SUPPLEMENTAL INFORMATION

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

Section 1

Supplemental Methods

Inclusion and exclusion criteria

Inclusion criteria

1. Age > 25 years.
2. Meet DSM-IV criteria for anxiety disorder as indicated by the SCID-IV or have a score of at least 40 on the state- or trait STAI scale at study inclusion.
3. 40% or more of the participants should have a diagnosis of advanced-stage potentially fatal illness (autoimmune, neurological, or cancer without CNS involvement). Patients should be ambulatory and not terminal and likely to have a roughly estimated life expectancy of > twelve months.
4. Patients without advanced-stage potentially fatal illness need to meet DSM-IV criteria for anxiety disorder (elevated STAI score not sufficient for inclusion)
5. Sufficient understanding of the study procedures and risks associated with the study.
6. Participants must be willing to adhere to the study procedures and sign the consent form.
7. Participants are willing to refrain from taking any psychiatric medications during the experimental session period. If they are being treated with antidepressants or are taking anxiolytic medications on a fixed daily regimen such drugs must be discontinued long enough before the LSD/placebo treatment session to avoid the possibility of a drug-drug interaction (the interval will be at least 5 times the particular drug's half-life [typically 3-7 days]).
8. If in ongoing psychotherapy, those recruited into the study may continue to see their outside therapist, provided they sign a release for the investigators to communicate directly with their therapist. Participants should not change therapists, increase or decrease the frequency of therapy or commence any new type of therapy during the study (not including the follow-up).
9. Participants must also refrain from the use of any psychoactive drugs, with the exception of the long term pain medication or caffeine or nicotine, within 24 hours of each LSD/placebo treatment session. They must agree not to use nicotine for at least 2 hours before and 6 hours after each dose of LSD. They must agree to not ingest alcohol-containing beverages for at least 1 day before each LSD treatment session. Non-routine medications for treating breakthrough pain taken in the 24 hours before the LSD treatment session may result in rescheduling the treatment session to another date, with the decision at the discretion of the investigators after discussion with the participant.
10. Participants must be willing not to drive a traffic vehicle or to operate machines within 24 h after LSD/placebo administration.

Exclusion criteria

1. Women who are pregnant or nursing, or of child bearing potential and are not practicing an effective means of birth control (double-barrier method, i.e. pill/intrauterine device and preservative/diaphragm).
2. Past or present diagnosis of a primary psychotic disorder. Subjects with a first degree relative with psychotic disorders are also excluded.
3. Past or present bipolar disorder (DSM-IV)
4. Current substance use disorder (within the last 2 months, DSM-IV, except nicotine)
5. Somatic disorders including CNS involvement of the cancer, severe cardiovascular disease, untreated hypertension, severe liver disease (liver enzymes increase by more than 5 times the upper limit or normal) or severely impaired renal function (estimated creatinine clearance <30 ml/min), or other that in the judgement of the investigators pose too great potential for side effects
6. Weight < 45 kg
7. Suicide risk or likely to require psychiatric hospitalization during the course of the study
8. Requiring ongoing concomitant therapy with a psychotropic drug (other than as needed, anxiety medications, and pain control medications) and unable or unwilling to comply with the washout period.

Procedures

Treatment Sessions

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). The treatment sessions began at 8:00 AM. LSD or placebo was administered at 9:00 AM. The

therapists and patients were in the same room for the whole treatment session, and a common meal was provided at approximately 6:00 PM. Afterward, acute subjective drug effects were assessed using the 5D-ASC and MEQ30 at the end of the session. At 8:00 PM, the patients were sent home in the company of a partner or friend. If necessary, then the patients could spend the night at the research facility, in which case an assistant was always on call who was ready to spend the night in the facility.

Randomization and study drug

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. Computerized block randomization (balanced blocks of 2 and 4 patients) was conducted by group (with or without a life threatening illness) and center and counter-balanced within group and center. 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(1). Inactive placebo consisted of identical units that were filled with ethanol only. For allocation concealment medication was prepackaged and numbered by Patient-ID and Session (1-4). Randomization and production according to good manufacturing practice (GMP) were performed by a licensed GMP facility (Apotheke Dr. Hysek, Biel, Switzerland).

Measures

Psychometric assessments

Spielberger's State-Trait Anxiety Inventory (STAI)

The STAI is a widely used and validated self-report instrument for assessing anxiety in adults. The STAI has been shown to be sensitive for the effects of LSD in a pilot study(2) and sensitive for psilocybin in several previous studies (3-6). The STAI is available in many languages including a validated German version. It includes separate measures of state and trait anxiety.(7) The STAI evaluates essential qualities of feelings of apprehension, tension, nervousness, and worry. The STAI differentiates between the temporary condition of state anxiety and the more general and long-standing quality of trait anxiety. The STAI state anxiety (STAI-S) subscale asks about feelings at the moment of completing the questionnaire. The STAI trait anxiety (STAI-T) subscale asks subjects to indicate how they generally view themselves. For both subscales, scores from 20 to 39 indicate mild anxiety, scores from 40 to 59 indicate moderate anxiety, and scores from 60 to 80 indicate severe anxiety. Both the STAI-S and STAI-T are commonly used as outcome measures in studies of patients with anxiety disorders.(8, 9) An STAI global (STAI-G) score can be derived by adding STAI-S and STAI-T scores (range: 40-160 points). The scoring in the present study was performed according to a previous study.(7)

Hamilton Depression Rating Scale (HAM-D)

The study psychiatrists assessed the patients' depression severity using the 21-item HAM-D (HAM-D-21).(10, 11) This rating scale consists of 21 items (3- to 5-point ratings) that ask about symptoms related to depression, such as low mood, suicidality, irritability, tension, loss of appetite, insomnia, loss of interests, somatic symptoms, and similar. The summary scores were calculated as described previously.(10)

Beck Depression Inventory (BDI)

The BDI consists of 21 questions that were developed to measure the severity of depression.(12) The German version of the BDI-II(13, 14) was used as a self-assessment. The BDI previously revealed an improvement of mood 6 months after psilocybin-assisted psychotherapy for anxiety in patients with advanced-stage cancer.(3) Summary scores were calculated as described previously.(13)

Symptom-Check-List-90-R (SCL-90-R)

The SCL-90-R is a widely used psychological status symptom inventory(15, 16). We used the German version(16). Outcome measures are the global severity index (SCL-90-R-GSI), positive symptom distress index (SCL-90-R-PSDI), and positive symptom total (SCL-90-R-PST). Reductions of these SCL-90-R scores were previously observed after LSD-assisted psychotherapy in patients with a life-threatening illness(2). SCL-90 scores were calculated according to a previous study.(17)

Subjective drug effect measurements

Previous studies showed that positively experienced acute effects of psilocybin on the 5D-ASC and MEQ30 were associated with long-term therapeutic effects on anxiety and depression.(4, 5, 18) Therefore, we hypothesized that acute effects of LSD on 5D-ASC Oceanic Boundlessness but not Anxious Ego-

Dissolution(18) and MEQ30 total scores would correlate with reductions of anxiety on the STAI-G scale 16 weeks after LSD.

5 Dimensions of Altered States of Consciousness (5D-ASC) scale

The 5D-ASC scale(19, 20) was administered once at the end of each treatment session to retrospectively rate peak drug effects. The 5D-ASC scale measures altered states of consciousness and contains 94 items that are assessed on visual analog scales. The instrument consists of five subscales/dimensions(19) and 11 lower-order scales.(20) The 5D-ASC Oceanic Boundlessness (OB) dimension (27 items) measures derealization and depersonalization that are associated with positive emotional states, ranging from heightened mood to euphoric exaltation. The corresponding lower-order scales include Experience of Unity, Spiritual Experience, Blissful State, Insightfulness, and Disembodiment. The Anxious Ego Dissolution (AED) dimension (21 items) summarizes ego disintegration and loss of self-control phenomena that are associated with anxiety. The corresponding lower-order scales include Impaired Control of Cognition and Anxiety. The Visionary Restructuralization (VR) dimension (18 items) consists of the lower-order scales Complex Imagery, Elementary Imagery, Audio-Visual Synesthesia, and Changed Meaning of Percepts. Two additional dimensions describe Auditory Alterations (AA; 15 items) and Reduction of Vigilance (VIR; 12 items). The total 3D-ASC (OAV) score is the total of the three main dimensions OB, AED, and VR and can be used as a measure of the overall intensity of alterations of mind.(21) The scale is well-validated in German(19) and many other languages and widely used to characterize subjective effects of various psychedelic drugs. The scale has been used by most research groups to psychometrically assess effects of LSD.(22-27) Furthermore, acute positive effect ratings on the 5D-ASC (OB but not AED scores) after psilocybin administration have been used to predict long-term effects of psychedelic treatments in patients.(18) Ratings on the 5D-ASC have been shown to closely correlate with ratings on the Mystical Effects Questionnaire (MEQ; see below),(21) which is primarily used by research groups in the United States.(5)

Mystical Effects Questionnaire

Mystical experiences were assessed once at the end of the treatment sessions using the 100-item States of Consciousness Questionnaire (SOCQ)(21, 28) that includes the 30-item Mystical Effects Questionnaire (MEQ30).(29) The published German version was used.(21) The MEQ has been used in numerous experimental and therapeutic trials with psilocybin.(4, 5, 28, 30-35) The MEQ items provide scale scores for each of seven domains of mystical experiences: internal unity, external unity, sacredness, noetic quality (as real as or more real than everyday reality), deeply felt positive mood, transcendence of time and space, and ineffability/paradoxicality (difficulty describing the experience in words). The total of all scale scores was used as an overall measure of the mystical-type experience. We also derived the four scale scores of the newly validated revised 30-item MEQ: mystical, positive mood, transcendence of time and space, and ineffability.(29) Additionally, some aspects of the LSD experience may be better captured with this scale. For scale validation, see a previous study.(29) For the German translation of the MEQ30, see the online supplement in a previous study.(21)

Autonomic effects

Blood pressure and heart rate were assessed repeatedly over time at baseline and up to 12 h after substance administration at intervals of 2 h using an automatic oscillometric device (OMRON Healthcare Europe NA, Hoofddorp, Netherlands).

Section 2

Therapeutic Methods/Manual

Purpose of this manual

The purpose of this short manual is to enable already psychotherapeutically trained or active personnel who are also familiar with the method of psycholytic (i.e. psychedelic) therapy, at least theoretically, to agree on a common guideline and to coordinate the therapeutic procedure for the study.

General principles and background

Psycholytic therapy consists of the experience accompanied by mind-altering substances and accompanying psychotherapeutic conversations. Both experiences and conversations depend on the needs of the patient and requirements for the therapeutic process.

In a catamnestic survey of ~120 female patients who underwent psycholytic therapy between 1988 and 1993, the roughly assumed average therapy duration was 3 years, including seven experiences with methylenedioxymethamphetamine (MDMA) or LSD and ~70 therapeutic conversations.

Such therapy within a Phase II research project is understandable hardly feasible and also not financeable. Here, we reduced LSD-assisted psychotherapy to a very short treatment phase with a few LSD experiences with the assumption that even with a short treatment duration, already observable results will be shown. The short duration is also suitable for studying safety aspects of the therapy because critical events would be more likely to arise in a phase of the therapy in which the patient is not yet as familiar with the LSD experience.

In a study that was designed as a drug trial to prove the safety and efficacy of the substance (so-called Phase II study), the double-blind, placebo-controlled, randomized design is currently the gold standard and a requirement for scientifically well-conducted research. We are well aware that this implies certain limitations and problems in an LSD-assisted study. LSD therapy is not simply a drug treatment; it is also a psychotherapy with the aid of a drug catalyst (LSD) for the psychotherapy process. From this perspective, it would be better to compare LSD psychotherapy with other psychotherapy methods. However, different effects between the test substance (LSD) and placebo are usually obvious to both the patient and the therapist. Thus, double-blind allocation is very quickly unblinded. Nevertheless, we decided to adhere to the design of a drug trial at this stage of the newly restarted research on LSD-assisted psychotherapy. Only in the last few years has it become possible to research such substances as LSD, psilocybin, and MDMA with regard to their therapeutic applicability. At this stage, we believe it is important to conduct scientifically sound and methodologically well-established research.

Role of the therapist

Christian Scharfetter writes in the foreword to the book, *Therapy with Psychoactive Substances*, the following: "*However, if a therapist expects too high, idealistic goals from his work, he not only overtaxes the patient, but also inwardly abandons the attitude of a psychotherapist who accompanies the patient along the way.*" This already essentially outlines the ethical orientation of our therapy approach. The enormously regressive and transcending character of the LSD experience often makes the person accompanying such a journey appear to the patient in a fantastic, even magical exaggeration. "*He does 'exactly the right thing at exactly the right time.' The music fits 'exactly' into the individual process.*" Such a strong positive bond with the therapist is helpful support for the therapy process because it enables trust and openness. However, it is not an expression of a therapist's psychic powers; at best, it is an expression of experience, empathy, and familiarity with such situations. The therapist must be aware of this.

Moreover, the compelling and in a certain sense unpredictable LSD experience makes it necessary for the therapist to learn accompanying a process that he does not know in detail. The patient may be lying still and experience something within her- or himself that does not show itself on the outside. They do not have to constantly report what is happening, which would disturb their own process. Therefore, the therapist is a kind of "free rider," alert and aware of the atmosphere in the room, aware of the patient's small movements, breathing, and movements, and always ready to become active with (hopefully) appropriate music, a gentle noninvasive physical touch (holding hands, holding feet, etc.), or a short conversation, often introduced with an open question ("How are you?," "Where are you right now?," or similar).

This therapeutic attitude of a clear ethic of non-harming and non-activist accompaniment is the basis of the therapeutic identity. Additionally, there are more technical aspects, such as familiarity with the LSD experience, if possible from self-experience, medical and pharmacological knowledge for normal and emergency situations, dealing with music in a therapeutic setting, or being able to touch in a therapeutic way.

Accompanying psychotherapy

After the screening phase of the study, where it is clarified whether the patient can be included in the study or not, the actual therapy begins. This can be didactically divided into three phases. The first discussions serve to establish a working alliance and prepare the patient for the therapy element "LSD experience." The second part of therapy is the actual all-day LSD or placebo experience sessions. The third phase of therapy includes further discussions that serve the purpose of integrating these experiences into everyday life, their suitability for reality, and the issue of how one can draw a benefit for normal life from such a non-ordinary experience.

Preparatory visits

The first phase before the first LSD session serves to establish the therapeutic relationship. The patient and therapist get to know each other, the anamnesis is taken in depth, the therapist gets to know the so-called "set" of the patient, including life situation, beliefs, burdens, and resources, and the patient's wishes, hopes, and fears about the upcoming LSD session and how he or she deals with the illness for which they come to therapy. The therapist answers the patient's questions about the substance and setting so that the first LSD session can occur in a situation of sufficient clarification and preparation.

Integrative visits

Integration (the post-processing of the LSD experience) is an important part of therapy. This is also the difference between self-experience, the recreational use of LSD, and therapy with LSD. Here, a therapist is present who helps to order, understand, deepen, and help answer "Why?," "What for?," and "What do I do with it?" questions.

The number of integration sessions is limited in the research project but can be increased if necessary. After 26 weeks, the first part of the therapy (depending on whether two LSD or two placebo sessions have taken place) is ended with a final interview, and then the same procedure (this time with two placebo or two LSD sessions) takes place. Thus, after 52 weeks, the whole treatment has finished.

LSD/placebo sessions

In the pilot study, "Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases,"(2) all treatments were conducted by the same co-therapists (female and male). The therapeutic discussions were conducted by the male therapist, and both therapists were present together for each of the LSD experiences. This guaranteed a certain uniformity in treatment methodology but has the disadvantage that the influence of different therapist personalities is uncertain. In the LSD study that now follows, several male and female therapists will conduct the treatments. Thus, a greater variety of therapeutic styles is available. These are not quantified in the context of this study. Nevertheless, it becomes apparent whether the results that are related to the different therapists are very heterogeneous. The LSD sessions are conducted as individual therapies (not as group therapy) and with generally only one patient and a female or male therapist present but not both at the same time. The reason to take two therapists of different sexes in some studies/settings is based on the idea that for transference processes, maternal and paternal figures should be present. This consideration is certainly understandable. However, we did not encounter any situation in the pilot study(2, 36) in which the participant explicitly referred to the preference of this situation or where we as therapists were convinced that this was now indispensable for the psychotherapeutic process. It also does not correspond to the setting of other psychotherapy methods. Certainly, it is good support for long therapeutic accompaniment when there are two therapists. However, the effort and costs are high for such a setting in individual therapy.

In the double-blind crossover procedure that was chosen for this study, each participant will complete two LSD sessions and two placebo sessions. At random, they will either first undergo two LSD sessions and then two placebo sessions, or vice versa (first placebo and then LSD). The session procedure is necessarily the same for all four sessions, based on the assumption of blinding. This means that the structure is identical, but logically the content of the sessions is not, which is individual. The therapist's interventions are individual, and the choice of music also depends at least partly on the individual process.

Requirements

The participant must be willing to have an LSD experience of his or her own free will. They can also decide at short notice to postpone the date (or drop out of the study altogether). Before taking the substance, all outstanding questions and concerns should be clarified. The therapist must also be convinced that the participant can have the LSD experience on that day. The therapist must be able to clinically rule out psychological or physical impediments.

Set, setting, and substance

The terms "set and setting" that are often quoted in this context have existed since the late 1950s and early 1960s. While initially the substance LSD was administered like a normal drug, the patients ingested it and were then left alone (e.g., in the ward of the psychiatric hospital).(37) It soon became clear that this strongly psychoactive substance required a suitable environment and care (setting) and also some internal conditions beyond the diagnosis in the narrower sense (set).

The elements of the setting for the study that is discussed here include the specific attitude and person of the therapist and the room where the approximately 9-h session will occur. This room should be comfortably furnished with shielding from excessive sound and light from outside. The patient should be able to both lie down and sit. Sleep masks (like those offered on airplanes) can be provided. Music, alternating with periods of silence, is played over a stereo system. Depending on the therapist's training, such instruments as drums, monochords, or singing bowls may also be played.

The therapist will be present with the patient during the whole time of LSD's effects, which lasts approximately 9 h.

Conduct of LSD/placebo sessions

It is planned to establish two treatment centers (Solothurn and Basel) within the framework of the study. The Basel treatment site will be defined by one therapist who will fully handle the treatments that occur there. The treatment site in Solothurn will comprise several therapists who will conduct the therapies according to the plan after the screening procedure.

Phases of the session

There is something artificial about dividing an experience that proceeds along a continuum into phases. It serves here only a didactic purpose. The LSD experience has something unpredictable about it, which does not mean that it is dangerous. But it does mean that it is only very limitedly predictable in its course and content. Even if a participant inwardly sets herself up to relax and let go, it does not mean that this is what will happen. Perhaps the experience goes in a completely different direction. "*To have an intention and yet to be completely open to what is happening as inner process"* is a motto of any LSD experience.

The first time after taking the drug consists of waiting for its effect. This begins usually after approximately 30-60 min. During this time, it is helpful to play soft and longer lasting music. It should help the participant relax and "glide" into the experience. In the beginning, before the effect sets in, helpful behavioral rules can be repeated, such as returning to breathing whenever one is internally agitated or accepting feelings as mental-bodily processes and welcoming them into the body rather than avoiding or fleeing. However, one should avoid overwhelming the participants with well-intentioned advice.

After 45-75 min, the effect begins to fully unfold itself. This is also referred to as a *plateau phase* or *main effect*. This stage lasts approximately 3-4 h. During this period, the patient will be in a deep inner process and particularly responsive to music and inner stimuli, thoughts, feelings, and perceptions. The therapist supports this process with appropriate music. This music can be powerful and evocative, but it should not manipulate the participant or force him into an emotional process. Periods of silence are valuable because they help to center. The togetherness of the therapist and participant is largely non-verbal. In this phase of the experience, it is even more pronounced. It would be an overload to have to speak in the midst of an abundance of thoughts, feelings, and perceptions. For the therapist, this means that they sometimes cannot know exactly what the participant is experiencing. They also do not know whether the music chosen is appropriate. Therefore, the music should not be too programmatic and should not be too text-heavy during this phase.

Approximately 5 h after taking the substance, the main effect will be over. The patient may become slightly restless, start to feel more physically active, or want to go to the toilet or drink something. Of course, they should be able to satisfy these needs, but it is important to support them in a further very introspective and another 3-4 h slow process of the weakening effect. During this time, patients relive many aspects of the experience from the main effect, or they can put into thought what previously had been an overwhelming perceptual process. Remaining slow and gentle with oneself also prevents overwhelming and difficult emotional breaks.

Approximately 8 h after taking the substance, a break can be made. Short conversations are possible, with a little food and drink. After another hour, the patient can go home if they are psychically and physically stable and accompanied. They are not fit to drive at this stage, and public transportation is not advisable. If the participant is not yet in a stable condition, then care must be prolonged. In that case, there will be another sitter ready to come for an overnight stay of the participant.

Intervention

First of all, the therapeutic work consists of a friendly and reserved presence and a calm competence that allows the patient to go through a very own process with the help of the substance and to be sure that there

is always someone present who can help and intervene if necessary. In this friendly presence, it is also possible to intervene actively, to address the patient, to touch them, and to accompany a process for which the presence of a therapist is helpful, perhaps even necessary. If one is disturbing, then the participant can say so, and the therapist will withdraw a little from direct contact.

Intervision

All therapists who are active in this study will participate in regular (three times per year) intervision meetings. In those meetings, technical aspects and therapeutic aspects of the study will be discussed. Every therapist is encouraged to share challenging and successful experiences. The need for these intervision meetings is given because therapists mostly act on their own. This proceeding is comparable to therapeutic work outside a clinical study, where therapists mostly act by themselves as well and attend regular intervision meetings.

Table S1. Listing of all therapists involved in the study, including professional background and specialization of psychotherapy (if applicable).

	Background	**Trained Psychotherapist? (If yes, specialization)**	**No. of patients treated**	**Conducted Screening and end of study visits**
Therapist 1	MD, Psychiatrist	Problem-oriented therapy, contextualized family therapy (Boszormeny- Nagy) psycholytic psychotherapy, bioenergetics analysis and therapy	6	yes
Therapist 2	MD, Psychiatrist	Psychodynamic psychotherapy	2	yes
Therapist 3	MD, Psychiatrist	Bioenergetics, group psychotherapy (S.H. Foulkes), oecologic-systemic couple therapy, trauma therapy, ego-state therapy, life-span integration, narrative exposition therapy	5	no
Therapist 4	MD, Homeopathy	No	5	no
Therapist 5	MD, Psychiatrist	Problem-oriented therapy, psychoanalytic group therapy, psycholytic psychotherapy, unitive body therapy humanistic psychology, topic-centered interaction, biodynamic psychology	6	no
Therapist 6	MD, General practician	No	6	no
Therapist 7	Psychologist	Bioenergetics, biosynthesis	4	no
Therapist 8	Mental health professional (nurse)	Transactional analysis	5	no
Therapist 9	Other discipline	Conversational psychotherapy, depth psychology oriented group therapy, medical hypnosis	5	no

Section 3

Supplemental Results

Patients

Table S2. Diagnoses of patients in the subgroup of patients with a severe life-threatening illness.

Diagnoses of Life-threatening Illnesses	
Cancer	
Year of primary diagnosis	
2015	Testicular cancer (metastatic) Tumor relapse in 2017
2010	Chronic lymphatic leukemia
2006	Adult acute myeloid leukemia with stem cell transplant
2014	Bladder carcinoma Tumor relapse 2018 non-metastasizing.
2019	Metastasizing colon carcinoma
2018	Colon carcinoma, large, colonoscopy, non-metastasizing
2012	Breast cancer (right-sided) Cancer relapse 2017 (left-sided)
2020	Breast cancer (left-sided)
2019	Metastasizing bronchus carcinoma
2020	Metastasizing cervical cancer
2006	Multiple myeloma
2016	Colon carcinoma non-metastasizing
Non-Cancer	
2017	Parkinson's disease First symptoms in 2010
1992	Marfan syndrome
2012	Multiple sclerosis
2015	Consecutive blindness due to ocular damage as prematurely born
1997	Morbus Boeck, kidney transplantation (cirrhotic kidney)
2017	Guillain Barré syndrome with partial remission
2014	Human immunodeficiency virus
1992	Multiple sclerosis
1998	Juvenile arthritis with secondary consecutive blindness

Use of medication at screening and end of study

At screening, 12 patients were treated with a short-acting anxiolytic (e.g., lorazepam, alprazolam; five patients using it regularly and seven patients using it only as back-up medication). During the study, one of the patients who was regularly taking an anxiolytic before the study stopped completely. Seven patients newly started anxiolytic medications during the study (six patients who were using it as back-up medication and for a short time during the study and one patient who started regular use during the placebo period with continued use at the end of the study). At the end of the study, 12 patients were treated with anxiolytics.

At screening, 17 patients were treated with an antidepressant. Three patients stopped antidepressant treatment completely, and one patient stopped one of two antidepressants during the study. Four patients newly started an antidepressant treatment during the course of the study (three during placebo periods and one during LSD periods). At the end of the study, 18 patients were treated with antidepressants.

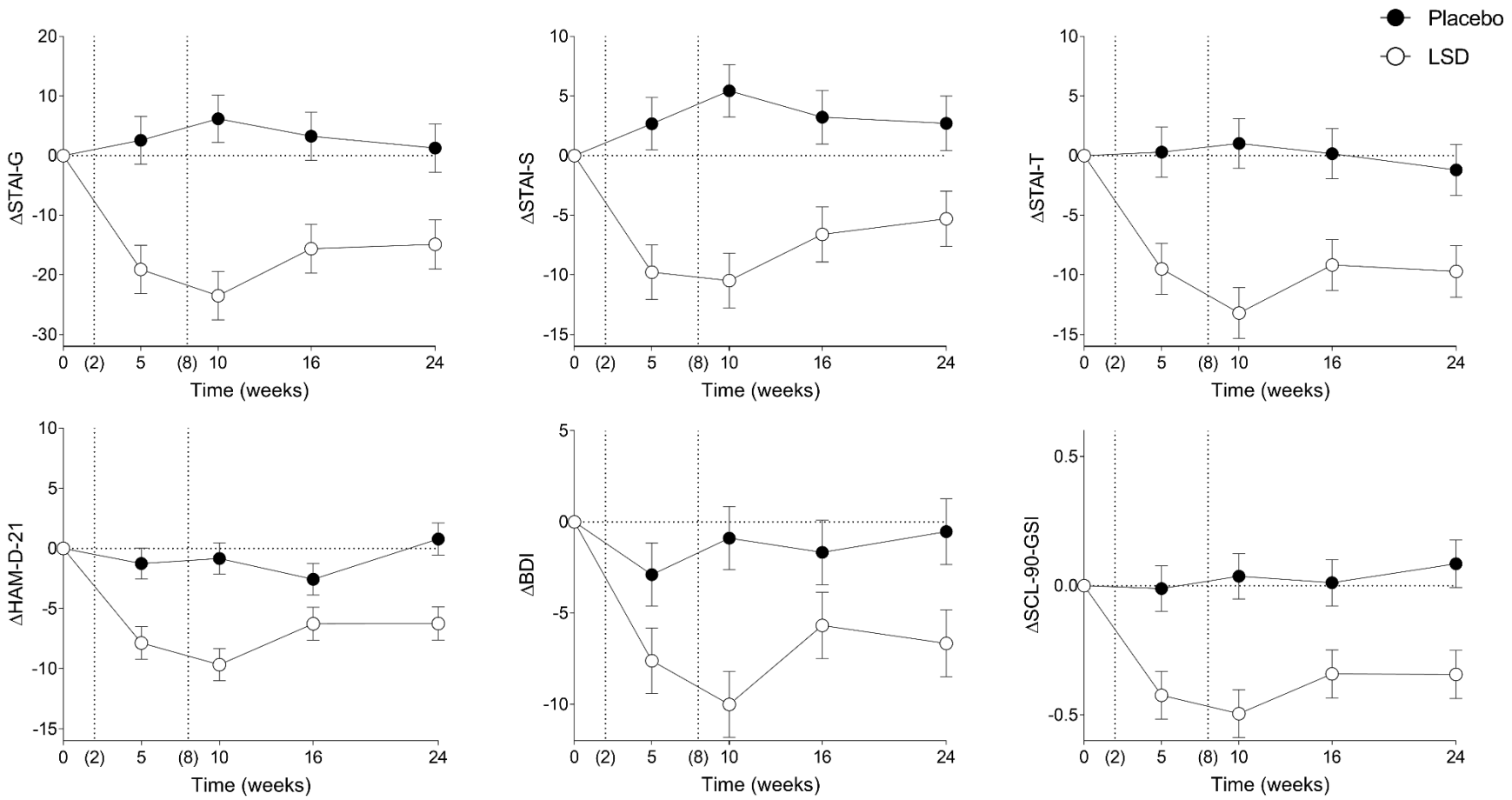

Figure S1. Outcomes from between-subjects analysis in first treatment period. LSD produced strong and sustained reductions of all outcome measures compared between-subjects with placebo and during the first treatment period. Treatment sessions with either LSD (two sessions) or placebo (two sessions) occurred at weeks 2 and 8. Outcome measures were assessed between sessions (btw visit, week 5) and 2 weeks (week 10), 8 weeks (week 16), and 16 weeks (week 24) after the second treatment session (w2, w8, and w16 visits, respectively). Values are score changes from baseline, expressed as least square means and standard errors in 42 patients (20 LSD, 22 placebo).

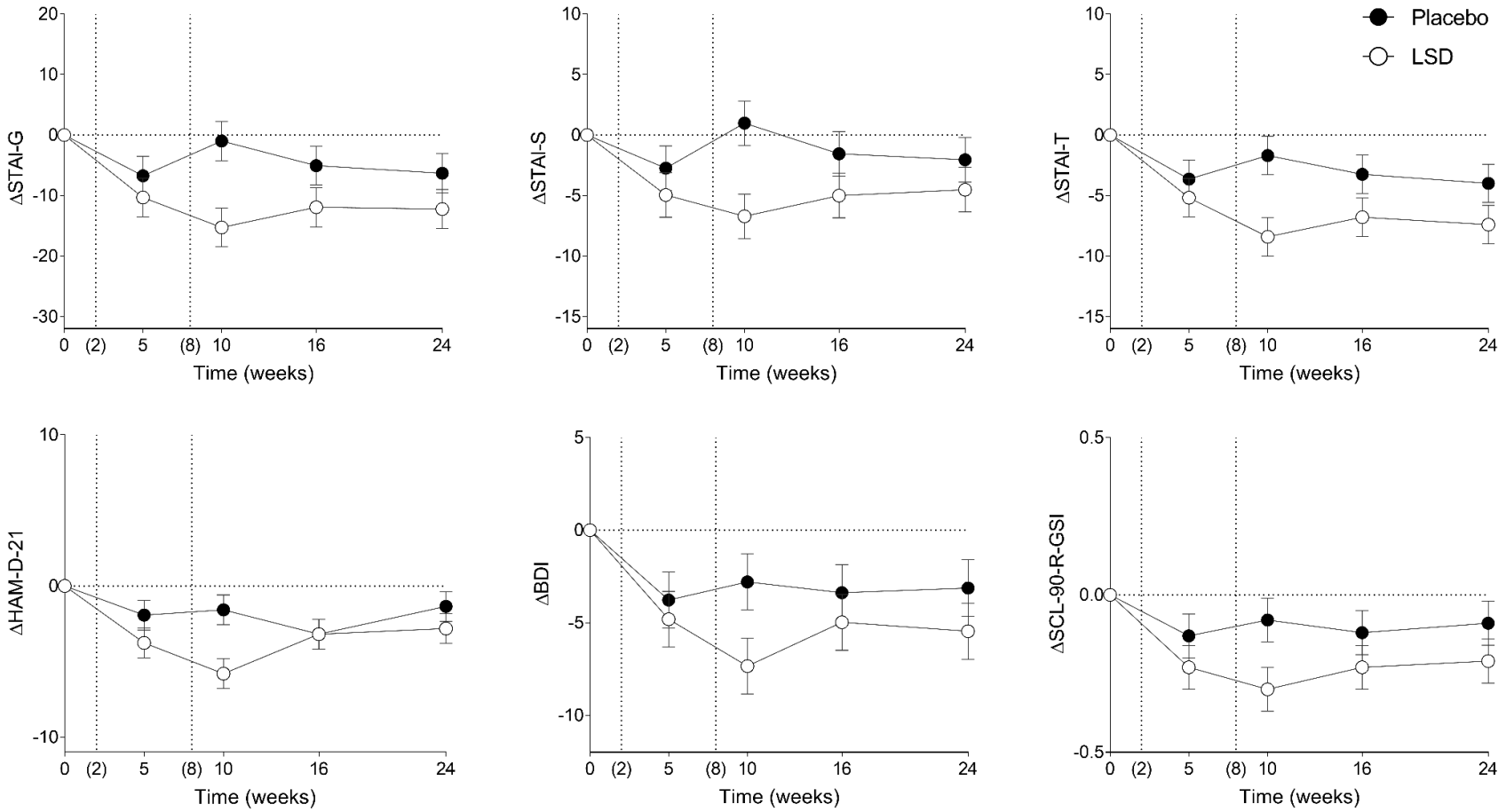

Figure S2. Effects of LSD and placebo on study outcome measures compared within-subjects. Data are changes from baseline expressed as least square means and standard errors and across both periods in the same 37 patients (n = 37/group). The STAI-G and STAI-T were only assessed in 36 patients because of missing values. Treatment sessions with LSD (two sessions) and placebo (two sessions) occurred at weeks 2 and 8 during both periods. Outcome measures were assessed between sessions (btw visit, week 5) and 2 weeks (week 10), 8 weeks (week 16), and 16 weeks (week 24) after the second treatment session (w2, w8, and w16 visits, respectively).

Table S3. Outcomes from the crossover 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‡	-3.6 (-9.8, 2.67)	-0.19	0.26	-14.3 (-20.5, -8.0)	-0.75	<0.0001	-6.9 (-13.1, -0.6)	-0.36	0.032	-5.9 (-12.2, 0.3)	-0.31	0.060
STAI-S	-2.2 (-5.9, 1.5)	-0.19	0.25	-7.7 (-11.4, -4.0)	-0.67	<0.0001	-3.5 (-7.2, 0.3)	-0.30	0.072	-2.5 (-6.3, 1.3)	-0.21	0.20
STAI-T‡	-1.5 (-4.7, 1.6)	-0.16	0.33	-6.7 (-9.8, -3.6)	-0.71	<0.0001	-3.5 (-6.7, -0.4)	-0.37	0.027	-3.4 (-6.5, -0.3)	-0.36	0.03
Depression Scales												
HAM-D-21	-1.8 (-4.1, 0.5)	-0.26	0.11	-4.2 (-6.5, -1.9)	-0.60	0.0003	0.0 (-2.3, 2.3)	0.00	1.0	-1.5 (-3.8, 0.8)	-0.21	0.21
BDI	-1.0 (-3.8, 1.7)	-0.12	0.46	-4.6 (-7.3, -1.8)	-0.54	0.001	-1.6 (-4.4,1.2)	-0.19	0.26	-2.3 (-5.1, 0.4)	-0.27	0.10
General Psychiatric Symptomatology												
SCL-90-R-GSI	-0.10 (-0.24, 0.04)	-0.24	0.15	-0.22 (-0.36, -0.08)	-0.51	0.002	-0.11 (-0.25, 0.03)	-0.25	0.13	-0.12 (-0.26, 0.02)	-0.27	0.11
SCL-90-R-PST	-2.9 (-7.5, 1.6)	-0.21	0.21	-4.1 (-8.7, 0.5)	-0.29	0.083	-2.2 (-6.8, 2.4)	-0.16	0.35	-0.8 (-5.5, 3.7)	-0.07	0.69
SCL-90-R-PSDI	-0.07 (-0.22, 0.08)	-0.16	0.34	-0.24 (-0.39, -0.09)	-0.51	0.002	-0.11 (-0.26, 0.05)	-0.23	0.17	-0.20 (-0.35, -0.05)	-0.43	0.010
SCL-90-R-GS	-9.6 (-22.4, 3.2)	-0.24	0.14	-19.4 (-32.3, -6.5)	-0.49	0.003	-10.4 (-23.0, 2.9)	-0.25	0.13	-12.9 (-25.8, 0.05)	-0.32	0.051

*values are score changes from baseline shown as differences between LSD and placebo reported as least square mean (95% confidence interval) in 37 patients.‡Only for 36 patients due to missing values; *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 Inventory); 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; w 2 session = 10 weeks; w 8 = 16 weeks; w 16 = 24 weeks.

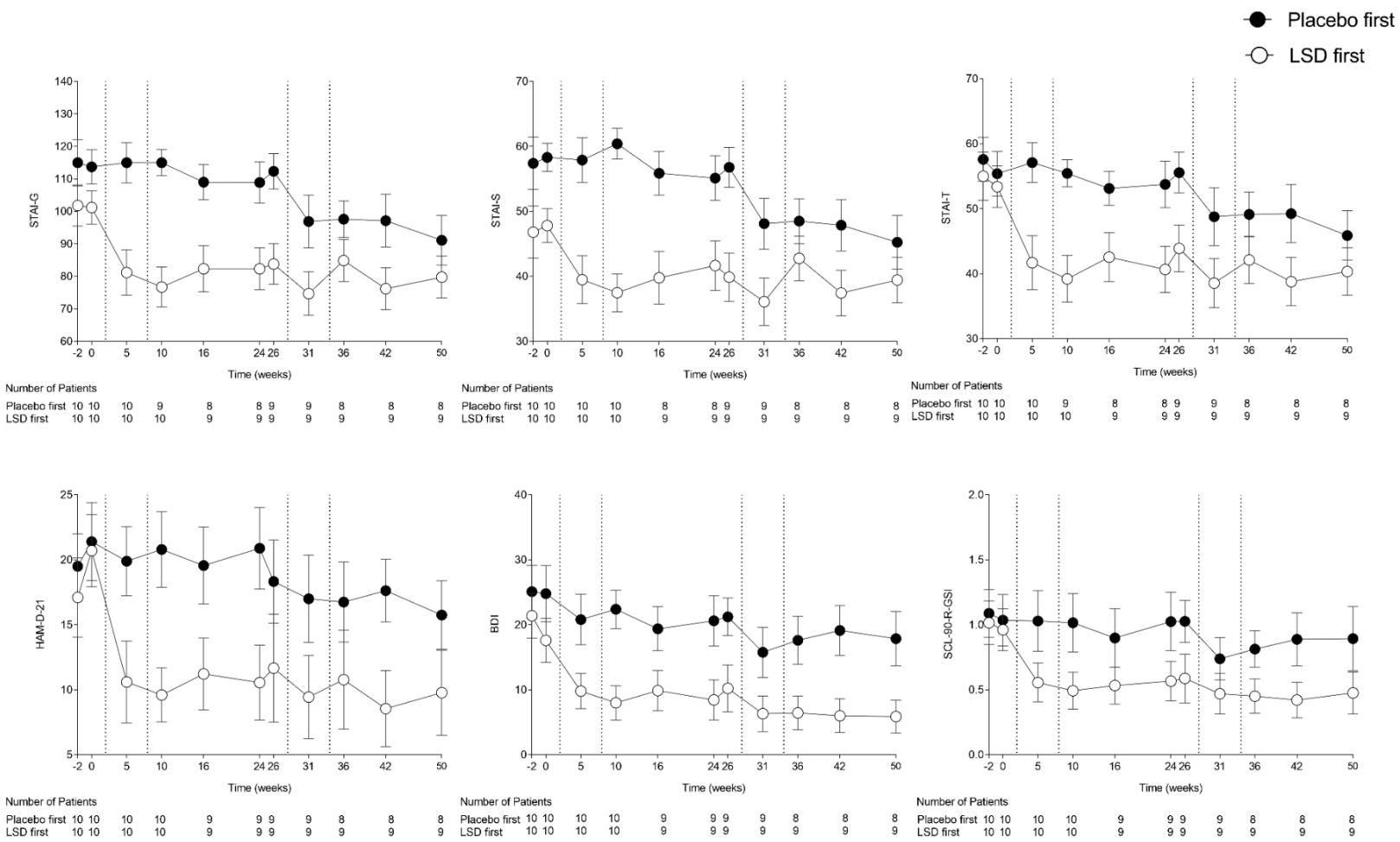

Figure S3. Outcome progress over entire study duration in patients with a life-threatening illness. Effects of LSD and placebo on study outcome measures over time and during both treatment periods are shown. The total number of patients who are shown in the graph was 20 at the start (week -2) and declined to 17 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 period and in weeks 28 and 34 in the second 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 (week 24 and 50) after the second treatment session per period. Values are absolute scores expressed as means and standard errors.

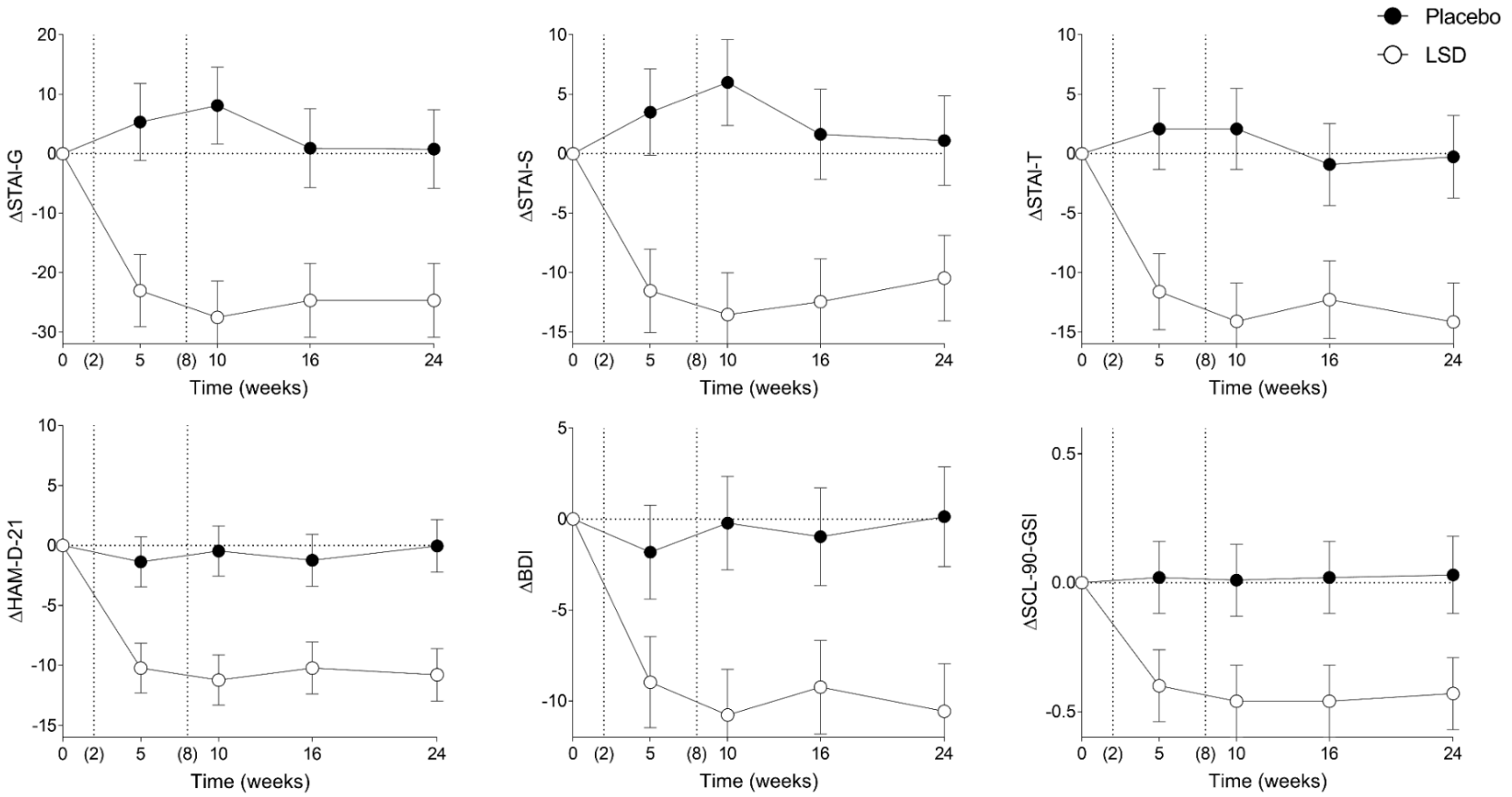

Figure S4. Outcomes from the between-subjects analysis in the first treatment period in patients with a life-threatening illness. LSD produced strong and sustained reductions of all outcome measures compared between-subjects with placebo and during the first treatment period. Treatment sessions with either LSD (two sessions) or placebo (two sessions) occurred at weeks 2 and 8. Outcome measures were assessed between sessions (btw visit, week 5) and 2 weeks (week 10), 8 weeks (week 16), and 16 weeks (week 24) after the second treatment session (w2, w8, and w16 visits, respectively). Values are score changes from baseline expressed as least square means and standard errors in 20 patients (10 LSD, 10 placebo).

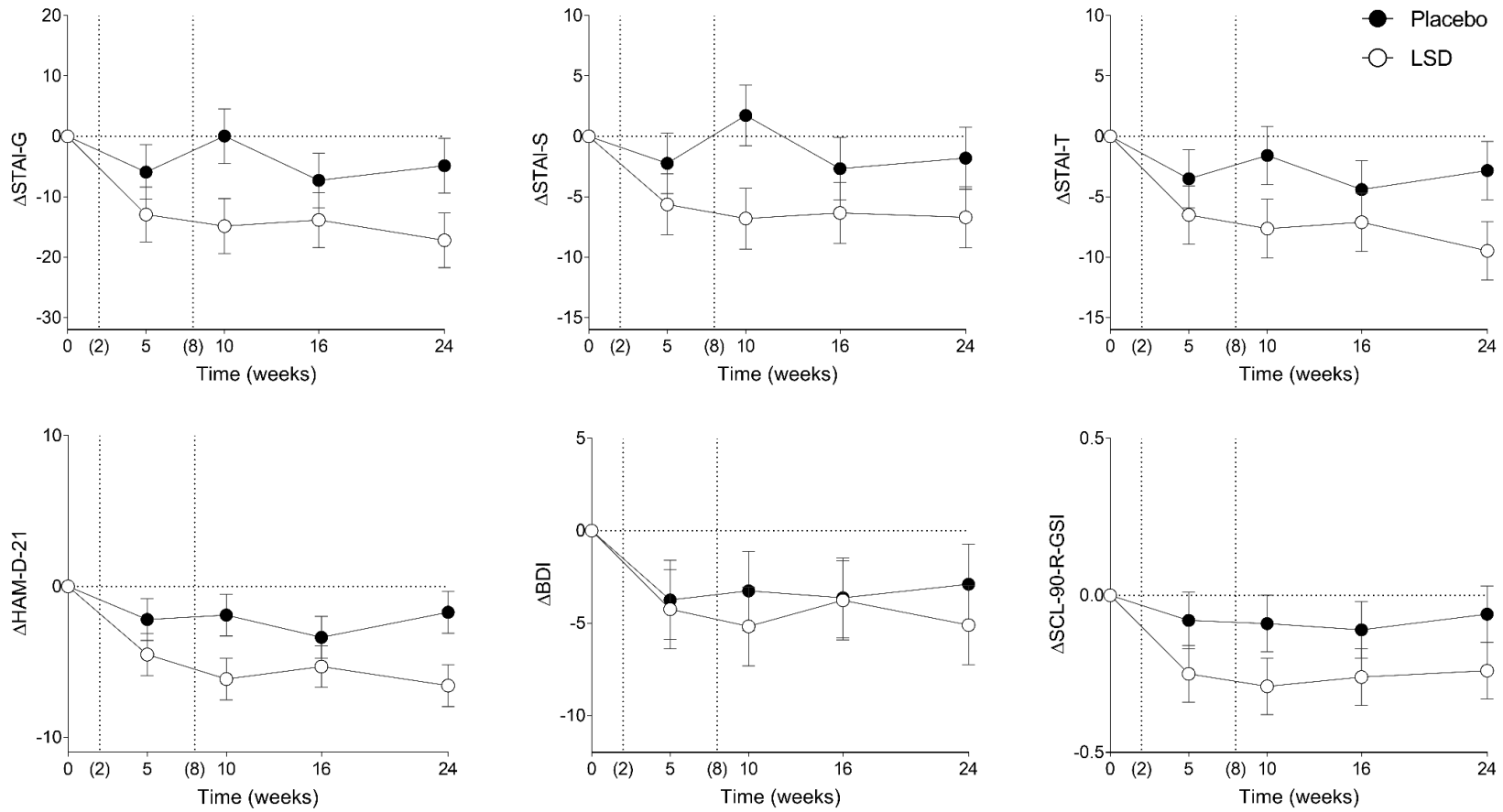

Figure S5. Outcomes from the within-subjects analysis in both treatment periods in patients with a life-threatening illness. Effects of LSD and placebo on study outcome measures compared within-subjects are shown. Data are changes from baseline expressed as least square means and standard errors and across both periods in the same 17 patients (n = 17/group). The STAI-G and STAI-T were only assessed in 16 patients because of missing values. Treatment sessions with LSD (two sessions) and placebo (two sessions) occurred at weeks 2 and 8 during both periods. Outcome measures were assessed between sessions (btw visit, week 5) and 2 weeks (week 10), 8 weeks (week 16), and 16 weeks (week 24) after the second treatment session (w2, w8, and w16 visits, respectively).

Table S4. Outcomes from the parallel analysis in patients with a life-threatening illness*

	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	-28.4 (-47.2, -9.5)	-1.44	0.0052	-35.6 (-54.5, -16.8)	-1.81	0.0008	-25.6 (-44.8, -6.4)	-1.27	0.011	-25.5 (-44.7, -6.3)	-1.26	0.012
STAI-S	-15.0 (-26.2, -3.8)	-1.23	0.011	-19.5 (-30.7, -8.3)	-1.60	0.0014	-14.1 (-25.7, -2.5)	-1.11	0.019	-11.6 (-23.1, -0.03)	-0.92	0.049
STAI-T	-13.7 (-23.5, -3.9)	-1.35	0.0084	-16.2 (-26.0, -6.4)	-1.59	0.0025	-11.4 (-21.3, -1.5)	-1.10	0.026	-13.9 (-23.8, -3.9)	-1.34	0.0086
Depression Scales												
HAM-D-21	-8.9 (-14.9, -2.8)	-1.34	0.0052	-10.8 (-16.8, -4.7)	-1.63	0.0009	-9.0 (-15.2,-2.8)	-1.31	0.0059	-10.7 (-17.0, -4.4)	-1.55	0.0014
BDI	-7.2 (-14.7, 0.4)	-0.88	0.063	-10.6 (-18.1, -3.0)	-1.29	0.0084	-8.3 (-16.1,-0.5)	-0.98	0.039	-10.7 (-18.6, -2.8)	-1.24	0.010
General Psychiatric Sympomatology												
SCL-90-R-GSI	-0.42 (-0.82, -0.02)	-0.97	0.041	-0.47 (-0.87, -0.07)	-1.08	0.024	-0.48 (-0.89, -0.06)	-1.06	0.025	-0.45 (-0.87, -0.04)	-1.00	0.034
SCL-90-R-PST	-13.7 (-27.3, -0.10)	-0.93	0.048	-15.6 (-29.2, -2.0)	-1.05	0.026	-17.0 (-31.1, -2.8)	-1.10	0.020	-16.8 (-31.0, -2.5)	-1.07	0.023
SCL-90-R-PSDI	-0.32 (-0.74, 0.10)	-0.70	0.13	-0.41 (-0.83, -0.01)	-0.90	0.054	-0.28 (-0.73, 0.16)	-0.59	0.20	-0.44 (-0.90, 0.01)	-0.89	0.055
SCL-90-R-GS	-37.7 (-73.5, -2.0)	-0.97	0.040	-42.4 (-78.2, -6.7)	-1.09	0.022	-41.4 (-78.6, -4.3)	-1.02	0.030	-48.6 (-86.4, -10.8)	-1.18	0.014

*values are score changes from baseline shown as differences between LSD and placebo reported as least square mean (95% confidence interval) in 20 patients (10 LSD, 10 placebo). *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 Inventory); 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; w 2 session = 10 weeks; w 8 = 16 weeks; w 16 = 24 weeks.

Table S5. Outcomes from the crossover analysis in patients with a life-threatening illness*

	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‡	-7.0 (-16.1, 2.0)	-0.39	0.13	-14.9 (-24.0, -5.9)	-0.82	0.0015	-6.6 (-15.6, 2.5)	-0.36	0.15	-12.3 (-21.4, -3.3)	-0.68	0.0080
STAI-S	-3.4 (-8.7, 1.9)	-0.31	0.20	-8.5 (-13.8, -3.3)	-0.78	0.0018	-3.5 (-9.1, 1.7)	-0.33	0.18	-2.5 (-10.3, 0.5)	-0.44	0.075
STAI-T‡	-3.0 (-7.6, 1.6)	-0.32	0.20	-6.1 (-10.7, 1.4)	-0.65	0.011	-2.7 (-7.3, 1.9)	-0.29	0.25	-6.7 (-11.3, -2.0)	-0.71	0.0053
Depression Scales												
HAM-D-21	-2.3 (-5.5, 0.8)	-0.36	0.14	-4.2 (-7.4, -1.1)	-0.65	0.0084	-1.9 (-5.1, 1.2)	-0.30	0.23	-4.9 (-8.0, -1.7)	-0.75	0.0026
BDI	-0.5 (-3.9, 2.9)	-0.07	0.77	-1.9 (-5.4, 1.5)	-0.27	0.27	-0.1 (-3.6, 3.4)	-0.02	0.94	-2.2 (-5.7, 1.3)	-0.30	0.21
General Psychiatric Sympomatology												
SCL-90-R-GSI	-0.18 (-0.40, 0.04)	-0.38	0.12	-0.20 (-0.43, 0.02)	-0.44	0.072	-0.15 (-0.38, 0.08)	-0.31	0.20	-0.18 (-0.41, 0.06)	-0.37	0.13
SCL-90-R-PST	-6.2 (-14.4, 1.9)	-0.37	0.13	-5.0 (-13.1, 3.2)	-0.29	0.23	-6.9 (-15.3, 1.4)	-0.40	0.10	-7.6 (-16.0, 0.7)	-0.44	0.073
SCL-90-R-PSDI	-0.06 (-0.30, 0.17)	-0.13	0.61	-0.25 (-0.49, -0.01)	-0.51	0.038	-0.09 (-0.33, 0.15)	-0.18	0.45	-0.24 (-0.49, 0.00)	-0.49	0.048
SCL-90-R-GS	-16.8 (-37.1, 3.6)	-0.40	0.11	-19.2 (-39.6, 1.1)	-0.45	0.064	-14.2 (-35.1, 6.7)	-0.33	0.18	-21.0 (-41.9, -0.1)	-0.48	0.049

*values are score changes from baseline shown as differences between LSD and placebo reported as least square mean (95% confidence interval) in 17 patients. ‡Only for 16 patients due to missing values; *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 Inventory); 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.

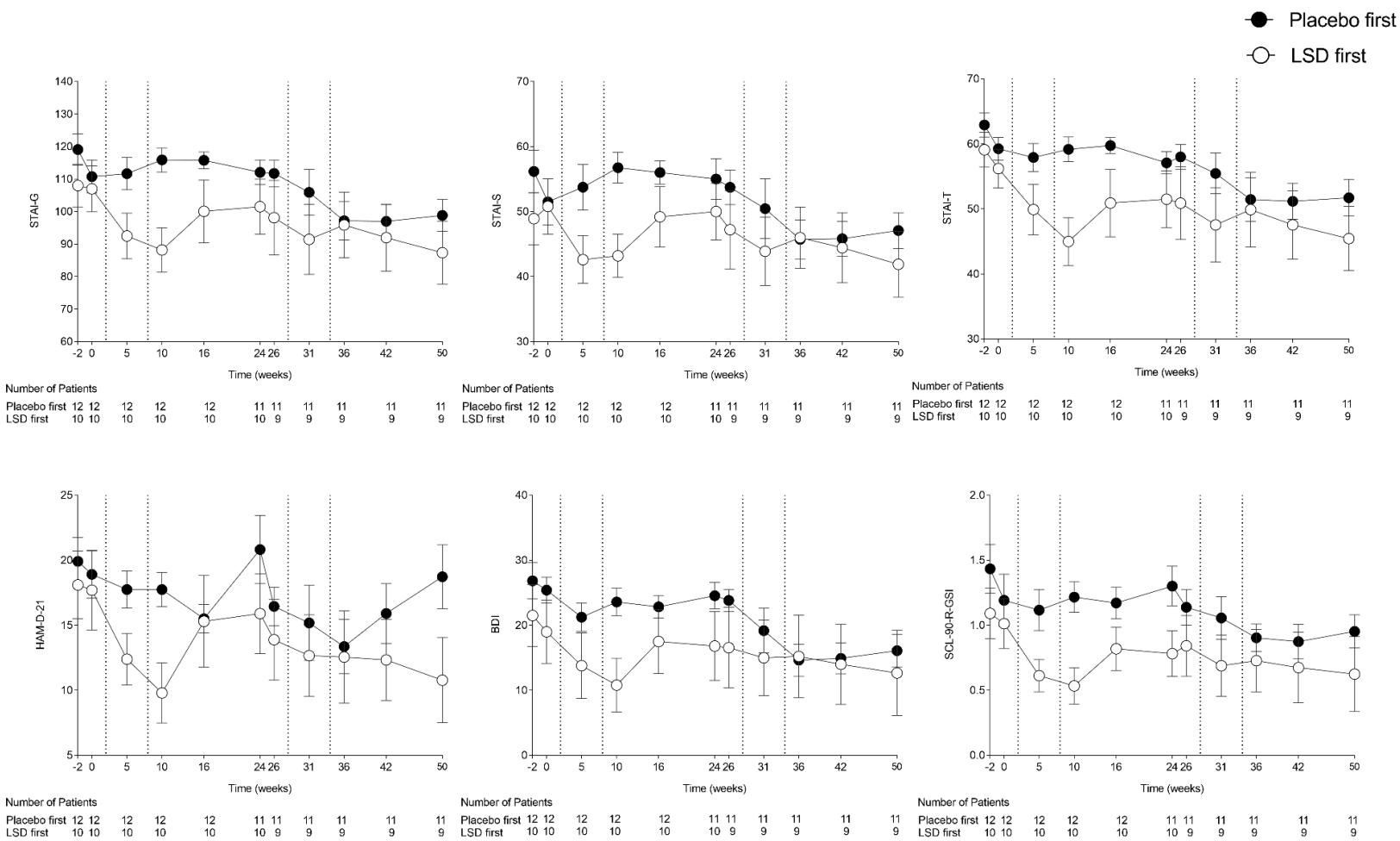

Figure S6. Outcome progress over entire study duration in patients without a life-threatening illness. Effects of LSD and placebo on study outcome measures over time and during both treatment periods are shown. The total number of patients who are shown in the graph was 22 at the start (week -2) and declined to 20 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, week 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. Values are absolute scores expressed as means and standard errors.

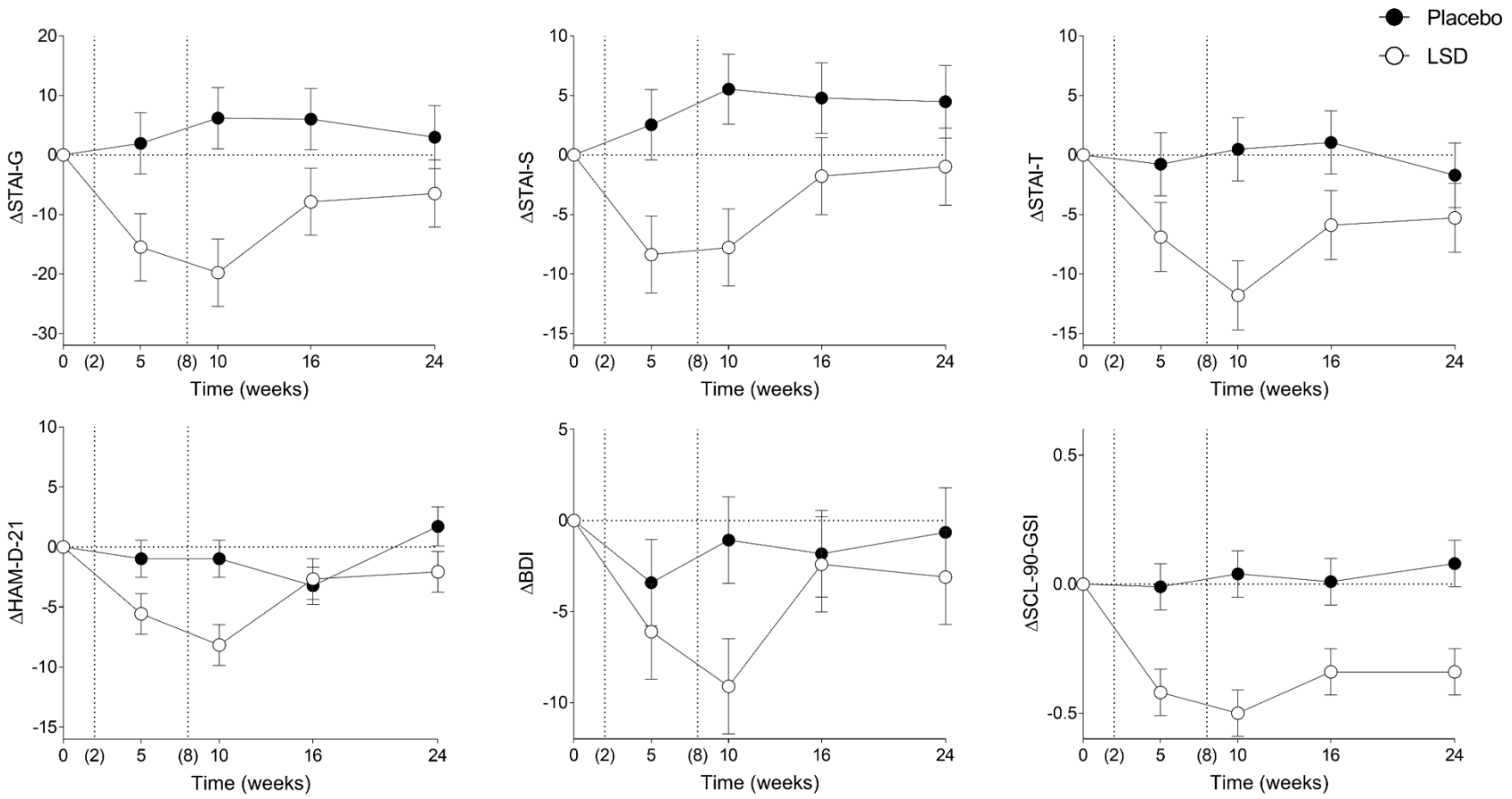

Figure S7. Outcomes from the between-subjects analysis in the first treatment period in patients without a life-threatening illness. LSD produced reductions of all outcome measures compared between-subjects with placebo and during the first treatment period. Treatment sessions with either LSD (two sessions) or placebo (two sessions) occurred at weeks 2 and 8. Outcome measures were assessed between sessions (btw visit, week 5) and 2 weeks (week 10), 8 weeks (week 16), and 16 weeks (week 24) after the second treatment session (w2, w8, and w16 visits, respectively). Values are score changes from baseline expressed as least square means and standard errors in 22 patients (10 LSD, 12 placebo).

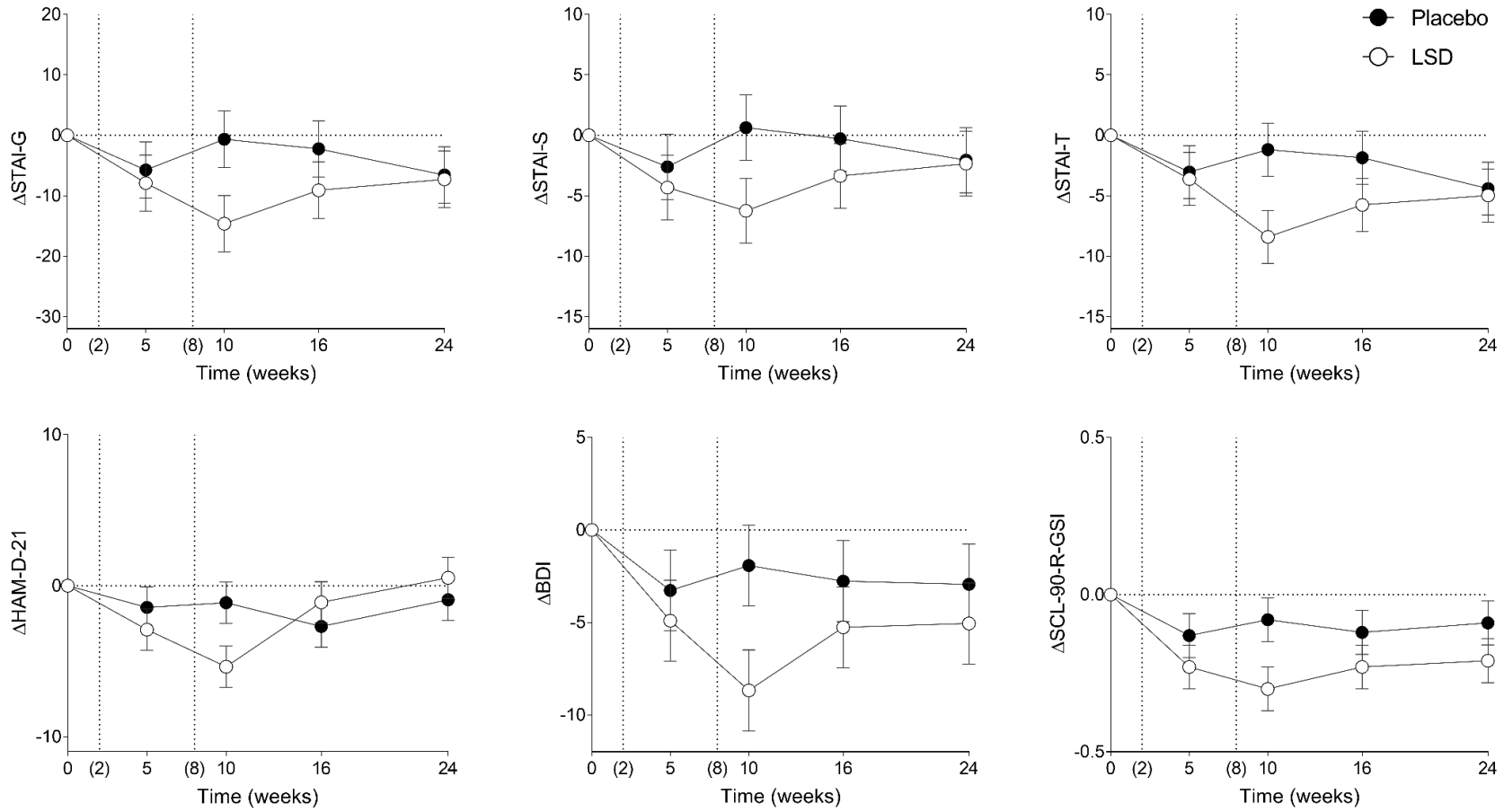

Figure S8. Outcomes from the within-subjects analysis in both periods in patients without a life-threatening illness. Effects of LSD and placebo on study outcome measures compared within-subjects are shown. Data are changes from baseline expressed as least square means and standard errors and across both periods in the same 20 patients (n = 20 per group). Treatment sessions with LSD (two sessions) and placebo (two sessions) occurred at weeks 2 and 8 during both periods. Outcome measures were assessed between sessions (btw visit, week 5) and 2 weeks (week 10), 8 weeks (week 16), and 16 weeks (week 24) after the second treatment session (w2, w8, and w16 visits, respectively).

Table S6. Outcomes from the parallel analysis in patients without life-threatening illness*

	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	-17.4 (-33.0, -1.9)	-0.97	0.029	-26.0 (-41.5, -10.4)	-1.45	0.0018	-13.9 (-29.5, 1.7)	-0.78	0.078	-9.5 (-25.2, 6.3)	-0.52	0.23
STAI-S	-10.9 (-19.7, -2.1)	-1.07	0.017	-13.3 (-22.1, -4.5)	-1.30	0.0039	-6.6 (-15.4, 2.3)	-0.64	0.14	-5.5 (-14.4, 3.5)	-0.52	0.23
STAI-T	-6.1 (-14.2, 2.0)	-0.66	0.13	-12.3 (-20.4, -4.2)	-1.32	0.0042	-7.0 (-15.1, 1.2)	-0.75	0.10	-3.6(-11.8, 4.6)	-0.38	0.38
Depression Scales												
HAM-D-21	-4.6 (-9.2, 0.0)	-0.85	0.051	-7.2 (-11.8, -2.6)	-1.34	0.0027	0.6 (-4.1, 5.2)	0.10	0.81	-3.8 (-8.5, 0.9)	-0.69	0.11
BDI	-2.7 (-10.0, 4.6)	-0.32	0.46	-8.0 (-15.3, -0.8)	-0.96	0.031	-0.6 (-7.8, 6.7)	-0.07	0.87	-2.5 (-9.8, 4.9)	-0.29	0.50
General Psychiatric Symptomatology												
SCL-90-R-GSI	-0.42 (-0.77, -0.08)	-1.07	0.012	-0.60 (-0.95, -0.26)	-1.52	0.0012	-0.27 (-0.62, 0.07)	-0.69	0.12	-0.40 (-0.75, -0.05)	-1.00	0.025
SCL-90-R-PST	-20.9 (-36.3, -5.6)	-1.20	0.0097	-26.4 (-41.8, -11.0)	-1.52	0.0016	-16.3 (-31.6, -0.9)	-0.94	0.039	-16.2 (-31.6, -0.8)	-0.93	0.041
SCL-90-R-PSDI	-0.27 (-0.58, 0.04)	-0.75	0.085	-0.48 (-0.78, -0.17)	-1.31	0.0032	-0.15 (-0.46, 0.16)	-0.40	0.35	-0.34 (-0.65, -0.02)	-0.91	0.037
SCL-90-R-GS	-38.2 (-69.2, -7.2)	-1.07	0.017	-54.1 (-85.2, -23.1)	-1.52	0.0012	-24.6 (-55.7, 6.5)	-0.69	0.12	-36.5 (-67.9, -5.1)	-1.01	0.024

*values are score changes from baseline shown as differences between LSD and placebo reported as least square mean (95% confidence interval) in 22 patients (10 LSD, 12 placebo). *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 Inventory); 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.

Table S7. Outcomes from the crossover analysis in patients without life-threatening illness*

	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	-2.2 (-11.1, 7.0)	-0.11	0.63	-13.9 (-22.9, -5.0)	-0.69	0.0026	-6.8 (-15.8, 2.1)	-0.34	0.13	-0.7 (-9.7, 8.3)	-0.04	0.86
STAI-S	-1.7 (-7.2, 3.7)	-0.14	0.53	-6.7 (-12.3, -1.4)	-0.56	0.014	-3.1 (-8.5, 2.4)	-0.25	0.26	-0.3 (-5.7, 5.2)	-0.02	0.92
STAI-T	-0.6 (-5.0, 3.8)	-0.06	0.80	-7.2 (-11.6, -2.8)	-0.72	0.0016	-3.9 (-8.3, 0.5)	-0.39	0.083	-0.6 (-5.0, 3.9)	-0.06	0.80
Depression Scales												
HAM-D-21	-1.5 (-4.8, 1.9)	-0.20	0.38	-4.2 (-7.6, -0.9)	-0.57	0.013	1.6 (-1.7, 4.9)	0.21	0.34	1.5 (-1.9, 4.8)	0.20	0.38
BDI	-1.6 (-5.9, 2.6)	-0.17	0.45	-6.8 (-11.0, -2.5)	-0.70	0.0022	-2.5 (-6.8, 1.8)	-0.26	0.25	-2.1 (-6.4, 2.1)	-0.22	0.33
General Psychiatric Sympomatology												
SCL-90-R-GSI	-0.09 (-0.28, 0.10)	-0.20	0.36	-0.27 (-0.46, -0.08)	-0.62	0.0064	-0.11 (-0.30, 0.08)	-0.25	0.26	-0.10 (-0.30, 0.09)	-0.24	0.28
SCL-90-R-PST	-3.7 (-9.34, 2.0)	-0.29	0.20	-6.7 (-12.4, -1.0)	-0.52	0.023	-1.4 (-7.0, 4.3)	-0.11	0.63	1.7 (-3.9, 7.3)	0.13	0.55
SCL-90-R-PSDI	-0.10 (-0.30, 0.10)	-0.22	0.32	-0.24 (-0.45, -0.04)	-0.52	0.022	-0.11 (-0.32, 0.09)	-0.25	0.27	-0.18 (-0.39, 0.02)	-0.40	0.077
SCL-90-R-GS	-8.1 (-25.3, 9.2)	-0.21	0.36	-23.1 (-40.6, -5.6)	-0.59	0.010	-9.7 (-26.9, 7.6)	-0.25	0.27	-9.6 (-26.8, 7.7)	-0.25	0.28

*values are score changes from baseline shown as differences between LSD and placebo reported as least square mean (95% confidence interval) in 20 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 Inventory); 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; w 2 session = 10 weeks; w 8 = 16 weeks; w 16 = 24 weeks.

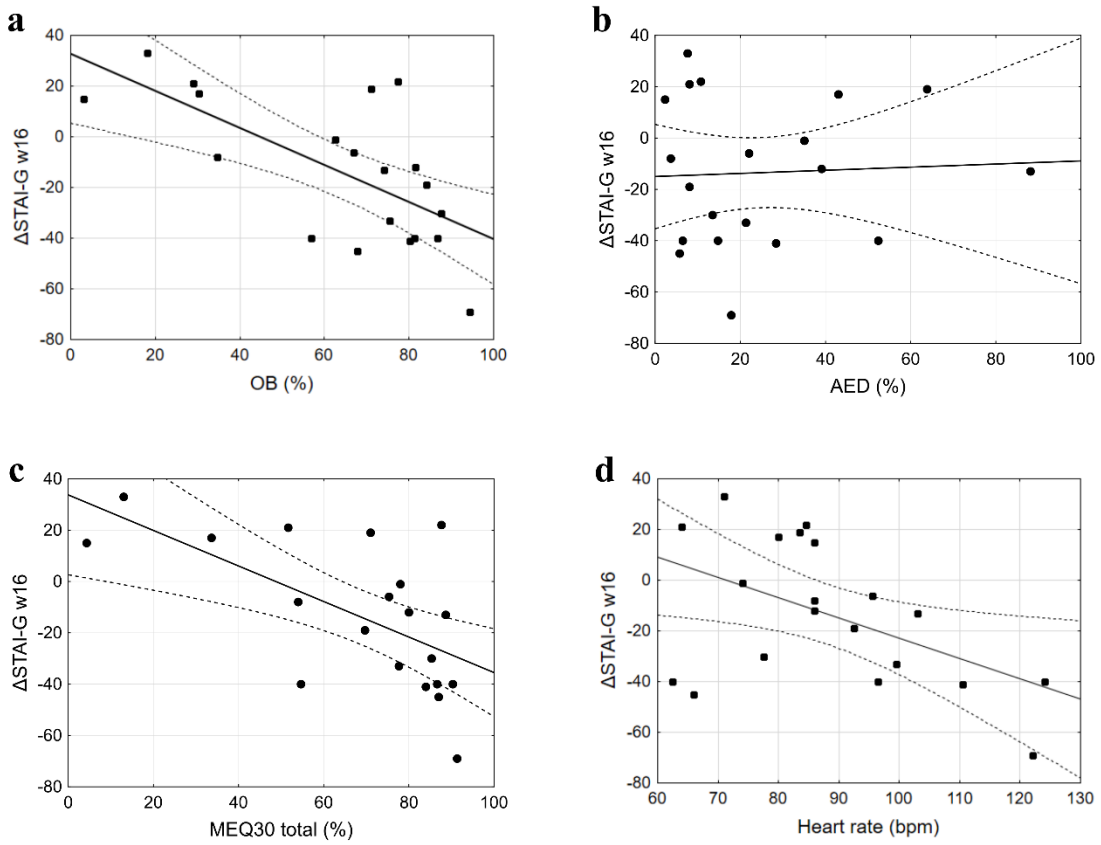

Figure S9. Correlations between acute drug effects and therapeutic outcomes in first treatment period. Acute positive but not negative changes in state of consciousness and mystical-type experiences induced by LSD correlated with therapeutic outcomes at w16 in the first treatment period. **a** Correlation between STAI-G and Oceanic Boundlessness (OB) on the 5D-ASC (r = -0.67, p = 0.001). **b** Correlation between STAI-G and Anxious Ego Dissolution (AED) on the 5D-ASC (r = 0.049, p = 0.83). **c** Correlation between STAI-G and Mystical Effects Questionnaire, 30 item version (MEQ30), total score (r = -0.62, p = 0.003). **d** Correlation between STAI-G and hear rate (Emax) (r = -0.49, p = 0.026). Data are expressed as score change from baseline on the STAI-G and percentage of total score on OB, AED, and MEQ30 total score (average of both LSD sessions) in 20 patients. The lines indicate regression and 95% confidence intervals

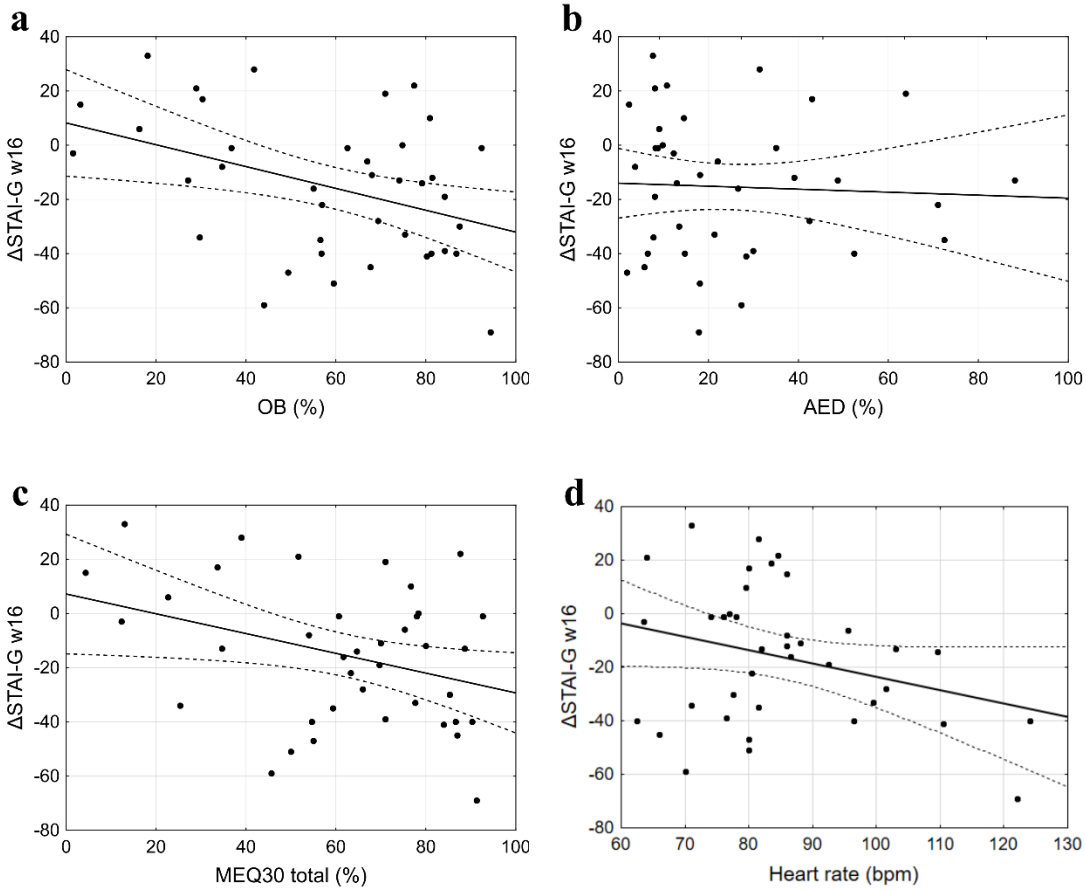

Figure S10. Correlations between acute drug effects and therapeutic outcomes over both treatment periods. Acute positive (Oceanic Boundlessness [OB]) but not negative (Anxious Ego Dissolution [AED]) changes in state of consciousness and mystical-type experiences (MEQ) induced by LSD correlated with therapeutic outcomes at w16 over both periods. **a** Correlation between STAI-G and OB on the 5D-ASC scale (r = -0.40, p = 0.01). **b** Correlation between STAI-G and AED on the 5D-ASC scale (r = 0.05, p > 0.05). **c** Correlation between STAI-G and Mystical Effects Questionnaire, 30 item version (MEQ30), total score (r = -0.34, p = 0.03). **d** Correlation between STAI-G and hear rate (Emax) (r = -0.29, p = 0.077). Data are expressed as score change from baseline on the STAI-G and percentage of total score on OB, AED, and MEQ30 total score (average of both LSD sessions) in 37 patients. The lines indicate regression and 95% confidence intervals.

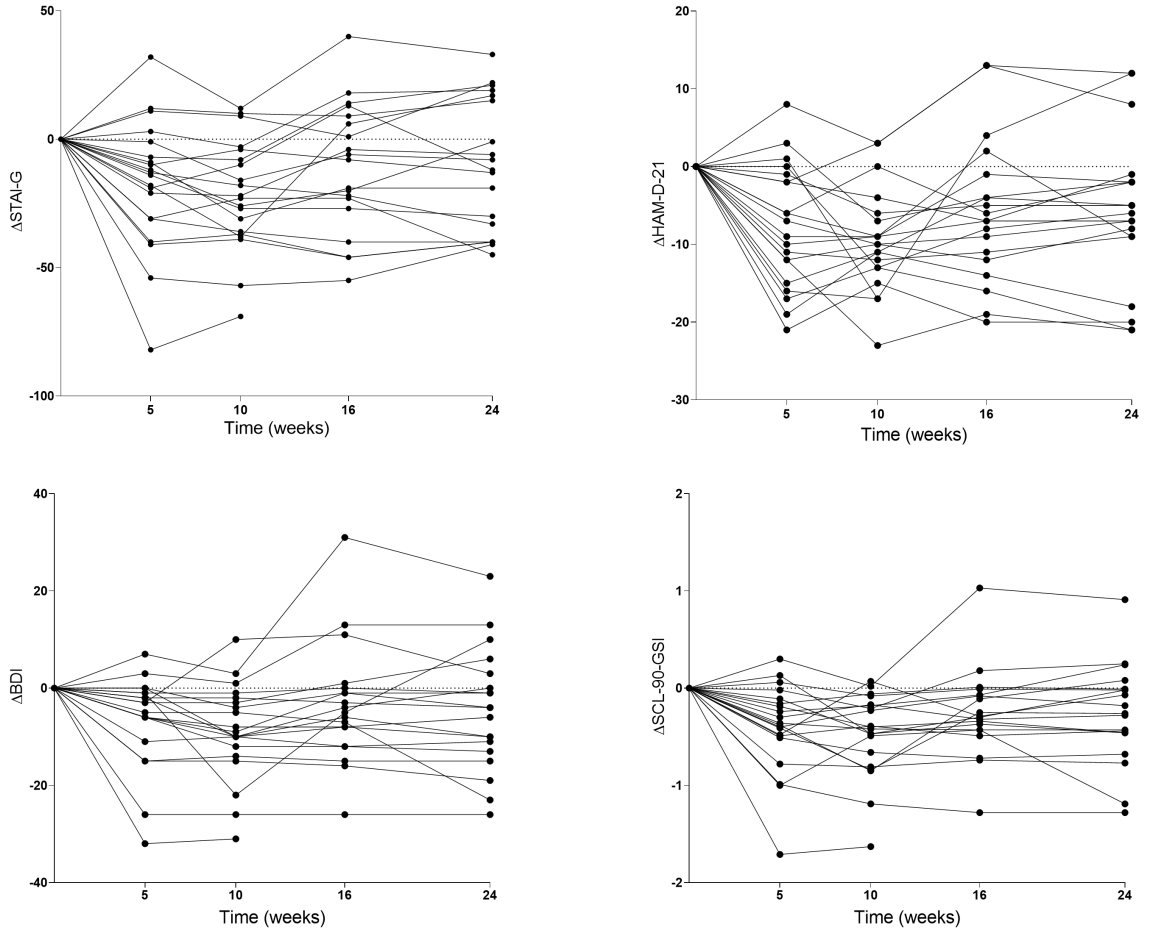

Figure S11. Individual curves. Individual curves for individual outcome ratings from all patients who were included in the between-subjects analysis in the LSD group in the first treatment period. Data are expressed as changes from baseline and for each subject. LSD was administered at weeks 2 and 8.

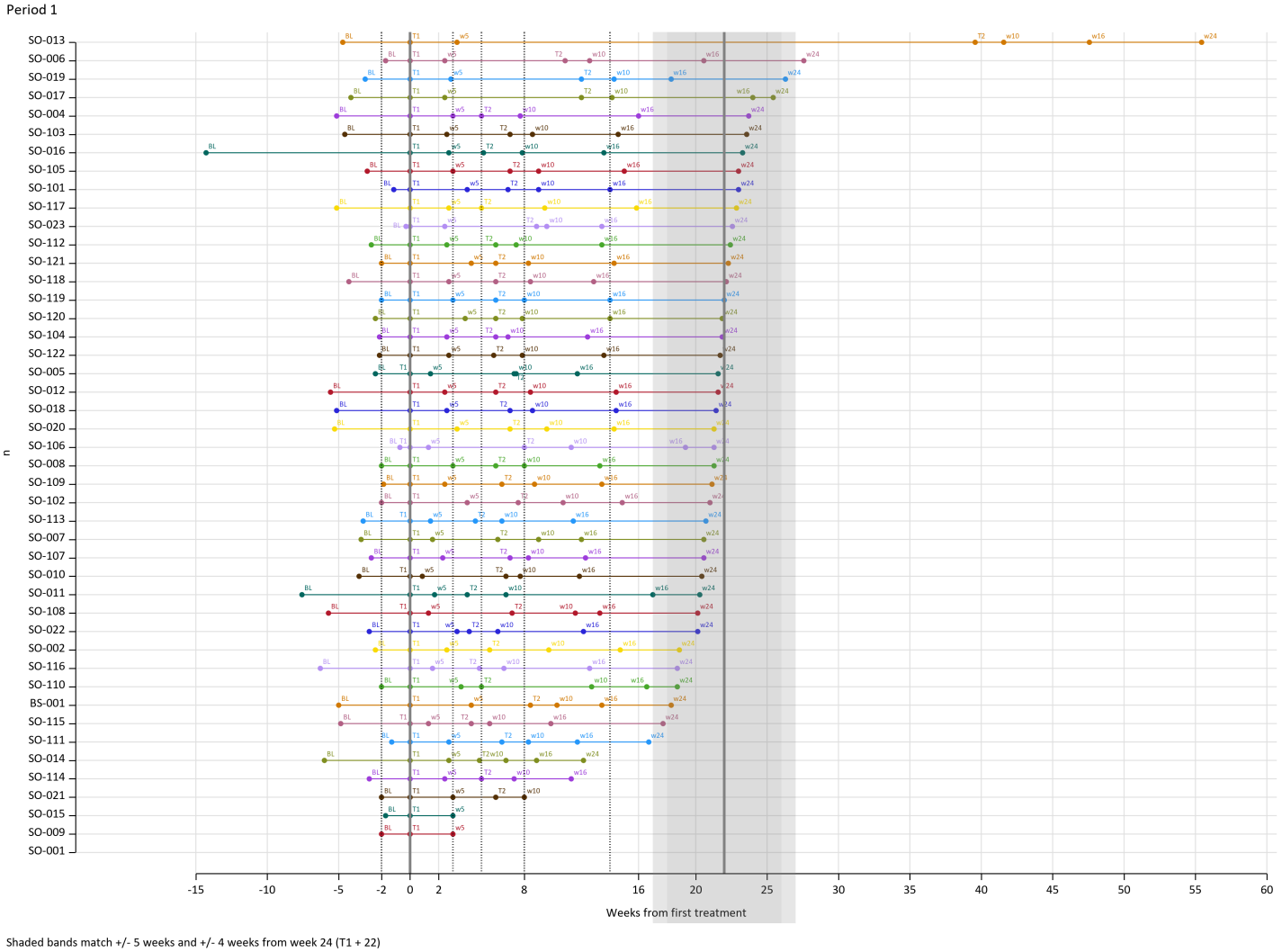

Figure S12. Time course. Time courses of sessions and visits for each individual patient, indicating durations between visits normalized to the first treatment session in the first treatment period (period 1). The second treatment session for patient SO-013 was delayed because of COVID-19 pandemic and the resulting lock-down.

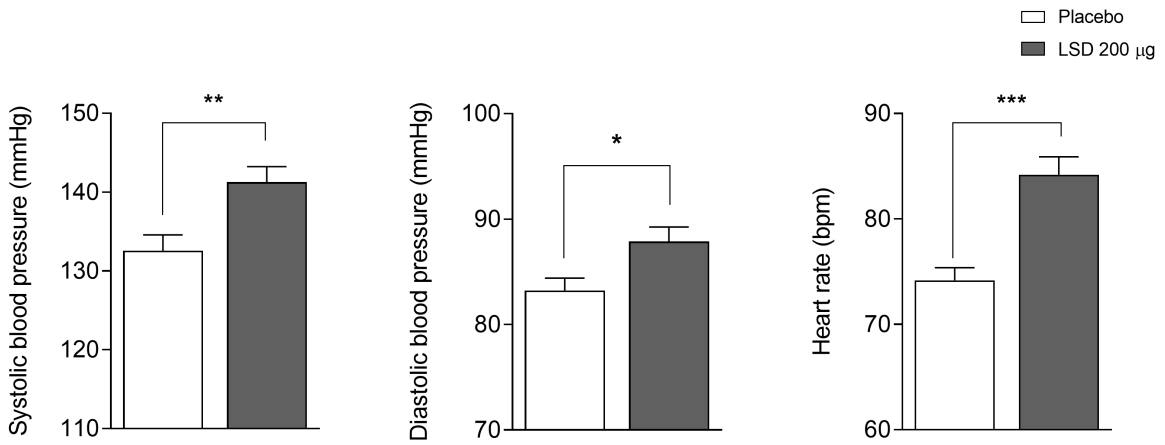

Figure S13. Autonomic effects. Effects of LSD on blood pressure and heart rate are presented as maximal values (E_{max}) of heart rate and blood pressure induced by LSD and compared with placebo. Data are expressed as the mean ± SEM in 42 patients and include both treatment periods with a total of 80 and 81 LSD and placebo sessions, respectively. Proportions of systolic blood pressure > 140 mmHg were significantly higher in LSD sessions ($n = 42$) compared with placebo ($n = 27$; $p = 0.020$). Similarly, for heart rate, where values > 80 bpm were reached in 38 cases for LSD compared with 20 cases for placebo ($p = 0.002$), and heart rate values > 100 bpm were reached in 10 cases for LSD compared with 1 case for placebo ($p = 0.004$). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Table S8. Adverse Events

		Period 1						Period 2					
		LSD Group			Placebo Group			LSD Group			Placebo Group		
	Total (n)	Total	Between	w 2	Total	Between	w 2	Total	Between	w 2	Total	Between	w 2
Reported Adverse Events during whole study duration													
Psychiatric													
Insomnia	7	1	0	0	2	0	0	2	0	0	2	1	0
Depression	3	2	0	0	0	0	0	0	0	0	1	0	0
Anxiety attack	2	1	0	0	0	0	0	1	0	0	0	0	0
Compulsive thoughts	1	1	0	0	0	0	0	0	0	0	0	0	0
Confusion	1	0	0	0	1	1	0	0	0	0	0	0	0
Restlessness	1	1	0	0	0	0	0	0	0	0	0	0	0
Psychosomatic complaints	1	0	0	0	1	1	0	0	0	0	0	0	0
Depression, suicidal thoughts	1	0	0	0	0	0	0	1	0	0	0	0	0
Nightmares	1	0	0	0	0	0	0	1	0	0	0	0	0
Due to underlying life-threatening illness													
Tumorrelapse	1	0	0	0	1	1	0	0	0	0	0	0	0
Rejection reaction	1	0	0	0	0	0	0	0	0	0	1	0	0
Tumorprogression	1	0	0	0	1	0	1	0	0	0	0	0	0
Polyneuropathy	1	0	0	0	1	0	0	0	0	0	0	0	0
Hemoglobin decrase	1	0	0	0	0	0	0	1	1	0	0	0	0
Alopecia	1	0	0	0	1	0	0	0	0	0	0	0	0
Gynecomastia	1	0	0	0	0	0	0	1	0	0	0	0	0
Hand-foot syndrome	1	1	0	0	0	0	0	0	0	0	0	0	0
Other													
Fatigue	45	9	2	2	13	6	2	14	4	1	9	2	1
Headache	40	6	4	0	21	9	2	9	1	2	4	1	1
Difficulty to concentrate	23	2	0	0	7	2	1	9	2	2	5	2	0
Nausea	19	1	1	0	7	3	2	7	2	1	5	1	0
Dizziness	18	4	1	0	7	3	2	5	2	0	2	1	0
Common cold	15	3	0	0	4	2	0	5	2	0	3	1	1
Diarrhea	5	0	0	0	1	0	1	2	0	1	2	0	0
Cough	4	1	0	0	0	0	0	2	0	0	1	0	0
Abdominal cramps	2	2	0	0	0	0	0	0	0	0	0	0	0
Abdominal pain	2	0	0	0	1	0	0	1	0	1	0	0	0
Lumbalgia	2	0	0	0	2	0	1	0	0	0	0	0	0
Mastitis	2	0	0	0	0	0	0	2	0	0	0	0	0
Weight gain	2	0	0	0	1	0	0	0	0	0	1	1	0
Viral eye infection	1	0	0	0	1	0	0	0	0	0	0	0	0
Bronchitis	1	0	0	0	0	0	0	0	0	0	1	0	0
Sigmoiditis	1	1	0	0	0	0	0	0	0	0	0	0	0
Insect bite	1	0	0	0	0	0	0	0	0	0	1	0	0
Torticollis	1	0	0	0	0	0	0	0	0	0	1	0	0
Eczema	1	1	1	0	0	0	0	0	0	0	0	0	0
Vaginalmycosis	1	0	0	0	1	0	0	0	0	0	0	0	0
Urinary infection	1	0	0	0	0	0	0	0	0	0	1	0	1
Toothache	1	0	0	0	1	0	0	0	0	0	0	0	0
Dizziness after deduction of escitalopram	1	0	0	0	0	0	0	1	0	0	0	0	0
Groin and testicle pain	1	1	0	0	0	0	0	0	0	0	0	0	0
Shingles	1	0	0	0	0	0	0	0	0	0	1	0	0
Ischialgia	1	0	0	0	1	1	0	0	0	0	0	0	0
Whiteness tooth dissection	1	0	0	0	0	0	0	0	0	0	1	0	1
Fall	1	0	0	0	0	0	0	1	0	0	0	0	0
Hypercholesterinemia	1	0	0	0	0	0	0	0	0	0	1	0	0
Dog bite	1	1	0	0	0	0	0	0	0	0	0	0	0
Norovirus	1	0	0	0	0	0	0	0	0	0	1	0	0
Swollen hand	1	0	0	0	0	0	0	0	0	0	1	0	0
Asthma bronchiale	1	0	0	0	1	0	0	0	0	0	0	0	0
Vitamin B12 deficiency	1	0	0	0	0	0	0	1	0	0	0	0	0
Sore throat	1	0	0	0	0	0	0	1	0	0	0	0	0
Muscular complaints (thorax)	1	0	0	0	1	0	0	0	0	0	0	0	0
Loss of appetite	1	0	0	0	0	0	0	0	0	0	1	1	0

Between = visit between sessions (week 5); w 2= week2 (=week 10)

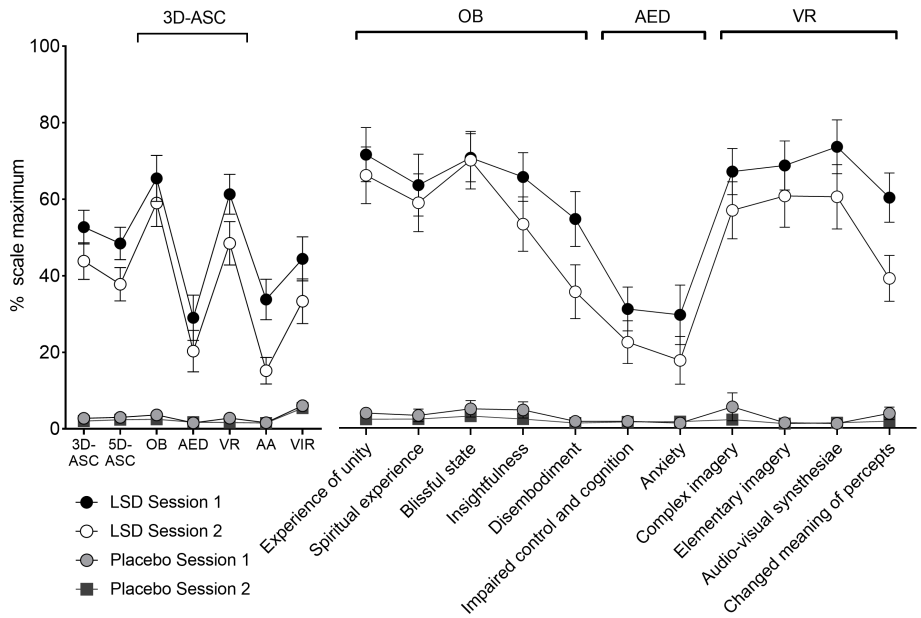

Figure S14. Acute alterations of mind on the 5 Dimensions of Altered States of Consciousness (5D-ASC) scale induced by LSD (n = 20) and placebo (n = 22) in the first treatment period. The data are expressed as the mean ± SEM percentage of maximally possible scale scores. OB, Oceanic Boundlessness; AED, Anxious Ego Dissolution; VR, Visionary Restructuralization; AA, Auditory Alterations; VIR, Vigilance Reduction. The 3D-ASC score includes the OB, AED, and VR scores. The 5D-ASC score includes all five sub-scores. LSD mainly induced a positive alteration of mind with high OB and relatively low AED scores.

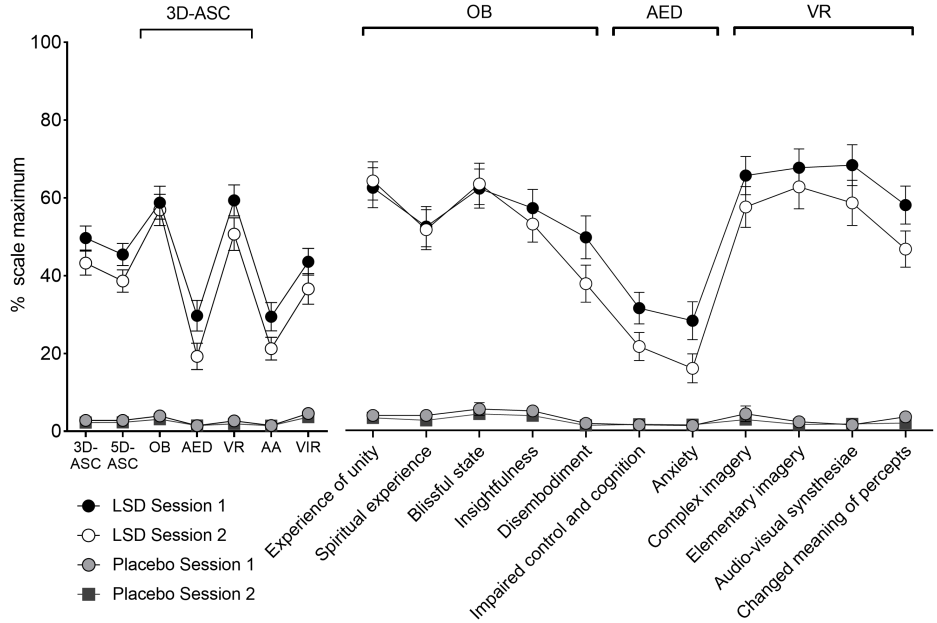

Figure S15. Acute alterations of mind on the 5 Dimensions of Altered States of Consciousness (5D-ASC) scale induced by LSD (n = 37) and placebo (n = 37) over both treatment periods. The data are expressed as the mean ± SEM percentage of maximally possible scale scores. OB, Oceanic Boundlessness; AED, Anxious Ego Dissolution; VR, Visionary Restructuralization; AA, Auditory Alterations; VIR, Vigilance Reduction. The 3D-ASC score includes the OB, AED, and VR scores. The 5D-ASC score includes all five sub-scores.

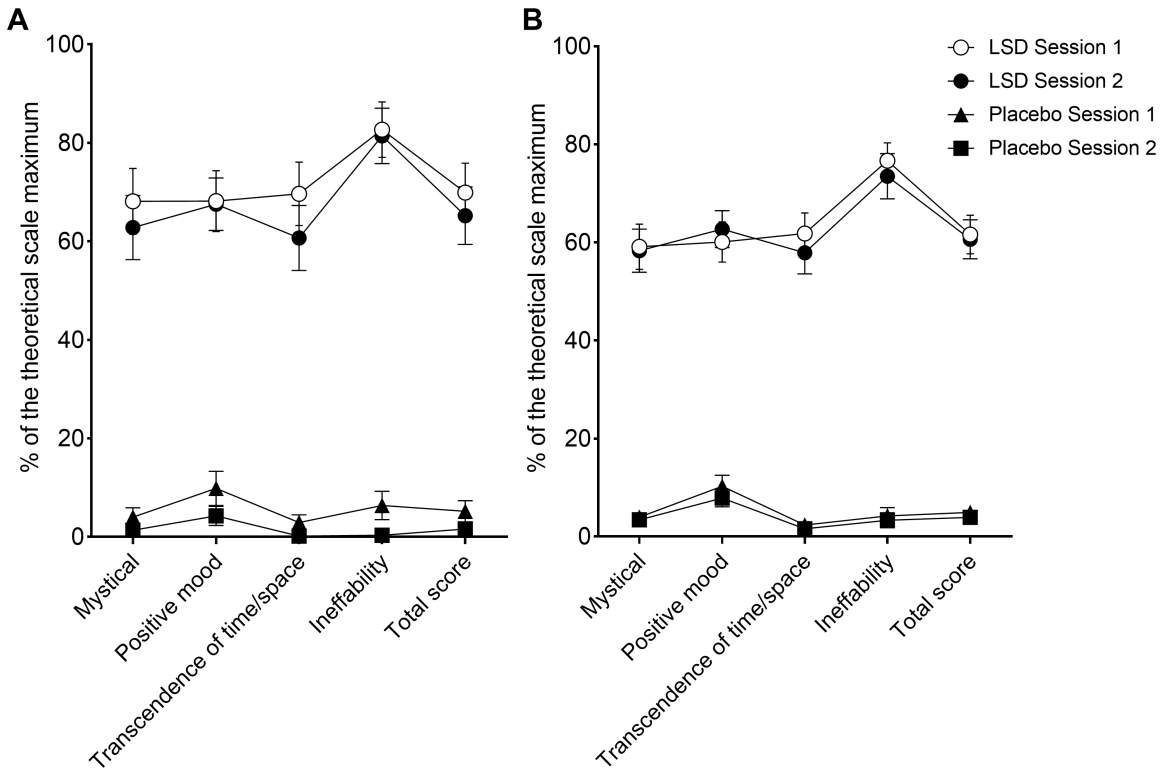

Figure S16. Acute mystical-type experiences on the Mystical Effects Questionnaire (MEQ30) induced by LSD (n = 20) and placebo (n = 22) **A** in the first treatment period (n = 20 LSD, n = 22 placebo) and **B** over both treatment periods (n = 37 LSD, n = 37 placebo). The data are expressed as the mean ± SEM percentage of maximally possible scale scores.

Table S9. Listing of all serious adverse events and their relationship to study treatment

Listing of serious adverse events			
Event	**Relation to study drug**	**Occurrence**	**Commentary**
Acute hospitalisation due to obsessive-compulsive disorder	Non-related	Period 2 (Placebo) Between treatment sessions	Worsening of preexisting condition approximately 6 months after last LSD treatment. No temporal relationship
Surgical correction of nasal septum deviation	Non-related	Period 2 (LSD) 11 weeks after last LSD treatment	Planned surgery
Unexpected pregnancy followed by sponaneous abortion	Non-related	Period 2 (LSD) Approx. 12 weeks after last LSD treatment	Spontaneous bleeding after pregnancy was noticed (approximately 6th week of pregnancy)
Unexpected pregnancy followed by sponaneous abortion	Non-related	Period 1 (LSD) Between treatment sessions	Patient was suffering from cervix-carcinoma
Acute transient anxiety and delusions	related	Period 1 (LSD) During Session	The patient was successfully treated with lorazepam and olanzapine. Consequently, the second LSD dose was reduced to 100 µg.
Suspected transient ischemic attack	Non-related	Period 2 (LSD) 2 weeks after last LSD treatment	Patient was suffering from Marfan syndrome and had experienced several similar attacks (>4) before.
Deceased due to cancer progression	Non-related	Period 1 (Placebo) 10 weeks after last treatment session	Metastasizing bronchus carcinoma, deceased before LSD treatment
Radiusfracture	Non-related	Period 2 (LSD) 16 weeks after last LSD treatment	Occurred during a private party 16 weeks after last LSD treatment
Acute hospitalisation due to disorientation	Non-related	Period 1 (Placebo) 6 weeks after last treatment session	Attributable to chemotherapy, occurred before LSD treatment.

Table S10. Response and remission rates

		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			Any time		
	total n (LSD/placebo)	n (%) LSD	n (%) placebo	*p*-value	n (%) LSD	n (%) placebo	*p*-value	n (%) LSD	n (%) placebo	*p*-value	n (%) LSD	n (%) placebo	*p*-value	n (%) LSD	n (%) placebo	*p*-value
Anxiety Response*																
STAI-G																
between-subject analysis (period 1)	42 (20/22)	7 (35)	0 (0)	0.0029	10 (50)	0 (0)	0.0001	7 (37)†	0 (0)†	0.0022	8 (42)††	2 (10)††	0.031	13 (65)	2 (9)	0.003
cross-over analysis (period 1 and 2)	36 (36/36)	10 (28)	5 (14)	0.25	16 (44)	2 (6)	0.0002	14 (39)	2 (6)	0.0013	15 (42)	7 (19)	0.072	22 (61)	11 (31)	0.017
Depression Remission‡																
HAM-D-21																
between-subject analysis (period 1)	36 (16/20)	8 (50)	1 (5)	0.0046	6 (38)	1 (5)	0.030	6 (40)**	1 (5)**	0.028	7 (47)***	0 (0)***	0.0015	9 (56)	2 (10)	0.0042
cross-over analysis (period 1 and 2)	31 (31/31)	9 (29)	7 (23)	0.77	9 (29)	8 (26)	1.0	9 (29)	9 (29)	1.0	9 (29)	8 (26)	1.0	15 (48)	10 (32)	0.30
BDI																
between-subject analysis (period 1)	38 (16/22)	8 (50)	2 (9)	0.0082	9 (56)	0 (0)	<0.0001	6 (40) ‡‡	1 (5) ‡‡	0.027	6 (40) ‡‡‡	1 (5) ‡‡‡	0.028	9 (56)	3 (14)	0.012
cross-over analysis (period 1 and 2)	32 (32/32)	10 (31)	11 (34)	1.0	12 (38)	8 (25)	0.42	11 (34)	8 (25)	0.59	12 (38)	9 (28)	0.60	15 (47)	11 (34)	0.45

*response was defined as STAI-G score reduction of ≥30%; ‡ Remission was defined as score <10 for the BDI and the HAM-D-21, only patients with a score of ≥10 at screening were included; † in 40 patients (19 LSD/ 21 placebo); †† in 39 patients (19 LSD / 20 placebo) ** in 34 patients (15 LSD / 19 placebo); *** in 33 patients (15 LSD/18 placebo); ‡‡ in 35 patients (15 LSD / 20 placebo); ‡‡‡ in 34 patients (15 LSD/19 placebo); STAI-G (Spielberger's State-Trait Anxiety Inventory Global Score); HAM-D-21 (Hamilton Depression Scale 21 item version); BDI (Beck Depression Inventory); btw visit = 5 weeks; w2 session = 10 weeks; w8 = 16 weeks; w16 = 24 weeks. Proportions of response/remission were compared using Fisher's exact test.

Table S11. CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-4
	2b	Specific objectives or hypotheses	3-4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	4-5 + Suppl.
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5-7, Fig. 1
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6-7 + Suppl.
	6b	Any changes to trial outcomes after the trial commenced, with reasons	7-8
Sample size	7a	How sample size was determined	7
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	Suppl.
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Suppl.

Allocation Concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5 + Suppl.
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Suppl.
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	4
	11b	If relevant, description of the similarity of interventions	5 + Suppl.
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	7-8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	7-8
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	8
	13b	For each group, losses and exclusions after randomisation, together with reasons	8. Fig. 2
Recruitment	14a	Dates defining the periods of recruitment and follow-up	8
	14b	Why the trial ended or was stopped	9
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	8-10, Table 2
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Supplement
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	10 + Suppl.
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13-14

Generalisability	21	Generalisability (external validity, applicability) of the trial findings	10-14
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13-14
Other information			
Registration	23	Registration number and name of trial registry	2, 4
Protocol	24	Where the full trial protocol can be accessed, if available	NA
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	14-15

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Section 4

Supplemental References

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