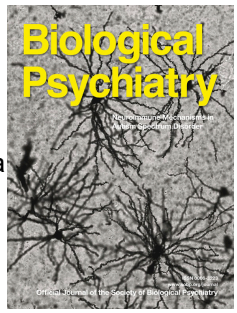

Lysergic acid diethylamide-assisted therapy in patients with anxiety with and without a life-threatening illness A randomized, double-blind, placebo-controlled Phase II study

Friederike Holze, Peter Gasser, Felix Müller, Patrick C. Dolder, Matthias E. Liechti

PII: S0006-3223(22)01553-0

DOI: https://doi.org/10.1016/j.biopsych.2022.08.025

Reference: BPS 14974

To appear in: *Biological Psychiatry*

Received Date: 13 June 2022

Revised Date: 5 August 2022

Accepted Date: 26 August 2022

Please cite this article as: Holze F., Gasser P., Müller F., Dolder P.C. & Liechti M.E., Lysergic acid diethylamide-assisted therapy in patients with anxiety with and without a life-threatening illness A randomized, double-blind, placebo-controlled Phase II study *Biological Psychiatry* (2022), doi: https://doi.org/10.1016/j.biopsych.2022.08.025.

Archival Report

Lysergic acid diethylamide-assisted therapy in patients with anxiety with and without a life-threatening illness

A randomized, double-blind, placebo-controlled Phase II study

Friederike Holze,[1, 2, *], Peter Gasser,[3, *] Felix Müller,[4] Patrick C. Dolder,[1, 2] Matthias E. Liechti[1, 2, +]

[1]Clinical Pharmacology and Toxicology, Department of Biomedicine and Department of Clinical Research, University Hospital Basel, Basel, Switzerland; [2]Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland; [3]Clinic Dr. Peter Gasser, Solothurn, Switzerland; [4]Psychiatric University Hospital, University of Basel, Basel, Switzerland

*Friederike Holze and Peter Gasser contributed equally and share first authorship

[+]Correspondence: Prof. Matthias E. Liechti, MD, Clinical Pharmacology, University Hospital Basel, Schanzenstrasse 55, Basel, CH-4056, Switzerland; E-mail: matthias.liechti@usb.ch; Phone: +41 61 328 68 68; Fax: +41 61 265 45 60

Short Title: LSD-assisted therapy in anxiety patients

Word counts: Manuscript: 3984; Abstract: 248

References: 25

Tables: 2

Figures: 3

Supplemental Material Online: One Word File containing 11 Tables and 16 Figures

Keywords: LSD; anxiety; life-threatening-illness; RCT; psychedelics; depression

Abstract

Background: This study aimed to investigate the efficacy and safety of lysergic acid diethylamide (LSD)-assisted therapy in patients who suffered from anxiety with or without association to a life threatening illness.

Methods: The study is an investigator-initiated two-center trial that used a double-blind, placebo-controlled, two-period, random-order, crossover design with two sessions with either oral LSD (200 µg) or placebo per period. The primary endpoint was anxiety symptoms 16 weeks after the last treatment session, assessed by Spielberger's State-Trait Anxiety Inventory–Global (STAI-G) score in 42 patients. Further outcome measures included ratings for depression symptoms (BDI [Beck Depression Inventory] and HAM-D-21 [Hamilton Depression Rating Scale]) and ratings for acute subjective drug effects. The outcomes for the first period, (between-subjects analysis) are primarily shown due to carry-over effects.

Results: LSD treatment resulted in significant reductions of STAI-G scores up to 16 weeks after treatment (least square mean (± SE) change from baseline difference = -16.2 (5.8), 95% CI=-27.8 to -4.5, *d*=-1.18, *p*=0.007). Similar effects were observed for ratings of comorbid depression on the HAM-D-21 (-7.0 (1.9), 95% CI=-10.8 to -3.2, *d*=-1.1, *p*=0.0004) and the BDI (-6.1 (2.6), 95% CI=-11.4 to -0.9, *d*=-0.72, *p*=0.02). Positive acute subjective drug effects and mystical-type experiences correlated with the long-term reductions in anxiety symptoms. Transient, mild, acute untoward effects of LSD treatment were reported by eight patients (19%). One treatment-related serious adverse event (acute transient anxiety) occurred (2%).

Conclusion: LSD produced long-lasting and notable reductions of anxiety and comorbid depression symptoms up to 16 weeks.

Trial registration: Clinicaltrials.gov Identifier: NCT03153579

Introduction

Anxiety is a common symptom of several mental illnesses and the leading symptom of anxiety disorders (1). Additionally, cancer and other life-threatening diseases are commonly associated with anxiety (2). Treatment options include mainly selective serotonin reuptake inhibitors and psychotherapy. However, antidepressants need to be administered daily and have limited efficacy. Therefore, alternative treatment options are needed.

Lysergic acid diethylamide (LSD) is a well-known classic psychedelic substance. Psychedelics, including LSD and psilocybin, induce profound acute alterations of mind and mystical-type experiences primarily by interacting with the serotonin 5-hydroxytryptamine-2A ($5\text{-}HT_{2A}$) receptor (3-5). LSD has a more turbulent history than psilocybin. Additionally, acute LSD effects last longer compared to those of psilocybin. However, a recent study documented otherwise comparable acute subjective effects and tolerability of LSD and psilocybin in healthy subjects (6). In the 1950s to 1970s, LSD was used in patients with end-stage cancer to improve mood and reduce anxiety (7-9). However, these studies did not use rigorous trial methods. Modern research on the therapeutic potential of psychedelics mostly used psilocybin. A small pilot study reported the safety of a moderate dose of psilocybin in patients with advanced-stage cancer (10). Two randomized, placebo-controlled trials in patients with life-threatening cancer reported significant reductions of anxiety and depression up to 5 and 6 weeks after a single dose of psilocybin (11, 12). A small pilot study for the present trial used two high doses of LSD (200 µg) or active placebo (20 µg LSD) in patients with life-threatening illness (LTI). The study found trends toward reductions of anxiety up to 2 months compared with placebo (13, 14). Therefore, the aim of the present larger study was to corroborate these findings in patients with LTI. Additionally, psychedelics have not yet been investigated in patients with psychiatric anxiety disorders in the absence of a LTI. Therefore, the present trial investigated effects of LSD on anxiety, depression, and overall psychiatric symptomatology in patients with anxiety with and also without a LTI using the Spielberger's State-Trait Anxiety Inventory (STAI), the Hamilton Depression scale (HAM-D-

21), the Beck Depression Inventory (BDI), and the Symptom-Check-List-90-R (SCL-90-R). Previous studies showed that acute effects of psilocybin on the 5 Dimensions of Altered States of Consciousness scale (5D-ASC; Oceanic Boundlesness but not Anxious Ego-Dissolution ratings) (15) and Mystical Experience Questionnaire (MEQ30, total scores) were associated with long-term therapeutic effects on anxiety and depression (11, 12, 15). Therefore, we hypothesized that acute effects of LSD on these 5D-ASC and MEQ30 scores would similarly correlate with long-term reductions of anxiety.

Methods and Materials

Study design and participants

The study used a double-blind, placebo-controlled, two-period, random-order, crossover design, with two LSD (200 µg) sessions and two placebo sessions and five study visits per period. The order of administration was random and counter-balanced. The study was an investigator-initiated two-center trial, with one study center at the University Hospital Basel, Switzerland, and one study center at the Clinic Dr. Peter Gasser, Solothurn, Switzerland. The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Guidelines in Good Clinical Practice and approved by the Ethics Committee of Northwest Switzerland (EKNZ), Swiss Federal Office for Public Health, and Swissmedic. Clinicaltrials.gov Identifier: NCT03153579.

Patients were recruited through an advertisement that was placed on the homepages of the University Hospital Basel and Swiss Medical Society for Psycholytic Therapy (SAePT) trial registries or by word of mouth. All patients provided written informed consent before study inclusion. Written informed consent was obtained by the study psychiatrist who conducted the screening visit. Both, patients and investigators were aware of the 2-period, placebo-controlled study design. Patients were informed that the study would investigate possible therapeutic benefits. The goal was to include patients with anxiety disorders or significant anxiety that was associated with a life-threatening somatic illness. LTI was

defined as any severe somatic disease, such as a diagnosis of cancer or another advanced-stage potentially fatal illness. Patients with a LTI had to meet Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), criteria for an anxiety disorder, including generalized anxiety disorder, social phobia, and panic disorder, as indicated by the SCID-IV or have a score ≥ 40 on the state or trait STAI scale at study inclusion. Patients without a LTI had to meet DSM-IV criteria for at least one anxiety disorder. Thus, in patients without a LTI, elevated STAI scores were not sufficient for inclusion.

The exclusion criteria included age < 25 years, past or present diagnosis of a primary psychotic disorder, patients with a first-degree relative with psychotic disorders, past or present bipolar disorder (according to the DSM-IV), current substance use disorder (within the last 2 months according to the DSM-IV, except nicotine), suicide risk, likely to require psychiatric hospitalization during the course of the study, and central nervous system involvement of the cancer (Supplementary Methods). Patients were allowed to be in ongoing psychotherapy and were asked not to change therapists, not to increase or decrease the frequency of their therapy, not to commence any new type of therapy during the study, and generally to keep their psychiatric medications. Psychiatric medications, such as antidepressants, neuroleptics, and anxiolytic medications, on a fixed regimen were tapered off typically 2 weeks before each LSD/placebo treatment session (i.e., five times the duration of a particular drug's half-life). Patients were instructed to refrain from using any psychoactive drugs, with the exception of long-term pain medication, within 24 h of each LSD/placebo treatment session.

After study inclusion, the patients were randomly assigned to LSD or placebo in the first treatment period and vice versa in the second treatment period by order of enrollment and group. LSD free base (> 99% purity; Lipomed AG, Arlesheim, Switzerland) was administered as an oral solution in units that contained 100 µg LSD in 1 ml of 96% ethanol (16). Inactive placebo consisted of identical units that were filled with ethanol only. Randomization and production according to good manufacturing practice (GMP) were performed by a licensed GMP facility (Apotheke Dr. Hysek, Biel, Switzerland).

Procedures

The study included a screening visit and two 24-week treatment periods per participant. Each treatment period consisted of two treatment sessions and five study visits. Treatment sessions were separated by 6 weeks (± 2 weeks). Study visits were conducted at baseline (bl visit), between the sessions (btw visit), and 2, 8, and 16 weeks after the second treatment session (w2, w8, and w16 visits). The w16 visit in the second period also served as the end-of-study visit (shown in Fig. 1). Patients were generally called by phone by the therapists within the next few days after treatment sessions for a brief follow-up.

Screening consisted of written informed consent, an evaluation of the patient's physical and mental health background, a psychiatric interview (SCID-IV), an assessment of anxiety severity (STAI), an assessment of depression (HAM-D-21 and BDI), and an assessment of further psychiatric symptomology (SCL-90-R) and a physical check-up. After successful screening, each patient was assigned to one investigator/therapist (shown in Table S1) for the whole duration of the study who conducted all treatment sessions and study visits. Treatment sessions lasted approximately 12 h, and study visits lasted approximately 1 h (Supplemental Methods).

Study visits consisted of talking psychotherapy (Supplementary Methods) followed by an assessment of adverse events, changes in general medication, and administration of the STAI, HAM-D-21, BDI, and SCL-90-R.

Treatment sessions were conducted in a calm hospital room (University Hospital Basel) or in a calm practice room (Clinic Dr. Peter Gasser). Only one patient and one investigator/therapist were present during the treatment sessions (exceptions of more than one therapist being present were made upon request by the therapist or patient; Supplementary Methods).

Outcome Assessments

The predefined primary endpoint of the study per protocol was the change in STAI-G

score from baseline at w16 after LSD compared with placebo within-subjects. Because of the long-lasting effects of LSD and resulting carryover effects (shown in Fig. 3) from the first to the second treatment period, the primary outcome analysis of the crossover (i.e., every patient served as his/her own control) was changed to w16 after LSD compared with placebo in the first period (between-subjects). Secondary endpoints were STAI scores at the btw, 2w, and 8w visits and HAM-D-21, BDI, and SCL-90-R scores at the btw, 2w, 8w, and 16w visits. Clinical response was defined as a STAI-G score reduction $\geq$ 30%. Further secondary endpoints were acute subjective drug effects during treatment sessions, assessed by the 5D-ASC and the MEQ30, acute autonomic drug effects during the treatment session (systolic and diastolic blood pressure and heart rate), adverse events, and serious adverse events (SAEs; during treatment sessions and during the entire study duration). Additionally, correlations between acute LSD effects (MEQ30 total score, Oceanic Boundlessness, Anxious Ego Dissolution, heart rate) and long-lasting therapeutic effects (16w) on the STAI-G were assessed (Supplementary Methods).

Statistical analyses

The sample size, was calculated based on the pilot study (14) and using PASS® (Kaysville, UT, USA) that required 80% power at a two-sided alpha of 0.05 using a 10% difference in anxiety scores with a standard deviation of 15%, was estimated to be 40 patients, allowing for 10 non-evaluable patients. Outcomes were analyzed using a Mixed Model for Repeated Measures (MMRM; SAS 9.4 software, SAS Institute, Cary, NC, USA), including treatment, visit, treatment $\times$ visit interaction, period, and sequence as fixed factors and patient as the random factor. Baseline values of the periods were considered covariates (change from baseline values for the respective period). LTI was used as a stratification factor. The crossover analysis was planned, but in case of being not fully valid because of carryover effects and withdrawals, a between-subjects analysis that was restricted to the first-period data was foreseen to substitute for the primary analysis of the full crossover data

using the MMRM without the period and sequence factors. Outcomes were predefined and preregistered in Clincaltrials.gov and analyses were predefined a priori in the protocol. Pearson correlations were used to describe relationships between acute effects of LSD on the 5D-ASC and MEQ30 and change in STAI-G score from baseline at wk16. The criterion for significance was $p < 0.05$.

Results

Enrollment began on June 23, 2017, and finished on February 1, 2021. The trial ended as planned with last patient last visit on December 15, 2021. Detailed numbers of participants and reasons for dropouts are shown in Fig. 2-3. All patients who completed both treatment sessions and at least one outcome visit (up to w2) of the first period were included in the between-subjects analysis ($n = 42$; shown in Fig. 2). Patients' demographic and clinical characteristics are shown in Table 1 and Table S2. Of the 42 patients who were included in the final analysis, 20 had a LTI and 22 had an anxiety disorder that was not associated with a somatic illness.

LSD produced strong reductions of anxiety, depression, and general psychiatric symptomatology compared with placebo in the first treatment period (shown in Fig. S1, Table 2). The least square mean (± SE) changes from baseline in the STAI-G score at 16 weeks after the last session were -14.9 (4.1) in the LSD group and 1.3 (4.1) in the placebo group (difference = -16.2, 95% confidence interval [CI] = -27.8 to -4.5, $p = 0.007$), indicating a significant difference between treatment groups (shown in Fig. S1, Table 2). Effects were maximal 2 weeks after the second LSD session and sustained up to 16 weeks. Thirteen of 20 patients (65%) in the LSD group and two of 22 patients (9%) in the placebo group showed a clinical response at any outcome visit (≥ 30% reduction of STAI-G scores, $p = 0.003$; Table S10). The secondary endpoint measurements, including the STAI-S, STAI-T, HAM-D-21, BDI, and SCL-90-R scores, all showed similarly rapid and sustained responses (shown in Fig. S1, Table 2) that were consistent with a lasting treatment effect on anxiety,

depression, and general psychiatric symptomatology. Outcomes of the crossover analysis and the subgroups can be found in Table S2-S7 and Figure S4-S8. Proportions of patients with the remission of depression are shown in Table S10. Individual responses and the time course can be found in Figure S11 and S13.

Acute subjective effects of LSD during the sessions of the first treatment period were significantly associated with the long-term outcome of a reduction of anxiety (shown in Fig. S9, S10, S14, S15, S16). Specifically, Oceanic Boundlessness and MEQ30 total score but not Anxious Ego Dissolution (average scores of both sessions) correlated with changes in STAI-G scores from baseline at w16 in the between-subjects analysis (r = -0.67, p = 0.001, r = -0.62, p = 0.003, and r = 0.049, p = 0.83, respectively; n = 20). Heart rate (Emax) during the acute LSD experience also correlated with long-term therapeutic outcome (r = -0.49, p = 0.026, n=20) when analyzed between subjects and for the first treatment period. There were no associations if only the data from the second treatment period was analyzed.

During the entire study duration, a total of nine (21%) SAEs occurred. Six SAEs occurred during the LSD period, and three occurred during the placebo period. Only one SAE (2%) was considered related to treatment and consisted of acute transient anxiety and delusions during an LSD session. The patient was successfully treated with lorazepam and olanzapine. A single dose of olanzapine was administered because lorazepam alone was not effective enough to fully block all symptoms. The patient was kept overnight and discharged in the morning and experienced no further long-term symptoms. Consequently, the second LSD dose was reduced to 100 µg for this patient. Additional non-treatment-related SAEs in the LSD period that occurred outside study visits are described in Table S9. During the LSD sessions, eight (19%) patients reported untoward effects, including anxiety (three patients [7%]), nausea (four patients [10%]), and headache (one patient [2%]). In a total of three patients (7%), LSD in the second session was reduced to 100 µg (one patient mentioned above and two other patients) because effects during the first session were considered too strong by the patient and therapist. There were no untoward effects during placebo sessions. A total of 229 additional adverse events were reported during the entire

trial duration (105 during the LSD period and 124 during the placebo period). None of these adverse events were considered related to treatment. A detailed listing of all adverse events is presented in Table S8. Autonomic effects are shown in Figure S15.

Outcome measures did not differ in patients with or without antidepressant co-treatment. The use of anxiolytic and antidepressant medications did not change substantially during the study (Supplementary Results).

Discussion

In this double-blind, placebo-controlled, randomized trial, LSD administration during two treatment sessions induced rapid and lasting reductions of anxiety, depression, and general psychiatric symptomatology up to 16 weeks. There was a significant reduction of the primary outcome measure of anxiety on the STAI-G at 16 weeks after the last LSD treatment and compared with placebo. Secondary outcome measures confirmed reductions of anxiety symptoms already after the first LSD session and reductions of depression (BDI, HAM-D-21) and reductions of general psychiatric symptomatology (SCL-90-R) up to 16 weeks after the last LSD administration compared with placebo. The present study confirms and expands previous findings from a small pilot study that used two administrations of LSD (200 µg) in patients with LTI (13, 14). The present findings are also consistent with a pilot study that used psilocybin in patients with advanced-stage cancer (10) and documented trends toward improvements in mood and anxiety. Additionally, the findings of our study align with two randomized, placebo-controlled trials that used single administrations of psilocybin (22 or 30 mg/70 kg or 0.3 mg/kg) in patients with life-threatening cancer. These studies reported comparable reductions of anxiety and depression 5-6 weeks after the psilocybin session compared with an active placebo (1 or 3 mg/70 kg psilocybin or 250 mg niacin) (11, 12). Effect sizes were comparable to the present study, whereas very high and higher effect sizes than those herein were reported for reductions of depression in studies that used psilocybin without a placebo control group (17, 18). However, trials that include a placebo condition likely more realistically reflect the benefits of psychedelic treatments. Reduction on

the SCL-90-R overall scores indicate that psychedelic treatment might be transdiagnostically effective (19).

LSD was generally well tolerated in the present study. However, one SAE was related to LSD (i.e., transient anxiety and delusion reaction during the session). LSD may produce acute anxiety in some people, particularly at high doses (4, 20). Specifically, effects of LSD at the dose and formulation that were used in the present study have been characterized very well in healthy subjects, and the dose could be considered high and have a greater risk of acute anxiety (4, 6). Transient anxiety and confrontation with a fear of death were also reported in the pilot study. Similar challenging emotions were also reported with psilocybin in cancer patients (11, 12) and patients with major depressive disorder (18). According to our clinical impression, the 200 µg dose of LSD might be too high for some patients, especially if they are not experienced with the effects of psychedelic drugs. Thus, a first dose of 100 or 150 µg LSD may be more adequate in future studies, with an optional increase to 150-200 µg for further doses. The 200 µg dose of LSD that was used in the present study can be considered equivalent to 40 mg of psilocybin (6) and higher than the psilocybin doses of 15-30 mg that have been used in clinical trials to date. Additionally, the high LSD dose was administered twice. The use of two doses has been strongly recommended (10, 13), allowing patients to become more familiar with the effects of a psychedelic and potentially have different experiences, particularly in cases in which the first dose produced a challenging experience.

The safety of LSD has been documented in healthy subjects (21). In the present study, LSD moderately increased blood pressure and heart rate during the sessions compared with placebo and similar to studies in healthy subjects (4, 6, 21). In the present study, no perceptual alterations were reported beyond the acute effects of LSD, consistent with the absence of clinically relevant flashback phenomena in controlled studies with LSD in healthy subjects (22). No participants reported acute suicidality at any time. One patient with a diagnosis of major depression reported transient feelings of depression, including suicidal thoughts (but no acutely increased suicidality including preparation), 8 weeks after the last

LSD treatment. Adverse events were comparable in the LSD and placebo periods.

In the present study, LSD produced marked alterations of mind and overall very positive acute experiences, indicated by high Oceanic Boundlessness ratings in the upper range of those in patients in limited LSD use programs (23) or in healthy subjects(4, 6, 20). Importantly, the present study found that LSD-induced acute positive subjective effects (Oceanic Boundlessness score) and mystical-type experiences (MEQ30 total score) were associated with the long-term therapeutic outcome as similarly shown for psilocybin (11, 12, 15), indicating that acute positive effects of psychedelics may serve as a treatment response predictor and biomarker. Similarly, acute mystical-type effects of LSD (200 µg) correlated with changes in well-being/life satisfaction in healthy subjects (24). However, heat rate (Emax) as an autonomic measure of the acute drug response also correlated with the therapeutic effects, although this association was weaker.

In the present study, there were differences in the treatment response between the groups that received LSD in the first period and those who received LSD in the second period. The LSD first group showed an overall stronger response with a partial relapse after week 10, whereas the LSD second group showed an overall weaker response with less relapse. Additionally, the correlations between acute effects and therapy outcomes were seen only in the group that received LSD in the first period. This raises questions about the interactions between expectancies, psychotherapy, and pharmacological treatments that require more investigation.

The present study has several strengths. It was relatively large. A total of 161 full-day sessions (80 LSD, 81 placebo) were conducted, and the study duration per patient was 12 months. The study used a randomized double-blind placebo-controlled design with a long 16-week follow-up for both treatments. Additionally, all patients were intended to be treated with both treatments within the crossover design. Previous studies with psychedelics in patients with anxiety or depression used no or not a sufficiently large placebo control group (14, 17, 18) or used relatively short follow-up times after the last treatment session of only 2 weeks (10), 3 weeks (25), 4 weeks (18), 5 weeks (11), and 6 weeks (12) during the phase of

the trial when a placebo group was run in parallel. Thus, the time course of effects and sustained effects up to 16 weeks after a psychedelic-assisted treatment session could be documented for the first time in a clinical trial compared with a placebo control group. Additionally, symptom scores remained low in the LSD-first group until the end of the trial, potentially indicating persisting effects up to 12 months (without a control). Finally, it was the first study with a psychedelic including patients with anxiety without a LTI.

The present study also has limitations. We used inactive placebo as the control condition. The characteristic effects of LSD unblinded the treatment order assignment in most patients once the effects of LSD were perceived. Only one patient in the LSD-first group mistook LSD as placebo and realized that he had LSD the first time only when he received placebo during the second study phase. Measures of subjective expectancy were not included. Other studies with psychedelics used an “active” placebo, such as niacin or a low dose of the psychedelic (e.g., 25 µg LSD) as the control condition. It remains to be shown whether blinding can be improved with these active placebo approaches and valid blinding remains a challenge in any trials that use psychedelics as well as in many other clinical trials. The use of a crossover design can also be problematic. Patients in the LSD-first group showed therapeutic effects that persisted into the second period, thereby lowering baseline ratings of this period. Additionally, placebo in the second period tended to further improve outcome ratings. This finding may be explained by the intensive entire-day one-to-one patient-therapist interactions, potentially including partial re-experience of the LSD sessions and integrating and consolidating its effects. Such a consolidation response was not possible in the placebo-first group. In the placebo-first group, the patients and therapist spent more time together before the LSD sessions, but this seemed not to positively influence the responses to LSD treatment. Thus, carryover and order effects in the crossover occurred. A possible advantage of the crossover design was that each patient was sure to receive LSD at some point during the study. Notably, retention in the study was also high in patients who received LSD first. Another limitation is related to the setting and experience of the investigators and therapists. The therapists were mostly highly motivated and also very

experienced with psychedelic-assisted therapy and had previously treated patients with LSD within limited use programs (23) and the pilot study (13, 14). The therapist treated the patients one-to-one within a highly-intensive treatment setting that may not be generally available in other trials and future settings of psychedelic-assisted therapy. Patients were also motivated, reflected by the relatively low dropout when considering the long study duration and inclusion of a placebo period. Only motivated patients were included who initiated contact with the study team on their own. Patients were allowed to continue their treatments, including psychotherapy and drug therapy, with the exception of pausing serotonergic agents before treatment sessions for safety reasons. Thus, although many patients were already receiving treatment for their anxiety disorder, LSD-assisted treatment further improved their symptomatology.

In conclusion, the present study suggests long-term benefits of LSD-assisted therapy in patients with anxiety disorders. Further, larger trials are needed to confirm these findings.

Final Disclosures

The authors thank Markus Baumann, Ose Hein, René Kostka, Claudia Möckel, Anke Röskamp, Barbara Speich, and Iga Zawadynska for their work as study therapists, Kathrin Haenseler for helping with conducting the study, Cedric Hysek and Corinne Grossenbacher for preparing the study medication, Manuel Strebel for help with data entry, Maurizio Rainisio for statistical support, Michael Arends for proofreading the manuscript, and particularly our generous donators for financial support.

Conflict of Interest Statement

The study was funded by the University Hospital Basel and the Swiss Medical Society for Psycholytic Therapy (SAePT). The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing the report.

MEL and PG are consultants for Mind Medicine, Inc. The other authors report no biomedical

financial interests or potential conflicts of interest. Knowhow and data associated with this work and owned by the University Hospital Basel were licensed by Mind Medicine, Inc.. Mind Medicine, Inc., had no role in financing, planning, or conducting the present study or the present publication.

References

1. Bandelow B, Michaelis S (2015): Epidemiology of anxiety disorders in the 21st century. *Dialogues in clinical neuroscience*. 17:327-335.
2. Mitchell AJ, Chan M, Bhatti H, Halton M, Grassi L, Johansen C, et al. (2011): Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. *Lancet Oncol*. 12:160-174.
3. Vollenweider FX, Vollenweider-Scherpenhuyzen MF, Babler A, Vogel H, Hell D (1998): Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. *Neuroreport*. 9:3897-3902.
4. Holze F, Vizeli P, Ley L, Muller F, Dolder P, Stocker M, et al. (2021): Acute dose-dependent effects of lysergic acid diethylamide in a double-blind placebo-controlled study in healthy subjects. *Neuropsychopharmacology*. 46:537-544.
5. Preller KH, Herdener M, Pokorny T, Planzer A, Kraehenmann R, Stämpfli P, et al. (2017): The fabric of meaning and subjective effects in LSD-induced states depend on serotonin 2A receptor activation. *Curr Biol*. 27:451-457.
6. Holze F, Ley L, Muller F, Becker AM, Straumann I, Vizeli P, et al. (2022): Direct comparison of the acute effects of lysergic acid diethylamide and psilocybin in a double-blind placebo-controlled study in healthy subjects. *Neuropsychopharmacology*. 47:1180-1187.
7. Grof S, Goodman LE, Richards WA, Kurland AA (1973): LSD-assisted psychotherapy in patients with terminal cancer. *International pharmacopsychiatry*. 8:129-144.
8. Kast E (1966): LSD and the dying patient. *Chic Med Sch Q*. 26:80-87.
9. Pahnke WN, Kurland AA, Goodman LE, Richards WA (1969): LSD-assisted psychotherapy with terminal cancer patients. *Current psychiatric therapies*. 9:144-152.

10. Grob CS, Danforth AL, Chopra GS, Hagerty M, McKay CR, Halberstadt AL, et al. (2011): Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. *Archives of general psychiatry*. 68:71-78.

11. Griffiths RR, Johnson MW, Carducci MA, Umbricht A, Richards WA, Richards BD, et al. (2016): Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: a randomized double-blind trial. *J Psychopharmacol*. 30:1181-1197.

12. Ross S, Bossis A, Guss J, Agin-Liebes G, Malone T, Cohen B, et al. (2016): Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. *J Psychopharmacol*. 30:1165-1180.

13. Gasser P, Kirchner K, Passie T (2015): LSD-assisted psychotherapy for anxiety associated with a life-threatening disease: a qualitative study of acute and sustained subjective effects. *J Psychopharmacol*. 29:57-68.

14. Gasser P, Holstein D, Michel Y, Doblin R, Yazar-Klosinski B, Passie T, et al. (2014): Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. *The Journal of nervous and mental disease*. 202:513-520.

15. Roseman L, Nutt DJ, Carhart-Harris RL (2017): Quality of acute psychedelic experience predicts therapeutic efficacy of psilocybin for treatment-resistant depression. *Front Pharmacol*. 8:974.

16. Holze F, Duthaler U, Vizeli P, Muller F, Borgwardt S, Liechti ME (2019): Pharmacokinetics and subjective effects of a novel oral LSD formulation in healthy subjects. *British journal of clinical pharmacology*. 85:1474-1483.

17. Carhart-Harris RL, Bolstridge M, Rucker J, Day CM, Erritzoe D, Kaelen M, et al. (2016): Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. *The Lancet Psychiatry*. 3:619-627.

18. Davis AK, Barrett FS, May DG, Cosimano MP, Sepeda ND, Johnson MW, et al. (2021): Effects of psilocybin-assisted therapy on major depressive disorder: a randomized clinical trial. *JAMA Psychiatry*. 78:481-489.

19. Kocarova R, Horacek J, Carhart-Harris R (2021): Does psychedelic therapy have a transdiagnostic action and prophylactic potential? *Front Psychiatry*. 12:661233.

20. Schmid Y, Enzler F, Gasser P, Grouzmann E, Preller KH, Vollenweider FX, et al. (2015): Acute effects of lysergic acid diethylamide in healthy subjects. *Biol Psychiatry*. 78:544-553.

21. Holze F, Caluori TV, Vizeli P, Liechti ME (2022): Safety pharmacology of acute LSD administration in healthy subjects. *Psychopharmacology (Berl)*. 239:1893-1905.

22. Muller F, Kraus E, Holze F, Becker A, Ley L, Schmid Y, et al. (2022): Flashback phenomena after administration of LSD and psilocybin in controlled studies with healthy participants. *Psychopharmacology (Berl)*. 239:1933-1943.

23. Schmid Y, Gasser P, Oehen P, Liechti ME (2021): Acute subjective effects in LSD- and MDMA-assisted psychotherapy. *J Psychopharmacol*. 35:362-374.

24. Schmid Y, Liechti ME (2018): Long-lasting subjective effects of LSD in normal subjects. *Psychopharmacology (Berl)*. 235:535-545.

25. Carhart-Harris R, Giribaldi B, Watts R, Baker-Jones M, Murphy-Beiner A, Murphy R, et al. (2021): Trial of psilocybin versus escitalopram for depression. *N Engl J Med*. 384:1402-1411.

Figure Legends

Figure 1. Study trial design and timeline. Timeline from screening to end of study visit with two identical periods (period 1: week 0-24; period 2: week 26-50) with the crossover from period 1 to period 2 between weeks 24 and 26. Each period consisted of two sessions (LSD/LSD or placebo/placebo) and five study visits that are indicated as baseline (bl; period week 0), between (btw; period week 5), week 2 (w2; period week 10), week 8 (w8; period week 16), and week 16 (w16; period week 24). The Spielberger's State-Trait Anxiety Inventory (STAI), Hamilton Depression Scale, 21 item version (HAM-D-21), Beck Depression Inventory (BDI), and Symptom-Check-List-90-R (SCL-90-R) were administered during study visits. The 5 Dimensions of Altered State of Consciousness (5D-ASC), Mystical Effects Questionnaire, 30 item version (MEQ30), blood pressure (BP), and heart rate (HR) were assessed during study sessions.

Figure 2. CONSORT trial profile. A total of 243 people contacted the study team and were prescreened. Of these people, 62 attended a screening visit, and 46 were enrolled in the study. Two patients withdrew consent after enrollment and before randomization, resulting in 44 randomized patients. Twenty-one patients were assigned to the treatment group that received LSD in the first period, and 23 patients were assigned to the group that received placebo in the first period. There was a total of seven dropouts.

Figure 3. Outcome progress over entire study duration. Effects of LSD and placebo on study outcome measures over time and during both treatment periods. In the LSD-first group, LSD produced strong effects that carried over into the second treatment period. In the placebo-first group, there were no relevant changes in scores in the first treatment period, and LSD was effective in the second treatment period. The total number of patients that are shown on the graph was 42 at the start (week -2) and declined to 37 until the end of the study (week 50). Treatment sessions with either LSD (two sessions) or placebo (two sessions) occurred at weeks 2 and 8 in the first treatment period and at weeks 28 and 34 in the second

treatment period. The treatment crossover occurred after week 24. Outcome measures were assessed between sessions (btw visit, weeks 5 and 31) and 2 weeks (weeks 10 and 36), 8 weeks (weeks 16 and 42), and 16 weeks (weeks 24 and 50) after the second treatment session per period. **A** Spielberger's State-Trait Anxiety Inventory Global Score(STAI-G) **B** Spielberger's State-Trait Anxiety Inventory State Score (STAI-S) **C** Spielberger's State-Trait Anxiety Inventory Trait Score (STAI-T) **D** Hamilton Depression Scale, 21 item version (HAM-D-21) **E** Beck Depression Inventory (BDI) **F** Symptom-Check-List-90-R (SCL-90-R). Values are absolute scores expressed as means and standard errors.

.

Table 1. Characteristics of patient population at inclusion

	Total* n=42	LSD first n=20	Placebo first n=22	With life-threatening illness n=20	Without life-threatening illness n=22
General Information					
Sex					
female/male (n(%))	20/22 (48/52)	9/11 (45/55)	11/11 (50/50)	11/9 (55/45)	11/11 (50/50)
Age (mean ± SD)	45±12	45±12	46±13	46±13	45±13
Weight (mean ± SD)	71±15	71±14	71±16	70±14	72±15
Primary Diagnosis					
Life-threatening Illness (n(%))	20 (48)	10 (50)	10 (45)	20 (100)	0 (0)
Cancer (n(%))	11 (26)	5 (25)	6 (27)	11 (55)	0 (0)
Non-cancer (n(%))	9 (21)	5 (25)	4 (18)	9 (45)	0 (0)
Anxiety disorder (n(%))	36 (86)	17 (85)	19 (86)	14 (70)	22 (100)
Generalized anxiety disorder (n(%))	26 (62)	11 (55)	15 (68)	9 (45)	17 (77)
Social Phobia (n(%))	15 (36)	8 (40)	7 (32)	4 (20)	11 (50)
Panic disorder (n(%))	10 (24)	5 (25)	5 (23)	4 (20)	6 (27)
Additional Psychiatric Diagnoses					
Obsessive-compulsive disorder (n(%))	5 (12)	4 (20)	1 (5)	1 (5)	4 (18)
Major depression (n(%))	9 (21)	3 (15)	6 (27)	5 (25)	4 (18)
Medication/Therapy					
Antidepressants (n(%))	17 (40)	8 (40)	9 (40)	7 (35)	10 (45)
Anxiolytics (n(%))	12 (29)	5 (25)	7 (32)	7 (35)	5 (23)
Psychotherapy (n(%))	27 (64)	12 (60)	15 (68)	10 (50)	17 (77)
Scores at Inclusion (mean ± SD)					
STAI-G	111±20	105±20	117±19	108±22	114±19
STAI-S	53±13	48±12	57±12	52±14	53±12
STAI-T	59±10	57±10	61±9	56±11	61±7
HAM-D-21	19±8	18±9	20±7	18±8	19±7
BDI	24±12	21±13	26±12	23±12	24±12
SCL-90-R-GSI	1.2±0.6	1.1±0.6	1.3±0.7	1.1±0.6	1.3±0.6

*total of patients included in the between-subjects analysis of the first period; STAI-G (Spielberger's State-Trait Anxiety Inventory Global Score); STAI-S (Spielberger's State-Trait Anxiety Inventory State Score); STAI-T (Spielberger's State-Trait Anxiety Inventory Trait Score); HAM-D-21 (Hamilton Depression Scale 21 item version); BDI (Beck Depression Inventory); SCL-90-R-GSI (Symptom-Check-List-90-R Global Severity Score)

Table 2. Main Outcomes from the between-subject analysis*

	between session (btw) visit			2 weeks after second session (w2) visit			8 weeks after second session (w8) visit			16 weeks after second session (w16) visit		
	Difference (95% CI)	*d*	*p*-value	Difference (95% CI)	*d*	*p*-value	Difference (95% CI)	*d*	*p*-value	Difference (95% CI)	*d*	*p*-value
Anxiety Scale												
STAI-G	-21.7 (-33.1, -10.2)	-1.2	0.0004	-29.7 (-41.1, -18.2)	-1.6	<0.0001	-18.9 (-30.4, -7.3)	-1.0	0.0018	-16.2 (-27.8, -4.5)	-0.87	0.0074
STAI-S	-12.5 (-18.8, -6.1)	-1.2	0.0002	-15.9 (-22.3, -9.6)	-1.5	<0.0001	-9.8 (-16.3, -3.3)	-0.93	0.0035	-8.0 (-14.6, -1.5)	-0.75	0.017
STAI-T	-9.8 (-15.8, -3.8)	-1.0	0.0019	-14.2 (-20.2, -8.2)	-1.5	<0.0001	-9.3 (-15.4, -3.3)	-0.97	0.0031	-8.5 (-14.6, -2.4)	-0.87	0.0071
Depression Scales												
HAM-D-21	-6.6 (-10.3, -2.9)	-1.1	0.0006	-8.8 (-12.5, -5.1)	-1.5	<0.0001	-3.7 (-7.5, 0.1)	-0.60	0.056	-7.0 (-10.8, -3.2)	-1.1	0.0004
BDI	-4.7 (-9.8, 0.4)	-0.57	0.068	-9.1 (-14.2, -4.0)	-1.1	0.0007	-4.0 (-9.2,1.2)	-0.48	0.13	-6.1 (-11.4, -0.9)	-0.72	0.022
General Psychiatric Sympomatology												
SCL-90-R-GSI	-0.41 (-0.67, -0.16)	-1.0	0.0019	-0.53 (-0.79, -0.28)	-1.3	<0.0001	-0.35 (-0.61, -0.10)	-0.84	0.0082	-0.43 (-0.69, -0.17)	-1.0	0.0018
SCL-90-R-PST	-17.5 (-27.6, -7.4)	-1.1	0.001	-21.2 (-31.3, -11.1)	-1.3	<0.0001	-16.6 (-26.8, -6.4)	-1.0	0.0020	-16.6 (-26.8, -6.3)	-1.0	0.0021
SCL-90-R-PSDI	-0.29 (-0.53, -0.05)	-0.7	0.019	-0.45 (-0.69, -0.21)	-1.1	0.0004	-0.22 (-0.47, 0.03)	-0.54	0.086	-0.38 (-0.64, -0.13)	-0.94	0.0032
SCL-90-R-GS	-37.2 (-60.3, -14.1)	-1.0	0.0021	-47.9 (-71.0, -24.8)	-1.3	0.0001	-31.7 (-55.2, -8.3)	-0.84	0.0088	-41.4 (-65.1, -17.7)	-1.1	0.0009

*values are score changes from baseline shown as differences between LSD and placebo reported as least square mean (95% confidence interval) in 42 patients. *d*: effect size, Cohen's *d;* STAI-G (Spielberger's State-Trait Anxiety Inventory Global Score); STAI-S (Spielberger's State-Trait Anxiety Inventory State Score); STAI-T (Spielberger's State-Trait Anxiety Inventory Trait Score); HAM-D-21(Hamilton Depression Scale 21 item version); BDI (Beck Depression Index); SCL-90-R-GSI (Symptom-Check-List-90-R Global Severity Score); SCL-90-R-PST (Symptom-Check-List-90-R Positive Symptom Total); SCL-90-R-PSDI (Symptom-Check-List-90-R Positive Symptom Distress Index); SCL-90-R-GS (Symptom-Check-List-90-R Global Score); btw visit = 5 weeks; w2 session = 10 weeks; w8 = 16 weeks; w16 = 24 weeks.