Modern Clinical Research on LSD

Matthias E Liechti

Abstract

All modern clinical studies using the classic hallucinogen lysergic acid diethylamide (LSD) in healthy subjects or patients in the last 25 years are reviewed herein. There were five recent studies in healthy participants and one in patients. In a controlled setting, LSD acutely induced bliss, audiovisual synesthesia, altered meaning of perceptions, derealization, depersonalization, and mystical experiences. These subjective effects of LSD were mediated by the 5-HT_{2A} receptor. LSD increased feelings of closeness to others, openness, trust, and suggestibility. LSD impaired the recognition of sad and fearful faces, reduced left amygdala reactivity to fearful faces, and enhanced emotional empathy. LSD increased the emotional response to music and the meaning of music. LSD acutely produced deficits in sensorimotor gating, similar to observations in schizophrenia. LSD had weak autonomic stimulant effects and elevated plasma cortisol, prolactin, and oxytocin levels. Resting-state functional magnetic resonance studies showed that LSD acutely reduced the integrity of functional brain networks and increased connectivity between networks that normally are more dissociated. LSD increased functional thalamocortical connectivity and functional connectivity of the primary visual cortex with other brain areas. The latter effect was correlated with subjective hallucinations. LSD acutely induced global increases in brain entropy that were associated with greater trait openness 14 days later. In patients with anxiety associated with life-threatening disease, anxiety was reduced for 2 months after two doses of LSD. In medical settings, no complications of LSD administration were observed. These data should contribute to further investigations of the therapeutic potential of LSD in psychiatry.

Introduction

The present article reviews studies on the clinical pharmacology and use of lysergic acid diethylamide (LSD) in psychiatry research, with a focus on recent clinical studies. Older studies that were published in the 1950s–1970s before the prohibition of LSD are summarized elsewhere (Passie *et al*, 2008). All modern controlled clinical studies of LSD published in the past 25 years were included in the present review based on medline and clinicaltrials.gov database searches. Other authors have reviewed serotonergic hallucinogens, including LSD (Dos Santos *et al*, 2016; Nichols, 2016; Passie *et al*, 2008), but did not cover the recent experimental clinical LSD research.

History

LSD was first synthesized in 1938, and its psychoactive properties were discovered in 1943. The similarity between the subjective psychotomimetic effects of LSD and schizophrenia were noted in 1947, leading to the experimental use of LSD to model psychosis. From 1949 to 1966, LSD (Delysid, LSD 25) was provided to psychiatrists and researchers 'to gain insights into the world of mental patients' and to assist psychotherapy. In the 1950s–1960s, LSD and LSD-associated psychotherapy were investigated with regard to anxiety associated with terminal cancer, alcoholism, opioid use disorder, and depression (Passie *et al*, 2008). LSD is a well-studied pharmacological substance, with more than 1000 published reports (Nichols, 2016). LSD has been an important tool in neuroscience and drug development (Nichols, 2016) and has influenced the arts and society. Clinical research on LSD came to a halt in the early 1970s because of political pressure following its widespread uncontrolled use. Nevertheless, the recreational use of LSD has remained high. In 2010, an estimated 32 million US residents reported lifetime use of LSD (Krebs and Johansen, 2013). In the 1990s, clinical hallucinogen research very slowly began again with experimental studies of psilocybin and dimethyltryptamine (DMT) (Gouzoulis-Mayfrank *et al*, 2005; Strassman and Qualls, 1994a; Strassman *et al*, 1994b). The first modern research findings from studies of LSD (Gasser *et al*, 2014, 2015), psilocybin (Carhart-Harris *et al*, 2016a; Griffiths *et al*, 2016; Grob *et al*, 2011; Johnson *et al*, 2014; Ross *et al*, 2016), and ayahuasca (which contains DMT) (Osorio *et al*, 2015) in psychiatric patients have only very recently been published. Legally authorized LSD-assisted psychotherapy is currently offered to very few patients in Switzerland in the context of compassionate use and based on case-by-case authorizations by the Federal Health Office. In addition, experimental research on LSD in healthy subjects has gained new momentum and resulted in novel findings, which are reviewed herein.

Receptor interaction profile and mechanism of action

Serotonergic hallucinogens can be classified based on their chemical structure as phenethylamines and tryptamines. Within the tryptamines, there are the simple tryptamines including the classic natural hallucinogens psilocybin (the prodrug for

psilocin), DMT, and mescaline and the ergolines including mainly LSD. Table 1 shows the human receptor interaction profile for LSD compared with that of other classic serotonergic hallucinogens obtained with the same assays (Table 1). LSD potently binds to human serotonin (5-hydroxytryptamine (5-HT)) 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, dopamine D_2, and α_2 adrenergic receptors and less potently to α_1 adrenergic, D_1, and D_3 receptors (Rickli *et al*, 2015, 2016) (Table 1). LSD also activates rat and mouse trace amine-associated receptor 1 ($TAAR_1$) but not human $TAAR_1$ (Simmler *et al*, 2016). LSD is a partial agonist at 5-HT_{2A} receptors (Rickli *et al*, 2016) (Table 1). 5-HT_{2A} receptors primarily mediate the hallucinogenic effects of LSD (Nichols, 2016; Preller *et al*, 2017; Vollenweider *et al*, 1998; Kraehenmann *et al*, 2017). The affinity of hallucinogens for 5-HT_{2A} receptors but not 5-HT_{1A} receptors is correlated with psychoactive potency in humans. Although the subjective effects of LSD in humans can be blocked by pretreatment with a 5-HT_{2A} receptor antagonist (Preller *et al*, 2017; Kraehenmann *et al*, 2017) and are therefore clearly mediated by 5-HT_{2A} receptor activation, the signaling pathways and downstream effects that mediate the effects of LSD have not been conclusively identified (Nichols, 2016). A key mechanism of action of LSD and other serotonergic hallucinogens is the activation of frontal cortex glutamate transmission secondary to 5-HT_{2A} receptor stimulation. However, interactions between the 5-HT and glutamate systems are unclear (Nichols, 2016). Increases in glutamatergic activity in the prefrontal cortex may result in downstream modulatory effects in subcortical areas and alterations in the gating functions of sensory and cognitive processing. Some notable differences can be seen between the pharmacological profiles of LSD and other serotonergic hallucinogens. First, LSD more potently binds 5-HT_{2A} receptors than psilocybin, mescaline, and DMT (Rickli *et al*, 2016) (Table 1). Second, LSD is more potent at 5-HT_1 receptors (Rickli *et al*, 2016), which may contribute to the effects of hallucinogens. However, there are no studies on the role of the 5-HT_1 receptor in the effects of LSD in humans. Third, LSD binds adrenergic and dopaminergic receptors at submicromolar concentrations, which is not the case for other classic serotonergic hallucinogens (Rickli *et al*, 2016) (Table 1). In animals, dopamine D_2 receptors were shown to contribute to the discriminative stimulus effects of LSD in the late phase of the acute response (Marona-Lewicka and Nichols, 2007). In humans, LSD may indirectly enhance dopamine neurotransmission (Nichols, 2016), with no role of direct D_2 receptor stimulation (Preller *et al*, 2017; Kraehenmann *et al*, 2017). Serotonergic hallucinogens presumably produce overall similar acute subjective (Hollister and Hartman, 1962; Wolbach *et al*, 1962) and potential therapeutic effects in humans. The early clinical trials used mostly LSD while most of the recent hallucinogen studies used psilocybin because of its ease of use due to the shorter action and less controversial history (Nichols *et al*, 2017; Nutt, 2016). However, modern studies need to directly investigate whether the effects of LSD in humans differ qualitatively from those of psilocybin and DMT, notwithstanding LSD's longer duration of action.

Table 1

Receptor Interaction Profiles for LSD and Other Classic Serotonergic Hallucinogens at Human Receptors

Studies in healthy subjects

Five novel experimental placebo-controlled studies have been conducted in Basel, London, and Zurich in a total of 95 normal subjects (Table 2). All studies used a crossover design and were placebo-controlled. The Basel and Zurich studies were randomized and double-blind, whereas the London studies were non-randomized and single-blind. Low–moderate doses of LSD base of 40–80 μg intravenously (London) or 100 μg orally (Basel and Zurich) were used in studies including brain imaging and a relatively high dose of 200 μg LSD base was used in one study in Basel without brain imaging. A full LSD reaction is expected at doses of 100–200 μg (Pahnke *et al*, 1969; Passie *et al*, 2008). Similar and higher doses of LSD were used in patients in the 1950s–1970s (Krebs and Johansen, 2012; Pahnke *et al*, 1970).

Table 2

Modern Clinical Placebo-Controlled LSD Studies

Subjective Effects

Modern placebo-controlled studies using validated psychometric scales have only recently been conducted (Carhart-Harris *et al*, 2016b; Kraehenmann *et al*, 2017; Preller *et al*, 2017; Schmid *et al*, 2015). In a controlled setting, the subjective effects of LSD were predominantly positive (Dolder *et al*, 2016; Schmid *et al*, 2015). Mean group ratings of 'good drug effect' and 'drug liking' on visual analog scales (VASs) reached 90% of maximal possible VAS scores after administration of 200 μg LSD (Schmid *et al*, 2015). In contrast, LSD produced only small (<25%) mean group increases in 'negative drug effect' and 'fear' (Dolder *et al*, 2017; Schmid *et al*, 2015). However, transiently greater ratings of negative drug effects (>50%) are seen in approximately half of the subjects at a 200 μg dose of LSD (Dolder *et al*, 2017). Thus, within a session all subjects experience positive drug effects but some also negative drug effects. Profound anxiety or panic was not experienced, and pharmacological sedation was not

needed (Dolder *et al*, 2016; Schmid *et al*, 2015). LSD increased ratings on all dimensions and subscales of the 5-dimension altered states of consciousness (5D-ASC) scale that has been used in all modern studies (Carhart-Harris *et al*, 2016b; Kraehenmann *et al*, 2017; Liechti *et al*, 2017; Preller *et al*, 2017; Schmid *et al*, 2015) (Figure 1). LSD mainly induced a blissful state, audiovisual synesthesia, changes in the meaning of perceptions, and positively experienced derealization and depersonalization (Carhart-Harris *et al*, 2016b; Liechti *et al*, 2017; Schmid *et al*, 2015). An oral dose of 200 μg LSD produced significantly greater bliss, changes in the meaning of perceptions, and insightfulness compared with 100 μg (Liechti *et al*, 2017). Intravenous LSD at a dose of 75 μg (Carhart-Harris *et al*, 2016b) produced similar ratings on the 5D-ASC as an oral dose of 100 μg (Liechti *et al*, 2017) but lower ratings compared with an oral dose of 200 μg (Schmid *et al*, 2015) (Figure 1). Pretreatment with the 5-HT_{2A} receptor antagonist ketanserin fully prevented the effects of 100 μg LSD on the 5D-ASC (Kraehenmann *et al*, 2017; Preller *et al*, 2017), indicating that the mind-altering effects of LSD in humans are primarily mediated by 5-HT_{2A} receptors. LSD elicited spontaneous synesthesia-like experiences (Carhart-Harris *et al*, 2016b; Liechti *et al*, 2017; Preller *et al*, 2017; Schmid *et al*, 2015), but it did not induce more vivid color experiences in response to grapheme or sound stimuli (Terhune *et al*, 2016). These findings indicate that LSD alters spontaneous processes rather than induced responses (Terhune *et al*, 2016). LSD at 40–80 μg, i.v., increased suggestibility (vividness of imagination) but not cued imagery (Carhart-Harris *et al*, 2015). LSD at 200 μg, p.o. acutely induced mystical experiences in healthy subjects and patients during LSD-assisted psychotherapy (Liechti *et al*, 2017). Studies of psilocybin showed that greater acute mystical experiences were significantly associated with positive long-term effects on mood and personality in healthy subjects (Griffiths *et al*, 2011) and better therapeutic outcomes in patients with anxiety, depression, and substance use disorder (Garcia-Romeu *et al*, 2015; Griffiths *et al*, 2011, 2016; Ross *et al*, 2016). Thus, acute substance-induced mystical-type effects during therapeutic sessions appear to predict the long-term effects of hallucinogens. However, LSD-induced mystical-type effects were highly correlated with other alterations of consciousness and particularly the blissful state on the 5D-ASC (Liechti *et al*, 2017), indicating that greater positive acute responses to hallucinogens and not specifically mystical-type effects may generally be associated with any better long-term effects on mood. Furthermore, LSD increased feelings of well-being, happiness, closeness to others, openness, and trust (Dolder *et al*, 2016; Schmid *et al*, 2015). Such empathogenic effects on mood are typically produced by 3,4-methylenedioxymethamphetamine (MDMA; ecstasy) (Hysek *et al*, 2014a) and may facilitate psychotherapy. A 200 μg dose of LSD produced greater feelings of closeness to others, happiness, openness, and trust than a 100 μg dose (Dolder *et al*, 2016). Consistently, an LSD dose of 200 μg is currently used in LSD-assisted psychotherapy in Switzerland (Gasser *et al*, 2014, 2015).

Figure 1
Effects of LSD on the 5D-ASC scale. The data are derived from three studies using doses of 75 μg i.v. (Carhart-Harris *et al*, 2016b), 100 μg p.o. (Liechti *et al*, 2017), and 200 μg p.o. (Schmid *et al*, 2015 ...

No differences in subjective VAS-rated responses to LSD were found between subjects with no prior hallucinogen use and subjects with moderate experience (1–3 prior uses) (Schmid *et al*, 2015). The effects of LSD on the 5D-ASC were also similar between subjects with no prior hallucinogen use (n=21) (Dolder *et al*, 2016) and subjects who had used LSD 14±18 times (mean±SD) (Carhart-Harris *et al*, 2016b). No correlations were found between past LSD use and the acute effects of LSD on functional magnetic resonance imaging (fMRI) study outcomes across subjects with prior LSD use (Speth *et al*, 2016; Tagliazucchi *et al*, 2016).

Music has typically been used in substance-assisted psychotherapy (Gasser *et al*, 2014, 2015; Johnson *et al*, 2008). Several modern studies assessed the interactive effects of LSD and listening to music. LSD enhanced the emotional response to music and produced greater feelings of wonder and transcendence compared with listening to music after placebo (Kaelen *et al*, 2015). LSD increased eyes-closed imagery or seeing scenes from the past, but listening to music did not interact with these subjective effects of LSD on imagery (Kaelen *et al*, 2016). Other researchers found that LSD significantly increased ratings of music excerpts that were previously rated as personally meaningless or neutral (Preller *et al*, 2017). Thus, LSD attributed meaning to previously meaningless stimuli (Preller *et al*, 2017).

Autonomic and Adverse Effects

LSD moderately increased blood pressure, heart rate, body temperature, and pupil size (Dolder *et al*, 2016; Kaelen *et al*, 2015; Schmid *et al*, 2015). The sympathomimetic effects of 100 and 200 μg doses of LSD were similar (Dolder *et al*, 2016, 2017) and less pronounced than those of MDMA and stimulants (Hysek *et al*, 2014b). Acute adverse effects up to 10–24 h after LSD administration included difficulty concentrating, headache, dizziness, lack of appetite, dry mouth, nausea, imbalance, and feeling exhausted. Headaches and exhaustion may last up to 72 h (Dolder *et al*, 2016; Schmid *et al*, 2015). No severe adverse reactions were reported in modern LSD studies (Carhart-Harris *et al*, 2016b; Dolder *et al*, 2016; Kaelen *et al*, 2015; Preller *et al*,

2017; Schmid *et al*, 2015). This is consistent with the view that LSD is relatively safe when used in medical settings and according to safety guidelines (Johnson *et al*, 2008). LSD is physically non-toxic, but there are psychological risks especially when it is used in unsupervised settings. In addition, it is important to note that many novel hallucinogens are being used and may even be sold as LSD but have a different pharmacology and possibly risk profile than LSD (Rickli *et al*, 2015, 2016). LSD has typically been reported to produce flashbacks. Flashbacks after LSD can be defined as episodic and short (seconds or minutes) replications of elements of previous substance-related experiences (Holland and Passie, 2011). In a web-based survey among hallucinogen users, greater past LSD use was a predictor of the probability of experiencing unusual substance-free visual experiences (Baggott *et al*, 2011). Clinically significant flashbacks are also defined as hallucinogen persisting perception disorder (HPPD). This disorder is considered rare and occurs almost exclusively in the context of illicit recreational use or/and in patients with anxiety disorders and it typically will have a limited course of months to a year (Halpern and Pope, 1999; Holland and Passie, 2011; Johnson *et al*, 2008). In controlled non-therapeutic research settings, psilocybin did not produce HPPD or flashbacks (Studerus *et al*, 2011). However, the prevalence and relevance of HPPD is unclear and needs to be studied (Halpern *et al*, 2016).

Endocrine Effects

LSD acutely increased plasma concentrations of cortisol (Strajhar *et al*, 2016), prolactin, oxytocin, and epinephrine (Schmid *et al*, 2015). LSD does not increase plasma concentrations of norepinephrine (Schmid *et al*, 2015), testosterone, or progesterone (Strajhar *et al*, 2016). The endocrine effects of LSD are consistent with those of other serotonergic substances including psilocybin, DMT, and MDMA (Hasler *et al*, 2004; Hysek *et al*, 2014b; Seibert *et al*, 2014; Strassman and Qualls, 1994a).

Model Psychosis

LSD (75 μg, i.v.) increased subjective ratings of cognitive disorganization and delusional thinking (Carhart-Harris *et al*, 2016b). Disordered cognition has been suggested to be a more fundamental characteristic of LSD's effects than positive or negative mood (Carhart-Harris *et al*, 2016b). Nevertheless, the LSD experience was not dominated by unpleasant psychosis-like phenomena but rather characterized by an overall positive mood state in the majority of subjects (Carhart-Harris *et al*, 2016b). Investigators rated subjects as more distant from reality and happy after administration of 200 μg LSD, whereas ratings of anxiety and paranoid thinking did not increase (Schmid *et al*, 2015). Patients with schizophrenia present deficits in sensorimotor gating, reflected by prepulse inhibition (PPI) of the startle response. LSD acutely disrupts PPI in both animals (Halberstadt and Geyer, 2010) and healthy human subjects (Schmid *et al*, 2015), producing deficits in information processing that are similar to those observed in schizophrenia. Similarly, inhibitory processes are impaired in schizophrenia and in healthy subjects after administration of LSD (Schmidt *et al*, 2017).

Emotional Processing

LSD impaired the recognition of sad and fearful faces (Dolder *et al*, 2016) and enhanced emotional empathy (Dolder *et al*, 2016), similar to psilocybin (Kometer *et al*, 2012; Preller *et al*, 2015) and MDMA (Hysek *et al*, 2014a; Kuypers *et al*, 2017). These effects of LSD on emotion processing may be considered useful in LSD-assisted psychotherapy. However, LSD also impaired the identification of complex emotions (Dolder *et al*, 2016).

Functional Brain Imaging

LSD acutely decreased the functional integrity of brain networks (Figure 2a) and the separation between networks (Carhart-Harris *et al*, 2016c; Tagliazucchi *et al*, 2016) (Figure 2b). At the whole-brain level, LSD increased functional connectivity between various brain regions (Figure 3). LSD also increased measures of functional 'brain entropy' (ie, the predictability of resting-state fMRI time series) across many functional systems (Lebedev *et al*, 2016). The acute LSD-induced global increase in 'brain entropy' was associated with trait openness that was assessed 14 days later (Lebedev *et al*, 2016). LSD increased thalamocortical resting-state functional connectivity (RSFC) (Mueller *et al*, 2017b; Tagliazucchi *et al*, 2016), overall connectivity in high-level cortical regions and the thalamus, and connectivity between normally more dissociated resting-state networks (Tagliazucchi *et al*, 2016). These findings indicate more globally synchronized activity within the brain and a reduction of network separation while under the pharmacological effects of LSD. Similar decreases in within-network integrity (Carhart-Harris *et al*, 2014; Muthukumaraswamy *et al*, 2013) and increases in between-network connectivity (Carhart-Harris *et al*, 2013; Roseman *et al*, 2014) have been observed under psilocybin. The LSD-induced increases in global connectivity, particularly in the temporo-parietal junction and insular cortex, correlated with feelings of moderate 'ego dissolution' that were produced by LSD (Tagliazucchi *et al*, 2016). 'Ego dissolution' refers to a disintegration of the sense of possessing a 'self' or identity that is

distinct from others and from the environment (Preller and Vollenweider, 2016; Tagliazucchi *et al*, 2016). In addition, LSD-induced RSFC between the thalamus and right fusiform gyrus and insula correlated with subjective visual and auditory alterations, respectively (Mueller *et al*, 2017b). Remaining to be determined is the way in which LSD-induced increases in thalamocortical connectivity may be linked to the thalamic gating of perceptions (Mueller *et al*, 2017b). In contrast to the higher connectivity between neural networks while under the effects of LSD, LSD globally decreased within-network RSFC (integrity) and within-network signal variance (Carhart-Harris *et al*, 2016c) (Figure 2a). Specifically, LSD decreased default mode network (DMN) integrity (Carhart-Harris *et al*, 2016c) as previously shown for psilocybin (Carhart-Harris *et al*, 2014), and this LSD-induced disintegration of the DMN correlated with ratings of ego dissolution (Carhart-Harris *et al*, 2016c; Tagliazucchi *et al*, 2016). Furthermore, reductions of RSFC in the DMN (ie, DMN disintegration) were associated with fewer mental spaces for the past (ie, decreased mental time travel to the past) while under the effects of LSD (Speth *et al*, 2016). Increases in DMN RSFC have been described in depression, and decreases in DMN RSFC that are induced by LSD may be linked to its potential antidepressant effects (Carhart-Harris *et al*, 2016a).

Figure 2
(a) Mean percentage differences (+SEM) in CBF (red), integrity (blue), and signal variance (green) in 12 different resting-state networks (RSNs) under LSD relative to placebo (red asterisks indicate statistical significance, **P*<0.05; ***P*<0.01, ...

Figure 3
Connectome ring showing functional connectivity between 132 regions covering the whole brain. Contrast LSD *vs* placebo, *P*<0.05, FDR. Yellow-red indicates increased functional connectivity, blue indicates decreased connectivity. Figure provided ...

Arterial spin labeling analyses revealed greater cerebral blood flow in the visual cortex that was induced by LSD, and this increase was associated with ratings of complex imagery on the 5D-ASC (Carhart-Harris *et al*, 2016c). LSD also strongly increased RSFC between the primary visual cortex (V1) and cortical and subcortical brain regions, and this effect correlated with 5D-ASC ratings of elementary or complex hallucinations (Carhart-Harris *et al*, 2016c). Greatly expanded V1 functional connectivity that is induced by LSD may indicate that a greater proportion of the brain processes visual information than under normal conditions (Carhart-Harris *et al*, 2016c). Further analyses found that LSD administration altered eyes-closed spontaneous activity within retinotopically organized patches of the V1 and neighboring visual regions (V3), similar to visual stimulation (Roseman *et al*, 2016). Thus, the primary visual system is altered by LSD and behaves as if it perceives spatially localized visual information when in fact there is none (Roseman *et al*, 2016), which is consistent with the notion of 'seeing with the eyes shut' (Carhart-Harris *et al*, 2016c; Roseman *et al*, 2016).

LSD-induced decreases in RSFC between the parahippocampus and the rest of the brain (particularly the retrosplenial and posterior cingulate cortex) correlated with VAS ratings of ego dissolution and altered meaning on the 5D-ASC (Carhart-Harris *et al*, 2016c). Similarly, psilocybin altered activity in parahippocampal-retrosplenial cortex circuit measured with EEG and this effect correlated with spirituality and insigthfulness ratings on the 5D-ASC (Kometer *et al*, 2015). LSD increased blood oxygen-level-dependent activity of the supplementary motor area and prefrontal cortex in response to music without personal meaning or relevance compared with personally meaningful and neutral music, indicating enhanced activity in brain areas that are involved in self-referential cognition and processing (Preller *et al*, 2017). LSD reduced left amygdala reactivity to the presentation of fearful faces (Mueller *et al*, 2017a). Psilocybin similarly decreased amygdala reactivity to negative facial expressions (Kraehenmann *et al*, 2015). Lower fear perception (Dolder *et al*, 2016) and amygdala reactivity may be useful during psychotherapy. Magnetoencephalography showed that LSD decreased oscillatory power throughout the brain during eyes-closed rest (Carhart-Harris *et al*, 2016c) as similarly shown for psilocybin (Kometer *et al*, 2015; Muthukumaraswamy *et al*, 2013) and ayahuasca (Riba *et al*, 2002). After LSD administration, lower alpha power correlated with subjective ratings of simple hallucinations (Carhart-Harris *et al*, 2016c). Lower alpha power in occipital sensors correlated with increases in primary visual cortex RSFC (Carhart-Harris *et al*, 2016c). Modern positron emission tomography (PET) and single-photon emission computed tomography studies of LSD have not yet been conducted. Other 5-HT hallucinogens, such as psilocybin, ayahuasca, and mescaline, increased metabolic indices in frontal brain areas Hallucinogen-induced hyperfrontality is hypothesized to reflect increased frontal activity due to flooding with information (Geyer and Vollenweider, 2008; Vollenweider *et al*, 1997). In contrast, in an fMRI study, psilocybin decreased blood flow and BOLD signal in the thalamus, anterior cingulate, medial prefrontal, and cingulate cortices (Carhart-Harris *et al*, 2012). It is not yet clear what the different imaging modalities represent and how these inconsistencies can be explained. It has been proposed that the PET study

findings of hyperfrontality reflect the increased neuronal firing activity while fMRI BOLD measures correlate with cortical oscillatory activity (Halberstadt, 2015). Altogether, the first modern imaging studies of LSD have provided preliminary information on the neural correlates of altered states of mind that are induced by LSD. However, there are many limitations. Much data have been derived from only a few small studies. Chance findings should be expected especially with regard to the RSFC data. LSD may also have direct actions on vascular resistance and blood flow that may confound neuroimaging data. These preliminary findings need to be confirmed in larger studies and by different research groups.

Clinical Pharmacology

The pharmacokinetics of LSD have been well investigated only for oral doses of 100 and 200 μg (Dolder *et al*, 2015b, 2017; Steuer *et al*, 2016). LSD concentration-time and subjective effect-time curves are shown in Figure 4. No data are available on the concentration-time course of the intravenous dose of 75 μg LSD that was used in the London studies. The pharmacokinetics of LSD are dose-proportional, and elimination kinetics are linear up to 12 h (Dolder *et al*, 2015b, 2017; Steuer *et al*, 2016). Maximal plasma concentrations are reached 1.5 h after oral administration (Dolder *et al*, 2015b, 2017) (Figure 4). The elimination half-life is ~3 h (Dolder *et al*, 2015b, 2017). LSD can be detected in blood plasma up to 12–24 h after administration, depending on the dose (Dolder *et al*, 2017). 2-Oxo-3-hydroxy-LSD (Oxo-HO-LSD) is the major metabolite of LSD and is detectable in urine for a longer time than LSD (Dolder *et al*, 2015a; Steuer *et al*, 2016). Oxo-HO-LSD and minor metabolites of LSD can only be detected at very low concentrations in blood plasma and serum (<0.3 ng/ml) (Dolder *et al*, 2015a; Steuer *et al*, 2016) but are present at higher concentrations in urine (Dolder *et al*, 2015a). The intravenous dose of 75 μg LSD that was used in the London studies likely corresponds to the oral dose of 100 μg that was used in the Basel and Zurich studies, based on the comparable effects on the 5D-ASC (Carhart-Harris *et al*, 2016b; Liechti *et al*, 2017) (Figure 1). The subjective, cognitive, and sympathomimetic effects of oral LSD closely reflected the time course of LSD concentrations in plasma (Dolder *et al*, 2015b, 2017) (Figure 4). Subjective effects of LSD peaked 2.5 h after administration and lasted for 8 h and 12 h after administration of 100 μg and 200 μg, respectively (Dolder *et al*, 2017) (Figure 4). After intravenous administration of 75 μg LSD, subjective effects peaked at 45–120 min and lasted 7–8 h (Carhart-Harris *et al*, 2016b; Kaelen *et al*, 2015). After a single dose of LSD, the pharmacodynamic effects lasted as long as LSD was present in the body, with no evidence of acute tolerance to the effects of LSD (Dolder *et al*, 2017). Tolerance has been reported with repeated daily LSD administration over 3–7 days (Belleville *et al*, 1956).

Figure 4
Pharmacokinetics and pharmacodynamics of LSD. LSD concentration-time (a) and subjective effect-time (b) curves. LSD was administered at a dose of 100 and 200 μg p.o. to 24 and 16 healthy subjects, respectively, at the time point *t*=0. Subjective ...

Mid- and Long-Term Effects

In comparison to other illicit substances, epidemiological studies indicate that the use of classic hallucinogens is associated with lower psychological distress, lower suicidality, and lower mental health problems (Hendricks *et al*, 2015). Long-lasting positive effects were documented in modern studies after controlled administration of psilocybin (Griffiths *et al*, 2011; MacLean *et al*, 2011) and ayahuasca (Bouso *et al*, 2012) but have not yet been reported in modern experimental laboratory studies of LSD. Controlled administration of LSD in healthy subjects increased optimism and trait openness 2 weeks after administration and produced trends toward decreases in distress and delusional thinking (Carhart-Harris *et al*, 2016b). In addition, the greatest increases in openness were observed in subjects who presented both the highest acute LSD-induced enhancements of ego dissolution during music listening and greater brain entropy in frontal areas (Lebedev *et al*, 2016). However, the reported increases in optimism and personality trait openness 14 days after LSD administration were observed in subjects with on average already 14 previous uses of LSD (Carhart-Harris *et al*, 2016b; Lebedev *et al*, 2016) raising the question of how open and optimistic participants can actually become or whether these effects are rather transient.

Studies in patients

Early studies from the 1950s to 1970s indicated that LSD may have antidepressive and anxiolytic properties (Dos Santos *et al*, 2016; Passie *et al*, 2008; Rucker *et al*, 2016). LSD-assisted psychotherapy was often performed in patients with anxiety and cancer (Pahnke *et al*, 1969; Sheehan, 1972) and in patients with depression or related disorders (Rucker *et al*, 2016). These early practices and studies were relatively poorly documented methodologically, and replication in modern studies is needed. Single or few doses of LSD also reportedly lessened cluster headache and induced remission more effectively than conventional

medications (Schindler *et al*, 2015). However, no controlled studies have been conducted. LSD was also well studied as treatment for alcohol use disorder (Krebs and Johansen, 2012). LSD and other hallucinogens are misused but are not addictive substances leading to compulsive drug taking, withdrawal or self-administration in animals (Fantegrossi *et al*, 2008; Nichols, 2004). Recent trials investigated psilocybin in patients with alcohol and nicotine use disorder (Bogenschutz *et al*, 2015; Johnson *et al*, 2014), major depression, and anxiety (Carhart-Harris *et al*, 2016a; Griffiths *et al*, 2016; Grob *et al*, 2011; Ross *et al*, 2016). However, in the past 40 years, no studies of LSD have been conducted in humans until very recently, and only one modern trial evaluated LSD in patients (Gasser *et al*, 2014, 2015) (Table 2). The trial assessed the effects of LSD-assisted psychotherapy on anxiety in 11 patients with life-threatening diseases (eight with cancer). Eight patients received 200 μg LSD twice, and three patients received active placebo (a low dose of 20 μg LSD) twice in two sessions 2–3 weeks apart, with an open-label crossover to 200 μg LSD after the first randomized double-blind treatment phase. At study entry, all of the patients presented higher ratings of anxiety on the state-trait anxiety inventory (STAI), six were diagnosed with generalized anxiety disorder, and seven were diagnosed with major depression. The study found a significant decrease in STAI anxiety 2 months after the two LSD sessions compared with baseline anxiety scores. STAI scores did not decrease in the placebo group. However, the placebo control group was too small for statistical comparisons with the treatment group and therefore a valid control was missing. The study also found non-significant decreases in depression and increases in quality of life (Gasser *et al*, 2014). A follow-up study at 12 months in nine patients reported sustained decreases in anxiety, an increase in quality of life, and no lasting adverse reactions after LSD, but the follow-up lacked a control group (Gasser *et al*, 2015). No drug-related severe adverse effects were reported, with no panic reactions or other medical or psychiatric complications. Prolonged psychotic reactions were reportedly rare in patients who received LSD during psychotherapy (Passie *et al*, 2008). Because the therapist used effective existential and meaning-based psychotherapeutic methods in both the treatment and control groups, the possible added benefits of LSD are not yet known. In addition, different and mostly non-evidence-based therapies have been used in psychedelic-assisted therapy trials making comparisons between studies difficult. A larger trial that uses LSD in patients who suffer from anxiety associated with severe somatic disease and anxiety disorder is conducted in Switzerland (NCT03153579). In addition, two high-quality studies recently reported the efficacy of psilocybin in the treatment of anxiety and depression associated with life-threatening cancer (Griffiths *et al*, 2016; Ross *et al*, 2016).

Future directions

New areas of research on hallucinogens, including LSD, have just recently opened, and many questions remain unanswered. With regard to potential therapeutic long-term effects of single-dose hallucinogen administration, unclear is whether these effects depend on a direct pharmacological action or on the acute psychological response. Differential indications might be associated with different aspects of mechanisms of action. Novel dose–response studies of the acute effects of LSD are lacking, and direct comparisons with psilocybin need to be made. Neuroimaging studies may help determine whether long-term changes in mood can be linked to changes in brain activity and how such patterns change before, during, and after the acute effects of LSD and other hallucinogens. The dissociable effects of the substance itself and psychotherapy on outcomes also need to be elucidated, in addition to their interactive effects. Larger studies need to validly define the benefits of using hallucinogens as an adjunct to psychotherapy and the patient characteristics that may predict such additional benefits of hallucinogens. Unclear are the aspects of the acute response to hallucinogens that best predict good long-term therapeutic outcomes. Acute mystical-type effects of psilocybin have been associated with greater reductions of anxiety and depression in patients (Garcia-Romeu *et al*, 2015; Griffiths *et al*, 2016; Ross *et al*, 2016). This association, however, may not imply causation. Other aspects of the acute peak response to hallucinogens could be equally important (Dolder *et al*, 2016; Liechti *et al*, 2017). Many practical aspects of clinical trials that evaluate the effects of LSD also need to be resolved. Clinical studies have generally become extremely costly because of overregulation. This is especially problematic for LSD research because industry funding is unlikely. In many countries, the scheduling of LSD still impedes or prohibits clinical research.

The mechanism of the therapeutic actions of LSD is unclear. The acute psychedelic or mystical peak experience characterized by a loss of usual sense of self, sense of unity, transcendence of time and space, and feelings of positive mood, awe, and meaning (Pahnke *et al*, 1970) may restructure patients' emotional trust, situational understanding, habits, and views (Gasser *et al*, 2015). Lower RSFC in the DMN may be linked to lower rumination and depression (Carhart-Harris *et al*, 2016c). Enhanced neurogenesis may be associated with antidepressant effects. Acutely reduced fear recognition and amygdala reactivity may facilitate the processing of negative information (Dolder *et al*, 2016; Mueller *et al*, 2017a), and feelings of closeness and trust enhance the patient–therapist relationship (Dolder *et al*, 2016; Schmid *et al*, 2015). Irrespective of the mechanism, if LSD in only a few doses may indeed improve health, this novel treatment paradigm needs to be studied further in modern clinical studies.

Conclusions

A few single administrations of LSD or related substances within a therapeutic setting may be beneficial for patients with anxiety associated with severe illness, depression, or addiction. These old–new treatments may have a potential in psychiatry. As professionals, we should actively study these new options so patients who are in need will not look elsewhere for unproven treatments from unregulated sources. More methodologically sound research on the psychological and biological mechanisms and therapeutic potential of LSD in psychiatry is needed.

Funding and disclosure

The authors declare no conflict of interest.

Acknowledgments

The author acknowledges P Dolder and F Mueller for comments on the manuscript, F Muller and P Vizeli for assistance with figure design, and M Arends for text editing. This work was funded by the Swiss National Science Foundation (Grant no. 320030_170249).

Article information

Neuropsychopharmacology. 2017 Oct; 42(11): 2114–2127.

Published online 2017 Jun 14. Prepublished online 2017 Apr 27. doi: 10.1038/npp.2017.86

PMCID: PMC5603820

PMID: 28447622

Matthias E Liechti[1,2,3,*]

[1]Psychopharmacology Research, Clinical Pharmacology and Toxicology, Department of Biomedicine, University Hospital Basel, University of Basel, Basel, Switzerland

[2]Psychopharmacology Research, Clinical Pharmacology and Toxicology, Department of Clinical Research, University Hospital Basel, University of Basel, Basel, Switzerland

[3]Psychopharmacology Research, Clinical Pharmacology and Toxicology, Department of Internal Medicine, University Hospital Basel, University of Basel, Basel, Switzerland

[*]Psychopharmacology Research, Clinical Pharmacology and Toxicology, Department of Biomedicine, University Hospital Basel, University of Basel, Schanzenstrasse 55, Basel CH-4056, Switzerland. Tel: +41 61 328 68 68, Fax: +41 61 265 45 60, E-mail: matthias.liechti@usb.ch

Received 2017 Feb 6; Revised 2017 Apr 19; Accepted 2017 Apr 20.

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