Original Paper

Acute subjective effects in LSD- and MDMA-assisted psychotherapy

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Abstract

Background: Lysergic acid diethylamide (LSD) and 3,4-methylenedioxymethamphetamine (MDMA) were used in psychotherapy in the 1960s–1980s, and are currently being re-investigated as treatments for several psychiatric disorders. In Switzerland, limited medical use of these substances is possible in patients not responding to other treatments (compassionate use).

Methods: This study aimed to describe patient characteristics, treatment indications and acute alterations of mind in patients receiving LSD (100–200 µg) and/or MDMA (100–175 mg) within the Swiss compassionate use programme from 2014–2018. Acute effects were assessed using the 5 Dimensions of Altered States of Consciousness scale and the Mystical Experience Questionnaire, and compared with those in healthy volunteers administered with LSD or MDMA and patients treated alone with LSD in clinical trials.

Results: Eighteen patients (including 12 women and six men, aged 29–77 years) were treated in group settings. Indications mostly included posttraumatic stress disorder and major depression. Generally, a drug-assisted session was conducted every 3.5 months after 3–10 psychotherapy sessions. LSD induced pronounced alterations of consciousness on the 5 Dimensions of Altered States of Consciousness scale, and mystical-type experiences with increases in all scales on the Mystical Experience Questionnaire. Effects were largely comparable between patients in the compassionate use programme and patients or healthy subjects treated alone in a research setting.

Conclusion: LSD and MDMA are currently used medically in Switzerland mainly in patients with posttraumatic stress disorder and depression in group settings, producing similar acute responses as in research subjects. The data may serve as a basis for further controlled studies of substance-assisted psychotherapy.

Keywords

Lysergic acid diethylamide, 3,4-methylenedioxymethamphetamine, psychedelics, substance-assisted psychotherapy, compassionate use

Introduction

The prototypical serotonergic hallucinogen lysergic acid diethylamide (LSD) (Nichols, 2004; Passie et al., 2008; Preller et al., 2016) was used in the 1950s–1970s as an adjunct to psychotherapy (Passie et al., 2008). LSD has been investigated as treatment for several psychiatric disorders, including alcoholism (Krebs and Johansen, 2012), opioid addiction, and anxiety and depression associated with terminal illness (Grof et al., 1973; Pahnke et al., 1969), before clinical research with LSD ended in the 1970s due to regulatory restrictions. Similar to LSD, 3,4-methylenedioxymethamphetamine (MDMA; 'ecstasy') was used as an adjunct in psychotherapy (Greer and Tolbert, 1986, 1998; Sessa et al., 2019; Stolaroff, 2004) before it was placed on Schedule I (no accepted medical use and high potential for abuse) in the 1980s.

Lately, interest in the therapeutic potential of hallucinogens such as LSD and psilocybin, but also for entactogens such as MDMA, has resumed. Recent preliminary data suggest that hallucinogenic drugs may reduce depressive symptoms in patients with unipolar depression (Carhart-Harris et al., 2016a, 2017; Osorio et al., 2015), improve anxiety and depressive symptoms associated with life-threatening somatic diseases (Gasser et al., 2014, 2015; Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016), may decrease symptoms of obsessive-compulsive disorder (OCD) (Moreno et al., 2006), and may increase abstinence in patients suffering from substance abuse (Bogenschutz et al., 2015; Johnson et al., 2014). MDMA-assisted psychotherapy reduced posttraumatic stress disorder (PTSD) symptoms in randomised controlled studies (Mithoefer et al., 2013, 2018, 2019; Sessa et al., 2019), and was granted breakthrough therapy designation by the Food and Drug Administration (FDA) (MAPS, 2016).

In Switzerland, LSD- and MDMA- assisted psychotherapy was conducted from 1988–1993 by several psychiatrists and psychotherapists with a special permission of the Swiss Federal Office for Public Health (FOPH) (Gasser, 1994). Since 2014, LSD and MDMA are being re-used in Switzerland in substance-assisted psychotherapy in patients with various treatment-resistant psychiatric disorders (compassionate use). To our knowledge, Switzerland is the only country where compassionate use of LSD and MDMA is possible.

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In a follow-up evaluation after the early substance-assisted psychotherapy, 84% of 121 patients reported an improved quality of life with greatest impact on their emotional lives (Gasser, 1994). Self-reported feeling of unity and love, religious and spiritual experiences, visions, and experience of intense and unfamiliar sense perceptions subjectively contributed to their therapeutic experience (Gasser, 1994), however this has not been objectively assessed with validated measures. In clinical studies in healthy volunteers, both LSD and MDMA produced empathogenic effects (Schmid et al., 2014, 2015a), reduced the perception of negative emotions, and enhanced empathy (Bedi et al., 2009; Dolder et al., 2016; Hysek et al., 2014a; Kuypers et al., 2017). Thus, LSD and MDMA acutely induce prosocial effects, which may be beneficial during substance-assisted psychotherapy. Additionally, hallucinogen-induced mystical-type experiences have been associated with persisting positive changes in healthy volunteers (Griffiths et al., 2006, 2008, 2018; Nicholas et al., 2018; Schmid and Liechti, 2018;) and patients (Garcia-Romeu et al., 2015, 2019; Griffiths et al., 2016), and acute substance-induced effects may mediate persisting therapeutic effects (Griffiths et al., 2016). While the research subjects were tested alone in the clinical studies, therapy sessions are conducted in a group setting in the Swiss compassionate use programme.

Even though there is a revived interest in the use of psychoactive substances as treatment of several disorders, to our knowledge there is no published data on the acute effects of LSD and MDMA in patients treated outside rigorously controlled clinical studies in therapeutic group settings. Moreover, it is of interest to know for what indications LSD and MDMA are being used clinically, and whether the acute effects of LSD and MDMA vary between patients and healthy subjects treated in different settings, though such information can currently only be derived from different populations.

Thus, we primarily aimed to describe the patient characteristics and acute subjective effects of LSD and MDMA in patients included in the compassionate use group therapy in Switzerland. Assessments of the acute mind-altering effects of LSD and MDMA were performed using validated psychometric instruments. Secondarily, the acute effects were compared with the acute responses to LSD or MDMA assessed in healthy subjects treated alone in experimental studies and patients in single therapy in therapeutic clinical trials.

Material and methods

Study design

In Switzerland, LSD and MDMA are medically used in patients with treatment-resistant disorders (compassionate use) based on individual authorizations by the FOPH, Bern, Switzerland. The present prospectively designed study assessed the patient characteristics, diagnoses, and acute subjective responses to LSD and/or MDMA (as assessed immediately after the treatment session) from December 2014–March 2018 in patients treated in compassionate use group therapy in Switzerland. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Canton of Basel, Switzerland (EKNZ 2018-00091). The administration of LSD and MDMA was authorised by the FOPH. All of the subjects provided written informed consent and agreed that their data can be included into the present analysis. Additionally, we compared the subjective effects of LSD and MDMA as assessed with the 5 Dimensions of Altered States of Consciousness (5D-ASC) scale (Dittrich, 1998; Studerus et al., 2010) and the Mystical Experience Questionnaire (MEQ) (Barrett et al., 2015; Griffiths et al., 2006; Liechti et al., 2017; MacLean et al., 2012; Pahnke, 1969) in the compassionate use patients with those in healthy subjects. Specifically, data in healthy subjects on the subjective effects of LSD on the 5D-ASC scale and on the MEQ were each pooled from two sets of published studies ([Dolder et al., 2015; Liechti et al., 2017; Schmid et al., 2015a) and (Holze et al., 2020; Schmid et al., 2015a; Liechti et al., 2017], respectively). Data on the subjective effects of MDMA on the 5D-ASC scale was pooled using data from nine previously published studies in healthy subjects (Dolder et al., 2018; Holze et al., 2020; Hysek et al., 2011, 2012a, 2012b, 2012c, 2013, 2014b; Schmid et al., 2015b). Additionally, data on the subjective effects of MDMA on the MEQ was used from one published study in healthy subjects (Holze et al., 2020). Furthermore, subjective effects of LSD on the MEQ were compared with those in patients treated with LSD in a clinical trial (Gasser et al., 2014; Liechti et al., 2017).

Participants

Patients in compassionate use group therapy. Patient characteristics, treatment indications, comorbidities, and concomitant medication are described in the results and in Table 1.

Healthy subjects comparator group. A total of 67 healthy subjects (33 male) aged 25–60 years (mean ± standard deviation (SD) = 30 ± 7.9 years) were included in the LSD studies (Dolder et al., 2015; Holze et al., 2019; Schmid et al., 2015a). Sixteen subjects had previous experience with hallucinogens, and nine subjects used LSD prior to inclusion in the LSD studies. Effects on the 5D-ASC scale after 200 µg LSD were assessed in 16 healthy subjects (eight male) aged 25–51 years (mean ± SD = 29 ± 6.2 years) (Schmid et al., 2015a), and in 24 healthy subjects (12 male) aged 25–60 years (mean ± SD = 33 ± 11 years) after 100 µg LSD (Dolder et al., 2015). Effects on the MEQ after 100 µg LSD were evaluated in 27 healthy subjects (13 male) aged 25–45 years (mean ± SD = 28 ± 4.2 years) (Holze et al., 2019).

A total of 164 healthy subjects (82 male) aged 18–45 years (mean ± SD = 25 ± 4.2 years) were administered 125 mg MDMA (Dolder et al., 2018; Holze et al., 2020; Hysek et al., 2011, 2012a, 2012b, 2012c, 2013, 2014b; Schmid et al., 2015b). Thirty-four subjects had previously used MDMA. All 164 participants completed the 5D-ASC scale, and effects on the MEQ were evaluated in 28 healthy subjects (14 male) aged 25–45 years (mean ± SD = 28 ± 4.2 years) (Holze et al., 2020).

All studies in healthy subjects were conducted at the University Hospital Basel. Informed consent was obtained from all of the participants. The detailed exclusion criteria are reported elsewhere (Hysek et al., 2011; Schmid et al., 2015b), including a history of psychiatric disorders.

Study patients treated alone comparator group. In this study, 11 patients (five male) aged 39–64 years (mean ± SD = 50 ± 9 years) suffering from anxiety associated with life-threatening diseases were included. Half of the patients were

Table 1. Patient characteristics.

	Total ($n=18$)	LSD ($n=11$)	MDMA ($n=11$)
Sex			
Female, *n* (%)	12 (67)	6 (55)	8 (73)
Male, *n* (%)	6 (33)	5 (46)	3 (27)
Age (years; median, range)	49 (29–77)	49 (29–77)	52 (37–77)
Marital status			
Single, *n* (%)	9 (50)	5 (46)	5 (46)
Married/living with partner, *n* (%)	5 (28)	3 (27)	4 (36)
Divorced/separated, *n* (%)	4 (22)	3 (27)	2 (18)
Spiritual orientation			
Protestant, *n* (%)	6 (33)	4 (36)	4 (36)
Roman Catholic, *n* (%)	4 (22)	1 (9.1)	4 (36)
Buddhist, *n* (%)	1 (5.6)	1 (9.1)	0 (0)
Jewish, *n* (%)	1 (5.6)	1 (9.1)	0 (0)
Not religious, *n* (%)	6 (33)	4 (36)	3 (27)
Engagement in meditation, n (%)	5 (28)	3 (27)	4 (36)
Educational level (highest)			
Obligatory school, *n* (%)	1 (5.6)	1 (9.1)	0 (0)
Professional degree, *n* (%)	6 (33)	2 (18)	5 (46)
High school, *n* (%)	1 (5.6)	1 (9.1)	0 (0)
Master degree, *n* (%)	6 (33)	3 (27)	4 (36)
Doctoral degree, *n* (%)	4 (22)	4 (36)	2 (18)
Work status			
On disability, *n* (%)	1 (5.6)	0 (0)	1 (9.1)
Limited employment, *n* (%)	5 (28)	2 (18)	3 (27)
Working full time, *n* (%)	10 (56)	7 (64)	6 (55)
Retired, *n* (%)	2 (11)	2 (18)	1 (9.1)
Indication for treatment [a]			
PTSD, *n* (%)	11 (61)	4 (36)	9 (82)
Major depression, *n* (%)	4 (22)	2 (18)	2 (18)
Personality disorder			
Anxious personality disorder, *n* (%)	1 (5.6)	1 (9.1)	0 (0)
Narcissistic personality disorder, *n* (%)	2 (11)	1 (9.1)	2 (18)
Obsessive compulsive disorder, *n* (%)	1 (5.6)	1 (9.1)	0 (0)
Dissociative disorder, *n* (%)	2 (11)	2 (18)	0 (0)
Eating disorder			
Anorexia nervosa, *n* (%)	0 (0)	0 (0)	0 (0)
Bulimia, *n* (%)	2 (11)	1 (9.1)	1 (9.1)
Autism spectrum disorder, *n* (%)	1 (5.6)	1 (9.1)	1 (9.1)
ADHD, *n* (%)	0 (0)	0 (0)	0 (0)
Social anxiety disorder, *n* (%)	1 (5.6)	1 (9.1)	1 (9.1)
Psychogenic aphonia, *n* (%)	1 (5.6)	1 (9.1)	0 (0)
Cluster headache, *n* (%)	1 (5.6)	1 (9.1)	0 (0)
Life threatening disease, *n* (%)	1 (5.6)	1 (9.1)	0 (0)
History of substance abuse/dependency[a]			
Alcohol, *n* (%)	3 (17)	2 (18)	2 (18)
Illegal drugs, *n* (%)	0 (0)	0 (0)	0 (0)
Other, *n* (%)	1 (5.6)	1 (9.1)	1 (9.1)
History of suicidal tendencies, n (%)	8 (44)	3 (27)	6 (55)
Comorbid disorder[a]			
Multiple sclerosis, *n* (%)	1 (5.6)	1 (9.1)	0 (0)
Progressive eye disorder, *n* (%)	1 (5.6)	1 (9.1)	0 (0)
ADHD, *n* (%)	2 (11)	2 (18)	2 (18)
Recurrent depression, *n* (%)	7 (39)	3 (27)	6 (55)

(Continued)

Table 1. (Continued)

	Total ($n=18$)	LSD ($n=11$)	MDMA ($n=11$)
Autism spectrum disorder, *n* (%)	2 (11)	2 (27)	2 (18)
Vitiligo, *n* (%)	1 (5.6)	0 (0)	1 (9.1)
Allergic asthma, *n* (%)	1 (5.6)	1 (9.1)	1 (9.1)
Coeliac disease, *n* (%)	1 (5.6)	0 (0)	1 (9.1)
Eating disorder, *n* (%)	1 (5.6)	0 (0)	1 (9.1)
Arterial hypertension, *n* (%)	2 (11)	1 (9.1)	2 (18)
Glaucoma, *n* (%)	1 (5.6)	1 (9.1)	1 (9.1)
Concomittant medication[a]			
Antidepressant, *n* (%)	4 (22)	2 (18)	3 (27)
Antianxiety/sedatives, *n* (%)	2 (11)	0 (0)	2 (18)
Neuroleptic, *n* (%)	1 (5.6)	0 (0)	1 (9.1)
ADHD drugs, *n* (%)	1 (5.6)	1 (9.1)	1 (9.1)
Analgesic, *n* (%)	0 (0)	0 (0)	0 (0)
St John's wort, *n* (%)	1 (5.6)	0 (0)	1 (9.1)
Other, *n* (%)	5 (28)	3 (27)	4 (36)
None, *n* (%)	9 (50)	6 (55)	4 (36)

ADHD: attention deficit hyperactivity disorder; LSD: lysergic acid diethylamide; MDMA: 3,4-methylenedioxymethamphetamine; PTSD: posttraumatic stress disorder.
[a]Multiple answers per patient possible.

diagnosed with generalised anxiety disorder (GAD) (Gasser et al., 2014). All of the participants provided written informed consent. The detailed exclusion criteria are reported elsewhere (Gasser et al., 2014), including a current alcohol or drug dependence, primary psychotic, bipolar I affective or dissociative disorders. None of the subjects had prior experience with LSD.

Drugs

In the compassionate use group, the substance used and the corresponding dosages were determined individually by the treating psychotherapist according to the patient's diagnoses and previous use or experiences with psychoactive substances. In patients in the compassionate use group therapy, LSD was administered orally in absolute doses of 100, 150, 175 and 200 µg LSD. Doses of 100 and 200 µg LSD were used in healthy subjects (Dolder et al., 2016; Holze et al., 2020; Liechti et al., 2017; Schmid et al., 2015a) and a dose of 200 µg LSD was used in the clinical study with LSD-assisted psychotherapy (Gasser et al., 2014). In patients in the compassionate use group therapy, MDMA was administered in doses of 100, 125 and 175 mg MDMA. In the clinical studies in healthy volunteers, MDMA was used at a dose of 125 mg. LSD and/or MDMA was repeatedly administered in patients in compassionate use group therapy (mean drug-assisted sessions ± SD 5.7 ± 0.8, range 2–12), whereas healthy subjects and patient in the clinical trial received LSD only once and MDMA once or twice.

Drug preparation

LSD was formulated as gelatine capsules that contained 100 µg LSD (Lipomed AG, Arlesheim, Switzerland) (Schmid et al., 2015a) or an oral solution containing 25 µg or 100 µg of LSD in 1 mL of 96% ethanol (Holze et al., 2019). MDMA was administered as gelatine capsules containing 100 or 25 mg MDMA hydrochloride (Lipomed AG, Arlesheim, Switzerland) (Vizeli and Liechti, 2017). The same formulations were used in patients in the compassionate use group therapy, in healthy subjects, and in patients in a clinical trial.

Study procedures

Compassionate use group therapy. In the compassionate use group, a group therapy setting was used, allowing the patients to interact with the present investigators (trained psychiatrists and psychologists) and other patients. Groups consisted of 3–13 patients and 1–3 investigators. Drug-assisted sessions were conducted in a quiet meditative setting, with music and silence alternating with about one-third music and two-thirds silence. The patients present were not all administered the same compound or dose levels. However, the group was led by trained investigators accordingly to minimise disturbances of individual dynamics of MDMA and LSD within the group. During the first hours of the drug action, there was no or not much interaction between the patients, and patients were encouraged to focus inwards. Setting and procedures have previously been described in detail in (Gasser, 2017).

Healthy subjects. In contrast, the sessions in the clinical studies in healthy subjects were conducted in a standard hospital room. Only one subject (receiving LSD) or at most two subjects (receiving MDMA) were present during the acute drug effects and constantly supervised by only one investigator per participant. The participants rested in hospital beds, could interact with the investigator, and were provided verbal or non-verbal support when needed. They could listen to their own music via headphones, but no other distraction was provided (Hysek et al., 2011; Schmid et al., 2015a).

Study patients treated alone. Experimental sessions in study patients were conducted in a quiet room in a private practice office. Patients laid on a mattress on the floor or were sitting on a

chair, and stayed in the treatment room during acute drug effects with one investigator present. Setting and procedures have previously been described in (Gasser et al., 2014, 2015) and were similar to the compassionate use setting except for the absence of other patients.

Measures

5D-ASC. The 5D-ASC rating scale measures altered states of consciousness (ASC) and contains 94 items (visual analogue scales). The 5D-ASC scale measures alterations in mood, perception, experience of self in relation to environment, and thought disorder. The 5D-ASC scale was administered at the same day after drug effects had faded or one day after drug administration in patients and in healthy volunteers, and all participants were asked to retrospectively rate drug effects during peak drug effects. The instrument is constructed of five dimensions (Dittrich, 1998), and 11 lower-order scales (Studerus et al., 2010). The 5D-ASC dimension 'oceanic boundlessness' (27 items) summarises derealization and depersonalization phenomena associated with positive emotional states, ranging from heightened mood to euphoric exaltation. The corresponding lower-order scales include 'experience of unity,' 'spiritual experience,' 'blissful state', and 'insightfulness'. The dimension 'anxious ego dissolution' (21 items) measures ego-disintegration and loss of self-control phenomena associated with anxiety. The corresponding lower-order scales include 'disembodiment,' 'impaired control of cognition', and 'anxiety'. The dimension 'visionary restructuralization' (18 items) consists of the lower-order scales 'complex imagery', 'elementary imagery', 'audio-visual synaesthesia', and 'changed meaning of percepts'. Two additional dimensions describe 'auditory alterations' (15 items) and 'reduction of vigilance' (12 items). The scale is well-validated and has been used to characterise the subjective effects of various psychedelic drugs (Hasler et al., 2004; Hysek et al., 2011; Liechti et al., 2017; Vollenweider and Kometer, 2010; Vollenweider et al., 2007; Schmid et al., 2015a; Studerus et al., 2010).

MEQ. Mystical experiences were assessed using a German version of the 43-item MEQ (Griffiths et al., 2006; Liechti et al., 2017; MacLean et al., 2012; Pahnke, 1969) embedded in the 100-item States of Consciousness Questionnaire (SOCQ; (Griffiths et al., 2006)). The MEQ was administered at the same day when drug effects had faded or one day after drug administration in healthy volunteers, and patients, respectively, and all participants were asked to retrospectively rate drug effects during peak drug effects. The MEQ has been used in numerous experimental and therapeutic trials with psilocybin (Garcia-Romeu et al., 2015; Griffiths et al., 2006, 2008, 2011; Johnson et al., 2014; MacLean et al., 2011) and in healthy volunteers with LSD and MDMA (Liechti et al., 2017). The 43-item MEQ (Griffiths et al., 2006; MacLean et al., 2012; Pahnke, 1969) provides seven domains of mystical experiences (internal unity, external unity, sacredness, noetic quality, deeply felt positive mood, transcendence of time/space, and ineffability). Additionally, we derived the four scale scores of the revised 30-item MEQ (mystical, positive mood, transcendence of time and space, and ineffability (Barrett and Griffiths, 2017; Barrett et al., 2015; Liechti et al., 2017)).

The total of all scale scores was used as an overall measure of the mystical-type experience, and a complete mystical experience was defined as scores ⩾60% on all MEQ30 factors (Barrett et al., 2015).

Data analysis

The data were analysed using Statistica 10 software (StatSoft, Tulsa, Oklahoma, USA). Significance of drug effects on the 5D-ASC scale and MEQ in patients in the compassionate use group therapy was compared with zero (i.e. no change compared with everyday life) using one-sample *t*-tests because there was no placebo comparator, and previous studies in healthy subjects receiving placebo have repeatedly shown no changes in these scales (Holze et al., 2020; Schmid et al., 2015a). To account for order effects and habituation, only the first assessment was used for the analysis if patients completed the questionnaires repeatedly in multiple sessions. Based on previous research in healthy volunteers, we hypothesised that LSD and MDMA would increase ratings on all dimensions and subscales of the 5D-ASC with less pronounced increases after MDMA in patients in the compassionate use group therapy (Holze et al., 2020). Further, we hypothesised that LSD, contrary to MDMA, would induce mystical-type experiences on the MEQ (Holze et al., 2020; Liechti et al., 2017). Finally, we postulated that acute effects of LSD and MDMA on the 5D-ASC scale and the MEQ would not significantly differ in patients within the compassionate use group therapy compared with healthy subjects and patients treated alone.

Differences between patients in the compassionate use group therapy receiving LSD (doses of 100–200 µg in one group), healthy volunteers (LSD 100 µg and 200 µg in two separate groups), and patients (only LSD 200 µg) participating in trials were analysed with ANOVA with group as between-subjects factor. Differences between patients in the compassionate use group therapy and healthy volunteers receiving MDMA (125 mg) were assessed using a *t*-test (two-tailed). Within the compassionate use group, additional ANOVAs were conducted to assess differences between different doses of LSD or MDMA. Tukey post-hoc comparisons were performed based on significant main effects. Differences in frequency of complete mystical experiences were evaluated using a Chi-square test. The criterion for statistical significance was $p < 0.05$.

Results

Patient characteristics in compassionate use group therapy

Patient characteristics, treatment indications, comorbidities and concomitant medication are described in Table 1. A total of 18 patients (12 women and six men; median age 49 years; range: 29–77 years) were included in this study. Patients with psychotic disorders or patients not capable to attend group meetings were excluded. All patients were Caucasian. Seven patients had prior drug experience (1–5 times), with three patients using MDMA (1–5 times), one patient using LSD (five times), one patient using cannabis, and two patients using ayahuasca (both one time). Eleven patients received LSD, and 11 patients received MDMA. Four patients received LSD after several sessions of MDMA (mean sessions ± SD: 4.75 ± 2.5, range 2–8 sessions). Patients who received both substances were usually first treated with MDMA, as this sequential approach may help patients to engage in the LSD

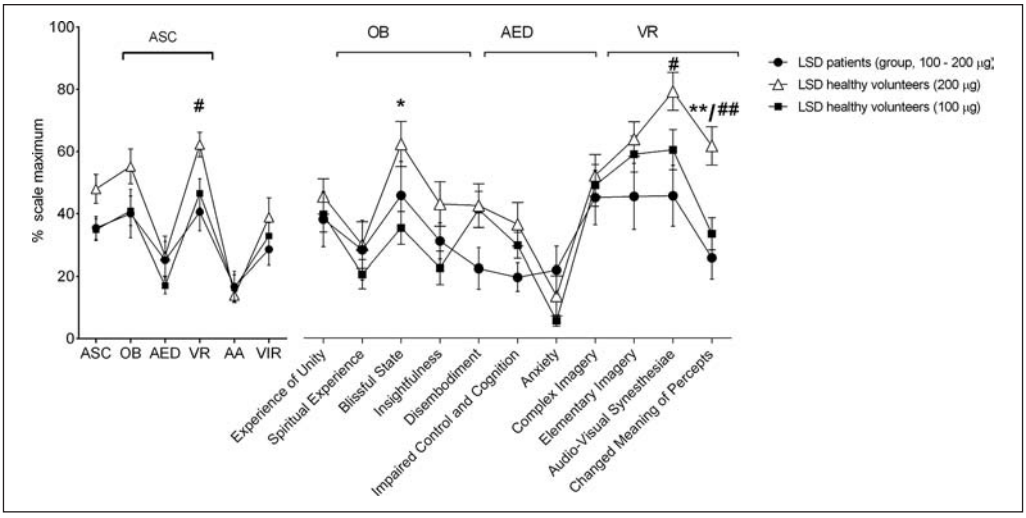

Figure 1. Effects of lysergic acid diethylamide (LSD) on the first completed 5 Dimensions of Altered States of Consciousness (5D-ASC) scale in patients in the compassionate use group therapy ($n=11$) and in healthy volunteers ($n=40$). The data are expressed as the mean ± standard error of the mean (SEM) of a total of 11 patients receiving LSD at different doses of 100 µg ($n=2$), 150 µg ($n=6$) and 200 µg ($n=3$); corresponding to a mean group-size-adjusted dose of approximately 150 µg LSD. For comparison, data expressed as the mean ± SEM of 24 healthy volunteers receiving 100 µg LSD, and of 16 healthy volunteers receiving 200 µg LSD are shown. Overall, LSD produced similar effects in patients in the compassionate use group therapy and healthy volunteers. LSD predominantly increased ratings of 'oceanic boundlessness' (OB) and 'visionary restructuralization' (VR) in all subjects. However, increases in VR were significantly greater in healthy subjects receiving 200 µg LSD compared with patients ($p<0.05$). Ratings of 'audio-visual synaesthesia' were higher after 200 µg LSD compared with patients ($p<0.05$), and ratings of 'changed meaning of percepts' were higher after 200 µg LSD compared with patients ($p<0.01$), but also compared with 100 µg LSD in healthy subjects ($p<0.01$). Ratings for 'blissful state' were significantly greater in healthy subjects receiving 200 µg LSD than 100 µg LSD ($p<0.05$). LSD produced only very little 'auditory alterations' (AA), and similarly elevated ratings in 'anxious ego dissolution' (AED) and "reduced vigilance" (VIR) in all groups. The global altered states of consciousness (ASC) score consists of the summation of the OB, AED and VR scores. #$p<0.05$, ##$p<0.01$ LSD in patients in the compassionate use group therapy compared with LSD 200 µg in healthy volunteers; *$p<0.05$, **$p<0.01$ LSD 100 µg compared with LSD 200 µg in healthy volunteers.

experience. Antidepressants ($n=4$), neuroleptics ($n=1$), St John's wort ($n=1$) and inhalative β-agonists ($n=1$) were paused during the sessions. On average, patients participated in a drug-assisted session with LSD or MDMA every 3.5 months (mean days between drug-assisted sessions ± SD: 105 ± 51, range 35–343 days) after attending 3–10 non-drug psychotherapy sessions.

Acute effects of LSD on the 5D-ASC

Acute effects of LSD on the 5D-ASC scale are shown in Figure 1 and Table 2. In patients in the compassionate use group therapy, LSD induced pronounced alterations of waking consciousness, with significant increases in all dimensions and all subscales of the 5D-ASC (all $t_{10}>3.0$, $p<0.05$). Higher doses of LSD did not produce greater effects than lower doses in patients in the compassionate use group (Supplementary Material Figure S1). Effects of LSD over time were similar in the same subject (Supplementary Material Figure S5). LSD produced overall comparable effects in patients and healthy subjects as evidenced by similar ASC global scores.

Acute effects of LSD on the MEQ

Acute effects of LSD on the MEQ are shown in Table 2. In patients in the compassionate use group therapy, LSD produced a mystical-type experience with significant increases in all MEQ scales (all $t_{10}>4.9$, $p<0.001$). Higher doses of LSD did not produce greater effects than lower doses in the compassionate use group (Supplementary Material Figure S2). LSD produced similar effects in patients in the compassionate use group therapy, in study patients treated alone, and healthy subjects with the exception of lower 'ineffability' ratings in the MEQ30 in the study patients treated alone compared with healthy subjects (main effect: $F_{3,62}=4.67$; $p=0.005$; both $p<0.05$). In healthy subjects, the 200 µg dose produced greater 'positive mood' on the MEQ30 than the 100 µg dose (main effect: $F_{3,62}=3.73$; $p<0.05$; $p=0.02$). Total mystical experiences occurred in 3 of 11 patients in the compassionate use group therapy, in five of 27 healthy subjects with the 100 µg dose, in two of 16 healthy subjects with the 200 µg dose, and in two of 11 study patients treated alone. There was no difference in the proportion of complete mystical experiences between groups ($\chi^2_{(3,4)}=0.96$, not significant (NS)).

Acute effects of MDMA on the 5D-ASC

Acute effects of MDMA on the 5D-ASC scale are shown in Figure 2 and Table 3. In patients in the compassionate use group therapy, MDMA produced significant increases in all dimensions (all $t_8>2.9$; $p<0.05$) except for 'auditory alterations'. MDMA significantly increased ratings for 'blissful state', 'insightfulness', 'impaired control and cognition', 'complex imagery', and 'anxiety' (all $t_8>2.4$; $p<0.05$). Increases in the 5D-ASC ratings were overall less pronounced after MDMA than after LSD. Effects of MDMA did not differ between MDMA dosages (Supplementary

Table 2. Acute effects of lysergic acid diethylamide (LSD) on the 5 Dimensions of Altered States of Consciousness (5D-ASC) scale and on the Mystical Experience Questionnaire (MEQ).

	Patients in compassionate use group therapy (100–200 µg)	Healthy volunteers (100 µg)	Healthy volunteers (200 µg)	Study patients treated alone (200 µg)	*F (2,48)*	*p*
	n = 11	*n* = 24	*n* = 16	*n* = 11		
5-D ASC scale						
Total ASC score	35 ± 3.7°°°	35 ± 3.5	48 ± 4.6	–	3.16	NS
Oceanic boundlessness	40 ± 7.8°°°	41 ± 4.7	55 ± 5.6	–	2.09	NS
Anxious ego dissolution	25 ± 6.1°°	17 ± 2.6	26 ± 6.4	–	1.33	NS
Visionary restructuralization	41 ± 6.1°°°†	47 ± 4.7	62 ± 3.9	–	4.36	0.018
Auditory alterations	17 ± 5.0°°	16 ± 4.3	14 ± 2.3	–	0.10	NS
Vigilance reduction	29 ± 5.0°°°	33 ± 4.3	39 ± 6.3	–	0.75	NS
Experience of unity	42 ± 9.7°°	43 ± 6.2	50 ± 6.2	–	0.32	NS
Spiritual experience	31 ± 10°	22 ± 5.1	33 ± 8.1	–	0.66	NS
Blissful state	50 ± 12°°	39 ± 5.7	68 ± 8.0*	–	4.05	0.023
Insightfulness	34 ± 6.3°°°	25 ± 5.8	47 ± 7.8	–	2.94	NS
Disembodiment	24 ± 7.2°°	45 ± 6.4	46 ± 7.6	–	2.14	NS
Impaired control and cognition	21 ± 4.9°°	32 ± 4.5	40 ± 7.6	–	1.83	NS
Anxiety	24 ± 8.3°	6 ± 2.0	15 ± 7.0	–	2.74	NS
Complex imagery	49 ± 9.5°°°	54 ± 7.4	57 ± 7.4	–	0.18	NS
Elementary imagery	50 ± 12°°	64 ± 6.3	70 ± 6.1	–	1.44	NS
Audio-visual synaesthesia	50 ± 11°°° †	66 ± 7.0	86 ± 6.7	–	4.28	0.019
Changed meaning of percepts	28 ± 7.3°° ††	36 ± 5.7	67 ± 6.7**	–	8.69	0.001
	n = 11	*n* = 27	*n* = 16	*n* = 11	*F (3,62)*	*p*
MEQ43						
Internal unity	42 ± 16°°°	41 ± 5.6	40 ± 6.2	41 ± 8.2	0.02	NS
External unity	35 ± 7.3°°°	36 ± 5.1	43 ± 6.8	38 ± 6.9	0.35	NS
Sacredness	50 ± 9.5°°°	36 ± 5.0	44 ± 6.3	50 ± 6.2	1.50	NS
Noetic quality	53 ± 9.5°°°	35 ± 6.0	40 ± 6.8	47 ± 7.7	1.27	NS
Deeply felt positive mood	54 ± 10°°°	41 ± 4.6	60 ± 5.1	53 ± 7.2	2.75	NS
Transcendence of time/space	58 ± 7.2°°°	64 ± 4.5	56 ± 5.1	51 ± 6.6	0.58	NS
Ineffability	56 ± 6.8°°°	59 ± 4.1	65 ± 3.9	44 ± 6.0	2.10	NS
MEQ30						
Mystical	43 ± 9.8°°°	37 ± 5.4	40 ± 6.3	44 ± 7.3	0.36	NS
Positive mood	62 ± 8.5°°°	45 ± 4.2	65 ± 4.2*	58 ± 7.0	3.73	0.016
Transcendence of time/space	62 ± 6.1°°°	65 ± 4.1	59 ± 4.9	49 ± 6.3	1.16	NS
Ineffability	74 ± 7.3°°°	76 ± 4.2#	82 ± 3.2##	50 ± 7.1	4.67	0.005
MEQ30 total score	60 ± 5.6°°°	48 ± 4.1	61 ± 3.8	50 ± 5.5	2.55	NS

ASC: altered states of consciousness; NS: not significant.
Data represent mean ± standard error of the mean (SEM) of the theoretical scale maximum.
°$p < 0.05$, °°$p < 0.01$, and °°°$p < 0.001$ compared with 0.
*$p < 0.05$, and **$p < 0.01$ compared with LSD 100 µg in healthy volunteers.
†$p < 0.05$, and ††$p < 0.01$ compared with LSD 200 µg in healthy volunteers.
#$p < 0.05$, and ##$p < 0.01$ compared with LSD study patients treated alone.

Material Figure S3). MDMA produced overall comparable effects in patients and healthy subjects as evidenced by similar ASC global scores. However, higher ratings for 'anxious ego dissolution' ($t_{171} = 2.851$, $p = 0.005$) including higher ratings of 'anxiety' ($t_{171} = 4.029$, $p < 0.001$) were observed in patients in the compassionate use group therapy compared with healthy volunteers. Additionally, MDMA produced greater increases in 'visionary restructuralization' ($t_{171} = 2.871$, $p = 0.005$) including 'complex imagery' ($t_{171} = 4.241$, $p < 0.001$) in patients. Ratings of 'oceanic boundlessness' did not differ, but patients reported greater 'spiritual experience' ($t_{171} = 3.326$, $p = 0.001$) and 'insightfulness' ($t_{171} = 2.891$, $p = 0.004$) compared with healthy volunteers.

Acute effects of MDMA on the MEQ

Acute effects of MDMA on the MEQ are shown in Table 3. In patients in the compassionate use group therapy, MDMA produced significant increases in all MEQ scales (all $t_8 > 2.7$, $p < 0.05$), except for ratings of 'internal unity' on the MEQ43 ($t_8 = 2.3$, $p = 0.06$). Higher doses of MDMA did not produce

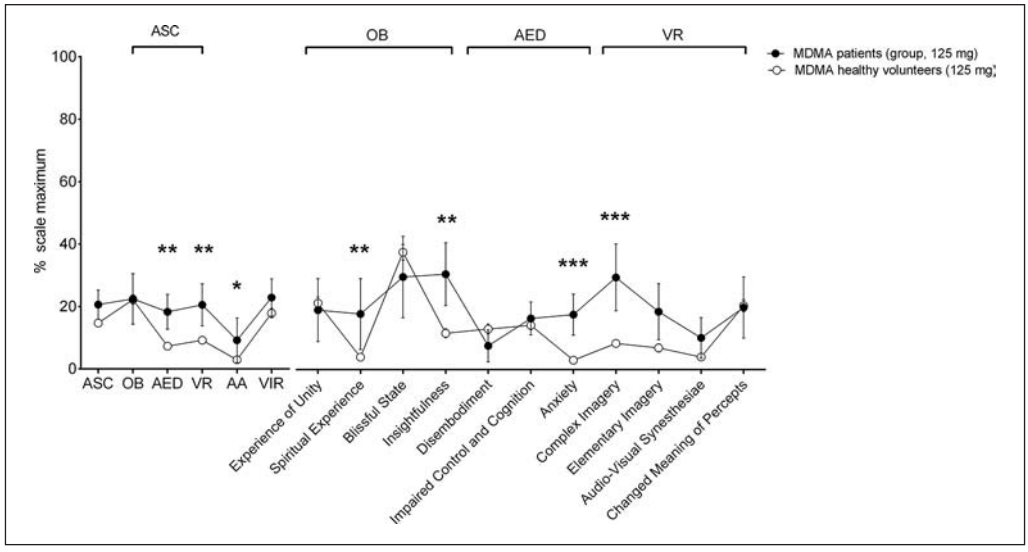

Figure 2. Effects of 125 mg 3,4-methylenedioxymethamphetamine (MDMA) on the first completed 5 Dimensions of Altered States of Consciousness (5D-ASC) scale in patients in the compassionate use group therapy ($n = 9$) and in healthy volunteers ($n = 164$). Overall, MDMA produced similar effects in patients in the compassionate use group therapy and healthy volunteers, and both groups displayed similar altered states of consciousness scale (ASC) global scores. However, ratings for 'anxious ego dissolution' (AED) and 'visionary restructuralization' (VR) were significantly higher in patients compared with healthy volunteers (both $p < 0.01$), predominantly due to significantly higher ratings of 'anxiety' and 'complex imagery', respectively (both $p < 0.001$). Additionally, ratings in 'auditory alterations' (AA, $p < 0.05$), 'spiritual experience' and 'insightfulness' (both $p < 0.01$) were higher in patients in the compassionate use group therapy compared with healthy volunteers. The data are expressed as the mean ± standard error of the mean (SEM) of the theoretical scale maximum. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ MDMA 125 mg in patients in the compassionate use group therapy compared with MDMA 125 mg in healthy volunteers. The global ASC score consists of the summation of the "oceanic boundlessness" (OB), AED and VR scores. VIR: reduced vigilance.

greater effects than lower doses (Supplementary Material Figure S4). MDMA produced greater effects in patients in the compassionate use group therapy compared with healthy volunteers as evidenced by a greater MEQ30 total score ($t_{35} = 4.1$, $p < 0.001$). In patients, ratings were higher in all dimensions (all $t_{35} > 2.5$, $p < 0.05$) except for 'positive mood' and 'internal unity'. However, total mystical experiences did neither occur in patients in the compassionate use group therapy nor in healthy subjects.

Discussion

In the present study we primarily described patient characteristics, treatment indications and acute subjective responses to LSD and MDMA in patients with treatment-resistant disorders in a group psychotherapy setting within the compassionate use programme in Switzerland.

Treatment indications included mostly PTSD and major depression, but also patients with other disorders such as personality disorders, dissociative disorder and cluster headache received compassionate use group therapy. Currently, the most promising results for MDMA-assisted psychotherapy were observed for PTSD (Amoroso and Workman, 2016; Mithoefer et al., 2010, 2018, 2019; Sessa et al., 2019), whereas serotonergic hallucinogens showed the most promising effects in the treatment of mood disorders (Carhart-Harris et al., 2016a, 2017; Osorio et al., 2015). Accordingly, most patients in the compassionate use group suffering from trauma-associated disorders including PTSD were primarily treated with MDMA, and patients diagnosed with major depression or OCD were primarily treated with LSD. Nevertheless, patients diagnosed with PTSD were also treated with LSD, and patients diagnosed with major depression were also treated with MDMA. Several patients were sequentially administered MDMA and LSD, particularly patients suffering from complex PTSD and comorbid personality disorders, as this may have prepared them to the more confrontational and transformative effects of LSD. However, the present exploratory study was not designed to assess efficacy and the use of psychoactive substances for a broader range of indications needs further confirmation in larger, placebo-controlled studies for each substance and indication.

Overall, LSD produced pronounced alterations of waking consciousness, and mystical-type experiences similar to those previously observed in healthy subjects and patients treated alone. MDMA induced largely comparable mind-altering effects, but produced greater mystical-type experiences in the present patients treated in a group setting.

On the 5D-ASC scale, LSD produced similar elevations on the global ASC score in patients in the compassionate use group therapy and healthy subjects in clinical trials. Still, significantly lower increases in perceptual alterations including prototypical hallucinogenic audio-visual synaesthesia and changed meaning of percepts were observed in patients compared with healthy volunteers. However, this difference was only noted when comparing the effects of different LSD doses corresponding to a mean group-size-adjusted dose of approximately 150 µg LSD in patients with the higher dose of 200 µg LSD in healthy volunteers. Nevertheless, higher doses of LSD did not produce greater

Table 3. Acute effects of MDMA on the 5 Dimensions of Altered States of Consciousness (5D-ASC) scale and on the Mystical Experience Questionnaire (MEQ).

	Patients in compassionate use group therapy (125 mg)	Healthy volunteers (125 mg)	***t* (171)**	***p***
	n = 9	*n* = 164		
5-D ASC scale				
Total ASC score	21 ± 4.7°°	15 ± 1.0	1.39	NS
Oceanic boundlessness	22 ± 8.1°	22 ± 1.5	0.01	NS
Anxious ego dissolution	18 ± 5.6°°	7.3 ± 0.9	2.85	0.005
Visionary restructuralization	21 ± 6.8°°	9.2 ± 0.9	2.87	0.005
Auditory alterations	9.2 ± 7.2	3.0 ± 0.5	2.40	0.020
Vigilance reduction	23 ± 6.0°°	18 ± 1.5	0.77	NS
Experience of unity	19 ± 10	21 ± 2.0	–0.25	NS
Spiritual experience	18 ± 11	4.0 ± 0.8	3.33	0.001
Blissful state	30 ± 13°	38 ± 2.5	–0.71	NS
Insightfulness	31 ± 10°	12 ± 1.4	2.89	0.004
Disembodiment	7.6 ± 5.1	13 ± 1.6	–0.77	NS
Impaired control and cognition	16 ± 5.3°	14 ± 1.3	0.37	NS
Anxiety	18 ± 6.6°	3.0 ± 0.8	4.03	<0.001
Complex imagery	29 ± 11°	8.4 ± 1.0	4.24	<0.001
Elementary imagery	19 ± 9.0	6.9 ± 1.4	1.92	NS
Audio-visual synaesthesia	10 ± 6.6	4.0 ± 0.8	1.61	NS
Changed meaning of percepts	20 ± 9.8	20 ± 1.9	–0.07	NS
	n = 9	*n* = 28	***t* (35)**	***p***
MEQ43				
Internal unity	20 ± 9.3	7.0 ± 2.7	1.85	NS
External unity	23 ± 9.2°	5.8 ± 1.9	3.00	0.005
Sacredness	29 ± 10°	6.6 ± 1.8	3.69	<0.001
Noetic quality	47 ± 13°°	9.8 ± 3.8	3.93	<0.001
Deeply felt positive mood	29 ± 9.9°	30 ± 3.9	–0.13	NS
Transcendence of time/space	27 ± 6.2°°	9.5 ± 2.2	3.50	0.001
Ineffability	37 ± 6.2°°°	14 ± 3.1	3.55	0.001
MEQ30				
Mystical	29 ± 11°	7.2 ± 2.6	2.96	0.006
Positive mood	36 ± 10°°	28 ± 3.3	1.06	NS
Transcendence of time/space	29 ± 6.5°°	11 ± 2.3	3.50	0.001
Ineffability	47 ± 7.7°°°	23 ± 4.9	2.50	0.017
MEQ30 total score	35 ± 5.8°°°	14 ± 2.4	4.14	<0.001

ASC: altered states of consciousness; NS: not significant.

Data represent mean ± standard error of the mean (SEM) of the theoretical scale maximum. °$p < 0.05$, °°$p < 0.01$, °°°$p < 0.001$ compared with zero.

effects on the 5D-ASC scale in patients within the compassionate use programme. Ratings on the 5D-ASC scale were similar over time in the same subjects, indicating no tolerance, contrary to other reports (Passie et al., 2008). However, LSD was only administered every 3.5 months on average.

LSD induced similar mystical-type experiences in patients treated in the compassionate use group therapy, in healthy subjects and patients treated alone in an experimental setting as evidenced by similar MEQ30 total scores. Higher mystical-type experiences would have been expected in the compassionate use group therapy compared with healthy subjects, as effects of psilocybin on the MEQ30 and the 5D-ASC dimension 'oceanic boundlessness' were greater in healthy subjects receiving high spiritual practice and psychological support compared with standard-support groups (Griffiths et al., 2018). However, participants in these studies may have generally been more spiritually involved, and the setting was highly optimised for the occurrence of mystical experiences (Griffiths et al., 2018). In the compassionate use programme, only 28% of the patients were engaged in meditation, and 33% of the patients were not religious. Besides, interactions within the group may have reduced mystical-type experiences, although patients have been encouraged to focus inwards. Nonetheless, LSD produced a numerically higher proportion of complete mystical experiences in the compassionate use group than in healthy volunteers and in patients in the laboratory setting. Positive long-term effects of

hallucinogens have been associated with their ability to acutely induce profound insights and mystical-type experiences (Nicholas et al., 2018; Schmid and Liechti, 2018), but whether these and which particular aspects of mystical-type experiences are critical for a possible therapeutic effect needs further evaluation. Similarly as on the 5D-ASC scale, quality and extent of ratings on the MEQ did not significantly differ between several doses of LSD doses in patients in the compassionate use group. In contrast, hallucinogen dose strongly predicted mystical-type experiences (Lyvers and Meester, 2012; Studerus et al., 2012) and a dose response in MEQ total score was observed in healthy participants after psilocybin (Nicholas et al., 2018). With regard to the extent of mystical-type experiences and acute alterations of consciousness, the present data suggest that lower doses of LSD could be used to achieve similar acute effects in this setting. However, a direct within-subjects comparison with administration of different doses of LSD in a larger patient sample would be needed to determine a possible dose response. Additionally, in healthy subjects, 200 µg of LSD produced greater empathogenic effects than 100 µg of LSD (Dolder et al., 2016), which may facilitate therapeutic alliance. However, empathogenic effects and social connectedness, which may contribute to therapeutic effects (Carhart-Harris et al., 2018), have not been assessed in this study.

MDMA generally produced similar alterations of consciousness in patients in the compassionate use group therapy and in healthy volunteers in a laboratory setting. Overall, MDMA-induced increases on the 5D-ASC scale were smaller than after administration of LSD, and MDMA did not produce prototypical hallucinogenic effects such as audio-visual synaesthesia or changed meaning of percepts. However, MDMA also yields small LSD-like perceptual alterations, likely via similar 5-hydroxytryptamine-2A (5-HT_{2A}) receptor stimulation (Liechti et al., 2000b). In patients, MDMA induced greater perceptual alterations including complex imagery than in healthy volunteers. Greater visionary restructuralization may partly result from the different settings, as the clinical studies were conducted in a hospital room with no visual distraction. Furthermore, this may be explained by the fact that more women than men were included and treated with MDMA in the compassionate use group therapy. MDMA-induced perceptual changes seem to be more intense in women than in men (Liechti et al., 2001). In the compassionate use group therapy, MDMA predominantly produced a blissful state, in line with previous reports in healthy volunteers (Greer and Tolbert, 1986; Schmid et al., 2014). Interestingly, the prototypical entactogen MDMA did not produce a statistically significant increase in experience of unity in the compassionate use group therapy, whereas this has repeatedly been demonstrated in healthy subjects (Hysek et al., 2012c; Schmid et al., 2014; Studerus et al., 2010). This may reflect the small sample size, as no significant difference was observed compared with the pooled data of healthy subjects. In contrast, LSD produced significant elevations in the experience of unity in patients treated in the group setting. Seventy-one per cent of the patients treated with LSD and/or MDMA during the early substance-assisted psychotherapy in Switzerland subjectively rated 'experience of unity' and 'complete love' as very important factors having long-lasting consequences (Gasser, 1994). Hallucinogens reliably produce feelings of loss of self-consciousness, and feelings of unity with everything, particularly at higher doses (Carhart-Harris et al., 2016b; Liechti et al., 2017; Millière, 2017; Schmid et al., 2015a). Hence, ratings of experience of unity on the 5D-ASC scale do not only reflect empathogenic effects, but also abnormalities in self-experience or some aspects of mystical experience (Barrett and Griffiths, 2017). LSD primarily acts as a direct partial agonist at the 5-HT_{2A} receptor (Nichols, 2004; Preller et al., 2017; Rickli et al., 2016; Titeler et al., 1988) whereas MDMA mostly acts as an indirect serotonergic agonist by releasing serotonin via the serotonin transporter (Hysek et al., 2012c), which may explain lower increases in the experience of unity after MDMA on the 5D-ASC scale. However, a direct comparison of this effect within the same studies and subjects is lacking so far, and other measurements seem more suited to represent empathogenic effects.

In the compassionate use group, MDMA produced only small, though significant, increases on the MEQ, and contrary to those observed with LSD, most ratings were higher than those of healthy subjects. Nonetheless, no total mystical experiences were observed in both groups with MDMA, in line with previous reports (Liechti et al., 2017; Lyvers and Meester, 2012). Experience of oceanic boundlessness, unity and positive mood seem necessary, but not sufficient for a complete mystical experience (Barrett and Griffiths, 2017). However, patients in the compassionate use programme also displayed greater ratings of spiritual experience and insightfulness on the 5D-ASC scale than healthy subjects after MDMA, indicating that the group setting may be more appropriate to induce at least some aspects of mystical-type experiences. Nevertheless, administration of LSD did not produce higher ratings on the MEQ and on these 5D-ASC subscales in the compassionate use group therapy compared with healthy subjects and patients treated alone, altogether suggesting that mystical experiences are primarily influenced by the administered substance itself, and less by the setting.

Similarly as for LSD, effects on the 5D-ASC scale and on the MEQ did not differ between several doses of MDMA. Yet, these findings have to be considered with caution, as only very few patients were tested with the corresponding doses. In healthy volunteers, 125 mg of MDMA yielded significantly greater mind-altering effects than 75 mg of MDMA (Schmid et al., 2014). Overall, it is unclear whether different dosages not only affect the acute but also the therapeutic effects. Interestingly, no significant dose response was observed in the acute reduction of OCD symptoms after psilocybin (Moreno et al., 2006). Likewise, no differences in PTSD scale scores were observed between patients suffering from treatment-resistant PTSD administered a supplemental dose of MDMA (62.5 mg) and those receiving only an initial dose of 125 mg MDMA (Mithoefer et al., 2010).

Of note, half of the patients in the present study had very limited prior drug experience. We found no differences in the quality and extent of the response to LSD or MDMA between the hallucinogen-naive and moderately experienced subjects, consistent with findings in healthy subjects (Schmid et al., 2015a).

Drugs possibly interfering with LSD or MDMA, mostly antidepressants, were paused before substance administration in patients in the compassionate use group therapy. Previous reports indicate that chronic administration of monoamine oxidase and serotonin reuptake inhibitors may diminish the subjective experience to LSD (Bonson et al., 1996) and MDMA (Liechti et al., 2000a) whereas lithium or tricyclic antidepressants may increase responses to LSD (Bonson and Murphy, 1996). Beta-agonists were paused as not only MDMA, in particular, but also LSD produce sympathomimetic effects (Hysek et al., 2011; Schmid et al.,

2015a). However, recommendations or controlled studies assessing effects of concomitant medication on the effects of LSD and MDMA are mostly missing so far.

Safety aspects in the use of psychedelics primarily concern psychological adverse effects (Parrott, 2014; Passie et al., 2008). Acute, mostly transient, anxiety was infrequently reported when LSD or MDMA were administered in a laboratory setting, which resolved without pharmacological intervention (Schmid et al., 2015a; Vizeli and Liechti, 2017). Likewise, no intervention was needed in the compassionate use group therapy. Interestingly, MDMA produced significantly higher ratings of ego dissolution and anxiety in patients in the compassionate use group compared with healthy subjects. One could argue that this is due to the fact that on the one hand psychiatrically healthy subjects and on the other hand patients with psychiatric disorders with probable pre-existing anxiety were tested. However, anxiety was not increased in patients in the compassionate use group receiving LSD compared with healthy volunteers. As mostly patients suffering from PTSD were treated with MDMA, increased anxiety may have been the result of re-experience and confrontation with previous traumatic events. Additionally, women seem more prone to bad drug effects of MDMA including acute anxiety (Vizeli and Liechti, 2017).

In the clinical studies, mostly younger and healthy subjects received LSD or MDMA. In the compassionate use group, LSD or MDMA was administered in patients aged from 29–77 years, including patients with somatic comorbidities such as arterial hypertension (under drug treatment), glaucoma, allergic asthma, coeliac disease and multiple sclerosis. However, vital signs or course of comorbidities were not determined, and the sample size is too small to draw conclusions about safe administration within these patients. Side effects and safety of LSD and MDMA administration in psychiatric patients, including those with different somatic comorbidities, still remain to be investigated in larger controlled studies. In particular it should be noted, that both substances produce cardiovascular stimulation, likely resulting in higher risk in patients with pre-existing cardiovascular disease (Dolder et al., 2016; Vizeli and Liechti, 2017). In the present study, data concerning continued substance use outside or after the compassionate use was not collected. Nevertheless, in the follow-up after the psycholytic therapy in the 1990s, no patient reported an increase in drug use after the therapy (Gasser, 1994).

The present study has several limitations. First, acute effects were only determined in a relatively small number of patients in the compassionate use therapy, and the results should be replicated in a larger study sample. The study sample is underpowered to reliably assess differences in acute effects between drug doses. Second, treatment efficacy was not determined, meaning that self-evaluation or objective improvement during and after treatment was not assessed. Hence, an exploration of associations of acute effects and therapeutic outcomes was not possible. However, the main goal of the study was to describe characteristics and acute effects in patients suffering from various treatment-resistant disorders treated outside a controlled study and within a group setting. Furthermore, no placebo condition was used in this observational study. Expectations may have influenced the psychological effects of the drugs because all of the subjects were informed about the possible effects prior to their first substance administration. Finally, the comparisons of the acute effects of LSD and MDMA made between the patients in a group therapy setting and in healthy volunteers and patients in a laboratory setting were based on data from different studies. However, there are at present no data from controlled studies directly comparing effects of LSD or MDMA between patients and healthy subjects within the same study and using different settings. Additionally, the comparison was not the main focus of the study.

In conclusion, both LSD and MDMA induced altered states of waking consciousness, and produced mystical-type experiences in patients suffering from a broad range of psychiatric disorders in the Swiss compassionate use group therapy. Overall, acute responses to LSD were greater compared with MDMA including more pronounced perceptual effects and occurrences of complete mystical experiences. The present study data also indicates that LSD and MDMA may produce largely comparable acute subjective effects on the 5D-ASC scale and the MEQ in patients and healthy volunteers in different settings. However, this finding and how the treatment response for different indications is affected by different settings needs further evaluation. The present observational data may serve as a basis for further studies of substance-assisted psychotherapy.

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Supplemental material

Supplemental material for this article is available online.

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