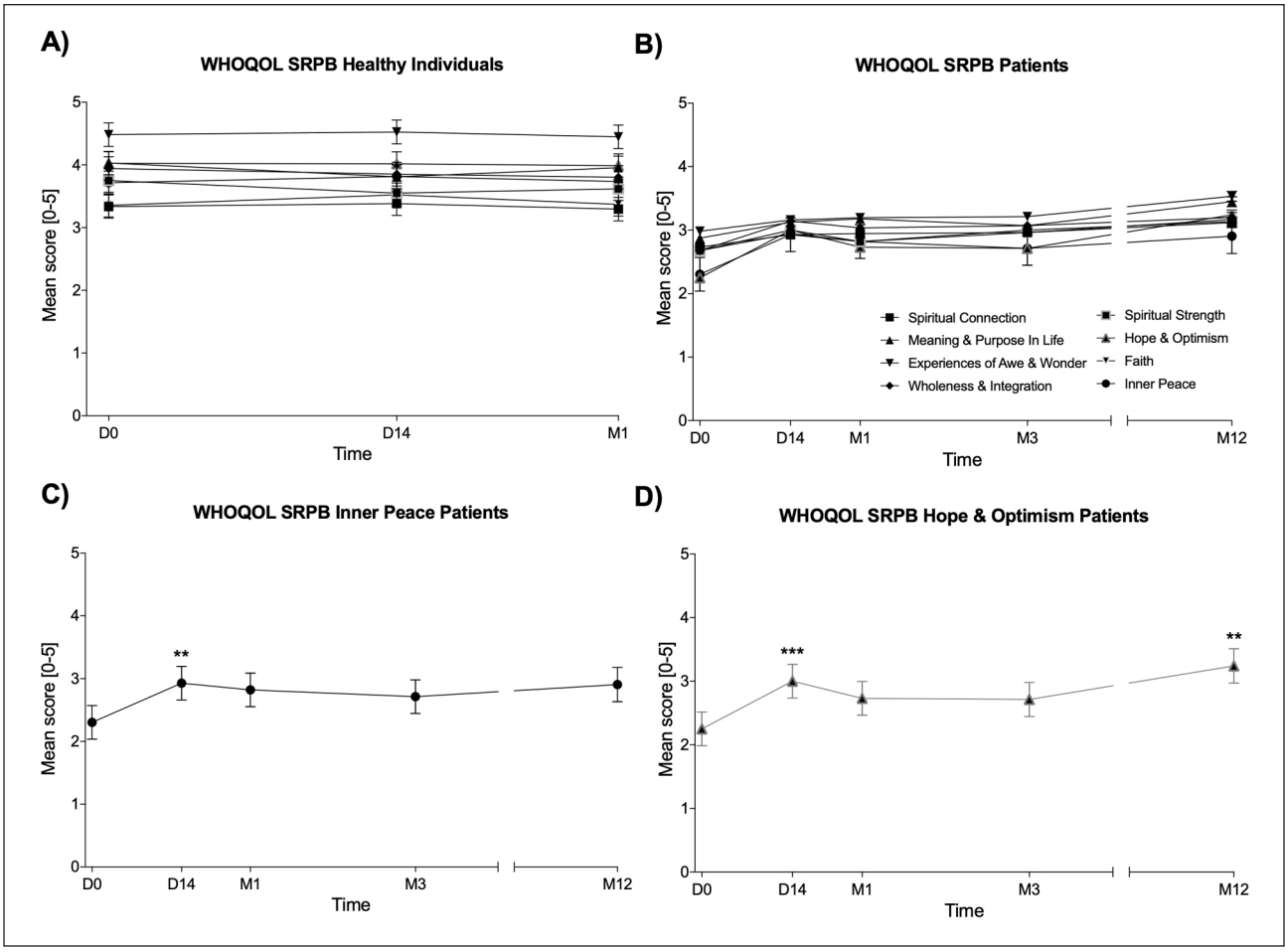

Figure 4. DMT enhanced long-term hope, optimism, and peace in patients with depression. (a) Healthy individuals showed no changes. (b) TRD patients demonstrated increases in quality of life related to spirituality, religiousness, and personal beliefs. Specifically, compared to baseline, patients showed improved (c) Inner Peace after 14 days and (d) Hope & Optimism after 14 days and 12 months. Data represent mean ± SEM of the WHOQOL-SRPB.

$^{**}p < 0.01$. $^{***}p \leq 0.001$ (Bonferroni-corrected post hoc pairwise comparisons).

D0, baseline; D14, 14 days post-administration; M1, 1 month post-administration; M3, 3 months post-administration; M12, 12 months post-administration; DMT, N,N-dimethyltryptamine; TRD, treatment-resistant depression; SEM, standard error of the mean; WHOQOL-SRPB.

of thought and emotion (Vollenweider and Preller, 2020; Wießner et al., 2022b). Neurobiological models further suggest that psychedelics induce transient increases in brain entropy and flexible network dynamics, opening a therapeutic window for adaptive learning and emotional processing (Carhart-Harris and Friston, 2019; Viol et al., 2023). Similarly, preclinical work indicates that psychedelics promote neuroplasticity through modulation of glutamatergic signaling and upregulation of brain-derived neurotrophic factor (De Almeida et al., 2019; De Sousa et al., 2022; Hutten et al., 2021).

Life satisfaction and quality of life have become increasingly central in psychiatric research, marking a shift from symptom-focused to recovery-oriented paradigms (Keyes, 2007). In our patients with depression, open-label inhaled DMT combined with psychological support was related to sustained long-term improvements across all WHOQOL-BREF domains of physical and psychological health, social relationships, and environment, indicating broad changes beyond affective symptom reduction. Notably, gains in spiritual and personal belief dimensions, particularly peace, hope, and optimism, suggest the exploratory potential of DMT interventions to promote existential well-being, a domain often critical for individuals with chronic mental illness or end-of-life distress (Maia et al., 2021; Roseman et al., 2017). Nevertheless, although these changes may suggest improvements beyond symptom reduction, they should be interpreted in light of the open-label design, lack of placebo control, and possible influence of contextual factors, such as expectancy effects, regression to the mean, and natural illness course, which may account for these improvements in addition to the treatment itself. Furthermore, patients continued their usual clinical treatment during follow-up, including ongoing pharmacological treatment, which may also have contributed to longer-term outcomes, particularly at later time points such as M12. In addition, other factors occurring up to 12 months, including psychotherapy, new pharmacological treatments, and relevant life events, were not examined in the present quantitative report and may also have

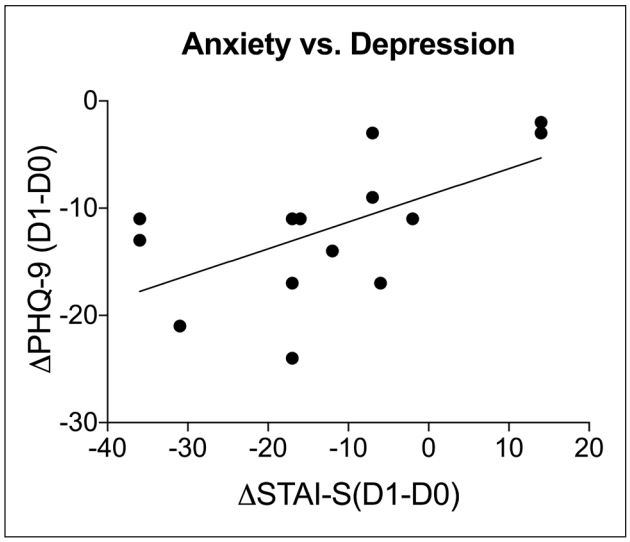

Figure 5. Correlation between reductions in anxiety and depression. A positive correlation was found between reduced state anxiety and reduced depressive symptoms 1 day after DMT administration compared to baseline. Negative values indicate symptom decreases.
PHQ-9, Patient Health Questionnaire – 9 item version; STAI-S, State-Trait Anxiety Inventory – state version; D1, 1 day post-administration; D0, baseline.

influenced these long-term changes. Moreover, the psychotherapeutic management aimed at integrating the experience, along with expressive and musical resources, may have contributed to the reported changes in quality of life and spiritual well-being (Koolen et al., 2025; Stroud et al., 2018).

The findings are consistent with systematic reviews showing that psychedelics can enhance well-being and psychosocial functioning (Aday et al., 2020; Van Elk and Yaden, 2022). Importantly, improvements in quality of life and life satisfaction are increasingly recognized as stronger predictors of long-term recovery, resilience, and functional reintegration than symptom reduction alone, especially in TRD (Ryff, 2014). Beyond that, the unchanged quality of life in healthy individuals may be explained by ceiling effects with high levels throughout all assessment points, while the improvements in life satisfaction in this sample may suggest the potential of DMT interventions to improve these specific, subjective aspects of well-being beyond psychiatric disorders. Along these lines, our results align with findings that 5-methoxy-DMT decreases anxiety and stress and enhances life satisfaction and mindfulness in recreational users (Uthaug et al., 2019).

The indication that DMT combined with psychological support is linked not only to improved depressive and anxious symptoms but also to quality of life carries implications for clinical practice and public health. Depression is among the leading causes of disability worldwide, and traditional treatments often fail to restore functioning or well-being even when symptoms remit (Rush et al., 2008). Interventions that address broader dimensions of recovery could therefore substantially reduce disease burden. For public health systems such as Brazil's Unified Health System (SUS), which prioritize cost-effective and scalable interventions, the potential of DMT as a rapid-acting antidepressant could be particularly relevant as a viable addition to public treatment options with short duration and the potential to promote well-being beyond symptom reduction.

Despite promising findings, several limitations warrant caution in this exploratory study. First, our study lacked a placebo-control condition, leaving open the possibility of expectancy effects or regression to the mean. In addition, the open-label designs limit causal inference, particularly given the subjective nature of self-reported outcomes, which may be especially susceptible to expectancy-related inflation, including participant and therapist effects, on domains such as quality of life and spiritual well-being, rather than evidence of benefit. Recent FDA advisory reviews have underscored that open-label or functionally unblinded designs substantially weaken causal inference, particularly in subjective outcomes, emphasizing a more cautious interpretation. Second, participants received multiple psychological components, including preparation, guided sessions, structured integrations, music, and expressive tasks, making this intervention a combined approach of DMT and psychological support. As such, these elements cannot be fully disentangled from the purely pharmacological effects, a point also raised by the FDA Regulatory Reviews, emphasizing the need to treat this therapeutic context as an additional mechanism of change. Accordingly, improvements, particularly in subjective domains such as quality of life and spiritual well-being, may partly reflect social and contextual influences (e.g., therapeutic attention, repeated clinical contact, and meaning-making processes), an interpretation that is further supported by similar short-term changes observed in healthy participants. Third, the sample size was relatively small, which reduces representativeness and statistical power, and increases the risk of errors. Given these limitations, especially the 12-month assessment, it should be interpreted with caution, since these long-term improvements may be influenced by attrition bias, self-selection effects, and uncontrolled changes in participants' life circumstances over time, such as engagement in psychotherapy or other relevant life events. Fourth, the study populations were restricted to healthy individuals and patients with TRD, limiting generalizability to other populations such as primary anxiety disorders or subclinical distress. Moreover, the healthy and patient samples were small and highly selective, drawn from the same national and institutional contexts and requiring prior DMT experience for the healthy participants, which further may have introduced expectancy and self-selection biases. The FDA Regulatory critiques of psychedelic research have emphasized that such narrow samples constrain interpretation, particularly regarding findings on well-being and long-term effects. Lastly, this secondary analysis includes data from two trials with differing follow-up timepoints and dosing protocols, introducing methodological heterogeneity. The findings should therefore be considered a complementary analysis with additional outcomes rather than a fully harmonized pooled trial presenting new clinical evidence. As a result, this work does not provide new clinical trial evidence, but it expands on previous findings by exploring additional outcomes and conducting a longer follow-up, offering a more comprehensive understanding of the effects of inhaled DMT combined with psychological support.

Conclusion

In an exploratory open-label study, inhaled DMT combined with psychological support was associated with reduced anxiety up to 1 day post-administration in both healthy volunteers and TRD patients, and with sustained increases in life

satisfaction in healthy volunteers up to 14 days. Beyond that, DMT was related to self-reported long-term improvements in life satisfaction and sustained improvements in quality of life among patients with TRD. These multidimensional improvements are consistent with the notion that psychedelics are related to better psychological functioning and recovery, including existential and functional domains often overlooked by conventional treatments. Given the exploratory nature and open-label design, future studies employing more rigorous placebo-controlled, double-blind methodologies with larger sample sizes and broader outcome measures will be essential to further clarify DMT's therapeutic profile and inform its potential integration into health systems.

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Supplemental material

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