Progress in Neuropsychopharmacology & Biological Psychiatry 81 (2018) 1–10

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Serotonergic hallucinogens in the treatment of anxiety and depression in patients suffering from a life-threatening disease: A systematic review

Simon Reiche[a], Leo Hermle[b], Stefan Gutwinski[c], Henrik Jungaberle[d], Peter Gasser[e], Tomislav Majić[c,*]

[a] Charité - Universitätsmedizin, Berlin, Germany
[b] Clinic for Psychiatry and Psychotherapy, Christophsbad, Göppingen, Germany
[c] Department of Psychiatry and Psychotherapy, Charité - Universitätsmedizin Berlin, Campus Mitte, Psychiatric University Hospital Charité at St. Hedwig, Berlin, Germany
[d] MIND European Foundation for Psychedelic Science, Germany
[e] Medical Office for Psychiatry and Psychotherapy, Solothurn, Switzerland

ARTICLE INFO

Keywords:
Hallucinogen
LSD
Psilocybin
Anxiety
Life-threatening disease
Cancer

ABSTRACT

Anxiety and depression are some of the most common psychiatric symptoms of patients suffering with life-threatening diseases, often associated with a low quality of life and a poor overall prognosis. 5-HT_{2A}-receptor agonists (serotonergic hallucinogens, 'psychedelics') like lysergic acid diethylamide (LSD) and psilocybin were first investigated as therapeutic agents in the 1960s. Recently, after a long hiatus period of regulatory obstacles, interest in the clinical use of these substances has resumed. The current article provides a systematic review of studies investigating psychedelics in the treatment of symptoms of existential distress in life-threatening diseases across different periods of research, highlighting how underlying concepts have developed over time. A systematic search for clinical trials from 1960 to 2017 revealed 11 eligible clinical trials involving a total number of N = 445 participants, of which 7 trials investigated the use of lysergic acid diethylamide (LSD) (N = 323), 3 trials investigated the use of psilocybin (N = 92), and one trial investigated the use of dipropyltryptamine (DPT) (N = 30). The 4 more recent randomized controlled trials (RCTs) (N = 104) showed a significantly higher methodological quality than studies carried out in the 1960s and 1970s. Evidence supports that patients with life threatening diseases associated with symptoms of depression and anxiety benefit from the anxiolytic and antidepressant properties of serotonergic hallucinogens. Some studies anecdotally reported improvements in patients´ quality of life and reduced fear of death. Moreover, low rates of side effects were reported in studies that adhered to safety guidelines. Further studies are needed to determine how these results can be transferred into clinical practice.

1. Introduction

Receiving a diagnosis of a life-threatening physical disease is usually a shocking event, associated with a significant degree of emotional suffering including fear, anger, despair, and social withdrawal. While some patients are capable of coping effectively with the challenges of their disease and the associated 'existential distress', others develop a broad range of psychological problems (Teunissen et al., 2007; Van Lancker et al., 2014), with a high prevalence of anxiety and depressive symptoms (Mitchell et al., 2011; Watts et al., 2015, 2014; Wilson et al., 2007). *Existential distress* includes core phenomena like feelings of hopelessness, a loss of will to live, a loss of meaning and sense of dignity, and a sense of being a burden to others and a desire for a hastened death (Boston et al., 2011; Boston and Mount, 2006; Chochinov et al., 2005a; Jaiswal et al., 2014; Kissane et al., 2001). These problems are often associated with poor treatment adherence (Arrieta et al., 2013) and higher mortality rates (Brown et al., 2003). In palliative care, there is a growing consensus that existential distress is a core determinant of

Abbreviations: 5HT, 5-hydroxytryptamine (= serotonin); 5-HT_{2A}, 5-hydroxytryptamine (serotonin) receptor 2A; ASC, altered states of consciousness; BDI, Beck Depression Inventory; DMT, *N,N*-dimethyltryptamine; DPT, *N,N*-dipropyltryptamine; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; ECRS, Emotional Condition Rating Scale; HADS, Hospital Anxiety and Depression Scale; HAM-A, Hamilton Rating Scale for Anxiety; HAM-D, Hamilton Rating Scale for Depression; HPPD, Hallucinogen Persisting Perception Disorder; LSD, lysergic acid diethylamide; MEQ30, Mystical Experience Questionnaire; SAP, Substance-assisted psychotherapy; STAI, State-Trait Anxiety Inventory; PDT, psychedelic (peak) therapy; POI, Personal Orientation Inventory; POMS, Profile of Mood States; QoL, Quality of life

* Corresponding author at: Department of Psychiatry and Psychotherapy, Charité - Universitätsmedizin Berlin, Campus Mitte, Psychiatric University Hospital Charité at St. Hedwig, Berlin, Grosse Hamburger Str. 5-11, 10115 Berlin, Germany.
E-mail address: tomislav.majic@charite.de (T. Majić).

http://dx.doi.org/10.1016/j.pnpbp.2017.09.012
Received 17 August 2017; Received in revised form 13 September 2017; Accepted 16 September 2017
Available online 22 September 2017
0278-5846/

poor well-being and quality of life (QoL) in patients with a life-threatening disease, determining the effectiveness in coping with the challenges of the disease (Breitbart et al., 2005, 2000; Edwards et al., 2010; Jones et al., 2003; Kandasamy et al., 2011; McClain et al., 2003; Puchalski, 2012; Rodin et al., 2009). Thus, an increasing number of psychotherapeutic interventions are approaching existential distress by meaning-enhancing interventions like the 'Meaning-centered Group Psychotherapy' (Breitbart et al., 2015, 2010), 'Dignity Therapy' (Chochinov et al., 2005b) or 'Supportive-expressive Group Therapy' (Reuter, 2010) (for a review see LeMay and Wilson, 2008). In contrast, there are currently no specific pharmacological treatment options regarding this particular type of distress (Breitbart et al., 2010). So far, treatment strategies mainly focus on reduction of symptoms like pain or sleep disturbances. Recently, the interest in the therapeutical potential of classic serotonergic hallucinogens (5-HT_{2A} receptor agonists; 'psychedelics') has resumed, and there is some evidence for efficacy in certain indications (Majić et al., 2017). In the following we will give an overview over this group of substances and outline the history of using these substances in the treatment of anxiety and depression in patients suffering from life-threatening diseases.

1.1. Substance class and historical background

The naturally occurring alkaloid psilocybin (4-phosphoryloxy-*N,N*-dimethyltryptamine) and the semisynthetic lysergic acid diethylamide (LSD) belong to the group of the classic or serotonergic hallucinogens ('psychedelics'), which can be divided into phenethylamines and tryptamines, including its subset of ergolines (Nichols, 2004). Besides mescaline (3,4,5-trimethoxyphenethylamine) and DMT (*N,N*-dimethyltryptamine), LSD and psilocybin constitute the most representative compounds of this substance class (Nichols, 2016; Passie et al., 2008, 2002). The chemical structure of the tryptamines resembles the neurotransmitter and tissue hormone serotonin (5-hydroxytryptamine, 5-HT) (Nichols, 2004) (see Fig. 1). Moreover,

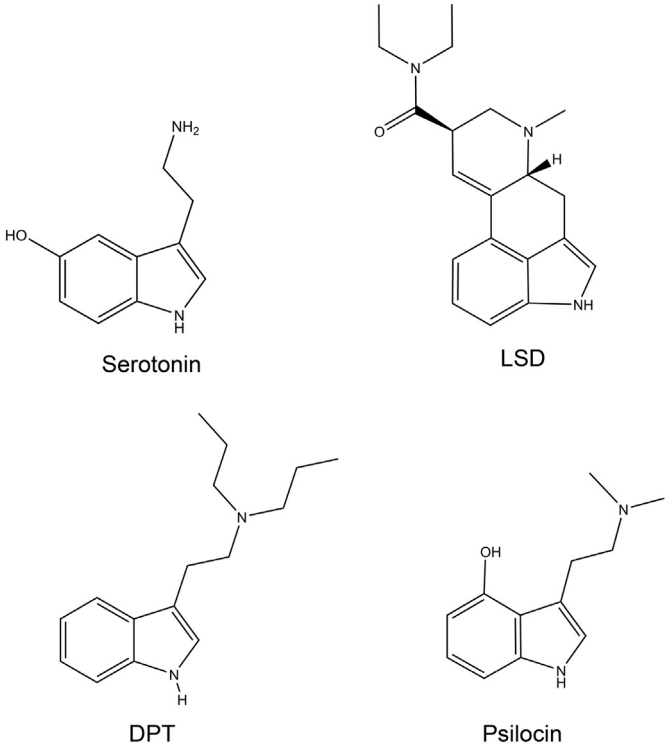

Fig. 1. Structural formula of serotonin (hydroxytryptamine, 5-HT) and related tryptamines psilocin (*N,N*-dimethyl-4-hydroxytryptamine, active metabolite of psilocybin), DPT (*N,N*-dipropyltryptamine) and LSD (lysergic acid diethylamide).

psychedelics share a common mechanism of action at different 5-HT receptors, primarily the 5-HT_{2A} receptor (Geyer and Vollenweider, 2008), which appears to be crucial for the specific psycho-vegetative effects, probably by activating a complex signal cascade (Halberstadt, 2015; Vollenweider and Kometer, 2010).

The treatment strategies presented in the current article originally emerged in the 1950s and 1960s. The idea of treating existential anxiety and depression in terminally ill patients with serotonergic hallucinogens was first suggested in an interview by the physician Valentina Wasson after participation in a ceremony involving 'magic mushrooms' containing psilocybin in 1957 and then some years later by the writer Aldous Huxley (Halifax and Grof, 1977). Subsequently, clinical trials evaluating psychedelic-assisted therapy in this indication have been carried out by different research groups in the U.S., however, initiating in the 1960s until the mid 1970s, when research on psychedelics came to a halt due to regulatory restrictions. However, after a hiatus period of > 30 years, LSD and psilocybin are currently being re-evaluated for the treatment of anxiety and depression, or 'existential distress' in patients with a life-threatening disease (Griffiths and Grob, 2010; Grob et al., 2013).

1.2. Studies in healthy volunteers

Scientific interest in serotonergic hallucinogens emerged due to the observation that a dosis of 200 to 500 µg of LSD may be capable of inducing 'unique, profound, overwhelming, otherworldly and impressive' (Sherwood et al., 1962) altered states of consciousness (ASCs), sometimes labelled as 'peak experiences'. Effects are sometimes followed by profoundly positive and potentially therapeutic after-effects (Maslow, 1962, 1959; Osmond, 1957) termed as 'psychedelic afterglow' (for a review see Majić et al., 2015) and described as 'elevated and energetic mood with a relative freedom from concerns of the past and from guilt and anxiety' (Pahnke, 1969a). One study administered a relatively high dose of psilocybin (30 mg) to a group of 20 students of theology before they attended a religious service in a private chapel ('Good Friday Experiment', Pahnke, 1963). When compared to the control group that received nicotinic acid as an active placebo, the psilocybin group experienced a high rate of profound experiences (30–40%), similar to the characteristics of nondrug-related 'mystical-type' experiences, described in the literature of theology (Hood, 1975; Pahnke, 1969b, 1967; Pahnke and Richards, 1966) (see Table 1). In a more recent study, psilocybin (30 mg/70 kg) or methylphenidate (40 mg/70 kg, as active control) were administered to a sample of healthy hallucinogen-naïve subjects in a double-blind, cross-over design (Griffiths et al., 2006). Out of the 36 subjects who received each substance in individual sessions conducted in specific setting, 22 subjects fulfilled Pahnke's criteria for having a 'mystical' peak experience. Positive after-effects were measured at 14-month follow-up with an observation of increased well-being or life satisfaction in 64% of the subjects (Griffiths et al., 2008). Respectively, 58% of subjects rated the experience as one of the most personally meaningful and 67% rated the

Table 1
Phenomenological features of a mystical-type experience—either naturally occurring or occasioned by a classical hallucinogen.
(Pahnke, 1963; Pahnke and Richards, 1966; Adapted from Grob et al., 2013).

- *Unity*: A core feature—a strong sense of the interconnectedness of all people and things—All is one—sometimes a sense of pure consciousness or a mind all things are alive
- *Transcendence of time and space*: A sense of timelessness, when the past and future collapse into the present moment—an infinite realm with no space boundaries
- *Deeply felt positive mood*: Universal love, joy, peace, tranquillity
- *Sense of sacredness*: Reverence, awe, or holiness
- *Noetic quality*: A sense of encountering ultimate reality
- *Ineffability and paradoxicality*: The feeling that the experience cannot be adequately described in words—a sense of the reconciliation of paradoxes
- *Transient experience with persisting positive changes in attitude and behavior*

experience as one of the most spiritually significant experiences of their lives (Griffiths et al., 2008).

As existential distress and spiritual crises belong to the core issues of patients suffering from depression and anxiety with life-threatening disease, the above-mentioned findings play a major role for the rationale of the treatment approach described in the current study.

In the following, the overall evidence for the efficacy of serotonergic hallucinogens in the treatment of patients with a life-threatening disease will be presented, including studies from 1960 to 2017. Moreover, potential safety issues will be critically discussed, and changes in the conceptual framework for the use of psychedelics in this indication will be highlighted.

2. Methods

A systematic literature review was conducted on the electronic databases MEDLINE (PubMed), Embase, Cochrane Library, Google Scholar in line with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009). Literature search was restricted to the period from January 1st 1960 to January 31st 2017. Clinical trials published in peer-reviewed journals were included, in which serotonergic hallucinogens (LSD, psilocybin, DMT or others) were administered to subjects aged 18 or older diagnosed with a diagnosis of advanced or terminal life-threatening disease. The following search strings were used: *(lysergic acid diethylamide OR LSD OR Psilocybin OR Psilocin OR mescaline OR DMT OR dimethyltryptamine OR psychedelic* OR hallucinogen*) AND (cancer OR life-threatening OR dying OR terminal OR palliative OR hospice OR advanced) AND (anxiety OR depression OR psychosocial distress OR psychotherapy OR therapy OR therapeutic OR treatment)*. Reference lists of identified articles were screened to identify articles missed in the database searches. Two investigators independently screened titles and abstracts (see Fig. 2).

3. Results

The electronic searches resulted in 1674 hits. After screening the title and removing duplicates, abstracts of 89 publications were screened and publications of non-clinical trials were excluded. We assessed the full text of the remaining 33 publications and excluded case reports (Frederking, 1955; Kurland, 1985; Pahnke et al., 1971, 1970a, 1970b; Sevanick, 2014), publications that investigated sample of patients previously described (Griffiths, 2016; Grob, 2012; Kurland et al., 1972; Richards et al., 1972, 1977; Richards, 1980), studies with non-eligible populations (Carhart-Harris et al., 2016; Soskin, 1973) and review articles (N = 8) (see Fig. 2).

Overall, 11 clinical trials (N = 445) were identified in which the treatment of patients with a life-threatening disease with serotonergic hallucinogens was evaluated. Studies are summarized in Tables 2 & 3 and discussed in detail in this section. Six studies (N = 341) were published between 1960 and 2000, whereas five studies (N = 104) were published between 2000 and 2017. While nine out of 11 studies only included patients suffering from cancer, one study and its follow-up study also included patients with non-malignant life-threatening diseases (Gasser et al., 2014a, 2014b).

3.1. Clinical trials from 1960 until 2000

The first clinical trial investigating the therapeutic use of LSD in patients with terminal cancer (N = 50) focused exclusively on analgesic effects of LSD, compared to the effects of opioids (Kast and Collins, 1964). The anesthetist Eric Kast and his co-workers reported that LSD, while slower in onset, produced a greater degree of pain relief than the opioids (pethidine or hydromorphone) ($p > 0.001$). In addition, the duration of pain relief after LSD was reported to last longer (up to three weeks) when compared to opioids. Surprisingly, many patients reported to have gained more open and positive attitudes about their

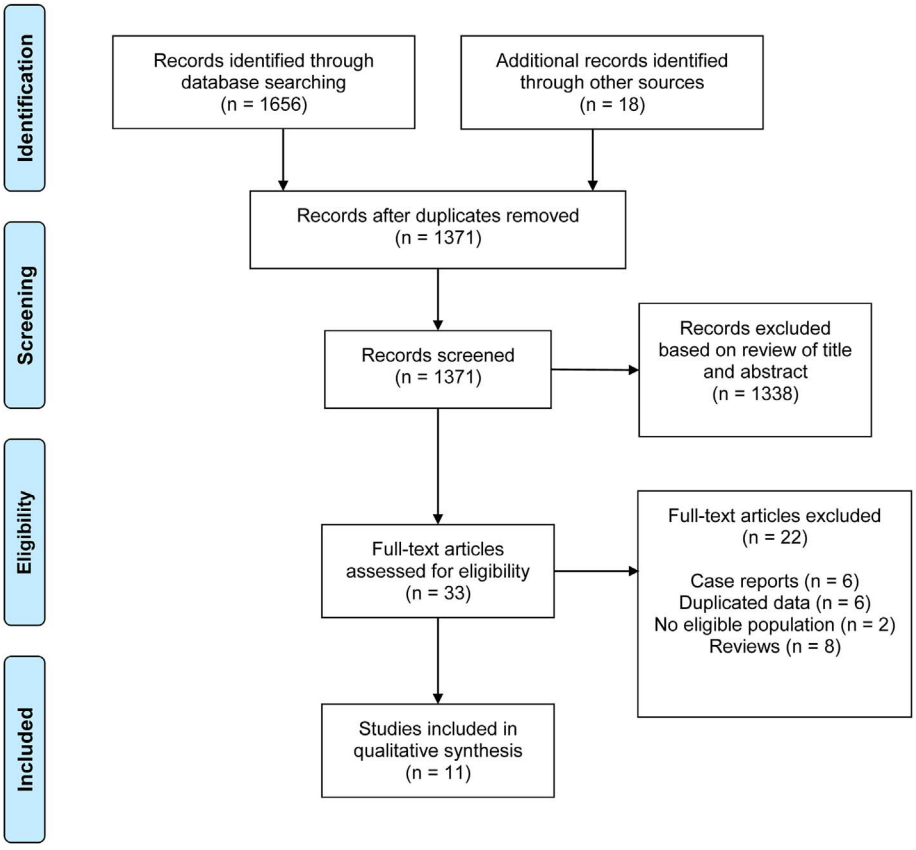

Fig. 2. PRISMA flow diagram of study selection.

Table 2
Summary of clinical trials included in the systematic review between 1960 and 2000.

Study	Substance	Sample size	Design	Dosage	Outcome criteria
Kast and Collins, 1964	LSD Opiods (hydro-morphone, pethidine)	N = 50	Open-label	$V_{(LSD)}$: 100 μg $V_{(Hydromorphone)}$: 2 mg $V_{(Pethidine)}$: 100 mg	▪ Acute analgesic effects (up to 3 weeks) superior to opiods ▪ Anecdotal reports of positive effects on mental health
Kast, 1966	LSD	N = 80	Open-label	V: 100 μg (moderate dose)	▪ Improvement of mood for up to 2 weeks ▪ 89% of patients reported to have gained valuable insights ▪ 90% of sessions were terminated with chlorpromazine
Kast, 1967	LSD	N = 128	Open-label	V: 100 μg (moderate dose)	▪ Analgesic effects (up to 3 weeks) ▪ Only acute improvements of mood ▪ Improvement of sleep and concern about illness and death
Pahnke et al., 1969	LSD	N = 22 MA = 50.7	Open-label; 1–2 LSD Session; psychotherapeutic preparation (10 h); post-integrative psychotherapy	V: 200–300 μg (high dose)	▪ ECRS: Positive change in 14 patients ▪ Degree of positive change correlates with the occurrence of 'mystical' experiences
Grof et al., 1973	LSD	N = 31 MA = 54	Open-label, psychotherapeutic preparation (10 h); post-integrative psychotherapy	V: 200–500 μg (high to very high dose)	▪ ECRS: Significant decreases in depression (t = 10.05; p = 0.001) and anxiety (t = 3.27; p = 0.001) ▪ Reduction of fear of death, pain and feelings of psychological isolation
Richards et al., 1980	DPT	N = 30 MA = 52.6	Open-label, psychotherapeutic preparation (10 h); post-integrative psychotherapy	V: 75–127.5 mg (moderately high dose)	▪ ECRS: Significant decreases in depression (t = 2.31; p = 0.03) and anxiety (t = 2.71; p = 0.01) ▪ Mini-Mult: Improvements in hypochondria (t = 3.01; p = 0.006) and psychasthenia (t = 3.32; p = 0.004) ▪ POI: Patients documented to be more self-assertive, confident and living more in the present moment ▪ Improvement correlated with occurrence of 'mystical' experience during drug effect (Richards et al., 1977)

Vertical Column: Study, Substance, Sample size, Design, Dosage, Outcome criteria. Horizontal lines: LSD (Lysergic acid diethylamide); DPT (Dipropyltryptamine). MA: mean age; V: Verum; ECRS: Emotional Condition Rating Scale (13-point (± 6) rating scale (depression, psychological isolation, anxiety, difficulty in medical management, fear of death and preoccupation with pain); Mini-Mult: questionnaire to assess personal traits (shortened version of MMPI), Hypochondria: concern with bodily symptoms; Psychasthenia: worry, anxiety, tension, doubts, and obsessiveness; POI: Personal Orientations Inventory.

Table 3
Summary of clinical trials included in the systematic review between 2000 and 2017.

Study	Substance	Sample size	Design	Dosage	Outcome
Grob et al., 2011	Psilocybin	N = 12 MA: 36–58	Double-blind RCT, Cross-over; 6-month follow-up	V: 0.2 mg/kg (moderate dose) P: Niacin (250 mg)	■ Significant reductions in anxiety after 1- (t = 4.36; p = 0.001) and 3-months (t = 2.55; p = 0.03) ■ Sign reductions measured by BDI at 6-months (t = 2.71, p = 0.03)
Gasser et al., 2014a, 2014b	LSD	N = 12 MA: 49.6	Double-blind RCT, Cross-over; 2 LSD-Session in 2–3 week interval; 6–8 session preparatory psychotherapy; 3 session post-integrative psychotherapy; 12-month follow-up	V: 200 µg (high dose) AP: 20 µg (very low dose)	■ Significant anxiety reductions at 2-month in STAI-state (d = 1.1; p = 0.033) and STAI-trait (d = 1.2; p = 0.021), that sustained for 12-month ■ 6 of 9 patients described facilitated access to emotions and important introspection or insights, ■ 7 patients reported sustained reductions in anxiety and fear of death and an improved quality of life
Griffiths et al., 2016	Psilocybin	N = 51 MA: 56.3	Double-blind RCT, Cross-over; preparatory psychotherapy (8 h); post-integrative psychotherapy (7 h); 6-month follow-up	V: 22 or 30 mg/70 kg (high dose) AP: 1 or 3 mg/70 kg (very low dose)	■ Immediate and large reductions in depression and anxiety after administration of high-dose Psilocybin ■ At 6-month follow-up about 80% show clinically significant reductions in depression and anxiety ■ Decreases in death anxiety; Increases in quality of life, life meaning and optimism ■ Improvement correlates with occurrence of 'mystical' experience during drug effect
Ross et al., 2016	Psilocybin	N = 29 MA: 56.3	Double-blind RCT, Cross-over; preparatory psychotherapy (6 h); post-integrative psychotherapy (6 h); 6.5-month follow-up	V: 0.3 mg/kg (high dose) P: Niacin (250 mg)	■ Primary outcome measures HADS, BDI, STAI showing immediate significant improvements ■ 60–80% of patients showing a clinically significant anxiolytic or anti-depressive response[a] after 6.5 month ■ Sustained improvements in existential distress, quality of life and spiritual well-being; Decreases in cancer-related demoralization, hopelessness and death anxiety ■ Improvement correlates with occurrence of 'mystical' experience during drug effect

Vertical Column: Study, Substance, Sample size, Design, Dosage, Outcome criteria. Horizontal lines: Psilocybin, LSD (Lysergic acid diethylamide). MA: mean age; RCT: randomized controlled trial; V: Verum; P: Placebo; AP: Active placebo; BDI: Beck Depression Inventory; STAI: State-Trait Anxiety Inventory; HADS: Hospital Anxiety and Depression Scale; d = cohen's d (effect size).

[a] Defined as ≥ 50% decrease relative to baseline.

condition, outlasting the immediate analgesic effects (Kast and Collins, 1964). Thus, in subsequent trials by the same research group, psychological aspects were increasingly considered, including the influence of LSD on mood or patients´ attitudes towards illness and death. In addition, the setting was given increasing importance. In another subsequent trial, a sample of terminal-cancer patients (N = 80) were treated with 100 μg of LSD, with 72 patients (89%) reporting to have gained valuable insights through the experience (Kast, 1966). In another subsequent trial by the same working group, cancer patients (N = 128) were administered 100 μg of LSD in a more carefully arranged setting (Kast, 1967). Prior to the drug session, daily interviews were held for one week to establish a trustful relationship with the patients and discuss relevant personal issues. Moreover, a variety of mostly psychological hypotheses were proposed to explain the analgesic actions of LSD: most importantly, Kast proposed the concept of *'attenuation of anticipation'*, in which he suggested that patients benefit from 'the loss of the ability to anticipate' pain and death, at the same time experiencing an 'expansion of immediate sensory life' (Kast, 1967).

At the same time, another working group at the Spring Grove Hospital (Baltimore, Maryland) had carried out trials evaluating LSD in the treatment of alcohol dependency (Kurland et al., 1971, 1967) in the framework of substance-assisted psychotherapy (SAP). With the impetus of Kast's studies, the SAP technique was transferred to the treatment of anxiety and depression in patients with a life-threatening disease (Kurland, 1985; Pahnke et al., 1970b), resulting in a total of three open-label pilot studies with terminal cancer patients (N = 112) (Grof et al., 1973; Pahnke et al., 1969; Richards et al., 1980). In contrast to earlier studies by Kast where LSD was administered without any specific psychological preparation, a series of drug-free interviews (average of 10 h, over a period of 2 or 3 weeks) were conducted before the substance was applied, in order to establish a therapeutic relationship with the patients and prepare them for the drug-assisted session. In addition, LSD and its acute effects on the psyche were openly discussed with the patients prior to the sessions. Sessions took place in a physically safe and psychologically supportive environment with additional positive stimuli (music, personal objects, etc.) and with two therapists of both sexes present. During the sessions, the therapists' role was mostly supportive with a limited amount of interventions, whereas the experience itself and enduring psychological effects were discussed in drug-free therapy sessions afterwards (for a review see Halifax and Grof, 1977; Kurland, 1985).

In the first study (Pahnke et al., 1969), a sample of terminally-ill cancer patients (N = 22) received a high dosage of 200–300 μg of LSD. Psychological symptoms were assessed with the 'Emotional Condition Rating Scale' (ECRS, an instrument specifically developed for this purpose) including the following six categories: depression, psychological isolation, anxiety, difficulty in medical management, fear of death and preoccupation with pain (Richards et al., 1972). In 14 patients, positive changes were documented, of which six showed a dramatic improvement. Furthermore, peak experiences were associated with a pronounced benefit (5 out of 6 patients with a dramatic improvement also fulfilled the criteria of a peak experience). Another study (Grof et al., 1973) investigated a group of terminal cancer patients (N = 31) that received a high to very high dose of LSD (200–500 μg). Assessment was carried out a day before and three days after treatment. In nine patients, a pronounced improvement and in 13 patients, a moderate improvement was described. Seven patients showed no improvement and in two patients, negative effects were reported. In detail, improvements were documented in all six categories ($t = 9.8$; $p = 0.001$). In the last trial, the therapeutic use of dipropyltryptamine (DPT) was investigated in terminal cancer patients as an alternative to LSD (N = 30) (Richards et al., 1980). DPT was used due to its shorter duration of action compared to LSD, in a moderately high dosage range of 75–127.5 mg. In addition to the ECRS, other psychological tests used to assess patients were the 'Mini-Mult' and 'Personal Orientation Inventory' (POI). In the ECRS, depression ($t = 2.31$; $p = 0.03$) and anxiety ($t = 2.71$; $p = 0.01$) were significantly improved, whereas the POI showed significant positive changes in the categories of 'Time-Competence' ($t = 2.22$; $p = 0.03$) and 'Inner-Directedness' ($t = 2.75$; $p = 0.01$), suggesting that patients were able to be more aware of the present moment, more self-assertive and confident. In another publication, describing the same sample of patients, the occurrence of 'mystical' experiences correlated with a positive outcome (Richards et al., 1977).

3.2. Clinical trials from 2000 until 2017

After a hiatus period of > 25 years due to regulatory restrictions, the first double-blind, placebo-controlled trial (N = 12) investigated the safety and therapeutic effects of psilocybin in patients with advanced-staged cancer and associated mental health problems (Grob et al., 2011). These included DSM-IV diagnoses of acute stress disorder, generalized anxiety disorder, anxiety disorder due to cancer, or adjustment disorder with anxiety. Psilocybin was chosen due to its shorter duration of action (4–6 h) in comparison to LSD (8–12 h) and because it has a far less negative reputation than LSD, which has been intensively associated with counter-culture (Clark, 1968; Leuner, 1968; Passie et al., 2002; Passie and Metzner, 2004). In a cross-over design with two experimental sessions several weeks apart, patients received a moderate dose of psilocybin (0.2 mg/kg) or niacin (250 mg). Niacin was used as an active placebo due to its mild stimulating properties. The patient's biographical and medical history, their intention to participate, treatment goals, and the structure of the sessions were discussed prior to the sessions in order to establish a trustful relationship between patient and researcher. Experimental sessions took place in a specifically prepared hospital room to provide a pleasant and comfortable setting. Reductions in 'State-Trait Anxiety Inventory' (STAI) reached significance at one month ($t = 4.36$; $p = 0.001$) and three months ($t = 2.55$; $p = 0.03$) after the second treatment session, whereas depressive symptoms (assessed with the 'Beck Depression Inventory' (BDI)) were reduced by nearly 30% one month after the second treatment session, reaching significance at six months ($t = 2.71$, $p = 0.03$). Anecdotal reports describe some patients to have gained new insights about how their illness impacted their lives, to experience improved social interactions and to have gained more positive attitudes towards their limited life expectancy. Small sample size and the applied cross-over design have to be considered as limitations of this study.

Another double-blind, randomized, active placebo-controlled pilot study (N = 12) examined the safety and efficacy of LSD-assisted psychotherapy for the treatment of anxiety and depression in patients with a life-threatening disease (Gasser et al., 2014a). Patients received two LSD-sessions at a 4–6-week interval, embedded in a 3-month treatment process that included 6–8 drug-free preparatory and follow-up psychotherapy sessions. Patients received either an experimental dose of 200 μg of LSD (N = 8) or 20 μg of LSD as active placebo (n = 4). Two months after the second LSD-session the study was unblinded, and the placebo group did crossed over to an open-label treatment with two full-dose LSD-sessions. Significant reductions were observed in STAI-state ($d = 1.1$; $p = 0.033$) and STAI-trait ($d = 1.2$; $p = 0.021$) subscales after 2-months, and reductions were sustained for 12 months (Gasser et al., 2014b). Follow-up qualitative semi-structured interviews were carried out with six of the nine patients who had survived at that point and who described facilitated access to emotions and enhanced introspective abilities, seven patients reported sustained reductions in anxiety and fear of death, and also improved quality of life. Additionally, five patients reported an improvement in their physical well-being (Gasser et al., 2014b). In consideration of the small sample size, generalization of reported results is limited.

In another recent trial (N = 51), the treatment protocol included one psilocybin-assisted treatment session where a high dosage of psilocybin (22 or 30 mg/70 kg) was administered, compared to a low

dosage (1 or 3 mg/70 kg) (Griffiths et al., 2016). Within a randomized cross-over design, each patient received both the experimental high dose and the control low dose as an active placebo in a randomized fashion, with patients serving as their own controls. Several preparatory and follow up drug-free sessions were conducted. Results are summarized in Table 3. After 6 months, 78% of the patients had responded clinically significantly (defined as ≥ 50% decrease of HAM-D score relative to baseline) and 65% of the patients showed symptom remission to normal range (defined as ≥ 50% decrease relative to baseline and a total score of ≤ 7). HAM-A scores showed 82.5% of patients with a clinically significant response and 56.5% of patients with symptom remission at 6-months. Additional follow-up measures also revealed significant improvements in the domains of overall quality of life, purpose in life, and acceptance of death and optimism ($p < 0.001$). In another recent trial with a similar setting (N = 29), a relatively high dose of psilocybin (0.3 mg/kg) was compared to the active placebo niacin (250 mg) in a cross-over design with two dosing sessions in conjunction with psychotherapy (Ross et al., 2016). Prior to, between and after the two drug administrations, three drug-free two-hour psychotherapy sessions (18 h in total) were conducted over a period of 4 months, followed by ongoing supportive sessions as part of the 6.5-month follow-up. Outcomes were documented primarily with HADS (Hospital Anxiety and Depression Scale), BDI and STAI at baseline, 1 day prior to and after the first dose, 2 weeks and 6 weeks after the first dose, 7 weeks after the first dose (1 day before the second dose) and 1 day, 6 weeks and 26 weeks after the second dose. Results are summarized in Table 3. Seven weeks after the first dose of psilocybin BDI scores decreased in 83% of the patients by half or more, whereas HADS anxiety score decreased in 58% of the patients to a comparable extent. Overall, 6.5 months after both groups had received psilocybin therapy, approximately 60–80% of patients exhibited a clinically significant anxiolytic or anti-depressive response (defined as ≥ 50% decrease relative to baseline).

In both studies, the occurrence of mystical-type experiences as assessed by mystical experience scores (MEQ30) correlated significantly with positive therapeutic outcomes, which is consistent with prior studies in healthy volunteers (Griffiths et al., 2008, 2006) and studies with cancer patients (Pahnke et al., 1969; Richards et al., 1980).

Consistent with prior studies the applied cross-over design is also a limitation of recent studies. Furthermore, the inadequate blinding in consequence of the obvious drug effects, the strict exclusion criteria and the high percentage of people with prior hallucinogen use limits the generalizability.

3.3. Adverse events (AE)

In some studies, transient physiological symptoms such as nausea or vomiting, headaches, tremor and breathing difficulties were reported during the drug-assisted sessions (Grof et al., 1973; Kurland, 1985; Richards et al., 1980). All recent studies reported transient, moderate increases in systolic and diastolic blood pressure with no need for a medical intervention (Gasser et al., 2014a; Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016). None of the studies reported serious medical complications. In one earlier study, 90% of the patients were treated with benzodiazepines because of anxiety and panic reactions (Kast, 1966). However, psychological effects of the substances had not been considered when the study was designed, and the important variables of set and setting had been disregarded, so that the patients had not been psychologically prepared for the effects. In a subsequent study of the same working group, patients were more intensively prepared and a decreased number of psychiatric side effects were reported: in seven out of 128 patients, panic reactions were reported, and 42 exhibited mild anxiety responses. All reactions responded to follow-up psychotherapy, and no patient had to be treated with benzodiazepines (Kast, 1967). In a recent study, a transient paranoid episode was reported in one patient (Griffiths et al., 2016). None of the studies reported clinical relevant flashback phenomena, Hallucinogen Persisting Perception Disorder (HPPD) (Hermle et al., 2013) or cases of prolonged psychosis. No further relevant complications were reported.

4. Discussion

Eleven clinical trials were identified in which therapeutic effects of serotonergic hallucinogens were evaluated in patients with a life-threatening disease. Studies can be divided into three major subgroups: 1) initial trials which focused on analgesic effects of psychedelics, where psychological effects were merely considered as side effects, sometimes surprisingly associated with improved disease coping strategies and attitudes (Kast, 1967, 1966; Kast and Collins, 1964); 2) clinical trials conducted during the 1960s and 1970s, mostly at Spring Grove, where psychological effects of psychedelics were primarily focused in the framework of 'Psychedelic (Peak) Therapy' (PDT). In these studies, the classical variables of 'set' (referring to the patient's mindset, history, health, personality, social and emotional situation), 'setting' (referring to the physical environment, study personnel, music selection and other stimulus during the session) and 'substance' (referring to type, dosage and frequency of the employed psychoactives) were carefully considered (Grof et al., 1973; Pahnke et al., 1969; Richards et al., 1980), and preparatory and post-treatment therapy sessions were understood as a vital part of the treatment process (Halifax and Grof, 1977; Kurland, 1985; Maslow, 1962; Sherwood et al., 1962). In the course of this close meshed patient care, fewer psychological adverse events such as panic reactions were described and up to two-thirds of the patients experienced reductions in anxiety and depressive symptoms, indicating that psychedelic-assisted psychotherapy showed effective and promising results. 3) A third group includes recent clinical trials, carried out after a long hiatus period of legal restrictions (Gasser et al., 2014a, 2014b; Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016), in which previous methods were reconsidered, aiming to induce insightful psychological experiences at somewhat lower dosages and with psilocybin being the predominant substance. These trials do not exhibit any fundamentally new conceptual framework, but they are of a substantially increased methodological quality (placebo control, randomization, double-blinding, use of modern psychiatric diagnostic classification and rating scales and long-term follow up). Mystical-type experiences have been repeatedly suggested as mechanisms of action, showing a conceptual proximity to the historical concept of 'Psychedelic (Peak) Therapy' (PDT) (Grof, 1980). However, PDT has been predominantly carried out in the US until the 1970s involving high dosages of psychedelics aiming to induce 'peak experiences'. In contrast, in Europe, traditionally lower dosages have been employed in the framework of 'Psycholytic Therapy' (PLT), not necessarily aiming at inducing peak experiences (Majić et al., 2015). On the other hand, it has been reported that patients might have mystical experiences without profound impact on their lives and, vice versa, others might not have made these kind of experiences but still have profoundly benefitted from the treatment. Thus, we believe that mystical or peak experiences might be important, but there are other important factors as well that are responsible for the therapeutic effects of psychedelic-assisted therapy.

4.1. Limitations

From today's viewpoint, most of the studies before the year 2000 show strong methodological limitations. While early results were mainly based on anecdotal evidence, later results were based on non-standardized outcome criteria and were not compared with any control group. Additionally, no long-term follow-up studies of the patients were carried out. In regard to the open study design the trials carry a high risk of bias. Most studies also lack detailed methodical descriptions of the populations, diagnosis methods, psychotherapeutic interventions and statistical analysis.

Nevertheless, recent double-blind, randomized and controlled studies show some limitations in their study set-up. The blinding process is only possible to a limited extent since psychedelics produce unique characteristic psychoactive effects, which reveal the allocation in treatment or control group to patient and therapist (Gasser et al., 2014a; Grob et al., 2011; Mogar, 1967; Salzman and Hicks, 1969). Methods to counteract this phenomenon are the administration of the active placebo niacin or small dosages of the psychedelic compound but are only successful to a limited extent. Therefore, in combination with the subjective outcome measures based on clinician- and patient-administered rating scales, recent studies still carry a risk of bias. Furthermore, the obtained follow-up data are only conclusive to a limited extent, after control groups have also received an active therapeutic dose of the psychedelic compound within the applied cross-over design. The authors argued that the reason for the uncontrolled study design in the early studies and the cross-over design in more recent studies, were also because of ethical reasons, since it would be ethically questionable to withhold a potential beneficial treatment concept or to run a placebo control group over such a long period in regard to the patient's severe illness and reduced life expectancy (Gasser et al., 2014b; Grob et al., 2013, 2011). With regard to the generalizability of the results, the strict exclusion criteria (see below) under which the patients for the studies have been recruited constitute a restriction. Also, the high percentage of highly educated people in the population and the fact that around half of the patients reported a prior history of hallucinogen use in recent studies (Griffiths et al., 2016; Ross et al., 2016), further limits the generalizability.

4.2. Safety and further research

Serotonergic hallucinogens show a reasonable safety profile when administered in a clinical research setting. Except for transient physiological symptoms including nausea, headaches and a moderate increase in blood pressure (Griffiths et al., 2006; Hasler et al., 2004; Passie et al., 2002; Schmid et al., 2015; Strassman and Qualls, 1994), no serious medical adverse effects have yet been described (Gable, 2004; Halpern et al., 2005; Halpern and Pope, 1999; Hasler et al., 2004; Nichols, 2016, 2004; Strassman, 1984). A review of 8 double-blind experimental studies in healthy individuals (N = 110) (Studerus et al., 2011) between 1999 and 2008 reported temporary adverse reactions such as dysphoria, anxiety and panic attacks without lasting somatic or psychiatric problems and concludes that psychedelics can be safely administered in healthy, well prepared volunteers within a controlled clinical environment. Notably, in patients with a life-threatening disease, a broader range of medical symptoms has been observed, which may be associated with their primary disease (Kurland et al., 1973; Kurland, 1985). For instance, patients with a malignant disease might experience more symptoms of fatigue during the drug-assisted therapy session than other groups of patients (Richards et al., 1972).

Psychedelics are capable of producing dose-dependent intense experiences, sometimes accompanied by acute transient anxiety and panic reactions or even transient psychotic symptoms with delusional and disorganized thinking. In some very rare cases, even long-term psychotic reactions have been reported (Strassman, 1984). Moreover, there are anecdotal reports of dangerous behaviors following recreational use of psychedelics, associated with accidents or even suicide attempts (Keeler and Reifler, 1967; Reynolds and Jindrich, 1985). In clinical environments, however, the risk of severe complications can be minimized by implementing appropriate safety guidelines such as careful screening of patients regarding counterindications, establishing strong interpersonal support prior to the drug session, and trustworthy and safe physical environments (Johnson et al., 2008).

Rare cases of prolonged psychosis after administration of psychedelics have been observed in clinical environments in the 1960s and 1970s (Cohen, 1960; McGlothlin and Arnold, 1971), when appropriate safety guidelines were not yet available. In addition, Hallucinogen Persisting Perception Disorder (HPPD) is a probably rare disorder, which is characterized as re-experiencing predominantly visual effects of psychedelics in the absence of an acute substance effect (i.e. flashbacks) (Majić et al., 2016). HPPD is often attributed to non-clinical recreational use, frequently associated with polydrug use patterns (Halpern and Pope, 2003), and specific incidences of HPPD are inconclusive due to low epidemiological data (Litjens et al., 2014), but is less relevant for clinical use in a therapeutic environment (Hermle et al., 2015, 2013, 2008). Nowadays, the overall probability of long-term adverse reactions seems subtle to not relevant (Halpern and Pope, 1999; Nichols, 2004; Strassman, 1984).

Moreover, retrospective population studies on U.S. adults failed to find any association between the lifetime use of serotonergic psychedelics and a mental health problems (Johansen and Krebs, 2015; Krebs and Johansen, 2013). Instead, a life-time use of psychedelics was linked to a lower likelihood of inpatient mental health treatment and a reduced incidence of suicidal behavior (Hendricks et al., 2015; Johansen and Krebs, 2015). In addition, psychedelics are currently also under investigation for the treatment of substance use disorders such as alcohol (Bogenschutz et al., 2015), tobacco (Johnson et al., 2014) and cocaine dependence (ClinicalTrials.gov, number NCT02037126) (for a review see Bogenschutz and Johnson, 2016). Other potential indications include obsessive-compulsive disorder (Moreno et al., 2006), cluster headache (Schindler et al., 2015; Sewell et al., 2006) and treatment-resistant depression (Carhart-Harris et al., 2016).

4.3. Conclusion

In conclusion, there is some evidence that substance-assisted psychotherapy with serotonergic hallucinogens is effective in the treatment of mental health problems in patients with a life-threatening disease and is well tolerated. Moreover, there is some evidence that psychedelic-induced mystical-type peak experiences mediate not only reduction of psychiatric symptoms in these patients, but may also be helpful for these patients by improving disease coping and quality of life when facing a life-threatening condition. Given the reasonable safety profile of serotonergic hallucinogens in a controlled clinical environment, psychedelic-assisted psychotherapy could be a promising treatment option in this context – especially for patients where other approaches have been ineffective. Hence, additional trials are needed to evaluate whether the presented results can be transferred in to clinical practice.

Acknowledgments

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

Arrieta, O., Angulo, L.P., Nunez-Valencia, C., Dorantes-Gallareta, Y., Macedo, E.O., Martinez-Lopez, D., Alvarado, S., Corona-Cruz, J.-F., Onate-Ocana, L.F., 2013. Association of depression and anxiety on quality of life, treatment adherence, and prognosis in patients with advanced non-small cell lung cancer. Ann. Surg. Oncol. 20, 1941–1948. http://dx.doi.org/10.1245/s10434-012-2793-5.

Bogenschutz, M.P., Johnson, M.W., 2016. Classic hallucinogens in the treatment of addictions. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 64, 250–258. http://dx.doi.org/10.1016/j.pnpbp.2015.03.002.

Bogenschutz, M.P., Forcehimes, A.A., Pommy, J.A., Wilcox, C.E., Barbosa, P.C.R., Strassman, R.J., 2015. Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. J. Psychopharmacol. 29, 289–299.

Boston, P.H., Mount, B.M., 2006. The caregiver's perspective on existential and spiritual distress in palliative care. J. Pain Symptom Manag. 32, 13–26. http://dx.doi.org/10.1016/j.jpainsymman.2006.01.009.

Boston, P., Bruce, A., Schreiber, R., 2011. Existential suffering in the palliative care setting: an integrated literature review. J. Pain Symptom Manag. 41, 604–618. http://dx.doi.org/10.1016/j.jpainsymman.2010.05.010.

Breitbart, W., Rosenfeld, B., Pessin, H., al, et, 2000. Depression, hopelessness, and desire for hastened death in terminally ill patients with cancer. JAMA 284, 2907–2911.

Breitbart, W., Gibson, C., Chochinov, H., 2005. Palliative care. In: Levenson, J.L. (Ed.), Am. Psychiatr. Publ. Textb. Psychosom. Med. Am. Psychiatr. Publ, Washington, DC.

Breitbart, W., Rosenfeld, B., Gibson, C., Pessin, H., Poppito, S., Nelson, C., Tomarken, A.,

Timm, A.K., Berg, A., Jacobson, C., Sorger, B., Abbey, J., Olden, M., 2010. Meaning-centered group psychotherapy for patients with advanced cancer: a pilot randomized controlled trial. Psychooncology 19, 21–28. http://dx.doi.org/10.1002/pon.1556.
Breitbart, W., Rosenfeld, B., Pessin, H., Applebaum, A., Kulikowski, J., Lichtenthal, W.G., 2015. Meaning-centered group psychotherapy: an effective intervention for improving psychological well-being in patients with advanced cancer. J. Clin. Oncol. 33, 749–754. http://dx.doi.org/10.1200/JCO.2014.57.2198.
Brown, K.W., Levy, A.R., Rosberger, Z., Edgar, L., 2003. Psychological distress and cancer survival: a follow-up 10 years after diagnosis. Psychosom. Med. 65.
Carhart-Harris, R.L., Bolstridge, M., Rucker, J., Day, C.M.J., Erritzoe, D., Kaelen, M., Bloomfield, M., Rickard, J.A., Forbes, B., Feilding, A., Taylor, D., Pilling, S., Curran, V.H., Nutt, D.J., 2016. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. Lancet Psychiatry 3, 619–627. http://dx.doi.org/10.1016/S2215-0366(16)30065-7.
Chochinov, H.M., Hack, T., Hassard, T., Kristjanson, L.J., McClement, S., Harlos, M., 2005a. Understanding the will to live in patients nearing death. Psychosomatics 46, 7–10.
Chochinov, H.M., Hack, T., Hassard, T., Kristjanson, L.J., McClement, S., Harlos, M., 2005b. Dignity therapy: a novel psychotherapeutic intervention for patients near the end of life. J. Clin. Oncol. 23, 5520–5525.
Clark, B., 1968. Some early observations on the use of psilocybin in psychiatric patients. Brit. J. Soc. Psychiatry 2, 21–25.
Cohen, S., 1960. Lysergic acid diethylamide: side effects and complications. J. Nerv. Ment. Dis. 130, 30–40.
Edwards, A., Pang, N., Shiu, V., Chan, C., 2010. Review: the understanding of spirituality and the potential role of spiritual care in end-of-life and palliative care: a meta-study of qualitative research. Palliat. Med. 24, 753–770. http://dx.doi.org/10.1177/0269216310375860.
Frederking, W., 1955. Intoxicant drugs (mescaline and lysergic acid diethylamide) in psychotherapy. J. Nerv. Ment. Dis. 121, 262–266.
Gable, R.S., 2004. Comparison of acute lethal toxicity of commonly abused psychoactive substances. Addiction 99, 686–696.
Gasser, P., Holstein, D., Michel, Y., Doblin, R., Yazar-Klosinski, B., Passie, T., Brenneisen, R., 2014a. Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. J. Nerv. Ment. Dis. 202.
Gasser, P., Kirchner, K., Passie, T., 2014b. LSD-assisted psychotherapy for anxiety associated with a life-threatening disease: a qualitative study of acute and sustained subjective effects. J. Psychopharmacol. 29, 57–68. http://dx.doi.org/10.1177/0269881114555249.
Geyer, M.A., Vollenweider, F.X., 2008. Serotonin research: contributions to understanding psychoses. Trends Pharmacol. Sci. 29, 445–453.
Griffiths, R., 2016. A single dose of psilocybin produces substantial and enduring decreases in anxiety and depression in patients with a life-threatening cancer diagnosis: a randomized double-blind trial. Neuropsychopharmacology. http://dx.doi.org/10.1038/npp.2015.324.
Griffiths, R.R., Grob, C.S., 2010. Hallucinogens as medicine. Sci. Am. 303, 76–79.
Griffiths, R.R., Richards, W.A., McCann, U., Jesse, R., 2006. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. Psychopharmacology 187, 268–283.
Griffiths, R.R., Richards, W.A., Johnson, M.W., McCann, U.D., Jesse, R., 2008. Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. J. Psychopharmacol. 22, 621–632.
Griffiths, R.R., Johnson, M.W., Carducci, M.A., Umbricht, A., Richards, W.A., Richards, B.D., Cosimano, M.P., Klinedinst, M.A., 2016. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: a randomized double-blind trial. J. Psychopharmacol. 30, 1181–1197.
Grob, C., 2012. Psilocybin treatment for anxiety in patients with advanced-stage cancer. Neuropsychopharmacology 38, S15.
Grob, C.S., Danforth, A.L., Chopra, G.S., Hagerty, M., McKay, C.R., Halberstadt, A.L., Greer, G.R., 2011. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. Arch. Gen. Psychiatry 68, 71–78.
Grob, C.S., Bossis, A.P., Griffiths, R.R., 2013. Use of the classic hallucinogen psilocybin for treatment of existential distress associated with cancer. In: Psychological Aspects of Cancer. Springer, pp. 291–308.
Grof, S., 1980. LSD-Psychotherapy. Hunter House, New York.
Grof, S., Goodman, L.E., Richards, W.A., Kurland, A.A., 1973. LSD-assisted psychotherapy in patients with terminal cancer. Int. Pharmacopsychiatry 8, 129–144.
Halberstadt, A.L., 2015. Recent advances in the neuropsychopharmacology of serotonergic hallucinogens. Behav. Brain Res. 277, 99–120.
Halifax, J., Grof, S., 1977. The Human Encounter with Death. EP Dutt, New York.
Halpern, J.H., Pope, H.G., 1999. Do hallucinogens cause residual neuropsychological toxicity? Drug Alcohol Depend. 53, 247–256.
Halpern, J.H., Pope, H.G., 2003. Hallucinogen persisting perception disorder: what do we know after 50 years? Drug Alcohol Depend. 69, 109–119.
Halpern, J.H., Sherwood, A.R., Hudson, J.I., Yurgelun-Todd, D., Pope, H.G., 2005. Psychological and cognitive effects of long-term peyote use among Native Americans. Biol. Psychiatry 58, 624–631.
Hasler, F., Grimberg, U., Benz, M.A., Huber, T., Vollenweider, F.X., 2004. Acute psychological and physiological effects of psilocybin in healthy humans: a double-blind, placebo-controlled dose–effect study. Psychopharmacology 172, 145–156.
Hendricks, P.S., Thorne, C.B., Clark, C.B., Coombs, D.W., Johnson, M.W., 2015. Classic psychedelic use is associated with reduced psychological distress and suicidality in the United States adult population. J. Psychopharmacol. 29, 280–288.
Hermle, L., Kovar, K.A., Hewer, W., Ruchsow, M., 2008. Halluzinogen-induzierte psychische Störungen. Fortschritte der Neurol. Psychiatr. 76, 334–342. http://dx.doi.org/10.1055/s-2008-1038191.
Hermle, L., Melanie, S., Martin, R., Anil, B., Martin, G., 2013. Hallucinogen persisting perception disorder (HPPD) and flashback-are they identical? J Alcohol. Drug Depend 1, 2.
Hermle, L., Ruchsow, M., Täschner, K.L., 2015. Halluzinogen-induzierte Persistierende Wahrnehmungsstörung (HPPD) und Flashback-Phänomene – Differenzialdiagnose und Erklärungsmodelle TT - Hallucinogen Persisting Perception Disorder (HPPD) and Flashback Phenomena – Differential Diagnosis and Explanatio. Fortschr. Neurol. Psychiatr. 83, 506–515. http://dx.doi.org/10.1055/s-0035-1553717.
Hood Jr., R.W., 1975. The construction and preliminary validation of a measure of reported mystical experience. J. Sci. Study Relig. 29–41.
Jaiswal, R., Alici, Y., Breitbart, W., 2014. A comprehensive review of palliative care in patients with cancer. Int. Rev. Psychiatry 26, 87–101.
Johansen, P.-Ø., Krebs, T.S., 2015. Psychedelics not linked to mental health problems or suicidal behavior: a population study. J. Psychopharmacol. 29, 270–279.
Johnson, M.W., Richards, W.A., Griffiths, R.R., 2008. Human hallucinogen research: guidelines for safety. J. Psychopharmacol. 22, 603–620.
Johnson, M.W., Garcia-Romeu, A., Cosimano, M.P., Griffiths, R.R., 2014. Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. J. Psychopharmacol. 28, 983–992.
Jones, J.M., Huggins, M.A., Rydall, A.C., Rodin, G.M., 2003. Symptomatic distress, hopelessness, and the desire for hastened death in hospitalized cancer patients. J. Psychosom. Res. 55, 411–418.
Kandasamy, A., Chaturvedi, S.K., Desai, G., 2011. Spirituality, distress, depression, anxiety, and quality of life in patients with advanced cancer. Indian J. Cancer 48, 55.
Kast, E., 1966. LSD and the dying patient. Chic. Med. Sch. Q. 26, 80–87.
Kast, E., 1967. Attenuation of anticipation: a therapeutic use of lysergic acid diethylamide. Psychiatr. Q. 41, 646–657.
Kast, E.C., Collins, V.J., 1964. Study of lysergic acid diethylamide as an analgesic agent. Anesth. Analg. 43, 285–291.
Keeler, M.H., Reifler, C.B., 1967. Suicide during an LSD reaction. Am. J. Psychiatry 123, 884–885.
Kissane, D.W., Clarke, D.M., Street, A.F., 2001. Demoralization syndrome—a relevant psychiatric diagnosis for palliative care. J. Palliat. Care 17, 12.
Krebs, T.S., Johansen, P.-Ø., 2013. Psychedelics and mental health: a population study. PLoS One 8, e63972.
Kurland, A.A., 1985. LSD in the supportive care of the terminally ill cancer patient. J. Psychoactive Drugs 17, 279–290.
Kurland, A.A., Unger, S., Shaffer, J.W., Savage, C., 1967. Psychedelic therapy utilizing LSD in the treatment of the alcoholic patient: a preliminary report. Am. J. Psychiatry 123, 1202–1209.
Kurland, A., Savage, C., Pahnke, W.N., Grof, S., Olsson, J.E., 1971. LSD in the treatment of alcoholics. Pharmacopsychiatry 4, 83–94.
Kurland, A.A., Grof, S., Pahnke, W.N., Goodman, L.E., 1972. Psychedelic drug assisted psychotherapy in patients with terminal cancer. J. Thanatol. 2 (1–2), 644–691.
Kurland, A., Grof, S., Pahnke, W.N., Goodman, E.L., 1973. Psychedelic drug-assisted psychotherapy in patients with terminal cancer. In: Goldb, I.K., Malitz, S., Kutscher, A.H. (Eds.), Psychopharmacol. Agents Termin. Ill Bereaved, Found. Thanatol. Columbia Univ. Press. Distrib, New York, pp. 86–133.
LeMay, K., Wilson, K.G., 2008. Treatment of existential distress in life threatening illness: a review of manualized interventions. Clin. Psychol. Rev. 28, 472–493.
Leuner, H., 1968. Is the use of LSD-25 in experimental psychiatry and psychotherapy today still justifiable? Nervenarzt 39, 356–360.
Litjens, R.P.W., Brunt, T.M., Alderliefste, G.-J., Westerink, R.H.S., 2014. Hallucinogen persisting perception disorder and the serotonergic system: a comprehensive review including new MDMA-related clinical cases. Eur. Neuropsychopharmacol. 24, 1309–1323.
Majić, T., Schmidt, T.T., Gallinat, J., 2015. Peak experiences and the afterglow phenomenon: When and how do therapeutic effects of hallucinogens depend on psychedelic experiences? J. Psychopharmacol. 29, 241–253.
Majić, T., Schmidt, T.T., Hermle, L., 2016. Flashbacks und anhaltende Wahrnehmungsstörungen nach Einnahme von serotonergen Halluzinogenen. In: von Heyden, M., Jungaberle, H., Majić, T. (Eds.), Handbuch Psychoaktive Substanzen. Springer Berlin Heidelberg, pp. 1–13. http://dx.doi.org/10.1007/978-3-642-55214-4_63-1.
Majić, T., Jungaberle, H., Schmidt, T.T., Zeuch, A., Hermle, L., Gallinat, J., 2017. Psychotherapy with adjuvant use of serotonergic psychoactive substances: possibilities and challenges. Fortschr. Neurol. Psychiatr. 85, 383–392. http://dx.doi.org/10.1055/s-0043-103085.
Maslow, A.H., 1959. Cognition of being in the peak experiences. J. Genet. Psychol. 94, 43–66.
Maslow, A.H., 1962. Lessons from the Peak-Experiences. J. Humanist. Psychol. 2 (1), 9–18.
McClain, C.S., Rosenfeld, B., Breitbart, W., 2003. Effect of spiritual well-being on end-of-life despair in terminally-ill cancer patients. Lancet 361, 1603–1607.
McGlothlin, W.H., Arnold, D.O., 1971. LSD revisited: a ten-year follow-up of medical LSD use. Arch. Gen. Psychiatry 24, 35–49.
Mitchell, A.J., Chan, M., Bhatti, H., Halton, M., Grassi, L., Johansen, C., Meader, N., 2011. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. Lancet Oncol. 12, 160–174.
Mogar, R., 1967. Psychedelic (LSD) research: a critical review of methods and results. Challenges Humanist. Psychol. 135Y146.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., Group, P, 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 6, e1000097.

Moreno, F.A., Wiegand, C.B., Taitano, E.K., Delgado, P.L., 2006. Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. J. Clin. Psychiatry 67, 1735–1740.
Nichols, D.E., 2004. Hallucinogens. Pharmacol. Ther. 101, 131–181. http://dx.doi.org/10.1016/j.pharmthera.2003.11.002.
Nichols, D.E., 2016. Psychedelics. Pharmacol. Rev. 68, 264–355. http://dx.doi.org/10.1124/pr.115.011478.
Osmond, H., 1957. A review of the clinical effects of psychotomimetic agents. Ann. N. Y. Acad. Sci. 66, 418–434.
Pahnke, W.N., 1963. Drugs and Mysticism: An Analysis of the Relationship Between Psychedelic Drugs and the Mystical Consciousness. PhD Dissertation. Harvard University, Cambridge, MA.
Pahnke, W.N., 1967. LSD and Religious Experience. LSD Man Soc. Wesley. Univ. Press, Middletown, CT, pp. 60–85.
Pahnke, W.N., 1969a. The psychedelic mystical experience in the human encounter with death. Harv. Theol. Rev. 62, 1–21.
Pahnke, W.N., 1969b. Psychedelic drugs and mystical experience. Int. Psychiatry Clin. 5, 149.
Pahnke, W.N., Richards, W.A., 1966. Implications of LSD and experimental mysticism. J. Relig. Health 5, 175–208.
Pahnke, W.N., Kurland, A.A., Goodman, L.E., Richards, W.A., 1969. LSD-assisted psychotherapy with terminal cancer patients. Curr. Psychiatr. Ther. 9, 144–152.
Pahnke, W.N., Kurland, A.A., Unger, S., Savage, C., Grof, S., 1970a. The experimental use of psychedelic (LSD) psychotherapy. JAMA 212, 1856–1863.
Pahnke, W.N., Kurland, A.A., Unger, S., Savage, C., Wolf, S., Goodman, L.E., 1970b. Psychedelic therapy (utilizing LSD) with cancer patients. J. Psychedelic Drugs 3, 63–75.
Pahnke, W.N., Kurland, A.A., Unger, S., Savage, C., Grof, S., 1971. The experimental use of psychedelic (LSD) psychotherapy. Int. Z. Klin. Pharmakol. Ther. Toxikol. 4, 446–454.
Passie, T., Metzner, R., 2004. A history of the use of psilocybin in psychotherapy. In: Teonanacatl Sacred Mushroom Vision. CA Four Trees, El Verano, pp. 109–134.
Passie, T., Seifert, J., Schneider, U., Emrich, H.M., 2002. The pharmacology of psilocybin. Addict. Biol. 7, 357–364.
Passie, T., Halpern, J.H., Stichtenoth, D.O., Emrich, H.M., Hintzen, A., 2008. The pharmacology of lysergic acid diethylamide: a review. CNS Neurosci. Ther. 14, 295–314.
Puchalski, C.M., 2012. Spirituality in the cancer trajectory. Ann. Oncol. 23, 49–55.
Reuter, K., 2010. Supportive-expressive Gruppentherapie. PiD-Psychotherapie im Dialog 11, 125–129.
Reynolds, P.C., Jindrich, E.J., 1985. A mescaline associated fatality. J. Anal. Toxicol. 9, 183–184.
Richards, W.A., 1980. Psychedelic drug-assisted psychotherapy with persons suffering from terminal cancer. J. Altered States Conscious. 5, 309–319.
Richards, W., Grof, S., Goodman, L., Kurland, A., 1972. LSD-assisted psychotherapy and the human encounter with death. J. Transpers. Psychol. 4, 121.
Richards, W.A., Rhead, J.C., DiLeo, F.B., Yensen, R., Kurland, A.A., 1977. The peak experience variable in DPT-assisted psychotherapy with cancer patients. J. Psychedelic Drugs 9, 1–10.
Richards, W.A., Rhead, J.C., Grof, S., Goodman, L.E., Di Leo, F., Rush, L., 1980. DPT as an adjunct in brief psychotherapy with cancer patients. OMEGA-Journal of Death and Dying 10, 9–26.
Rodin, G., Lo, C., Mikulincer, M., Donner, A., Gagliese, L., Zimmermann, C., 2009. Pathways to distress: the multiple determinants of depression, hopelessness, and the desire for hastened death in metastatic cancer patients. Soc. Sci. Med. 68, 562–569.
Ross, S., Bossis, A., Guss, J., Agin-Liebes, G., Malone, T., Cohen, B., Mennenga, S.E., Belser, A., Kalliontzi, K., Babb, J., 2016. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. J. Psychopharmacol. 30, 1165–1180.
Salzman, C., Hicks, R.E., 1969. Controlled therapy research with psychedelic drugs: a critique. Psychedelic Drugs 23Y32.
Schindler, E.A.D., Gottschalk, C.H., Weil, M.J., Shapiro, R.E., Wright, D.A., Sewell, R.A., 2015. Indoleamine hallucinogens in cluster headache: results of the clusterbusters medication use survey. J. Psychoactive Drugs 47, 372–381. http://dx.doi.org/10.1080/02791072.2015.1107664.
Schmid, Y., Enzler, F., Gasser, P., Grouzmann, E., Preller, K.H., Vollenweider, F.X., Brenneisen, R., Müller, F., Borgwardt, S., Liechti, M.E., 2015. Acute effects of lysergic acid diethylamide in healthy subjects. Biol. Psychiatry 78, 544–553.
Sevanick, L., 2014. Psilocybin-assisted psychotherapy in the treatment of cancer-related psychosocial distress/anxiety. Pscyho-oncology 23, 73–74.
Sewell, R.A., Halpern, J.H., Pope, H.G.J., 2006. Response of cluster headache to psilocybin and LSD. Neurology 66, 1920–1922. http://dx.doi.org/10.1212/01.wnl.0000219761.05466.43.
Sherwood, J.N., Stolaroff, M.J., Harman, W.W., 1962. The psychedelic experience—a new concept in psychotherapy. J. Neuro-Oncol. 4, 69.
Soskin, R.A., 1973. The use of LSD in time-limited psychotherapy. J. Nerv. Ment. Dis. 157, 410–419.
Strassman, R.J., 1984. Adverse reactions to psychedelic drugs. A review of the literature. J. Nerv. Ment. Dis. 172, 577–595.
Strassman, R.J., Qualls, C.R., 1994. Dose-response study of N, N-dimethyltryptamine in humans: I. Neuroendocrine, autonomic, and cardiovascular effects. Arch. Gen. Psychiatry 51, 85–97.
Studerus, E., Kometer, M., Hasler, F., Vollenweider, F.X., 2011. Acute, subacute and long-term subjective effects of psilocybin in healthy humans: a pooled analysis of experimental studies. J. Psychopharmacol. 25, 1434–1452.
Teunissen, S.C.C.M., Wesker, W., Kruitwagen, C., de Haes, H.C.J.M., Voest, E.E., de Graeff, A., 2007. Symptom prevalence in patients with incurable cancer: a systematic review. J. Pain Symptom Manag. 34, 94–104.
Van Lancker, A., Velghe, A., Van Hecke, A., Verbrugghe, M., Van Den Noortgate, N., Grypdonck, M., Verhaeghe, S., Bekkering, G., Beeckman, D., 2014. Prevalence of symptoms in older cancer patients receiving palliative care: a systematic review and meta-analysis. J. Pain Symptom Manag. 47, 90–104.
Vollenweider, F.X., Kometer, M., 2010. The neurobiology of psychedelic drugs: implications for the treatment of mood disorders. Nat. Rev. Neurosci. 11, 642–651.
Watts, S., Leydon, G., Birch, B., Prescott, P., Lai, L., Eardley, S., Lewith, G., 2014. Depression and anxiety in prostate cancer: a systematic review and meta-analysis of prevalence rates. BMJ Open 4, e003901.
Watts, S., Prescott, P., Mason, J., McLeod, N., Lewith, G., 2015. Depression and anxiety in ovarian cancer: a systematic review and meta-analysis of prevalence rates. BMJ Open 5, e007618.
Wilson, K.G., Chochinov, H.M., Skirko, M.G., Allard, P., Chary, S., Gagnon, P.R., Macmillan, K., De Luca, M., O'Shea, F., Kuhl, D., 2007. Depression and anxiety disorders in palliative cancer care. J. Pain Symptom Manag. 33, 118–129.