Acute Effects and Pharmacokinetics of LSD after Paroxetine or Placebo Pre-Administration in a Randomized, Double-Blind, Cross-Over Phase I Trial

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Psychedelics, such as psilocybin and lysergic acid diethylamide (LSD), are being investigated for the treatment of depressive and anxiety disorders, for which concomitant treatment with selective serotonin reuptake inhibitors (SSRIs) is prevalent. The present study investigated the acute response to single doses of LSD (100 µg) after daily administration of paroxetine (10 mg for 7 days, followed by 20 mg for 35 days) or placebo (42 days) using a randomized, double-blind, cross-over design in 23 healthy participants. Paroxetine did not alter pleasant subjective effects of LSD but significantly reduced "bad drug effect," "anxiety," and "nausea." No differences in autonomic effects or QTc interval after LSD administration were found between both conditions. The strong cytochrome P450 2D6 (CYP2D6) inhibitor paroxetine led to higher maximal concentrations and total exposures of LSD (geometric mean ratios of 1.4 and 1.5, respectively) indicating relevant involvement of CYP2D6 in its metabolism. The extent of this inhibition was nominally highest in genetic CYP2D6 normal metabolizers and lowest in poor metabolizers. The present findings suggest that add-on treatment with LSD to an SSRI is well-tolerated. The pharmacokinetic and pharmacodynamic interactions indicate that no dose adjustment of LSD seems necessary in the presence of an SSRI that inhibits CYP2D6. For SSRIs that do not relevantly inhibit CYP2D6, a dose increase of LSD might be appropriate, but due to lacking data and potential other pharmacokinetic interactions with these compounds, no definitive dose recommendation can be made.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Psychedelics are being investigated as a treatment for depressive and anxiety disorders. Data on the interaction of selective serotonin reuptake inhibitors (SSRIs) with psychedelics are scarce. A first study in healthy participants showed that 2-week pre-administration of the SSRI escitalopram did not alter the acute pleasant subjective effects of the psychedelic psilocybin but reduced subjective "bad drug effect" and "anxiety" compared with placebo.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ The present study investigated the pharmacokinetic and pharmacodynamic interaction between a 6-week pre-treatment of the SSRI paroxetine (or placebo) and LSD (100 µg).

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ The SSRI paroxetine did not alter the acute pleasant subjective effects of LSD but significantly reduced "bad drug effect," "anxiety," and "nausea" compared with placebo. The CYP2D6 inhibitor paroxetine increased peak plasma LSD concentrations 1.4-fold and total exposure 1.5-fold.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Antidepressant treatment with SSRIs may not need to be discontinued before psychedelic-assisted therapy, pending further studies in patients. LSD doses may need to be increased when combined with SSRIs that do not strongly inhibit CYP2D6.

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Classic psychedelics, such as lysergic acid diethylamide (LSD) and psilocybin, induce acute alterations of mind via serotonin 5-hydroxytryptamine-2A (5-HT_{2A}) receptor activation.[1,2] LSD and psilocybin are being investigated as potential treatments for depressive and anxiety disorders and are thus intended to be used in patients who are often already treated with antidepressants, typically selective serotonin reuptake inhibitors (SSRIs). Several modulating effects of SSRIs on the number and/or activity of 5-HT_{2A} receptors have been described, including receptor down-regulation.[3] Case reports and surveys indicate that SSRIs attenuate the response to psychedelics.[4–7] In a previous controlled Phase I trial, we observed a reduced response to psilocybin after escitalopram pre-administration.[8] Theoretical risks concerning QT-time prolongation and serotonergic toxicity, were considered low, however clinical data was lacking.[9] Therefore, SSRI therapy has been discontinued before psychedelic administration in clinical Phase II trials, with the exception of one open-label trial.[10] However, SSRI discontinuation carries the risk of symptom relapse and withdrawal symptoms, including depressed mood.[11] In healthy participants, mood states before the administration of a psychedelic have been shown to influence its acute effects.[12–14] Transient feelings of discomfort (herein assessed as "bad drug effect") and anxiety are common during the acute effect phase, though they are typically mild in intensity and often co-occur with pleasant effects.[15,16] However, anxiety might limit treatment efficacy in patients, whereas acute pleasant effects, such as mystical-type experiences, have been positively associated with the therapeutic response.[17–21] One Phase II trial showed a lower antidepressant response to psilocybin when SSRI treatment was discontinued compared with unmedicated patients.[22] However, in another trial, psilocybin efficacy was unaffected by antidepressant drug discontinuation in patients.[23]

Altogether, it is unclear whether an antidepressant should be discontinued prior to administration of a psychedelic. Studies on interactions between SSRIs and psychedelics are limited, with no controlled data on LSD. We, therefore, investigated whether 6-week pre-administration to paroxetine alters acute subjective and adverse effects of a typical therapeutic dose of LSD in healthy participants.[24,25] We used paroxetine, a strong cytochrome P450 2D6 (CYP2D6) inhibitor, thereby allowing for additional investigation of the role of CYP2D6 in LSD metabolism.[26,27] Genetic polymorphisms in CYP2D6 significantly affect the pharmacokinetics and subjective effects of LSD. Individuals with nonfunctional CYP2D6 (poor metabolizers) exhibited longer LSD half-lives and approximately 75% higher area under the plasma concentration-time curve (AUC) values of LSD and its inactive metabolite 2-oxo-3-hydroxy LSD (O-H-LSD) compared with those with functional CYP2D6.[27,28] CYP2D6 genotype has also been shown to influence the metabolism of paroxetine.[29]

The primary study hypotheses were that (1) LSD would produce similar alterations of mind (3D-OAV total score ratings on the 5 Dimensions of Altered States of Consciousness [5D-ASC] scale) and (2) similar single-item visual analog scale (VAS) "good drug effect" peak ratings after paroxetine and placebo. Consistent with our previous findings on the interaction of escitalopram and psilocybin, we expected to observe a reduction of "bad drug effect" and "anxiety" ratings in response to LSD after paroxetine compared with placebo.[8] We expected paroxetine to increase the exposure of LSD, consistent with a relevant contribution of CYP2D6 to LSD metabolism, thereby compensating for any lower pharmacodynamic effects of the combination.

MATERIALS AND METHODS

Study design

The present study used a double-blind, placebo-controlled, cross-over design with two experimental test sessions to investigate the response to open-label single doses of LSD (100 µg base equivalent). Participants received either daily paroxetine (10 mg for 7 days, followed by 20 mg for 35 days) or a placebo for 42 days prior to each LSD administration. The order of conditions was random and counterbalanced, with the final dose of paroxetine/placebo given on site 1 h before LSD. Compliance with the self-administration regimen was monitored by pill counting and measuring plasma levels of paroxetine before the last administration. The first test session and the start of the second self-administration phase were separated by a washout period of at least 2 days. No placebo for LSD was used because the effects of LSD vs. placebo have been extensively described previously and were not the focus of the present study.[1,24,25,30] The study adhered to the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice Guidelines and was approved by the Ethics Committee of Northwest Switzerland (BASEC-2021-02223) and the Swiss Federal Office for Public Health. The study was registered at ClinicalTrials.gov on December 12, 2021 (NCT05175430).

Study sample

Healthy volunteers, 25–65 years of age, were recruited via advertisement or self-referred from ClinicalTrials.gov. Exclusion criteria were pregnancy (determined by urine drug pregnancy tests), breastfeeding, first-degree relative history of psychotic disorders, suspected noncompliance, past or current presence of any major psychiatric disorder (assessed by a semi-structured interview by a psychologist/psychiatrist), the use of medications that may interfere with the study medication, chronic or acute physical illness (e.g., abnormalities in physical exam, electrocardiogram [ECG], and hematological and chemical blood analyses), excessive tobacco smoking (>10 cigarettes/day), excessive alcohol consumption (>20 standard beverages/week), lifetime psychedelic drug use >20 times, and illicit drug use within the last 2 months (except cannabis). Participants were required to refrain from any illicit drug use during the study period (determined by urine drug tests) and have no more than one alcoholic beverage on the day before the test sessions. Further details are described in the **Supplementary Methods**. All participants provided written informed consent and received payment for their participation.

Study procedures

The present study involved a screening visit, two 26-h test sessions, and an end-of-study visit at the University Hospital Basel. Participants were instructed to set a daily reminder on their mobile device to take the paroxetine/placebo capsules in the morning, starting 42 days before the planned test session. Test sessions started at 8 AM and were conducted in a calm hospital room that was equipped with a bed. Only one participant and one or two trained investigators were present during each test session. At the beginning of each test session, urine pregnancy and/or drug tests were performed. Participants underwent baseline safety measurements (assessing adverse events since the last visit, vital parameters, and ECG) and were administered the last paroxetine/placebo capsule at 8:30 AM. Afterward, a standardized breakfast was served. LSD was administered at 9:30 AM, whereupon outcome measures were repeatedly assessed for 24 h. Participants remained under constant supervision during the acute effect phase. During the night, an investigator was available in a room next to the participants. Test sessions ended the next day at approximately 10 AM.

Study drugs

The study medication was produced according to Good Manufacturing Practice. LSD D-tartrate (146 µg, >99% purity; Lipomed AG, Arlesheim, Switzerland), corresponding to 100 µg LSD base, was prepared as a drinking solution in 1 ml of purified water with 20% ethanol. Paroxetine was obtained as the marketed drug 10 mg caplet (Paroxetin beta, betapharm Arzneimittel GmbH, Augsburg, Germany) and 20 mg caplet (Deroxat, GlaxoSmithKline AG, Münchenbuchsee, Switzerland) and encapsulated to ensure blinding. Corresponding placebo capsules were filled with mannitol. To assess blinding, participants guessed their condition at the beginning of each test session.

Subjective effects

The time course of subjective effects of LSD was assessed with 17 VASs before and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, and 24 h after LSD administration. Items included "any drug effect" to measure the overall effect. The VAS item "good drug effect" served as a primary endpoint of pleasant subjective effects. Other VAS items included "bad drug effect," "anxiety," "ego dissolution" (loss of sense of self), and the altered perception of vision, hearing, and time. Changes in mood were also assessed with the Adjective Mood Rating Scale (AMRS) before and 3, 6, 12, and 24 h after LSD administration.[31]

More complex aspects of the psychedelic experience were assessed with comprehensive standardized questionnaires after the acute effects had subsided. This involved the 5D-ASC, which includes the 3D-OAV total score. It is derived from the three main dimensions ("Oceanic Boundlessness," "Anxious Ego Dissolution," and "Visionary Restructuralization") and served as a primary endpoint to measure the overall mind-altering effect of LSD.[32] Moreover, mystical-type experiences were assessed using the States of Consciousness Questionnaire (SOCQ), comprising the Psychedelic Experience Scale (PES48) and 30-item Mystical Experience Questionnaire (MEQ30).[33–35] All subjective effect measurement tools are described in detail in the **Supplementary Methods**. At the end-of-study visit, participants retrospectively rated maximum effects in each test session on four VASs. Moreover, they indicated which study day they found to be more pleasant and which to be more valuable as an experience as not only patients, but also healthy participants often find psychedelic experiences personally meaningful.[36,37]

Adverse and autonomic effects

Acute adverse effects during test sessions were systematically assessed with the List of Complaints (LC) before LSD administration and 12 and 24 h afterward.[38] Adverse effects of at least moderate severity (e.g., if a concomitant medication was administered) and/or not covered by the LC were documented as adverse events (AEs) on separate forms. Nausea is a known frequent side effect of psychedelics; therefore, it was additionally assessed with a single-item VAS during the test sessions.[15,16]

Blood pressure, heart rate, and tympanic body temperature were repeatedly measured at the same timepoints as the single-item VAS assessments. ECG was recorded before and 3.5 h after LSD administration. Further details on the assessment of autonomic effects are described in the **Supplementary Methods**.

Pharmacokinetics

Repeated blood sampling was performed at the same time points as the VAS measurements. Blood was collected into lithium heparin tubes via an intravenous catheter. Samples were immediately centrifuged, and plasma was subsequently stored at −80°C until analysis. Plasma concentrations of LSD and O-H-LSD were determined by a fully validated high-performance liquid chromatography–tandem mass spectrometry (LC–MS/MS) method.[39] An LC–MS/MS method for paroxetine was set up by adapting the LC–MS/MS method used to quantify LSD. The lower limit of quantification (LLOQ) was 10 pg/mL for LSD and O-H-LSD and 1 ng/mL for paroxetine.

Pharmacokinetic analyses were conducted using non-compartmental analysis (NCA) in Phoenix WinNonlin 8.4 (Certara, Princeton, NJ, USA) using the exact time of each sample collection. Peak plasma concentration (C_{max}) and time to C_{max} (T_{max}) were obtained directly from the observed data. The terminal elimination rate constant (λ_z) to calculate half-life ($t_{1/2}$) was estimated by log-linear regression after semilogarithmic transformation of the data using at least three data points of the linear phase of the concentration-time curve. The AUC was computed using the linear-up log-down method. The infinite AUC (AUC_∞) was derived by extrapolating the AUC_{24} using the constant λ_z. To further characterize the pharmacokinetic–pharmacodynamic (PK–PD) relationship, we performed sequential compartmental pharmacokinetic and PK–PD modeling of the data. Detailed descriptions of these analyses are provided in the **Supplementary Methods**.

Genotyping and gene expression

We performed CYP2D6 genotyping in all participants to characterize the influence of the CYP2D6 genotype on the pharmacokinetics of LSD and paroxetine and on the paroxetine-LSD interaction. Whole-blood gene expression was determined to assess the effects of paroxetine on the expression of genes that encode the serotonin transporter (*SLC6A4*) and $5HT_{2A}$ receptor (*HTR2A*).[8] BDNF gene *(BDNF)* expression was chosen as an additional marker for potential paroxetine-related neuroadaptation because *BDNF* expression was upregulated after paroxetine in animals.[40] Moreover, there is evidence of genetic epitasis between *BDNF* and *SLC6A4* in humans.[41] Details on the assessment of genotyping and gene expression are described in the **Supplementary Methods**.

Data analysis

Peak (E_{max} and/or E_{min}), peak change from baseline (ΔE_{max}), and area under the effect curve (AUEC) values were determined for repeated measures. Data were analyzed with RStudio (version 2024.07.0-daily+174, RStudio, PBC, Boston, MA, USA) using paired two-sided *t*-tests. The criterion for significance was $p < 0.05$.

Pharmacokinetic parameters of LSD were analyzed according to Food and Drug Administration guidance for drug–drug interaction studies.[42] Geometric mean ratios (GMRs) and their corresponding 90% confidence intervals (CIs) were calculated for the total exposure (AUC_∞) and maximal concentrations (C_{max}) of LSD with and without paroxetine. A default 0.8–1.25 range for the CI was applied in the absence of otherwise specified no-effect boundaries.

RESULTS

Participants

Among 37 screened individuals, 27 met the criteria for study inclusion. There were three dropouts. Two participants dropped out because of personal reasons (one before any study drug was administered and one after the first LSD administration). One participant dropped out after taking paroxetine for 6 days due to adverse effects. One further participant was excluded from the analysis set because of a non-detectable plasma paroxetine level at the beginning of the test session, indicating noncompliance. The final data set comprised 23 participants (sex: 12 male, 11 female; age: 31 ± 8 years [mean ± SD], range: 25–55 years; body weight: 68 ± 11 kg, range: 48–96 kg). Ten participants had taken psychedelic substances before the study (6 ± 5 times). Four women used a hormonal contraceptive, and one was postmenopausal.

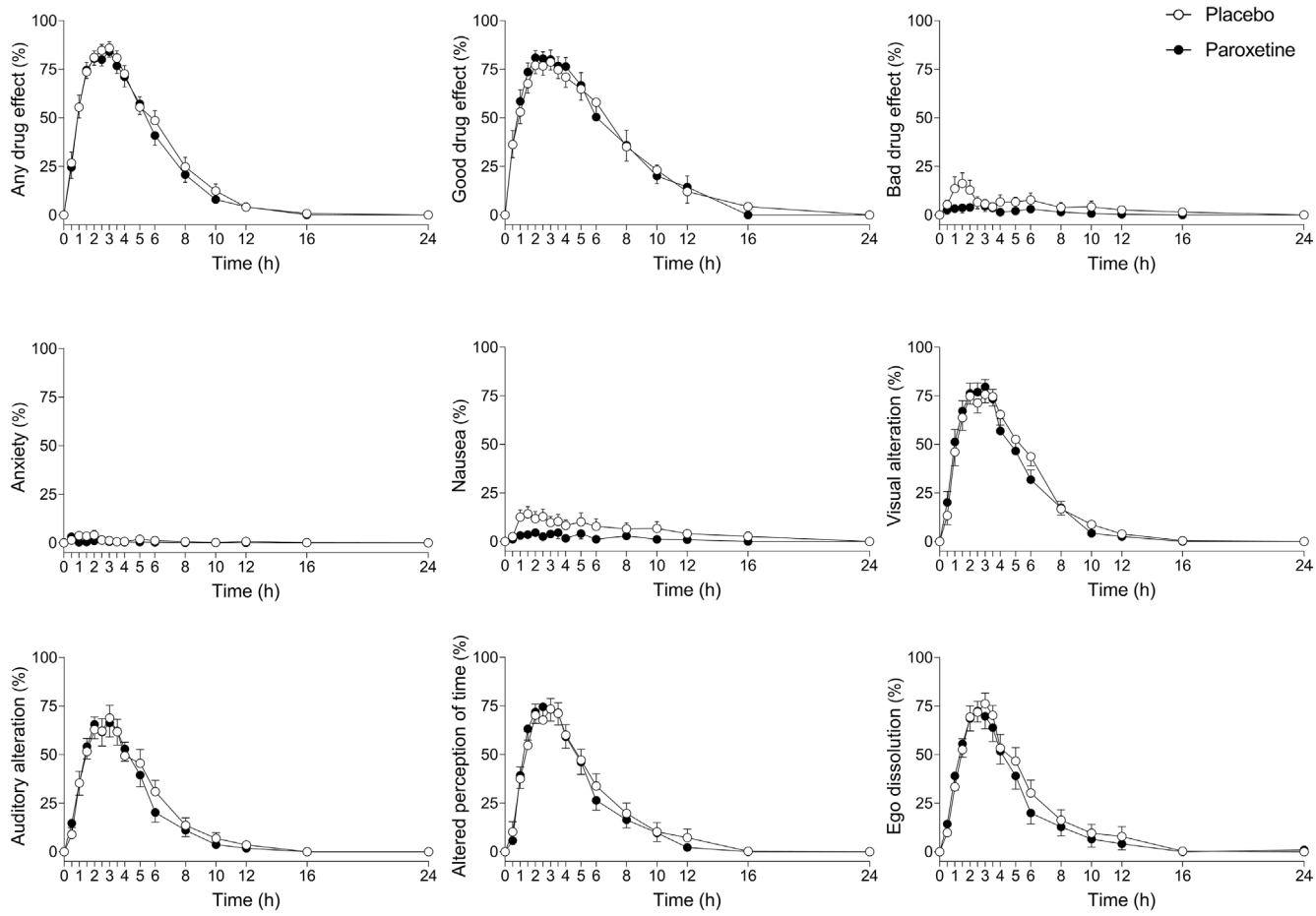

Figure 1 Acute subjective effects of LSD over time on single-item visual analog scales (VASs). Paroxetine significantly reduced LSD-induced increases in ratings of "bad drug effect" (E_{max}: $p=0.04$), "anxiety" (E_{max}: $p=0.04$, AUEC: $p=0.01$), and "nausea" (E_{max}: $p=0.02$, AUEC: $p=0.03$). LSD was administered at $t=0$ h. The data are expressed as the mean ± standard error of the mean (SEM) in 23 participants. Additional VAS measurements over time are shown in **Figure S1**. Maximal responses and statistics for all VAS items are shown in **Table S1**.

Subjective effects

Consistent with our hypotheses, paroxetine significantly reduced LSD-induced single-item VAS ratings of "bad drug effect" and "anxiety," while having no effect on any other items, including "good drug effect" (**Figure 1**; **Table S1**). The duration of the overall LSD effect ("any drug effect") was similar after paroxetine (mean ± SD: 9.1 ± 2.3 h) and placebo (9.6 ± 2.4 h). Paroxetine had no effect on 3D-OAV total score ratings on the 5D-ASC compared with placebo (**Figure 2**; **Table S2**). Moreover, no significant differences were found between paroxetine and placebo in any of the 5D-ASC dimensions or factors. However, there was a trend for LSD to induce more pleasant subjective effects (e.g., "blissful state") after paroxetine compared with placebo, which was also reflected in the PES48 (**Figure S2**, **Table S2**). There were no differences in LSD-induced changes in mood on the AMRS between paroxetine and placebo (**Figure S3**, **Table S3**).

Adverse and autonomic effects

Overall, similar acute (0–12 h) and subacute (12–24 h) adverse effects after LSD administration were reported on the LC across both conditions (**Tables S4 and S5**). A tendency toward a lower total number of adverse effects of LSD after paroxetine was observed both acutely (placebo: 181; paroxetine: 158) and subacutely (placebo: 52; paroxetine: 27). The most frequently reported adverse effect was headache (placebo: 13 participants; paroxetine: 16 participants). Nausea was reported by 13 participants on the LC after placebo and 6 after paroxetine. This finding was also reflected on the VAS, where peak and overall nausea were significantly lower after paroxetine compared with placebo (**Figure 1**; **Table S1**). Pronounced nausea persisted in two participants for multiple hours and led to emesis but only in the placebo condition (**Table S6**). In one case, domperidone (10 mg) was administered, with no improvement. In each condition, there were three cases for which paracetamol (500 or 1,000 mg) was administered because of persistent headaches, which responded to treatment in all cases. No severe AEs occurred during the study.

Paroxetine significantly reduced LSD-induced elevations of heart rate but not blood pressure compared with placebo (**Figure S4**, **Table S4**). LSD did not increase the QTc interval at its peak effect at 3.5 h after administration compared with 1 h before in either the paroxetine or placebo condition. There were no cases of QTc time increases >450 ms.

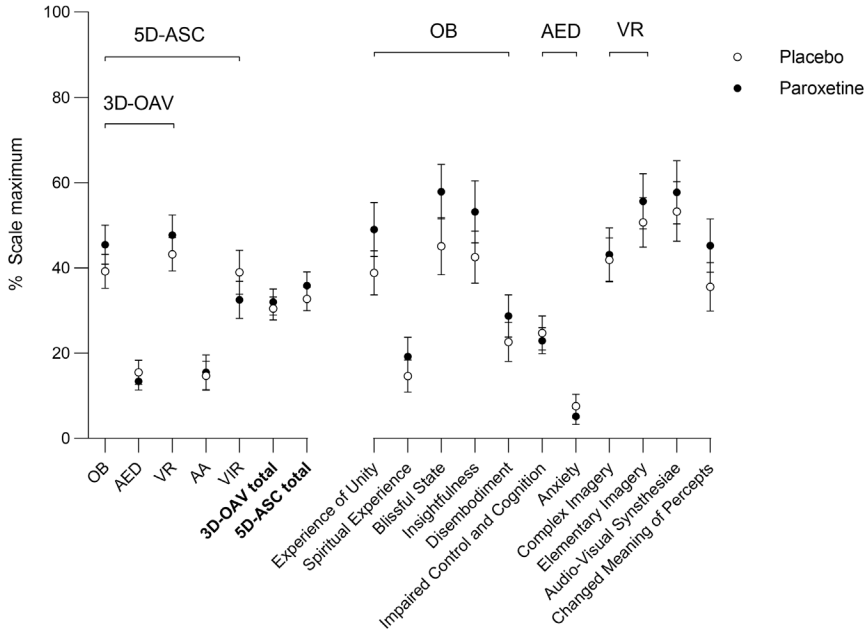

Figure 2 Acute alterations of mind on the 5 Dimensions of Altered States of Consciousness (5D-ASC) scale. Paroxetine pre-treatment had no effect on the 3D-OAV or 5D-ASC total score, reflecting overall alterations of mind, compared with placebo. The 3D-OAV total score comprises the three main dimensions "Oceanic Boundlessness" (OB), "Anxious Ego-Dissolution" (AED), and "Vigilance Reductions" (VIR). The 5D-ASC total score additionally comprises "Auditory Alterations" (AA) and "Vigilance Reductions" (VIR). The data are expressed as the mean ± SEM percentage of the maximal possible score in 23 participants. Corresponding statistics are shown in **Table S2**.

Pharmacokinetics, genotyping, and gene expression

Pharmacokinetic parameters of LSD and O-H-LSD are summarized in **Table 1**. Mean plasma concentrations over time are shown in **Figure 3**. Individual parameters and LSD concentration-time profiles are provided in **Table S10** and **Figure S6a–h**. Paroxetine significantly increased the AUC_{∞} (GMR: 1.47; 90% CI: 1.29–1.68), C_{max} (1.41; 1.24–1.60), and half-life (1.24; 1.17–1.31) of LSD which was outside the default no-effect boundaries. Paroxetine concentrations before the final administration were 17.0 ng/mL (geometric mean).

The participant's CYP2D6 genotypes are summarized in **Table S11**. There were 11 normal metabolizers (NM), 9 intermediate metabolizers (IM), and 3 poor metabolizers (PM). **Table 2** shows the pharmacokinetic parameters of LSD and O-H-LSD according to the CYP2D6 genotype. AUC_{∞} and C_{max} values of LSD were highest in PMs and decreased with

Table 1 Pharmacokinetic parameters calculated using non-compartmental analyses

	Placebo		Paroxetine		Ratio
	Geometric mean (95% CI)	Range	Geometric mean (95% CI)	Range	GMR (90% CI)
LSD					
C_{max} (ng/mL)	2.0 (1.7–2.3)	1.2–4.5	2.8 (2.5–3.2)	1.9–5.4	1.41 (1.24–1.60)
T_{max} (h)	1.8 (1.4–2.3)	0.50–4.0	1.7 (1.3–2.1)	0.50–3.5	0.92 (0.75–1.13)
$t_{1/2}$ (h)	3.5 (3.2–3.8)	2.6–6.1	4.3 (3.9–4.8)	3.0–9.3	1.24 (1.17–1.31)
AUC_{∞} (ng·h/mL)	15 (13–17)	8.2–31	22 (19–25)	11–48	1.47 (1.29–1.68)
CL/F (L/h)	6.8 (5.9–8.0)	3.2–12	4.6 (4.0–5.4)	2.1–9.2	0.68 (0.60–0.77)
V_z/F (L)	34 (31–38)	18–56	29 (25–33)	14–48	0.84 (0.74–0.95)
O-H-LSD					
C_{max} (ng/mL)	0.16 (0.14–0.18)	0.10–0.34	0.21 (0.19–0.23)	0.14–0.31	1.27 (1.18–1.38)
T_{max} (h)	4.9 (4.4–5.4)	3.5–8.0	4.3 (3.7–5.0)	1.5–8.0	0.88 (0.77–1.01)
$t_{1/2}$ (h)	7.8 (7.1–8.5)	5.7–14.2	9.0 (8.1–10)	5.8–8.9	1.16 (1.08–1.25)
AUC_{∞} (ng·h/mL)	2.5 (2.2–2.8)	1.6–4.4	3.6 (3.3–3.9)	2.4–5.3	1.44 (1.31–1.58)

AUC, area under the plasma concentration-time curve; AUC_{∞}, AUC from time zero to infinity; CI, confidence interval; CL/F apparent total clearance; C_{max}, maximum observed plasma concentration; GMR, geometric mean ratio (paroxetine/placebo); T_{max}, time to reach C_{max}; $t_{1/2}$, plasma half-life; V_z/F, apparent volume of distribution; $N = 23$.

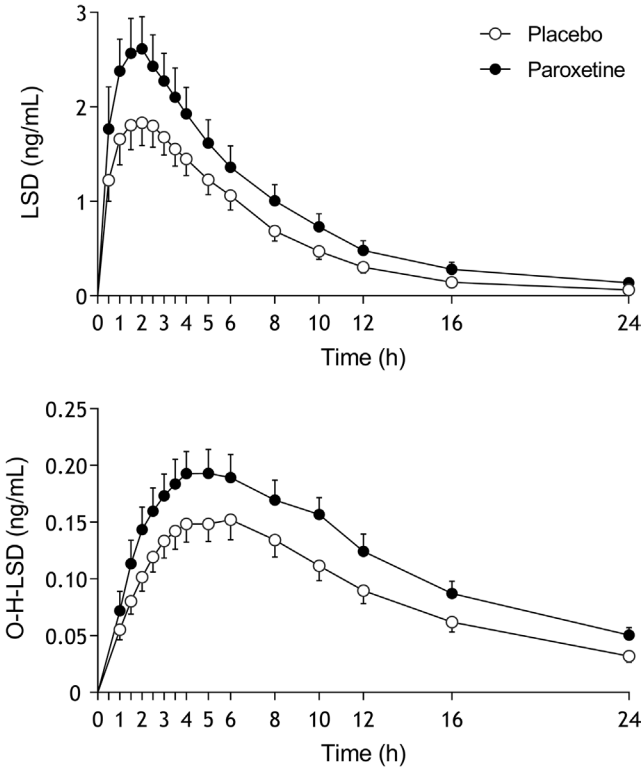

Figure 3 Pharmacokinetics of LSD and O-H-LSD. A pharmacokinetic interaction between paroxetine and LSD was observed, in which paroxetine increased the exposure of LSD and O-H-LSD in plasma. The data are expressed as the geometric mean ± 95% confidence interval (CI) in 23 participants. LSD was administered at $t = 0$ h. Corresponding pharmacokinetic parameters are listed in **Table 1**.

increasing CYP2D6 function. The CYP2D6 inhibitor paroxetine did not alter the AUC_{∞} or C_{max} values of LSD in PMs. However, paroxetine increased LSD concentrations in IMs and NMs. Similar effects were observed for O-H-LSD. Reduced genetically-predicted CYP2D6 activity also increased paroxetine plasma concentrations (**Table S9**).

Pharmacokinetics and PK–PD modeling findings are presented in **Tables S12** and **S13**, respectively. **Figure S8A–C** illustrates the individual estimated LSD plasma concentrations and estimated subjective effects over time, respectively. Diagnostic plots and individual model fit plots are provided in **Figure S9A,B**. The pharmacokinetics model results are closely aligned with those obtained from NCA. The mean (95% CI) PK-PD model-derived EC_{50} value for the LSD "any drug effect" was 1.7 (1.0–1.4) ng/mL and 1.2 (1.5–2.0) ng/mL following paroxetine and placebo, respectively, consistent with reduced potency of LSD in the presence of paroxetine.

Paroxetine did not affect the whole-blood gene expression of *HRT2A*, *SLC6A4*, or *BDNF* compared with placebo (**Table S7**).

Blinding and end-of-study visit assessments

The participants correctly identified their assigned condition in 83% of cases, mostly because of paroxetine's side effects (**Table S8**). However, the unblinding rate can be assumed to not relevantly influence the subjective outcome measurements of this trial. Expectations of paroxetine's potential influence on LSD were systematically and qualitatively assessed at the screening visit, and none of the participants stated specific expectations about substance interactions.

Ratings of maximum subjective effects of LSD on VASs at the end-of-study visit showed no significant differences between conditions (**Table S8**). However, 70% of the participants stated that LSD after paroxetine was overall more pleasant than LSD after placebo. Sixty-one percent stated that the LSD-after-placebo session was a more valuable experience than the LSD-after-paroxetine session, but these differences were not statistically significant.

DISCUSSION

The present study confirmed the hypotheses that 6 weeks of paroxetine pre-administration compared with placebo resulted in an equivalent overall intensity of LSD-induced subjective effects and equivalent pleasant subjective effects. Clinically relevant scores for acute effects in psychedelic-assisted therapy, such as the MEQ30 factors and 5D-ASC "Oceanic Boundlessness," were not affected by paroxetine. Paroxetine significantly reduced LSD-induced "bad drug effect" and "anxiety" compared with placebo. These findings are in line with our previous study, where we assessed the acute response to psilocybin (25 mg) after 2 weeks of escitalopram vs. placebo in healthy participants.[8] Escitalopram also had no relevant effect on the pleasant effects of psilocybin but significantly reduced subjective "bad drug effect," and "anxiety" compared with placebo. In addition to fewer LSD-induced unpleasant subjective effects, paroxetine markedly reduced nausea. In our previous study, we observed a similar trend with 10 participants who reported psilocybin-induced nausea after placebo compared with only three participants after escitalopram.[8] No signs of serotonergic toxicity occurred in either study. SSRIs did not increase the psychedelic-induced cardiovascular stimulation or elevation of body temperature. The present study was the first to evaluate changes in QTc interval before and after LSD administration. LSD did not alter the QTc time regardless of whether it was administered after paroxetine or placebo. No prolonged QTc intervals were observed.

The CYP2D6 inhibitor paroxetine significantly increased the peak plasma LSD concentration and overall exposure by 41% and 47%, respectively. In CYP2D6 PMs, paroxetine did not alter LSD exposure. However, the extent of inhibition, as indicated by the paroxetine/placebo ratios for AUC_{∞} and C_{max}, increased with higher CYP2D6 activity. This confirms and quantifies the relevance of the CYP2D6-mediated metabolism of LSD.[12,26,27,30] A similar relationship could be observed for O-H-LSD. We therefore conclude that this metabolite is not formed mediated by CYP2D6, in line with previous in vitro data.[26]

The higher EC_{50} for the subjective effect of LSD observed after paroxetine indicates a reduced potency of LSD in the presence of an SSRI (paroxetine) compared to a placebo due to a pharmacodynamic interaction. However, in the present study, a pharmacokinetic CYP2D6-mediated interaction compensated for the reduced pharmacodynamic response to LSD. Therefore, clinical implications could be derived from the present findings. No adjustment of the LSD dose seems necessary when combined with

Table 2 Pharmacokinetic parameters from non-compartmental analyses according to CYP2D6 genotype

	Placebo		Paroxetine		Ratio
Parameter (Unit)	Geometric mean (95% CI)	Range	Geometric mean (95% CI)	Range	GMR (90% CI)
LSD					
Normal metabolizer, *N* = 11					
AUC_∞ (ng·h/mL)	12 (11–14)	8.2–17	22 (17–28)	11–48	1.76 (1.44–2.14)
C_{max} (ng/mL)	1.8 (1.6–2.1)	1.3–2.4	3.0 (2.4–3.7)	2.0–5.4	1.62 (1.32–1.99)
$t_{1/2}$ (h)	3.3 (3.0–3.5)	2.6–3.9	4.2 (3.7–4.7)	3.0–5.6	1.28 (1.20–1.36)
Intermediate metabolizer, *N* = 9					
AUC_∞ (ng·h/mL)	15 (11–19)	9.1–26	20 (16–25)	12–31	1.35 (1.11–1.62)
C_{max} (ng/mL)	2.0 (1.5–2.6)	1.2–4.5	2.6 (2.1–3.2)	1.9–4.6	1.32 (1.08–1.60)
$t_{1/2}$ (h)	3.5 (3.0–4.0)	2.8–4.7	4.1 (3.7–4.7)	3.4–5.9	1.19 (1.06–1.34)
Poor metabolizer, *N* = 3					
AUC_∞ (ng·h/mL)	28 (21–36)	25–31	28 (24–34)	26–30	1.02 (0.84–1.24)
C_{max} (ng/mL)	3.0 (1.8–5.0)	2.6–3.8	3.2 (1.5–6.5)	2.3–4.1	1.05 (0.82–1.33)
$t_{1/2}$ (h)	4.7 (2.6–8.5)	3.9–6.1	5.8 (2.1–16)	4.4–9.3	1.23 (0.87–1.74)
O-H-LSD					
Normal metabolizer, *N* = 11					
AUC_∞ (ng·h/mL)	2.1 (1.9–2.4)	1.6–3.0	3.6 (3.2–4.1)	2.7–4.6	1.71 (1.51–1.93)
C_{max} (ng/mL)	0.1 (0.1–0.2)	0.097–0.21	0.2 (0.2–0.2)	0.15–0.31	1.43 (1.29–1.58)
$t_{1/2}$ (h)	7.2 (6.2–8.3)	5.4–12	9.5 (7.7–12)	6.0–17	1.32 (1.18–1.47)
Intermediate metabolizer, *N* = 9					
AUC_∞ (ng·h/mL)	2.7 (2.2–3.5)	1.7–4.4	3.7 (3.1–4.5)	2.5–5.3	1.35 (1.17–1.56)
C_{max} (ng/mL)	0.2 (0.1–0.2)	0.12–0.34	0.2 (0.2–0.3)	0.14–0.28	1.23 (1.11–1.36)
$t_{1/2}$ (h)	8.0 (7.0–9.0)	6.4–10	9.7 (7.9–12)	6.0–13	1.21 (1.03–1.42)
Poor metabolizer, *N* = 3					
AUC_∞ (ng·h/mL)	3.3 (2.7–4.1)	3.0–3.6	3.4 (2.5–4.7)	3.1–4.0	1.04 (0.95–1.13)
C_{max} (ng/mL)	0.2 (0.1–0.2)	0.16–0.19	0.2 (0.1–0.2)	0.14–0.18	0.94 (0.89–1.00)
$t_{1/2}$ (h)	10 (4.6–22)	7.1–13	11 (4.4–25)	8.5–16	1.06 (0.72–1.57)

AUC_∞, area under the plasma concentration-time curve from time zero to infinity; CI, confidence interval; C_{max}, maximum observed plasma concentration; GMR, geometric mean ratio (paroxetine/placebo); $t_{1/2}$, plasma half-life.

an SSRI strongly inhibiting CYP2D6, for example, paroxetine or fluoxetine. In contrast, a higher dose of LSD might be required in the presence of SSRIs that do not significantly inhibit CYP2D6. Since all marketed SSRIs inhibit various CYP enzymes to differing extents, whose influence on LSD metabolism remains unclear, no definitive dosing recommendations can currently be made.

The present study indirectly confirmed the hypothesis of a mildly lower response to LSD after pre-administration of an SSRI. Despite a 41% higher peak concentration of LSD after paroxetine compared with placebo, an equivalent overall response was observed. The mechanisms behind the SSRI-induced reduction of the pharmacodynamic response to psychedelics remain to be investigated. We did not find differences in gene expression of the $5\text{-}HT_{2A}$ receptor after paroxetine compared with placebo. Peripheral and central gene expression are generally associated, however, it remains unclear if this was the case in the present study. Neuroimaging trials have reported contradictory findings in $5\text{-}HT_{2A}$ binding potential after SSRI treatment.[43–45]

The generalizability of the present study to a clinical population is still limited because patients usually receive SSRI therapy for months or years. Only a few studies have investigated the effects of psychedelics in patients who undergo antidepressant treatment. A retrospective survey found that approximately half of patients who used SSRIs or serotonin-norepinephrine reuptake inhibitors (SNRIs) reported weaker-than-expected subjective effects of psilocybin compared with either the same dose before SSRI treatment or unmedicated people who took the same dose.[5] Another survey assessed the subjective effects of different psychedelics in patients with and without current SSRI or SNRI treatment using a prospective design.[7] The authors found lower rates of challenging experiences in patients who used SSRIs or SNRIs compared with unmedicated patients. Well-being and depressive symptoms improved similarly in both groups over 4 weeks. An exploratory one-arm open-label Phase II trial found that a single dose of 25 mg psilocybin during SSRI treatment showed therapeutic efficacy.[10] The safety profile of psilocybin with an SSRI was comparable to

the safety profiles of similar trials that investigated psilocybin in patients with no SSRI treatment.[46,47] The combined administration of an SSRI and LSD or psilocybin in patients could be favorable because the risk of SSRI discontinuation symptoms is eliminated, while the therapeutic effects of both substances appear to be maintained. Moreover, the combination could have a complementary effect, in which SSRIs would increase the capacity for passive coping (i.e., tolerating stressors), and psychedelics would increase the capacity for active coping (i.e., actively addressing stressors).[48] Controlled studies in patients are needed to determine whether antidepressant medication can be maintained during LSD-assisted therapy.

The present study has considerable strengths. The interaction between paroxetine and LSD was assessed using a robust study design in a highly controlled setting, investigating clinically relevant doses of LSD and paroxetine. A run-in period of 6 weeks was used, likely allowing for clinically relevant neuroadaptations to occur, since SSRI efficacy studies have observed improvements over a period of up to 6 weeks.[49,50] We comprehensively assessed the psychological and physiological effects of LSD using established measurement tools, confirming the safety and feasibility of LSD and SSRI co-administration.

Limitations of the present study include the mostly young age of the participants and the still short run-in period when compared with clinical populations. Older people may be more vulnerable to adverse effects, such as SSRI-related QTc prolongation. Future research should investigate the interaction between other antidepressants and LSD, psilocybin, or other psychedelics. Lastly, Phase II trials should compare the therapeutic efficacy of psychedelics in patients with and without concomitant antidepressant pharmacotherapy.

CONCLUSION

Paroxetine had no influence on the acute pleasant subjective effects of LSD but significantly reduced LSD-induced "bad drug effect," "anxiety," and "nausea." As a strong CYP2D6 inhibitor, paroxetine increased plasma concentrations of LSD, confirming the involvement of CYP2D6 in the metabolism of LSD.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

M.E.L. is a consultant for Mind Medicine, Inc. All other authors declare no competing interests for this work.

AUTHOR CONTRIBUTIONS

A.M.B. and M.E.L. wrote the manuscript with input from all the other authors. All authors gave final approval for the manuscript. M.E.L. and A.M.B. designed the research. A.M.B., M.H.D., A.J., A.T., I.S., I.A., L.E., and J.T. performed the research. A.M.B., L.M., J.T., D.L., E.G., H.M.S., and M.E.L. analyzed the data.

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