Journal of Psychopharmacology

Safety, Tolerability, Pharmacokinetics, and Subjective Effects of 50 µg, 75 µg, and 100 µg LSD in Healthy Participants

Journal:	*Journal of Psychopharmacology*
Manuscript ID	JOP-2021-4627
Manuscript Type:	Original Paper
Date Submitted by the Author:	20-Jan-2021
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Please list at least 3 keywords which relate to your manuscript::	Lysergic acid diethylamide, LSD, psychedelic, hallucinogen, implementation science
Abstract:	Background. Emerging clinical evidence suggests that classic psychedelics hold promise in treating a range of psychiatric disorders, but require scalable interventional protocols. This study evaluated the safety, pharmacokinetics, and subjective effects of 50 µg, 75 µg and 100 µg lysergic acid diethylamide (LSD) in healthy adults within an interventional paradigm. This data is required as a foundation for future clinical research Methods. This was a phase 1, dose-escalation study: one part with an open-label design and another with a double-blind placebo-controlled crossover design. Results. Thirty-two adults (mean age = 28·8 years) received 50 µg (n = 3), 75 µg (n = 7), 100 µg (n = 3) LSD, 50 µg followed by 75 µg LSD (n = 9) one week apart, or placebo followed by a 75 µg LSD (n = 10) one week apart. Twenty-eight percent of subjects experienced at least one mild adverse event, with one adverse event classified as moderate in severity. Maximum blood plasma levels occurred between 1·2 and 2 hours post-administration, with an apparent half-life between 2·8 to 4·3 hours. In most comparisons, doses of LSD induced greater subjective effect ratings relative to placebo. Conclusion. The results suggest 50 µg, 75 µg and 100 µg LSD are tolerable doses with a favorable safety profile in this population, with only mild adverse events during the day of drug effects. Future clinical

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Abstract

Background. Emerging clinical evidence suggests that classic psychedelics hold promise in treating a range of psychiatric disorders, but require scalable interventional protocols. This study evaluated the safety, pharmacokinetics, and subjective effects of 50 µg, 75 µg and 100 µg lysergic acid diethylamide (LSD) in healthy adults within an interventional paradigm. This data is required as a foundation for future clinical research

Methods. This was a phase 1, dose-escalation study: one part with an open-label design and another with a double-blind placebo-controlled crossover design.

Results. Thirty-two adults (mean age = 28·8 years) received 50 µg (n = 3), 75 µg (n = 7), 100 µg (n = 3) LSD, 50 µg followed by 75 µg LSD (n = 9) one week apart, or placebo followed by a 75 µg LSD (n = 10) one week apart. Twenty-eight percent of subjects experienced at least one mild adverse event, with one adverse event classified as moderate in severity. Maximum blood plasma levels occurred between 1·2 and 2 hours post-administration, with an apparent half-life between 2·8 to 4·3 hours. In most comparisons, doses of LSD induced greater subjective effect ratings relative to placebo.

Conclusion. The results suggest 50 µg, 75 µg and 100 µg LSD are tolerable doses with a favorable safety profile in this population, with only mild adverse events during the day of drug effects. Future clinical work will evaluate similar paradigms to evaluate safety and tolerability in clinical populations.

Funding. This study was funded by Eleusis Health Solutions Ltd.

Introduction

Lysergic acid diethylamide (LSD) is a classic psychedelic that induces profound alterations in consciousness at the doses currently being considered for treatment of psychiatric disorders (Hintzen and Passie, 2010; Nichols, 2016; Liechti, 2017). LSD was the focus of nearly ten thousand 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 favorable 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 (Peter Gasser, Kirchner and Passie, 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; NCT03866252). Nevertheless, the profound and protracted sensoriperceptual effects of classic psychedelics like LSD at moderate to high doses could limit their viability as universally accessible treatments in psychiatric care. Developing approaches to ensure the safety and cost-efficiency of classic psychedelic therapies is essential to guaranteeing broad 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 (i.e., 100 µg and higher), LSD reliably produces transcendent mystical-type experiences characterized by pseudo-hallucinations and feelings of awe, unity, insight, positive mood, and transcendence of time and space (Johnson *et al.*, 2019). Other effects include emotional lability, sensitivity to surroundings, and a reduction in vigilance. Reported adverse events through 24 hours post-drug administration include anxiety, derealization, depersonalization, emotional distress, feeling abnormal, feeling cold, having illusions, difficulty concentrating, and headache (Passie *et al.*, 2008; Gasser *et al.*, 2014; 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 (Hartogsohn, 2016; Carhart-Harris *et al.*, 2018).

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 include multiple preparatory sessions over several days prior to drug administration, the oversight of two attendants (typically one man and one woman) present during the entire drug session that can last from 4-12 hours, and multiple follow-up psychotherapy sessions with these attendants in the days and weeks following the drug session. Some of these guidelines may render classic psychedelic therapies impractical for broad use within psychiatry. Scalable approaches that ensure patient safety and support are needed to make classic psychedelic drug therapy a practical and affordable therapeutic alternative.

The goal of this phase 1, single-center, dose-escalation study was to evaluate the safety, tolerability, pharmacokinetics, and subjective effects of 50 µg, 75 µg, and 100 µg LSD among healthy participants in a scalable intervention paradigm. 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 (these results reported elsewhere). 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; Schmid *et al.*, 2015; Robin L Carhart-Harris *et al.*, 2016; Dolder *et al.*, 2017a; Preller *et al.*, 2019), 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, Richards and Griffiths, 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 µg, 75 µg, 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; P. Gasser, Kirchner and Passie, 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 crossover design. The purpose of having an open-label lead to the study was to evaluate the tolerability and 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 crossover 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. Other exploratory endpoints, such as measures of creativity and qualitative analyses of study participants' experiences, are reported elsewhere.

Methods

This was a phase 1, single-center, dose-escalation study that used both open-label and double-blind placebo-controlled crossover designs to evaluate the safety and tolerability of doses of LSD ranging from 50 µg to 100 µg in healthy 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 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 adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study.

Study design

This phase 1, single-center, dose-escalation study used both open-label and double-blind placebo-controlled crossover designs to evaluate the safety and tolerability of doses of LSD ranging from 50 µg to 100 µg in healthy participants. Two sub-studies in different populations of healthy participants were carried out as follows: part 1 was an open-label dose-escalation study in hallucinogen non-naïve participants, and part 2 was a double blind, placebo controlled, randomized, crossover study in hallucinogen naïve participants. Hallucinogen non-naïve participants were those who previously used LSD or any other classic psychedelic drug on more than 3 occasions during their lifetime. Hallucinogen naïve participants were defined as those who had not used LSD or any other classic psychedelic during the past 7 years. Only participants in part 1 of the study provided pharmacokinetics (PK) data.

In part 1, participants were randomly assigned to one of 5 cohorts (i.e., maximum 3 participants per cohort) and received a single dose of 50 µg, 75 µg, or 100 µg LSD, each member of a cohort receiving the same dose. In part 2, participants were assigned to one of 8 cohorts (i.e., maximum 3 participants per cohort), and then randomly assigned to the experimental non-crossover treatment group or the placebo-controlled crossover group. In part 2, they received their assigned study treatment on 2 separate occasions, as follows: participants either received 50 µg LSD followed by 75 µg LSD (experimental non-crossover group), or placebo followed by 75 µg LSD (placebo-controlled crossover group), with dosing separated by 7 days.

Participants received their assigned LSD doses in an in-patient setting. All participants had a baseline day prior to the drug dosing day (for part 2 participants, this occurred the day before the first dosing day), during which they completed baseline assessments, received an orientation session about potential drug effects, underwent a brief breathing exercise, which helped build rapport with their attendant. On each dosing day, participants were encouraged to lie down with eyeshades and listen to a set music playlist for the first 3-4 hours after drug administration, then they were encouraged to work on their work-related problem during the afternoon, and completed several assessments. On the day following dosing, participants completed assessments, a semi-structured interview was conducted (for part 2, this occurred after the second dosing day), and they were released at mid-day. A follow-up visit was conducted approximately 1-week and 1-month after the last dose.

D-lysergic acid diethylamide hydrate (d-LSD, HPLC purity >99%, Onyx Scientific Limited, United Kingdom) was dissolved in ethanol at 25mg/ml and prepared as a solution 50 µg 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 hours 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 to 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 use of LSD or any other classic 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 classic psychedelic drug, including psilocybin, mescaline, and ayahuasca during the past 7 years. Exclusion criteria for both parts included: 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 140mmHg (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. In practice, none of the participants

received concomitant CNS (central nervous system) medications during the trial period. Participants were administered the Columbia-Suicide Severity Rating Scale (C-SSRS) and the SCID-CT (First *et al.*, 2007) (Clinical Trials Version) as a screening tool, modified based on guidelines described by Johnson and colleagues (2008).

Safety and tolerability profile assessments

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., hematology, blood chemistry, urinalysis) were carried out at screening, baseline, and one-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 dose group.

Pharmacokinetics: Blood sampling

Blood samples for plasma analysis of LSD were collected within 15 minutes prior to dosing and at 30 minutes and 1, 2, 4, 8, 12, and 24 hours post dosing. Post-dose samples were taken ± 10% of scheduled time or ± 30-minute window around the scheduled time, whichever was narrower. Immediately after blood collection, two lithium heparin tubes (1 x 4 mL and 1 x 6 mL - BD Diagnostics - Vacutainer®) were kept on wet ice until centrifuged. Within 30 minutes of blood collection, samples were separated by centrifugation for 10 minutes (1000 - 1200 g) at approximately 4°C. The resultant plasma was withdrawn in approximately equal volumes of 1·5 mL into 2 appropriately labelled polypropylene tubes for pharmacokinetic (PK) assay and stored (within 1 hour 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). 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. Drug levels determination 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. Maximum measured concentration C_{max} and peak time T_{max} were obtained directly from concentrations over the 24-hour 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 logconcentration vs. time curve with a $1/Y^2$ weighting method, and $T_{½}$ (elimination half-life) was derived as ln(2)/ λz. The AUC_{0-t} were 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 200pg/mL, were treated as missing and excluded except for those recorded pre-dosing (Time 0h). 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 dose group using descriptive statistics of the arithmetic mean, standard deviation, coefficient of variation (CV%), geometric mean, median, minimum and maximum and number of observations. With 7 participants or 3 participants per treatment dose group of 75 µg or 50 µg and 100 µg LSD, 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 minutes pre-dose and then at 0·5, 1, 2, 4, 8, and 12 hours 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.*, 2014) and 3,4-Methylenedioxymethamphetamine (Farré *et al.*, 2007).

For both part 1 and part 2, altered states of consciousness were measured using three questionnaires administered at the end of the day of the drug administration session: 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) (MacLean *et al.*, 2012; Barrett, Johnson and Griffiths, 2015). All questions were completed on Psytools (Delosis, London) via laptop computer.

The ASC is a self-report questionnaire that can be used to measure subjective experiences induced by psychedelic drugs. 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, Gamma and Vollenweider, 2010).

The EDI is an 8-item questionnaire designed to measure ego-dissolution. Each item is scored on a 5-point Likert 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 scale, and derived scores for the MEQ include a total score as well as four scales: Mystical, Positive Mood, Transcendence of Time and Space, and Ineffability. Additionally, 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 µg, 75 µg, and 100 µg conditions are presented for descriptive purposes. To compare ASC, EDI, and MEQ scale scores between participants who received placebo, 50 µg, 75 µg, 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 posthoc tests conducted for those scale scores with unequal variances and Fisher's ANOVA followed by Hochberg GT2 posthoc tests for those scale scores with equal variances. 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 Part 2, a mixed effect ANOVA tested the interaction between experimental condition (50 µg/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 µg/75 µg condition and the placebo/75 µg condition.

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 µg/75 µg condition in Part 2 were evaluated with Kendall's tau, a non-parametric 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).

Results

Study Population

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

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

---------- Table 1 goes here ----------

Safety and Tolerability

LSD was found to be well tolerated in the population studied. Twenty-eight percent of participants (n = 9) experienced at least 1 TEAE. All TEAEs are presented in Table 2.

---------- Table 2 goes here ----------

The only AEs that were reported for more than 1 participant were nausea, vomiting, and headache (2 participants each). All AEs were reported as mild in severity, except for one. This TEAE, "Euphoric Mood," occurred in an LSD naïve participant in Part 2 (50 µg/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 AE was marked as "resolved," and he completed a physical examination, chemistry, haematology, and urinalysis, results of which were within 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 µg and 100 µg groups.

Other safety assessment results support the conclusion that LSD at the doses used in this study did not present a safety concern. No clinically significant abnormalities based on vital signs, physical examinations, ECG measurements, and laboratory results were found in clinical review. The C-SSRS and psychiatrist interview administered at the end of each study day revealed that no participant was suicidal and that all participants were recommended for release.

Pharmacokinetics

Drug levels were quantifiable for each of the 50 µg and 75 µg LSD conditions in average until the 8-hour sampling time points, and until the 12-hour time point for 100 µg LSD. Drug levels were below LLOQ (200 pg/ml) at the 24-hour sampled time points for all doses. Plots of concentration in pg/ml by participant are presented in Figure 1 for each dose group.

---------- Figure 1 goes here ----------

Fig. 1 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 12h post-dose is represented.

The PK parameters AUC_{0-24}, C_{max}, T_{max}, and terminal half-life $T_{1/2}$ are summarized for LSD 50 µg, 75 µg and 100 µg in Table 3. The C_{max} was 1088 ± 219 pg/ml for the 50 µg LSD group with a peak time at 2 hours. The C_{max} was 1712 ± 417 pg/ml for the 75 µg LSD group with a peak time at 1·2 hours. The C_{max} was 3034 ± 664 pg/ml for the 100 µg LSD group with a peak time at 1·7 hour. 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 µg and 100 µg LSD dose groups. The apparent half-life for 50 µg, 75 µg and 100 µg LSD averaged at 2·8, 3·2 and 4·3 hours, respectively. The estimation of the actual elimination phase and corresponding elimination half-life was limited by the small sample size and the absence of timepoints in between 4 and 8 hours, and apparent half-life is provided instead.

---------- Table 3 goes here ----------

Pharmacodynamics: Subjective Drug Effects

Figure 2 displays means for VAS items. As seen in the figure, effects were somewhat variable both between and within items, though generally peaked 120 minutes to 240 minutes postbaseline.

---------- Figure 2 goes here ----------

Fig. 2 Mean value of VAS questions plotted over time for each group from baseline to 12h post-dose, for 50 µg LSD (N=3), 75 µg LSD (N=7), and 100 µg LSD (N=3).

Table 4 displays means (SDs) of ASC, EDI, and MEQ scale scores of participants who received placebo, 50 µg, 75 µg, and 100 µg as their first or only LSD dose. Differences between conditions were observed for all scales of the ASC (all Welch's F statistics > 5·54, all p-values < .02), with Games-Howell posthoc tests indicating greater ratings on the Oceanic Boundlessness scale among those who received 50 µg (p = ·00009), 75 µg (p = ·049), and 100 µg (p = ·006) as compared to those who received placebo; greater ratings on the Dread of Ego Dissolution (p = ·0003) and Auditory Alterations (p = ·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 µg (p = ·0000001) and 75 µg (p = ·008) as compared to those who received placebo; and greater ratings on the Vigilance Reduction

scale among those who received 50 µg (p = ·01) and 100 µg (p = ·02) as compared to those who received placebo. Differences between conditions were also observed for the Ego Dissolution Inventory (Welch's F [3, 6·64] = 12·23, p = ·004), with a Games-Howell posthoc test indicating greater ratings among those who received 50 µg (p = ·001) as compared to those who received placebo.

---------- Table 4 goes here ----------

Finally, differences between conditions were observed for all scales of the MEQ (all Welch's or Fisher's F statistics > 7·20, all p-values < .001), with Games-Howell or Hochberg GT2 posthoc tests indicating greater ratings on the Mystical scale among those who received 50 µg (p = ·0004) and 75 µg (p = ·02) as compared to those who received placebo (100 µg vs. placebo p = ·10); greater ratings on the Positive Mood scale among those who received 50 µg (p = ·0000004), 75 µg (p = ·0003), and 100 µg (p = ·00009) as compared to those who received placebo; greater ratings on the Transcendence of Time and Space scale among those who received 50 µg (p = ·000009), 75 µg (p = ·01), and 100 µg (p = ·00007) as compared to those who received placebo; greater ratings on the Ineffability scale among those who received 50 µg (p = ·0000000001) and 75 µg (p = ·0003) as compared to those who received placebo (100 µg vs. placebo p = ·08); and greater Total scale scores among those who received 50 µg (p = ·000009) and 75 µg (p = ·005) as compared to those who received placebo (100 µg vs. 50 µg p = ·07). Differences in percentage of participants meeting criteria for a complete mystical experience on the MEQ among those who received placebo (0%), 50 µg (25%), 75 µg (0%), and 100 µg (33·3%) approached statistical significance ($\chi 2$ [3, N = 32] = 6·79, p = ·07).

---------- Figure 3 goes here ----------

Fig. 3 ASC, EDI, and MEQ scale for the 50 µg /75 µg and placebo/75 µg groups on Day 1 vs. Day 8.

Figure 3 display means of ASC, EDI, and MEQ scale scores across experimental condition (50 µg /75 µg vs. placebo/75 µg) and day of drug administration (Day 1 vs. Day 8). There were significant experimental condition by day of drug administration interactions for every scale of the ASC (all F [1,15] statistics > 9·52, all p-values < ·008) with the exception of Auditory Alterations (F [1, 15] = 3·36, p = ·08), which approached significance. There were also significant experimental condition by day of drug administration interactions for the EDI (F [1,15] = 7·87, p = ·01), and every scale of the MEQ (all F [1, 15] statistics > 16·86, all p-values < .004). As shown in the figures, whereas those in the 50 µg /75 µg condition reported greater scale scores than those in the placebo/75 µg condition

on Day 1 (all Welch's or Fisher's F statistics > 12·74, all p-values < .002), there were no significant differences between conditions on Day 8. Moreover, whereas there were no differences on scale scores between Day 1 and Day 8 among those in the 50 µg/75 µg condition, there were significant differences on all scale scores between Day 1 and Day 8 among participants in the placebo/75 µg condition (all F [1, 8] statistics > 15·22, all p-values < .004), with the exception of Auditory Alterations scale of the ASC (F = 2·59, p = ·15). Finally, among participants in the 50 µg/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 = ·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 = ·06).

---------- Table 5 goes here ----------

Tables 5 and 6 present relationships between Day 1 and Day 8 ASC and MEQ scale scores, respectively, among participants in the 50 µg/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 = ·21).

---------- Table 6 goes here ----------

Discussion

The goal of this phase 1, single-centre, dose-escalation study was to evaluate the safety and tolerability of doses of LSD ranging from 50 µg to 100 µg among healthy participants in a scalable intervention paradigm. This study used both open-label and double-blind placebo-controlled crossover designs. A total of 23 participants (13 from Part 1, and 10 from Part 2) each received a single dose of LSD, and 8 participants in Part 2 each received two doses of LSD.

Overall clinical review of adverse events, vital signs, ECGs, laboratory safety tests, concomitant medications, and physical examination identified no concerns with doses of 50 µg, 75 µg and 100 µg LSD in the 31 healthy participants, aged 23 to 54 years.

The single moderately-rated adverse event reported by one participant was *Euphoric Mood*. This adverse event, reported in Part 2 of the study one week after dosing, 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 (Pahnke and Richards, 1970; Pahnke *et al.*, 1971; Halpern, 1996; Majić, Schmidt and Gallinat, 2015). 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 a patient at-risk to such complications. It is noted that in the current study, the participant reporting *Euphoric Mood* did not exhibit any 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 $AUC_{0\text{-}24h}$ curve values in the 50 µg, 75 µg , 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 hyrdate 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.*, 2017b). 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 25mg/ml and then diluted in water with a final volume of 25 ml and a shelf life of 78 hours only. Thus, the apparent higher drug exposure trends in our study could be due to the small sample size, with 3 participants each in the 50 µg and 100 µg LSD dose groups, and 7 participants in 75 µg LSD dose group, and could reflect as well an apparent higher bioavailability 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 hours and LSD had an apparent half-life ranging from 2·8 to 4·3 hours, similar to previously reported values for a dose of LSD of 100 or 200 µg (Dolder *et al.*, 2015, 2017b; 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 to placebo on the EDI, MEQ, and ASC measures between those who received 50 µg (n = 12), 75 µg (n = 7), and 100 µg (n = 3) LSD. This may simply be a function of greater power afforded by greater sample size, or because nine of the 12 participants who received 50 µg LSD were hallucinogen-naive whereas all participants who received 75 µg and 100 µg LSD had previously used a hallucinogen. That LSD produced elevations in ASC and MEQ scores relative to placebo is consistent with prior research evaluating LSD doses of an even lower dose of 10 µg (Bershad *et al.*, 2019), 75 µg (R. L. Carhart-Harris *et al.*, 2016), 100 µg (Liechti, Dolder and Schmid, 2017; Holze *et al.*, 2019), and 200 µg (Schmid *et al.*, 2014; Liechti, Dolder and Schmid, 2017). 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, Dolder and Schmid, 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 one week after receiving 50 µg LSD (50%), and 75 µg LSD one week after receiving placebo (55%) exceeded those of healthy 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. These findings indicate that safety guidelines for higher doses apply fully to these lower doses. Insofar as such experiences 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 one week after receiving 50 µg LSD and those who received 75 µg LSD one week after

receiving placebo. No within-subject differences were detected between 50 µg 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). 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 hallucinogen-naive whereas some participants in between-subject analyses were hallucinogen non-naïve.

In this study, the following aspects were implemented as part of a scalable intervention paradigm for classic psychedelic administration: abbreviated non-drug sessions (i.e. preparation, 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 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 psychoactive effects thought to mediate therapeutic outcomes (Johnson *et al.*, 2019). New, more efficient approaches to ensuring patient safety and clinician compliance with treatment guidelines, while providing support for patients following drug therapy, are needed to make psychedelic drug therapy a practical and affordable therapeutic to current treatments. The current trial provides a blueprint for a design that requires fewer resources without compromising safety or subjective effects.

This study has two important limitations. First, the sample size was low, especially for the higher 100 µg dose group (n = 3), and all conclusions will need to be further validated in a larger sample size. Second the population included only healthy participants, and all components of the study environment that were tested in this study would need to be re-evaluated before implementation in a patient population. Namely, future studies will investigate whether a similar preparatory session and staffing structure provides sufficient support for patient populations. A minor limitation is the low recruitment rate in this trial of female participants.

Conclusions

In summary, this was a phase 1, single-center, dose-escalation study that used both open-label and double-blind placebo-controlled crossover designs to evaluate the safety, tolerability, pharmacokinetics, and subjective effects of low to moderate doses of LSD ranging from 50 µg to 100 µg among healthy participants in a scalable intervention paradigm. The 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 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 each particular psychopathology.

References

Barrett, F. S., Johnson, M. W. and Griffiths, R. R. (2015) 'Validation of the revised Mystical Experience Questionnaire in experimental sessions with psilocybin', *Journal of Psychopharmacology*. doi: 10.1177/0269881115609019.

Bershad, A. *et al.* (2019) 'S125. Subjective and Behavioral Effects of Microdoses of LSD in Healthy Human Volunteers', *Biological Psychiatry*. doi: 10.1016/j.biopsych.2019.03.876.

Carhart-Harris, R. L. *et al.* (2015) 'LSD enhances suggestibility in healthy volunteers', *Psychopharmacology*, 232(4), pp. 785–794. doi: 10.1007/s00213-014-3714-z.

Carhart-Harris, Robin L *et al.* (2016) 'Neural correlates of the LSD experience revealed by multimodal neuroimaging', *Proceedings of the National Academy of Sciences* , 113(17), pp. 4853–4858. doi: 10.1073/pnas.1518377113.

Carhart-Harris, R. L. *et al.* (2016) 'The paradoxical psychological effects of lysergic acid diethylamide (LSD)', *Psychological Medicine*. doi: 10.1017/S0033291715002901.

Carhart-Harris, R. L. *et al.* (2018) 'Psychedelics and the essential importance of context', *Journal of Psychopharmacology*. doi: 10.1177/0269881118754710.

Dittrich, A. (1998) 'The standardized psychometric assessment of altered states of consciousness (ASCs) in humans', *Pharmacopsychiatry*, 31(S2), pp. 80–84. doi: 10.1055/s-2007-979351.

Dolder, P. C. *et al.* (2015) 'Pharmacokinetics and concentration-effect relationship of oral LSD in humans', *International Journal of Neuropsychopharmacology*. doi: 10.1093/ijnp/pyv072.

Dolder, P. C. *et al.* (2017a) 'Pharmacokinetics and Pharmacodynamics of Lysergic Acid Diethylamide in Healthy Subjects', *Clinical Pharmacokinetics*. doi: 10.1007/s40262-017-0513-9.

Dolder, P. C. *et al.* (2017b) 'Pharmacokinetics and Pharmacodynamics of Lysergic Acid Diethylamide in Healthy Subjects', *Clinical Pharmacokinetics*. Springer, 56(10), pp. 1219–1230. doi: 10.1007/s40262-017-0513-9.

Family, N. *et al.* (2020) 'Safety, tolerability, pharmacokinetics, and pharmacodynamics of low dose lysergic acid diethylamide (LSD) in healthy older volunteers', *Psychopharmacology*. doi: 10.1007/s00213-019-05417-7.

Farré, M. *et al.* (2007) 'Pharmacological interaction between 3,4-methylenedioxymethamphetamine (ecstasy) and paroxetine: pharmacological effects and pharmacokinetics.', *The Journal of pharmacology and experimental therapeutics*. doi: 10.1124/jpet.107.129056.

First, M. B. *et al.* (2007) 'SCID-I/P'.

Garcia-Romeu, A. *et al.* (2020) 'Persisting Reductions in Cannabis, Opioid, and Stimulant Misuse After Naturalistic Psychedelic Use: An Online Survey', *Frontiers in Psychiatry*. doi: 10.3389/fpsyt.2019.00955.

Gasser, P. *et al.* (2014) 'Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases', *Journal of Nervous and Mental Disease*. doi: 10.1097/NMD.0000000000000113.

Gasser, Peter, Kirchner, K. and Passie, T. (2015) 'LSD-assisted psychotherapy for anxiety associated with a life-threatening disease: A qualitative study of acute and sustained subjective effects', *Journal of Psychopharmacology*. doi: 10.1177/0269881114555249.

Gasser, P., Kirchner, K. and Passie, T. (2015) 'LSD-assisted psychotherapy for anxiety associated with a life-threatening disease: A qualitative study of acute and sustained subjective effects', *Journal of Psychopharmacology*. doi: 10.1177/0269881114555249.

Halpern, J. H. (1996) 'The use of hallucinogens in the treatment of addiction', *Addiction Research and Theory*. doi: 10.3109/16066359609010756.

Hartogsohn, I. (2016) 'Set and setting, psychedelics and the placebo response: An extra-pharmacological perspective on psychopharmacology', *Journal of Psychopharmacology*, 30(12), pp. 1259–1267. doi: 10.1177/0269881116677852.

Hintzen, A. and Passie, T. (2010) *The Pharmacology of LSD: A critical review*. Oxford University Press, USA.

Holze, F. *et al.* (2019) 'Pharmacokinetics and subjective effects of a novel oral LSD formulation in healthy subjects', *British Journal of Clinical Pharmacology*. John Wiley & Sons, Ltd (10.1111), p. bcp.13918. doi: https://doi.org/10.1111/bcp.13918.

Johnson, M., Richards, W. and Griffiths, R. (2008) 'Human hallucinogen research: guidelines for safety.', *Journal of psychopharmacology (Oxford, England)*, 22(6), pp. 603–20. doi: 10.1177/0269881108093587.

Johnson, M. W. *et al.* (2019) 'Classic psychedelics: An integrative review of epidemiology, therapeutics, mystical experience, and brain network function', *Pharmacology and Therapeutics*. Elsevier Inc., pp. 83–102. doi: 10.1016/j.pharmthera.2018.11.010.

Krebs, T. and Johansen, P.-Ø. (2012) 'Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials.', *Journal of psychopharmacology (Oxford, England)*, 26(7), pp. 994–1002. doi: 10.1177/0269881112439253.

Liechti, M. E. (2017) 'Modern Clinical Research on LSD OPEN', *Modern Clinical Research on LSD*. doi: 10.1038/.

Liechti, M. E., Dolder, P. C. and Schmid, Y. (2017) 'Alterations of consciousness and mystical-type experiences after acute LSD in humans', *Psychopharmacology*. doi: 10.1007/s00213-016-4453-0.

MacLean, K. A. *et al.* (2012) 'Factor Analysis of the Mystical Experience Questionnaire: A Study of Experiences Occasioned by the Hallucinogen Psilocybin', *Journal for the Scientific Study of Religion*. doi: 10.1111/j.1468-5906.2012.01685.x.

Majić, T., Schmidt, T. T. and Gallinat, J. (2015) 'Peak experiences and the afterglow phenomenon: When and how do therapeutic effects of hallucinogens depend on psychedelic experiences?', *Journal of Psychopharmacology*. doi: 10.1177/0269881114568040.

NCT03153579 (no date) *LSD Treatment in Persons Suffering From Anxiety Symptoms in Severe Somatic Diseases or in Psychiatric Anxiety Disorders*. Available at: https://clinicaltrials.gov/ct2/show/NCT03153579?term=lysergic+acid&phase=12&draw=2&rank=4 (Accessed: 23 July 2020).

NCT03781128 (no date) *Lysergic Acid Diethylamide (LSD) as Treatment for Cluster Headache*. Available at: https://clinicaltrials.gov/ct2/show/NCT03781128?term=lysergic+acid&phase=12&draw=2&rank=1 (Accessed: 23 July 2020).

NCT03866252 (no date) *LSD Therapy for Persons Suffering From Major Depression*. Available at: https://clinicaltrials.gov/ct2/show/NCT03866252?term=lysergic+acid&phase=12&draw=2&rank=3 (Accessed: 23 July 2020).

Nichols, D. E. (2016) 'Psychedelics', *Pharmacological Reviews*, 68(2), pp. 264–355. doi: 10.1124/pr.115.011478.

Nour, M. M. *et al.* (2016) 'Ego-dissolution and psychedelics: Validation of the ego-dissolution inventory (EDI)', *Frontiers in Human Neuroscience*. doi: 10.3389/fnhum.2016.00269.

Pahnke, W. N. *et al.* (1971) 'The experimental use of psychedelic (LSD) psychotherapy.', *Internationale Zeitschrift fur klinische Pharmakologie, Therapie, und Toxikologie. International journal of clinical pharmacology, therapy, and toxicology*. doi: 10.1001/jama.212.11.1856.

Pahnke, W. N. and Richards, W. A. (1970) 'Implications Of LSD and Experimental Mysticism', *Journal of Psychedelic Drugs*. Taylor & Francis, 3(1), pp. 92–108. doi: 10.1080/02791072.1970.10471366.

Passie, T. *et al.* (2008) 'The pharmacology of lysergic acid diethylamide: a review.', *CNS neuroscience & therapeutics*, 14(4), pp. 295–314. doi: 10.1111/j.1755-5949.2008.00059.x.

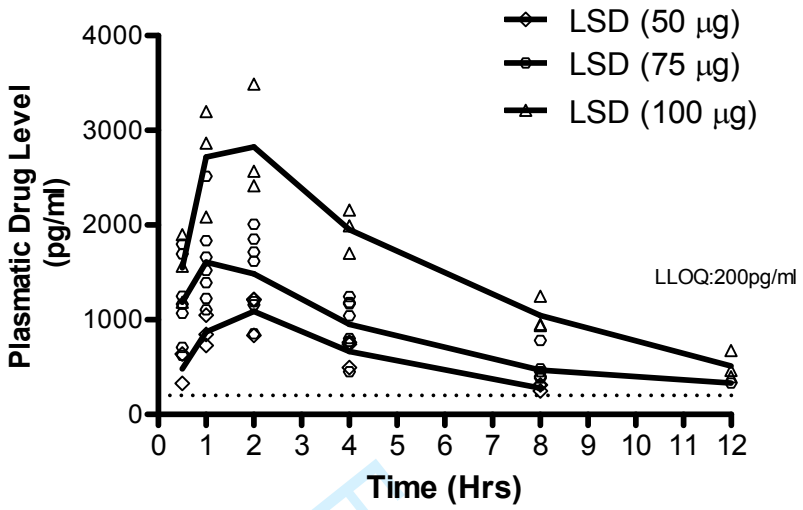
Preller, K. H. *et al.* (2019) 'Effective connectivity changes in LSD-induced altered states of consciousness in humans', *Proceedings of the National Academy of Sciences*. doi: 10.1073/pnas.1815129116.

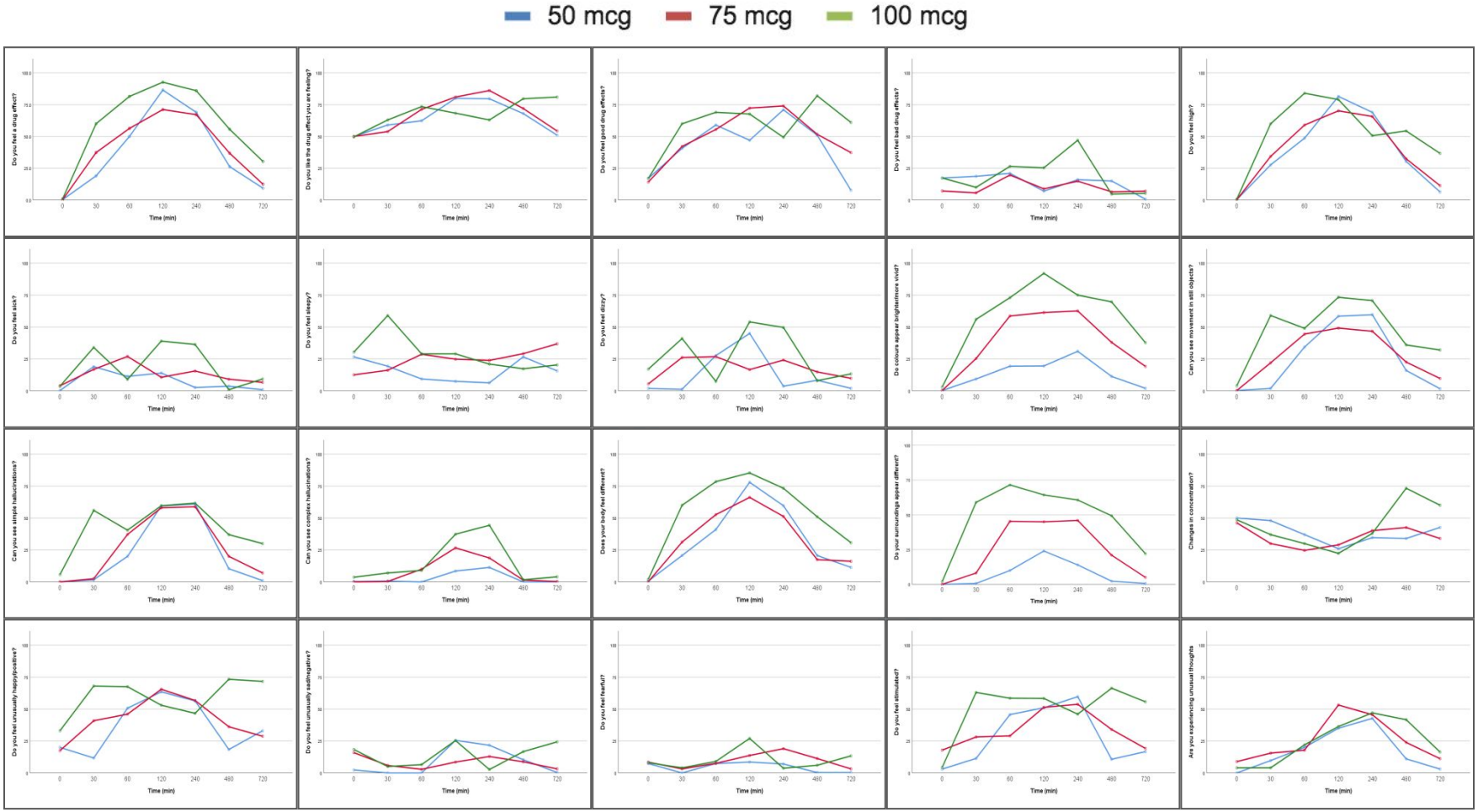
Schmid, Y. *et al.* (2014) 'Acute Effects of Lysergic Acid Diethylamide in Healthy Subjects', *Biological Psychiatry*. Elsevier, 78(8), pp. 544–53. doi: 10.1016/j.biopsych.2014.11.015.

Schmid, Y. *et al.* (2015) 'Acute effects of lysergic acid diethylamide in healthy subjects', *Biological Psychiatry*. doi: 10.1016/j.biopsych.2014.11.015.

Studerus, E., Gamma, A. and Vollenweider, F. X. (2010) 'Psychometric evaluation of the altered states of

consciousness rating scale (OAV).', *PloS one*, 5(8), p. e12412. doi: 10.1371/journal.pone.0012412.




50 mcg
75 mcg
100 mcg
Do you feel a drug effect?
Do you like the drug effect you are having?
Do you feel good drug effects?
Do you feel bad drug effects?
Do you feel high?
Do you feel sick?
Do you feel sleepy?
Do you feel dizzy?
Do colours appear brighter/more vivid?
Can you see movement in still objects?
Can you see simple hallucinations?
Can you see complex hallucinations?
Does your body feel different?
Do your surroundings appear different?
Changes in concentration?
Do you feel unusually happy/positive?
Do you feel unusually sad/negative?
Do you feel fearful?
Do you feel stimulated?
Are you experiencing unusual thoughts
Time (min)
0
30
60
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240
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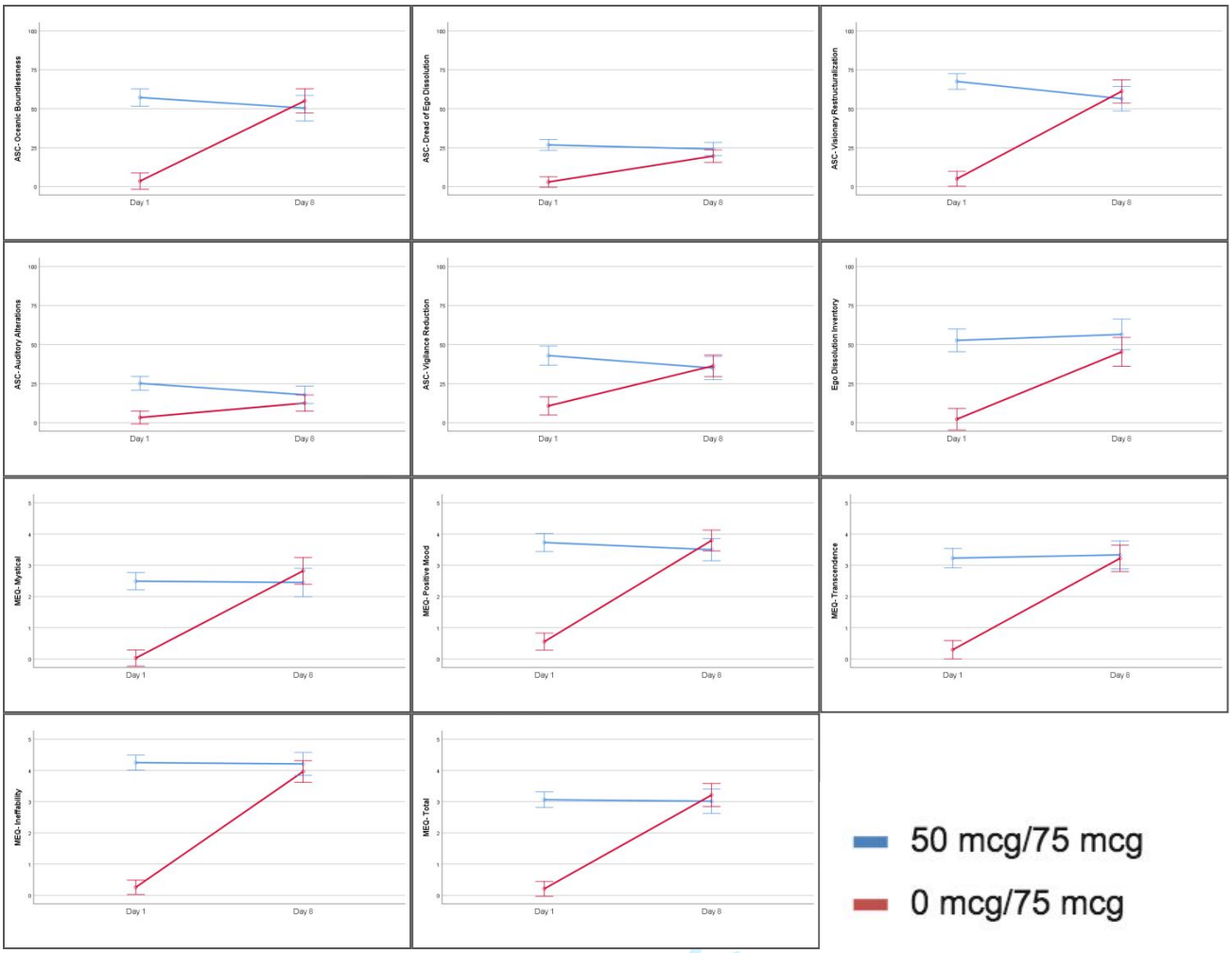
720



Error bars are +/- 1 SEM

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 50µg/ 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/m2)		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%)

Table 2. Treatment Emergent Adverse Events, listed by system organ class and preferred term, number of subjects (number of incidents)

System Organ Class Preferred Term	**Part 1**	**Part 2**				**Total n(freq)**
	LSD 50µg n(freq)	**LSD 75µg n(freq)**	**LSD 100µg n(freq)**	**Placebo/ LSD 75µg n(freq)**	**LSD 50µg/ LSD 75µg 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)	

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

		T_{max} (h)	C_{max} (pg/ml)	AUC_{0-24} (pg.h/ml)	Half-life ($T_{1/2}$(h))
LSD 50µg (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 75µg (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	11744	4·3
	Nbr Obs	7	7	7	7
LSD 100µg (N=3)	Mean	1·7	3034	17723	4·3
	Median	2	3199	17445	4·0
	SD	0·6	554	868	1·3
	CV (%)	35	18	5	30
	Minimum	1	2416	17028	3·2
	Maximum	2	3487	18695	5·7
	Nbr Obs	3	3	3	3

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

	ASC OBN	ASC DED	ASC VRS	ASC AUA	ASC VIR	EDI	MEQ MYS	MEQ POS	MEQ T/S	MEQ INF	MEQ TOT
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)	.02 (.06)	.60 (.56)	.45 (.62)	.23 (.38)	.24 (.22)
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 (.78)	2·87 (1·03)
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)	2·41 (1·01)
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)	3·75 (1·08)

Note. ASC = Altered States of Consciousness questionnaire; EDI = Ego Dissolution Inventory; MEQ = Mystical Experience Questionnaire; OBN = Oceanic Boundlessness; DED = Dread of Ego Dissolution; VRS = Visionary Restructuralization; AUA = Auditory Alterations; VIR = Vigilance Reduction; MYS = Mystical; POS = Positive Mood; T/S = Transcendence of Time and Space; INF = Ineffability; TOT = Total score.

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

	OBN	DED	VRS	AUA	VIR
OBN	0·0 (1·0)	.07 (.80)	-.42 (.13)	-.42 (.13)	.21 (.45)
DED	0·0 (1·0)	.21 (.45)	-.28 (.32)	-.14 (.62)	.35 (.21)
VRS	.14 (.62)	-.35 (.21)	.28 (.32)	.42 (.13)	.21 (.45)
AUA	-.28 (.32)	-.35 (.21)	-.14 (.62)	.14 (.62)	.35 (.21)
VIR	-.50 (.08)	0·0 (1·0)	-.21 (.45)	-.21 (.45)	**.71 (.01)**

Note. ASC = Altered States of Consciousness questionnaire; OBN = Oceanic Boundlessness; DED = Dread of Ego Dissolution; VRS = Visionary Restructuralization; AUA = Auditory Alterations; VIR = Vigilance Reduction. 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 µg/75 µg condition

	MYS	POS	T/S	INF	TOT	Complete Mystical Experience
MYS	-.07 (.80)	-.28 (.32)	-.40 (.17)	-.37 (.22)	-.07 (.80)	.09 (.77)
POS	-.03 (.89)	.11 (.70)	0·0 (1·0)	0·0 (1·0)	.11 (.70)	-.15 (.65)
T/S	.11 (.70)	-.11 (.70)	-.23 (.44)	-.17 (.58)	.11 (.70)	.20 (.55)
INF	-.04 (.89)	.20 (.50)	.04 (.89)	.14 (.66)	.12 (.68)	-.21 (.53)
TOT	0·0 (1·0)	-.07 (.80)	-.18 (.53)	-.20 (.50)	0·0 (1·0)	0·0 (1·0)
Complete Mystical Experience	.10 (.73)	-.10 (.73)	-.05 (.86)	-.06 (.85)	.10 (.73)	0·0 (1·0)

Note. MEQ = Mystical Experience Questionnaire; MYS = Mystical; POS = Positive Mood; T/S = Transcendence of Time and Space; INF = Ineffability; TOT = Total score. Reported statistic is Kendall's tau (p-value).