Clinical Study Protocol

LSD – unterstützte Psychotherapie
bei Personen mit Angstsymptomatik in Verbindung mit fortgeschrittenen lebensbedrohenden Erkrankungen. Eine doppelblinde, plazebokontrollierte Phase-II Dosis-Wirkungs-Pilotstudie

LSD – assisted psychotherapy
in persons suffering from anxiety associated with advanced-stage life threatening diseases. A phase-II, double-blind, placebo-controlled dose-response pilot study

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SPONSOR **MAPS**

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German Summary

Hintergrund

Nachdem LSD im Jahre 1943 durch den Schweizer Chemiker Albert Hofmann in Basel entdeckt wurde, erfolgte eine fast dreissig Jahre dauernde rege Forschungstätigkeit, die im psychiatrischen und psychotherapeutischen Kontext zum Ziel hatte, das therapeutische Potenzial dieser besonderen Substanz zu erforschen. Obschon es im therapeutischen und Forschungskontext zu keinen besonderen Komplikationen kam, wurde die Forschung mit LSD in den frühen 1970er Jahren de facto verboten, weil die Substanz als Folge des massiven Konsums in der Hippieszene praktisch weltweit als Betäubungsmittel ohne therapeutischen Nutzen deklariert wurde. In der Schweiz wird LSD als „verbotener Stoff, der weder verkehrs- noch verkaufsfähig ist“ auf der Betäubungsmittelliste aufgeführt. Diese Deklaration erfolgte aus gesundheitspolitischer Notwendigkeit und nicht auf Grunde wissenschaftlicher Erkenntnisse.
LSD ist eine gut erforschte psychoaktive Substanz, insbesondere sind die Daten ausreichend, um die pharmakologischen Parameter (Pharmakokinetik, -dynamik und Metabolismus) sowie die Wirkungsweise neurophysiologisch hinreichend zu beschreiben, obschon vieles noch ungeklärt ist. Die Toxikologie ist geklärt, Wirkungen und Nebenwirkungen psychisch und somatisch ausführlich an gesunden Probanden dargestellt. Die Frage der körperlichen und psychischen Abhängigkeit wird selbst von drogenkritischen Institutionen wie dem us-amerikanischen National Institute on Drug Abuse (NIDA) dahin gehend beantwortet, dass dieses Risiko als gering einzustufen ist (NIDA Info Facts, 2006). Wohlgemerkt sind diese Informationen für einen illegalen Rahmen geschrieben. Das Risiko in einem therapeutischen Kontext ist sicherlich als noch geringer einzustufen.
Die in diesem Protokoll beschriebene Studie hat zum Ziel, die seit langem unterbrochene Erforschung und Evaluation von LSD als unterstützendes Medikament im Rahmen einer Psychotherapie wieder aufzunehmen.
Menschen, die unter Krebs, schweren Autoimmunerkrankuungen, Infektionskrankheiten ohne kurative Möglichkeiten wie AIDS u.a.m. leiden, müssen sich mit Sterben und Tod in nächster Zukunft und in ihrem eigenen Leben auseinander setzen. Die Angst vor dem Tod an sich, die Angst vor Schmerzen und Leiden, unerledigte und nicht mehr erledigbare wichtige Angelegenheiten und Konflikte können einen erheblichen Stress und Zunahme von Aengsten bedeuten. LSD hat die Potenz – das wurde in früheren therapeutischen Studien wiederholt aufgezeigt (Grinspoon et al., 1986,1979; Grof, 1979,1980,1983,2000,2006; Leuner 1981, Kast, 1964, 1966, 1970; Kurland et al. 1969,1973,1985, Pahnke et al. 1969,1970) – Menschen einen vertieften Zugang zu sich und ihrer Geschichte aber auch zu ihrer Umwelt als soziale Umwelt und als Schöpfung zu ermöglichen. Vor allem letzter Aspekt, die Verbundenheit mit der Schöpfung als kognitiv-emotionelle und spirituelle Erfahrung kann erheblich zu einer Reduktion der Angst vor dem Sterben beitragen.

Ziel

Die vorliegende Studie hat zum Ziel in einem Pilotprojekt mit einer geringen Probandenzahl von 12 Probanden zu zeigen, dass LSD-unterstützte Psychotherapie sicher und wirksam ist. Als Indikator für die Wirksamkeit wurde Angstreduktion und Verbesserung der Lebensqualität bei Patienten mit todbringenden Krankheiten ausgewählt. Diese zwei Parameter, Angst und Lebensqualität, werden mit zwei standardisierten Selbstbewertungen in Form von Fragebogen gemessen. Zusätzliche Fragebogeninstrumente werden die Fragestellung einer Symptomreduktion und Verbesserung der Lebensqualität noch vertiefen.
Die Sicherheit der Methode wird gemessen an Art und Häufigkeit von leichten und schweren Nebenwirkungen wie vorübergehende Derealisation, Flashbacks, Schlafstörungen, Ängste, Suizidalität, Psychose und psychiatrische Hospitalisation. Die schweren und auch die leichten Nebenwirkungen werden protokolliert und ausgewertet.
Die Pilotstudie soll Hinweise geben können, ob es sich lohnt und ob es vertretbar ist, mit LSD-unterstützter Psychotherapie weiterzuforschen allenfalls auch in grösserem Rahmen mit grösseren Probandenzahlen.

Methode

Vorliegende Studie ist eine kontrollierte, randomisierte, doppelblinde Phase-II Untersuchung an 12 freiwilligen Probanden, die an Angstsymptomen leiden in Folge einer todbringenden Erkrankung.
Nach Indikationsstellung, Klärung von Ein- und Ausschlusskriterien, schriftlicher Patienteninformation durchlaufen die Probanden sechs (bei Bedarf auch mehr) Gesprächspsychotherapiesitzungen und zwei ganztägige, betreute LSD-Psychotherapiesitzungen. Die Verumgruppe erhält eine mittelhohe Dosis von 200 µg LSD, die Placebogruppe erhält 20 µg LSD. Die ca. 8-stündige Sitzung endet wenn der/die ProbandIn psychisch und somatisch in einem stabilen Zustand ist. Er/sie bleibt über Nacht in der Praxis, wo die Sitzung stattgefunden hat und wird kontinuierlich begleitet. Anderntags wird die Sitzung besprochen. Nach rund zwei Wochen folgt eine weitere experimentelle Sitzung nach dem gleichen Muster. Danach folgt eine Phase von rund zwei Monaten, in der weitere Gesprächspsychotherapiesitzungen stattfinden, die der weiteren Integration der LSD-Erfahrung dienen. Nach etwas mehr als drei Monaten erfolgt eine Abschlussuntersuchung. Die Gruppe der ProbandInnen, die Placebo erhielten, haben in einer zweiten Studienphase die Gelegenheit, die zwei LSD-Sitzungen (200 µg) nachzuholen, falls sie das wollen.
Dass die Placebogruppe nicht ein reines Placebo erhält, sondern ein aktives Placebo, von dem eine milde vegetative Wirkung, nicht aber die LSD-typischen psychischen Veränderungen zu erwarten sind hat folgenden Grund: Die Durchführung doppelblinder Untersuchungen ist der Goldstandard aller Medikamentenforschung. Bei psychoaktiven Substanzen ist aber die Gefahr der Entblindung recht gross, d.h. sowohl Proband wie auch Untersucher wissen, ob Placebo oder Verum zum Einsatz kommt. Mit der Entblindung

steigt die Gefahr von systematischen Fehlern (Bias). Ein aktives Placebo kann das Problem zwar nicht lösen, aber etwas verringern. Trotzdem ist das kontrollierte, randomisierte, doppelblinde Design für die vorliegende Studie das objektivste und geeignetste und wurde trotz des Risikos einer Entblindung beibehalten.

Erwarteter Nutzen des vorliegenden Projektes

Es ist kaum zu erwarten, dass bei einer so kleinen Untersuchung mit nur 12 Probanden (8 Probanden erhalten das Verumpräparat, 4 Probanden ein Placebo) statistisch signifikante Unterschiede entstehen. Das könnte nur geschehen, wenn die Gruppenunterschiede riesig wären. Vielmehr wird die statistische Auswertung Hinweise und Tendenzen aufzeigen können, die zeigen in welche Richtung zukünftige Forschung gehen könnte.
Der Nutzen der Studie dürfte darin liegen, dass nach so langer Zeit unseres Wissens weltweit erstmalig wieder eine psychotherapeutische Studie mit LSD durchgeführt wird. Obschon mit einer Pilotstudie eine kleine Untersuchung durchgeführt wird, genügt sie modernen Forschungsstandards (Good Clinical Practice). Sie wird wichtige Hinweise über Sicherheit und Wirksamkeit LSD-unterstützter Psychotherapie geben und bei positiven Resultaten eine neue Phase wissenschaftlich begleiteten Einsatzes von LSD begründen mit dem Ziel, die Frage beantworten zu können, wo denn der Nutzen von LSD zu suchen ist.

Ethics

The trial will not be initiated until appropriate EC approval of the protocol and the informed consent document. In addition, all documents will be submitted to other authorities in compliance with local jurisdictions. The EC and, if applicable, other authorities must be informed of protocol amendments in accordance with local legal requirements.

This trial will be conducted in accordance with the most recently acceptable version of the Declaration of Helsinki, Good Clinical Practice (GCP) according to International Conference on Harmonisation (ICH) guidelines, and applicable standard operating procedures (SOPs). The trial will be conducted under a protocol reviewed and approved by an EC; the trial will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; the physicians conducting the trial do not find the hazards to outweigh the potential benefits; each subject, or where applicable, each subject's legally acceptable representative(s) will give his or her written informed consent before any protocol-driven tests or evaluations are performed.

Informed Consent of Subject

The investigator is responsible to obtain informed consent in adherence to GCP and according to applicable regulations prior to entering the subject into the trial.
The information about the trial must be given orally and in an understandable form. Written information about the trial will also be provided. In addition to the explanation of the trial and of subject’s legal rights the information should comprise that access to original medical records and processing of coded personal information must be authorized. The informed consent discussion must be conducted by a person who is qualified according to applicable local regulations. The subject should have the opportunity to inquire about details of the trial and to consider participation.
The informed consent form (ICF) must be signed and dated by the subject and must be countersigned by the person who conducted the informed consent discussion (according to local laws and GCP).
If a subject is unable to read or write, oral consent in the presence of an impartial witness is possible, if this is permitted by local legislation. In this case, the witness is to be present during the meeting in which the significance of the informed consent will be orally explained. After the informed consent discussion and after the subject has orally consented to participate in the clinical trial the witness should sign and personally date the consent form to attest that information concerning the clinical trial and the subject’s rights was accurately explained to, and apparently understood by the subject and that informed consent was given freely.
The investigator will provide a copy of the signed informed consent to the subject, and will maintain the original in the investigator’s study file.

The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive EC's approval before use.
The subject should be informed in a timely manner if new information becomes available that may affect the decision to participate in the clinical trial. The communication of this information should be documented.

Subject names will not be supplied to the sponsor. Only the subject numbers and subject identification codes will be recorded in the case report form (CRF), and if a subject's name appears on any other document (e.g., pathologist report), it will be obliterated before the copy of the document is supplied to the sponsor.

Premature Discontinuation of the Study

The sponsor, or the investigator (following consultation with the sponsor) has the right to discontinue this study at any time. If the clinical study is prematurely terminated, the investigator is to promptly inform the study subjects and should assure appropriate therapy and follow-up for the subjects. If the study is prematurely discontinued, all procedures and requirements pertaining to the archiving of the documents will be observed. All other study materials (completed, partially completed and blank CRFs, study medication/vaccines etc.) will be returned to the sponsor.

Introductory Statement

This protocol is for a randomized, active placebo controlled double-blind dose-response, phase-II pilot study of Lysergic Acid Diethylamide-25 (LSD) - assisted psychotherapy in twelve subjects with anxiety related to advanced-stage illness (e.g. cancer, metabolic or autoimmune diseases). Subjects will have a shortened estimated life expectancy due to disease severity, and will either not have adequately responded to anxiolytic treatments, such as medication or psychotherapy, or who will have refused to take anxiolytic medications.

LSD is a semi-synthetic compound that was developed from ergot alkaloids. LSD was first synthesized in 1938 by the Swiss chemist Albert Hofmann at Sandoz pharmaceutical laboratories in Basel, Switzerland. Hofmann was investigating the therapeutic potential of ergot, a fungus that parasites cereal grains (Hofmann 1979), and was mainly searching for vasoactive compounds. LSD's highly specific actions on the brain and human consciousness were discovered by chance by Hofmann in 1943 (Hofmann 1979). Psychiatrists soon saw that there could be a therapeutic potential for this substance. The first therapeutic study was conducted at the Swiss Psychiatric University Hospital in Zurich (Burghoelzli) in 1946 (Stoll 1947; Stoll et al. 1949). At that time, the substance

was administered like any other medication and the concept that there must be guidance and constant care of the patient throughout the duration of drug action (i.e. 10 hours, sometimes up to 12 hours) only developed approximately 10 years later when Stanislav Grof (Grof 1983) first in Prague (Czech Republic) and later in the USA, Hanscarl Leuner (Leuner 1981) in Goettingen (Germany) and other psychotherapeutically-oriented psychiatrists began their work. Researchers used LSD in basic psychiatric research and in psychotherapy (Grinspoon and Bakalar 1979; Grof 2000; 1980; Nichols 2004). Psychiatric researchers examined LSD-assisted psychotherapy in the treatment of alcoholism, "neurotic disorders" and anxiety arising from terminal illness (Grinspoon and Bakalar 1979; Grof 2000; 1980; Jemsen 1962; Kast 1967; Kurland et al. 1971; Ling and Buckman 1963; Martin 1957; Nichols 2004; Pahnke 1973; Strassmann 1995). LSD appeared to reduce anxiety and depression in people with advanced stage cancer (Grof et al. 1973) and to produce long-lasting analgesia in people with advanced-stage cancer (Kast and Collins 1964). At least two-thirds of people with advanced stage cancer enrolled in psychotherapy using doses of 200 µg or more exhibited improved quality of life (Grof et al. 1973; Kurland et al. 1973; Pahnke et al. 1969). At the same time, other investigators treated LSD as representing a means of reproducing symptoms of psychosis in healthy individuals (Nichols 2004; Strassman 1995).

There is considerable previous human experience with the use of LSD in the context of psychotherapy. Psychiatrists, psychotherapists and researchers have administered LSD to thousands of people (Nichols 2004; Strassman 1994, see also "Previous Human Experience"). After a period of rich scientific activity in the 1950s and 1960s investigating the therapeutic potential of LSD, including its use in the treatment of dying people (Grinspoon and Bakalar 1986; Grof et al. 1973; Nichols 2004), this research came to a halt, chiefly as a result of political concerns and in response to large-scale use and abuse in subcultures at that time. Though some past research reported promising results, researchers did not conduct studies using optimal procedures (Nichols 2004). There has not been any prospective, double-blind, placebo-controlled LSD-assisted psychotherapy research completed since the early 1970s.

The last time LSD-assisted psychotherapy was legally possible in Switzerland was from 1988 to 1993. Within those five years, 170 patients with a wide range of clinical conditions were treated and the results of the treatments were summarized in a follow-up case series study (Gasser, 1996). However, the psychiatrists did not employ a control group and did not document the investigation or the process itself, because the treatments were understood as therapeutic and not part of a controlled study. The follow-up study suggested that the treatment may have been safe and efficacious, as more than 80% of patients who responded to the follow-up were satisfied with the result of the treatment, with no reported occurrence of severe persisting adverse effects. However, no information was obtained from non-responders to the follow-up, who might have had less positive results than the responders.

We will conduct this randomized, active-placebo controlled investigation in order to redevelop a treatment method of LSD-assisted therapy for people confronting anxiety relating to advanced-stage illnesses and to gather preliminary evidence on the safety and efficacy of this treatment in this population using current scientific standards. Eight of twelve participants will be assigned to the experimental intervention dose condition (called verum ("true") dose, 200 μg LSD), and four of twelve will be assigned to the low dose condition (called active placebo dose, 20 μg LSD). Participants enrolled in the study will receive two sessions of LSD-assisted psychotherapy separated by a two to four week interval. These experimental sessions will be embedded within a course of six to eight individual non-drug psychotherapy sessions that will first prepare participants for LSD-assisted therapy and then help participants integrate material from the LSD-assisted sessions.

An independent rater will assess anxiety levels, quality of life, and pain throughout the study and until two months after the second experimental session. The use of anxiety and pain medications will be assessed throughout the duration of the study via diaries kept by participants.

The proposed pilot study is part of a comprehensive plan by the sponsor, MAPS (Multidisciplinary Association for Psychedelic Studies, www.maps.org) to reevaluate the therapeutic potential of LSD-assisted psychotherapy and to develop a method that is safe and efficacious for patients with defined disturbances, with the goal of obtaining the prescription use of LSD-assisted psychotherapy by specially-trained and licensed psychiatrists and psychotherapists in specially regulated clinics (Doblin, 2001) Similar studies with patients suffering from anxiety related to advanced-stage cancer are being conducted in the USA. One study at Harbor-UCLA Medical Center is being sponsored by the Heffter Research Institute and is utilizing psilocybin-assisted therapy (Grob 2005). Psilocybin is the active compound in psychedelic mushrooms. It was first isolated by Hofmann in 1957 and it shares a similar pharmacological profile to LSD (Grob 2005). Another study at McLean Hospital, Harvard Medical School, with the design, approval process and funding coordinated by MAPS, is using the entactogen MDMA, to evaluate MDMA-assisted psychotherapy in subjects with anxiety associated with advanced-stage cancer (Halpern, 2006). We will be able to gather information about the safety and efficacy of each of the three substances in people with anxiety related to diagnosis with advanced-stage illnesses and short life expectancy.

Study Design

In the 1950s and 1960s, psychotherapy researchers extensively explored LSD-assisted psychotherapy in the treatment of patients facing death due to severe illness. Although these investigations did not always use methods that meet the requirements of modern psychiatric and psychotherapy research, early research found evidence that this treatment was efficacious. The proposed study is primarily intended to meet two goals. The first is to discover whether LSD-assisted psychotherapy can be safely administered to

individuals with a severe prognosis and short estimated life expectancy who suffer from anxiety related to their diagnosis and the severity of their disease or condition. The second goal is to determine whether this therapy will produce improvements in symptoms of anxiety.

The Spielberger State Trait Anxiety Inventory (STAI; see below under "Measures") will serve as a primary outcome measure of anxiety. Participants must have a score of 40 or higher on both State and Trait scales of the STAI in order to be enrolled in the study. Anxiety will be assessed at baseline prior to any intervention, approximately one hour before each experimental session, one day and one week after each experimental intervention session, at a follow-up evaluation conducted two months after the second experimental session, and across entries in a Daily Diary tracking use of anxiolytic and pain management medications.

A secondary aim of this proposed study is to evaluate whether the experimental intervention translates into meaningful improvements in quality of life. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire EORTC-QLQ-C30 will serve as a primary outcome measure of quality of life. Additional outcome measures include assessments of symptomatology (SCL-90R), global anxiety and depression (HADS), reductions in extent or intensity of experienced pain and resultant use of pain-relieving medications, and side effects for a week after each experimental session (VAPS, Daily Diary). In addition, the quality of the altered state during the LSD-session will be measured by the Peak Experience Profile (PEP).

Objectives:

1. To determine if LSD can be safely administered to participants with anxiety associated with advanced-stage illnesses, without serious adverse events related to the investigational product.
2. To measure if participants receiving LSD-assisted psychotherapy will experience dose-dependent decreases in anxiety after each experimental session and at two months after the second LSD session, as measured by STAI.
3. To measure if participants receiving LSD-assisted psychotherapy will experience dose-dependent improvements in quality of life extending to the follow-ups two months after the second LSD session, as measured by the EORTC QLQC30.

Background and Significance

As described above in the "Introductory Statement," LSD is a semi-synthetic alkaloid of the ergot fungus with a pharmacological profile that makes it well-suited as an adjunct to intensive psychotherapy. LSD is classified as a psychedelic or hallucinogen that chiefly acts as a partial $5HT_{2A}$ agonist, a property it shares with other compounds in this class,

such as the tryptamine psilocybin or the phenethylamine mescaline (Nichols 2004). In humans, LSD produces sometimes intense changes in perception, cognition and emotion that last for up to 12 hours after ingestion. LSD can alter the sense of self or ego as well as changing perceptions about the world (Nichols 2004). Before LSD was placed in the most restrictive category, Schedule 1, a substantial number of therapists employed it as an adjunct to psychotherapy in the United States and Europe (Grinspoon and Bakalar 1986; Nichols 2004; Strassman 1995). A number of psychotherapists concluded that LSD could safely be administered in an outpatient setting and was clinically useful in treating various psychiatric conditions, including anxiety associated with a diagnosis of advanced-stage cancer.

The subject population for this study was selected in part because patients with advanced-stage cancer and other potentially fatal illnesses often fail to obtain satisfactory relief from currently available treatments, or may find current treatments intolerable. Anxiety, depression, chronic pain, and unresolved family issues can become serious physical and mental health problems for individuals living with a life-threatening illness. End-of-life problems, including pain management, are increasingly understood by caregivers and the public as significant public health concerns (Potter et al. 2003; Randall-David et al. 2003; Shvartzman et al. 2003). Efforts to improve the quality of life for these individuals are clearly a public health priority. Recent efforts have been undertaken to devise more effective medication management for pain control (MacPherson 2002; Thomas and von Gunten 2003) and to improve family communication and support (Wells et al. 2003). McClain et al. (2003) support developing additional palliative care interventions to improve the well-being of people with advanced-stage cancer by "… keeping psychological distress of patients who are facing death to a minimum".

Clinical research and anecdotal reports of past experience with LSD-assisted psychotherapy suggest that it could serve as a treatment for psychiatric conditions that emerge after diagnosis with life-threatening illnesses. Patient and therapist reports of LSD-assisted psychotherapy conducted prior to the placement of LSD into Schedule I are suggestive of therapeutic benefits in subjects who have not found relief from other interventions. The qualities associated with LSD-assisted psychotherapy described in clinical research and anecdotal reports are changes in perceptions of the self and the world, including ego dissolution, feelings of transcendence or transformation, and increased and decreased distress that may assist people in facing and grappling with physical deterioration and impending death. While LSD can acutely produce both negative and positive emotions, it is expected that the combination of LSD within the therapeutic setting will reduce anxiety afterwards. That may be particularly useful in the treatment of anxiogenic cognitions, behaviors, and resultant emotions associated with life-threatening illness. Moreover, resultant decreased use of anxiolytic agents may better preserve cognition and sensorium, and therefore could significantly improve the individual's quality of life. Chronic use of benzodiazepines for the treatment of anxiety, for example, induces side effects of compromised sleep architecture, memory difficulties, a plethora of other cognitive impairments, and general lethargy. On the basis of past

reports of successful treatment of anxiety associated with advanced-stage cancer with LSD-assisted therapy (Grof 1970; Kurland 1973; Pahnke 1970), we hypothesize that psychotherapy conducted in combination with LSD will produce improvement in patients with advanced-stage life-threatening illnesses.

General Investigational Plan

Investigators

Dr. Peter Gasser is the principal investigator of the study. He is a psychiatrist and psychotherapist in a private practice in Solothurn, Switzerland. He has undergone training in psycholytic therapy during the five-year period (1988-93) when the Swiss government permitted working with LSD and MDMA for psycholytic therapy, with psycholytic therapy defined as the use of low to moderate doses of these drugs to facilitate psychotherapy. Dr. Gasser is president and member of the board of the Swiss Medical Association for Psycholytic Therapy (SAPT).

The cotherapist for the LSD-sessions is Barbara Speich. She is an experienced psychiatric nurse who is presently working as a teacher in the education of mental health professionals and as a supervisor in the same field. She also is a member of SAPT.

The independent rater will be an experienced psychiatrist/clinical psychologist.

Subjects

The researchers will enroll twelve subjects diagnosed with the advanced stage of an illness with a substantially reduced life expectancy who are experiencing anxiety as a result of their diagnosis and deteriorating health. Advanced-stage illness is defined specifically for each disease, but generally refers to a condition where the disease is considered incurable or inoperable and progressively debilitating. Individuals may be men or woman aged 18 or older. Participants will have symptoms of anxiety and/or panic associated with their diagnosis with an illness (as opposed to a history of an anxiety disorder distinct from the diagnosis) that are clinically significant enough that the subject has been offered and/or prescribed standard medications or psychotherapy for alleviating these symptoms. Participants must have a score of 40 or higher on both State and Trait scales of the Spielberger State Trait Anxiety Inventory (STAI). The first twelve individuals who meet inclusion criteria without meeting any exclusion criteria, and who consent to take part in the study, will be enrolled as participants. Potential participants will be referred from different institutions or practitioners (see below under recruitment of participants). Any participants who drop out or are removed from the study by the

investigators between the first and the second experimental intervention sessions will be replaced.

Inclusion Criteria

Compliance with inclusion criteria will be continually evaluated throughout the course of the study. Individuals will be included as potential participants if they meet the following conditions:

1. Have a diagnosis of advanced-stage potentially fatal illness.
2. Meet DSM-IV criteria for Anxiety Disorder Due to a General Medical Condition (Diagnosis Code 293.84) as indicated by the SCID and a score of at least 40 on each part of the STAI.
3. Have failed to respond adequately or at all to medication or psychotherapy intended to reduce anxiety, or have refused to take anxiolytic medication.
4. May be diagnosed with another affective disorder other than anxiety disorder, except bipolar-I disorder.
5. Are at least 18 years of age.
6. Are willing to commit to medication dosing, experimental sessions, follow-up sessions, and to complete evaluation instruments (although they may withdraw from the study at any time without cause).
7. Are willing to withdraw 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 at the time they are first evaluated, these potential participants should independently review their use of these medications with their treatment providers. Such drugs must be discontinued long enough before the first LSD 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).
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 until after the evaluation session 2 months after the second LSD treatment session.
9. Participants must agree that, for one week preceding each LSD treatment session:
    a. Clinical judgment will be used to determine permissible herbal supplements.
    b. They will not initiate any new prescription medications (except with prior approval of the research team).
    c. Clinical judgment will be used to determine permissible nonprescription medications.
10. Participants must agree to take nothing by mouth except for routine medications, non-alcoholic liquids and light food after 12 A.M. (midnight) the evening before each experimental intervention session. Participants must also refrain from the use

of any psychoactive drug, with the exception of the long term pain medication or caffeine or nicotine, within 24 hours of each LSD 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 PRN medications for treating breakthrough pain taken in the 24 hours preceding 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.

Exclusion Criteria

Compliance with exclusion criteria will be continually evaluated throughout the course of the study. Individuals will be excluded from study participation if they are /have :

1. Women who are pregnant or nursing, or of child bearing potential and are not practicing an effective means of birth control.
2. Anyone with past or present diagnosis with a primary psychotic disorder
3. Meeting DSM-IV criteria for Dissociative Disorder or Bipolar-I Affective Disorder
4. Meeting DSM-IV criteria for abuse of or dependence on any substance (other than caffeine or nicotine) in the past 60 days.
5. Diagnosed with significant somatic problems, that in the clinical judgment of the investigators poses too great a potential for side effects.
6. No sufficient liver function at the baseline examination or the day before the experimental sessions.
7. Having evidence of CNS affection from the primary disease (e.g. brain metastasis), shown by neurocognitive impairment.
8. Weighing less than 45 kg.
9. Reasonably judged to present a serious suicide risk or who are likely to require psychiatric hospitalization during the course of the study.
10. Unable to fully understand the potential risks and benefits of the study and give informed consent.
11. Requiring ongoing concomitant therapy with a psychotropic drug (other than as needed, anxiety medications, and pain control medications) and are unable or unwilling to comply with the washout period.

Prescreening and Informed Consent

The investigators will recruit participants from amongst patients receiving care at the practices of area oncologists, general practitioners, hospital outpatient services or organizations that care for people suffering from these diseases (e.g. Krebsliga, Selbsthilfegruppen), including patients of study collaborators or consultants. The investigators may also seek participants through sending letters asking for referrals to oncologists and other health professionals (see Appendix III), through reports about the

study in the scientific medical newspapers or through contact with caretakers, physicians or potential participants at medical meetings and congresses. There will be no advertisements for recruitment in the popular press.
Initial screening may be conducted via telephone and will involve gathering information regarding the type of disease, sites of disease spread or physiological deterioration, prior treatment, and expected prognosis.

Prospective participants who pass initial screening will be given written informed consent before undergoing baseline evaluations including the medical examination and completion of the STAI. These baseline evaluations may be completed over several days. If the STAI is administered while the participant is on a course of medication, then he or she will be assessed again prior to first experimental session, after having discontinued medication for at least 5 times the particular drug's half-life.

Each prospective candidate's general medical condition will be assessed and documented to determine suitability for study participation. This baseline exam (see time and events table) will be performed by the treating specialist. The baseline medical examination will involve the following procedures: general medical history and physical exam, and metabolic profile. Additional medical tests to further establish participant eligibility include ECG and thyroid hormone status.

If the applicant meets all study criteria without meeting any exclusionary criteria, and if the applicant is still interested in taking part in the study, the prospective participant will be contacted by the principal investigator to discuss the study procedure, answer questions about the study and the informed consent, and arrange for an initial non-drug psychotherapy appointment.

Evaluations performed by the independent rater are expected to last approximately two to three hours. The independent rater will commence with the baseline evaluation by administering the SCID, a structured psychiatric interview (First et al. 1997) to provide a DSM-IV diagnosis of Anxiety Disorder due to a General Medical Condition and to rule out the presence of exclusionary Axis I diagnoses (i.e., substance dependence, psychotic disorder, dissociative disorder, major affective disorder, or eating disorder). Other outcome measures administered at this baseline meeting include the second primary outcome measure, the EORTC-QLQ C30, and measures of anxiety and depression, HADS, and self-reported symptoms SCL-90. Participants will also be instructed on keeping the Daily Diary and measures of daily pain VAPS.

Subject Numbering

Prior to enrollment, subjects will be tracked with their initials and a screening number assigned sequentially starting at "001". Subjects who meet the study admission criteria will be enrolled into the study and will be assigned a 4-digit subject number. The first two digits identify the study site. The next two digits identify the subject within the site

and will be assigned sequentially, with 01 corresponding to the first subject enrolled, e.g. the first enrolled subject will be 0101, second 0102, etc.

Randomization

At the first experimental session each participant will be randomly assigned to one of two conditions, either active placebo (20 μg) or experimental intervention (200 μg). Four of twelve participants will be assigned to receive active placebo and eight will be assigned to receive the experimental intervention dose. Rudolf Brenneisen, Prof., PhD, University of Bern, Dept. of Clinical Research, Lab. for Phytopharmacology, Bioanalytics and Pharmacokinetics, Murtenstrasse 35, CH-3010 Bern, will generate and maintain the randomization code and procedure. Condition assignment will be maintained throughout the course of the study, since this study does not employ a crossover design. If there is an adverse event or other emergency requiring knowledge of participant's condition assignment, as when pharmacological intervention is necessary, the blind may be broken for an individual participant.

Removal of Subjects from Therapy or Assessment

The subject, or where applicable, the subject's legally acceptable representative(s) can withdraw consent for participation in the study at any time without prejudice. The investigator can withdraw a subject if, in his or her clinical judgment, it is in the best interest of the subject or if the subject cannot comply with the protocol.

The subject will be clinically monitored after withdrawal, the cause of which will be recorded on the "Study Termination" CRF and, where appropriate, on the subject's medical records. Where the withdrawal of a subject resulted from an adverse event, this will be documented in accordance with the procedures in section.

Whenever possible, the tests and evaluations listed for the termination and outcome visits will be carried out.

Psychotherapy

All participants will take part in at least two introductory psychotherapy sessions prior to the first experimental session, where they will review their disease-related anxiety and discuss what will occur during the experimental session. Non-drug assisted psychotherapy will occur with both therapist-investigators one day after each experimental session, and with just the principal investigator one week after each experimental session. Participants will complete outcome measures before undergoing each psychotherapy session. During psychotherapy occurring after experimental sessions, the participant and investigators will explore and discuss the events of the experimental session. The final psychotherapy session will occur two months after the second experimental session. (see time and events

table). If any additional psychotherapy sessions are conducted, participants will complete outcome measures before that session. If the participant's health precludes traveling to the practice of The principal investigator after the second experimental session, then meetings for administration of measures and psychotherapy (on Day 49 and Day 102) can be conducted at the participant's home.

At least one of the therapist-investigators will conduct each introductory psychotherapy session. While both investigators do not have to take part in introductory sessions, participants must meet both investigators before the experimental session occurs. During the introductory psychotherapy sessions, the investigators and the participant will review the participant's anxiety and will discuss any other issues or goals the participant has for the initial experimental session. Participants will learn more about the procedures occurring during and after each experimental session, and the investigators will discuss the effects of LSD and what might occur during an experimental session. The participant will also learn more about the rules and restrictions concerning the experimental sessions.

Psychotherapy follow-up sessions will be conducted in the morning on the day after the experimental sessions. The investigators and participant will review the events of the experimental session. They will seek to integrate the thoughts, feelings or insights that arose during the experimental session. Psychotherapy occurring after the first experimental session may also involve preparation for the second experimental session, if all involved have concluded that it is safe and appropriate for a second experimental session to occur. The participant will be instructed not to drive a motor vehicle or operate heavy machinery on the day after an experimental session. One week later, the participant and the investigators will continue to review, discuss and explore the events of the preceding experimental session. Psychotherapy will continue to focus on reducing anxiety, but may also address other issues that arose during or after the experimental sessions. Psychotherapy conducted a week after the second experimental session may encompass the events of both the first and the second experimental sessions. As noted above, the participant may request additional psychotherapy sessions during the course of the study.

The final meeting between the participant and the investigators will occur approximately two months after the second experimental session. After a final administration of all outcome measures, the investigators will speak with the participant about his or her anxiety level and quality of life in the interval between psychotherapy sessions. The investigator and participant may re-examine the goals set out for each experimental session, or they may return to the discussions and work that occurred during the previous psychotherapy session.

Psychotherapy During Experimental Session

The LSD treatment sessions will be supervised and facilitated by the principal investigator, psychiatrist (Dr. Peter Gasser) accompanied by an experienced female co-

investigator/co-therapist (B. Speich). Both therapists will be present throughout the experimental sessions. The sessions will be conducted following the principles developed by Grof for LSD psychotherapy (Grof 1980, pp. 123-147) and adapted by the Swiss Society for Psycholytic Therapy (Benz 1989). At the beginning of the session (approx. 11:00 A.M.), the therapists will discuss with the participant his or her intentions for the session, including intentions regarding working with psychological issues related to their episodes of anxiety. After the session begins, participants will recline in a comfortable position, with eyes closed most of the time. They will listen to a program of music designed to support their experimental session by initially promoting relaxation and later evoking and supporting deep emotions and the emergence of unconscious material (Bonny and Savary 1990; Grof 2000: pp.186-191; Grof 1980; Unkefer 1990). The participant may request a specific musical style for his or her session. After the first hour, if the participant has not spoken spontaneously, the investigators will check in with him/her about the nature of the experience. For the rest of the experimental session, as appropriate, the investigators will engage with the participant to support and encourage emotional processing and resolution of whatever psychological material is emerging. The investigators will also encourage periods of time in which the participant remains silent with eyes closed and with attention focused introspectively on his or her sense of self and life-history in order to increase the psychological insights mediated by the LSD treatment. The investigators may use physical touch, such as holding hands, at the request of and under the control of the participant. Non-alcoholic, non-caffeinated beverages, such as water or juices, will be freely available throughout the session. Food (fruit or crackers) will be available during the latter part of the session.

After approximately six to ten hours, if all medical and psychological parameters are acceptable and the participant is alert, ambulatory, and emotionally stable, the session will conclude. Participants will spend the night at the practice of The principal investigator, where the experimental LSD-assisted sessions have occurred. If possible, a relative or significant other will accompany the participant during his or her stay to assist him or her and to offer support, but if a participant cannot locate someone willing to stay with them and offer support, then a nurse will be available to accompany the participant. Participants will be able to contact at least one of the investigators throughout the night through telephone to answer questions or concerns. If necessary, the investigators may return to the practice within 15 minutes to assess or treat the participant if needed. The location will have appropriate furnishings.

Open Label Continuation for Active Placebo Patients

After each participant completes all outcome measures two months after the second LSD-assisted session (Day 102), the participant will have a meeting with the principal investigator. During this meeting, the blind will be broken. If a participant had received the low (“active placebo”) dose of LSD during the course of the study, she or he will be offered an opportunity to enroll in the open label study continuation. He or she would give written informed consent to take part in this second stage of the study, with

consenting to take part in this stage independent of consenting to taking part in the first stage. If the participant consents to take part in this stage of the study, he or she will receive the experimental intervention ("verum") dose of LSD (200 µg) during two experimental sessions scheduled two to four weeks apart. Experimental sessions will occur after a single introductory session scheduled no later than two weeks after breaking the blind for Stage 1. Outcome measures assessed two months after the second experimental (low or full dose LSD) session will serve as Stage 2 baseline measures. Participants will receive non-drug psychotherapy follow-up sessions 24 hours and one week after each LSD-assisted psychotherapy session. The independent rater will administer outcome measures one and two months after the second full-dose LSD-assisted psychotherapy session. If people are unable to complete outcome measures for whatever reason, the one-month follow-up will be considered the final assessment for the open-label study continuation.

Data Analysis

(written by A. Huesler, Inst. f. Statistik und Versicherungsmathematik, University of Bern)

The STAI and EORTC QLQC-C30 sub-scale scores will be analyzed by nonparametric methods for longitudinal data (cf. Brunner and Langer (1999), Brunner, Domhof and Langer (2002)). The nonparametric framework is chosen for two reasons, that of the sample size being too small to assess the assumptions that underlie a parametric model, and because the primary outcome measures only use an ordinal scale. We will also compute descriptive statistics for all time points and all participants. Any drop-outs, incomplete observations and serious adverse events will be reported.

The first step of the analysis will consist of descriptively summarizing the data by graphing the time course of STAI and EORTC QLQC-C30 (sub-scale) scores for each patient and by computing summary measures for these scores. The second step will consist of comparing the time courses of the control group and the treatment group. We will apply a so-called F1_LD_F1 model (cf. Brunner and Langer (1999), Brunner et al. (2002)) with experimental intervention condition (LSD versus active placebo) serving as a between-group factor and time of measurement serving as a within-subjects factor. We are mainly interested in testing an interaction between experimental intervention condition and time. We expect that participants given the fully active dose of LSD will have lower STAI and EORTC QLQC-C30 (sub-) scores than people given active placebo two months after the second experimental session than at baseline. Statistical significance will be set at 0.05. The study has sufficient power only to detect large effects because the sample size is very small. No adjustment for multiple testing will be done because the STAI score is the primary outcome. P-values and confidence intervals will be reported instead.

PEP scale scores will be computed and correlated with STAI and EORTC-QLQ scale scores assessed 24 hours and one week after each experimental session.

All data processing and statistical evaluation will be performed by the institute for statistics and mathematics of the University of Bern. CRF data, if necessary, can also be entered and analyzed by MAPS.

Drugs and Dosage

The experimental drug is lysergic acid diethylamide (LSD), an ergoline first synthesized by Albert Hofmann in 1938. At high doses, LSD is hallucinogenic, altering perception, cognition and emotion in humans, with effects most likely the result of its activity at serotonin 5-HT_{2A} receptors, followed by its activity at 5-HT_{1A} and 5-HT_{2C} receptors. The dose of LSD (20 µg) chosen for the active placebo dose condition has been selected on the basis of its ability to produce minimal but detectable subjective effects (Abramson et al. 1955). On the basis of previous research in healthy volunteers (Abramson et al. 1955) and in the treatment of cancer (Grof et al. 1973; Kurland et al. 1973), the LSD dose of the Experimental Condition (200 µg) is expected to produce most of the expected effects of LSD. Psychiatrists employing LSD-assisted psychotherapy in people with advanced stage cancer administered doses of 200 µg or higher to produce powerful alterations in consciousness and experiences of transcendence (Grof et al. 1973; Kurland et al. 1973).

Methods

The proposed study is a randomized, double-blind dose-response study of LSD-assisted psychotherapy in people with advanced-stage fatal disease and diagnosis-related anxiety. Four of twelve participants will be randomly assigned to the active placebo condition, and eight of twelve assigned to the Experimental Intervention Dose (see Table 1 below). Participants in the Low Dose condition will receive 20 µg LSD on each of two sessions. Participants in the Experimental Intervention condition will receive 200 µg LSD. The study includes eight conventional (non-drug assisted) psychotherapy sessions with The principal investigator, at least two also involving The co-therapist, with all sessions lasting one hour, two experimental (LSD-assisted) sessions with the principal investigator and the co-therapist, lasting 8 hours, and two administrations of outcome measures by the independent rater lasting from 60 to 90 minutes. A participant will have completed the active treatment phase of the study approximately three and a half months after screening, and two months after the second experimental session.

All LSD treatment sessions will begin at 11:00 AM and will take place in the private practice of The principal investigator. In case of emergency the practice is equipped with medical emergency equipment, i.e. appropriate medications, defibrillation kit, and respiration bag. A hospital with intensive care unit can be reached by car or ambulance in three minutes. The hospital staff will be/has been informed about the study and the drug sessions. Participants will have had nothing by mouth except alcohol-free liquids and a light breakfast since 12:00 AM the evening before. Participants will not have consumed caffeine or nicotine for two hours before or six hours after drug administration. They will

be asked to arrive at 9:00 AM for collection of a urine specimen for drug screening and, for females of childbearing potential, a pregnancy test. At this time, they will also complete measures of anxiety, quality of life, and pain (as outlined in Table 2 below).

Each experimental session will last up to ten hours. Experimental sessions are scheduled to occur after the independent rater has administered outcome measures. After both therapist- investigators have determined that the participant can undergo the experimental session, each participant will receive an initial dose of LSD, as described in "Drugs and Dosage" above. The participant will lie or sit comfortably while listening to a musical program designed to facilitate introspection and deep emotions, as described earlier in "Psychotherapy During Experimental Sessions." Blood pressure and heart rate will be measured at the outset of each treatment session, in the middle and at the end of the session.

The experimental session ends approximately six to ten hours after the administration of LSD. Participants will remain on-site for an overnight stay after the experimental session. They will stay in a comfortably furnished room with a kitchen and a shower. A relative or significant other will remain with them to assist them if needed, and if a relative or significant other cannot join the participant, a nurse will be in attendance with them instead. The participant, relative or significant other, or nurse can contact at least one of the investigators if necessary, and the investigators may return to the practice during the night if they are needed to help treat the participant.

Table 1. Schedule of Visits Timeline

Study Measure / Approx. Study Day[a]	Screening	Baseline (day - 14 to 0)	7	14	**21**	22	28	**42**	43	49[b]	50	102[b]
Informed Consent		X										
Inclusion / Exclusion Criteria	X	X										
SCID		X										
SCL-90		X										X
HADS		X			**X**		X	**X**		X		X
STAI		X*			**X**		X	**X**		X		X
EORTC-QLQ-C30		X			**X**		X	**X**		X		X
PEP						X			X			
Determine wash-out period for specified medications		X		X			X					
Conventional psychotherapy[d]			X	X		X	X		X	X		X
Experimental treatment session[e] (LSD or placebo)					**X**			**X**				
Both investigators present			X[c]	X[c]	**X**	X		**X**	X			
Independent rater evaluation		X										X
Unblinding (start of Phase II for Placebo Subjects)												X
Medical Exam / History		X									X	
Metabolic Profile		X									X	
Monitor vital signs					**X**			**X**				
Drug screen / Pregnancy test		X			**X**			**X**				
Daily Diary & VAPS			X	X	**X**	X	X	**X**	X	X	X	X
Changes to baseline prescription medications (pain / psychoactive)			X	X	**X**	X	X	**X**	X	X	X	X
Common side effects					**X**	X	X	**X**	X	X		
Adverse Events requiring physician visit					**X**	X	X	**X**	X	X	X	X
Serious Adverse Events		X	X	X	**X**	X	X	**X**	X	X	X	X

[a] Standard study windows are –2 / +3 days. Study days will be adjusted if extra visits are required.
[b] Day 49, Day 102, may alternately be performed at the participant's home.
[c] Participant meets second investigator during one of the introductory sessions.
[d] At any time during the study additional psychotherapy sessions may be scheduled.
[e] 6-8 hours session with overnight stay.
* may be repeated after washout period as per protocol.

Administration of Outcome Measures (Research Follow-Up)

Outcome measures will be administered by the independent rater on six occasions during Stage 1; once prior to the initial psychotherapy session, immediately before each experimental session prior to drug administration, prior to each psychotherapy session scheduled a week after an experimental session, on the final day of the study, two months after the second experimental session. The independent rater will be blind to condition assignment and will not be present during experimental or non-drug psychotherapy sessions. No outcome measures, except the daily anxiety and pain diaries will be administered prior to psychotherapy sessions conducted the day after each experimental session. Daily Diaries will also be reviewed during these meetings. Participants enrolled in the open-label study continuation ("Stage 2") will complete outcome measures on a nearly identical schedule to that of Stage 1. However, outcome measures completed two months after the second experimental session will be treated as baseline outcome measures, and participants will complete measures on an additional date one month after the second open-label LSD-assisted therapy session.

Outcome measures will include the participant-completed (self-report) EORTC QLQ-C30, HADS, STAI, and SCL-90-R, and the independent rater administered SCID (See Table 2). Participants will complete outcome measures on days when any additional psychotherapy sessions are scheduled (see "Psychotherapy.") More details about each measure can be found in "Measures" below. Daily Diaries for anxiety, pain, and side effects of the experimental session will also be reviewed at these meetings. The STAI will serve as the primary outcome measure of anxiety, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) will serve as the primary outcome measure of quality of life and the Daily Diary will serve as the measure of severe (and also light) side effects of the experimental session. The independent rater will complete the measures on Day 102 and check the Daily Diary in detail with the subject for side effects.

Participants will complete the PEP, a measure of altered states of consciousness the day after the experimental session prior to the non-drug psychotherapy session with both therapist-investigators.

Each experimental session will be recorded to audio. Comparison of information gathered from these recordings may be qualitatively or quantitatively examined in an attempt to gain a better understanding of the effects of LSD within a psychotherapeutic context.

Assessment / Measures

Outcome measures were selected primarily because they are well-validated, clinically relevant, and repeatable. These include observer-administered and rated measures of symptoms of anxiety, depression, and quality of life; self-report measures of symptoms, quality of life, daily pain, and daily diary (logging medication use); physician-rated

measures of physical health, review of laboratory values, and physical functioning; and psychiatrist administered tests of mental status and diagnosis. Self-report measures of anxiety and depression symptoms will be made at baseline, on the morning of each experimental session ("Day 21" and "Day 42"), one week after each experimental session ("Day 28" and "Day 49"), two months after the second experimental session ("Day 102"), and during the six-month and 12-month follow-up sessions. This will be the case for all measures except for SCID, administered only at baseline, and the SCL-90-R, administered only at baseline and two months following last experimental session. The STAI will be administered during screening in additional to the time points mentioned above.

All participants will undergo psychiatric screening with the SCID, a structured psychiatric interview. This will be done by an independent rater. Participants will be asked to keep a daily diary that logs daily use of all medications and need for symptom-specific medications for acute symptoms of anxiety and/or pain. Participants will also be asked to rate their prior 24 hours of pain each day using the VAPS. Side effects that may occur after the two experimental sessions will be logged in the daily diary as well.
The measures that will be used in the course of this study are in Table 2 and listed below.

Table 2. Test Measures

Assessment	**Abbreviation**	**Measure of**	**Time needed**	**Clinician rated**	**Participant Self-rated**	**Screening outcome measure**
Daily Diary	--	Anxiolytic and Pain Control Medication, Side effects	5 min.		X	Outcome
Europ. Organiz. For Research and Treatment of Cancer; Quality of Life Questionnaire [a]	EORTC QLQ-C30	Global quality of life	10-15 min.		X	Outcome
Hospital Anxiety and Depression Scale	HADS	Anxiety + Depression	5-10 min.		X	Both
Spielberger State Trait Anxiety Inventory [a]	STAI	Anxiety	5-10 min.		X	Both
Structured Clinical Interview for DSM-IV	SCID	Past and present psychiatric health	50-120 min.	X		Screening
Symptom Checklist 90	SCL-90-R	General current mental health and quality of life	10-15 min.		X	Both
Visual-Analog Pain Scale	VAPS	Rating of subjective pain experienced	2 min.		X	Outcome
Peak Experience Profile	PEP	Rating of altered states of consciousness	25 min		X	24 h post-Experimental Session only

[a]Primary outcome measures

1. Daily Diary. Participants will keep a daily log of medications taken while actively enrolled in the study protocol. Only changes to pain and psychoactive baseline medications will be recorded on the CRF. The forms provided to participants will also remind them to contact the investigators prior to initiation of any drug or medication not already reviewed during the intake evaluation. Participants will also complete the VAPS (see Visual Analog Pain Scale below) daily. The VAPS was originally developed for use in a study of MDMA-assisted psychotherapy in participants with anxiety arising from a diagnosis of advanced stage cancer. Starting on the day of each experimental session, participants describe and indicate the presence of LSD side effects for seven days after each experimental session.

2. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (Aaronson et al. 1993) has satisfactory psychometric properties and currently is one of the most widely accepted measures of quality of life. This instrument has 30 items yielding scores for five subscales (physical, role, emotional, social, and cognitive functioning) and 3 symptom subscales (fatigue, pain, and nausea/vomiting). This will be the primary outcome variable for quality of life.

3. Hospital Anxiety and Depression Scale (Zigmond and Snaith 1983) was developed to assess anxiety and depression in somatic patients. It is a 14 item self-report instrument. It is used for screening, diagnostic and follow-up purposes.

4. Peak Experience Profile. The original 180 item questionnaire was developed in the 1960ies for the description of psychedelic experiences. It covers so called peak experiences (delightful) and nadir experiences (distressful). In the study we will use a revised version of 100 items, who will be translated into German.

5. Spielberger State-Trait Anxiety Inventory differentiates “state anxiety” (i.e. anxiety dependent on a specific situation or stressor) from “trait anxiety” (longstanding anxious affect or disorder) and is considered the definitive instrument for measuring anxiety in adults (Spielberger et al. 1970). Extensive normative group data exists and the STAI has been administered to advanced-stage cancer patients with anxiety. The STAI has 40 questions with four possible answers each. A score of 40 or greater in each of the two sub-scales is associated with clinically significant symptoms of anxiety. This will be the primary outcome variable for cancer related anxiety.

6. Structured Clinical Interview for the DSM-IV: SCID-IV (First et al. 1994). The SCID is a semi-structured interview that permits accurate diagnosis of lifetime and current psychiatric disorders using DSM-IV criteria

7. Symptom Checklist 90 - Revised. This is a standardized instrument used to measure subjective feeling states (Derogatis 1994). Reliability, validity, and utility have been demonstrated across close to 1000 studies and normative data values have been

published. The SCL-90-R has subscales along 9 primary symptom dimensions (somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism) and 3 global indices (global severity index, positive symptom distress index, and positive symptom total). The SCL-90-R has 90 questions, and responses are made on a 5-point rating scale.

8. Visual Analog Pain Scale. This is a simple and efficient tool that consists of a drawn 10-cm line labeled at one end "no pain" and at the other end with "worst pain possible." Scoring is accomplished by having the participant mark the line to indicate pain intensity, and the line is then measured to the mark on a 0- to 10- point scale. Extensive prior research indicates that the VAPS is reliable and valid as both a sensitive measure of pain and as a measure of change in pain (Ohnhaus and Adler 1975). The current format for the daily analog pain scale was developed for a study of MDMA-assisted psychotherapy.

Monitoring for Risks

According to the most recent and comprehensive review, hallucinogenic drugs "are generally considered to be physiologically safe molecules whose principal effects are on consciousness" (Nichols 2004). Moreover, the author notes, "there is no evidence that any of the hallucinogens, even the very powerful semisynthetic LSD, causes damage to any human body organ". A series of searches of the electronic PubMed database made during 2005 and 2006 continue to confirm the lack of any serious adverse events associated with LSD used in nonmedical or recreational settings. The three key safety concerns with human use of LSD are behavioral changes, acute adverse psychological reactions, and prolonged or chronic reactions. These are summarized below. These concerns have also been systematically reviewed in several publications (Halpern and Pope 1999; Halpern and Pope 2003; Malleson et al. 1971; Strassman 1984; Strassman 1995).

Acute Psychological Distress

The investigators will discuss possible effects of study drugs with participants during introductory psychotherapy sessions and immediately before each experimental session to reduce the likelihood of a panic response. The intent of experimental psychotherapy sessions is to allow the participant whenever possible to confront and move through intense emotional changes or experiences evinced by LSD. Both investigator-therapists will remain with the participant for up to ten hours after drug administration, or until the participant is mentally stable or has returned nearly or wholly to baseline.

If after twelve hours the participant continues to exhibit extreme psychological distress, paranoia or lack of insight into his or her condition, at least one and possibly both investigators will remain with the participant until his or her anxiety and mental status has returned to baseline. If appropriate, the participant will receive a rescue medication, but with a preference for supportive care first, as described below.

If a participant exhibits signs of psychological distress, such as panic or paranoia or expressing delusions or lack of insight on the nature of his or her current situation, the investigators will first remind the participant that he or she has taken a psychoactive drug and that he or she can first stay with and work through the anxiety. The investigators can offer support and reassurance, and they may help reduce anxiety through reminding the participant of any relaxation techniques learned prior to the experimental session. Oral lorazepam (Temesta®, 1 - 3 mg) will also be available for on-site treatment of extreme acute anxiety if needed. Zolpidem (Stilnox® 10mg) may be given after the experimental session if the subject has difficulty sleeping. Benzodiazepines may be prescribed in the days following the experimental session, as a supplement to other non-drug methods of reducing anxiety. Sublingual olanzapine (Zyprexa®, 10 mg) will be available for treatment of psychosis or extreme distress that does not resolve with supportive care.

In recent research into the effects of 30 mg psilocybin (Griffiths et al. 2006), similar precautions were taken. There were no reactions requiring pharmacological intervention. Rescue medication will only be used if an individual is endangering him or herself or others, or at the discretion of the investigator. At least one of the investigators will be available by phone throughout the night after each drug administration. The use of prescribed rescue medicines during an experimental session is contraindicated because it can interrupt the therapeutic process, although it would not be expected to cause any physical harm to the subject. The goal of the process is to confront fears and to experience them fully as a means of coping with them.

The investigators will query subjects about suicidal thoughts or impulses, and if apparent, a way of handling them will be discussed with the participant. If he or she is unable to take responsability for him or herself during an experimental session, the investigators will hospitalize the participant for the next 24 hours or until he or she appears stable.

If a psychiatric hospitalization is necessary a hospital is ten minutes away from the practice. This hospital will be informed in advance about the study.

Medical Emergencies

Basic emergency equipment is available in the practice. The principal investigator's office is located three minutes away via car from the next hospital, the Bürgerspital Solothurn, which has an emergency room and an intensive care unit. The hospital will be informed in advance about the nature of this study.

There will be three routine blood pressure and pulse readings at the beginning, middle and end of each experimental session. The investigators will make additional readings on the basis of clinical judgment as to the severity of elevated blood pressure. If necessary, the investigator will seek to reduce elevated blood pressure via antihypertensive medication,

and if antihypertensives fail to significantly reduce blood pressure, then the subject will be transported to the hospital.

Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. An AE can, therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.

An *unexpected adverse event* is one that is not listed in the current Investigator's Brochure or an event that is by nature more specific or more severe than a listed event.

All AEs will be monitored until resolution or, if the AE becomes chronic, a cause identified. If an AE is unresolved at the conclusion of the study, a clinical assessment will be made by the investigator and Medical Monitor as to whether continued follow-up of the AE is warranted.

The severity of events reported on the "Adverse Events" CRF will be determined by the investigator as:
Mild: no limitation in normal daily activity.
Moderate: some limitation in normal daily activity.
Severe: unable to perform normal daily activity.

The relationship of the study treatment to an AE will be determined by the investigator based on the following definitions:
1. Not Related
The AE is not related if exposure to the investigational product has not occurred, **or** the occurrence of the AE is not reasonably related in time, **or** the AE is considered unlikely to be related to use of the investigational product, i.e. there are no facts (evidence) or arguments to suggest a causal relationship, or the AE is more likely related to the subject's pre-existing condition.
2. Possibly Related
The administration of the investigational product and AE are considered reasonably related in time **and** the AE could be explained by causes other than exposure to the investigational product.

3. Probably Related
Exposure to the investigational product and AE are reasonably related in time **and** the investigational vaccine is more likely than other causes to be responsible for the AE, **or** is the most likely cause of the AE.
The relationship of the study treatment to an AE will be determined by the investigator.

Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions)
- Results in a congenital anomaly/birth defect
- Requires intervention to prevent permanent impairment or damage
- Is an important and significant medical event that may not be immediately life threatening or resulting in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the patient/subject or may require intervention to prevent one of the other outcomes listed above.

Adverse events which do not fall into these categories are defined as **non-serious**. It should be noted that a severe adverse event need not be serious in nature and that a serious adverse event need not, by definition, be severe.
In addition, a pre-existing event or condition that results in hospitalization should be recorded on the medical history. The hospitalization would not result in the event or condition being reported as an on study SAE unless, in the view of the investigator, hospitalization was prolonged as a result of participation in the clinical trial or was necessary due to a worsening of the pre-existing condition. This is because the onset of the event (the reason for the procedure) occurred before the subject was entered in the trial. Hospitalization for cosmetics, non-emergency prophylaxis or abortion does not result in an SAE report unless, in the view of the investigator, hospitalization for these procedures was prolonged as a result of participation in the clinical trial.

Adverse Event Collection

All serious adverse events will be collected for the duration of the study. All SAEs which occur during the course of the trial, whether considered to be associated with the study IP or not, have to be reported **within 24 hours** or at the latest on the following working day by telephone or fax to either of the following:

Medical Monitor: Rick Doblin; rick@maps.org; (1) 617-484-8711
Study Monitor: Valerie Mojeiko; valerie@maps.org; (1) 831-336-4325

Adverse events that will be collected for the duration of the study are:

- Pain using the VAPS.
- Events requiring a physician visit or an intervention, not related to planned treatments for baseline conditions.
- Any adverse event leading to withdrawl from the study.

Additional adverse events collected for seven days after each experimental session are:

- Common side effects.
- Exacerbation of anxiety.

Collection of Concomitant Medications

All prescription concomitant medications will be recorded at baseline. During the study participants will keep a daily log of medications taken while actively enrolled in the study protocol. Only changes to anxiolytic and pain management baseline medications will be recorded on the CRF.

Laboratory Assessments

Before the study, the investigator will supply the sponsor with a list of the normal ranges for clinical laboratory assessments. All abnormal laboratory values require a comment on the laboratory report, regardless of the clinical significance.
After reviewing the laboratory report and evaluating any results that are outside the normal range, the investigator must sign and date the laboratory report. Any abnormal laboratory test result that warrants further investigation to guard the subject's safety will be repeated as appropriate and reviewed by the investigator.

Study Monitoring, Auditing and Documentation

Investigators and/or their study staff will be trained during the initiation visit. During each monitoring visit source data verification will be performed by qualified staff representing the sponsor. A CRF collation supplied by the sponsor will be completed for each subject. The entries will be checked by trained delegates of the sponsor.
Monitoring and auditing procedures of the sponsor will be followed, in order to comply with GCP guidelines and to ensure validity of the study data.
The sponsor will review the study documentation used for planning, conduct and monitoring of the study in order to ensure compliance with GCP and local regulations.

This documentation includes as a minimum: the Investigator's Brochure, the Study Protocol, the Case Report Forms and the Subject Information and Consent Form.

Risks to Participants

Risks and Discomforts Related to Screening and Baseline Examination

All participants will have to undergo a standard medical examination prior to study enrollment. The examination will involve drawing blood. A risk-benefit analysis suggests that the temporary discomfort from providing blood samples is outweighed by the need to ensure that participants are healthy enough to meet all inclusion criteria at screening. Participants may find discussing their anxiety and their illness upsetting, or they may find screening boring or tiring. Screening is necessary to assess participant eligibility for the study and to reduce risks associated with study procedures.

Risks and Discomforts of Psychotherapy

During non-drug and experimental sessions, participants will be asked to think about and discuss their thoughts and emotions about their illness, including anxiety and the impact the illness has had on their lives. They may experience intense emotional responses to speaking about these thoughts, feelings and concerns. Even in a therapeutic context, thinking about and discussing serious illness and impending death or the effects of disease progression on life function can produce distress during and immediately after non-experimental and experimental sessions. Psychotherapy is conducted as part of the research study, including the experimental intervention (LSD-assisted psychotherapy), and people undergoing psychotherapy are expected to confront unpleasant thoughts, feelings and memories in the process of therapy. Because psychotherapy is an integral part of the research study design, the potential distress arising from psychotherapy is unavoidable.

Risk of the Experimental Drug (LSD)

Transient anxiety and/or depressive reactions are not uncommon amongst non medical uses of LSD (Strassman 1984; Halpern and Pope 1999), and anxiety commonly reported by people given the related compound psilocybin in controlled settings (Hasler et al. 2004; Vollenweider et al. 1997). However, in most cases these transient effects do not prompt healthcare seeking behavior. Indeed, some users report value in such experiences. Such reactions that are encountered by health services typically resolve spontaneously with non-specific supportive care or, on occasions, sedative medication. Anxiety and depression rarely persist beyond acute drug intoxication (Gasser 1996; Grinspoon and Bakalar 1979; Grof 1980; 2000; Halpern and Pope 1999; Henderson and Glass 1994; Leuner 1981). All adverse effects will be recorded during experimental sessions and non-drug psychotherapy sessions when participants report these events. Participants will note any adverse effects into their diary. This form is shown in Appendix B. The investigator

will discuss the possible effects of LSD during introductory sessions so that participants are prepared for these experiences.

Panic attacks, severe generalized anxiety, or persisting insomnia.

As reported in several reviews, transient anxiety or depression after taking LSD has been reported in many cases (Grinspoon and Bakalar 1979; Grof 1980; Strassman 1984). These cases typically resolve spontaneously with supportive care, but in some cases involved the administration of anti-psychotic or sedative drugs as well. In most cases, emergency room admissions related to anxiety or psychological distress after LSD do not require continued hospitalization (Nichols 2004; Strassman 1984; Halpern and Pope 1999). Both acute and prolonged anxiety or psychotic reactions to LSD appear to be dose-dependent (Cohen 1960). The occurrence and intensity of anxiety or panic responses can be reduced through providing participants with information on potential drug effects, supervision and monitoring of participants for the duration of drug effects, and using ascending dose designs. There is a concept in this study of treating patients first by verbal and psychological interventions, and using anxiolytic medication only after verbal and psychological interventions have failed, and if participants are endangering themselves or others.

In case of insomnia the investigator may prescribe a benzodiazepine or zolpidem as a "rescue medication" for the day or night after an experimental session. Residual symptoms will be addressed during the frequent follow-up psychotherapy visits with the investigators.

Self-injurious behavior.

People who have taken LSD in uncontrolled settings may engage in reckless behavior, such as driving while intoxicated. The risk of reckless behavior occurring during controlled studies can be prevented or greatly reduced through continued supervision by the researchers and requiring all participants to remain at the practice for 24 hours after each drug administration.

Psychosis, suicidal thoughts or impulses.

There are reports of prolonged psychiatric symptoms after LSD use, but this response remains rare. In one survey of 5000 people administered LSD or mescaline in therapeutic and research settings, adverse psychiatric reactions lasting more than 48 hours were reported in 0.08% of research volunteers and 0.18% psychiatric patients (Cohen 1960). A survey of a different group of 4300 research volunteers who took part in LSD research reported a rate of 0.9% for serious, persistent psychiatric reactions (Malleson 1971). Early research with LSD related compounds did not apply as stringent criteria for participant selection or screening as would be used now, so the low rate of psychosis from these early

studies is liable to overestimate the rate of prolonged psychological responses that might occur in a study that screens for past or present psychotic disorders.

Researchers who reviewed case series and reviews of the relationship between LSD use and subsequent occurrence of psychosis note that evaluation of psychosis is made after LSD use only, and not prior to use (Strassman 1984), making it difficult to determine the degree of change after LSD use. After examining the literature, Strassman concluded that LSD might trigger psychotic episodes in people already vulnerable to psychosis rather than directly causing it. However, the most recently available U.S. data on LSD-related emergency department visits indicates there were 891 visits in 2002, or approximately 1 visit per 100,000 U.S. residents (Drug Abuse Warning Network, Emergency Department Trends From DAWN: Final Estimates 1995 - 2002. 2003, DHHS). Subjects with a history of psychosis (bipolar disorder or schizophrenia) or suicidal attempts will be excluded from this study.

These findings, in combination with more recent case series described above, indicate that while LSD can provoke psychosis or other psychiatric symptoms in a very small percentage of people, it does not do so often, and that receiving a hallucinogenic drug as part of a research study is extremely unlikely to trigger persistent, or even transient, psychosis. The occurrence of transient or persistent psychosis can be prevented or further reduced by screening subjects on the basis of past and current mental health. Individuals will be excluded from study participation on the basis of past or current psychotic disorders in the individual or in first-degree relatives, such as biological parent or sibling. If a participant should become psychotic or suicidal for a time exceeding the duration of drug effects, arrangements will be made for him or her to be admitted to the nearest inpatient psychiatric facility.

Chronic neuropsychological effects.

Earlier studies found changes in personality or neuropsychological function after frequent chronic LSD use. A review of these studies concluded that they all shared a number of methodological flaws (Halpern and Pope 1999) that included retrospective study design and failure to account for the effects from use of other drugs, possible pre-existing morbidity, and the association of LSD with subcultures that valued specific personality types. In their review and analysis, Halpern and Pope concluded that long-term changes in personality or psychological function, if they existed at all, were liable to be subtle or not clinically significant. It is notable that an investigation of the effects of psilocybin two months after administration to psilocybin-naïve individuals, found that people who knew the participants reported positive changes in their attitudes and behavior (Griffiths et al. 2006).

Some people who have used serotonergic hallucinogens, such as LSD or psilocybin, experience persistent and distressing alterations in mostly visual perception that last from weeks to years after use. This condition is now diagnosed as hallucinogen persistent

perception disorder (HPPD), and is not referred to by the term "flashbacks," which better describes an experience more akin to traumatic recall of an intensely upsetting experience, as a "bad trip." By contrast, HPPD involves changes in visual perception rather than a re-experiencing of feelings or memories. To date, there are no reports describing prevalence of HPPD in the general population, but an examination of previous reports and estimates of use of LSD and other hallucinogens use in the US suggests that HPPD is very rare (Halpern and Pope 2003; Johnson and O'Malley 2004). Halpern and Pope note that many to most previous studies were affected by selection bias. These reports also contained information supporting alternative explanations of flashbacks or HPPD, such as use of other drugs or the presence of other mental disorders, and found that people who had not used hallucinogens can also experience similar perceptual disturbances. In 2003, 9.7% of individuals reported at least some lifetime use LSD, (Johnston and O'Malley 2004), and 0.2% reported using LSD at least once in the past year (NSDUH, 2004), suggesting that if HPPD were a common outcome of LSD use, it would be reported more often in the literature. Preliminary data collected by Baggott suggests that no more than 1% of 1000 hallucinogen users surveyed experience HPPD (Baggott, personal communication).

The risk of HPPD occurring after LSD administration can be reduced by screening participants for potential risk factors such as substance dependence and through excluding people reporting HPPD after prior use of hallucinogens.

Reproductive and Developmental Risks.

Pregnant women will be excluded from participation in the proposed study. Women of childbearing potential enrolled in the study must practice a reliable method of birth control, and they must have a negative pregnancy screen before undergoing each experimental session. Although there is no evidence (see below under "reproductive toxicity") of a teratogenic or mutagenic potential of LSD, this precaution of excluding women who could become pregnant is a general ethical commitment.

Abuse Liability

Currently, LSD is placed in Switzerland and the USA in a schedule of narcotics defined as having no medical use and having high abuse liability. Despite this designation, examining use patterns in humans and self-administration and conditioned aversion in rodents and nonhuman primates suggest that LSD possesses little or no abuse liability (Nichols 2004). Only one study found that LSD produced conditioned place preference, an indicator of reward value, in rats, but only in males of a specific rat strain (Meehan et al. 1998; Parker 1996). Most drugs with similar pharmacological profiles, such as psilocybin, also fail to produce consistent self-administration in rodents or monkeys (Fantegrossi et al. 2004; Nichols 2004). Rhesus monkeys found LSD to be aversive, working to avoid a cue associated with LSD infusion (Hoffmeister 1975). There is no

human LSD dependence syndrome, and prevalence of LSD use in adolescents and young adults seems to remain relatively stable over time in the US (Johnston et al. 2004), as well as in Europe. Hence it appears that LSD has little to no abuse liability, and participants receiving LSD are highly unlikely to develop dependence on it after exposure.

Risks of Active Placebo dose of LSD

The 20 μg dose of LSD used in this study is expected to produce some but not most of the effects of the experimental intervention dose of 200 μg. These include slight changes in perception, cognition or mood. This dose is not expected to produce the intense experiences or insights that the therapists will use in combination with psychotherapy, so the active placebo dose is not expected to reduce anxiety to the same degree as the experimental intervention dose. It is necessary to employ an active placebo so as to have a controlled study and to maintain the blind concerning condition assignment. Participants who learn they received active placebo may decide to undergo an open-label study continuation.

Alternative Treatment and Procedures

The primary alternative to study participation is not to take part in the study. There are a number of recognized treatments for anxiety arising from a medical condition. Treatment often includes both psychotherapy and medication. Most commonly recommended psychotherapeutic treatments include anxiety management (stress inoculation training), cognitive therapy, exposure therapy, and psychodynamic psychotherapy. Medications that may ameliorate symptoms of anxiety include antidepressants (SSRI or tricyclic), benzodiazepines, buspirone, zolpidem, and mood stabilizers. Participation in this study is entirely voluntary, and refusing to take part in this study will not affect the care the participant is already receiving for anxiety arising from advanced stage illness. Nor will declining to participate affect any care for the advanced stage illness. Participants will not be penalized for withdrawing from the study.

Risk-Benefits Analysis

Anxiety arising from diagnosis with an advanced-stage illness places an additional burden upon people living with debilitating or potentially fatal diseases. Illness-related anxiety reduces quality of life and increases distress in people with short life expectancies, potentially further limiting their interpersonal relationships and activities. Even currently available methods of reducing anxiety in people with potentially fatal illnesses, such as use of benzodiazepines, have drawbacks such as over-sedation, and some individuals may decline these medications because of these or other side effects. LSD-assisted psychotherapy may increase quality of life by reducing need for daily anxiolytic or pain control medication in this population, and it may also improve other aspects of quality of life not addressed by currently available treatments, such as reducing fear in the face of

impending death and increased calm or ease with advanced stage illness. Developing a wider array of options for treating anxiety arising from experiencing the advanced stages of a potentially fatal illness would greatly benefit people suffering not only from deteriorating health but from anxiety and fear relating to their condition.

LSD and other compounds that share similar effects, such as psilocybin, can powerfully alter perception, emotion and cognition and can produce psychological distress, including panic reactions. In rare instances, these drugs can provoke or exacerbate psychosis or long-term alterations in perception. However, most of the changes are transient and treatable with supportive care. LSD does not have any demonstrable toxicity on physiological systems and organs, and it has a proven safety record as indicated from past human LSD research conducted in thousands of participants, including research involving people with cancer (Grof et al. 1973; Kast and Collins 1966; Kurland 1985; Pahnke et al. 1969). It is notable that people in the US and Europe have safely administered psilocybin to drug-naïve participants (for example Griffiths et al. 2006; Hasler et al. 2004) and an ongoing study continues to investigate the use of psilocybin in treating anxiety arising from advanced stage cancer and short estimated life expectancy (Grob 2005) without any resulting adverse effects. Careful screening prior to study participation and careful monitoring during each drug administration will greatly reduce the risks of LSD or psilocybin.

A third of the participants in this study will receive an “active placebo,” or a dose of LSD that is not expected to be efficacious in combination with psychotherapy. These participants will still receive a course of non-drug psychotherapy sessions and they will receive the same support and care from the therapists during the study. Once the blind has been broken for each individual, participants who received active placebo may return to undergo an open-label study continuation wherein they receive a fully active dose of LSD. A placebo group is required in order to properly assess the efficacy of study drugs, and an active placebo is required when dealing with strong psychoactives such as LSD.

After examining and carefully weighing the evidence concerning the risks and benefits of this study, we conclude that the benefits of developing a new treatment for anxiety arising from a potentially fatal illness outweigh the risks of 20 or 200 µg LSD administered in this study.

Confidentiality

Every effort will be made to strictly safeguard the confidentiality of all participants. Despite this, privacy cannot be guaranteed. Data collected from each participant will be identified only by the participant's initials and subject number on source documents. All communication concerning the participants, including communications relating to statistical data gathering from the tests and measurements, will use subject number only and not the participant’s name. All data, measures and records, and information linking subject numbers to the names of participants will remain at the office of the principal

investigator within a locked file cabinet. Access to measures will be limited to regulatory agencies and researchers assessing the participant for changes in symptoms and individuals analyzing data. Researchers with access to data will not be provided with any information that would identify participants by name or by other means.

Recording study procedures inevitably preserves participant identifying characteristics, such vocal timbre (voice quality) or tone of voice. Hence recording to audio poses a risk to confidentiality. Listening to audio recordings will be restricted to researchers working with the principal investigator or the sponsor. Audiotapes will be marked only with participant numbers and initials.

Costs to Participants

There will be no costs to participants for any of the study procedures, including receiving the study drug or remaining at the practice site for the duration of the experimental session and overnight after each drug administration day. The sponsor, MAPS, will pay for all study drugs and study procedures. Participants will not be paid for their participation in this study.

Patient's Rights / Insurance

All patients will receive the Informed Consent before enrolling in the study. In the first investigational interview, the investigators will ensure that participants understood the study design as described in consent documents. The investigators will let participants know that they can stop their participation at any point of the study without negative consequences for them and without giving any reason for their decision.

The study insurance is following the needs and guidelines of Swissmedic (http://www.swissmedic.ch/files/pdf/Schaeden_Rahmenbedingungen-D.pdf), the Swiss drug regulation authority.

The insurance was made with Zurich Insurance Company, the contract with the company is attached to this protocol.

Record Retention

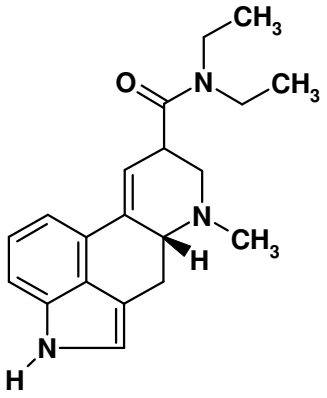
Investigators must retain all study records required by MAPS and by the applicable regulations in a secure and safe facility. The investigator must consult a MAPS representative before disposal of any study records. "Essential documents" are defined as documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the

investigational product. These documents should be retained for a longer period however, if required by the applicable regulatory requirements or by an agreement with the sponsor *or* The Committee for Human Medicinal Products (CHMP) requires retention for the maximum period of time permitted by the institution, but not less than 15 years. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

Chemistry, Manufacturing and Control Information

(written by Prof. Brenneisen, University of Bern, Dept. of Clinical Research, Lab. for Phytopharmacology, Bioanalytics and Pharmacokinetics)

The test substance is d-lysergic acid diethylamide (LSD, lysergamide, Delysid), an indole alkaloid first synthesized in 1938 by Albert Hofmann at Sandoz Laboratories. It will be used as hydrate, which is an off-white powder. The administration will be orally in form of capsules. The supplier of LSD is Lipomed AG, Fabrikmattenweg 4, 4144 Arlesheim. Product reference and batch no. are LSD-397-FB and 397.1B10.1. According the specification sheet the HPLC purity is >98.5%. Identitity is confirmed by IR, UV, and melting point vs. reference (see attached quality certification sheet no. QA-F-20.1, 15.9.2003). An indipendent quality control is performed at the University of Bern, DKF (Prof. Dr. R. Brenneisen) to check identity by GC/MS and purity by HPLC. The QC data will be submitted to Swissmedic after study notification.



LSD: $C_{20}H_{25}N_3O$, M.wt. 323.4

The formulation of 200-□g ("Verum") and 25-□g ("Active Placebo") tablets (weight of hydrate) is performed by the Grosse Apotheke Dr. G. Bichsel, Bahnhofstr. 5a, 3800 Interlaken. Dextrose tablets are impregnated by an ethanolic solution of LSD using an appropriate technique and under GMP conditions. Verum and Active Placebo are not differing in its appearance (weight, colour, size etc.) and taste. The quality control of the tablets, performed by the DKF, includes check of identity (GC/MS, HPLC), and content

(HPLC). The QC data will be submitted to Swissmedic after study notification. The LSD tablets are stored in a locked safe and only the investigator has access to the test preparations. Supply, handling, formulation, and the clinical use of LSD must follow the regulations of the Swiss Narcotics Law. A general narcotics permit of the Federal Office for Public Health (BAG), issued on Prof. Dr. R. Brenneisen, is already existing (AB-8/5-BetmG-/06.004679, valid until 12.2009). It allows the supply and handling of all substances (including LSD) scheduled according to Art. 4 Bst d ("Illicit Substances"). A special production permit for Bichsel and a LSD trial permit for Dr. P. Gasser (main investigator) are necessary, respectively, and must be applied at the BAG.

Pharmacokinetics and Pharmacodynamics

Lysergic acid diethylamide (d-lysergic acid diethylamide, lysergide, LSD), was first synthesized by Albert Hofmann in 1938. Hofmann was also the first to describe the subjective effects of LSD in 1943 (Hofmann 2005). LSD is an ergot derivative that possesses a complex pharmacology that includes direct activation of serotonin, dopamine and norepinephrine receptors, activation of secondary messengers and alteration in gene expression (Nichols 2004; Gonzalez-Maeso et al. 2003). Psychiatrists and psychotherapy researchers conducted human LSD studies prior to the discovery of many, if not most, serotonin receptors, and to date, human LSD research has not resumed. Consequently, the mechanisms of action for the subjective or physiological effects of LSD remain uncertain. However, it is likely that LSD shares mechanisms of action with tryptamine hallucinogens such as psilocybin (Aghajanian and Marek 1999; Nichols 2004), including agonism at (activation of) $5HT_{2A}$, $5HT_{2C}$ and $5HT_{1A}$ receptors. Studies in nonhuman animals support the significance of $5HT_{2A}$ receptors in producing stimulus components of LSD in rodents (Appel et al. 2004; Marona-Lewicka et al. 2005; Nichols 2004; Winter and Rabin 1988), and some later-appearing effects of LSD may be the result of indirect or direct action at dopamine receptors (Creese et al 1975; Marona-Lewicka et al. 2005; Minuzzi et al. 2005). The role played by $5HT_{1A}$ receptors is not entirely clear, as a $5HT_{1A}$ agonist only partially substitutes for LSD in rats trained to distinguish between LSD and saline (Cunningham and Appel 1987). In vitro studies found LSD to be a powerful 5HT2C agonist (Burris et al. 1991; Sanders-Bush et al. 2004). However, while LSD had high affinity for 5HT2C receptors, it has low efficacy (Fiorella et al. 1995; Egan et al. 1998). LSD acts on a wide array of receptors, as indicated below in Table 2. LSD acts as at least a partial agonist at nearly all serotonin receptors except for $5HT_3$ (Boess and Martin 1994; Egan et al. 2000; Eglen et al. 1997; Gerald et al. 1995; Hirst et al. 2003; Nichols et al. 2002) and it possesses affinity for several dopamine receptors (Creese et al. 1975; Nichols et al. 2002). There is some evidence that LSD also acts on $alpha_1$ adrenergic receptors (Marona-Lewicka and Nichols 1995; U'Prichard 1977). Clonidine, an alpha1 adrenergic agonist, potentiated the LSD stimulus in rats (Marona-Lewicka and Nichols 1995). By contrast, LSD appears to have little to no affinity for histamine receptors (Green 1979; Nichols et al. 2002), and the only evidence of LSD action at

acetylcholine sites is indirect and functional, with the muscarinic antagonists atropine and scopolamine intensifying LSD-induced catalepsy in rats (Chiu and Mishra 1980).

When it activates the $5HT_{2A}$ receptor, LSD stimulates arachidonic acid and phosophipase C (PLC), but it stimulates more PLC than the tryptamine psilocin (Kurrasch-Orbaugh et al. 2003). This compound-specific trigger of secondary messenger systems may play a role in producing physiological or subjective effects of LSD.

Research has begun to elucidate the intracellular signaling pathways affected by LSD in neurons. There are, however, not yet any indications as to which of these pathways, if any, are involved in producing the subjective or physiological effects of LSD and other hallucinogens. LSD acts on $5\text{-}HT_{2A}$ and perhaps other receptors, to affect several different intracellular pathways: (1) calcium release and phosphoinositide turnover; (2) DDARP32, which inhibits protein phosphatase-1 and its downstream effectors GSK-3, CREB and c-Fos; and (3) upregulation of aromatic L-amino acid decarboxylase (AADC) which produces 2-phenylethylamine (2PE). Detectable changes in gene expression involve several genes implicated in synaptic plasticity, glutamate signaling, and the cytoskeletal architecture (Nichols and Sanders-Bush 2002). These include serum glucocorticoid kinase (*sgk*), neuron-derived orphan receptor 1 (*Nor1*), *ania3*, *arc*, *krox*-20, *egr-1*, *egr-2*, and *period-1* (Nichols and Sanders-Bush 2002). These last three genes were found to be increased in the mouse somatosensory cortex after LSD but not after the structurally related non-hallucinogen lisuride (Gonzales-Maeso et al. 2003).

Table 4: Affinity of LSD for Various Receptors

Receptor	Ki (nM)	Hot Ligand	Species	Source	Reference
5-HT1A	1.1	3H-8-OH-DPAT	Human	Cloned	Nichols et al 2002
5-HT1B	3.9	3H-GR-125743	Rat	Cloned	Nichols et al. 2002
5-HT1D	14	3H-5-HT	Human	Cortex	Peroutka et al. 1989
5-HT1E	93	3H-5-HT	Rat	Cloned	Nichols et al. 2002
5-HT2A	2.7	3H-DOB	Human	Cloned	Egan et al. 2000
5-HT2B	30	3H-LSD	Rat	Cloned	Nichols et al. 2002
5-HT2C	5.5	125I-DOI	Rat	Cloned	Nichols et al. 2002
5-HT3	33000	3H-Quipazine	Rat	Cortex	Milburn and Peroutka 1989
5-HT4L	1000	3H-GR-113808	Rat	Cloned	Gerald et al. 1995
5-HT5A	9	3H-LSD	Rat	Cloned	Nichols et al. 2002
5-HT5B	3.23	3H-5CT	Rat	Cloned	Boess and Martin 1994
5-HT6	2.3	3H-LSD	Human	Cloned	Hirst et al. 2003
5-HT7	6.6	3H-LSD	Rat	Cloned	Nichols et al. 2002
5-HT7L	10	3H-5-HT	Rat	Cloned	Eglen et al. 1997
Adrenergic Alpha	220	3H-Clonidine	Rat	Brain	Prichard et al. 1977
Adrenergic Beta1	140	125I-Pindolol	Rat	Cloned	Nichols et al. 2002
Adrenergic Beta2	740	125I-Pindolol	Rat	Cloned	Nichols et al. 2002
Dopamine D1	180	3H-SCH23390	Rat	Cloned	Nichols et al. 2002
Dopamine D2	120	3H-NMSP	Rat	Cloned	Nichols et al. 2002
Dopamine D3	27	3H-NMSP	Rat	Cloned	Nichols et al. 2002
Dopamine D4	56	3H-NMSP	Rat	Cloned	Nichols et al. 2002
Dopamine D5	340	3H-SCH23390	Rat	Cloned	Nichols et al. 2002
Histamine H1	1540	3H-Pyrilamine	Rat	Brain	Nichols et al. 2002

Table adapted from Baggott, protocol for pilot LSD study, unpublished.

Primary Pharmacodynamics

Drug Activity Related to Proposed Action

LSD in combination with psychotherapy produces lasting reduction in anxiety and improves quality of life in people with potentially fatal illness partially or wholly through its hallucinogenic, or psychedelic, effects (Nichols 2004; see also Grof et al. 1973; Kurland et al. 1973; Pahnke et al. 1969). However, none of the human LSD studies sought out to determine the specific pharmacological mechanisms producing alterations in consciousness. Furthermore, the effects of LSD were considered within the context of a psychotherapeutic setting wherein the environment and therapist response to the participant helped produce and amplify the emotional intensity and sense of transformation occurring during LSD psychotherapy. As discussed above, it appears that LSD alters consciousness through its action on $5HT_{2A}$, $5HT_{2C}$ and $5HT_{1A}$ receptors. Future research may discover roles for other serotonin receptors, such as the $5HT_{5A}$ (Grailhe et al. 1999) or $5HT_6$ (Boess et al. 1997; Hirst et al. 2003) receptors, but to date

these actions are hypothetical and based on non-human animal or in vitro research only. Likewise, it is possible that compound-specific alterations in secondary messenger signaling after receptor activation ("allosteric receptor trafficking") might play a role in producing the subjective effects of LSD (Kurrasch-Orbaugh et al. 2003), but to date there is no support for these relationships.

Some previous research indicated that LSD produced analgesia that outlasted its subjective effects (Kast 1966). The mechanism of action for this effect is unclear, and might relate to direct receptor activation, allosteric modulation or changes in gene expression, described above. One possible candidate is an interactions between LSD and the neuropeptide Substance P, a modulator of pain perception. At least one study found that intrathecal (subarachnoid space) injections of 25 mcg/kg LSD (approximately 1750 mcg in an average person) prevented desensitization to repeated injections of substance P, so that pain-response behavior remained the same, but mice given Freund's adjuvant first and then LSD showed enhanced desensitization to substance P (Larson et al. 1989). It is not clear whether these changes are relevant to human LSD studies, given the high doses used and central route of administration.

Safety Pharmacology

Several hundred studies in various animal species have indicated the low toxicity of LSD. LD_{50} values for LSD are 50-60 mg/kg iv for mice, 16.5 mg/kg for rats, and 0.3 mg/kg for rabbits (Clark 1987: Haddad et al. 1998; Rothlin 1957). On the basis of a single case report, estimated lethal dose in humans is 0.2 mg/kg or about 14,000 mcg (Klock et al. 1975). All past and proposed human LSD research proposes administering doses that are a fraction of the doses listed above.

LSD is not associated with disease or damage to any organ or system (Nichols 2004), with most LSD distributed to plasma, liver and brain in cats given 1 mg/kg LSD (Axelrod et al. 1957). A recent search conducted on the PubMed database in September, 2005 using the words "LSD" or "lysergic acid diethylamide" and various organs or medical terms ("heart," "cardiac," "liver") and "adverse event", and an additional search conducted in August 2006 with the words "lysergic acid diethylamide" uncovered a single case report of a mesenteric mass in a repeated LSD user (Berk et al. 1999), and failed to find any case reports of serious adverse effects or adverse effects on the heart, liver or kidney. The lack of case reports describing serious adverse events is especially notable given that people have used LSD both within and outside the confines of medical research for over fifty years. Risk of acute or long term physiological adverse effects after administering sub-hallucinogenic or typical doses of LSD appears to be minimal.

To date, there have been only two fatalities deemed directly due to LSD (Fysh 1986; Griggs and Ward 1977). However, both cases were poorly or incompletely reported, and thus the role played by LSD is questionable. In one case, the fatality was discovered when the body was found one month after taking a dose of LSD estimated to be extremely high,

so the circumstances surrounding actual death are uncertain (Griggs and Ward 1977), and in the other case, the cause of death is unstated, and the author fails to provide any medical history or proximal cause of death in the individual (Fysh 1985). Aside from these incomplete and ambiguous reports, no other fatalities directly due to LSD have been reported. Animals given a lethal dose of LSD usually die from acute respiratory depression (Rothlin 1957; Haddad et al. 1998), and high doses of LSD can also produce hyperthermia in rodents (Clark 1987). Humans exposed to extremely high doses of LSD may respond similarly, with eight individuals exhibiting hyperthermia, bleeding and respiratory arrest and coma after unintentionally insufflating more than 1 mg/kg LSD (Klock et al. 1977).

The most common acute adverse effects of LSD are all psychological, and include anxiety or panic response, a prolonged unpleasant experience (or "bad trip") and psychotic reactions. As reported in several reviews, transient anxiety or depression after taking LSD has been reported in many cases (Grinspoon and Bakalar 1979; Grof 1980; Strassman 1984). These cases typically resolve spontaneously with supportive care, but in some cases included treatment with anti-psychotic or sedative drugs as well. In most cases, emergency room admissions related to anxiety or psychological distress after LSD do not require continued hospitalization (Nichols 2004; Strassman 1984; Halpern and Pope 1999). A case series not evaluated by Nichols (2004) described similar acute adverse effects in people reporting LSD use and reached similar conclusions to those of Nichols (Blaho et al. 1997). Both acute and prolonged anxiety or psychotic reactions to LSD appear to be dose-dependent (Cohen 1960). The occurrence and intensity of anxiety or panic responses can be reduced through providing participants with information on potential drug effects, supervision and monitoring of participants for the duration of drug effects, and using ascending dose designs.

People who have taken LSD in uncontrolled settings may engage in reckless behavior, such as driving while intoxicated. The risk of reckless behavior occurring during controlled studies can be prevented or greatly reduced through continued supervision by the researchers and by keeping participants within the confines of the clinic or laboratory where the study takes place for the duration of drug acute effects.

Some individuals enter transient and sometimes prolonged psychotic states after LSD use (Cohen 1960; Halpern and Pope 1999; Strassman 1984). Researchers who reviewed case series and reviews of the relationship between LSD use and subsequent occurrence of psychosis note in these studies, evaluation of psychosis is made after LSD use only, and not prior to use (Strassman 1984), making it difficult to determine the degree of change after LSD use. After examining the literature, Strassman concluded that LSD might trigger psychotic episodes in people already vulnerable to psychosis rather than directly causing psychosis. Research into the prevalence of prolonged psychiatric reactions (as lasting more than two days) reported rats ranging from 0.08% in healthy volunteers to 0.18% in psychiatric patients (Cohen 1960; Malleson 1971). These findings, in combination with more recent case series described above, indicate that the occurrence of

prolonged psychiatric symptoms after LSD is extremely rare. Early research with LSD related compounds did not apply as stringent criteria for participant selection or screening as would be used now, so the low rate of psychosis from these early studies likely overestimates the rate of prolonged psychological responses that might occur in a study that screens for past or present psychotic disorders. The occurrence of transient or persistent psychosis can be prevented or further reduced by screening subjects on the basis of past and current mental health and excluding people on the basis of the presence of past or current psychotic disorders or first-degree relatives, such as biological parent or sibling, with psychotic disorders.

Earlier studies found changes in personality or neuropsychological function after frequent chronic LSD use. A review of these studies concluded that they all shared a number of methodological flaws (Halpern and Pope 1999) that included retrospective study design and failure to account for the effects from use of other drugs. In their review and analysis, Halpern and Pope concluded that long-term changes in personality or psychological function, if they existed at all, were liable to be subtle or not clinically significant. Careful monitoring of participants during the course of a study could allow investigators to spot any indicators of personality change.

Some people who have used serotonergic hallucinogens, such as LSD or psilocybin, experience persistent and distressing alterations in mostly visual perception that last from weeks to years after use. This condition is now diagnosed as hallucinogen persistent perception disorder (HPPD), and is not referred to by the term “flashbacks,” which better describes an experience more akin to traumatic recall of an intensely upsetting experience, as a “bad trip.” To date, there are no reports describing prevalence of HPPD in the general population, but an examination of previous reports and estimates of use of LSD and other hallucinogens use in the US suggests that HPPD is very rare (Halpern and Pope 2003; Johnson and O’Malley 2004). Halpern and Pope note that many to most previous studies were affected by selection bias. These reports also contained information supporting alternative explanations of flashbacks or HPPD, described in more detail in the “Risks to Participants” section. Preliminary data collected by Baggott suggests that no more than 1% of 1000 hallucinogen users surveyed experience HPPD (Baggott M, personal communication to L Jerome October, 2006). The risk of HPPD occurring after LSD administration can be reduced by screening participants for potential risk factors such as substance dependence and through excluding people reporting HPPD after prior use of hallucinogens.

Abuse Liability

LSD possesses little or no abuse liability (Nichols 2004). Only one study found that LSD produced conditioned place preference, an indicator of reward value, in rats, but only in males of a specific rat strain (Meehan et al. 1998; Parker 1996). Most drugs with similar pharmacological profiles, such as psilocybin, also fail to produce consistent self-administration in rodents or monkeys (Fantegrossi et al. 2004; Nichols 2004). Rhesus

monkeys found LSD to be aversive, working to avoid a cue associated with LSD infusion (Hoffmeister 1975). There is no human LSD dependence syndrome, and prevalence of LSD use in adolescents and young adults seems to remain relatively stable over time in the US (Johnston and O'Malley 2003), as well as in Europe (see for instance Soellner 2005).

Pharmacokinetics/Toxicokinetics

Absorption, Distribution, Metabolism, Excretion

LSD is capable of eliciting pharmacological effects after oral doses as low as 0.26 µg/kg (Murphree 1962), but produces its distinctive effects at oral doses of about 1 µg/kg. Aghajanian and Bing (1964) administered 2 µg/kg intravenous LSD using a 1.5 min infusion to 5 male volunteers. They found LSD had an elimination half-life of 175 min, with kinetics well described by a two-compartment model (Wagner et al. 1968). Plasma levels, illustrated in Figure 1, correlated well with performance on an arithmetic task. More recently, Papac and Foltz (Papac and Foltz 1990) reported that 1 µg/kg oral LSD given to a single male volunteer had an apparent plasma half-life of 5.1 h with a peak plasma concentration of 1.9 ng/ml at 3 h post-dose. Comparison of this study with the earlier intravenous one indicates that LSD is well absorbed with a bioavailability that may be around 70%.

Several groups have characterized urinary metabolites. The main urinary metabolite in biosamples from two illicit LSD users was 2-oxo-3-hydroxy-LSD (Canezin et al. 2001). This metabolite may be as much as 16 to 43 times higher than LSD in blood and urine specimens (Poch et al. 1999; Cai and Henion 1996; Reuschel et al. 1999). Nor-LSD, Nor-iso-LSD, lysergic acid ethylamide, trioxylated-LSD, lysergic acid ethyl-2-hydroxyethylamide and 13 and 14-hydroxy-LSD and their glucuronide conjugates have also been detected in urine.

Cai and Henion investigated the in vitro metabolism of LSD using human liver microsomes and high-performance liquid chromatography and capillary electrophoresis coupled with tandem mass spectrometry (Cai and Henion 1996). Lysergic acid ethylamide and 2-oxo-LSD along with several mono- and trioxylated metabolites of LSD were identified. They concluded that de-ethylation is the major route of LSD metabolism by human liver microsomes. Klette and colleagues (Klette et al. 2000) studied the formation of 2-oxo-3-hydroxy-LSD and 2,3-dihydroxy-LSD in human liver microsomes and preserved hepatocytes, finding that both metabolites formed in a time-dependent manner that could be prevented with the nonspecific cytochrome P-450 inactivator 1-aminobenzotrizole. Klette et al. suggest three possible metabolic pathways, summarized in Figure 1.

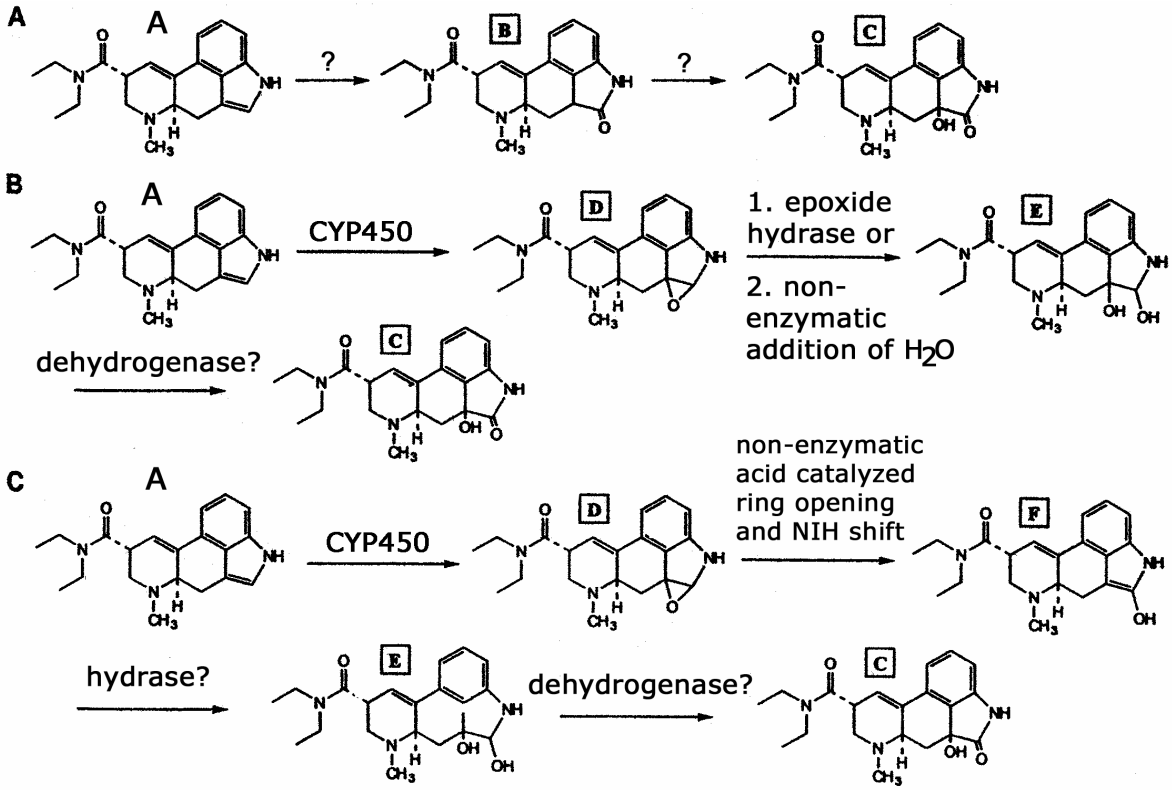


Figure 1. LSD metabolic pathways: A) via 2-oxo LSD intermediate; B) via epoxide intermediate and epoxide hydrase/nonenzymatic addition of water, unknown dehydrogenase activity; C) via epoxide intermediate, N.I.H. shift, Cyt P450, and unknown dehydrogenase activity. [A] LSD, [B] 2-oxo LSD, [C] 2-oxo-3-hydroxy-LSD, [D] LSD 2,3 epoxide, [E] 2,3-dihydroxy LSD, [F] 2-hydroxy LSD.
From Klette et al. 2000. Figure from Baggott, protocol for pilot LSD study, unpublished).

The distribution of LSD has been investigated in the mouse (Stoll et al. 1955, Haley and Rutschmann 1957); guinea pig, rhesus monkey, rat (Siddik 1979); and the cat (Axelrod 1957). Results from these latter two studies have been summarized in Tables 3 and 4, below.

Table 4: Tissue Distribution of LSD in the Rat*

Tissue	%	mg/kg
Gut Contents	70.2	…..
Liver	2.31	3.89
Spleen	0.08	1.33
Brain	0.02	0.21
Heart	0.03	0.55
Lung	0.12	1.13
Skeletal Muscle	0.09	0.4
Kidney	0.44	3.28
Uterus and Ovaries	0.06	0.74
Adipose Tissue	0.04	0.24
Gut (less contents)	10.2	17.8
Blood	…..	0.46
Rest of Carcass	7.55	0.53

*Measures were made three hours after administration of 1 mg/kg of labeled LSD intraperitoneally (from Boyd 1956). Table from Baggott, protocol for pilot LSD study, unpublished

Table 5: Tissue Distribution of LSD in the Cat*

Tissue	mg/kg
Plasma	1.75
Cerebrospinal fluid	0.36
Brain	0.52
Liver	0.67
Kidney	0.53
Muscle	0.2
Heart	0.3
Lung	0.87
Spleen	0.38
Intestine	0.39
Fat	0.2
Bile	1.85

*Measures were made 90 minutes after the intravenous administration of 1 mg/kg, of LSD (from Axelrod et al. 1957). Table from Baggott, protocol for pilot LSD study, unpublished

Toxicology

Acute toxicity

As noted in "Safety Pharmacology" above, LSD has little or no physical toxicity. LD_{50} values for LSD are listed above in "Safety Pharmacology" and far exceed doses administered in human LSD research.

Reproductive Toxicity

In vitro studies conducted in the 1960s and 1970s found signs of chromosomal damage from exposure to LSD (Cohen et al. 1967), but later investigations failed to support these claims (Dishotzky et al. 1971; Cohen and Shiloh 1977). A review of 4815 former participants in trials with LSD found that 170 infants of participants, or 0.03%, had two commonly occurring birth defects, syndactyly or congenital dislocation of the hip (Grinspoon and Bakalar 1979). Examination of 148 pregnancies in illicit LSD users and matched controls also failed to find an association between use of LSD and rate of birth defects (Grof 1980; 2000). It thus appears that LSD is neither mutagenic nor teratogenic. Some ergolines have been used to induce labor, and there is limited evidence that LSD might promote uterine contractions in uterine tissue (Zhang and Dyer 1993). Past research was often conducted in men only, and current or planned research will restrict study entry to women who are using an effective means of contraception.

Previous Human Experience

LSD was given to thousands of individuals in the context of psychiatric and psychological research or during psychotherapy in the 1950s and 1960s (Nichols 2004; Strassman 1995). At the time, some researchers believed that LSD and other hallucinogens produced a "model psychosis" that would allow them to experimentally reproduce and study this mental disorder. Researchers investigated LSD effects on affect, perception, cognition, creativity and sleep (Goldberger 1966; Jarvik et al. 1955; Muzio et al. 1966; Savage 1952; Zegans et al. 1967). These studies found that LSD made it difficult to concentrate and to perform some cognitive tasks. Others employed LSD as a psychotherapeutic adjunct in the treatment of anxiety, depression, neurotic disorders and alcoholism (Grof et al. 1973; Jensen 1962; Ling and Buckman 1963; Martin 1957; Pahnke et al. 1970; Savage and McCabe 1973). There appears to be no investigations of the neuroendocrine effects of LSD in humans, perhaps because interest and capacity to assess these hormones arose after human LSD research had ceased. Research also examined the effects of LSD in people with cancer, reporting reduced anxiety and fear of death, and improved mood (Grof et al. 1973; Kurland 1973; Pahnke et al. 1969). People with cancer sometimes reported experiencing analgesia after receiving LSD, with analgesia outlasting subjective drug effects (Kast and Collins 1964; Kast 1966; Kast 1970). After a case series found that LSD and psilocybin partially or completely interrupted cycles of cluster headaches (Sewell and Halpern 2006), there are plans underway to perform controlled studies in treating this excruciating type of headache.

People have continued to self-administer LSD in non medical settings, as described earlier in "Abuse Liability," above. People have reported using LSD in non medical settings over the last forty years. When available, narrative reports of LSD experiences match findings from clinical trials (Hofmann 1979), with people reporting sometimes profound changes in perception, mood and cognition.

There is a large literature on LSD in therapeutic (Grinspoon and Bakalar 1979; Grof 2000; 1980; Mangini 1998; Strassman 1995) and research (Nichols 2004) contexts. Psychotherapists and psychotherapy researchers either used repeated low doses, or relied on larger single doses in the context of psychotherapy. These early studies reported successful treatment outcomes with LSD-assisted psychotherapy (Strassman 1995; Nichols 2004). However, researchers did not conduct or document these studies with the rigor expected of current psychiatric research, so that many question the evidence these studies provide for the efficacy of LSD in psychotherapy (Nichols 2004). There have been no new human LSD studies published in the last two decades, but the large number of previous human trials indicates that LSD can be safely administered within a research or psychotherapeutic setting.

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Signature Page:

LSD – assisted psychotherapy in persons suffering from anxiety associated with advanced-stage life threatening diseases. A phase-II, double-blind, placebo-controlled dose-response pilot study

I have read the foregoing protocol and agree to conduct the clinical trial as outlined. I agree to conduct the trial in compliance with all applicable regulations and guidelines as stated in the protocol and other information supplied to me, including ICH Topic E6.

_____ _____

Investigator Signature Date

Print name:_____

On behalf of MAPS, I confirm that the sponsor will comply with all obligations as detailed in all applicable regulations and guidelines. I will ensure that the investigator is informed of all relevant information that becomes available during the conduct of this clinical trial.

_____ _____

Medical Monitor Signature Date

Print name:_____

Appendix A: Investigators

Principal Investigator

Name:	Gasser	
Vorname:	Peter	
Adresse:	Hauptbahnhofstr. 5, 4500 Solothurn	
Geburtsdatum:	10. Februar 1960	
Zivilstand:	verheiratet, 3 Kinder	
Berufl. Ausbildung:		
Studium:	1980 - 1986	Humanmedizin in Fribourg und Bern
	1986	Staatsexamen in Bern
Dissertation:	1987	Ein Ansatz zur Erfassung von Gesundheitsproblemen in der ambulanten Versorgung aus der Sicht von Patienten und ihren Ärzten (Leitung Prof. Th. Abelin, Bern)
Weiterbildung:	1987	Assistenzarzt Medizinische Klinik Bürgerspital Solothurn (Prof H. Bürgi)
	1988 - 1989	Assistenzarzt Psychiatrische Universitätspoliklinik Bern (Prof E. Heim)
	1990 – 1991	Assistenzarzt Kantonale Psychiatrische Klinik Solothurn (Dr. med. F. Vadasz)
	1992	Facharzt FMH für Psychiatrie und Psychotherapie
	1992 - 1996	Oberarzt Kantonale Psychiatrische Klinik Solothurn
	seit 1997	eigene psychiatrisch-psychotherapeutische Praxis
Psychotherapeutische Ausbildung:	1988	Ausbildung in Problemorientierter Therapie (POT, Kurztherapie)
	1989	Ausbildung in kontextueller Familientherapie (nach Boszormeny-Nagy)
	1989 - 1992	Ausbildung in Psycholytischer Psychotherapie bei der Schweizerischen Ärztegesellschaft für Psycholytische Psychotherapie (SÄPT)
	seit 1997	Präsident dieser Gesellschaft
	1995 - 2000	Ausbildung in Bioenergetik bei Schweiz. Gesellschaft f. Bioenergetische Analyse und Therapie
Publikationen zum Thema:	- Die Psycholytische Psychotherapie in der Schweiz 1988 – 1993 Eine katamnestische Erhebung. In: Jahrbuch für transkulturelle Medizin und Psychotherapie 1995, S. 143-162.	
	- Die Psycholytische Psychotherapie in der Schweiz von 1988 – 1993. Eine katamnestische Erhebung. Schweizer Archiv für Neurologie und Psychiatrie 147 (1996), S. 59-65.	

Co-Therapist

Name:	Speich
Vorname:	Barbara
Adresse:	Haldenweg 52; 4500 Solothurn
Geburtsdatum:	11. April 1954
Zivilstand:	ledig

Diplomausbildungen:	1971 – 1974	Laborantin
	1984 – 1987	Pflegfachfrau DN II Schwerpunkt Psychiatrie
	1993 – 1995	Berufsschullehrerin im Gesundheitswesen,
	2001 – 2004	Supervisorin und Organisationsentwicklerin BSO / EAS
Weiterbildung:	1988	Führungsgrundsätze
	1989	Managementausbildung für Stations- und Abteilungsleitung
	1992 – 1993	Weiterbildung zur Unterrichtsassistentin,
	1994	Grundkurs Kinästhetik,
	1999	TA – 101 – Grundlagenkurs wpi
	2005 – 2007	Transaktionsanalyse
berufliche Tätigkeiten:	1974 – 1976	Laborantin, Müller AG Seon
	1977 – 1978	Instruktorin, Arova Schaffhausen
	1978 – 1980	Laborantin, Cardinal Brauerei Wädenswil
	1980 – 1981	Laborantin, Schöller Hardturm AG Zürich
	1981 – 1982	Hilfsarbeiterin Bauarbeiten, Umbuu AG Engi
	1982 – 1983	Elektro-Hilfsmonteurin, Elektrizitätsversorgung Engi
	1987 – 1988	Psychiatrieschwester, Psychiatrische Klinik Schlössli Oetwil am See
	1988 – 1990	Stellvertretung Abteilungsleitung, Psychiatrische Klinik Schlössli Oetwil am See
	1990 – 1992	Abteilungsleitung, Psychiatrische Klinik Solothurn
	1992 – 1993	Unterrichtsassistentin, Kantonale Pflegeschule LaSol Solothurn
	1995 - 1999	Berufsschullehrerin im Gesundheitswesen, Kantonale Pflegeschule LaSol Solothurn
	1999 – 2000	Berufsschullehrerin im Gesundheitswesen, Bildungszentrum für Gesundheitsberufe, Olten
	2000 – heute	Berufsschullehrerin im Gesundheitswesen, Psychiatrische Dienste, Solothurner Spitäler AG Solothurn
	2002 – heute	Selbständige Tätigkeit als Supervisorin und Organisationsentwicklerin

Appendix B: Daily Diary - example

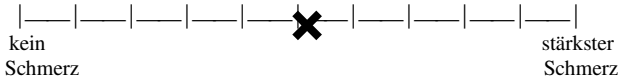
A diary card which collects the following information will be handed out. For ease of completion by the subject the format will be in a larger size.

LSD – unterstützte Psychotherapie

Tagebuch von ProbandIn Nr.

Erklärung:

1. Nummerieren Sie die Tage fortlaufend, beginnend mit dem Tag 1, dem Tag an dem Sie die Einverständniserklärung unterzeichnet haben.
2. Bitte tragen Sie für jeden Tag ein, welche Schmerz- und Beruhigungsmedikamente Sie eingenommen haben. Wenn sich gegenüber dem Vortag nichts verändert hat, können Sie Gänsefüsschen (〃) machen.
3. Wenn Sie nach der ersten (und natürlich auch nach der zweiten) ganztägigen Sitzung mit LSD (oder Placebo) unerwünschte Wirkungen dieser Behandlung verspüren, so tragen Sie diese bitte ein. Tragen Sie sie auch ein, wenn sie nicht sicher sind, ob ein Zusammenhang zwischen dem Problem und der Sitzung besteht.
4. Tragen Sie für jeden Tag auf der Schmerzskala ein, wie starke Schmerzen Sie im Ganzen gesehen in den letzten 24 Stunden hatten. Dabei steht das linke Ende der Skala für „keine Schmerzen“ und das rechte Ende für „stärkste Schmerzen“, die Sie sich auszuhalten vorstellen können. Die Skala geht von null bis zehn. Sie ist ca. 10 cm lang, d.h. jede Verschiebung um einen cm nach rechts bedeutet eine Schmerzzunahme um eine Einheit oder 10%. In der Mitte würden Sie ein Kreuz für mittelstarke Schmerzen machen. Schmerzempfindung ist etwas Subjektives. Tragen Sie den Schmerz so ein, wie Sie ihn empfinden. Bei unten stehendem Beispiel wird mit dem Kreuz (**X**) ausgedrückt, dass die betreffende Person an diesem Tag mittelstarke Schmerzen verspürte.



5. Bei Fragen wenden Sie sich bitte an Dr. P. Gasser (Tel. 032 622 40 20).
6. Um die Anonymität Ihrer Angaben zu wahren, sollte oben auf dem Blatt nur die Ihnen für diese Studie zugeteilte Nummer dastehen

LSD – unterstützte Psychotherapie

Tagebuch von ProbandIn Nr.

Tag Nummer	Eingenommene Medikamente	Festgestellte unerwünschte Wirkungen der LSD-Sitzung	Schmerzbeurteilung und Schmerzveränderung
			|——|——|——|——|——|——|——|——|——|——| kein Schmerz … stärkster Schmerz
			|——|——|——|——|——|——|——|——|——|——| kein Schmerz … stärkster Schmerz
			|——|——|——|——|——|——|——|——|——|——| kein Schmerz … stärkster Schmerz
			|——|——|——|——|——|——|——|——|——|——| kein Schmerz … stärkster Schmerz
			|——|——|——|——|——|——|——|——|——|——| kein Schmerz … stärkster Schmerz

Appendix C: Letter for Recruitment of Participants

This letter is reduced in size here for better presentation

Dr. med. Peter Gasser
Psychiatrie + Psychotherapie FMH
Hauptbahnhofstr. 5
4500 Solothurn

Abs.: Dr. P. Gasser, Hauptbahnhofstr.5, 4500 Solothurn
An allgemeinmedizinisch, internistisch
und onkologisch tätige AerztInnen.
An Beratungsstellen und Selbsthilfe-
Gruppen der Schweiz

LSD – unterstützte Psychotherapie
bei Personen mit Angstsymptomatik
in Verbindung mit fortgeschrittenen lebensbedrohenden Erkrankungen

Solothurn, Datum des Poststempels

Sehr geehrte Damen und Herren

- Seit dem (Datum) führe ich eine psychotherapeutische Studie durch, bei welcher unter Zuhilfenahme der bewusstseinserweiternden Substanz LSD (Lysergsäurediäthylamid) in einem kontrollierten therapeutischen Rahmen Patientinnen und Patienten behandelt werden können, welche unter Angstsymptomen leiden im Rahmen von fortgeschrittenen, potentiell tödlich verlaufenden Erkrankungen. Am ehesten kommen Menschen mit metastasierenden Krebserkrankungen in Frage, aber auch solche mit nicht weiter behandelbaren Autoimmunerkrankungen oder Infektionserkrankungen wie AIDS, sofern eine Angstsymptomatik vorhanden ist und herkömmliche Behandlungsformen nicht erfolgreich waren oder nicht gewünscht werden. In erster Linie geht es um die Themen Angst vor dem Sterben, dem Leiden und dem Tod, um nicht bearbeitete und nicht mehr bearbeitbare Probleme und Konflikte und um den Wunsch nach einer spirituellen Erfahrung, welche in dem hier vorgestellten Kontext behandelt werden sollen.

- Die Studie, die ich durchführe, ist eine Untersuchung mit insgesamt 12 Probanden. Sie wurde von der zuständigen Ethikkommission, von Swissmedic (Heilmittelkontrolle) und dem Bundesamt für Gesundheit geprüft und zugelassen.

- Psychotherapie mit Zuhilfenahme von LSD als Sterbebegleitung bei Krebskranken wurde bereits in den sechziger und Anfang siebziger Jahre des letzten Jahrhunderts durchgeführt mit guten Ergebnissen, was Reduktion von Angst und Zunahme der Lebensqualität anbetrifft. Bei der hier vorgestellten Studie werden sie PatientInnen zwei ganztägige Sitzungen mit LSD in Einzelbehandlung mit permanenter therapeutischer Begleitung absolvieren. Die Sitzungen finden im Abstand von etwa 4 Wochen statt. Die ganze Behandlung ist eingebettet in sechs bis acht einstündige Gesprächspsychotherapiesitzungen.

- Bei Interesse oder weiterführenden Fragen bitte ich Sie, mit mir Kontakt aufzunehmen. Gerne werde ich Sie persönlich mündlich informieren oder Sie mit dem benötigten schriftlichen Material beliefern.

Freundliche Grüsse

Dr. med. Peter Gasser

Tel.: 032 622 40 20 • Fax: 032 622 42 81 • e-Mail: pgasser@gmx.net • EAN-Nr.:7601000147660