Review

Peak experiences and the afterglow phenomenon: When and how do therapeutic effects of hallucinogens depend on psychedelic experiences?

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Abstract

Interest in the therapeutic potential of psychedelic substances has recently resumed. During an early phase of human psychedelic research, their therapeutic application in different pathologies had been suggested, and the first evidence for efficacy was provided. The range of recent clinical applications of psychedelics spans from cluster headaches and obsessive-compulsive disorder to addiction and the treatment of fear and anxiety in patients suffering from terminal illness, indicating potentially different therapeutic mechanisms. A variety of approaches in psychotherapy emphasize subjective experiences, such as so-called peak experiences or afterglow phenomena, as differentially mediating therapeutic action. This review aims to re-evaluate earlier and recent concepts of how psychedelic substances may exert beneficial effects. After a short outline of neurophenomenological aspects, we discuss different approaches to how psychedelics are used in psychotherapy. Finally, we summarize evidence for the relationship between subjective experiences and therapeutic success. While the distinction between pharmacological and psychological action obviously cannot be clear-cut, they do appear to contribute differently from each other when their effects are compared with regard to pathologies.

Keywords

Hallucinogens, psychedelics, serotonin, psilocybin, ketamine, LSD, substance-assisted psychotherapy, psychedelic therapy, psycholytic therapy, obsessive-compulsive disorder, substance addiction

Introduction

In the last 15 years, hallucinogenic substances such as psilocybin and ketamine have been rediscovered by researchers in neuroscience and psychiatry (Langlitz, 2010). With the rise of modern neuroimaging methods, new hypotheses regarding the mechanism of action of these substances in the central nervous system have been suggested (Carhart-Harris et al., 2012; Nichols and Chemel, 2006; Vollenweider and Kometer, 2010). In parallel, the therapeutic potential of psychedelics has also been reconsidered (Griffiths and Grob, 2010). Thus, in light of the need for new treatment options for psychiatric disorders, a colorful, but almost forgotten, chapter of psychiatric history has been facing a revival (Barrau-Alonso et al., 2013; Sessa, 2012).

While modern psychopharmacologic drug development primarily targets biological mechanisms, psychedelics have been assumed to exert their therapeutic actions by facilitating different types of therapeutically useful states of consciousness (Chandler and Hartman, 1960; Savage et al., 1964). In contrast, some recent approaches have increasingly suggested other therapeutic mechanisms of action, especially when considering ketamine treatment in depression (Aan Het Rot, 2012; Zarate et al., 2006).

The current re-evaluation of clinical usage of psychedelics includes the treatment of cluster headache (Frood, 2006), obsessive-compulsive disorder (OCD) (Moreno et al., 2006), addiction (Ross, 2012), depression (Zarate et al., 2006) and anxiety in terminally ill patients (Grob et al., 2011). However, the hypotheses on how psychedelics might exert their therapeutic potential have been inconclusive. Since the discovery of lysergic acid diethylamide (LSD) in 1943, three main aspects have been of major scientific interest.

First, the observation that mescaline could induce psychosis-like states (Beringer, 1927) and mescaline's structural similarity to norepinephrine led to a paradigm shift regarding the neurobiological underpinnings of schizophrenic symptoms (Osmond, 1957; Osmond and Hoffer, 1959). The concept of 'model psychosis' marked a turning point in modern psychopharmacology as it suggested that states of consciousness are associated with chemical processes.

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Secondly, psychedelic substances such as LSD-25 induce powerful subjective experiences and altered states of consciousness (ASCs) perceived as the ability to 'expand consciousness' (Watts, 1968). This triggered their use outside the scientific environment as tools for spiritual practice, so-called self-actualization or enhanced creativity (Harman et al., 1966; Krippner, 1964;).

Thirdly, drug-facilitated states of 'expanded consciousness' were found to lead to persisting changes in the perception of oneself, others and the environment (Savage et al., 1966). This observation was one of the initial rationales for employing hallucinogens in the treatment of mental disorders in the 1950s (for a comprehensive bibliography, see Passie, 1997).

During the first period of psychedelic research, altered or non-ordinary states of consciousness, referred to as *psychedelic experiences*, were considered to be the key mechanism and the sine qua non for proclaimed therapeutic effects, often with an exclusive emphasis on psychological aspects (Grinspoon and Bakalar, 1979, 1981; Grof, 1979; Harman et al., 1966; Savage et al., 1963, 1966; Sherwood et al., 1962). In the mid-1970s, clinical psychedelic research came to a standstill due to regulatory restrictions. After a hiatus of more than 20 years, interest has re-emerged, but under different conditions: methodological quality standards have improved and neurobiological methods, above all, neuroimaging, have gained increasing importance in psychiatric research (Gallinat et al., 2012; Hermle et al., 1992; Juckel et al., 2007; Langlitz, 2010; Vollenweider, 2001). In parallel, the interest of the neurosciences in subjective experience was fostered, reflected in the concept of 'neurophenomenology' (Cardeña et al., 2012; Lloyd, 2002).

This review focuses on current clinical psychedelic research, re-evaluating former and recent concepts of how psychedelic substances may exert their therapeutic effects. We focus on the classical hallucinogens, which have been traditionally used in psychedelic-assisted psychotherapy, and include a special reference to ketamine. We will not discuss 3,4-methylenedioxy-methamphetamine (MDMA) here as it is not considered to be a hallucinogen in the narrow sense, but rather an entactogen (Nichols, 1986) or empathogen (Nichols, 2004). It is of note that ibogaine has been investigated in the treatment of substance addiction (Alper et al., 1999; for a review, see Mash et al., 1998), but it will not be discussed here since its complex biological mechanisms of action involve a number of additional pathways, making it more difficult to localize the role of psychedelic experiences in their potential anti-addictive effects. After a short outline of methodological and neurophenomenological aspects, we discuss different therapeutic approaches and relate them to the question of how subjective experiences contribute to the therapeutic outcome.

Neurophenomenology of psychedelic states

Variable terminology has been used in the description of psychedelic experiences. Referring to phenomenological considerations, we will discuss the temporal profiles of drug-facilitated ASCs as they pertain to the therapeutic applications. We refer to conceptualizations of ASCs and finally suggest a basic operationalization for depicting peak or mystical type experiences in future research.

The study of drug-facilitated states and their subjective experience is challenging. Besides general epistemic limitations on the assessment of qualitative experiences, additional difficulty is created by the fact that these experiences often go beyond the previously experienced epistemic range. It is not surprising that highly metaphoric terminology was suggested to approximate *new* qualities of experience for which other verbal labels appear inappropriate. A further limitation is that 'online' (while experiencing drug effects) evaluation suffers from acute drug effects, such as problems in verbalization or attentional and motivational fluctuations. Additionally, purposeful introspection may interfere with the experience as such; thus, the assessment is usually done retrospectively. Appropriate operationalizations and means of quantification form the basis for developing therapeutic approaches where therapeutically desirable experiences are fostered while alleviating others. Finally, it has to be acknowledged that the drug-facilitated subjective experiences limit the validity of double-blind, placebo-controlled studies as designed for drugs without obvious psychotropic properties (Oram, 2012).

Currently, the use of questionnaires or structured interviews remains the method of choice to quantify between- and within-subject differences in ASCs. Agreement on common standard assessment tools is desirable, as it enables the pooling of data for joint analysis and fosters comparability. This is crucial, as upon the administration of the same drug, psychedelic experiences may be markedly different when subjects undergo a positron emission tomography (PET) scan compared to a therapeutic session in a comfortable atmosphere (Studerus et al., 2012).

In the 1970s, Dittrich (1985) initially designed a questionnaire for 'Abnormal Mental States' (in German: Abnormer psychischer Zustand (APZ)) with 158 dichotomous items and tested 11 different induction methods, including hallucinogens (see also Studerus et al., 2010). Dittrich identified three oblique primary etiology-independent dimensions: 'oceanic boundlessness', 'dread of ego dissolution' and 'visionary restructuralization'. Meanwhile, several refinements of Dittrich's questionnaire were introduced, resulting in the Altered States of Consciousness Rating Scale (5D-ASC), which constitutes the most frequently used questionnaire and the current gold standard (Studerus et al., 2010). As well as the 5D-ASC, which is primarily used in Germany and Switzerland, other scales such as the Hallucinogen Rating Scale (Strassman et al., 1994) and the Phenomenology of Consciousness Inventory (Pekala et al., 1986) are also commonly used.

Types of psychedelic experiences

Different classification schemata have been developed in order to depict states of consciousness, including pathological states (for a review, see Passie, 2007). A basic distinction of psychedelic experiences has been suggested, to classify psychotic, psychodynamic, cognitive, aesthetic and psychedelic peak/mystical aspects (Pahnke, 1967). In his famous 'Good Friday Experiment', Pahnke (1966) administered a high dose of psilocybin (or nicotinic acid as an active control) to a group of divinity students before they attended a religious service. The experiment took place in a small basement chapel to which the service in the main sanctuary was transmitted. A high rate of profound mystical experiences was found in the psilocybin group when compared with the control group. Consequently, the idea evolved that hallucinogens may induce psycho-spiritual experiences with an impact on the profound belief and disbelief systems. Via this impact, the drug leads to therapeutic or transformative effects

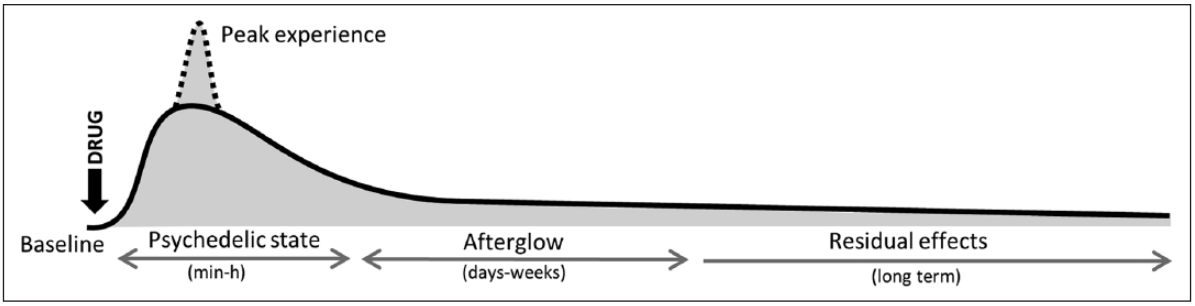

Figure 1. Time course of subjective experiences induced by psychedelics.
Psychotropic effects of psychedelic substances unfold over a timescale of several hours, which is dependent on the drug and dosage. Most therapeutic approaches make use of this window for psychotherapeutic interventions. On some occasions, subjective experiences include the so-called 'peak experience' (indicated by the dashed line), which is characterized by intense states, including mystical experiences. A persisting feeling of elevated and energetic mood is termed 'afterglow' and may persist for several days or even weeks. Long-term residual effects include therapeutically valuable changes of mindset as well as changes in personality traits, which have been often reported.

(Pahnke, 1969a; Sherwood et al., 1962) wherein the temporal mechanism of the drugs action contributes differently (Figure 1).

Grof's classification largely overlapped with Pahnke's; however, Grof additionally introduced the concept of 'perinatal matrices' emphasizing the occurrence of perinatal or birth phenomena in psychedelic sessions (Grof, 1979). Upon comparing and integrating their nomenclature one finds that Pahnke and Grof agree on a description of a highly intense component of the experience which only occurs on occasion. Pahnke referred to this as the *psychedelic peak experience*. He described nine characteristics that psychedelic peak experiences share with non-drug-related mystical experiences (Pahnke, 1966, 1969a): (1) a sense of unity; (2) the transcendence of time and space; (3) a deeply felt positive mood; (4) a sense of sacredness; (5) the noetic quality; (6) paradoxicality; (7) alleged ineffability; (8) transiency; and (9) persisting positive changes in different domains, including attitudes and behavior towards the self, others, life and the experience itself.

After the acute effects of the drug have subsided, a *psychedelic afterglow* has been described by several authors (Albaugh and Anderson, 1974; Krupitsky and Grinenko, 1997; Metzner, 1998; Pahnke, 1969a; Pahnke et al., 1970a; Sherwood et al., 1962). Pahnke described this as a state of 'elevated and energetic mood with a relative freedom from concerns of the past and from guilt and anxiety', furthermore, he notes that the willingness 'to enter into close interpersonal relationships is enhanced' (Pahnke, 1969a). During the afterglow period, the effectiveness of psychotherapeutic interventions is reported to be enhanced until the afterglow gradually subsides after a period of between two weeks and a month (Albaugh and Anderson, 1974; Pahnke, 1969a). Interestingly, within some ritual uses of hallucinogens such as those of the União do Vegetal, religious services are separated by intervals of two weeks, which is often the reported duration of the afterglow phenomenon (Grob et al., 1996).

Whether the changes in attitude and behavior following psychedelic experiences are limited to the timeframe of the afterglow or result in longer-lasting effects has been controversial (Grof, 1979; Pahnke et al., 1970a). A long-term follow-up report from the 1990s, interviewing subjects who had participated in Pahnke's Good Friday Experiment, came to the conclusion that no persisting dysfunction and even some beneficial effects could be observed after more than 25 years (Doblin, 1991), except for one subject who had sustained an acute psychotic episode during the study and had difficulty integrating the experience even years after the experiment had taken place. Several years later, a similar experiment was carried out by Griffiths et al. (2006) using a sophisticated design. In this study, different doses of psilocybin or methylphenidate (as active control) were administered to 30 healthy subjects. The authors reported that in the psilocybin group complete mystical experiences, as measured by the Pahnke-Richards Mystical Experience Questionnaire, occurred in 58% of the subjects (Griffiths et al., 2006). In a 14-month follow-up these were considered by more than 50% of subjects to be one of the most personally meaningful and spiritually significant experiences of their lives, and had increased well-being or life satisfaction in 64% of the subjects (Griffiths et al., 2008). Furthermore, enduring increases in the personality domain of openness were observed among those subjects who had a complete mystical experience (MacLean et al., 2011). Together these results suggest that beneficial effects of the experience had outlasted the afterglow phenomena.

To depict psychedelic peak experiences in future research, we propose a focus on the mystical aspect of the experience as reflected by scores on the 5D-ASC. On introducing the APZ questionnaire, Dittrich referred to the epistemological debate that one cannot ultimately clarify whether drug-facilitated ASCs are 'real' mystical experiences; he therefore proposed 'Oceanic Boundlessness' (OBN) as the label for one subscale. As OBN includes changes in the sense of time, depersonalization as well as derealization and a positive basic mood (Dittrich, 1985), this subscale's items partly overlap with items 1–3 of the psychedelic peak/mystical experience as categorized by Pahnke (1966, 1967): a sense of unity, the transcendence of space and time, and a deeply felt positive mood. After further refinement of the 5D-ASC questionnaire, one of 11 factors is now termed 'spiritual experiences' and a corresponding high cut-off score could be utilized as an operationalization for depicting a mystical experience (Studerus et al., 2010).

Neural substrates of psychedelic experiences

On the molecular level, the description of action of psychedelic substances has greatly progressed (for a review, see Nichols, 2004). In contrast, how substances alter neuronal networks or

system behavior has not been completely understood. However, the rise of neuroimaging techniques (e.g. functional magnetic resonance imaging (fMRI) electroencephalography (EEG) or magnetoencephalography (MEG)) has contributed new insights into the neural underpinnings of qualitative conscious experiences, including mystical-type experiences.

Evidence has converged that the 'core psychedelic effects' are transmitted via an action on 5HT-2A receptors, while substances interact with multiple receptor types (Aghajanian and Marek, 1999a; Geyer and Vollenweider, 2008; Halberstadt and Geyer, 2011; Nichols, 2004; Nichols and Chemel, 2006; Passie et al., 2002, 2008). This is best demonstrated by two studies in which administration of psilocybin was preceded by ketanserin, a 5HT-2A receptor blocker, and drug effects were diminished (Kometer et al., 2013; Vollenweider et al., 1998). As 5HT-2A receptors are expressed on pyramidal neurons as well as on GABAergic interneurons, it is challenging to distinguish which cell population contributes more (Lee and Roth, 2012). A recent psilocybin study used dynamic causal modelling to link cell populations with whole-brain MEG recordings and indicated that the modulation of pyramidal cells best explained the given data (Muthukumaraswamy et al., 2013).

Despite the pivotal role of serotonergic receptors, interactions with other transmitter systems (e.g. dopamine or norepinephrine) may contribute to differences in a substance's action (Halberstadt and Geyer, 2011; Marona-Lewicka et al., 2005; Nichols, 2004; Passie et al., 2008). Characterization of the psychedelic effects of ketamine (an N-methyl-D-aspartate (NMDA) receptor antagonist) points towards a shared glutamatergic pathway for serotonergic psychedelics and ketamine (Aghajanian and Marek, 1999b, 2000; Anand et al., 2000; Deakin et al., 2008; Vollenweider and Kometer, 2010, Vollenweider et al., 1997a, 1997b). The precise mechanisms of interaction between the transmitter systems remain a focus for future research.

The recent shift in human neuroimaging from mere activation studies towards network analyses is also reflected in psychedelic studies. Carhart-Harris et al. (2012, 2013) investigated connectivity changes of major brain networks during psychedelic-facilitated states. They observed distinct decreases of activity in anterior and posterior cingulate cortices that related to a decreased coupling between medial prefrontal cortex and the posterior cingulate cortex. A general disturbance of normal network interaction was also indicated in an MEG study (Muthukumaraswamy et al., 2013).

The conceptualization of the Bayesian brain hypothesis', such as the predictive coding framework (Friston, 2005), has gained prominence in neuroimaging, including in relation to psychosis and drug-facilitated ASCs. In short, it is assumed that the brain constantly generates an implicit future model to predict sensory inputs. Whenever sensory input contradicts the model's predictions, a prediction error is generated that is important to update the model for learning and for filtering sensory information. The hierarchical ordering of the neocortex is assumed to reflect these functions anatomically by means of microscopic and macroscopic connectivity principles (Bastos et al., 2012). Corlett et al. (2007) formulated causal hypotheses for drug-facilitated states when NMDA- and AMPA-mediated signaling is manipulated. Experimentally, mismatch paradigms were tested in combination with psilocybin and ketamine (Umbricht et al., 2003, Schmidt et al., 2012, Schmidt et al. 2013). Such studies contribute mechanistic views on network interactions that might ultimately enable the tracking of causative mechanisms in consciousness research.

The question of whether spiritual experiences facilitated by psychedelics are identical to those that occur spontaneously is quite controversial, yet they have repeatedly been suggested as a model for religious experience (Dittrich, 1985; Griffiths et al., 2011; Maslow, 1964; Masters and Houston, 1966; Nichols and Chemel, 2006; Pahnke, 1969a; Watts, 1968). Nevertheless, on the level of biological research, it is difficult to compare findings from non-drug-related mystical states to psychedelic-facilitated states due to various confounders such as trait and state and pharmacological side effects, among others. The authors of the present review do not know of any study that specifically investigated the neural basis of peak experiences. This might be for several reasons: (1) spiritual experiences have been reported to occur only sometimes, and in a subset of subjects (Grof, 1979; Nichols, 2004); (2) when considered as setting variables, PET, EEG, fMRI or other experimental settings may decrease the probability of experiencing spiritual states (Studerus et al., 2012); and (3) as mentioned above, spiritual states are highly subjective and individual experiences (MacLean et al. 2012). Using OBN as an indicator for spiritual experiences, a PET study suggested a correlation with changes in a fronto-limbic-striato-parietal network, whereas 'Dreadful Ego Dissolution' (DED) was associated with thalamic hyperactivity and a decrease of orbitofrontal activity (Vollenweider, 2001, 2008).

Concepts of hallucinogen-assisted therapy

Psychedelic healing in the context of religious rituals

The medical use of hallucinogenic plants has been reported for different indigenous cultures, for example, Amazonian shamans (Andritzky, 1989; Naranjo, 1979) and Southern Mexican indigenous people (Bruhn et al., 2002). Plant-derived serotonergic hallucinogens such as psilocybin, N,N-dimethyltryptamine (DMT) and mescaline have been used safely in ritual contexts, probably for thousands of years, and this fact has been used as an argument for the harmlessness and safety of these substances when used in a specific setting (Bouso et al., 2012; dos Santos, 2013; Grob et al., 1996; Halpern et al., 2005, 2008). The use of mescaline-containing peyote cacti in the Native American Church is a current example of such a practice (Halpern et al., 2005). In highly ritualized settings, peyote has been reported to increase the openness of the individual to cultural messages by enhancing suggestibility and inducing a state of enhanced perception of spiritual and self-reflective issues (Calabrese, 1997). Via this mechanism, psychopharmacology and psychotherapy have been suggested to become partners in a 'tandem strategy' (Calabrese, 2007) in which both rely highly on the other. Analogously, in the Amazonian basin, plant-derived concoctions containing DMT (ayahuasca, hoasca or yage) are ingested in religious healing ceremonies within the framework of shamanic medicine (Grob et al., 1996; Naranjo, 1979).

Furthermore, syncretic churches from Brazil, such as Santo Daime and the União do Vegetal, use ayahuasca in regular religious

Table 1. Comparison of psycholytic and psychedelic therapy in terms of dosage, psychological effects, mechanism of action, number of sessions, setting, integration to reality, goal and indications. Adapted from Leuner (1967).

	Psycholytic therapy (PLT)	Psychedelic therapy (PDT)
Dosage	Low doses (30–200 µg LSD equivalent)	High doses (200–1500 µg LSD equivalent)
Psychological effects	Symbolic images, regression, transference phenomena	Cosmic-mystic experiences, experiences of oneness and ecstatic joy
Mechanism of action	Activation and deepening of the psychoanalytic process	No foundation in classical psychological theories. Parallels to religio-psychological experiences
Number of sessions	Numerous sessions	The aim is to create one single 'overwhelming' experience
Setting	Analytic discussion of material experienced in individual and group sessions	Extremely suggestive preparation and use of specific surroundings and music. No detailed discussion of the experience
Integration into reality	Reality comparison, attempt to adapt experience to everyday life	Adaptation to reality not desired, but rather the fixation of the psychedelic experience
Indications	Classical indications for psychotherapy: neuroses, psychosomatic cases; in addition, cases of psychopathy, sexual perversion, borderline cases. Not alcoholism or psychosis	Alcoholism and drug addiction, anxiety and depression in terminal phases of somatic illness

services (Grob et al., 1996). Initial reports indicated beneficial effects, however, placebo-controlled studies are lacking (Halpern et al., 2008; Santos et al., 2007). Moreover, when comparing the use of hallucinogenic substances in indigenous rituals with use in modern psychotherapeutic settings, it is crucial to bear in mind the distinct concepts of mind and illness in these cultures (Metzner, 1998). In contrast to the psychedelic treatment concepts in psychiatry, religious services involving hallucinogens are performed regularly, weekly or monthly (Calabrese, 1997; 2007; Halpern et al., 2005), possibly providing a state of constant afterglow.

Modern forms of psychedelic-assisted psychotherapy

Among the different historic concepts of psychedelic-assisted psychotherapy, *psycholytic therapy* (PLT) and *psychedelic (peak) therapy* (PDT) have been most intensively practiced and studied (Grinspoon and Bakalar, 1979; Passie, 1997) (Table 1).

The term *psycholytic*, meaning 'soul-dissolving', or 'mind-loosening', was first introduced by RA Sandison. In PLT, serotonergic hallucinogens were used in low doses of 50–200 µg LSD equivalent in repeated sessions over a period of months to several years, embedded within a form of psychodynamic psychotherapy (Gasser, 1995; Leuner, 1967; Sandison, 1963). The psychedelics were used to facilitate and intensify psychodynamic psychotherapy, with markedtly more drug-free sessions than substance-assisted sessions (Chandler and Hartman, 1960). In this method, the psychedelic effects were used in order to facilitate the loosening of defensive mechanisms, the revival and abreaction of childhood experiences, the release of associated emotions and a deepening of introspective insight, all of which was mediated by the interpretation of unconscious material by the therapists (Eisner and Cohen, 1958; Leuner, 1963, 1981; Sandison, 1959), which would have been 'worked through' in a psychoanalytic manner (Sandison, 1963). Another aim of using hallucinogens in PLT was the enhancement of the relationship between patients and therapists (Eisner and Cohen, 1958), including the intensification of transference and counter-transference phenomena (Abramson, 1956). Analogous to psychoanalytically oriented psychotherapy, the indications of PLT were in the field of neurotic disorders as well as personality disorders or psychosomatic diseases (Gasser, 1995; Grinspoon and Bakalar, 1979).

The term *psychedelic*, meaning 'mind-manifesting', was introduced by Osmond (Dyck, 2008). The PLT approach was grounded in the European psychoanalytic tradition, whereas PDT has been practiced mostly by North American therapists and scientists (Dyck, 2008). The most extensively studied indications for PDT include alcohol and drug addiction and anxiety in terminally ill cancer patients. In PDT, high to very high doses (ranging from 250–450 µg LSD equivalent or sometimes even higher, depending on indication, set and setting variables) were administered to the patient in order to induce a psychedelic peak experience in an environment of permissiveness, friendliness and psychological safety (Blewett and Chwelos, 1959; Savage et al., 1964). Originally, the drug session was embedded within a standardized procedure that included three inter-correlated phases (Blewett and Chwelos, 1959; MacLean et al., 1961; Sherwood et al., 1962): (1) preparation; (2) the drug session; and (3) work on integrating the experience. First, several interviews were carried out to establish a stable relationship of mutual regard and trust between therapist and patient and to learn about the patient's specific problems (Pahnke et al., 1970a). Special consideration was given to aspects of the personality structure that may have emerged as barriers for a fruitful psychedelic experience (MacLean et al., 1961). Symptoms of the underlying problems of the patient were regularly, but only very gently, addressed, as therapeutic interventions were of second priority to the establishment of a solid relationship (Savage and McCabe, 1973) and to open the possibility for a 'significant encounter' (Kurland et al., 1967). The drug session itself was guided by at least two therapists, preferentially of both genders, who were present throughout the session (Blewett and Chwelos, 1959; MacLean et al., 1961). A harmonious, careful, tasteful and quiet atmosphere was created in which the patients received 'a heavy dose of tender, loving care' (Kurland et al., 1967). Patients listened to carefully selected music via headphones and wore eyeshades to facilitate release into the unfolding inner experience and intense emotional processes (Bonny and Pahnke, 1972). The third phase focused on

the integration of the experience and consisted of a series of drug-free interviews of variable frequency, mostly not exceeding a few weeks (Savage and McCabe, 1973).

In addition to the effects observed when using lower-dosage techniques, the psychedelic peak experience has been described as so 'unique, profound, overwhelming, otherworldly and impressive' (Sherwood et al., 1962) that it was believed to be able to change a person's underlying system of beliefs and disbeliefs, to transform his view on the self, the others and the environment. It has therefore been compared to religious conversion (Pahnke, 1967, 1969a, 1969b; Pritchard, 1974). Even more importantly, the administration of the substances was restricted to one or only a few times, and usually terminated when a 'peak experience' had been successfully induced.

Therefore, besides dosages and frequencies of psychedelic-assisted sessions, the most prominent difference between the two concepts lies in the significance given to peak experiences, which are considered as key mechanisms of action in PDT but as much less important and sometimes even as side effects without any therapeutic significance in PLT (Leuner, 1967). However, despite several obvious differences between PLT and PDT, there are many overlaps and shared positions. Integrative approaches have been suggested by different authors (Grof, 1979; Halpern, 2007; Strassman, 1995), and recent studies investigating the therapeutic use of hallucinogens have mostly left behind the distinction between these two classical concepts (e.g. Grob et al., 2011; Moreno et al., 2006). In addition, the concept of 'psychodelytic therapy', introduced by Arendsen-Hein, Grof and others, combined aspects of PDT and PLT, including a series of low-dose psycholytic sessions followed by one or more high-dose psychedelic sessions with differentially arranged settings (Grof, 1969).

History and present psychiatric research with psychedelics

In the following section we review current research regarding possible indications for the therapeutic use of psychedelic substances. Reference is given to the most investigated disorders: substance-related addiction, treatment of depression and anxiety in patients suffering from terminal somatic illness, major depression, OCD and cluster headache.

Treatment of substance addiction

Alcoholism and other substance-related addictions have been among the first and most extensively studied indications for treatment with psychedelic agents from the 1950s to the early 1970s (Grof et al., 1973b; Hoffer and Osmond, 1968; Kurland et al., 1967; Ludwig et al., 1969; Osmond, 1969; Pahnke et al., 1970a; Savage, 1962; Savage and McCabe, 1973; Smith, 1958; for a review, see Mangini, 1998). The concept of using psychedelics in this context originally arose from the observation that LSD-facilitated states of consciousness somewhat resembled delirium tremens in alcohol withdrawal syndrome (Ditman and Whittlesey, 1959). Due to the highly aversive nature of the experience, some alcohol addicts had quit drinking after experiencing a first episode of delirium tremens. Thus, the initial psychedelic treatment concept in alcoholism was to induce such a highly aversive but spontaneously reversible and controllable state (Hoffer, 1967; Osmond, 1969). Surprisingly, in many of the treated individuals the experiences under psychedelic drugs were not purely negative. This led to a different approach, in which 'thought-provoking' instead of frightening experiences were considered as a means of therapeutic action (Smith, 1958).

Traditionally, a high-dose approach with the induction of mystic experience has been related to the treatment of addiction (Grof et al., 1973b; Kurland et al., 1967; Ludwig et al., 1969; Pahnke et al., 1970a). It has been suggested that dysfunctional self-concepts are made visible through the psychedelic peak experience. The notion that one is 'infinite in essence', leading to a conversion-like state of self-acceptance and self-surrender, has transcended, which is in line with therapeutic approaches involving spiritual or religious elements such as Alcoholics Anonymous (Blewett and Chwelos, 1959). Some authors reported that patients with a peak experience ('peakers') displayed a better clinical outcome; however, these findings are inconclusive (Grof et al., 1973b; Kurland et al., 1967; Pahnke et al., 1970a; Richards et al., 1977). It has also been suggested that only positive reactions to LSD are of therapeutic value, whereas contrary reactions such as sensory distortions and negative reactions like panic and fear were assumed to be irrelevant. Psychotic reactions may have explicit anti-therapeutic consequences (Pahnke et al., 1970a). On the other hand, painful psychodynamic reactions have also been considered integral and fruitful elements by the majority of authors when embedded within a therapeutic procedure of preparation and integration of the experience. In interviews with 121 patients who had undergone PLT with LSD, several had fearful or other negative experiences, but only one considered these experiences negative for their own therapeutic outcome (Gasser, 2008).

It has been repeatedly emphasized that the majority of the studies conducted before the 1970s were methodically weak and therefore do not allow conclusions regarding therapeutic efficacy to be drawn (Abbuzahab and Anderson, 1971; Mangini, 1998; Ross, 2012). However, a recent meta-analysis (Krebs and Johansen, 2012) identified six randomized controlled trials (from 1966–1970) evaluating the effects of a single dose of LSD on alcohol abuse with an overall sample of 536 participants. Beneficial effects of LSD treatment were reported at the first follow-up assessment, which ranged from 4 weeks to 12 months after treatment. All of the included studies employed dosages between 450 and 800 μg LSD, which is considered to be a high or even very high dose, with sample sizes ranging from 10–132. The authors reported that the effect size of a single dose of LSD in a therapeutic setting was comparable to the effect of naltrexone, acamprosate or disulfiram applied daily over the same period of time. However, the authors emphasized that in those studies that showed an effect in the treatment group, therapeutic preparation and follow-up had been carried out, whereas in the groups that showed no beneficial effects the presence of a therapist was minimal. For instance, in two of the studies, participants had been left alone during a long period of the LSD effect.

It was alternatively hypothesized that serotonergic psychedelics act via experience-independent mechanisms. It has been suggested that serotonergic hallucinogens exert anti-addictive effects by normalizing functional connectivity in the prefrontal-limbic network through glutamate-dependent neuroplastic adaptation, as serotonergic hallucinogens increase extracellular glutamate levels in these areas (Ross, 2012).

Finally, ketamine psychedelic psychotherapy (KPT) has been investigated for the treatment of alcoholism and heroin addiction since the 1980s (Krupitsky and Grinenko, 1997; Krupitsky et al.,

2002, 2007). This approach initially combined the induction of peak experiences and afterglows with aversive elements during the drug session (Krupitsky and Grinenko, 1997); however, these elements were dropped in subsequent KPT studies. A standardized procedure for a single session, or repeated sessions, uses ketamine at a sub-anesthetic (= psychotomimetic) dose embedded within up to 15 sessions of drug-free, 'existentially oriented' psychotherapy as preparation and follow-up (Krupitsky and Grinenko, 1997; Krupitsky et al., 2002). In a double-blind, randomized, active placebo-controlled sample of 70 heroin addicts, psychedelic experiences occurred only in the high-dose ketamine group, followed by significantly higher rates of abstinence during the subsequent 23 months after treatment (Krupitsky et al., 2002). Compared to the control group, which received non-psychedelic ketamine doses, longer-lasting reductions in drug craving and improvement of the anhedonia syndrome were reported (Krupitsky et al., 2002). Patients from the high-dose group also showed improvement in nonverbal unconscious emotional attitudes and appeared to be more self-confident and emotionally open. In line with traditional psychedelic therapy of addiction, the authors hypothesized that psycho-spiritual experiences had led to positive changes in the patients' attitude towards the meaning of life, life purposes and spiritual development (Krupitsky et al., 2007). Furthermore, it has also been suggested that ketamine shares its antagonistic properties on NMDA neurotransmission with non-psychedelic drugs that also exhibit anti-addictive properties, such as acamprosate, lamotrigine and topiramate, leading to the conclusion that more than psychological effects may at least partly contribute to the anti-addictive effects (Ross, 2008).

In conclusion, the data pertaining to the efficacy of psychedelic-assisted therapy for the treatment of substance-related disorders are conflicting and recent research has been scarce; however, some current approaches are encouraging for future research. Regarding the mechanisms of action, the traditional view of hallucinogens exerting their putative anti-addictive effects primarily via psycho-spiritual conversions has been contested, however, this hypothesis still holds strong arguments.

Terminally ill cancer patients

The treatment of anxiety and depression in cancer patients in preterminal states of illness has been among those indications with the most promising benefits from a treatment with serotonergic hallucinogens (Grob et al., 2011; Grof and Halifax, 1977; Grof et al., 1973a; Kast, 1966, 1967; Pahnke, 1969a, 1970b; Richards, 1978; Richards et al., 1979). The idea to treat patients with LSD originated from attempts to reduce cancer-related pain (Kast and Collins, 1964). Promising analgesic effects were found for LSD, which outlasted the acute psychedelic state and the analgesic effects of opioids (Kast, 1966; Kast and Collins, 1964). Surprisingly, although these studies had focused primarily on analgesia, and psychotherapeutic preparation or follow-up had not been conducted, they reported patients having gained profound insight and a changed attitude towards the self and their social surroundings, which alleviated their anxiety towards dying (Kast, 1966, 1967). In the first reported study, many patients' experiences were too aversive and many of them said they would not have agreed to use the substance again (Kast and Collins, 1964). However, the results of further studies were more promising, possibly because the patients had been better prepared (Kast, 1966, 1967). Two mechanisms of the psychedelic experience were proposed to be therapeutically crucial: (1) a reduction of the anticipative cognition of death and enhancement of immediate sensory life; and (2) the loosening of ego boundaries, which offers a possibility to escape from the inevitability of the anticipated context (Kast, 1967).

From 1965 until the 1970s several studies on the use of LSD and dipropyltryptamine (DPT) for the treatment of depression and anxiety in terminally ill cancer patients were carried out at Spring Grove Hospital in Maryland (for a summary, see Grof and Halifax, 1977). In contrast to the previously discussed studies by Kast and colleagues, more consideration was given to set and setting and the patients' potential reactions to the substance. Also, follow-up psychotherapy sessions were carried out and the setting of the psychedelic sessions was carefully arranged (Pahnke, 1967). In an initial study, the authors found that one-third of the patients improved dramatically in regard to fear, anxiety, worry, depression, pain and, most importantly, fear of death, one-third improved moderately, and one-third did not improve (Pahnke, 1969a). The effect of psychedelics on the fear of death was reported to be most dramatic if a psychedelic mystical experience had occurred. The author reported that through this experience the patients had gained some sense of transcendence and security, which had diminished their fear of death and deepened their pre-existing interpersonal relationships and thereby enhanced the quality of life of the patients and their families. However, it was emphasized that these therapeutic effects depended strongly on set, setting, and preparatory and follow-up sessions that allowed the integration of the experience. Similar observations regarding the relationship between the 'peak experience variable' and therapeutic effects have been reported in later studies using LSD and DPT (Grof and Halifax, 1977; Grof et al., 1973a; Pahnke, 1969b; Richards et al., 1977). Grof emphasized mystical aspects linked to the experience of (ego-) death and rebirth to be of a crucial therapeutic value for the terminally ill cancer patient (Grof, 1979; Grof and Halifax, 1977).

A recent study investigated psilocybin in a sample of 12 patients with advanced-stage cancer and reactive anxiety using a within-subject, double-blind, placebo-controlled design (Grob et al., 2011). The treatment model and setting were similar to those employed by the Spring Grove clinic in the 1960s and 1970s. A low to moderate dosage of psilocybin was given only once. While no direct influence on pain was found, it was reported that anxiety was reduced at 1 and 3 months after treatment and that mood was improved even 6 months after treatment. In addition, the authors reported that the patients had gained insights into how their illness had changed their lives, social relationships and feelings of security. The psilocybin experience had induced feelings of strong empathic rapport and strengthened relationships with close relatives and friends. The authors suggested that the experience, via the treatment, of an 'ego-free state' and of transcendence of physical existence had led to a loss of fear of death. In line with previous reports, this study suggests that psilocybin facilitates therapeutic bonds and diminishes feelings of hopelessness. That overall effects were only moderate was ascribed to the cases that had used only low doses of psilocybin. It could be speculated that high doses, as utilized in the studies from the 1960s and 1970s, may be capable of inducing more profound psycho-spiritual experiences, potentially fostering beneficial effects.

Analogously, promising effects were also found when treating anxiety in patients with life-threatening diseases in the framework

of LSD-assisted psychotherapy (Gasser et al., 2014). In this study, moderate doses of LSD were administered on a single occasion embedded within a series of drug-free psychotherapeutic sessions. Participants exhibited a reduction of anxiety, which remained significant after 12 months. Both studies, however, were not placebo-controlled due to ethical considerations.

OCD

Moreno and Delgado (1997) reported the case of a patient with OCD who had recreationally used psilocybin-containing mushrooms and realized that his OCD-symptoms were diminished. The patient used psilocybin daily for four years and found that his OCD symptoms improved, while he lacked ASC experiences due to the effects of tolerance. Two years after he had discontinued the use of this substance, his symptoms returned to their previous intensity. Moreno et al. (2006) conducted a controlled study of psilocybin with treatment-resistant OCD patients. A sample of nine subjects was exposed to four single-dose psilocybin sessions with low to very high doses in a standardized setting in an outpatient clinic where no specific psychotherapeutic procedures were performed. The authors reported a consistent reduction of OCD core symptoms in all of the patients. In contrast to the delayed effects of selective serotonin reuptake inhibitors (SSRIs), this effect on OCD symptoms was immediate and the effects persisted after acute effects had subsided, but were still highly transient, lasting somewhat longer than 24 hours. The authors suggest a rapid, adaptive cascade including postsynaptic serotonin receptor down-regulation or early gene expression as the underlying mechanism. However, all subjects also experienced moderate to severe psychedelic states, making it difficult to determine the extent to which subjective experiences may have contributed to the treatment effects. To our knowledge this is the only controlled study on the effectiveness of serotonergic hallucinogens for OCD, with the conclusion being highly limited due to the small sample size and the lack of a control group.

Studies from the first period of intensive psychedelic research are limited to a few anecdotal accounts of LSD and psilocybin (Brandrup and Vanggaard, 1977; Leonard and Rapoport, 1987; Savage et al., 1962) as OCD sufferers were considered to be resistant to the psychological effects of LSD (Grof, 1979), with much higher dosages of up to 1500 µg LSD equivalent being necessary to induce the effective psychedelic responses. Interestingly, subjects with a highly rationalistic personality structure or those who placed a strong emphasis on structure and control (McGlothlin et al., 1967) were also reported to be less prone to psychedelic states.

Additionally, ketamine was reported to induce anti-obsessive effects; however, these findings remain controversial. One study found anti-obsessive effects that did not last any longer than the acute drug effects (Bloch et al., 2012), whereas another study found that the effects of ketamine on constant intrusive thoughts lasted for 7 days post-treatment (Rodriguez et al., 2013).

Converging evidence suggests that serotonergic neurotransmission plays a key role in the pathophysiology of OCD. Animal models of OCD identified 5-HT2 receptors to be critically involved in OCD-like behaviors in mice (Shanahan et al., 2011), and serotonergic agents such as SSRIs or clomipramine are the standard treatment for OCD. Studies show that LSD rapidly down-regulates 5-HT2 receptors in the rat brain, which partly explains the rapid tolerance to LSD that develops with repeated usage (Buckholtz et al., 1990). Furthermore, it has been reported that LSD enhances neuronal responsiveness to serotonin in the orbitofrontal cortex of rats independently from the psychedelic state, which potentially relates to OCD pathology (Zghoul and Blier, 2003). In addition, the 5HT-2 agonist psilocybin was found to reduce marble-burying behavior in mice, an animal model of OCD (Matsushima et al., 2009). This corroborates the idea that the effects of serotonergic hallucinogens are at least partially mediated by direct pharmacological mechanisms of action.

Depression

In the past decade, a large body of research has been done on the use of ketamine in depression (for reviews, see Aan het Rot et al., 2012; Mathews and Zarate, 2013). Strong but short-lasting effects have been found for treatment-resistant unipolar depression (Zarate et al., 2006) and bipolar depression (DiazGranados et al., 2010a) as well as suicidal ideation (DiazGranados et al., 2010b). However, in this approach, the application of ketamine has not been connected to any specific psychotherapeutic context or to a consciously experienced psychedelic state of mind. On the contrary, direct pharmacodynamic effects upon the neurobiological correlates of depression have been suggested to explain the observed symptom reduction, independent of any subjective effects of ketamine (Zarate et al., 2006). One study found a correlation between psychotomimetic effects of ketamine and its effects on depression; however, these effects were found to be independent of any specific therapeutic context (Sos et al., 2013). To our knowledge, there has been no study investigating the effects of a ketamine-assisted psychotherapy for depression that focuses on inducing psychedelic experiences. In addition to the treatment of depression and anxiety in patients suffering terminal somatic illness, serotonergic substances have sometimes been mentioned for the treatment of depression, in both a psychedelic and a psycholytic approach (Grof, 1979) in the context of endogenous or neurotic depression. The results of these studies were nevertheless controversial, sometimes even mentioning negative effects, as the substances tended to aggravate the present mood rather than ameliorating it.

Other clinical applications of psychedelic substances

In the 1990s, a sufferer of cluster headaches accidentally discovered that the recreational use of LSD prevented expected cluster periods from occurring and that magic mushrooms containing psilocybin taken in sub-hallucinogenic dosages every 3–6 months drastically reduced the frequency of further periods (Sewell, 2008; Sewell et al., 2006). The patient shared his experience via the internet, resulting in the formation of a group of cluster headache patients called ‘Clusterbusters’ who promoted the use of serotonergic psychedelics (Frood, 2006). In an online survey, 53 cluster headache sufferers who had taken LSD or psilocybin reported that both substances were highly effective in aborting acute attacks, terminating cluster periods and extending periods of remission, i.e. reducing the frequency of cluster headache periods (Sewell et al., 2006). Thus, it appears that cluster headache is one of the most strikingly effective indications for serotonergic psychedelics (Sewell, 2008),

as the relationship between efficacy and the low rate of adverse effects has not been observed in any of the other treatments. Interestingly, the therapeutic effects in cluster headache appear to be completely independent of the psychedelic experience (Sewell et al., 2006). Recently, non-hallucinogenic ergoline derivatives such as 2-bromo-lysergic acid diethylamide (BOL-148) have been investigated, with promising results (Karst et al., 2010).

In Switzerland, a large sample of patients was legally treated using a substance-assisted therapy with LSD, psilocybin and MDMA from 1989–1993 (Gasser, 1995). Among these patients, the most frequent diagnosis was narcissistic personality disorder; this indication for the therapy might be explained by the ego-dissolving properties of hallucinogens, which have also been referred to as 'narcissilytic' or as 'humility agonists' (Halpern, 2003). Other previous indications include the broad spectrum of neurotic disorders, above all those with a psychosomatic component, sexual dysfunctions and post-traumatic stress disorder, among others (Gasser, 1995; Oehen, 2008).

Conclusions

Systematic assessment of drug-facilitated ASCs in controlled clinical trials is required to ultimately argue what experiences contribute to therapeutic outcomes. Despite political hurdles, several studies have investigated neuronal correlates of psychedelic-facilitated ASCs. However, it remains a goal for future research to elucidate the relationship between subjective experiences and the neuronal mechanisms that underlie long-term therapeutic effects.

How are therapeutic effects related to subjective experiences?

The most extensively studied conditions for therapy with psychedelics – involving the induction of a psychedelic (peak) experience – are addiction and the treatment of terminally ill patients. For both conditions, psycho-spiritual aspects have proven helpful in drug-free treatment approaches. The idea of achieving conversion to a state of permanent abstinence from addiction with a 'single, overwhelming experience' has proven to be too optimistic (Albaugh and Anderson, 1974; MacLean et al., 1961). However, indigenous use of high doses in ritualized contexts has been associated with higher abstinence rates and reduced high-risk behaviors (Albaugh and Anderson, 1974; Halpern et al., 2008; Thomas et al., 2013). The use of psychedelics in these rituals is closely intertwined with an enhancement of social interactions and pro-community attitudes, and this has been reported to be part of the more holistic understanding of treating illness. From this standpoint, the notion of mere pharmacological effects appears controversial, especially when considering that non-drug-related treatments involving spirituality are among the most fruitful strategies for treating addiction (Galanter et al., 2013; Kelly et al.; 2011).

Conversely, OCD has been described as highly resistant to the acute psychotropic effects of serotonergic psychedelics. Specifically, Grof (1979) reported LSD-assisted psychotherapy in OCD as 'problematic'. However, recent studies have reported a reduction of OCD symptoms in patients after administration of psilocybin (Moreno et al., 2006) or ketamine (Rodriguez et al., 2013) without any psychotherapeutic session. These studies lead to the conclusion that the potential therapeutic effects of psychedelics in OCD may occur independently of psychedelic experiences.

Interestingly, therapeutic effects of NMDA receptor agonists also appear to be not directly related to subjective experiences. Recently, ketamine has been applied to elicit short-term antidepressive effects in major depression and bipolar disorder. These effects appear to be for the most part independent of psychedelic states, as the dosages used were mostly sub-psychedelic. More studies are required to determine the relationship between the psychotomimetic and antidepressant properties of ketamine. To date, studies on serotonergic hallucinogens in depression are sparse and not too promising. Nevertheless, anecdotal reports of PLT or PDT with beneficial effects do exist (Baker, 1964). Thus, only well-designed studies could inform future applications.

One of the most outstanding and unique properties of psychedelic drugs resides in their ability to create states of mind that resemble mystical experiences. This cannot be reproduced in animal models, as these experiences are dependent on the self-reflective abilities of humans. Importantly, these specific states of mind may imply the existence of therapeutic options on the level of subjective experience, which deserve further investigation in clinical trials, as well as an opportunity for the understanding of psychoses. At the same time, they appear to be represented by neurobiological correlates that deserve further investigation in brain imaging studies.

Pharmacotherapy or psychotherapy, or both?

In the majority of the work mentioned in this review, classical psychedelics such as LSD have been proposed to facilitate and intensify ongoing therapeutic processes, but not to replace them. It has been repeatedly emphasized in both major approaches to psychedelic-assisted therapy that set and setting are of great significance for the outcome. Metzner (1998) considered the drug a 'catalyst or trigger', not in itself a healing entity. This is in line with metaphors that psychedelics work as 'unspecific amplifiers' (Grof, 1979) or 'microscopes' (Watts, 1962) to assess unconscious intra-psychic material. Given the ineffability and overwhelming intensity of some drug-facilitated states and the complex interactions between drug, set and setting, it has been suggested that the personal psychedelic experience of the therapist is a prerequisite for all treatment approaches (Blewett and Chwelos, 1959; Gasser, 1995; Masters and Houston, 1966; Pahnke et al., 1970a).

In contrast to traditional psychiatric drugs such as antipsychotics or antidepressants, psychedelic agents are not to be ingested regularly but only once or a few times. Most notably, ketamine – although it is not a classical psychedelic – illustrates two different aspects of the potential mechanisms of action. In KPT, as implemented in the treatment of substance addiction, psychedelic experiences are put at the center of the hypothesis of how symptoms improve (Krupitsky and Grinenko, 1997). In addition, it has been reported that anti-addictive effects may be associated with the mystical-type effects of ketamine, independently of a therapeutic framework (Dakwar et al., 2014). In contrast, recent studies on depression have suggested ketamine as a treatment option for affective disorders in a genuinely pharmacological sense where psychedelic effects are not considered or where they are regarded as adverse reactions (for a review, see Aan Het Rot et al., 2012).

Two different positions can be distinguished when considering current research on the beneficial effects of psychedelics. In the first, psychedelic drugs are administered on only one or a few occasions, aiming at facilitating a mystical or peak experience with long-lasting beneficial effects similar to those gained by religious conversion. This strategy has been the basis for PDT and PLT upto the 1970s, and it holds some evidence from current research. The second approach involves the repeated or sustained use that mostly occurs in ritual contexts. It has been associated with beneficial effects on substance addiction and other psychiatric conditions, often without any predefined therapeutic goal.

In conclusion, psychedelic drugs are unique in the sense that they might have at least four distinct therapeutic effects: (1) as medicaments in the sense of agents with neurochemical and pharmacodynamic effects, e.g. in the above-mentioned treatment contexts of depression and possibly OCD; (2) as tools for facilitating and supporting various types of psychotherapy, with special consideration of indications and counter-indications, mindset and setting variables, e.g. in the treatment of terminal illness; as (3) analgesics, e.g. for the treatment of headache or other pain syndromes; and (4) as facilitators of self-experiences in spiritual or other contexts. Furthermore, these dimensions overlap, such as when spiritual experiences are considered as tools for therapy of terminally ill patients or for addiction, or when psychotherapy involves the exploration of subconscious aspects. Therefore, more research is required to outline other potential indications and define the overlap of the different dimensions and the relation to personalized treatment, since these effects will strongly depend on the individual.

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