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LSD-assisted psychotherapy for anxiety associated with a life-threatening disease: A qualitative study of acute and sustained subjective effects

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Abstract

Objective: A recently published study showed the safety and efficacy of LSD-assisted psychotherapy in patients with anxiety associated with life-threatening diseases. Participants of this study were included in a prospective follow-up.

Method: 12 months after finishing LSD psychotherapy, 10 participants were tested for anxiety (STAI) and participated in a semi-structured interview. A Qualitative Content Analysis (QCA) was carried out on the interviews to elaborate about LSD effects and lasting psychological changes.

Results: None of the participants reported lasting adverse reactions. The significant benefits as measured with the STAI were sustained over a 12-month period. In the QCA participants consistently reported insightful, cathartic and interpersonal experiences, accompanied by a reduction in anxiety (77.8%) and a rise in quality of life (66.7%). Evaluations of subjective experiences suggest facilitated access to emotions, confrontation of previously unknown anxieties, worries, resources and intense emotional peak experiences à la Maslow as major psychological working mechanisms. The experiences created led to a restructuring of the person's emotional trust, situational understanding, habits and world view.

Conclusions: LSD administered in a medically supervised psychotherapeutic setting can be safe and generate lasting benefits in patients with a life-threatening disease. Explanatory models for the therapeutic effects of LSD warrant further study.

Keywords

LSD, psycho-oncology, psycholytic therapy, psychedelics, hallucinogens

Clinical Trial Registration

ClinicalTrials.gov identifier: NCT00920387

Introduction

The use of mind-altering drugs for religious and healing purposes has been known for thousands of years. The drug-induced altered state of consciousness is used to travel to other realms of consciousness to integrate and heal the state of disorder (Eliade, 1975; Schultes and Hofmann, 1980).

When the intense psychological effects of LSD were discovered in 1943, a rich period of scientific and therapeutic investigations into mind-altering substances started (Hintzen and Passie, 2010). LSD was used in the treatment of anxiety, depression, psychosomatic diseases and addiction (Abramson, 1967). After Kast's accidental discovery of LSD's effects on pain alleviation and psychological well-being in patients with end-stage cancer (Kast, 1967), some studies on LSD-assisted psychotherapy were conducted in this group of patients (e.g. Kurland, 1985; Pahnke, 1969; Richards et al. 1977).

Psychological treatment of people experiencing the existential challenge of suffering from a life-threatening disease and those who are in the process of dying is still mostly inadequate. Typically, these patients suffer from isolation, anxiety and depressive symptoms. There is obviously a need for more effective treatments (Schweizer Krebsliga, 2005).

The present study was designed to investigate one approach to this dilemma that appears promising: sensible and carefully supervised use of LSD in conjunction with intensive psychotherapy. In line with another recent investigation (Grob et al., 2011), the present pilot study included patients suffering from existential anxiety induced by a life-threatening disease. Results relating to safety and efficacy have already been published (Gasser et al., 2014). In the present study, we evaluate long-term effects on anxiety and explore subjective experiences and lasting psychological changes.

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Psychological effects of LSD

At a psychological level, the action of LSD (100–250 μg p.o.) increases sensory perception with illusionary changes of perceived objects, synesthesia, and enhanced mental imagery. Affectivity is intensified. Thoughts are accelerated, with their scope usually broadened to include new associations and altered interpretation and meanings of relationships and objects. LSD induces a dream-like alteration of consciousness with increased affectivity and enhanced production of inner stimuli. Without any clouding of consciousness, the dream-like altered state is experienced with full awareness of the self and good memory of the experience. Hypermnesia and enhanced memory processes typically occur. Ego identification and ego boundaries are weakened (Grof, 1980; Leuner, 1962). The effects of LSD last for 6–9 h (Passie et al. 2008).

LSD has been described as a 'non-specific amplifier of the unconscious' (Grof, 1975; Leuner 1981), because it promotes the latent psychodynamics of the patients and enables access to thoughts, associations, feelings and inner processes, which are usually excluded from consciousness. Some individuals report deeply touching, 'religious–mystical' and perspective-altering experiences on LSD/psilocybin (Griffiths et al., 2006; McGlothlin et al., 1967).

Neurobiological effects of LSD-like hallucinogens

Indolealkylamine hallucinogens such as LSD and psilocybin have high affinity to 5-HT receptors (Nichols, 2004; Pierce and Peroutka, 1989) with the 5-HT2A receptor as the primary site of action and significant modulation by 5-HT2C and 5-HT1A receptors (Fiorella et al., 1995; Vollenweider et al., 1998). Many indolealkylamine hallucinogens have higher affinity at other 5-HT receptors than at 5-HT2A as well as effects on dopamine and adrenergic receptors (Nichols, 2004). The activation of the 5-HT2A receptor may therefore be a necessary but not sufficient condition for eliciting their effects (Halberstadt and Geyer, 2011; Meert, 1996).

Experimental results by Béïque et al. (2007) suggest that 5-HT2A activation directly enhances the activity of neuronal networks in the prefrontal cortex, with some subpopulations of 5-HT2A-activated pyramidal cells playing a significant role (Halberstadt and Geyer, 2011). This (excessive) activation may destabilize prefrontal recurrent circuits, which then facilitates the sensory/cognitive effects of hallucinogens. By means of 5-HT2A activation, hallucinogens enhance glutamatergic transmission in the prefrontal cortex (PFC) which may also contribute to the effects of hallucinogens by altering cortico-cortical and cortico-subcortical transmissions (Martín-Ruiz et al., 2001; Winter et al., 2004). Activation of 5-HT2A and 5-HT1A receptors in the medial PFC (mPFC) also has downstream effects on serotonergic and dopaminergic activity by means of descending projections to the dorsal raphe and the ventral tegmental area (Puig et al., 2003) and of dopamine in mesocortical areas in animals (Vazquez-Borsetti et al., 2009) and humans (Vollenweider et al., 1999). 5-HT2A receptors are also widely expressed in the thalamus (Cyr et al., 2000). The reticular nucleus of the thalamus serves as a sort of gate for processing signals to the cortex (Behrendt, 2003) and its 'filtering' function might be altered by hallucinogen-induced 5-HT2A activation (Vollenweider and Geyer, 2001).

Neurometabolic and cerebral blood flow studies with hallucinogens in humans showed partially incongruent results (e.g. Carhart-Harris et al., 2012a; Gouzoulis-Mayfrank et al., 1999; Vollenweider et al., 1997). Significant changes in brain activity were shown in the right hemisphere, some limbic/paralimbic structures, and the PFC.

Materials and methods

Ethics

The initial phase II double-blind, active placebo-controlled, randomized clinical trial (MAPS, 2007) was approved by the Ethics Committee of the Canton of Aargau, Switzerland; Swissmedic, the drug regulation authority; the Swiss Federal Office for Public Health (BAG) and US Food and Drug Administration (IND # 101,825) and was conducted in accordance with Good Clinical Practices (GCP). The Long-Term Follow-Up investigation (LTFU) was designed when the study was already running and was implemented as an amendment to the initial study.

Procedure

The participants underwent a 3 month treatment phase with 6–8 psychotherapy sessions in order to build up a therapeutic relationship. Two LSD experiences were embedded in the therapeutic process at a 4–6-week interval (Figure 1). Two therapists guided the session, which lasted 8–10 h, with music, short talks and other interventions. The participants stayed overnight in the physician's office. After an integrative talk the following morning, the participant was released home (Gasser et al., 2014).

Participants

Twelve participants qualified to participate in the initial study. Details of recruitment are described elsewhere (Gasser et al., 2014). They were randomly assigned to a full-dose group (N=8) with two guided LSD sessions (LSD 200 μg) or to an active placebo group (N=4) with two guided active placebo sessions (LSD 20 μg). A dose of 200 μg was chosen so as not to overwhelm the patients, but being high enough to allow psychedelic peak experiences. The initial study was controlled for, but LTFU did not look for the concomitant use of other medications.

When unblinding the assignments at the 2 month follow-up therapy session, those who learned that they had been in the placebo group could choose to crossover to two guided sessions with 200 μg of LSD.

Participant #2 chose not to crossover (= no full dose) and did not qualify for LTFU. Participant #4 died 6 months after end of the initial study. The remaining 10 participants qualified for LTFU. Participant #3 did not send back the STAI questionnaire and was excluded from the quantitative analysis. Participant #9 did not allow audio recording of the LTFU interview thus was not included in the qualitative analysis.

Seven of the 10 participants (four females, six males; 39–64 yrs., mean = 51.1 yrs.) had life-threatening cancer as primary diagnosis. The other participants suffered from life-threatening autoimmune, neurological and rheumatological diseases. Participant #5

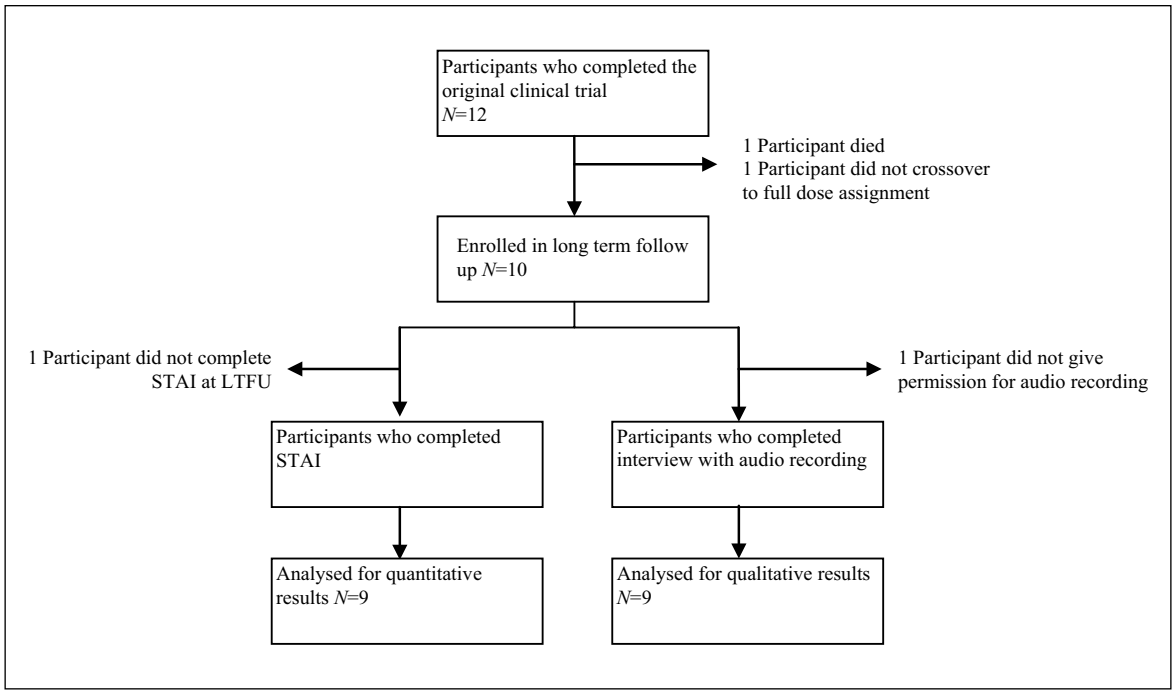

Figure 1. Flow chart for LTFU.

had previous experience of LSD; all others were naïve to the drug. Table 1 shows the demographic data.

Psychometric measures for LTFU

The Spielberger State and Trait Anxiety Inventory (STAI) Form X served as the primary outcome measurement of anxiety (Spielberger et al., 1970). Measurements were taken at the baseline, 1 week after experimental sessions, and at 2-month and 12-month follow-ups. Other measures were carried out during the treatment phase of the study (European Organization for the Research and Treatment of Cancer, Quality of Life Questionnaire, 30 items; Hospital Anxiety and Depression Scale; Symptom Check List, 90 items; State of Consciousness Questionnaire). These were not repeated in the LTFU.

Qualitative measures

To explore subjective experiences and elements of the therapeutic process of the participants in more detail, qualitative semi-structured interviews were conducted to gain a more holistic understanding from a client-centred perspective (Maxwell, 2009; Weiss, 1995).

The interviews were held at the home of the participant or via telephone. All interviews were recorded and transcribed. Interviews focused on subjective experiences, changes in daily life, quality of life, anxiety, attitudes and values as related to the LSD-assisted psychotherapy.

The Qualitative Content Analysis (QCA) summary type (Mayring and Glaeser-Zikuda, 2008) was used as method for evaluating the interviews. The QCA leads to a reduction of the text material by systematically building main categories from the material. Parts of the transcripts were then ordered by how they fit into the categories. This process leads to an extraction of the essential structural contents/elements as given in the interviews. In addition, the interviews are specifically formatted to allow comparisons between different participants' experiences, impressions and statements. MAXQDA (cf. www.maxqda.com), a piece of software used for content analysis, was used to assign parts of the transcripts to certain categories (Kirchner, 2010).

Statistical analysis

We used repeated measurement analysis of variance (ANOVA) to analyse changes in the STAI scores over time using time as within-subject factor (levels: baseline, end of study, and follow-up) followed by Tukey post hoc tests based on significant main effects of time.

Results

Quantitative measures, STAI

Nine participants who received two doses of LSD (200 µg) were evaluated. LTFU results demonstrated that STAI state and STAI trait scores did not rise after end of the study. For STAI state, repeated ANOVA measurements showed a significant main effect of time $F(2.16)=15.7$, $p=0.0002$ and significant reductions between baseline and end of study ($p=0.0008$) and follow-up ($p=0.0005$, Tukey post hoc tests) (Gasser et al., 2014). For STAI trait scores, the main effect of time was $F(2.16)=9.5$, $p=0.002$. Post hoc test confirmed significant reductions at the end of study ($p=0.006$) and follow-up ($p=0.004$) (Gasser et al., 2014) (Figure 2).

Table 1. Demographic data of the participants.

Participant number	1	3	5	6	7	8	9	10	11	12
Study condition	full dose	placebo / crossover	placebo / crossover	full dose	full dose	full dose	placebo / crossover	full dose	full dose	full dose
Follow-up interval (m)	25	9	12	12	12	12	12	12	14	15
Gender	m	m	f	m	f	f	m	m	f	m
Age (y)	44	46	62	46	62	39	64	59	43	46
Marital status	Single	Married	Single	Single	Single	Married	Married	Living with partner	Married	Living with partner
Work status (FT=Full time; PT=Part time)	Nurse, FT	Office manager, FT	Office manager, PT	Physiotherapist, FT	Counselor, PT	On disability	Retired	On disability	Office manager, PT	Social worker, PT
Diagnosis (M=Metastasis)	Esophagus cancer	Celiac disease	Breast cancer, M	Plasmocytoma	Breast cancer	Breast cancer, M	Non Hodgkin Lymphoma	Parkinson's disease	Breast cancer, M	Bechterew disease
Prior use of mind-altering drugs	MDMA once, 5 y ago	None	LSD 4 times, 40 y ago	None	None	Cannabis; Psilocybin once, 10 y ago	None	None	None	None
Comorbid disorder										
Major depression	x	x		x	x	x			x	x
Panic disorder			x	x	x					
Gen. anxiety disorder	x	x			x	x			x	x
Dysthymia		x								x
Reactive depression			x							
Social phobia					x					
PTSD										x

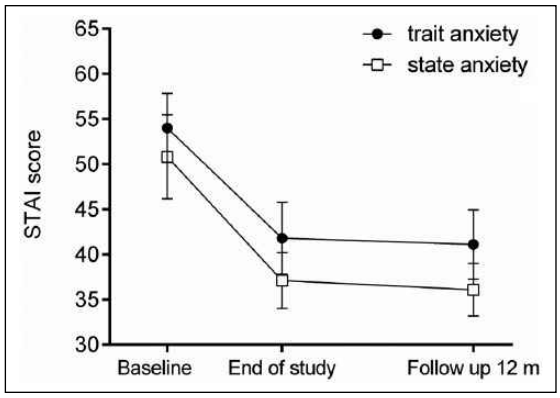

Figure 2. LTFU results of STAI state and trait scores.
STAI measurements, max. score 80 points in each branch trait anxiety and state anxiety), 20 items 4-points Likert scale). *N*=9, i.e. all participants who received two full-dose LSD sessions. Data are mean ± SEM.

Qualitative measures: semi-structured interviews

The interviews conducted with the nine participating subjects found that all of them reported benefits from the LSD-assisted psychotherapy. Data from the interviews confirm the data obtained with the STAI. Of the nine participants, 77.8% reported sustained reductions in anxiety. Seven participants (77.9%) reported less fear of death and an improved quality of life (66.7%) (Table 2). Most reported (subjectively perceived) positive personality changes such as increased openness and deepened awareness. Generally, the research participants stated that they felt more relaxed and patient with themselves and others. These findings are congruent with the stable improvement in STAI scores between the end of the study and the LTFU. These results are even more impressive in light of the awareness that all participants were experiencing an ongoing severe somatic disease. Three participants died a few months after the LTFU.

None of the participants reported lasting negative effects from the LSD sessions. Beyond the temporary difficulty reported by some in dealing with the initial effects of LSD (e.g. intense emotions, alteration in self-control), no adverse events were mentioned. This finding is congruent with surveys on LSD-assisted therapy, which have reported adverse events (psychotiform reactions, suicides etc.) in numbers comparable with psychotherapy without LSD (Cohen, 1960; Gasser, 1996; Malleson, 1971).

It would go beyond the scope of this paper to list all the significant statements given in the interviews. The following quotes were chosen to illustrate the core elements of the subjective experiences and some of the sustained changes reported. We have collated them under a number of subheadings based on the implications of the statements.

Facilitated access to emotions and catharsis

It is well known that LSD enhances affectivity. There is no specific preference for the kind of emotions intensified, whether they subjectively are experienced as positive or negative. This effect can be especially relevant in significant situations such as when confronting an existential threat such as a life-threatening disease. A usual psychological reaction to such a threat is to tend to isolate and go into a kind of inner withdrawal. Intensification of emotions often leads to their cathartic expression, e.g. crying. This may be interpreted as a psychological tightening up induced by grave anxiety and fear. The quotes chosen indicate that LSD is opening up the patients to the experience of emotions that in the usual frame of consciousness/self-experience were partially excluded from perception. The quotes suggest that the patients did profit from the intensified experience of emotions.

> I had the strong impression that things can be seen, which usually rest under the surface. … a lot of emotions were hidden for a long time that are usually not noticed at all became very, very present in that state when you have a break-through somehow… (#12).

> It encouraged me to let the feelings flow … to free myself from my fears. To look at my grief. It was necessary. It was relieving. Afterward I was able to laugh about it. It is a fluctuating world of emotions you have to pass during these eight hours … Except the feeling of grief and fear … there were other sequences and nuances. … A lot is happening there (#1).

> The LSD session sets things free in my mind, which under normal conditions may not have appeared, because they might have been suppressed. I mean I did sense certain freeing moments for myself. That I could let go of the weight of the fear … Well I was surprised to find real stirring of emotions, which I usually would not have felt with all my self-control and restraint (#5).

> I was very very sad, I cried, never desperate, but a lot of sad things came up. And that resolved later on and became lightness. But at the beginning, at first I did not go 'in' for long, but then I dove away. … I was very sad. … What was very, very important to me was that I got access to my emotions, I went relatively deep inside. I went through heaviness and sadness. But I felt all emotions very intensely (#7).

It seems possible that the confrontation with intensified emotions or thoughts (more or less excluded from the usual frame of consciousness) can disturb an individual and interfere with the ability to cope with a difficult situation. But it is known from the extensive experience with LSD-assisted psychotherapy during the 1960s that (if dosing and setting are appropriate) only those emotions/thoughts/memories come up into consciousness which can be coped with by the psychological capacities of the individual patient (Grof, 1980; Leuner 1981). The quotes appear to confirm this observation. Virtually all patients valued the intensified emotional experiences as positive, in spite of sometimes coping with difficult emotional experiences. None of the patients interviewed reported any serious psychological problems resulting from their LSD treatments.

De-schematizing and viewing experiences in another perspective

LSD is known for its capacitiy to alter the usual frame of reference, especially in respect to cognitive concepts and habits and by altering contextualizations and validations of persons and events (Grof, 1975). One important aspect of this 'de-schematizing' is a change in perspective, i.e. the frame in which an individual perceives him/

Table 2. Quantitative evaluation of semi-structured interviews.

Effects of LSD in the therapeutic setting.			
Effect	*Participant no.*	*n*	*%*
Facilitated access to emotions	1, 5, 7, 11, 6, 12	6	66.7
Important introspection/insights	1, 6, 7, 8, 11, 12	6	66.7
Faster progress	1, 6, 7, 10	4	44.4
Easier 'letting go'	5, 1, 11	3	33.3
Lasting benefits mentioned			
Effects	*Participant no.*	*n*	*%*
Effects on psychopathology			
Increased access to emotions	1, 12, 7	3	33.3
Reduced anxiety/fear of death	1, 3, 5, 6, 8, 10, 11	7	77.8
Other improved psychopath. symptoms (includes better sleep, no more suicidal thoughts, less depressed feelings)	8, 3, 12	3	33.3
Positive psychological effects			
More relaxed	5, 6, 8, 1, 3	5	55.6
Physical well-being	3, 5, 7, 12	4	44.4
Increased quality of life	1, 3, 5, 8, 7, 10	6	66.7
Increased awareness	6, 1,8, 10	4	44.4
Increased equanimity	6, 8, 5	3	33.3
Increased self-assurance	8, 10, 11	3	33.3
Increased capability to draw boundaries	11, 3, 7	3	33.3
Increased mental strength	5, 11	2	22.2
Effects on personality and values			
Change in habit patterns	7, 11, 10	3	33.3
Less career-focused	1, 3	2	22.2
Increased patience	8, 1	2	22.2
Increased importance of family	3, 1	2	22.2
Other changes in personality and values (includes less materialism, less self-centred, more outspoken, more open).	3, 1, 8,11,5,10	6	66.7

Total number of participants *n*=9; Full-dose LSD *n*=7; crossover placebo/LSD *n*=2.

herself and others. An appropriate metaphor for these changes in perspective could be a set of photographic lenses, that can focus, either bringing things nearer than usual or enabling the observation of them from a much more distant perspective, i.e. a mountain-top. Also, there appears to be the experience of a wide-angle lens giving a much broader picture, providing the opportunity to see many different aspects and/or dimensions of situations, persons, etc., at once (Leuner, 1981). The following examples convey an idea about such changes in concepts and perspectives:

> …The things you normally consider as reality are just not as they seem to be (#6).

> I believe that the amygdala is out of order. This switch, which right away judges: *good or bad* experience. That it is simply cut out. That things rush towards them and they have to look at what to do with them. Without LSD or techniques which you might be able to learn, that is impossible (#6).

> I had the opportunity to relax. I rather connected to my inner world. Closed eyes. It was less about my illness. I was able to put it into perspective. … Not to see oneself with one's sickness as centre. There are more important things in life. … The evolution of humankind for example. … Your Inner Ego gets diminished, I believe, and you are looking at the whole … you are indeed starting to build relations with plants or with the entire living world around. You think less about yourself, you are thinking – across borders (#1).

> Dying is as usual or unusual as life itself. You cannot separate it. I simply have to familiarize myself with the idea and the process. And for that an LSD session is of priceless worth (#10).

Changes of basic emotions during the LSD experiences

Some of the patients reported impressive changes in their emotional state during the LSD experiences. Some experienced these changes during the experience itself; or even manipulate the emotional state in the second LSD session after getting accustomed to the state during their first LSD experience.

> Emotionally it was a roller coaster ride. … The first time it was very brutal, painful, at least emotionally very painful. I could not even say in which direction – it just hurt, like heartache, like being disappointed, like everything you once had experienced as a negative feeling. … It was pure pain. Pain of memories, well, or memory of pain. … it was quite hard. During the second time it was sublime. Really. Love,

expansion, holding, I knew that this sometimes happens, that participants talk about spiritual experiences. I thought they just meant this dissolution of oneself – everything is okay, everything is great. That was a very important experience for me. Very, very important (#6).

The first trip was a panic trip. With almost pure fear of death. It was agony … Really, I had the feeling 'that I am dying'. Yes, it was just really black, the black side. I was afraid, shaking. … It was total exhaustion, not seeing an exit, no escape. It seemed to me like an endless marathon … that was a big part of the trip until it finally led to relaxation … During the second trip the dark side also showed up at the beginning, but for a rather short time. I was a little tensed, sweating, but not for so long and suddenly a phase of relaxation came. Completely detached. It became bright. Everything was light. It became a pleasant feeling, a warm feeling. No pain. Almost a little floating, clear, being carried and together with the music… It was really gorgeous. … The key experience is when you get from dark to light, from tension to total relaxation (#3).

During the session the thoughts were … 'Do I travel the right path'? That was my question. Not dealing with death during the session but if I am on the right path. LSD gave me the feeling intensively that I am on the right path. That was nice. I was just floating for six hours, but felt a total assurance inside. That everything I do is actually good. … It gave me assurance. I was content. I had to giggle a lot and smile and I knew it is the right path. … everything will be fine (#8).

It appears from the quotes that the patients initially were confronted with aspects of their situation related to 'negative' emotions such as anxiety, depression, hopelessness and feeling tortured by the gravity of their situation, etc. Later during the course of their experience (or during their second LSD experience), the basic experience transformed to a much more positive basic emotional tone. The patients described this as an intensity that never was experienced before and that gave them 'a new baseline' for how to feel in their life situation. Other interviewees suggested that there is a transformation of the basic pattern in or with which the whole situation of the person is experienced. Interestingly, in all patients the connotations were on the positive side. Patients reported a core experience resulting in a sustainable state of feeling much more safe and secure. Their experiences during LSD inspired much more confidence and trust in their situation and how they can deal with it.

Long-term after-effects: changes in perspectives, attitudes, values

I think right after the trips … certain changes happened. … Same things were not equally important anymore. A shift in values. … To take time to listen to music, to listen to music consciously. Maybe that material values were not that important anymore. That other values have priority. Health and family, such things… When you have a job and the job has priority and the family comes last. You don't even notice it anymore. To realize there, stop, what is actually important? That the family is fine, that the kids are doing well… (#3).

Something changed in the relationship to my biological daughter. More like, it helped me to draw boundaries. … That is my big worry, that is my big topic. ‚Do I behave correctly? Do I do it right? Am I a good mother?' In the session I realized if I do it like this or like that, it won't change, but it burdens me less (#7).

I believe that the LSD experience was very, very important for me. … I was able to really take a lot of things with me into my daily life. … I did some steps along that path even before, and LSD gave me total confidence that it is okay to be on this path. I was just floating for six hours, but felt a total assurance inside. That everything I do is actually good (#8).

In my mother's family there is a Nazi past history, that also played a role, I thought about that. And after these six hours I was able to just let go of it. That was fascinating. To realize that also this path that I am going is okay, that I should not condemn my family, my grandfather and that it is not my fault. That was great … During the second time it intensified even more and really all thoughts that came up, I was able to take with me and put them into practice and I did not have problems anymore… [I am] More relaxed, more patient. … I have less blockages and I believe LSD helps to realize that it is okay. Looking back, almost a year later, … I believe I changed quite a bit. In a spiritual way, in the way of thinking. I became relaxed, I am not so afraid anymore, no bad conscience anymore… (#8).

Increases in quality of life

Another frequently mentioned benefit was the long-term increase in quality of life. Quality of life is complex to measure, and the few quotes here only can provide a tentative idea about a few aspects.

Participant #3 said that his quality of life had improved immensely due to the disappearance of his suicidal thoughts since the LSD-assisted psychotherapy.

Quality of life changed extremely insofar as I became calmer, that I take things easier. It makes a difference if I look upon death with stress or with equanimity. I believe that is an enormous difference in quality of life. That I don't have to cry every night like in the first months. Instead I laugh and the illness, well the pain, when I get up and walk like an old grandmother I have to giggle and think 'What is this?'. Well I think quality of life has changed (#8).

Furthermore she was able to express herself much more freely and was not afraid anymore of saying things in community with others. Her quality of life improved enormously due to being calmer, taking things easier and approaching death with equanimity. She also mentioned being more patient and less stressed as a benefit.

Participant #6 had intense experiences of joy, which he did not know from daily life and which he he called 'desirable', very pleasant and very important. He added that the dissolution of oneself and the entire experience was so strong that 'everything else seems banalities.'

Participant #8 noticed that falling asleep was possible again without having revolving thoughts that kept her from sleeping.

Participant #5 found improvement in personal strength resulting from the LSD psychotherapy: "I personally believe that my mental strength is related to the LSD sessions."

Comparing LSD in psychotherapy with usual psychotherapy

When the clients were asked about the specific effects of LSD in psychotherapy in comparison with usual psychotherapy, most of them mentioned facilitated access to emotions, important insights, faster progress, accessing feelings of safety and facilitation of 'letting go' as the main features.

> It is really difficult to explain, but it was something that I had not experienced before and that really opened certain doors, which might have opened as well if I would have gone 20 times [to usual psychotherapy], but it was very fast and easy. It helped a lot (#7).

> In usual psychotherapy it is mainly about talking, about words. In LSD-assisted psychotherapy it is mainly about inner processes, inner change, inner experience, it gets enriched by it (#1).

Possible negative aspects of the treatment

All patients interviewed reported that there were no negative effects that lasted beyond the duration of the sessions. A few mentioned that during the initial phase of the LSD experience they experienced difficulty in 'letting go' or giving up some of the usual self-control ("some distrust in the beginning"). Some subjects felt a little threatened "… when the feelings came, but it did not last. It dissolved. It was never desperate …" (#11).

> It was more the feeling of something unpleasant, which is anyway always there, which you are normally able to take care of. To be stuck in a condition where you have to endure it for hours. This is not really a problem, but just straining and no easy way to come back to a relaxation. Both times I was quite relaxed at last … (#12).

For some others it was a difficult experience to feel their emotions with more intensity and to be confronted with anxiety, hopelessness and fear of death. But all patients were able to handle these unusually intense emotions and reported that a lot of tension was dissolved afterwards.

In respect to sub-acute after-effects, a few participants mentioned being tired and slightly destabilized the first days after their LSD experiences. One patient stated:

> It felt like when you take a glass of water and stir it with a hand full of mud. As if everything is still mixed with the water and only later on it sinks to the ground, like a sediment. That is the resting period. But shortly after sinking and also the next day it was more like being stirred. … I don't mean that you don't capture reality anymore … you would not run through a red light, but everything feels like one is mollycoddled. … But of course you are able to follow your daily life (#6).

Observations on headaches

Two of the study participants had serious migraine cycles during the years before treatment. At the LTFU, participant #3 reported that his migraine cycles and the accompanying pain had been significantly reduced for a number of months after the LSD treatments. Participant #12 reported no migraine in the 12 months up to the LTFU. This incidental observation may be an indication to support some recent studies (Sewell et al., 2006).

Discussion

The present study has shown that psychological improvement as achieved during 3 months of LSD-assisted psychotherapy is stable over a 12-month period. The condition of the patients was serious in that they were facing a life-threatening illness and the anticipation of possible death. The results from the QCA suggest that the improvement (as demonstrated by the significantly lower STAI trait scores) is also perceived as valid in personal statements (Table 2). Interestingly, the improvement in psychopathological symptoms was accompanied by positive psychological changes in the subjects (e.g. increases in relaxation, equanimity, self-assurance, mental strength), which we were not able to detect in the original study due to the focus on pathology-oriented measures (Gasser et al., 2014).

One important distinction that has to be made at this point is about the paradigms of *psycholytic therapy* (low-dose serial sessions in a psychoanalytic frame for treating neuroses) and *psychedelic therapy* (one or two high-dose sessions directed to mystical peak experiences to initiate a personality change). Even if the typical dose in typical psychedelic therapy sessions (200–500 mcg LSD; Grof, 1980) is somewhat higher and the setting more structured (e.g. music played throughout), the present study is in some major components equivalent to the psychedelic approach, but did allow for more cognitive, psychodynamic and interpersonal aspects. Up to now, only the psychedelic approach was used in treatment of en-of-life anxiety (e.g. Grob et al., 2011; Grof et al., 1973; Kurland, 1985).

A typical psychological reaction to a life-threatening disease is an anxiety/depression-driven tendency for interpersonal isolation and the attempt to harden oneself against the threat triggered by the anticipation of severe suffering and possible death.

As studies in the past, as well as the present study, have shown, this situation appears to be essentially changed by the effects of treatment with LSD (Gasser et al., 2014; Grob et al., 2011; Grof et al., 1973; Kurland, 1985; Pahnke, 1969).

Unfortunately, there is not much knowledge about the effects of LSD-like hallucinogens in psychotherapy, especially at a neurobiological level. We will give an outline of some ideas relating to possible mechanisms of action in the following paragraphs.

Possible mechanisms of action at a psychological level

It appears that LSD-assisted psychotherapy involves a combination of mechanisms operating in conventional psychotherapy, such as a facilitated access to emotions, relieving of traumatic memories, abreaction and catharsis, facilitation of emotional and intellectual insights (Grof, 1980; Leuner, 1981). The most

significant effects of LSD in psychotherapeutic contexts can be described as follows:

1. The *cognitive experience*, with astonishingly lucid thoughts and altered associations, with problems seen from novel perspectives, and relationships of many levels seen at once;
2. The *psychodynamic experience*, characterized by an emergence of material into consciousness that was previously excluded. A symbolic portrayal of important conflicts as well as abreaction and catharsis are elements of a (sometimes hypermnestic) reliving of incidents from the past;
3. The *psychedelic peak experience*, with (i) loss of usual sense of self with positive ego transcendence, (ii) transcendence of time and space, (iii) sense of awe and reverence, and (iv) meaningful new insights.

All of these dimensions of the LSD experience may contribute to treatment effects, especially within the psychedelic approach. Studies in the past have demonstrated more treatment effects for individuals who had psychedelic peak experiences, but those without them have also found significantly bettered (Pahnke et al., 1970; Richards et al., 1977).

In terms of a possible mechanism of action, the changes reported in the present study seem to be not so much dependent on cognitive or psychodynamic experiences (which were regularly mentioned). Virtually all of the patients reported their most moving subjective events were intense emotional experiences. These were characterized at first by a tense and anxiety-laden confrontation with emotions and aspects of their actual life situation, sometimes accompanied by appropriate memories. These somewhat burdening experiences in most cases happened during the first (phase of the) LSD experience. The basic emotional experience then changed to a much more positive emotional tone:

> … suddenly a phase of relaxation came. Completely detached. It became bright. Everything was light. It became a pleasant feeling, a warm feeling. No pain. Almost a little like floating, clear, being carried and together with the music… It was really gorgeous. The key experience is when you get from dark to light, from tensed to total relaxation (#3).

Another typical example is this:

> … it was sublime. Really. Love, expansion, holding, I knew that this sometimes happens, that participants talk about spiritual experiences. I thought they just meant this dissolution of the self – everything is okay, everything is great. That was a very important experience for me (#6).

It seems that the core of these deeply affecting experiences is a tension-free state of well-being or a positive experience of 'pure existence in the here and now' accompanied by a relative freedom from concerns of the past as well as from guilt, depression and anxiety. As the results of the QCA suggest, these experiences inspired much more confidence and trust for the patients in their situation and how it can be dealt with. These observations are congruent with those in earlier studies in which patients reported sustained decreases in anxiety, worry and depression as well as increases in serenity, peace and calmness and an accentuated orientation in the here and now (Grof et al., 1973; Kurland, 1985; Richards et al., 1977).

Several authors focus on the fact that LSD-like substances can facilitate 'peak experiences' or 'mystical experiences'. Even just one of these experiences was proven to have an inherent potential to change the psychological make-up of the person (Griffiths et al., 2006; McGlothlin et al., 1967; Savage et al., 1966). It appears that the changes observed by our patients were mainly dependent on a related encompassing of emotional experiences, but these do not match the criteria for mystical experiences on the Pahnke–Richards Mystical Experience Scale set out in the State of Consciousness Questionnaire (SCQ) (=60% positive answers) as applied in another part of this study (Diesch, 2014). This suggests 'incomplete' mystical experiences. These may be better described as 'peak experiences' in accordance with Maslow's definition as "moments of pure, positive happiness when all doubts, all fears, all inhibitions, tensions, all weaknesses were left behind … All separateness and distance from the world disappeared as they felt one with the world, fused with it, really belonging in it and to it, instead of being outside and looking in" (Maslow, 1962: 9). Maslow made a conscious division between mystical *or* peak experiences (Maslow, 1970: 75), with the latter being similar in many respects, but without some essential features of mystical experiences. Equivalent peak experiences under the influence of LSD were also called 'intuitive-intellectual effects' and described as a combination of emotional and intellectual functions (Terrill, 1962). The prominent American scholar of religious experience, William James, describes the core features of these kind of peak experiences:

> The central [characteristic] is the loss of all worry, the sense that all is ultimately well with one, the peace, the harmony, the willingness to be … The second feature is the sense of perceiving truths not known before … insight into depths of truth unplumbed by the discursive intellect. … The mysteries of life become lucid … illuminations, revelations, full of significance and importance, all inarticulate though they remain" (James, 1902: 242-243).

From the subjective descriptions evaluated in the present study it appears that intellectual functions were to a greater degree intact during these experiences, not suspended as often is reported during full-blown mystical experiences (e.g. Griffiths et al., 2006; Pahnke, 1969). Ego boundaries were certainly loosened, but not completely absent. Throughout an altered basic emotional experience, loosening of ego functions combined with pronounced self-referential processing of significant (intellectual/emotional) content, patients may gain a new perspective on themselves and a reduction of ruminations and ego-centredness (Leuner, 1967; Northoff, 2007; Pizzagalli, 2011). Even if this may not be easy to translate to patients with severe somatic diseases, equivalent psychological changes have been found in recent experiments on psilocybin-induced peak experiences, with a specific increase of the personality trait of openness on the NEO-FFI (MacLean et al., 2011).

James also gives a description of changes in the mental or intellectual sphere, which may apply to the effects seen in our patient population.

> A mind is a system of ideas, each with the excitement it arouses, and with tendencies impulsive and inhibitive, which mutually check or reinforce one another. … A new perception, a sudden emotional shock … will make the whole fabric fall together, and then the centre of gravity sinks into an attitude more stable, for the new ideas that reach the centre in the rearrangement seem now to be locked there, and the new structure remains permanent" (James, 1902: 190f.).

Such cognitive/psychological mechanisms may (partially) explain the nature as well as the durability of the changes observed in psychopathological measures, personal habits and values as well as intellectual contextualization.

Psychophysical mechanisms of the revealed changes in psychological traits (e.g. STAI trait scores) are essentially unknown, but it may be related to an alteration of the homoeostasis of the individual's psychological system, resulting in a breaking up of fixated psychological habits, defence mechanisms and entrenched thought patterns. These patterns maybe also pre-exist on a neurobiological level. The patients interviewed in the present study referred to 'de-pattering' in terms of previously fixated physical, psychological and thought patterns, which led to increases in relaxation, an imperturbable calmness and an acceptance of their own self and basic situation. Another usable concept for understanding of these processes may be to view psychedelic peak experiences as a kind of '*super*reinforcement' associated with an enhancement of 'heuristic' mediating processes leading to transformations of basic concepts of the self (Unger, 1963).

Possible neurobiological mechanisms of action

The following more or less hypothetical mechanisms may contribute to the improvement of the psychological state of the patients in the present study.

Neuroimaging studies suggest that the LSD-like hallucinogen psilocybin makes a greater repertoire of functional connectivity in the brain's networks available than in normal waking consciousness. Brain regions implicated as the base for the normal state of consciousness are represented in the default-mode network (DMN), which also hosts important 'connector hubs' (Hagmann et al., 2008) that allow communication and integration between different brain regions (Bullmore et al., 2009). The highly organized activity within the DMN is a requirement for mood regulation and high-level constructs, such as the self (Gusnard et al., 2001) or 'ego' (Carhart-Harris and Friston, 2010) as well as the ability for self-reference (Raichle, 1998). Psilocybin-induced reduction of blood flow in DMN regions alters the integrity of the DNM and thereby leads to 'unconstrained cognition' and changes in the experience of the self (Carhart-Harris et al., 2012a). Changes in functional connectivity may contribute to changes in perspective and re-evaluations of situations and persons (Carhart-Harris et al., 2014; Vollenweider and Geyer, 2001), sometimes supported by intensified memory (Carhart-Harris et al., 2012b). However, some of these reductions in brain activity are not congruent with earlier findings (e.g. Vollenweider et al., 1997).

The long-term results of the present study as well as the impact of peak experiences in changing psychological traits, behaviour and basic emotional tone (Griffiths et al., 2006, 2011; MacLean et al., 2011) suggest sustained neurobiological alterations. Hypothetically, LSD-like hallucinogens in psychotherapy may improve the patients by 'breaking up' a more fixated and less dynamic neurobiological matrix of functioning, accompanied by emotional bias, altered responsiveness and reduced flexibility in the emotional and cognitive sphere (Carhart-Harris et al., 2014; Vollenweider and Geyer, 2001). Patients may regain mental flexibility as a result of treatment with LSD, which has been found to be reduced in depressive and anxiety disorders (Stuhrmann et al., 2011). Through intensification of affectivity and weakening of ego boundaries, LSD may also function as an 'opener' to another emotional basic experience, enabling subjects to have 'deeper' insights and perspective-altering outlooks. Future research is indicated to gain pre/post-treatment neuroimaging data on patients undergoing treatment with LSD.

Patients with depressive and anxiety disorders show reduced PFC activity and hyperactivity within the amygdala in response to negative stimuli (Hariri et al., 2006; Stuhrmann et al., 2011). Reduced prefrontal glutamate levels are associated with attenuated PFC activation and decreased top-down inhibition of amygdala activity. Stimulation of postsynaptic 5-HT2A receptors in the PFC by hallucinogenic indolealkylamines increases glutamatergic recurrent network activity and may reduce the emotional-cognitive bias by strengthening PFC activity and thereby reversing the depression/anxiety-driven disequilibrium between the PFC and the amygdala (Vollenweider and Kometer, 2010).

In terms of psychological long-term effects, it is worth noting that the administration of the hallucinogenic 5-HT2A agonist DOI increases the brain neurotrophic factor BDNF in different regions of rat brain (Vaidya et al., 1997). BDNF is expressed at high levels in the hippocampus and the cerebral cortex and regulates synaptic strength and neuronal morphology. Expression of BDNF mRNA is increased in response to stress, depression, and trauma (Jiang and Salton, 2013), and has been implicated in learning and memory (Adlam and Zaman, 2013). Repeat administration leads to rapid desensitization, but it appears to be possible that the effects of increased BDNF on neuronal and synaptic formation and functioning contribute to the sustained psychological effects of some hallucinogens (Vollenweider and Kometer 2010).

Rates of improvement

It is important to note that in studies in the past it was consistently demonstrated that approximatively one-third of patients with end-stage-cancer treated with LSD-assisted psychotherapy showed dramatic improvement, one-third moderate improvement, and one-third was essentially unchanged (Kurland, 1985). In contrast, in the present study no 'dramatic' improvement was seen, but moderate (high to low) improvement was observed in *all* of the patients. This difference in outcome is not easy to explain, but may possibly be explained through the use of a moderate dose of LSD (200 mcg), which may not easily induce a full-blown mystical state, but the experiences may have assimilated more aspects of the psychotherapeutic features of the LSD experience and therefore enabled the patients to surf though more

dimensions (e.g. cognitive, psychodynamic) of the LSD experience and benefit from this.

Possible harmful aspects of the LSD experience

It is possible that being confronted with intensified emotions/thoughts/experiences may disturb an individual's ability to cope with a difficult situation. However, it is well known from the vast experience with LSD-assisted psychotherapy during the 1960s that (if the dose and setting are appropriate) only those emotions/thoughts/memories enter the consciousness which can be coped with within the patient's psychological capacity (Grof, 1980; Leuner, 1981). The quotes given in the results section appear to confirm this observation.

Beyond a temporary difficulty experienced by a few subjects in dealing with some initial effects of LSD (e.g. intense emotions, alterations in self-control), no acute adverse effects were mentioned. Mild irritation (not interfering with everyday performance) for a day or two after the LSD session was reported by some subjects. No flashbacks or suffering from any other after-effects were reported 12 months after treatment. This confirms the findings of earlier surveys (Cohen, 1960; Gasser 1996; Malleson, 1971).

Limitations of the study

The limitations of the initial study are discussed in the previous publication (Gasser et al., 2014). For this LTFU, the small number of participants (N=10) is a further limitation. As a result of the crossover design there was no control group for the follow-up. It would be ethically problematic under European law to run a placebo control group over such a long time, so the the cross-over design was not merely a methodological decision, it was also an ethical one.

Conclusion

LSD-assisted psychotherapy in patients with life-threatening diseases demonstrated safety and positive stable treatment outcomes at LTFU. Systematic evaluations of semi-structured qualitative interviews with the participants point to cognitive, psychodynamic, and emotional experiences induced by LSD which contribute to sustained treatment effects. In particular, the emotional 'peak experiences' were deeply moving and established another inner frame for addressing and/or coping with the stressful situation. No serious adverse effects were reported.

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