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Safety, tolerability, pharmacokinetics, and subjective effects of 50, 75, and 100 µg LSD in healthy participants within a novel intervention paradigm: A proof-of-concept study

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Abstract

Background: Classic psychedelics hold promise as therapeutics for psychiatric disorders, but require scalable intervention protocols. This proof-of-concept study evaluated the safety, tolerability, pharmacokinetics, and subjective effects of 50, 75, and 100 µg lysergic acid diethylamide (LSD) in healthy adults within a novel intervention paradigm.

Methods: Up to three participants were administered LSD on the same day in separate rooms, each with a single attendant, after 1 day of preparation. An open-label design and a double-blind placebo-controlled design were used.

Results: Ninety-one percent of participants completed the study. Thirty-two adults (mean age = 28.8 years) received 50 (n = 3), 75 (n = 7), 100 (n = 3) LSD, 50 µg followed by 75 µg LSD (n = 9) 1 week apart, or placebo followed by a 75 µg LSD (n = 10) 1 week apart. There were no serious adverse events. Twenty-eight percent of participants experienced at least one expected mild adverse event, with one expected moderate adverse event. The maximum blood plasma levels occurred between 1.2 and 2 h post-administration, with an apparent half-life between 2.8 and 4.3 h. LSD largely induced greater subjective effects versus placebo.

Conclusion: In the current novel intervention paradigm, 50, 75, and 100 µg LSD are tolerable with favourable safety profiles in healthy adults, only mild adverse events during the day of drug administration, and mystical-type subjective experiences. Future studies are needed to evaluate safety, tolerability, subjective effects, and cost-effectiveness in clinical populations.

Keywords

Hallucinogen, implementation science, LSD, Lysergic acid diethylamide, psychedelic

Introduction

Lysergic acid diethylamide (LSD) is a classic psychedelic that induces alterations in consciousness at the doses currently being considered for treatment of psychiatric disorders (Hintzen and Passie, 2010; Liechti, 2017; Nichols, 2016). LSD was the focus of nearly 10,000 research papers in the 1950s and 1960s, and primarily used at moderate-to-high doses in experimental treatments for a number of indications, with much focus on alcohol use disorder and end-of-life distress (Passie et al., 2008). Recent clinical trials suggest LSD has a favourable safety profile in healthy participants at lower doses (i.e. up to 20 µg; Family et al., 2020) and at higher doses (i.e. up to 200 µg; Schmid et al., 2015), as well as in patients suffering from end-of-life distress at a dose of 200 µg (Gasser et al., 2014). Preliminary efficacy results suggest that LSD-assisted psychotherapy exerts robust and rapid relief for patients suffering from anxiety and depression related to their terminal illness (Gasser et al., 2014, 2015) and several clinical trials are currently underway focused on various indications of high unmet need, including anxiety disorders, major depressive disorder and cluster headaches (NCT03153579; NCT03781128; and NCT03866252). Nevertheless, the sensoriperceptual effects of classic psychedelics like LSD at moderate-to-high doses could limit their viability as accessible treatments in psychiatric care. Developing approaches to maximize the safety, cost-effectiveness and affordability of classic psychedelic therapies is essential to maximize patient access to these promising new therapeutic alternatives.

LSD is generally regarded as physiologically and psychologically safe when administered in clinical settings, and no serious adverse events have been reported to date (Liechti, 2017). At doses currently being explored for mental health treatment (i.e.

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100 µg and higher), LSD can produce transcendent mystical-type experiences characterized by pseudohallucinations and feelings of awe, unity, insight, positive mood, and transcendence of time and space (Dolder et al., 2017; Holze et al., 2020; Johnson et al., 2019). Other effects include emotional lability, sensitivity to surroundings, and a reduction in vigilance. Reported adverse events through 24 h post-drug administration include anxiety, derealization, depersonalization, emotional distress, feeling abnormal, feeling cold, having illusions, difficulty concentrating, and headache (Gasser et al., 2014; Passie et al., 2008; Schmid et al., 2015). LSD also increases suggestibility (Carhart-Harris et al., 2015), which may account in part for its therapeutic efficacy as well as the increase in general sensitivity and the intensification of emotional reactions during the acute phases of drug effects post-administration. This may also account for how the physical and social environment can affect the quality of the experience (Carhart-Harris et al., 2018; Hartogsohn, 2016).

Modern clinical studies involving LSD and other classic psychedelics generally follow safety guidelines articulated by Johnson and colleagues (2008). These guidelines serve as a backbone for patient interventions using high doses of a classic psychedelic, and they often include intensive preparation prior to drug administration, the oversight of two attendants present during the entire period of acute drug action, and multiple follow-up psychotherapy sessions with these attendants in the days and weeks following the drug session. For instance, in a study of psilocybin-assisted therapy for demoralization among AIDS survivor men, Anderson et al. (2020) administered one dose of psilocybin in a therapeutic paradigm that spanned 7 weeks and involved approximately 3 h of individual psychotherapy and up to 15 h of group psychotherapy. In a study of psilocybin versus escitalopram for depression, Carhart-Harris and colleagues (2021) administered two doses of psilocybin over approximately 6 weeks that included a 3-h in-person preparatory session, two in-person integration sessions and six 'debriefing' or integration sessions via telephone or mobile technology. Furthermore, in a study of psilocybin-assisted therapy in the treatment of major depressive disorder, Davis and colleagues (2020) administered two doses of psilocybin over an 8-week intervention period that involved at least 18 in-person visits, 8 h of preparation and up to 6 h of integration. Finally, in the only contemporary clinical trial of LSD published to date, Gasser et al. (2014, 2015) administered two doses of LSD to patients with end-of-life distress in an intervention 'lasting several months' (Gasser et al., 2014: 515) that included two preparatory sessions and six integrations sessions lasting 60–90 min. Unfortunately, these intensive approaches may render classic psychedelic therapies impractical for broader use within psychiatry. Indeed, it has been noted that the intensive nature of classic psychedelic therapies will almost surely render them expensive and difficult to access, especially for those living with economic disadvantage (Thrul and Garcia-Romeu, 2021). Scalable approaches that maximize patient safety and support are needed to make classic psychedelic drug therapy a more practical and affordable therapeutic alternative.

The goal of this phase 1 proof-of-concept, single-centre, dose-escalation study was to evaluate the safety, tolerability, pharmacokinetics, and subjective effects of 50, 75, and 100 µg LSD among healthy adult participants. This was done in an intervention paradigm conceptualized as more scalable that traditional approaches to administer classic psychedelics in clinical settings. Participants would spend full days at the research site, and their participation was framed around exploring creativity vis-à-vis a work-related problem they described at their screening visit. This framing required participants to focus on improving an aspect of their life (i.e. productivity on a professional problem) and provided an opportunity to develop an operational protocol for an interventional trial. The specific problem-solving aspect of this trial sets it apart from previous studies administering classic psychedelics to healthy participants (Carhart-Harris et al., 2015, 2016; Dolder et al., 2017; Holze et al., 2019, 2020; Preller et al., 2019; Schmid et al., 2015), which have mostly been laboratory-conducted studies with the sole objective of evaluating safety, pharmacokinetics, and related assessments and/or neuroimaging.

The current study design utilized a single attendant to assist each participant during each drug administration, employed remote monitoring of the rooms used for drug administration, fostered group interactions, and a strong collaborative 'interpersonal atmosphere' (Johnson et al., 2008) over a single day prior to drug administration and required no ongoing interaction between participants and attendants after the drug administration day. Up to three healthy participants received a dose of LSD on the same day in separate rooms using this approach.

The doses selected (50, 75, and 100 µg) were above the perceptual threshold (Passie et al., 2008), but also lower than some of the doses currently used for therapeutic intervention in recent clinical trials (i.e. 200 µg in the treatment of end-of-life distress; Gasser et al., 2014, 2015), anxiety disorders (NCT03153579), and major depressive disorder (NCT03866252). These lower doses were selected so that participants could complete planned protocol assessments during the acute period of drug action but may nevertheless be in the relevant range for other indications such as cluster headaches (NCT03781128) or neurorehabilitation.

The present study first used an open-label design followed by a double-blind placebo-controlled design. The purpose of having an open-label lead to the study was to evaluate the tolerability and pharmacokinetics (PK) of different LSD doses in a population that had prior experience with this drug class, and to determine the appropriate LSD doses for use in the subsequent double-blind placebo-controlled portion of the study. The placebo-controlled portion of the study allowed for comparison of protocol measurements taken during LSD administration to placebo as well as within-subject comparison of different LSD doses. Only safety, tolerability, pharmacokinetic, and subjective effect results will be presented here. Qualitative analyses of participants' experiences are reported in a separate article (Hendricks et al., in press) and measures of creativity will also be reported in a separate article. We hypothesized that LSD at the tested doses would be safe and tolerable, as determined by there being no serious or unexpected adverse events and a retention rate of ⩾80% of participants (Swift and Greenberg, 2012). Furthermore, we hypothesized that the exposure to LSD in the doses in our study would be congruent with previous studies that had reported plasma levels of LSD after oral administration. Finally, we hypothesized that the intervention programme used in this study would demonstrate evidence of potential efficacy by triggering transcendent mystical-type subjective experiences thought to mediate treatment outcomes (Johnson et al., 2019).

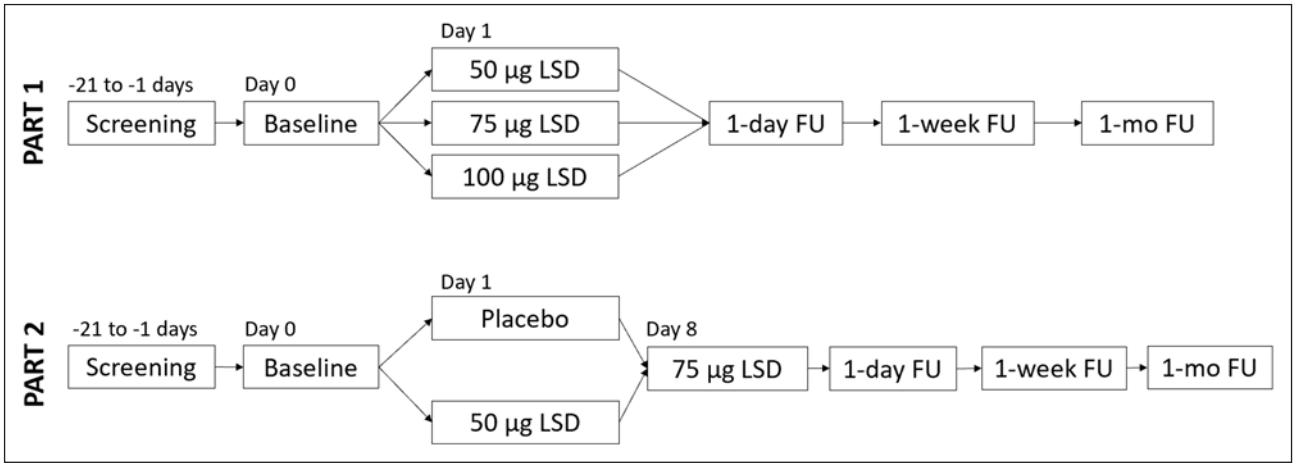


Figure 1. Schematic of trial design.

Methods

This was a phase 1 proof-of-concept, single-centre, dose-escalation study that used both open-label and double-blind placebo-controlled designs to evaluate the safety, tolerability, pharmacokinetics, and subjective effects of doses of LSD ranging from 50 to 100 µg in healthy adult participants. Given the stage of development, this investigation aimed to explore a range of secondary outcomes. Therefore, no adjustment was planned for the multiplicity of tests. The trial was carried out at an Early Phase Clinical Unit, Northwick Park Hospital, United Kingdom.

The study was conducted in accordance with Good Clinical Practice, as required by the United Kingdom Statutory Instrument 2004 No.1031, The Medicines for Human Use (Clinical Trials) Regulations, and subsequent amendments. It was also performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The study protocol and informed consent form were reviewed and approved by the independent ethics committee for the investigational site. The study was conducted in accordance with International Conference on Harmonisation harmonized tripartite guideline on Good Clinical Practice and UK law. Each participant provided written informed consent after an adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study.

Study design

Two sub-studies in different populations of healthy participants were carried out as follows: part 1 was an open-label dose-escalation study in psychedelic non-naive participants, and part 2 was a double-blind, placebo-controlled, randomized study in psychedelic naive participants. The schematic of the two designs is illustrated in Figure 1.

Observations of tolerability of different doses used in the first part informed the doses used in the second part of the study. Psychedelic non-naive participants were those who previously used LSD or any other classic psychedelic drug on more than three occasions during their lifetime. Psychedelic-naive participants were defined as those who had not used LSD or any other classic psychedelic during the past 7 years. In practice, only one of the participants in part 2 of the study who received placebo as his first dose had previously ingested a psychedelic: one instance of psilocybe mushrooms at age 14. Only participants in part 1 of the study provided PK data, as they were deemed to be less likely to have psychologically adverse reactions to blood draws at multiple time points during the acute effects of the drug.

In part 1, participants were assigned to one of five cohorts (i.e. maximum three participants per cohort), or groups of participants that were run in the same sessions, on a rolling basis and received a single dose of 50, 75 or 100 µg LSD, each member of a cohort receiving the same dose. In part 1, all participants in a cohort were assigned the same dose: the first two cohorts received 75 µg, the third received 50 µg, the fourth received 100 µg, and the final cohort received 75 µg. In part 2, participants were assigned to one of eight cohorts (i.e. maximum three participants per cohort), and then randomly assigned to the experimental treatment group or the placebo-controlled group. In part 2, they received their assigned study treatment on two separate occasions, as follows: participants either received 50 µg LSD followed by 75 µg LSD (experimental group), or placebo followed by 75 µg LSD (placebo-controlled group), with dosing separated by 7 days.

Participants arrived at the inpatient clinical trial unit late in the evening on the day prior to their pre-drug baseline assessment and preparation day and stayed overnight (part 2 participants arrived the night before their second dose on their second visit; it is noted that overnight stays served only to maximize adherence to the research protocol and were not conceptualized as necessary components of the intervention paradigm). The following day, participants completed pre-drug baseline assessment and preparation, which included: (1) a brief introduction to their attendant after breakfast in a communal area with other participants; (2) the completion of computer-based assessments in their room until lunch; (3) communal lunch with study administrators, other participants and attendants, with one of the study administrators presenting an overview of LSD effects, guidance with regard to navigating these effects including challenging experiences per Johnson et al. (2008), and instruction to remain lying down while wearing eyeshades and listening to a pre-determined music playlist with headphones for the first 4 h of acute drug action prior to initiating problem-solving; (4) an individual session with their

attendant after lunch that included 30 min discussing their work-related problem, 60 min of breathing exercises and 30 min of rapport-building in their room; (5) the completion of computer-based assessments in their room; and (6) dinner with study administrators, other participants and attendants. Participants stayed overnight once more, and were allowed to read, work and use their phones. The following day, after a light breakfast in a communal area with other participants, the study drug was administered at 9:00 AM. Each attendant remained in the room with his or her assigned participant until 6:30 PM, with brief breaks for food or bathroom use. A remote monitor was responsible for monitoring all three rooms via video and audio streaming and stepped into the rooms in the event the attendants needed a break and assist with any challenging experiences by stepping in or calling the psychiatrist (note: this was not necessary at any point during the study). At 6:30 PM, participants were provided dinner in a communal area with the study administrators, other participants and attendants, after which their attendants left, and the participants completed final computer-based assessments for the day. Participants remained in the clinical trial unit overnight one final time and were allowed to use their phones and work on their problems. The following day, they completed computer-based assessments and a semi-structured interview conducted by an external interviewer or study manager prior to departing before lunchtime. Part 2 participants completed the semi-structured interview after their second drug dose only. Follow-up assessment only visits were conducted approximately 1 week and 1 month after the last dose at the clinical trial unit, during which no study personnel was present. During these visits, medical assessments were carried out, and participants completed computer-based assessments that focused on secondary exploratory aims (these data not presented here).

D-lysergic acid diethylamide hydrate (d-LSD, HPLC purity > 99%, Onyx Scientific Limited, United Kingdom) was dissolved in ethanol at 25 mg/mL and prepared as a solution 50 or 4 µg d-LSD/mL in distilled water and completed to a final volume of 25 mL with the addition of distilled water for oral administration. A shelf life of 78 h was allocated to the doses, when stored in the defined container closure at a temperature of 2–8°C, with the start of the expiry period being defined as the time of combining the d-LSD with ethanol. LSD in solution has been found to be stable for much longer, and up to 2 months, in other studies (Holze et al., 2019). Placebo was distilled water only and presumed to be indistinguishable from the LSD solution.

Study participants

Participants were recruited via flyers posted on university campuses that framed the study around exploring the effects of LSD on creative problem-solving. Healthy men or women aged 21–65 years were screened within 28 days of randomization. Participants who met all inclusion and no exclusion criteria and provided written informed consent were assigned to a cohort (maximum of 3 participants per cohort) based on availability. Eligibility was also dependent on the outcome of an interview with a physician that was performed as part of the screening process.

Key inclusion criteria for part 1 was the use of LSD or any other psychedelic drug, including psilocybin, mescaline, and ayahuasca, on more than 3 occasions during their lifetime. Key inclusion criteria for part 2 was no use of LSD or any other psychedelic drug, including psilocybin, mescaline, and ayahuasca during the past 7 years. Exclusion criteria for both parts included: the presence or clinically relevant history of any psychiatric, respiratory, gastrointestinal, renal, hepatic, haematological, lymphatic, neurological, cardiovascular, musculoskeletal, genitourinary, immunological, dermatological, connective tissue diseases or disorders, as judged by the investigator, and blood pressure exceeding 140 mmHg (systolic) and 90 mmHg (diastolic). Key psychiatric exclusion criteria included a clinically relevant history of psychiatric disorder as judged by the investigator, first- or second-degree relative with schizophrenia, any manic or hypomanic episode, lifetime presence of any major depressive disorder, dependence on any substance in the past 5 years (part 2 only), current diagnosis of schizophrenia, obsessive-compulsive disorder, dysthymic disorder, panic disorder, anorexia, or bulimia or current symptoms of drug abuse. Current smokers were excluded as per phase 1 guidelines to avoid drug–drug interactions for pharmacokinetic and other measurements. Also excluded were participants receiving chronic or acute administration of tricyclic antidepressants or lithium, administration of selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, or other prescription drugs that may interact with the pharmacokinetics of LSD within 14 days of first dosing. A complete list of inclusion and exclusion criteria is included in the supplemental materials. In practice, none of the participants received concomitant central nervous system (CNS) medications during the trial period. Participants were administered the Columbia-suicide severity rating scale (C-SSRS) and the structured clinical interview clinical trials version (SCID-CT: First et al., 2002) as a screening tool, modified based on guidelines described by Johnson and colleagues (2008) to ask about family history of psychiatric disorders, any lifetime psychotic episode that is not substance-induced or due to a medical condition and hypomanic episode.

Safety and tolerability profile assessments

Dropout and adverse events (AEs) were recorded throughout a participant's participation in the study. During screening, baseline, treatment, and follow-up, all participants underwent a series of safety assessments including the C-SSRS, blood pressure and pulse rate. Clinical laboratory evaluations (i.e. haematology, blood chemistry, and urinalysis) were carried out at screening, baseline, and 1-month follow-up. Electrocardiogram (ECG) parameters were recorded for part 1 at screening, treatment day (for part 2, on both treatment days), the day following treatment and 1 month.

Safety was assessed by the clinical evaluation of AEs, vital signs, ECGs, laboratory safety tests, concomitant medications and physical examination, including C-SSRS. No formal analyses were performed, although descriptive summaries of AEs are presented for review. MedDRA coded (version 17.1 or higher) treatment-emergent adverse events (TEAEs) classified according to preferred term (PT) and system organ class (SOC) are summarized by the dose group.

Pharmacokinetics: Blood sampling

Blood samples for plasma analysis of LSD were collected within 15 min prior to dosing and at 30 min and 1, 2, 4, 8, 12, and 24 h post-dosing. Post-dose samples were taken ±10% of scheduled time or ±30 min window around the scheduled time, whichever was narrower. Immediately after blood collection, two lithium heparin tubes (1 × 4 mL and 1 × 6 mL, BD Diagnostics; Vacutainer®) were kept on wet ice until centrifuged. Within 30 min of blood collection, samples were separated by centrifugation for 10 min (1000–1200 g) at approximately 4°C. The resultant plasma was withdrawn in approximately equal volumes of 1.5 mL into two appropriately labelled polypropylene tubes for PK assay and stored (within 1 h of the blood sampling time) at –80°C or lower until shipment.

Pharmacokinetics: Drug levels determination

LSD drug-level determination in human plasma samples was performed at Analytical Services International Ltd (UK). Determination of drug levels was performed as described in Family and colleagues (2020).

Pharmacokinetics: Analysis

The PK parameters were derived, using non-compartmental methods, from plasma drug concentrations over time profiles for each individual participant. The maximum measured concentration C_{max} and peak time T_{max} were obtained directly from concentrations over the 24-h time profiles, as well as T_{first} and T_{last} (first and last quantifiable drug levels during the observation period). The lower limit of quantification (LLOQ) of LSD was 200 pg/mL. λz (terminal elimination rate constant) was calculated by linear regression of the terminal linear portion of the log concentration versus time curve with a $1/Y^2$ weighting method, and $T_{1/2}$ (elimination half-life) was derived as ln(2)/λz. AUC_{0-t} was calculated using trapezoidal summation of the plasma measurable concentrations over the observation period. Recorded drug levels below the level of quantification (BLQ), which included all values under 200 pg/mL, were treated as missing and excluded except for those recorded pre-dosing (time 0 h). For the purpose of calculating AUC_{0-t} when two consecutive plasma concentrations BLQ were encountered after T_{max}, all subsequent values were excluded from the analysis.

Individual plasma concentrations of LSD parent drug were summarized by the dose group using descriptive statistics of the arithmetic mean, standard deviation, coefficient of variation (CV%), geometric mean, median, minimum and maximum, and the number of observations. The form of the relationship between the administered dose and the extent of absorption (AUCs, C_{max}) was also investigated following each dose.

Subjective effects

For part 1, subjective drug effects were assessed during dose day at multiple time points via visual analogue scale (VAS). Time points were 15 min pre-dose and then at 0.5, 1, 2, 4, 8, and 12 h post-dosing. The 20 questions were selected from a range of different sources, including drug abuse liability measures (Shram et al., 2011), and subjective scales previously used to investigate LSD (Schmid et al., 2015) and 3,4-methylenedioxymethamphetamine (Farré et al., 2007).

For both parts 1 and 2, altered states of consciousness were measured using three questionnaires administered at the end of the day of the drug administration session after dinner: the five-dimensional altered states of consciousness (ASC) scale (Dittrich, 1998), the ego dissolution inventory (EDI; Nour et al., 2016), and the mystical experience questionnaire (MEQ; Barrett et al., 2015; MacLean et al., 2012). All questions were completed on Psytools (Delosis, London) via a laptop computer.

The ASC is a self-report questionnaire that can be used to measure subjective experiences induced by classic psychedelics. The dimensions on which this scale measures alterations in consciousness include: oceanic boundlessness, dread of ego dissolution, visionary restructuralization, auditory alterations, and vigilance reduction. The administration of the ASC requires participants to respond to 94 items on a VAS (Studerus et al., 2010).

The EDI is an eight-item questionnaire designed to measure ego dissolution. Each item is scored on a 5-point Likert-type scale, and the inventory includes a single factor.

The MEQ is a 30-item self-report questionnaire developed for detecting and characterizing mystical experiences induced by classic psychedelics. Each item is scored on a 5-point Likert-type scale, and derived scores for the MEQ include four scales: mystical, positive mood, transcendence of time and space, and ineffability. In addition, a response of more than or equal to 60% of each and every scale would classify an experience as a 'complete mystical experience'.

Mean values on VAS items for the 50-, 75-, and 100-µg conditions are presented for descriptive purposes. To compare ASC, EDI and MEQ scale scores between participants who received placebo, 50, 75 and 100 µg as their first (for part 2) or only (for part 1) dose, Levene's test for equality of variances was conducted to compare variances between these conditions, with Welch's ANOVA followed by Games–Howell post hoc tests conducted for those scale scores with unequal variances and Fisher's ANOVA followed by Hochberg GT2 post hoc tests for those scale scores with equal variances. Both post hoc tests control for the probability of making one or more type I errors. A chi-square test of independence compared percentage of participants meeting criteria for a complete mystical experience on the MEQ across the four conditions. For these calculations, every participant's first dose (i.e. only dose for part 1 participants) were used to increase power and make use of a placebo comparator.

For part 2, a mixed-effect ANOVA tested the interaction between experimental condition (50/75 µg vs. placebo/75 µg) and day of drug administration (day 1 vs. day 8) on ASC, EDI, and MEQ scale scores. Any significant interaction effects were subsequently explored with Welch's ANOVA (for unequal variances) or Fisher's ANOVA (for equal variances) comparing scale scores between and within experimental conditions. A McNemar test compared percentage of participants meeting criteria for a complete mystical experience on the MEQ between day 1 and day 8 for both the 50/75 µg and the placebo/75 µg conditions.

Finally, relationships between day 1 and day 8 ASC, EDI and MEQ scores (including the dichotomous complete mystical experience criterion) among participants in the 50/75 µg condition in part 2 were evaluated with Kendall's tau, a non-parametric

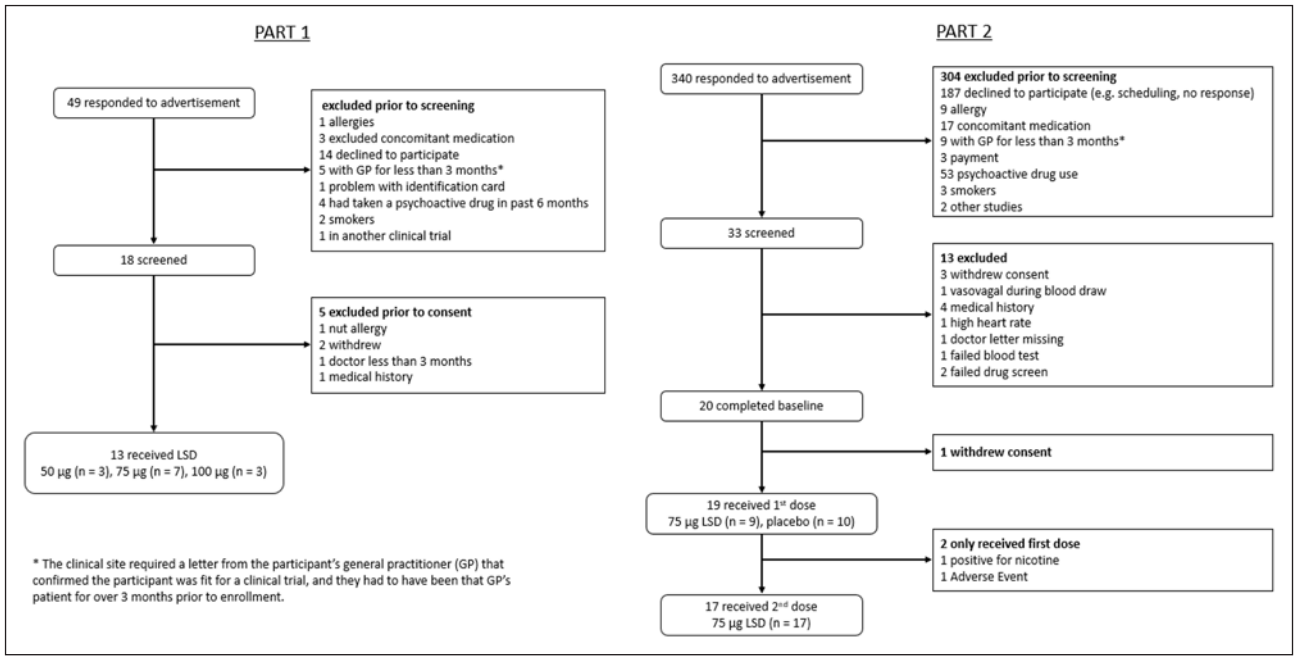


Figure 2. CONSORT flow diagram for part 1 (left) and part 2 (right) of the study.

correlation appropriate for small samples. To facilitate interpretation and reduce type I error, relationships were explored within the same questionnaires only (e.g. associations of ASC scale scores on day 1 were evaluated with ASC scale scores on day 8 only).

All analyses are reported with precise *p* values, allowing the reader to estimate a conservative Bonferroni-type correction by dividing α of 0.05 by the number of comparisons in the family of analyses of the reader's choosing, and then comparing the precise *p* values to the Bonferroni-corrected α.

Results

Study population

Figure 2 displays the CONSORT flow diagram. Thirty-three participants were determined eligible for this study. In part 1, 13 participants were enrolled and received 50 µg (n = 3, no women, mean age = 28), 75 µg (n = 7, one woman, mean age = 28) or 100 µg (n = 3, no women, mean age = 32) LSD on a single occasion. In part 2, the experimental group (n = 9, two women, mean age = 27) received two sequential single doses of LSD (50 µg followed by 75 µg), with dosing separated by seven drug-free days. The placebo-controlled group (n = 10, one woman, mean age = 31) received placebo followed, after seven drug-free days, by a single dose of 75 µg LSD. One participant withdrew from the study prior to drug administration. Two participants, one from each dose group, did not get dosed a second time: one participant in the placebo-controlled group was withdrawn from the study due to nicotine consumption, and one participant withdrew due to an AE (described below). These participants were dropped from analyses that required two time points.

Age, gender, and BMI were balanced across dose groups. The demographic and baseline characteristics for each dose group are summarized in Table 1.

Safety and tolerability

LSD was found to be well tolerated in the population studied, with 30 of 33 participants (91%) completing all aspects of the current study. There were no serious adverse events. Twenty-eight percent of participants (n = 9) experienced at least one expected TEAE. All TEAEs are presented in Table 2.

The only expected AEs that were reported for more than one participant were nausea, vomiting, and headache (two participants each). All expected AEs were reported as mild in severity, except for one. This expected TEAE, 'Euphoric Mood', occurred in an LSD-naive participant in part 2 (50/75 µg condition) and was classified as moderate in severity by the clinical staff. This participant opted to withdraw from the study after receiving 50 µg, forgoing a second LSD dose of 75 µg secondary to concerns that an elevated mood state might interfere with an upcoming job interview. The participant attended the clinical unit on the morning of the second dose, during which the expected AE was marked as 'resolved', and he completed a physical examination, chemistry, haematology and urinalysis, results of which were within the normal range. The participant also attended all subsequent follow-up visits, with no clinically relevant notes. No TEAEs were reported for the 50-µg group, and incidences of AEs were similar across the 75- and 100-µg groups.

No clinically significant abnormalities based on vital signs, physical examinations, ECG measurements or laboratory results were found in clinical review (note: physiological data are included for review as supplementary materials). The C-SSRS and psychiatrist interview administered at the end of each study

Table 1. Demographic and baseline characteristics of healthy participants (safety population).

Observation		Part 1			Part 2		Total
		LSD 50 µg	LSD 75 µg	LSD 100 µg	Placebo/LSD 75 µg	LSD 50 µg/LSD 75 µg	
		n = 3	n = 7	n = 3	n = 10	n = 9	N = 32
Age (years)		28.3 (SD = 1.53)	28 (SD = 3.79)	32 (SD = 9.54)	26.8 (SD = 1.99)	30.7 (SD = 9.49)	28.8 (SD = 6.05)
BMI (kg/m^2)		21.5 (SD = 1.55)	22.3 (SD = 2.74)	25.1 (SD = 1.44)	24.6 (SD = 3.13)	23.6 (SD = 4.35)	23.6 (SD = 3.29)
Gender	Female	0	1 (14.3%)	0	1 (10.0%)	2 (22.2%)	4 (12.5%)
	Male	3 (100.0%)	6 (85.7%)	3 (100%)	9 (90.0%)	7 (77.8%)	28 (87.5%)

BMI: body mass index; LSD: lysergic acid diethylamide.

Table 2. Treatment emergent adverse events, listed by system organ class and preferred term, number of subjects (number of incidents).

System organ class	Part 1			Part 2		Total, *n* (freq)
Preferred term	LSD 50 µg, *n* (freq)	LSD 75 µg, *n* (freq)	LSD 100 µg, *n* (freq)	Placebo/LSD 75 µg, *n* (freq)	LSD 50 µg/LSD 75 µg, *n* (freq)	
Gastrointestinal disorders		1 (1)	1 (1)		1 (2)	3 (4)
Vomiting		1 (1)			1 (1)	2 (2)
Nausea			1 (1)		1 (1)	2 (2)
Nervous system disorders			1 (1)	1 (1)	1 (1)	3 (3)
Headache				1 (1)	1 (1)	2 (2)
Sensory loss			1 (1)			1 (1)
General disorders and administration site conditions		1 (1)		1 (1)		2 (2)
Fatigue				1 (1)		1 (1)
Catheter site pain		1 (1)				1 (1)
Injury, poisoning and procedural complications				2 (2)		2 (2)
Skin abrasion				1 (1)		1 (1)
Injury				1 (1)		1 (1)
Infections and infestations					1 (1)	1 (1)
Nasopharyngitis					1 (1)	1 (1)
Musculoskeletal and connective tissue disorders				1 (1)		1 (1)
Myalgia				1 (1)		1 (1)
Psychiatric disorders					1 (1)	1 (1)
Euphoric mood					1 (1)	

LSD: lysergic acid diethylamide.

day revealed that no participant was suicidal. All participants were recommended for release.

Pharmacokinetics

Drug levels were quantifiable for each of the 50- and 75-µg LSD conditions in average until the 8-h sampling time points, and until the 12-h time point for 100 µg LSD. Drug levels were below LLOQ (200 pg/mL) at the 24-h sampled time points for all doses. Plots of concentration in pg/mL by participant are presented in Figure 3 for each dose group.

The PK parameters $AUC_{0–24}$, C_{max}, T_{max}, and terminal half-life $T_{1/2}$ are summarized for LSD 50, 75, and 100 µg in Table 3. C_{max} was 1088 ± 219 pg/mL for the 50-µg LSD group with a peak time at 2 h. C_{max} was 1712 ± 417 pg/mL for the 75-µg LSD group with a peak time at 1.2 h. C_{max} was 3034 ± 664 pg/mL for the 100-µg LSD group with a peak time at 1.7 h. The ratio between 50- and 75-µg dosing groups for C_{max} and $AUC_{0–24}$ was averaging at 1.6 and 1.7, respectively, whereas the ratio between 50- and 100-µg dosing groups for C_{max} and $AUC_{0–24}$ was averaging at 2.8 and 4, indicating a drug dose to plasma levels positive relationship but deviating from linearity between 50- and 100-µg LSD dose groups. The apparent half-life for 50, 75 and 100 µg LSD averaged at 2.8, 3.2 and 4.3 h, respectively. The estimation of the actual elimination phase and corresponding elimination half-life was limited by the small sample size and the absence of time points in between 4 and 8 h, and apparent half-life is provided instead.

Table 3. Pharmacokinetic parameters summary for 50, 75, and 100 µg LSD.

		T_{max} (h)	C_{max} (pg/mL)	AUC_{0-24} (pg h/mL)	Half-life ($T_{1/2}$ (h))
LSD 50 µg (*N*=3)	Mean	2	1088	4337	2.8
	Median	2	1213	5026	2.6
	SD	0	219	1723	0.3
	CV (%)	0	20	40	10
	Minimum	2	836	2376	2.6
	Maximum	2	1216	5609	3.1
	Nbr obs	3	3	3	3
LSD 75 µg (*N*=7)	Mean	1.2	1712	7577	3.2
	Median	1	1619	7587	3.1
	SD	0.5669	417	2880	0.7
	CV (%)	47	24	38	22
	Minimum	0.5	1248	2869	2.2
	Maximum	2	2516	11,744	4.3
	Nbr obs	7	7	7	7
LSD 100 µg (*N*=3)	Mean	1·7	3034	17,723	4.3
	Median	2	3199	17,445	4.0
	SD	0.6	554	868	1.3
	CV (%)	35	18	5	30
	Minimum	1	2416	17,028	3.2
	Maximum	2	3487	18,695	5·7
	Nbr obs	3	3	3	3

LSD: lysergic acid diethylamide; T_{max}: time to reach maximum plasma concentration; C_{max}: maximum drug plasma concentration; AUC_{0-24}: area under the plasma concentration-time course curve profiles from time zero to the last quantifiable concentration; CV: coefficient of variation; SD: standard deviation.

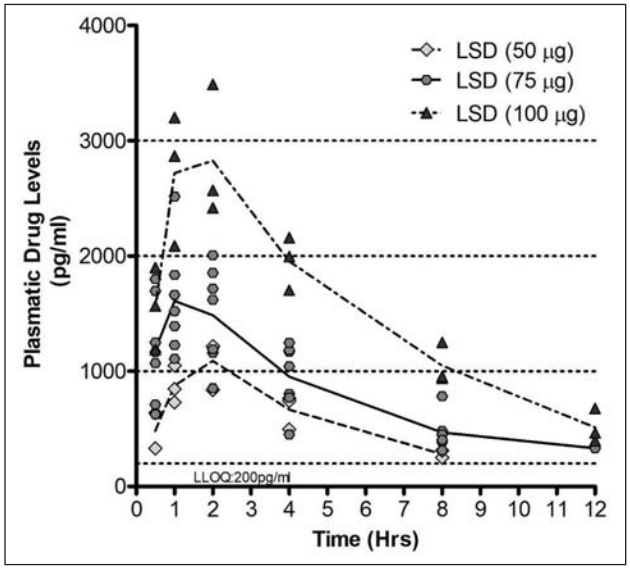


Figure 3. Plasma concentrations of LSD for each participant after 50 µg LSD (*N*=3), 75 µg LSD (*N*=7) and 100 µg LSD (*N*=3). Trace of the mean per dosing group from baseline to 12 h post-dose is represented.

Pharmacodynamics: Subjective drug effects

Figure 4 displays means for VAS items. As seen in the figure, effects were somewhat variable both between and within items, though generally peaked 120 to 240 min post-baseline.

Table 4 displays means (SDs) of ASC, EDI, and MEQ scale scores of participants who received placebo, 50, 75, and 100 µg as their first or only LSD dose, as well as results of ANOVAs comparing these four conditions. Differences between conditions were observed for all scales of the ASC, with post hoc tests indicating greater ratings on the oceanic boundlessness scale among those who received 50 (p=0.00009), 75 (p=0.049), and 100 µg (p=0.006) as compared to those who received placebo; greater ratings on the dread of ego dissolution (p=0.0003) and auditory alterations (p=0.004) scales among those who received 50 µg as compared to those who received placebo; greater ratings on the visionary restructuralization scale among those who received 50 (p=0.0000001), 75 (p=0.0002), and 100 µg (p=0.001) as compared to those who received placebo; and greater ratings on the vigilance reduction scale among those who received 50 (p=0.01) and 100 µg (p=0.02) as compared to those who received placebo. Differences between conditions were also observed for the ego dissolution inventory, with a post hoc test indicating greater ratings among those who received 50 µg (p=0.001) as compared to those who received placebo.

Finally, differences between conditions were observed for all scales of the MEQ, with post hoc tests indicating greater ratings on the mystical scale among those who received 50 (p=0.0004) and 75 µg (p=0.02) as compared to those who received placebo (100 µg vs. placebo p=0.10); greater ratings on the positive mood scale among those who received 50 (p=0.0000004), 75 (p=0.0003) and 100 µg (p=0.00009) as compared to those who received placebo; greater ratings on the transcendence of time and space scale among those who received 50 (p=0.000009), 75 (p=0.01) and 100 µg (p=0.00007) as compared to those who received placebo; and greater ratings on the ineffability scale among those who received 50 (p=0.0000000001) and 75 µg (p=0.0003) as compared to those who received placebo (100 µg vs. placebo, p=0.08). Differences in percentage of participants

Table 4. Mean (SDs) of ASC, EDI, and MEQ scale scores of participants who received placebo, 50, 75, and 100 µg as their first or only LSD dose, and results of ANOVAs comparing these four conditions.

	ASC OBN	ASC DED	ASC VRS	ASC AUA	ASC VIR	EDI	MEQ MYS	MEQ POS	MEQ T/S	MEQ INF
Placebo	3.73 (5.33)	3.14 (5.93)	6.84 (11.26)	3.78 (6.08)	12.68 (12.72)	2.36 (2.48)	0.02 (0.06)	0.60 (0.56)	0.45 (0.62)	0.23 (0.38)
50 µg	50.42 (23.38)	24.94 (12.56)	62.73 (17.24)	23.97 (15.48)	37.19 (20.21)	50.27 (30.31)	2.26 (1.28)	3.48 (1.00)	3.09 (1.13)	4.25 (0.78)
75 µg	35.39 (24.16)	18.84 (19.07)	47.83 (21.98)	21.99 (16.06)	31.60 (24.29)	24.96 (22.66)	2.13 (1.30)	2.78 (1.13)	2.19 (1.08)	3.57 (1.04)
100 µg	62.61 (7.51)	36.66 (34.49)	58.09 (21.85)	19.93 (24.28)	32.13 (5.67)	64.54 (38.53)	3.55 (1.28)	3.77 (1.10)	4.00 (1.45)	4.22 (1.34)
ANOVA results	Welch's F (3, 7.93) = 56.31, p=0.00001	Welch's F (3, 7.04) = 9.18, p=0.007	Fisher's F (3, 28) = 20.91, p=0.0000002	Welch's F (3, 7.13) = 6.62, p=0.018	Welch's F (3, 12.41) = 5.54, p=0.012	Welch's F (3, 6.64) = 12.23, p=0.004	Welch's F (3, 6.61) = 21.24, p=0.0008	Fisher's F (3, 28) = 20.55, p=0.0000003	Fisher's F (3, 28) = 16.16, p=0.000003	Welch's F (3, 7.20) =82.77, p=0.000006

ASC: altered states of consciousness questionnaire; AUA: auditory alterations; DED: dread of ego dissolution; EDI: ego dissolution inventory; INF: ineffability; MEQ: mystical experience questionnaire; MYS: mystical; OBN: oceanic boundlessness; POS: positive mood; T/S: transcendence of time and space; TOT: total score; VRS: visionary restructuralization; VIR: vigilance reduction.

meeting criteria for a complete mystical experience on the MEQ among those who received placebo (0%), 50 (25%), 75 (0%) and 100 µg (33.3%) approached statistical significance (χ^2 (3, N=32)=6.79, p=0.07).

Figure 4 displays means of ASC, EDI, and MEQ scale scores across experimental condition (50/75 µg vs. placebo/75 µg) and the day of drug administration (day 1 vs. day 8). There was a significant experimental condition by the day of drug administration interactions for every scale of the ASC (oceanic boundlessness F (1, 15)=17.14, p=0.0008; dread of ego dissolution F (1, 15)=9.52, p=0.007; visionary restructuralization F (1, 15)=33.58, p=0.00003; vigilance reduction F (1, 15)=15.21, p=0.001) with the exception of auditory alterations (F (1, 15)=3.36, p=0.08), which approached significance. There was also a significant experimental condition by the day of drug administration interactions for the EDI (F (1, 15)=7.87, p=0.01), and every scale of the MEQ (mystical F (1, 15)=14.02, p=0.001; positive mood F (1, 15)=30.98, p=0.00005; transcendence of time and space F (1, 15)=11.51, p=0.004; ineffability F (1, 15)=38.98, p=0.00001). As shown in the figures, those in the 50/75 µg condition reported greater scale scores than those in the placebo/75 µg condition on day 1 on the ASC (oceanic boundlessness Welch's F (1, 8.92)=57.38, p=0.00003; dread of ego dissolution Fisher's F (1, 17)=30.62, p=0.00003; visionary restructuralization Fisher's F (1, 17)=86.96, p=0.00000004; auditory alterations Welch's F (1, 10.09)=13.56, p=0.004; vigilance reduction Fisher's F (1, 17)=12.74, p=0.002), EDI (Welch's F (1, 8.08)=27.18, p=0.0007), and MEQ (mystical Welch's F (1, 8.04)=45.04, p=0.0001; positive mood Fisher's F (1, 17)=77.15, p=0.00000009; transcendence of time and space Fisher's F (1, 17)=46.33, p=0.000003; ineffability Welch's F (1, 10.94)=171.51, p=0.00000004), there were no significant differences between conditions on day 8. Moreover, there were no differences on scale scores between day 1 and day 8 among those in the 50/75 µg condition, but there were significant differences on all scale scores between day 1 and day 8 among participants in the placebo/75 µg condition on the ASC (oceanic boundlessness F (1, 8)=48.75, p=0.0001; dread of ego dissolution F (1, 8)=26.03, p=0.0009; visionary restructuralization F (1, 8)=40.74, p=0.0002; vigilance reduction F (1, 8)=15.22, p=0.004) with the exception of the auditory alterations scale (F (1, 8)=2.59, p=0.146), the EDI (F (1, 8)=22.83, p=0.001), and the MEQ (mystical F (1, 8)=47.62, p=0.0001; positive mood F (1, 8)=76.29, p=0.00002; transcendence of time and space F (1, 8)=40.18, p=0.0002; ineffability F (1, 8)=88.10, p=0.00001), as displayed in Figure 5. Finally, among participants in the 50/75 µg condition, 33.3% met criteria for a complete mystical experience on day 1 as compared to 50% on day 8 (McNemar test statistic=25, p=0.62). Among participants in the placebo/75 µg condition, 0% met criteria for a complete mystical experience on day 1 as compared to 55% on day 8, with this result approaching statistical significance (McNemar test statistic=3.20, p=0.06).

Tables 5 and 6 present relationships between day 1 and day 8 ASC and MEQ scale scores, respectively, among participants in the 50/75 µg condition. As seen in these tables, a significant correlation was found for the visionary restructuralization scale of the ASC only. The correlation of the EDI was also not significant (Kendall's tau=35, p=0.21).

Exploratory analyses

Although our a priori analytic strategy in comparing subjective responses to the first or only LSD dose was to collapse across participants in part 1 and part 2 (Table 4), one reviewer suggested that we evaluate responses from participants in part 1 and part 2 separately, as these data may have been affected by differences in sample characteristics (e.g. prior psychedelic use) or study procedure (e.g. blood draws). We therefore compared subjective drug effects between: (1) participants who received 50 µg LSD in part 1 to participants who received 50 µg LSD in part 2; and (2) participants who received 75 µg LSD in part 1 to participants who received 75 µg LSD 1 week after receiving placebo in part 2. These analyses failed to reveal any significant differences. Moreover, evaluating participants in part 1 and part 2 separately revealed no significant differences between those who received 50, 75, and 100 µg LSD in part 1 and significantly greater responses on all scales among those who received 50 µg LSD as compared to those who received placebo in part 2.

Discussion

The goal of this phase 1 proof-of-concept, single-centre, dose-escalation study was to evaluate the safety, tolerability, pharmacokinetics, and subjective effects of doses of LSD ranging from 50 to 100 µg among healthy participants in an intervention paradigm conceived as more scalable than traditional approaches to administering classic psychedelics. This study used both open-label and double-blind placebo-controlled designs. A total of 23 participants (13 from part 1 and 10 from part 2) each received a

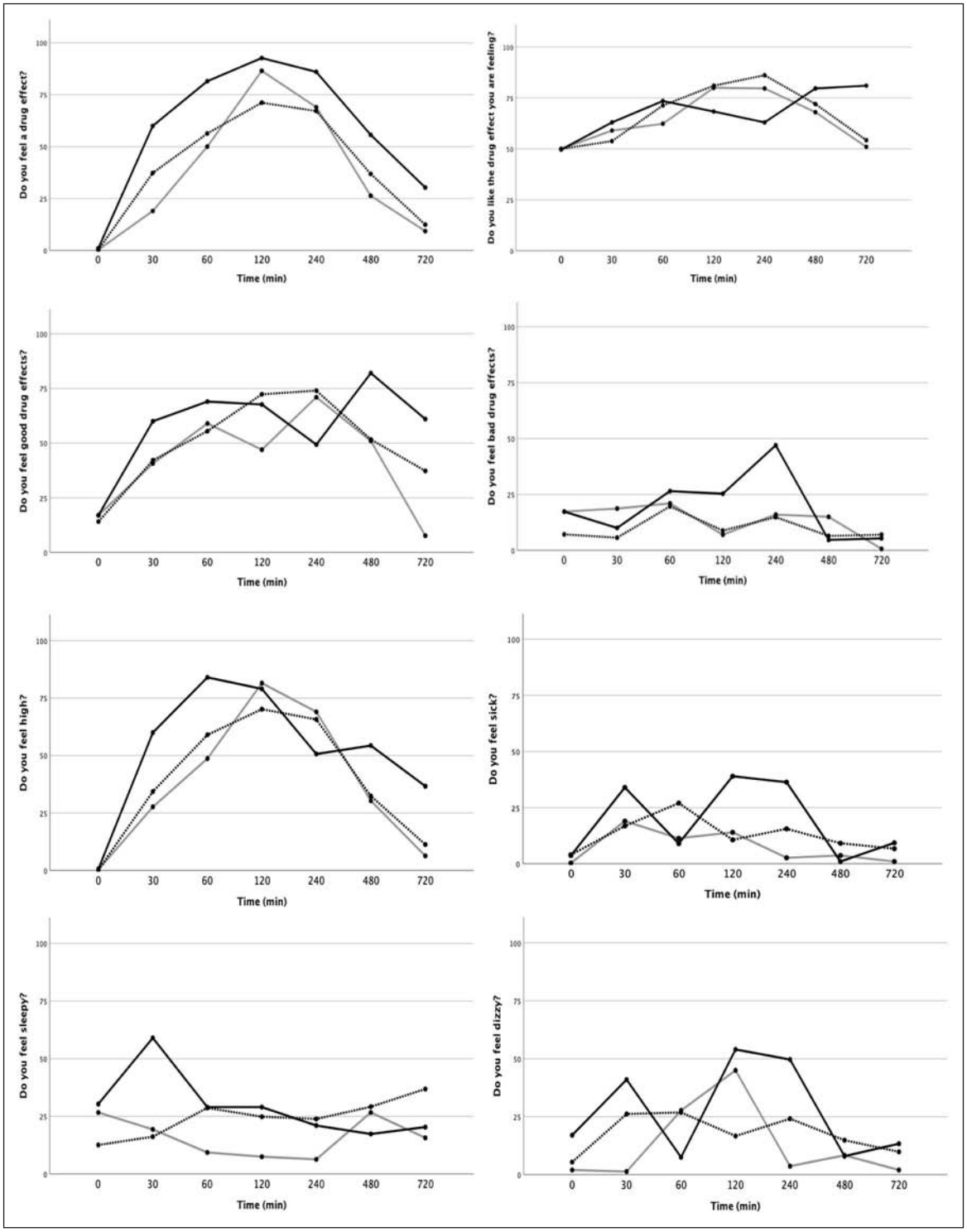
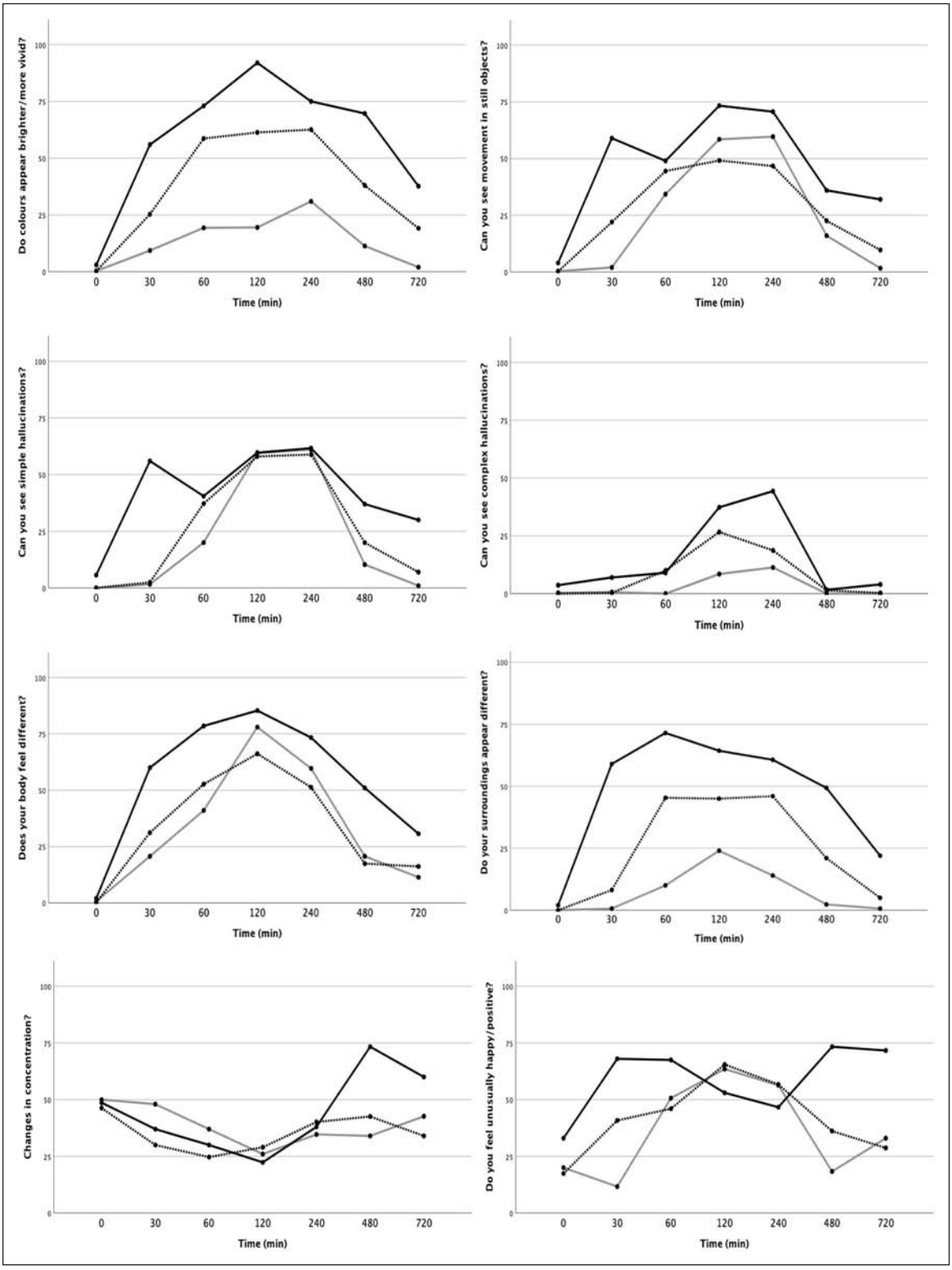


Figure 4. (Continued)



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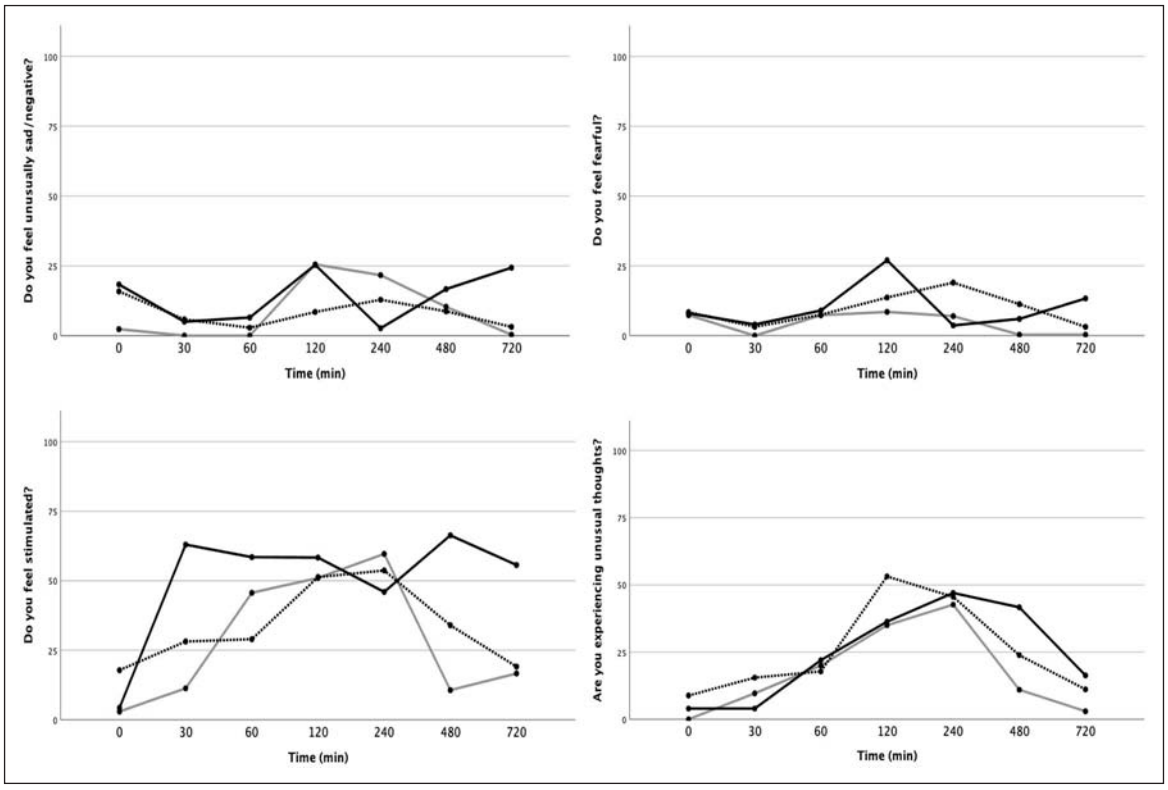

Figure 4. Mean value of VAS questions plotted over time for each group from baseline to 12 h post-dose, for 50 µg LSD ($N=3$), 75 µg LSD ($N=7$), and 100 µg LSD ($N=3$).
Note. Grey lines correspond to 50 µg LSD, dotted lines correspond to 75 µg LSD, and bold lines correspond to 100 µg LSD.

Table 5. Relationships between day 1 and day 8 ASC scale scores among participants in the 50/75 µg condition.

	OBN	DED	VRS	AUA	VIR
OBN	0.0 (1.0)	0.07 (0.80)	−0.42 (0.13)	−0.42 (0.13)	0.21 (0.45)
DED	0.0 (1.0)	0.21 (0.45)	−0.28 (0.32)	−0.14 (0.62)	0.35 (0.21)
VRS	0.14 (0.62)	−0.35 (0.21)	0.28 (0.32)	0.42 (0.13)	0.21 (0.45)
AUA	−0.28 (0.32)	−0.35 (0.21)	−0.14 (0.62)	0.14 (0.62)	0.35 (0.21)
VIR	−0.50 (0.08)	0.0 (1.0)	−0.21 (0.45)	−0.21 (0.45)	**0.71 (0.01)**

ASC: altered states of consciousness questionnaire; AUA: auditory alterations; DED: dread of ego dissolution; OBN: Oceanic boundlessness; VIR: vigilance reduction; VRS: visionary restructuralization. Reported statistic is Kendall's tau (p value). Findings in bold are significant.

Table 6. Relationships between day 1 and day 8 MEQ scores among participants in the 50/75 µg condition.

	MYS	POS	T/S	INF	TOT	Complete Mystical Experience
MYS	−0.07 (0.80)	−0.28 (0.32)	−0.40 (0.17)	−0.37 (0.22)	−0.07 (0.80)	0.09 (0.77)
POS	−0.03 (0.89)	0.11 (0.70)	0.0 (1.0)	0.0 (1.0)	0.11 (0.70)	−0.15 (0.65)
T/S	0.11 (0.70)	−0.11 (0.70)	−0.2 3 (0.44)	−0.17 (0.58)	0.11 (0.70)	0.20 (0.55)
INF	−0.04 (0.89)	0.20 (0.50)	0.04 (0.89)	0.14 (0.66)	0.12 (0.68)	−0.21 (0.53)
TOT	0.0 (1.0)	−0.07 (0.80)	−0.18 (0.53)	−0.20 (0.50)	0.0 (1.0)	0.0 (1.0)
Complete Mystical Experience	0.10 (0.73)	−0.10 (0.73)	−0.05 (0.86)	−0.06 (0.85)	0.10 (0.73)	0.0 (1.0)

INF: ineffability; MEQ: mystical experience questionnaire; MYS: mystical; POS: positive mood; TOT: total score; T/S: transcendence of time and space. Reported statistic is Kendall's tau (p value).

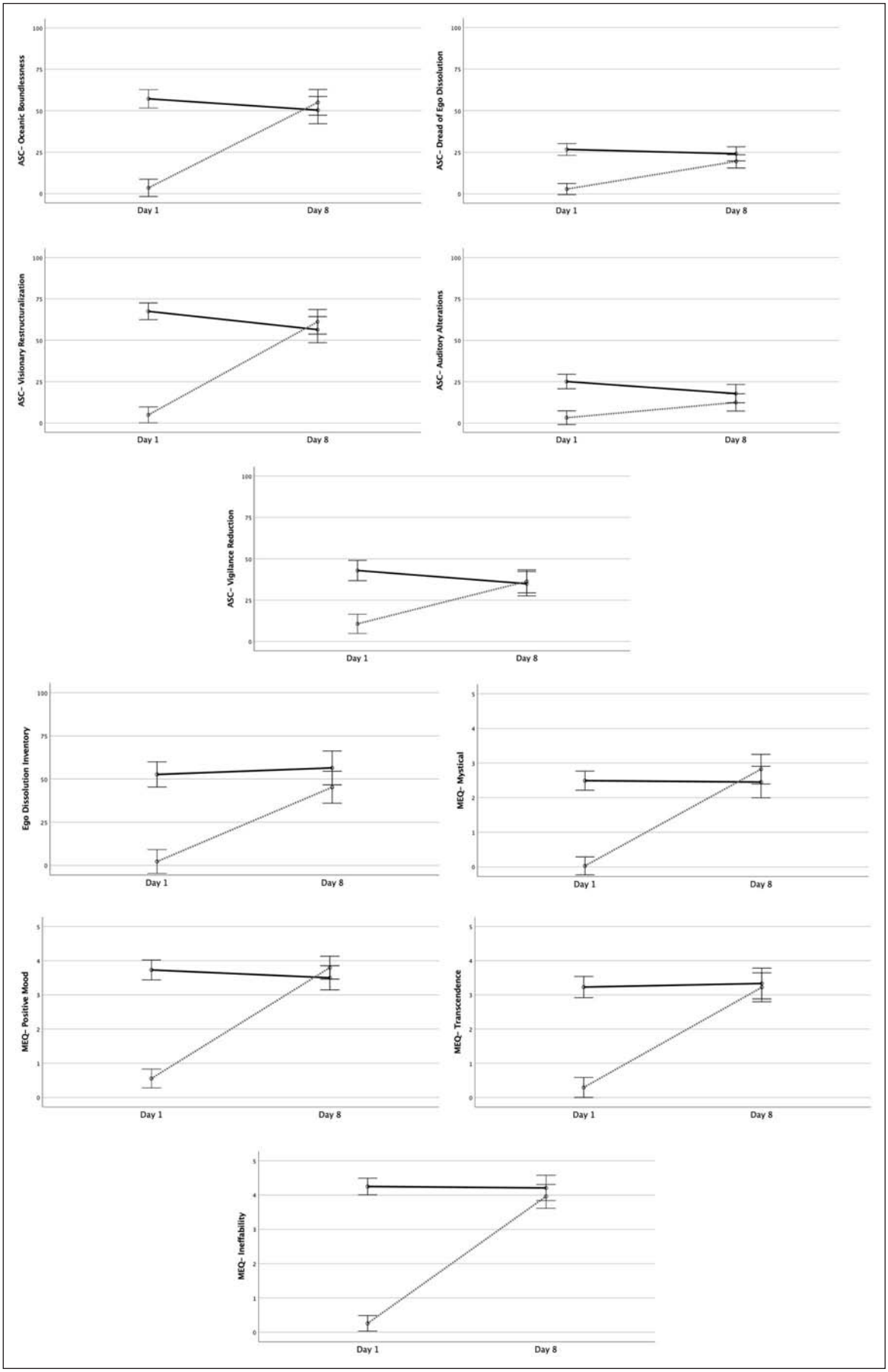

Figure 5. ASC, EDI, and MEQ scales for the 50/75 µg and placebo/75 µg groups on day 1 vs. day 8.

Note. Bold lines correspond to the 50 µg/75 µg condition and dotted lines correspond to the placebo/75 µg condition. Error bars are +/- 1 SEM.

single dose of LSD, and eight participants in part 2 each received two doses of LSD.

Participant retention and overall clinical review of adverse events, vital signs, ECGs, laboratory safety tests, concomitant medications and physical examination identified no concerns with doses of 50, 75, and 100 µg LSD in the 31 healthy participants who received at least one dose of LSD, aged 23–54 years. The single moderately rated adverse event reported by one participant was *Euphoric Mood*. This expected adverse event, reported by the clinical site in part 2 of the study 1 week after dosing, was noted as such since it resulted in the participant choosing to withdraw from the study after receiving 50 µg LSD and not receiving their second LSD dose of 75 µg. This participant opted to withdraw secondary to concerns that an elevated mood might interfere with an upcoming job interview.

Elevated mood after dosing is consistent with the 'afterglow' that occurs after the ingestion of a classic psychedelic, described as a persisting feeling of elevated and energetic mood for days to weeks after drug administration (Halpern, 1996; Majić et al., 2015; Pahnke and Richards, 1970; Pahnke et al., 1971). In a recent study in 12 healthy volunteers who were administered psilocybin, positive effect remained elevated and trait anxiety reduced at 1 month post-intervention (Barrett et al., 2020). Despite being noted as an expected adverse event in the current study, this post-acute period has also been suggested to be an ideal window for psychotherapeutic intervention and possibly a mechanism that aids abstinence in substance use patients (Garcia-Romeu et al., 2020). While this phenomenon may offer a suitable time for a therapeutic intervention, further investigations should focus on mitigating potential risks related to impulsive decision-making and triggering mania in patients at risk for such complications. It is noted that in the current study, the participant reporting *Euphoric Mood* did not exhibit any other indications of impulsivity or mania. Other safety assessments performed, including laboratory safety assessments, vital signs, and ECGs support the conclusion that the investigated doses of LSD do not present a safety concern.

The mean C_{max} and $AUC_{0–24h}$ curve values in the 50-, 75-, and 100-µg LSD dose groups were approximately 1.1, 1.7, and 3.0 ng/mL, and 4.3, 7.6, and 17.7 ng h/mL, respectively, consistent with dose-proportional pharmacokinetics. Our estimated C_{max} and AUC values appear higher than previously reported values for 100 µg LSD hydrate capsules where C_{max} was averaging at 1.3 ng/mL and the AUC value was averaging at 8.1 ng h/mL (Dolder et al., 2017). On the other hand, the same group reported noteworthy differences of apparent bioavailability and/or stability of a net 100 µg oral solution of LSD base in ethanol stored up to the duration of the study versus an oral capsule formulation of LSD hydrate with C_{max} values of 1.7 versus 1.3 ng/mL, and AUC 13.3 versus 8.1 ng h/mL (Holze et al., 2019). In our study, the active pharmaceutical ingredient d-LSD base was prepared as an aqueous oral solution by dissolution in ethanol at 25 mg/mL and then diluted in water with a final volume of 25 mL and a shelf life of 78 h only. Thus, the apparent higher drug exposure trends in our study could be due to the small sample size, with three participants each in the 50- and 100-µg LSD dose groups, and seven participants in the 75-µg LSD dose group, and could reflect an apparent higher bioavailability as well combined with the absence of significant degradation of the active drug product in our protocol. The mean T_{max} ranged from 1.2 to 2 h and LSD had an apparent half-life ranging from 2.8 to 4.3 h, similar to previously reported values for a dose of LSD of 100 or 200 µg (Dolder et al., 2015, 2017; Holze et al., 2019).

With regard to subjective effects, between-subjects analyses among participants who received LSD as their first (part 2) or only (part 1) dose revealed that not all mean scores were significantly different than placebo on the ASC, EDI, and MEQ among those who received 50 ($n=12$), 75 ($n=7$), and 100 µg ($n=3$) LSD. This may be a function of greater power afforded by greater sample size, or because nine of the 12 participants who received 50 µg LSD were psychedelic-naive whereas all participants who received 75 and 100 µg LSD had previously used a psychedelic. Nevertheless, that LSD largely produced elevations in ASC, EDI, and MEQ scores relative to placebo is consistent with prior research evaluating LSD at an even lower doses of 10 (Bershad et al., 2019), 75 (Carhart-Harris et al., 2016), 100 (Holze et al., 2019; Liechti et al., 2017) and 200 µg (Liechti et al., 2017; Schmid et al., 2015). However, to the best of our knowledge, the current report is the first to demonstrate such elevations produced by 50 µg LSD specifically.

In addition, the percentage of participants meeting criteria for a complete mystical experience after 50 µg (25%) and 100 µg (33·3%) LSD in the current study exceeded those of previous investigations evaluating 200 µg LSD among both healthy participants (Liechti et al., 2017; 12.5%) and patients with life-threatening illnesses (Gasser et al., 2014; 17%), though no participants who received 75 µg LSD in the current study met these criteria. The percentage of participants in part 2 meeting criteria for a complete mystical experience after 50 µg LSD (33.3%), 75 µg LSD 1 week after receiving 50 µg LSD (50%) and 75 µg LSD 1 week after receiving placebo (55%) exceeded those of participants in previous studies as well. These differences may reflect the small sample size in the current study, or differences between the studies in set, setting, or participant characteristics. Nevertheless, these findings indicate that safety guidelines for higher doses apply fully to these lower doses, as subjective effects are similar in intensity. Insofar as such experiences appear to underlie the therapeutic efficacy of LSD (Johnson et al., 2019), the current results suggest that doses as low as 50 µg may be sufficient for certain patients to induce such experiences in clinical application. However, patient populations may differ significantly in their perception of drug effects, and research into the use of LSD in the treatment of alcoholism (Krebs and Johansen, 2012) suggests that much higher doses may be required to effectively treat conditions such as substance dependence.

Consistent with between-subjects analyses described above, in part 2 of the current study those who received 50 µg LSD as their first dose reported greater scores on the EDI and all scales of the ASC and MEQ as compared to those who received placebo as their first dose. As expected, no differences were found in subjective effects between those who received 75 µg LSD 1 week after receiving 50 µg LSD and those who received 75 µg LSD 1 week after receiving placebo. No within-subject differences were detected between 50 and 75 µg LSD. These findings are the first to our knowledge demonstrating conspicuous subjective effects associated with 50 µg LSD, and are consistent with a prior study evaluating 75 µg LSD (Carhart-Harris et al., 2016). Furthermore, this lack of correlation indicates a variability in response in the same person in the same setting. That 75 µg LSD demonstrated more differences across self-report scales in within-subject analyses than in between-subject analyses

described above may be a consequence of greater power, or because all participants in within-subject analyses were psychedelic-naive, whereas some participants in between-subject analyses were psychedelic non-naive.

In this study, the following aspects were implemented as part of an intervention paradigm for classic psychedelic administration conceptualized as more scalable than traditional methods: abbreviated non-drug sessions (i.e. preparation and integration/follow-up), a single attendant in the treatment room with remote support from other team members, fostering group interaction, and dosing up to three participants per day. A review of the safety and tolerability results suggests that these changes may not affect the physical or psychological safety of healthy participants. Furthermore, a review of the subjective effects suggests these changes may not inhibit the transcendent, mystical-type experiences that are thought to mediate therapeutic outcomes (Johnson et al., 2019). Qualitative analyses of participants' experiences, which speak to the feasibility of the current paradigm from the participants' perspectives, are reported in a separate report (Hendricks et al., in press). New, more efficient approaches to ensure patient safety and clinician compliance with treatment guidelines, while providing support for patients following drug therapy, are needed to make classic psychedelic drug therapy a more practical and affordable therapeutic alternative to current treatments. The current trial provides a potential paradigm for a design that requires fewer resources without compromising safety or subjective effects. However, as noted below, evaluation of this intervention model in clinical samples is a critical question for future research.

This study has important limitations. First and most noteworthy, the sample included only healthy participants. This is significant because clinical populations might require more intensive support to maximize the safety and efficacy of classic psychedelic-assisted treatment. All components of the intervention paradigm that were tested in this study would need to be re-evaluated in clinical samples before implementation in patient populations. Namely, future studies will need to investigate whether a similar preparatory process, staffing structure, and abbreviated integration/follow-up provides sufficient support for the range of patient populations. Second, the sample size was low, especially for the higher 100-µg dose group ($n = 3$), and all conclusions should be considered preliminary until further validated in a larger sample, as some null findings may represent type II errors. The small sample is offset by the uniqueness of the current study, however, as administering LSD to human participants remains a challenge due to regulatory and funding restrictions, which is why only a handful of contemporary studies have been published on the matter. Third, participants were informed of the identity of the drug, raising the possibility of expectancies influencing the results. Fourth, though the current intervention was conceived as more scalable and appears less intensive than traditional approaches on its face, some of its components may in fact be more involved or costly (e.g. full days at the site and the provision of meals). No measurements of costs were calculated in the current study, and a cost-effectiveness analysis would need to be carried out for a full evaluation of the benefit of this paradigm, especially in comparison to more traditional approaches. Relatedly, the current study did not evaluate the acceptability or feasibility of the novel intervention paradigm from the perspective of care providers. Finally, the low recruitment rate in this trial of female participants limits the extent to which these findings may generalize to women.

Conclusion

In summary, this was a phase 1 proof-of-concept, single-centre, dose-escalation study that used both open-label and double-blind placebo-controlled designs to evaluate the safety, tolerability, pharmacokinetics, and subjective effects of low-to-moderate doses of LSD ranging from 50 to 100 µg among healthy participants in an intervention paradigm conceived as more scalable than traditional approaches to administering classic psychedelics. Findings support the feasibility of new treatment design protocols for drug administration and open the door for larger studies designed to evaluate further refinements and additions (e.g. treatments components specific to the mental health condition under consideration) to these new treatment designs for the safe and cost-efficient delivery of classic psychedelic drug therapy. These methods need to be tested in a controlled environment with a patient population for further refinement for the range of relevant mental health conditions.

Declaration of conflicting interests

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Supplemental material

Supplemental material for this article is available online.

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