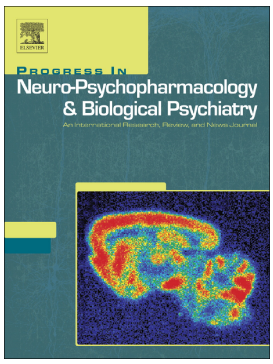

LSD microdosing for major depressive disorder: Mood and pharmacokinetic outcomes from a phase 2a trial

Dimitri Daldegan-Bueno, Carina Joy Donegan, Rachael Sumner, Anna Forsyth, Soo Hee Jeong, William Evans, Malak Alshakhouri, Robin J. Murphy, Lisa Reynolds, Nicholas Hoeh, Nathan Allen, Frederick Sundram, David Menkes, Suresh Muthukumaraswamy

PII: S0278-5846(26)00041-2

DOI: https://doi.org/10.1016/j.pnpbp.2026.111645

Reference: PNP 111645

To appear in: *Progress in Neuropsychopharmacology & Biological Psychiatry*

Received date: 2 October 2025

Revised date: 21 January 2026

Accepted date: 15 February 2026

Please cite this article as: D. Daldegan-Bueno, C.J. Donegan, R. Sumner, et al., LSD microdosing for major depressive disorder: Mood and pharmacokinetic outcomes from a phase 2a trial, *Progress in Neuropsychopharmacology & Biological Psychiatry* (2024), https://doi.org/10.1016/j.pnpbp.2026.111645

LSD microdosing for major depressive disorder: Mood and pharmacokinetic outcomes from a Phase 2a trial

Dimitri Daldegan-Bueno[a*] (d.daldegan@auckland.ac.nz), Carina Joy Donegan[b] (carina.donegan@auckland.ac.nz), Rachael Sumner[a] (r.sumner@auckland.ac.nz), Anna Forsyth[a] (a.forsyth@auckland.ac.nz), Soo Hee Jeong[c] (s.jeong@auckland.ac.nz), William Evans[d] (info@manahealth.co.nz), Malak Alshakhouri[a] (malak.alshakhouri@auckland.ac.nz), Robin J. Murphy[a] (robin.murphy@auckland.ac.nz), Lisa Reynolds[b] (l.reynolds@auckland.ac.nz), Nicholas Hoeh[b] (n.hoeh@auckland.ac.nz), Nathan Allen[e] (nathan.allen@aut.ac.nz), Frederick Sundram[b] (f.sundram@auckland.ac.nz), David Menkes[f] (david.menkes@auckland.ac.nz), Suresh Muthukumaraswamy[a] (sd.muthu@auckland.ac.nz)

[a] School of Pharmacy, Faculty of Medical and Health Sciences, University of Auckland, 85 Park Road, Grafton, Auckland, 1023, New Zealand.
[b] Department of Psychological Medicine, Faculty of Medical and Health Sciences, University of Auckland, 22 Park Avenue, Grafton, Auckland, 1023, New Zealand.
[c] Department of Pharmacology and Clinical Pharmacology, Faculty of Medical and Health Sciences, University of Auckland, 85 Park Road, Grafton, Auckland, 1023, New Zealand.
[d] Mana Health, 7 Ruskin St, Parnell, Auckland 1052, New Zealand.
[e] Department of Computer and Information Sciences, Auckland University of Technology, 6 St Paul Street, Auckland, 1010, New Zealand.
[f] Department of Psychological Medicine, Waikato Clinical Campus, University of Auckland, Pembroke Street, Hamilton 3240, New Zealand.

Word Count (text body): 3,584
Submitted to: *Progress in Neuro-Psychopharmacology & Biological Psychiatry* as an Original Research Article
Submission Date: October 3, 2025

*Corresponding author:
Dimitri Daldegan-Bueno
School of Pharmacy
The University of Auckland
Private Bag 92019, Auckland 1142, New Zealand.
Email: d.daldegan@auckland.ac.nz

Abstract
Introduction: Despite growing interest in microdosed psychedelics, clinical trial evidence remains limited. We present daily mood, subjective perception of effects, and pharmacokinetics from an 8-week regimen of microdosed lysergic acid diethylamide (LSD) as a treatment for major depressive disorder in an open-label trial in which participants reported a mean symptom reduction of 60%. Methods: Participants took 16 sublingual LSD doses: 8 μg onsite, with bloods collected at eight time-points, then twice weekly at home with titration (6–20 μg). Pharmacokinetic parameters were estimated using non-compartmental and compartmental modelling. Daily questionnaires were used to assess depression severity with the self-reported Hamilton Depression Rating Scale (HAM-D6), and mood with visual analogue scales (VAS). Drug effects were recorded with VAS scales on each dosing day. Linear mixed models were used to compare dosing days to one- and two-day post-dosing, and to identify linear trends (tolerance/sensitisation) of drug effects. Results: Nineteen participants (males n = 15, 79%) received the intervention. Daily VAS indicated increased scores of mood-related states (e.g., more creative, happier) on dosing days ($p = 0.009$ to 0.039), but not in depression ($p = 0.291$). There was no indication of tolerance or sensitisation ($p > 0.081$). Non-compartmental AUC0-tlast was 836±319 pg.h/mL, Cmax 212±77.7 pg/mL and Tmax 1.17±0.56 hours. Discussion: Results suggest short-term improvements in mood following microdosed LSD in people with depression, warranting confirmation in controlled trials. It provides the pharmacokinetic parameters of 8 μg of LSD in a sample of people with depression and indicates no tolerance or sensitisation to repeated microdoses of LSD, despite incremental dose titration.

Keywords
Microdosing; psychedelics; LSD; major depressive disorder; pharmacokinetics

1. Introduction

Classic psychedelics such as lysergic acid diethylamide (LSD), psilocybin, and N, N-dimethyltryptamine (DMT) can induce profound mind-altering effects associated with the activation of 5-HT2A receptors (Kwan et al., 2022). There is a growing body of research investigating the potential of psychedelics to treat or aid the treatment of a range of mental disorders (Andersen et al., 2021; Ko et al., 2023). A leading psychedelic therapeutic potential is in the treatment of depression (Ko et al., 2023; Yao et al., 2024), a condition prevalent in around 5% of the global adult population and the leading cause of the mental health burden of disease (GBD, 2022; WHO, 2023). Microdosing psychedelics, a practice that involves taking repeated doses of psychedelics in ranges below the threshold to induce substantial perceptual alterations, has recently increased in popularity amongst communities of people who may be seeking treatment or currently use drugs (Kuypers et al., 2019; Lea et al., 2020a). While considerable investigation has been conducted on full psychedelic doses, evidence for microdosing psychedelics for mental health purposes is comparatively scarce (Murphy et al., 2024; Polito & Liknaitzky, 2022). Despite this, there are numerous reports of microdosing being used to self-medicate, often as an attempt to treat depression (Lea et al., 2020b; Polito & Liknaitzky, 2022).

When considering LSD, acute doses of 5 to 20 µg reach their peak plasma concentration within 50 to 90 minutes after oral administration (Family et al., 2020; Holze et al., 2021; Morse et al., 2025), with a reported threshold of 5 to 10 µg required to cause noticeable subjective effects in healthy individuals (Holze et al., 2021; Murphy et al., 2024). Evidence from placebo-controlled studies indicates that doses as low as 20 µg or below can acutely affect neural connectivity, cognition and mood (Murphy et al., 2024). We previously reported transient, mood-enhancing effects acutely after 10 µg of LSD in a cohort of healthy males (Murphy et al., 2023). A similar mood-enhancing effect was reported for doses of 20 µg compared to placebo in people with mildly depressed mood (Molla et al., 2024). Taken together, these results suggest that these transient, mood-enhancing properties might have therapeutic value for people experiencing depression.

On this basis, we conducted an open-label phase 2A clinical trial to investigate the safety and tolerability of microdosing LSD at home in a sample of people with depression (Donegan et al., 2023) who also reported improvements in depression symptoms (Daldegan-

Bueno et al., 2025). Here we report further data from this trial, including changes in daily ratings of mood, subjective perception of microdosed LSD effects, and the pharmacokinetics of 8 µg of LSD administered in the laboratory.

2. Methods

This work is a secondary analysis of an open-label phase 2A trial (acronym: LSDDEP1) of microdosing LSD to treat depression (*N* = 19). Participants enrolled in this study met the DSM-5 diagnosis criteria of major depressive disorder (DSM-5 criteria) and had a Montgomery-Asberg Depression Rating Scale (MADRS) score between 18 and 35 at the time of screening. Participants in the trial attended three onsite visits: a baseline visit, followed by a first dosing visit (day 1; seven days after baseline), and a final visit scheduled two to seven days after taking the final microdose. Between the dosing visit and the final measure visits, each participant took a further 15 LSD doses twice a week for 8 weeks (16 doses in total). For each at-home dose, participants were encouraged to engage in a self-selected psychologically beneficial activity. At the end of the intervention, participants reported a mean reduction of 60% of depressive symptoms as measured with the MADRS. A full methods protocol for this study was published prospectively (Donegan et al., 2023), and safety and depression severity data are published elsewhere (Daldegan-Bueno et al., 2025).

Data for this trial were collected between 11 July 2023 and 18 April 2024; all onsite visits were conducted at the University of Auckland Clinical Research Centre in New Zealand. This trial was prospectively registered at the Australian New Zealand Clinical Trials Register (ANZCTR), reference: ACTRN12623000486628 (12 May 2023).

2.1 Study drug, dose & administration

The GMP-quality LSD hemitartrate Active Pharmaceutical Ingredient (API) from Psygen Ltd. (Calgary, Canada) was formulated according to GMP standards by Biocell Corp. (Auckland, New Zealand) to create MB-22001, a titratable liquid formulation of LSD used in this study. MB-22001 was taken sublingually by holding the liquid under the tongue for approximately 30 seconds and then swallowing it. On each dosing day, participants completed a five-point Likert scale indicating whether they thought the dose was too much, too little or adequate. They were instructed to decrease their next dose if they experience any disturbance of daily functioning.

The starting dose of LSD (onsite session) was 8 µg. The following 15 doses were taken at home and could be titrated within the limits of 4 to 20 µg based on the self-perception of the effects. During the trial, the titration scheme was amended and updated based on the observation that the first system was inefficient; participants took many doses before reaching their titrated dose. For the first titration scheme (7 participants), the dose could be increased by 1 µg at each dosing or decreased by 3 µg if the previous dose had tolerability issues. For the second titration scheme (12 participants), the dose could be increased by 2 or 1 µg increments at each dosing to a maximum of 20 µg and decreased by 2 µg or 1 µg if the previous dose had tolerability issues. The first and second titration schemes were based on three and five-point Likert scales, respectively, filled out at the end of every dosing day. For the first titration scheme, the following questions were used: "I felt too little of the effects" (+ 1 µg), "It was adequate" (+ 0 µg), and "I felt too much of the effects" (- 3 µg). For the second titration scheme, the following questions were used: "I felt no effect" (+ 2 µg), "I felt too little of the effects" (+ 1 µg), "It was adequate" (+ 0 µg), "I felt too much of the effects" (- 1 µg), and "I felt way too much of the effects" (- 2 µg).

2.2 Measures

2.2.1 Daily Questionnaires

During the dosing-at-home period, participants filled out a short survey daily using a customised phone application designed for this trial. The survey contained the HAM-D6 psychometric instrument, six visual-analogue rating scales (VAS) of mood, and an additional Likert-type scale rating their sleep. Surveys were unlocked at 7 pm (with a notification in the mobile phone app) and locked at midnight. If the participant didn`t fill out the survey within this time frame, the survey for the day was recorded as missing.

HAM-D6: a short, self-reported, unidimensional scale based on the Hamilton Depression Rating Scale provides a score (0 – 24) measuring depression severity (Bech et al., 2009). Questions are prompted on how the person has been feeling over the past three days.

SQS: The Sleep Quality Scale (SQS) is a single-item VAS scale rated from "Terrible" (0) to "Excellent" (10) assessing the overall quality of sleep over the past week (Snyder et al., 2018). The SQS question was adapted to refer to the sleep of the previous night.

Daily VAS: Daily VAS ratings consisted of six scales on which participants rated effects from "Less than usual" (-50) to "More than usual" (+50), with "Usual" (0) as the middle anchor point. Scale questions were: "How connected did you feel today?", "How creative did you feel today?", "How much energy did you feel today?", "How happy did you feel today?", "How irritable did you feel today?" and "How jittery did you feel today?". Data were analysed using the categorical variable "day" with three levels, dose day and the two subsequent non-dose days (dose/post1/post2), repeated through 16 cycles (Dose 1 to Dose 16).

2.2.2 Drug Effects Questionnaires

At the end of every dosing day at home, participants filled out a survey inquiring about their experience during the time they felt the most potent drug effect on that day. Like the daily questionnaire, this survey was unlocked at 7 pm and locked at midnight. Drug VAS ratings consisted of 16 scales on which participants rated effects from "Not at all" (0) to "Extremely" (100). As the first dose was taken onsite, only Drug Effects data from dosing-at-home were included in the analysis (Dose 2 to Dose 16). Items covered general drug effects (feeling a drug effect, feeling high, wanting more), valence of the effects (liking or disliking effects, feeling unusually happy, sad, or fearful), somatic (feeling sick, sleepy, dizzy), and perceptual changes (altered body sensations or surroundings, seeing movement in still objects). Additional items assessed arousal and cognition, including stimulation and unusual thoughts.

2.2.3 Pharmacokinetics Parameters

Blood samples were obtained during the first dosing session done at the laboratory before, at 20, 40, 60, 90, 120, 180, 240, and 360 minutes after receiving their first 8 µg dose. Blood samples were collected using 4 mL lithium heparin tubes (with the actual time recorded for each sample), and were centrifuged immediately at 1,500 *g* at 4 °C for 15 minutes, pipetted into 500 µL plasma aliquots and stored at -80 °C. Liquid chromatography-tandem mass spectrometry (LC-MS/S) analysis was performed as described in Morse et al. (2025). An ultra-high-pressure liquid chromatography coupled with tandem mass spectrometry was

performed using a Vanquish UHPLC system, coupled with a TSQ Quantiva triple quadrupole mass spectrometer, controlled by Xcalibur 4.3 software (Thermo Scientific), using a heated electrospray ionisation source (H-ESI) in positive ionisation mode. The assay's performance characteristics included a lower limit of quantification (LLOQ) of 25 pg/mL, an upper limit of quantification (ULOQ) of 1,000 pg/mL and a limit of detection (LOD) of 10 pg/mL for LSD, iso-LSD and 2-Oxo-3-hydroxy-LSD.

2.4 Analysis

For the Daily VAS measures, linear mixed-effects models were used to assess the effects of dosing days on each outcome. Dosing days were treated as a categorical variable (Dosing Day, Post 1, Post 2) and modelled as fixed effects; participants were modelled as random effects. Post hoc multiple comparisons were accounted for with a Bonferroni-adjusted alpha threshold for each domain (Dosing Day vs Post 1 and Post 2; $\alpha = 0.05/2 = 0.025$).

For the Drug VAS measures, linear mixed-effects models were used to assess whether there were linear trends over time for each outcome. Dosing days were treated as continuous variables (doses 2 to 16) and were modelled as random effects to account for dose variation, given the titration scheme; participants were also modelled as random effects. Due to the absence of post-hoc analysis in these models, the *p-value* was not corrected, and a threshold below 0.05 was considered statistically significant. For both the Daily VAS and Drug VAS models, C_{max} was then added as a fixed-effects covariate.

Non-compartmental analysis was performed using plasma drug concentration-time data for each participant with PKanalix (version 2024R1, Lixoft). The parameters derived were peak plasma concentration (C_{max}), time to maximum concentration (T_{max}), the area under the concentration curve from 0 to 6 hours ($AUC_{0\text{-}tlast}$; calculated using the trapezoidal linear/log method), the area under the curve to infinity ($AUC_{0\text{-}\infty}$), apparent total clearance (CL/F), and volume of distribution during the terminal (V_D/F). Non-compartmental pharmacokinetic parameters ($AUC_{0\text{-}\infty}$, $AUC_{0\text{-}tlast}$, C_{max}, and T_{max}) were correlated with dosing metrics (mean dose, total dose exposure, and most frequently dose taken) using the Spearman correlation. Visual plot inspection was performed with mean titrated dose, comparing low versus high $AUC_{0\text{-}tlast}$, C_{max} and T_{max}. Population modelling was then carried out in Monolix (version 2024Rq, Lixoft) using a one-compartment model with no delay, first-order absorption, and linear elimination based on previous research with micro LSD doses (Holze et al., 2021; Morse

et al., 2025); additional settings included oral/extravascular administration and clearance parameterisation. Simulations were performed in Simulx (version 2024R1, Lixoft).

All statistics were done in R (V. 2.5.1). Linear mixed-effects models were computed using the lmer function of the lme4 package.

3. Results

In total, 19 people received the intervention. Participants consisted mainly of males (n = 15, 78.94%), people of European descent (n = 13, 68.42%), with an undergraduate (n = 10, 52.63%) level of education, and with a mean age of 41.52 (SD = 11.67) years. Most participants were taking antidepressant medication when they started the trial (n = 15, 78.94%) and had at least one psychedelic experience in their lives (n = 11, 57.84%). A detailed report of safety, outcome and dosing is presented elsewhere (Daldegan-Bueno et al., 2025). Briefly, participants presented a 59.52% reduction of depression severity (assessed by MADRS), with a mean (SD) score of 23.7 ± 6.72 and 9.59 ± 7.67 at the start and end of intervention, respectively.

3.1 Daily Questionnaires

There was a total of 620 daily questionnaires: 244/275 (88.72%, missing n = 31 [11.27%]) on dosing days, 188/188 (100%) on the day after dosing, and 157/157 (100%) on the day after dosing. The ratings of Daily VAS are plotted in Figures 1 and 2. There was no effect of dosing day for HAM-D6 ($F_{(2, 569.08)}$ = 1.23, p = 0.291), and sleep quality ($F_{(2, 569.77)}$ = 1.15, p = 0.317) ratings. However, participants reported feeling more connected ($F_{(2, 570.11)}$ = 3.77, p = 0.023; post1: β = 3.49, SE = 1.33, t = 2.62, p = 0.008), more creative ($F_{(2, 570.04)}$ = 3.25, p = 0.039; post1: β = 3.13, SE = 1.4, t = 2.23, p = 0.025), and with more energy ($F_{(2, 569.99)}$ = 4.68, p = 0.009; post1: β = 4.30, SE = 1.46, t = 2.94, p = 0.003) on dosing days compared to one day after dosing. They also reported being less irritable ($F_{(2, 570.02)}$ = 3.96, p = 0.019) two days after dosing (β = -3.83, SE = 1.38, t = -2.78, p = 0.006), and happier ($F_{(2, 569.71)}$ = 6.93, p = 0.001) one (β = 3.95, SE = 1.28, t = 3.10, p = 0.002) and two (β = 4.26, SE = 1.34, t = 3.17, p = 0.001) days after dosing. Feeling more creative (β = 3.02, SE = 1.47, t = 2.05, p = 0.04) and with more energy (β = 3.04, SE = 1.54, t = 1.97, p = 0.04) on dosing day compared to two days after dosing was also significant but did not survive Bonferroni correction (p threshold = 0.025). There was no effect for feeling jittery ($F_{(2, 569.59)}$ = 0.13, p = 0.876). When added as a fixed-effect covariate

to the models, there was no significant effect of C_{max}, indicating no effect of maximal LSD plasma concentration, on any of the outcomes.

[INSERT FIGURE 1 HERE]

[INSERT FIGURE 2 HERE]

3.2 Drug Effects

The ratings of Drug VAS across 15 days are plotted in Figure 2. There were no linear trends in any of the Drug VAS measures throughout the dosing days, indicating no tolerance or sensitisation on the reported effects (β = -0.85 to 0.52, t = -1.87 to 0.78, *p* = 0.081 to 0.924). When adding C_{max} as a fixed-effect covariate, it had a significant effect on "Like" (β = -0.17, t = -3.01, *p* = 0.009) and "Drug Effect" (β = -0.13, t = -2.25, *p* = 0.040) measures, but it did not change the dosing day's effects, i.e., dosing days remained not significant.

[INSERT FIGURE 3 HERE]

3.3 Pharmacokinetic Parameters

The mean titrated dose was 14.61 µg (*SD* = 3.63), with a minimum and maximum titrated dose of 6 and 20 µg, respectively. The most frequently titrated dose was 15 µg (*n* = 6), with a total LSD mean dose across the 16 doses of 196.61 µg (*SD* = 52.07). Non-compartmental modelling indicated that the mean maximum concentration of LSD was 211.66 (± 77.7) pg/mL at 1.17 (± 0.56) hours post-dosing. Total mean exposure up to last time observed ($AUC_{0\text{-}tlast}$) was 836.25 (± 318.70) and to infinity 1,464 (± 767.24) pg.h/mL, with a mean apparent total clearance of 6.56 (± 2.53) L/h and a volume of distribution during the terminal phase of 46.63 (± 11.09) L. One compartmental modelling showed similar characteristics: $AUC_{0\text{-}tlast}$: 829 (± 288.93) pg.h/mL; $AUC_{0\text{-}\infty}$: 1,332.51 (± 465.51) pg.h/mL; C_{max}: 211.66 (± 77.7) pg/mL; T_{max}: 1.48 (± 0.71) hours; CL/F: 6.65 (± 2.05) L/h, and V_D/F: 36.3 (± 11.09) L. Raw and modelled peripheral blood concentrations are plotted in Figure 4, and pharmacokinetic parameters are described in Table 1.

[INSERT FIGURE 4 HERE]

[INSERT TABLE 1 HERE]

There were no significant correlations between non-compartmental pharmacokinetics characteristics ($AUC_{0-\infty}$, $AUC_{0-tlast}$, C_{max}, and T_{max}) and subsequent titrated dose (mean dose, dose mode, total dose administered) (R = -0.32 to 0.14, p = 0.21 to 0.92). Visual plot inspection indicates that participants with low versus high $AUC_{0-tlast}$ and C_{max}, but not T_{max} values titrated to higher doses (Figure 5).

[INSERT FIGURE 5 HERE]

4. Discussion

This work reported results of an open-label pilot trial of LSD microdosing at home in patients with major depressive disorder on daily ratings of mood, subjective perception of microdosed LSD effects taken repeatedly, and pharmacokinetics of 8 µg of LSD administered in the laboratory.

We identified transient improvements in mood evaluated by VAS items (increased connectedness, creativity, energy, happiness, and decreased irritability) on dosing days at home compared to one or two post-dosing days. These findings are aligned with those from our double-blind, placebo-controlled randomised trial of microdosing LSD at home with healthy, non-depressed male individuals (Murphy et al., 2023). Other trials report similar mood-enhancing effects in healthy populations (Bershad et al., 2019; Hutten et al., 2020) and an increased blissful state and spiritual experience in people with depression (Molla et al., 2024) with doses up to 20 µg. Taken together, this raises the possibility that LSD might have mood-enhancing effects of value for individuals with depression (Murphy et al., 2024). Accordingly, participants in this trial also experienced a 60% reduction in depression severity at the end of the intervention (Daldegan-Bueno et al., 2025).

While it is not possible to attribute the reduction in depression to LSD (due to the open-label nature of the study), the acute mood improvement reported here may help account for the observed improvement in depression in this sample. Specifically, enhanced feelings of connection, creativity, and energy on dosing days could aid in mitigating anhedonia, a core symptom of depression (APA, 2022; Serretti, 2023), by acutely promoting engagement

and enjoyment of social activities. Accordingly, qualitative data at the end of our intervention reports enhanced behavioural activation, feelings of connectedness and mental clarity, which, by presenting a bidirectional positive feedback loop, improved emotional well-being in some of the participants (Donegan et al., 2025b). Overall, these results add preliminary evidence that the mood-enhancing effects of LSD may have therapeutic value for individuals with depression. However, the daily depression score (HAM-D6) had no significant alteration, indicating that acute mood improvements are not necessarily reflected in a daily measure of depression. It should be noted that the way this tool was implemented in this study had some methodological issues, which are discussed in more detail in the limitations section below.

The pharmacokinetic parameters of sublingual LSD identified in this study were comparable to previously reported parameters of oral and sublingual LSD doses of 5 to 10 µg (Family et al., 2020; Holze et al., 2021; Morse et al., 2025), providing further data on dose-proportional changes in plasma LSD concentrations. It further adds, to the best of our knowledge, the first pharmacokinetic data of microdosed LSD administered sublingually in individuals with major depressive disorder. While no correlations between pharmacokinetics and titration parameters were found (possibly due to the small sample size), visual exploration suggests that participants with higher $AUC_{0\text{-}tlast}$ or C_{max} on a dosing day tended to be less likely to titrate their dose higher and vice versa. This suggests, not surprisingly, that the plasma concentration of LSD is related to the subjective perception of effects of the drug. Moreover, we have previously indicated that adding a titration protocol for LSD microdosing at home reduced the occurrence of adverse events leading to withdrawal (Daldegan-Bueno et al., 2025). These results provide preliminary evidence that a self-regulated dosage may help compensate for individual drug pharmacokinetics. It provides a rationale for continued investigations into predictors of individual concentration variations, such as genetic determinants of cytochrome P450 enzyme activity (Morse et al., 2025; Vizeli et al., 2021), and microdose-sensitive pharmacodynamic measures.

Ratings of the drug effects on dosing days throughout the 15-dose regimen at home were stable throughout time, indicating no tolerance or sensitisation to repeated LSD microdoses, despite the dose being incremented throughout the intervention. It also indicates that positive effects were more substantial than negative ones. Overall, our results add to the evidence that LSD subjective effects are reported at doses between 5 and 10 µg (Murphy et

al., 2024) by demonstrating this in individuals experiencing depression, most of whom were on concurrent antidepressant pharmacotherapy.

5. Limitations

The results reported in this work are from an uncontrolled, open-label, pilot trial with a small sample size and are exploratory. The lack of a control group is especially relevant to the daily mood results, which effects often are more pronounced on post-dosing days, hindering the interpretation of a direct dosing effect. Also, our daily measures of mood were based on single VAS items as opposed to psychometrically validated instruments. The HAM-D6 daily results do not corroborate the primary outcome measure (MADRS), which reported a substantial average reduction (60%) in depression severity. However, while the MADRS was conducted under optimal conditions in this study, with a structured interview guideline (Williams & Kobak, 2008), the HAM-D6 was not. Several participants reported struggling with completing the HAM-D6 daily because the items in this questionnaire asked about the past three days (data not presented), whereas in this study, the survey was filled out daily, so each report was overlaid with the previous one. Therefore, we adapted the HAM-D6 for our upcoming trial (Daldegan-Bueno et al., 2024) to have the questions based on the day the participants are responding. Another potential limitation is tolerance related to antidepressant use, as most participants were taking antidepressants; although dose titration may have partially mitigated this issue, the doses and subjective effects identified here may not generalise to individuals not using antidepressants. Finally, it is critical to consider the impacts of participant expectations when taking part in a trial using psychedelics (Donegan et al., 2025a) and the modulatory effect this may have on subjective ratings. Altogether, the mood-related results presented here should be interpreted as exploratory and warrant controlled trials.

6. Conclusion

This work adds preliminary evidence that microdosing LSD can acutely elevate mood in people with depression after an intervention of 16 LSD microdoses. It provides, for the first time, pharmacokinetic parameters of 8 µg of LSD in a sample of people with depression and indicates no tolerance or sensitisation effects of repeated microdoses of LSD.

7. Glossary

$AUC_{0\text{-}tlast}$: Area under the concentration curve from 0 to the last time measured

ANZCTR: Australian New Zealand Clinical Trials Register

API: Active Pharmaceutical Ingredient

$AUC_{0}\text{-}\infty$: Area under the curve to infinity

CL/F: Apparent total clearance

C_{max}: Peak plasma concentration

DMT: Dimethyltryptamine

GMP: Good Manufacturing Practice

HAM-D6 Hamilton Depression Rating Scale (short version)

HDEC: University of Auckland Health and Disability Ethics Committee

HRC: The Health Research Council

LC-MS/S: Liquid chromatography-tandem mass spectrometry

LLOQ: Lower limit of quantification

LSD: Lysergic Acid Diethylamide

LSDDEP1: Open-label pilot trial of LSD microdosing in patients with major depressive disorder

MADRS: Montgomery-Asberg Depression Rating Scale

SD: Standard deviation

SQS: The Sleep Quality Scale

T_{max}: Time to maximum concentration

ULOQ: Upper limit of quantification

VAS: Visual Analogue Scale

$\mathbf{V_D/F}$: Volume of distribution during the terminal

9. References

Andersen, K. A. A., Carhart-Harris, R., Nutt, D. J., & Erritzoe, D. (2021). Therapeutic effects of classic serotonergic psychedelics: A systematic review of modern-era clinical studies. *Acta Psychiatr Scand*, *143*(2), 101-118. https://doi.org/10.1111/acps.13249

APA. (2022). *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR)* [https://doi/book/10.1176/appi.books.9780890425787]. American Psychiatric Publishing, Inc. https://doi.org/10.1176/appi.books.9780890425787

Bech, P., Wilson, P., Wessel, T., Lunde, M., & Fava, M. (2009). A validation analysis of two self-reported HAM-D6 versions. *Acta Psychiatr Scand*, *119*(4), 298-303. https://doi.org/10.1111/j.1600-0447.2008.01289.x

Bershad, A. K., Schepers, S. T., Bremmer, M. P., Lee, R., & de Wit, H. (2019). Acute Subjective and Behavioral Effects of Microdoses of Lysergic Acid Diethylamide in Healthy Human Volunteers. *Biol Psychiatry*, *86*(10), 792-800. https://doi.org/10.1016/j.biopsych.2019.05.019

Daldegan-Bueno, D., Donegan, C. J., Forsyth, A., Sumner, R. L., Murphy, R. J., Menkes, D. B., Evans, W., Hoeh, N., Sundram, F., Reynolds, L. M., Ponton, R., Cavadino, A., Smith, T., Roop, P., Allen, N., Abeysinghe, B., Svirskis, D., Bansal, M., & Muthukumaraswamy, S. (2024). LSDDEP2: study protocol for a randomised, double-dummy, triple-blind, active placebo-controlled, parallel groups trial of LSD microdosing in patients with major depressive disorder. *Trials*, *25*(1), 560. https://doi.org/10.1186/s13063-024-08384-3

Daldegan-Bueno, D., Donegan, C. J., Sumner, R., Forsyth, A., Evans, W., Alshakhouri, M., Reynolds, L., Ponton, R., Smith, T., Roop, P., Hoeh, N., Allen, N., Sundram, F., Menkes, D., & Muthukumaraswamy, S. (2025). LSD microdosing in major depressive disorder: results from an open-label trial. *Neuropharmacology*, 110762. https://doi.org/https://doi.org/10.1016/j.neuropharm.2025.110762

Donegan, C. J., Daldegan-Bueno, D., Noorani, T., Sumner, R., Forsyth, A., Evans, W., Smith, T., Hoeh, N., Sundram, F., Menkes, D., Muthukumaraswamy, S., & Reynolds, L. (2025a). Qualitative Content Analysis of Expectations in participants with depression about to begin LSD microdosing treatment: Identifying the need for psychedelic expectancy measures. *Neuropharmacology*, 110670. https://doi.org/https://doi.org/10.1016/j.neuropharm.2025.110670

Donegan, C. J., Daldegan-Bueno, D., Sumner, R., Forsyth, A., Evans, W., Hoeh, N., Sundram, F., Menkes, D., Muthukumaraswamy, S., & Reynolds, L. (2025b). What is it like to Microdose LSD for Depression? A Thematic Analysis of Participant Interviews from an Open-Label Trial. *Unpublished results*. https://doi.org/https://doi.org/10.1016/j.neuropharm.2025.110670

Donegan, C. J., Daldegan-Bueno, D., Sumner, R., Menkes, D., Evans, W., Hoeh, N., Sundram, F., Reynolds, L., Ponton, R., Cavadino, A., Smith, T., Roop, P., Allen, N., Abeysinghe, B., Svirskis, D., Forsyth, A., Bansal, M., & Muthukumaraswamy, S. (2023). An open-label pilot trial assessing tolerability and feasibility of LSD microdosing in patients with major depressive disorder (LSDDEP1). *Pilot Feasibility Stud*, *9*(1), 169. https://doi.org/10.1186/s40814-023-01399-8

Family, N., Maillet, E. L., Williams, L. T. J., Krediet, E., Carhart-Harris, R. L., Williams, T. M., Nichols, C. D., Goble, D. J., & Raz, S. (2020). Safety, tolerability, pharmacokinetics, and pharmacodynamics of low dose lysergic acid diethylamide (LSD) in healthy older

volunteers. *Psychopharmacology (Berl)*, *237*(3), 841-853. https://doi.org/10.1007/s00213-019-05417-7

GBD. (2022). Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Psychiatry*, *9*(2), 137-150. https://doi.org/10.1016/s2215-0366(21)00395-3

Holze, F., Liechti, M. E., Hutten, N., Mason, N. L., Dolder, P. C., Theunissen, E. L., Duthaler, U., Feilding, A., Ramaekers, J. G., & Kuypers, K. P. C. (2021). Pharmacokinetics and Pharmacodynamics of Lysergic Acid Diethylamide Microdoses in Healthy Participants. *Clin Pharmacol Ther*, *109*(3), 658-666. https://doi.org/10.1002/cpt.2057

Hutten, N., Mason, N. L., Dolder, P. C., Theunissen, E. L., Holze, F., Liechti, M. E., Feilding, A., Ramaekers, J. G., & Kuypers, K. P. C. (2020). Mood and cognition after administration of low LSD doses in healthy volunteers: A placebo controlled dose-effect finding study. *Eur Neuropsychopharmacol*, *41*, 81-91. https://doi.org/10.1016/j.euroneuro.2020.10.002

Ko, K., Kopra, E. I., Cleare, A. J., & Rucker, J. J. (2023). Psychedelic therapy for depressive symptoms: A systematic review and meta-analysis. *Journal of Affective Disorders*, *322*, 194-204. https://doi.org/https://doi.org/10.1016/j.jad.2022.09.168

Kuypers, K. P., Ng, L., Erritzoe, D., Knudsen, G. M., Nichols, C. D., Nichols, D. E., Pani, L., Soula, A., & Nutt, D. (2019). Microdosing psychedelics: More questions than answers? An overview and suggestions for future research. *Journal of Psychopharmacology*, *33*(9), 1039-1057. https://doi.org/10.1177/0269881119857204

Kwan, A. C., Olson, D. E., Preller, K. H., & Roth, B. L. (2022). The neural basis of psychedelic action. *Nature Neuroscience*, *25*(11), 1407-1419. https://doi.org/10.1038/s41593-022-01177-4

Lea, T., Amada, N., & Jungaberle, H. (2020a). Psychedelic Microdosing: A Subreddit Analysis. *Journal of psychoactive drugs*, *52*(2), 101-112. https://doi.org/10.1080/02791072.2019.1683260

Lea, T., Amada, N., Jungaberle, H., Schecke, H., Scherbaum, N., & Klein, M. (2020b). Perceived outcomes of psychedelic microdosing as self-managed therapies for mental and substance use disorders. *Psychopharmacology*, *237*(5), 1521-1532. https://doi.org/10.1007/s00213-020-05477-0

Molla, H., Lee, R., Tare, I., & de Wit, H. (2024). Greater subjective effects of a low dose of LSD in participants with depressed mood. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*, *49*(5), 774-781. https://doi.org/10.1038/s41386-023-01772-4

Morse, J. D., Jeong, S. H., Murphy, R. J., Muthukumaraswamy, S. D., & Sumner, R. L. (2025). Pharmacokinetics and pharmacodynamics of sublingual microdosed lysergic acid diethylamide in healthy adult volunteers. *Journal of Psychopharmacology*, *0*(0), 02698811251330747. https://doi.org/10.1177/02698811251330747

Murphy, R., Muthukumaraswamy, S., & de Wit, H. (2024). Microdosing psychedelics: Current evidence from controlled studies. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*. https://doi.org/https://doi.org/10.1016/j.bpsc.2024.01.002

Murphy, R. J., Sumner, R., Evans, W., Ponton, R., Ram, S., Godfrey, K., Forsyth, A., Cavadino, A., Krishnamurthy Naga, V., Smith, T., Hoeh, N. R., Menkes, D. B., & Muthukumaraswamy, S. (2023). Acute Mood-Elevating Properties of Microdosed Lysergic Acid Diethylamide in Healthy Volunteers: A Home-Administered Randomized

Controlled Trial. *Biological Psychiatry*, *94*(6), 511-521. https://doi.org/https://doi.org/10.1016/j.biopsych.2023.03.013

Polito, V., & Liknaitzky, P. (2022). The emerging science of microdosing: A systematic review of research on low dose psychedelics (1955–2021) and recommendations for the field. *Neuroscience & Biobehavioral Reviews*, *139*, 104706. https://doi.org/https://doi.org/10.1016/j.neubiorev.2022.104706

Serretti, A. (2023). Anhedonia and Depressive Disorders. *Clin Psychopharmacol Neurosci*, *21*(3), 401-409. https://doi.org/10.9758/cpn.23.1086

Snyder, E., Cai, B., DeMuro, C., Morrison, M. F., & Ball, W. (2018). A New Single-Item Sleep Quality Scale: Results of Psychometric Evaluation in Patients With Chronic Primary Insomnia and Depression. *Journal of Clinical Sleep Medicine*, *14*(11), 1849-1857. https://doi.org/doi:10.5664/jcsm.7478

Vizeli, P., Straumann, I., Holze, F., Schmid, Y., Dolder, P. C., & Liechti, M. E. (2021). Genetic influence of CYP2D6 on pharmacokinetics and acute subjective effects of LSD in a pooled analysis. *Sci Rep*, *11*(1), 10851. https://doi.org/10.1038/s41598-021-90343-y

WHO. (2023). *Depressive disorder (depression)*. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/depression

Williams, J. B. W., & Kobak, K. A. (2008). Development and reliability of a structured interview guide for the Montgomery-Åsberg Depression Rating Scale (SIGMA). *British Journal of Psychiatry*, *192*(1), 52-58. https://doi.org/10.1192/bjp.bp.106.032532

Yao, Y., Guo, D., Lu, T.-S., Liu, F.-L., Huang, S.-H., Diao, M.-Q., Li, S.-X., Zhang, X.-J., Kosten, T. R., Shi, J., Bao, Y.-P., Lu, L., & Han, Y. (2024). Efficacy and safety of psychedelics for the treatment of mental disorders: A systematic review and meta-analysis. *Psychiatry Research*, *335*, 115886. https://doi.org/https://doi.org/10.1016/j.psychres.2024.115886

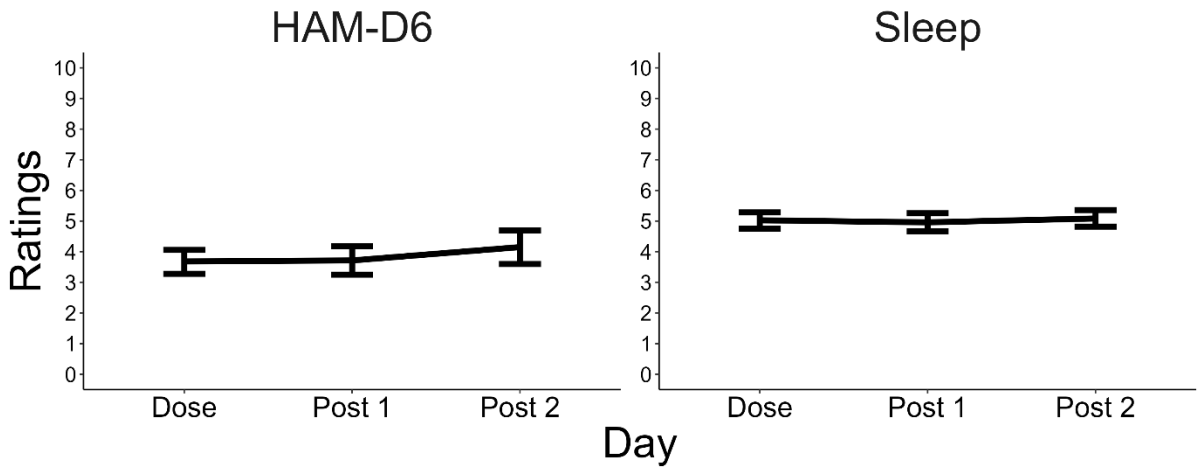

Figure 1. Daily ratings of Depression (HAM-D6) and sleep quality on dosing days, one day and two days post-dosing at home. Graphic points represent mean values, and error bars represent a 95% confidence interval bootstrapped 1,000 times.

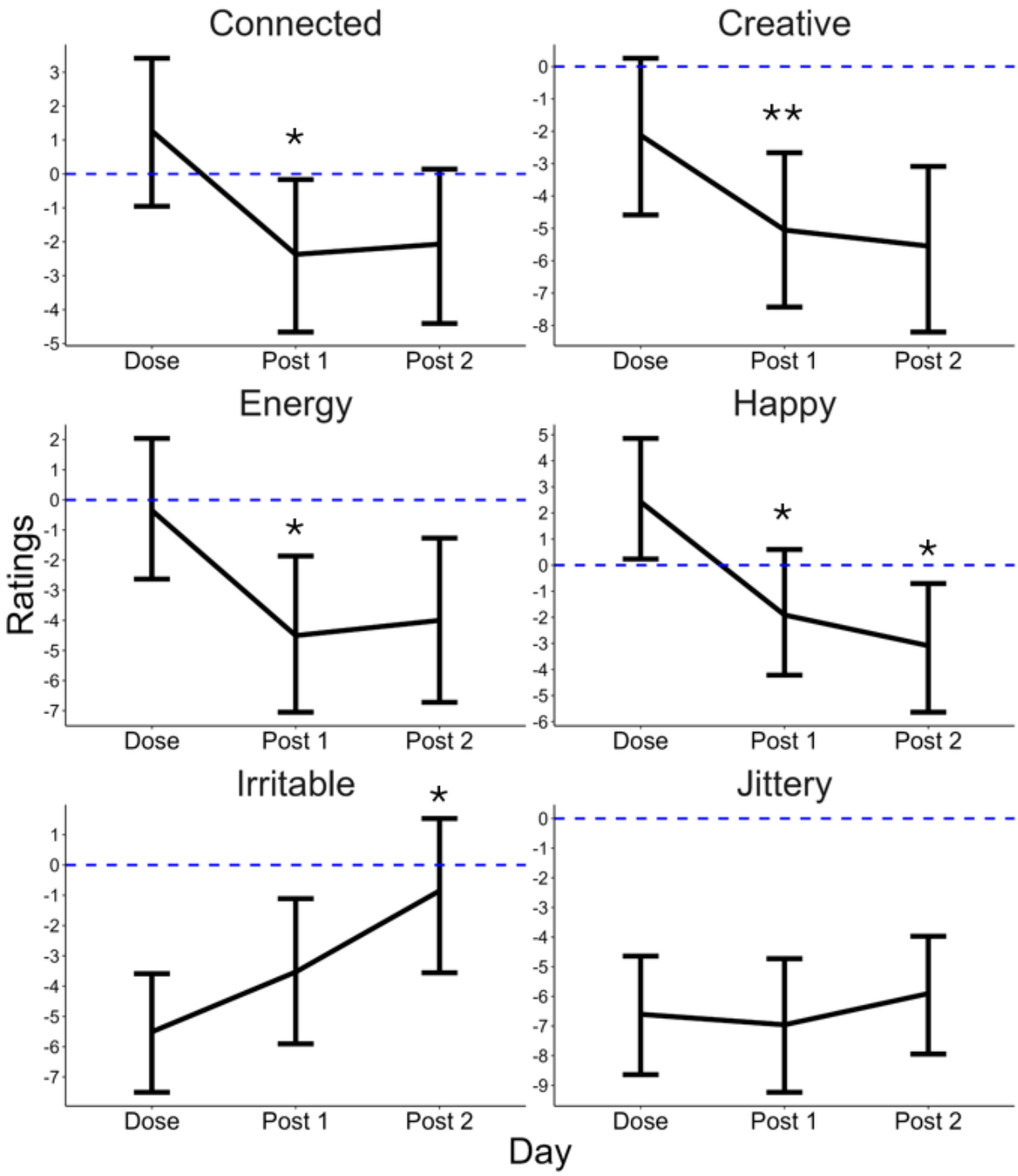

Figure 2. Daily VAS ratings on dosing days, one day and two days post-dosing at home. Graphic points represent mean values, and error bars represent a 95% confidence interval bootstrapped 1,000 times. The dashed line represents feeling as usual. *$p < 0.01$ and ** $p = 0.025$ compared to the dosing day.

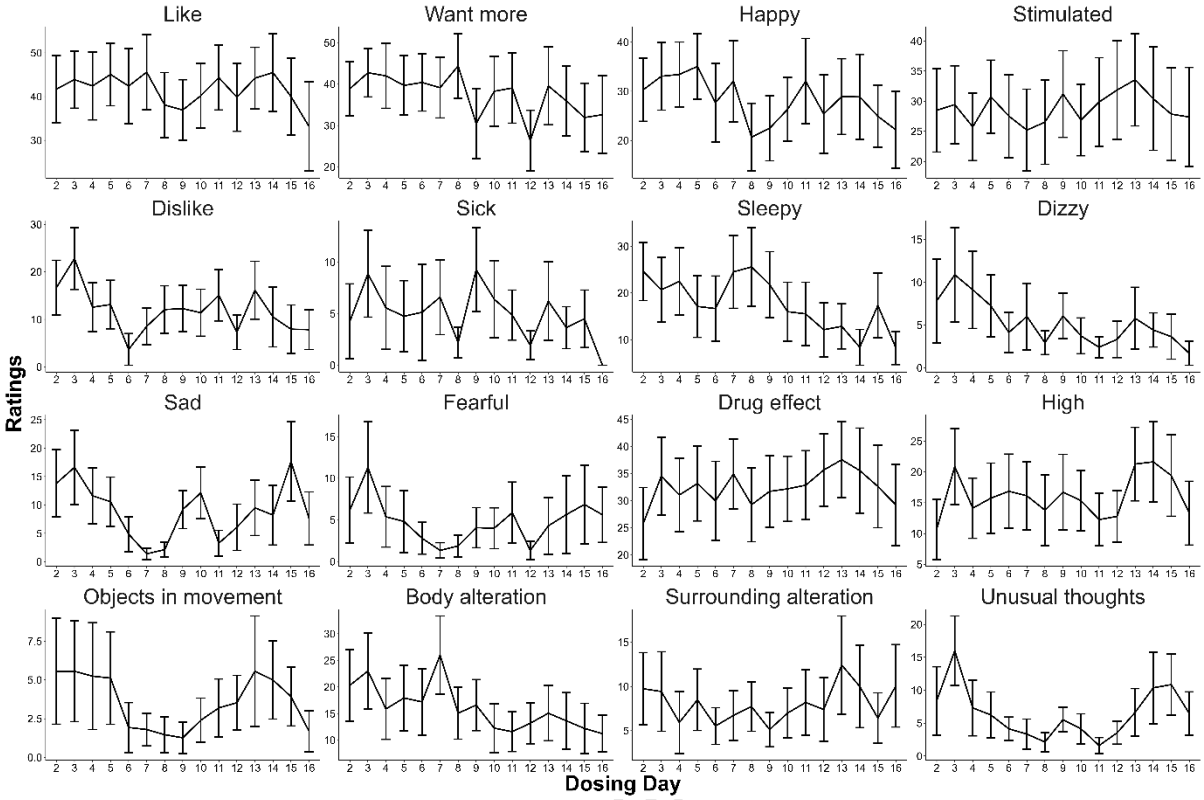

Figure 3. Mean and standard error of Drug Effects VAS ratings across 15 dosing days at home (n = 16). Two participants were removed from the analysis due to unreliable responses. No linear trends were identified throughout the dosing days in any of the VAS ratings.

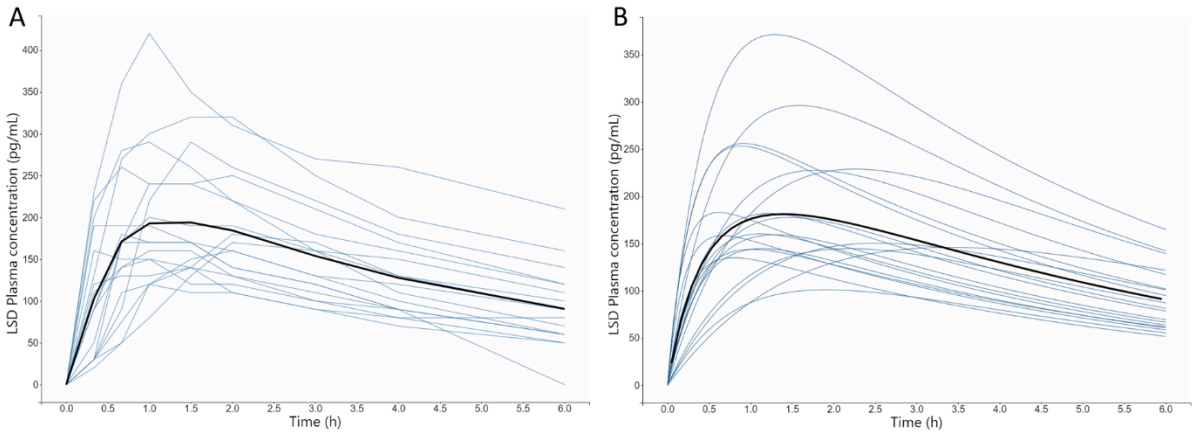

Figure 4. Plasma concentration-time profiles of LSD **A.** Observed plasma concentrations for each individual (blue lines) and mean concentration (black line) at 0 (pre-dose), 20, 40, 60, 120, 180, 240 and 360 minutes after sublingual administration of 8 µg of LSD. **B.** Predicted plasma concentration-time profiles of LSD based on a one-compartment model, showing individual (blue lines) and mean (black line) predictions.

Table 1. Pharmacokinetic parameters of sublingual LSD (8 µg).

		$AUC_{0-\infty}$ (pg.h/mL)	$AUC_{0-tlast}$ (pg.h/mL)	C_{max} (pg/mL)	T_{max} (h)	CL/F (L/h)	V_D/F (L)
Non-compartmental	**Mean (SD)**	1,464.79 (767.24)	836.25 (318.7)	211.66 (77.7)	1.17 (0.56)	6.56 (2.53)	36.63 (11.09)
	Range	707.77 – 3,899.2	455.83 – 1,649.17	120 – 420	0.33 - 2	2.05 - 11.30	20.34- 56.95
One compartment	**Mean (SD)**	1,332.51 (465.54)	829.96 (288.93)	190.53 (66.31)	1.48 (0.71)	6.65 (2.05)	35.94 (10.59)
	Range	772.56 – 2469.24	469.88 – 1,608.74	101.12 – 371.29	0.62 – 3.39	3.23 – 10.35	16.9 – 56.45

Legend: $AUC_{0-\infty}$, area under the plasma concentration-time curve from time zero to infinity; $AUC_{0-tlast}$, area under the plasma concentration-time curve from time zero to last time (6 hours) measured; C_{max}, maximum plasma concentration observed; T_{max}, time observed to reach C_{max}; CL/F, apparent total clearance; V_D/F, volume of distribution during the terminal phase.

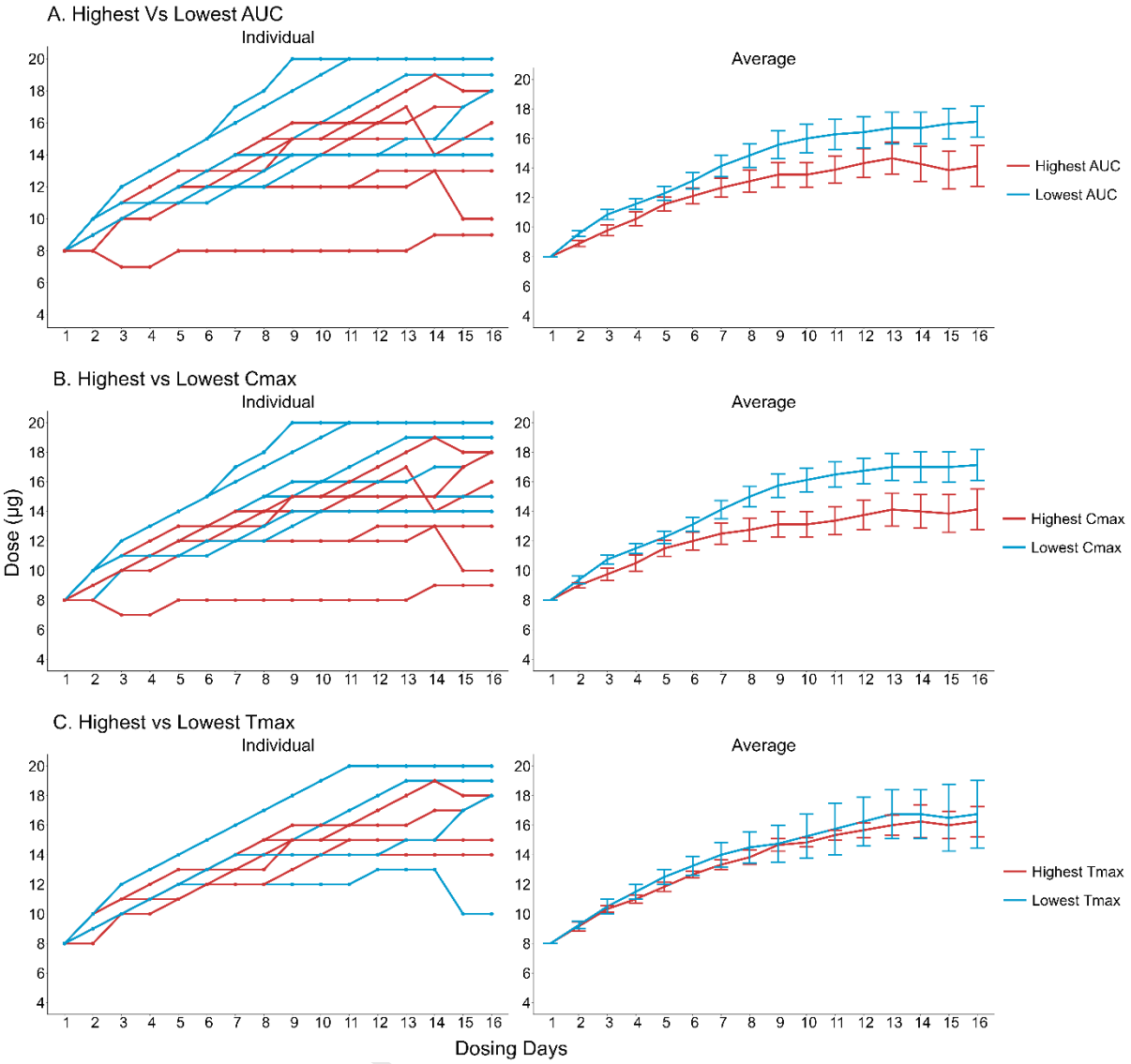

Figure 5. Mean titrated dose and standard errors for participants with high vs low $AUC_{0\text{-}tlast}$, C_{max} and T_{max} at the first, onsite dosing. Participants who did not complete the titration schedule (withdrawal, n = 1) and those with missing blood samples (n = 1) were excluded. **A.** Individual and average Highest vs lowest $AUC_{0\text{-}tlast}$ (n = 8/group). **B.** Individual and average Highest vs lowest C_{max} (n = 8/group). **C.** Individual and average Highest (n = 7) vs lowest (n = 4) T_{max}; participants with the median T_{max} (n = 5) were excluded. Highest vs lowest parameters determined by the median value ($AUC_{0\text{-}tlast}$ = 750 pg.h/mL; C_{max} = 185 pg/mL; T_{max} = 1 hour).

Authors' contributions

Dimitri Daldegan-Bueno: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Project administration. **Carina Joy Donegan:** Conceptualization, Methodology, Investigation, Writing - Review & Editing, Project administration. **Rachael Sumner:** Conceptualization, Methodology, Formal analysis, Validation, Investigation, Resources, Data Curation, Writing - Review & Editing, Visualization, Supervision. **Anna Forsyth:** Conceptualization, Methodology, Validation, Investigation, Resources, Data Curation, Writing - Review & Editing, Visualization, Supervision, Project administration. **Soo Hee Jeong:** Methodology, Validation, Formal analysis, Writing - Review & Editing. **William Evans:** Investigation, Writing - Review & Editing. **Malak Alshakhouri:** Validation, Investigation, Writing - Review & Editing. **Robin J. Murphy:** Data curation, Formal analysis, Methodology, Validation, Writing - Review & Editing. **Lisa Reynolds:** Validation, Writing - Review & Editing. **Nicholas Hoeh:** Investigation, Writing - Review & Editing. **Nathan Allen:** Software, Resources, Data Curation, Writing - Review & Editing. **Frederick Sundram:** Investigation, Writing - Review & Editing. **David Menkes:** Investigation, Writing - Review & Editing. **Suresh Muthukumaraswamy:** Conceptualization, Visualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing - Review & Editing, Supervision, Project administration, Funding acquisition.

Ethical Statement

Ethics approval was awarded by the University of Auckland Health and Disability Ethics Committee (HDEC) on the 14th of December 2022 (Reference: 13536) and the HRC Standing Committee on Therapeutic Trials (Online reference: 2022/SCOTT/13545; Department of Health reference TT55-0335 (2988)).

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Suresh Muthukumaraswamy reports financial support was provided by Health Research Council of New Zealand. Suresh Muthukumaraswamy reports financial support was provided by MindBio Therapeutics. Rachael Sumner reports financial support was provided by MindBio Therapeutics. Anna Forsyth reports financial support was provided by MindBio Therapeutics. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics approval and consent to participate

Ethics approval was awarded by the University of Auckland Health and Disability Ethics Committee (HDEC) on the 14th of December 2022 (Reference: 13536) and the HRC Standing Committee on Therapeutic Trials (Online reference: 2022/SCOTT/13545; Department of Health reference TT55-0335 (2988)).

Research material availability

The authors do not have permission to share data. Access to the final trial dataset is only available to the study investigators and any other relevant regulatory bodies.

Funding

This work was supported by the Health Research Council of New Zealand (Project Grant #22-076); MindBio Therapeutics Ltd, Melbourne, Australia, to fund the development of the Study Application, Formulation Development and Contract Manufacturing. The funders of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the reports.

Trial sponsor and role of sponsor

The study sponsor is the University of Auckland, contactable via the Office of Research Strategy and Integrity at humanethics@auckland.ac.nz. The study sponsor was not involved in the study design, collection, management, analysis, interpretation of the data, writing of the report, or the decision to submit the report for publication.

Acknowledgements

The authors would like to thank Eric Thorstensen and the Liggins Institute, University of Auckland, for performing the blood essays analysis.

Highlights (3/5 bullet points)

Preliminary evidence that microdosed LSD enhances mood acutely

No evidence of tolerance or sensitisation with repeated LSD microdoses

First pharmacokinetic data for 8 µg LSD in depression patients

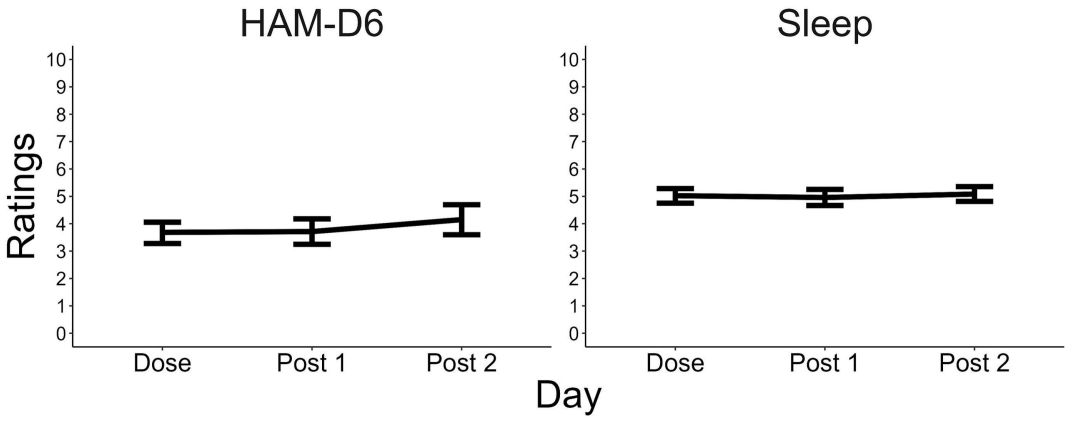

Figure 1

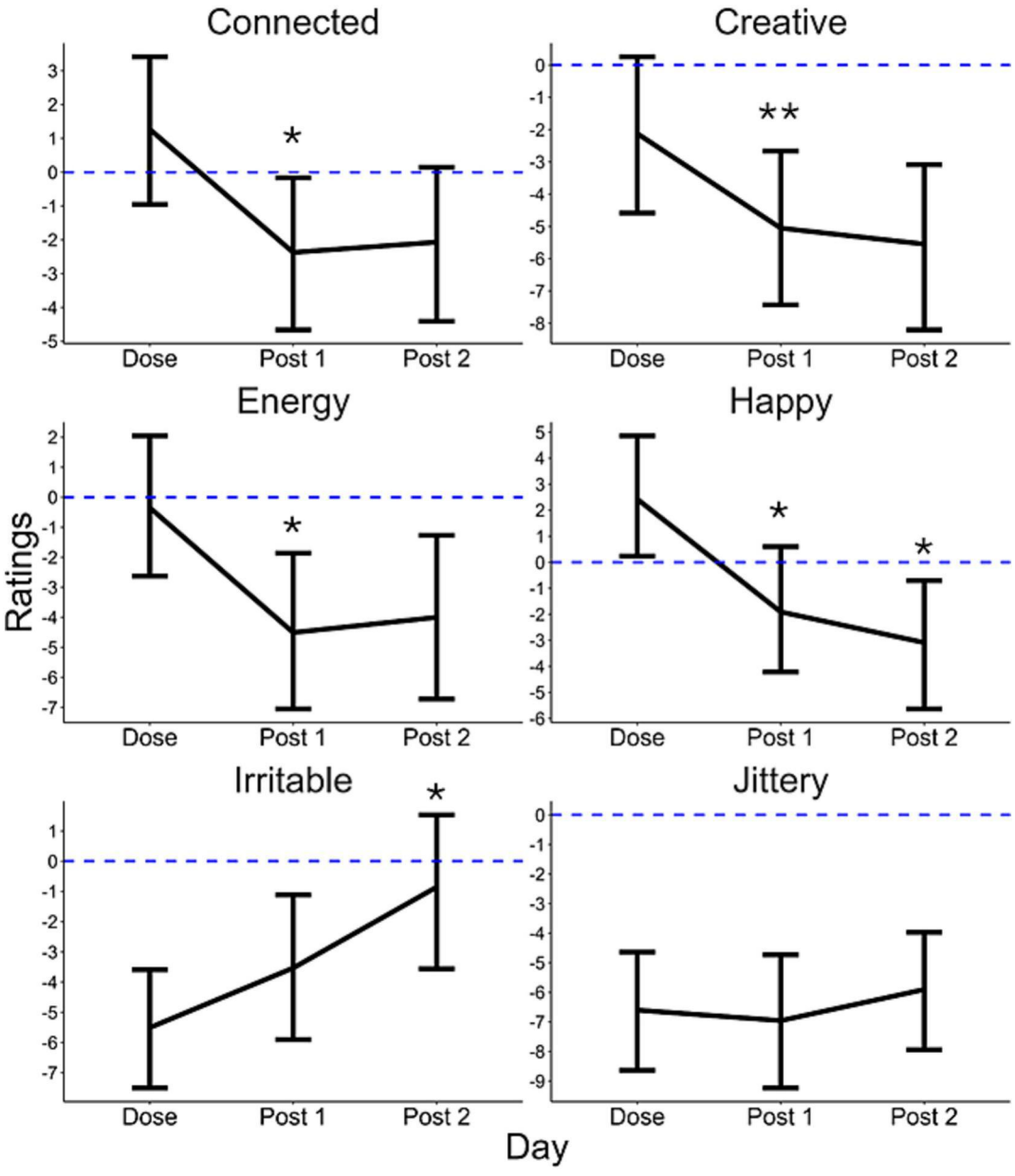
Connected
Creative
Energy
Happy
Irritable
Jittery
Ratings
Dose
Post 1
Post 2
Day
*
**

Figure 2

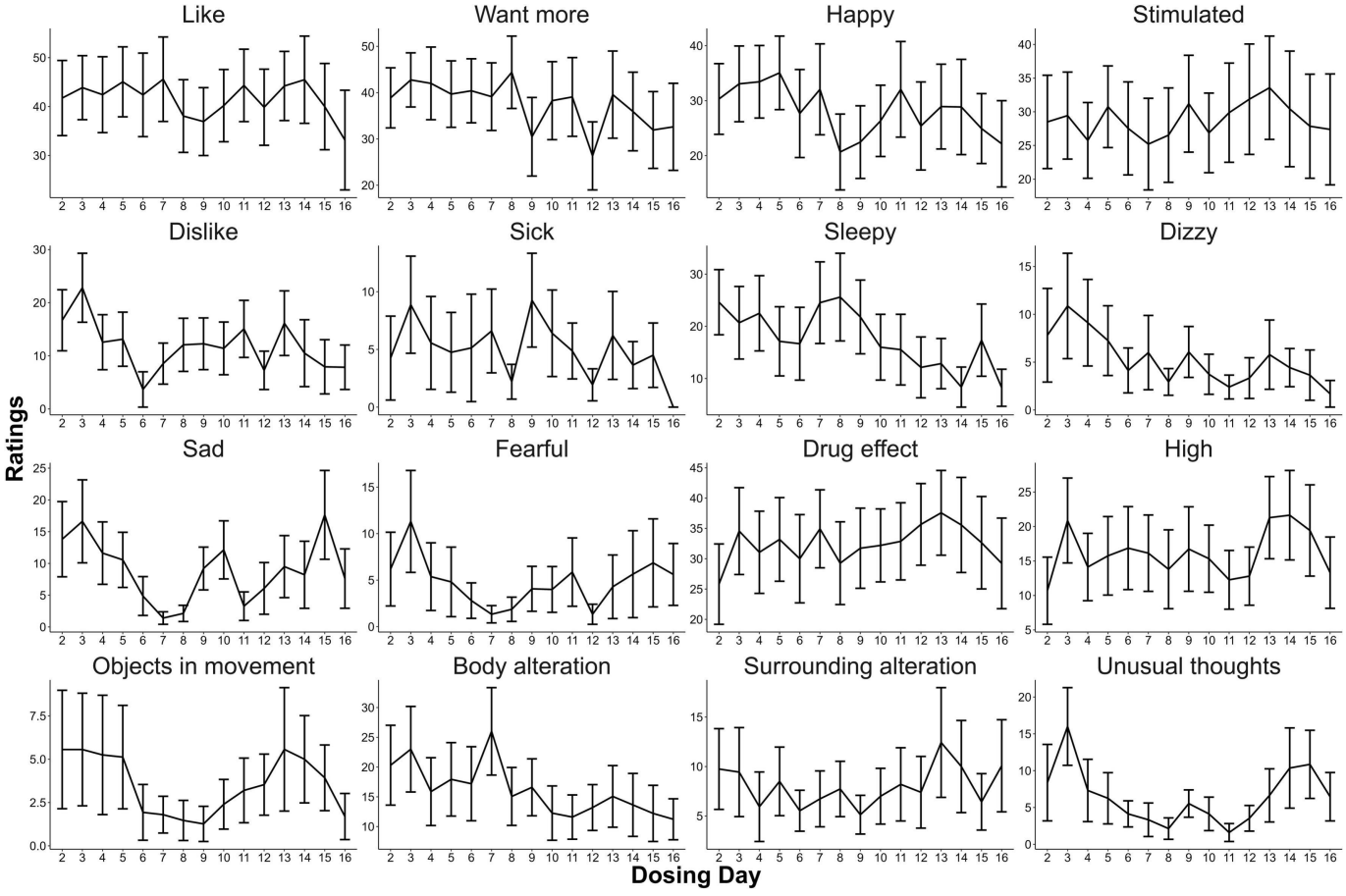
Like
Want more
Happy
Stimulated
Dislike
Sick
Sleepy
Dizzy
Sad
Fearful
Drug effect
High
Objects in movement
Body alteration
Surrounding alteration
Unusual thoughts
Ratings
Dosing Day

Figure 3

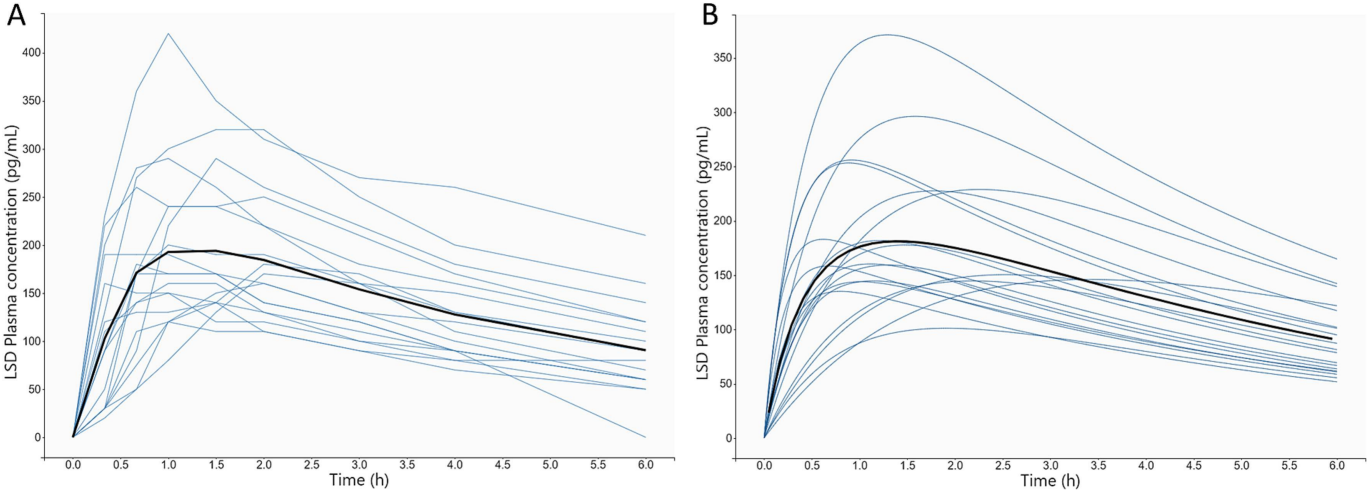
A
LSD Plasma concentration (pg/mL)
400
350
300
250
200
150
100
50
0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
Time (h)
B
LSD Plasma concentration (pg/mL)
350
300
250
200
150
100
50
0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
Time (h)

Figure 4

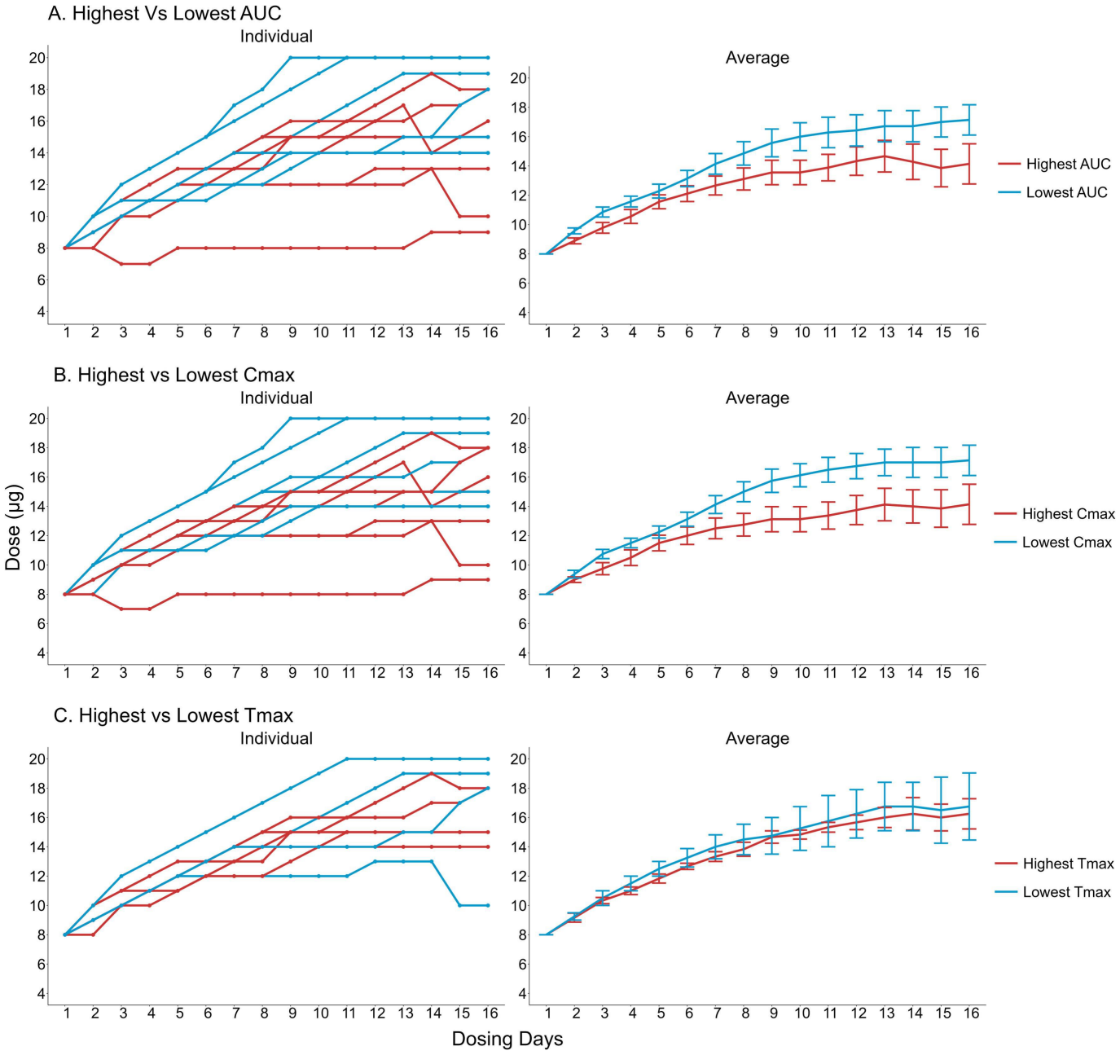
A. Highest Vs Lowest AUC
Individual
Average
Highest AUC
Lowest AUC
B. Highest vs Lowest Cmax
Individual
Average
Highest Cmax
Lowest Cmax
C. Highest vs Lowest Tmax
Individual
Average
Highest Tmax
Lowest Tmax
Dose (µg)
Dosing Days

Figure 5