



Novel Treatment Approaches for Substance Use Disorders: Therapeutic Use of Psychedelics and the Role of Psychotherapy

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Abstract

Purpose of Review The use of psychedelics in a therapeutical setting has been reported for the treatment of various diagnoses in recent years. However, as psychedelic substances are still commonly known for their (illicit) recreational use, it may seem counterintuitive to use psychedelic therapy to treat substance use disorders. This review aims to discuss how psychedelics can promote and intensify psychotherapeutic key processes, in different approaches like psychodynamic and cognitive behavioral therapy, with a spotlight on the treatment of substance use disorders (SUD).

Recent Findings There is promising evidence of feasibility, safety, and efficacy of psychedelic therapy in SUD. In the whole process of former and current psychedelic therapy regimes that have shown to be safe and efficacious, various psychotherapeutic elements, both psychodynamic and behavioral as well as other approaches, can be identified, while a substantial part of the assumed mechanism of action, the individual psychedelic experience, cannot be distinctly classified to just one approach.

Summary Psychedelic therapy consists of a complex interaction of pharmacological and psychological processes. When administered in well-defined conditions, psychedelics can serve as augmentation of different psychotherapy interventions in the treatment of SUD and other mental disorders, regardless of their theoretical origin.

Keywords Psychedelics · LSD · Psilocybin · Psychotherapy · Psychodynamic · CBT · Addiction

Introduction

Psychedelics, also known as serotonergic hallucinogens, exert their main effects via stimulation of the serotonin 5-HT_{2A} receptor [1]. Not included in the use of the term psychedelics in this article are dissociative anesthetics (e.g., ketamine), empathogen-entactogen stimulants (e.g.,

MDMA; 3,4-methylenedioxy-meth-amphetamine), ibogaine, or new psychoactive substances (NPS, “legal highs”). The best known psychedelics are LSD (5R,8R-lysergic acid diethylamide), psilocybin, DMT (*N,N*-dimethyltryptamine), and mescaline (3,4,5-trimethoxyphenethylamine). These substances cause an altered state of consciousness, usually lasting several hours, with profound changes in perception, including hallucinations, synesthesia, altered experience of time and space, and strong activation of emotions and emotionally formative memories [1]. In Europe, psychedelics are best known to be used in recreational settings, while overall lifetime-prevalence levels among young adults have been generally low and stable for a number of years between 1 and 2% [2]. While their individual and societal harm ranks the lowest among many illegal legal substances, and their addiction/dependence potential seems negligible, [3, 4], most psychedelics are controlled under the Convention on Psychotropic Substances of 1971. It might therefore seem counterintuitive to use these substances to treat addiction.

However, in this article, the authors present psychotherapeutic frameworks and possible mechanisms of action, in

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order to show why and how addiction treatment with psychedelics may be beneficial, which has been suggested in a number of epidemiological and observational trials [5–11], clinical trials [12–15], meta-analyses [16], and conceptual articles [17–21]. There is growing evidence that psychedelics can be used to intensify psychotherapy processes in certain conditions, and thus serve as a non-specific augmentation of certain psychotherapeutic processes, which play a role in different forms of psychotherapy. We put a focus on psychodynamic therapy and CBT in this article for the high availability of empirical data in reported trials, as well as for their well-known historical and conceptual differences, which makes the similarities concerning the combination with psychedelic even more striking. High quality empirical data about other psychotherapies (e.g., hypnotherapy, group therapy) in psychedelic therapy is sparse though, and would be worth being further investigated.

Psychedelic Use, Research, and Therapy

Psychedelics have been used for several millennia in the context of traditional practices and shamanic rituals, for healing physical and mental disorders, for religious reasons and divination [22]. Since the beginning of the twentieth century, psychedelics have aroused the interest of botanists, psychologists, and psychiatrists. This interest was reinforced by the discovery of the psychedelic effects of LSD in 1943 [23]. Along with the associated counterculture in the 1960s, psychedelics became increasingly popular for recreational use. It is estimated that more than 30 million people living in the USA have used LSD, psilocybin, or mescaline in their lifetime [24].

In a clinical and research context, these substances were initially used as an experimental disease model for research on psychotic disorders (“psychotomimetics”), and rarely for self-exploration among psychiatrists. Further aspects of their therapeutic potential in the treatment of mental disorders were recognized later [25]. In fact, investigators who first tried LSD as an alcoholism treatment hypothesized that a psychotic-like experience would mimic a safer version of delirium tremens, because delirium tremens often preceded sobriety, but were also frequently fatal. However, these investigators found that under interpersonally supportive conditions, instead of psychotic-type experiences, patients often had positively-valenced experiences, for example insightful, peak, or mystical-type effects (e.g., feeling at one with the universe) that led to sobriety [26–28]. It was psychiatrist Humphry Osmond who coined the term psychedelic in 1957 to describe the mind-manifesting, revealing properties of these substances, after having observed that high doses of LSD in patients with alcohol dependence lead to profound experiences and strong effects on alcohol relapse prevention [26]. Between the late 1950s and early

1970s, approximately 40,000 patients worldwide with different mental disorders (substance use disorders, affective disorders, neurosis etc.) were treated with psychedelics—primarily LSD, mescaline, and psilocybin—sometimes with reports of remarkable therapeutic success described in over 1000 publications [29]. Following the largely socially and politically motivated international ban on psychedelics in 1971, almost all research activity in this field came to a halt. It was not until the 1990s that interest in psychedelic research has resurged. Since about the year 2000, there has been an increasing number of basic science and clinical studies [23, 25].

Contemporary Clinical Studies

Recent clinical trials investigating for the efficacy of psychedelic therapy have been conducted as treatment of major depression [30–34], anxiety and depression associated with terminal illness [35–38], tobacco use disorder [14], alcohol use disorder [15], suicidality [39], and obsessive–compulsive disorder (OCD) [40].

Independent from the diagnosis which was intended to treat, these trials have generally been based on fairly similar study protocols that focused on the careful selection and preparation of patients (usually referred to as set) and the provision of a safe and trusting environment (usually referred to as setting) [23]. “Set” and “setting” are an expression going back to the 1950s/1960s and often used in general language. In the context of research, however, this expression might be replaced in the coming years while trials discover the complex interplay of environmental, individual, and pharmacological factors. The approach nowadays is similar to the historical model of psychedelic therapy, or psychedelic peak therapy [41, 42]. In this model, a moderate to high dose of a psychedelic (e.g., LSD ≥ 200 μ g; psilocybin ≥ 20 mg) is applied to provide an overwhelming, transformative experience [43, 44]. In current studies, a brief therapeutic intervention phase is conducted for a period of one to three months, of which only a small proportion of sessions is under the influence of psychedelics. Between one and four sessions are conducted with administration of a psychedelic, at intervals with one to several weeks in-between each session [23]. In contrast to established pharmacotherapies (e.g., with antidepressants), a continuous daily substance administration is not provided.

In recent clinical trials on psychedelic therapy, a study protocol is commonly applied in most trials, hereafter also referred to as the current standard model. In this carefully refined protocol with emphasis on safety issues, the treatment is usually divided into three phases: (1) preparation, (2) dosing sessions, and (3) integration of the psychedelic experience [4, 23]. In the preparation phase (1), patients are informed about the mechanisms of action of

the psychedelics, about possible aversive parts of the experience (fear, sadness, loss of ego-boundaries, somatic side effects) and how to deal with them if they should arise. Therapists will explore the biographical and motivational background and current stress factors, and will begin to establish a therapeutic alliance. During dosing sessions (2), the patient is lying down in a comfortably arranged room in the presence of one or two therapists, wearing eyeshades and listening to a playlist of specifically selected emotion-eliciting music. The patient is encouraged to surrender to the inner experience with a mindful, accepting attitude, and to interact as little as possible with the environment during the acute effect of the substance, which usually lasts several hours. In the integration phase (3), the subjective psychedelic experience is discussed with the therapists, with a special emphasis on its meaning for the current life situation and the symptoms (e.g., the addictive behavior), helping the patient to integrate the experience into his daily life and to find a way out of the addiction and towards mental well-being. In most of the mentioned studies, no or very few specific psychotherapeutic interventions took place according to the current standard model. A focus was put on the deliberate and standardized design of set and setting, whose crucial importance for the psychedelic experience and thus for the success of the therapy is becoming increasingly clear and which are the subject of current investigations [45–47]. However, as discussed below, the studies addressing alcohol and tobacco dependence included a variety of classical psychotherapeutic elements, which took place not in the dosing session itself but rather in the preparation and integration sessions [14, 15]. In the mentioned studies, there were different control conditions applied, ranging from non-controlled open-label [14, 15, 32] to randomized controlled trials, the latter with low-dose psilocybin or LSD [35], niacin [36–38, 40], a specially designed placebo [31] or methylphenidate as active placebo. One trial controlled with waiting list [30], and one study used a double-dummy RCT to compare psilocybin to 6 weeks of an SSRI [34]. Thus, recent trials adopted a fairly standardized therapeutic intervention, while many did not fulfil the criteria of the current gold standard of controlled clinical trials (RCTs), which is mostly due to difficulties in successfully blinding the psychedelic experience [48]. Another problem is the small sample size of the existing trials, and potential bias due to a high rate of self-referred, highly motivated patients, which—in combination with highly motivated researchers and therapists, and the lack of effective blinding procedures—could have overstated treatment effects. Some of the methodological challenges are being addressed by upcoming trials like the EPIsoDE-Study (ClinicalTrials.gov: NCT04670081).

Risk and Potential Harm of Psychedelic Therapy

As applied in modern clinical trials, the risk of psychedelics in the treatment of mental disorders incl. SUD is considered very low, if the crucial points of patient selection (e.g., no personal or family history of psychosis), control of individual (set), and environmental factors (setting) are carefully addressed [4]. Although challenging reactions including fear and anxiety are common even in controlled settings and can be managed appropriately, when ingested in uncontrolled settings, such effects sometimes lead to dangerous behavior that can harm the self or others. In those vulnerable to psychotic disorders, such experiences may be destabilizing and instigate or worsen such disorders. [49]. In the cited clinical trials since 2011, not a single case of persisting psychotic reaction is reported. The risk with regard to the development of an addiction is very low and considered negligible for classic psychedelics such as psilocybin and LSD [50].

Psychodynamic Approaches

As the first variant of psychedelic therapy, the so-called psycholytic (loosening the soul or mind) therapy developed in the 1950s, especially in Europe [41, 42]. Psycholytic therapy involved the repeated use of a low to moderate dose of a psychedelic (e.g., 50–200 µg LSD) as part of months to years of outpatient psychodynamic therapy [51, 52]. In substance-assisted sessions, an intensification of emotional experience, an alleviation of neurotic defense mechanisms such as repression, denial, rationalization, and a marked increase in the number of the patient's free associations have been observed regularly [51]. This may allow patients to re-surface long-forgotten, emotionally aversive memories or traumas, often resulting in a cathartic abreaction of the feelings that have come to consciousness. By using psychoanalytic techniques (e.g., confrontation, interpretation) during substance-free sessions in order to further process the content rising into the patient's consciousness during substance-assisted sessions, patients and therapists reportedly gained deeper insights into repressed neurotic conflicts and unconscious patterns of response and interaction [51, 53].

These elements are universal in the psychodynamic treatment of any given mental disorder, be it depression or substance use disorder/addiction. Only a few psychodynamic hypotheses can be found that are specific about addiction treatment with psychedelics. Early US and Canadian trials on treatment of alcohol dependence with high-dose LSD from the 1950s–1970s suggested that the peak experience—while often framed by therapists from the alcoholics anonymous movement, and perceived by patients as “spiritual awakening”—led to deep insights and instant psychological transformation, changing the patients' dysfunctional patterns, increasing self-esteem, revealing their true personal

values, and leading to a phase of profound well-being, so that imagining the return to alcohol consumption triggered feelings of disgust [26]. The proposed psychological factors share some commonalities with the general psychodynamic idea of making the unconscious conscious.

Recently, Moreton and colleagues suggested an increased confrontation with one's own dying and death during the substance-assisted sessions as a psychodynamic mechanism of action, as it can result in a reduction of the mostly repressed death anxiety inherent in humans and thus bring about a decrease in symptoms of various mental disorders [54]. This existential psychotherapy approach is in line of the Krupitsky's findings of high recovery rates in heroin and alcohol addicts after ketamine-assisted existentially oriented psychotherapy, which also provided "positive transformation of nonverbalized (mostly unconscious) self-concept and emotional attitudes to various aspects of self and other people, positive changes in life values and purposes, important insights into the meaning of life and an increase in the level of spiritual development." [55, 56]. Although ketamine is not a serotonergic hallucinogen, it nonetheless shows some overlapping effects, and thus Krupitsky's work is likely relevant.

Another psychodynamic element is the so-called age regression, as was concluded from patients' experience reports during the psychedelic experience. In addition to an increased ability to remember repressed and long-past events (facilitation of autobiographical memories [57]), this can also include an archaic mode of experience with symbolic imagery, which, depending on the psychoanalytic background of the therapist, was classified in terms of archetypes (C.G. Jung) or primary-process thinking (S. Freud) [51, 53]. Further therapeutically useful effects were described as an intensification of the therapeutic relationship and an increased transference and countertransference, all factors which can also play an important role in the psychodynamic treatment of drug addiction [58].

Finally, there are some interesting psychoanalytical hypotheses and theories about the development of substance use disorders which have not yet been connected to psychedelic therapy models. Winnicott, building on the framework of object relations theory, argued that addiction could be understood as "regression to the early stage at which the transitional phenomena are unchallenged" [59]; it would be reasonable that age regression during a psychedelic experience can help discover and understand the early developmental deficits on a cognitive and emotional level, and "work this through" in subsequent therapy sessions, in order to no longer depend on the (pseudo-)translational object, which is the drug of addiction. The self-medication theory by Khantzian was created from clinical observation of patients with substance use disorders, who showed difficulties in regulating affect, self-esteem, relationships, and

self-care, all of which result in strong painful affective states that are in turn being regulated in a dysfunctional way with substance abuse [60, 61]. The psychedelic state could help the patient find important insights about those supposedly repressed, shame-laden mechanisms and the related structural personality deficits, while providing a positive mood (feelings of unity, bliss, trust in the therapeutic relationship, etc.) to enable correcting emotional experiences with the therapist.

Figure 1 provides an overview of the psychodynamic processes and factors that are thought to be intensified and enhanced by psychedelic-assisted therapy sessions.

Most studies of psychedelic-augmented psychodynamic treatment date from the 1950–1970s, so the scientific standard and control of biases was heterogeneous and rather low. Methodological details cannot be provided, as the principal method was phenomenological observations and narratives on a single case base—a major problem in all psychodynamic therapy research. Further trials with more rigorous designs are needed to elucidate the proposed mechanisms.

Although in recent decades, some segments of psychological science have deemphasized psychoanalytic theory due to concern over a disprovable framework largely based on non-experimental clinical observation, psychodynamic models remain of interest. In fact, psychedelic research might itself constitute an experimental framework for investigating purported psychodynamic mechanisms. In the discussion about

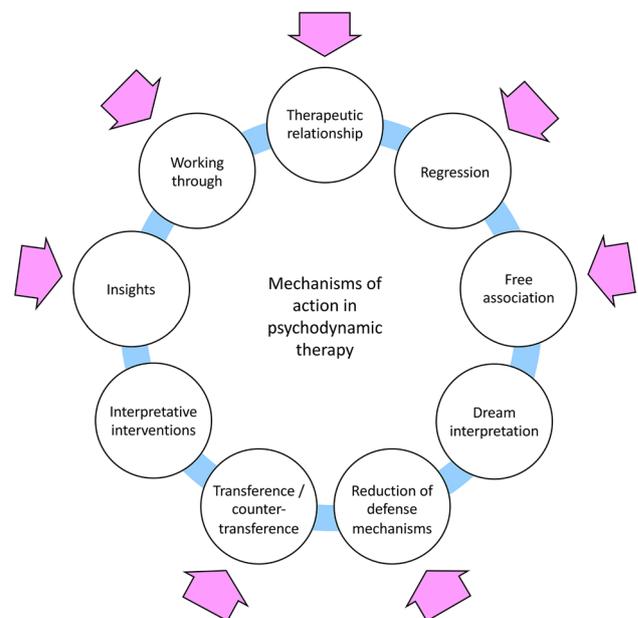


Fig. 1 Psychodynamic factors in psychedelic therapy, as described, e.g., by Leuner, Gasser, Cohen (for references see text). Colored flashes show factors and processes that are reported to be enhanced by psychedelics. The effect on the patient's dreams has not yet been sufficiently investigated; the therapist's interpretations should not be affected since he does not ingest any substances

the mechanisms of action of psychedelic therapy, psychoanalytic concepts have been revisited and modernized in recent years. One reason for this is the strong phenomenological similarity between the psychedelic experience and the dream experience [62]. Interpretation of dream content has been one of the central therapeutic techniques of psychoanalysis since the beginning of occidental psychotherapy. It was first outlined by Sigmund Freud in 1900 as the “royal road to the unconscious” [63]. Recent neurobiological and phenomenological studies have described the similarities of the psychedelic state with the dream state, e.g., in terms of perception, mental imagery, emotion activation, and self- and body experience [64]. Accordingly, primary-process thinking, which is characterized by fusion and transformations of mental images, bizarre experiential content, and illogical cognitions and emotions, can be understood as an organizing principle for both dreams and psychedelic states [65].

In summary, the psychedelic experience in a therapeutic setting has been reported to intensify key mechanisms of psychodynamic therapy like free association, regression, transference, weakened defense, deep insights, catharsis and exposure to existential themes, and thus augmenting the therapy process. With regard to SUD, psychedelics addressed processing of specific affects and thought patterns like guilt, grief, disgust, relational problems, and self-harm.

From Psychodynamic Theory to Predictive Processing

The abovementioned psychoanalytic perspective on the effects of psychedelics also serves as one conceptual framework in current neurobiological models, especially in the entropic brain theory and the REBUS (relaxed beliefs under psychedelics) model [66–68]. The authors describe a shift from rational-logical thinking (psychoanalytically: secondary process, “Ego”) to associative-instinctual thinking (primary process, “Id”), which can lead to an awareness of previously imperceptible (unconscious) psychological content.

As the REBUS model is based on the influential predictive processing (PP) theory from cognitive and brain science, it is worth exploring PP models for reward learning to better understand addiction. While some authors suggest that dopaminergic brain signaling coding for aberrant salience is a key mechanism in substance use disorder, other authors argue that compulsive drug seeking and taking is the behavioral consequence of high precision weighting of priors in the PP account, as a reaction to strong bodily sensations (craving), in order to reduce reward error signal [69]. One could suppose that psychedelics, by reducing the higher prior precision weighting, also reduces craving and drug seeking, not only during the acute experience, but also during the “neuroplastic window” of days or weeks after the intake, allowing new insights (e.g., about drug consumption,

personal values) to be processed if adequate psychotherapy is provided.

Krähenmann et al. note that, in the psychedelic state, the two cognitive modes described above (Ego/Id) can coexist in parallel, so that here most likely a hybrid state of dream and waking consciousness, similar to lucid dreaming, is present [64, 65, 70, 71]. The structural similarities between dreaming and psychedelic experience suggest that the images, emotions, and thoughts arising in the psychedelic state can be of therapeutic value for the further course of therapy in a manner similar to dreams and free associations in regular psychodynamic treatment. This theory is supported by work in the field of neuropsychanalysis demonstrating the compatibility of psychodynamic concepts and the entropic brain theory and predictive processing [72, 73].

Cognitive-Behavioral Approaches

Although the current standard model of psychedelic-assisted therapy largely refrains from applying targeted psychotherapeutic interventions, it is often considered that here, too, the therapeutic effect of the psychedelic experience is based on psychological mechanisms such as those generally effective in psychotherapy [74–76]. From the perspective of cognitive-behavioral therapy, one might assume that psychedelics can facilitate learning processes that ultimately lead to permanent changes in dysfunctional beliefs.

This assumption is in line with current neurobiological and information-theoretical theories of the acute effects of psychedelics. One currently influential approach is the REBUS model mentioned above [67]. According to this model, activation of 5-HT_{2A} receptors in cortical association areas such as those of the default mode network leads to a profound destabilization of assumptions about the world and the self (belief relaxation): assumptions that are rigid and barely modifiable in normal waking consciousness can be temporarily weakened in the psychedelic state while sensitivity to contradictory information is increased. When such destabilization affects, for instance, certain assumptions of the visual system (e.g., “sounds are not visible” or “light, in case of doubt, comes from above”), typical perceptual psychedelic phenomena such as synesthesia or the impression of wandering shadows and deforming objects may result. From a psychotherapeutic point of view, however, it appears more interesting to consider the destabilization of assumptions at higher levels of information processing—especially of dysfunctional belief structures that negatively affect the patient’s self-image and social and emotional experience [77].

According to the cognitive-behavioral model [74] illustrated in Fig. 2, metacognitive assumptions which are temporarily destabilized during the psychedelic state can be

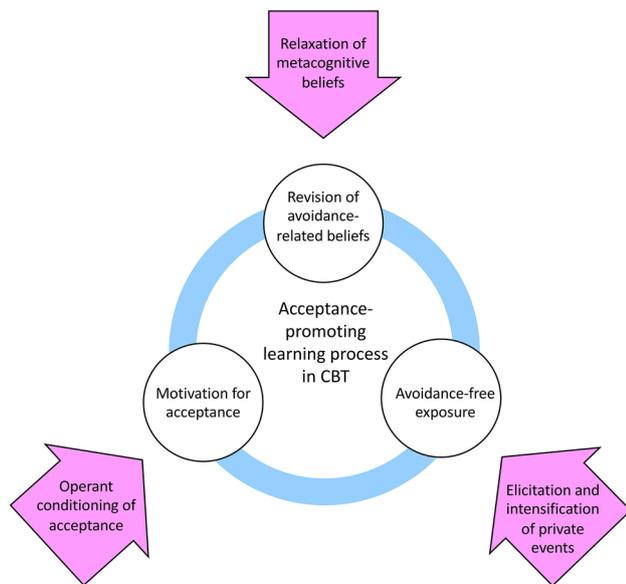


Fig. 2 Cognitive-behavioral model of the acceptance-promoting effects of psychedelic therapy (figure adapted from Wolff et al. 2020 [74]). Various interlocking aspects of an avoidance-reducing learning process, the promotion of which is the goal of many behavioral therapy interventions, are shown in the circle. The colored arrows represent proposed specific effect factors of psychedelic therapy

permanently and positively shifted by confrontation with previously avoided experiential content, as often appears to occur in psychedelic therapy even without specific intervention by the therapist [78–80]. Of central importance here is the observation that during the psychedelic experience, attempts to avoid aversive experiential content often lead to increased aversion, whereas a mindful, accepting attitude typically warrants a less tormenting experience [74, 78, 81–83]. Hence, a form of operant conditioning takes place, making possible deep and largely avoidance-free engagement with distressing feelings, thoughts, memories, and body perceptions. It appears likely that the revision of dysfunctional assumptions that may occur in this state is facilitated by psychedelic-induced belief relaxation. In a broader sense, this mechanism might reflect the psychedelic-related factors of cessation of substance abuse, which were reported e.g., by Noorani and colleagues. In this study, psychedelic therapy for smoking cessation and its perceived mechanisms of change were investigated. As essential factors to their efforts to quit smoking, participants reported valuable insights into a better, deeper or more essential understanding of themselves under the influence of psilocybin. These experiences were held accountable for the feeling of a decreased desire to smoke or the mere senselessness of smoking. Also, the holistic perception of oneself was described as a

mechanism, e.g., insights revealing how anxiety and fear contributed to their smoking [14, 84].

In conclusion, there seems to be a meaningful overlap between the mechanisms of action of psychedelic therapy and those of behavioral therapy, particularly with regard to the experiences made within the dosing sessions. Furthermore, embedding psychedelic interventions into behavioral therapy treatments before and after the actual psychedelic experience seems possible and reasonable, and has already been investigated in several studies [15, 85]. With regard to the existing studies addressing alcohol and tobacco dependence, several classical CBT elements have been used within preparation and integration sessions. Johnson et al. included the assignment of a target quit date, a contract to quit, a smoking diary and smoking cessation specific interventions (e.g., “NURD program card” was to be read each time a cigarette was smoked: “This cigarette is giving me no satisfaction;” “This is an unpleasant experience;” “This cigarette is making me feel rotten; I am losing the desire to smoke.” or WEST-D program card was to be read each time participants noticed an urge to smoke: “What’s the trigger? Each time I feel like smoking, Stop, Think, Deprogram.”) [14]. Bogenschutz et al. used Motivational Enhancement Therapy (MET) during preparatory sessions, which is a time-limited, usually four-session adaptation of motivational interviewing where the client is engaged to set goals, detect discrepancies between goals and the current situation, develop an intrinsic motivation to change, and is encouraged in her/his self-efficacy [15]. In these two clinical trials on SUD treatment, psychedelic sessions can be seen as enhancers of the manualized SUD psychotherapy. The exact interaction between the pharmacological and the psychological effects and their proportion in the symptom reduction are not well understood yet, and warrant further investigation.

Against the backdrop of increasing evidence for positive synergistic effects between psychedelic interventions and mindfulness practices, as well as acceptance-promoting effects of psychedelics [78, 86–89], efforts to combine psychedelic-assisted interventions with the so-called “third-wave procedures” within CBT have recently increased [90]. This is especially true for the combination of psilocybin with acceptance and commitment therapy (ACT), whose basic features and therapeutic goals show numerous overlaps with the phenomenology of psychedelic states [81, 91]. Correspondingly, sophisticated therapeutic concepts are currently being tested in clinical trials. Furthermore, the possibility of combining psychedelics with dialectical behavioral therapy (DBT) for the treatment of borderline personality disorder is also now being discussed [92].

The Subjective Experience

Since the early phase of psychedelic research, the observation has been made repeatedly that the experiences made under the substance's influence have an impact on the course and also on the success of the therapy. Modern research seems to support this. For example, a recent study identified certain experiential qualities of the substance's effects that were particularly associated with a response to therapy in depressed patients [93]. A similar picture emerged as in the studies with healthy subjects, in which the majority of participants had a so-called mystical-type experience due to a high dose of a psychedelic, phenomenologically comparable to reports of spiritual awakening experiences [44, 94, 95]. These experiences appeared to have long-term positive effects on well-being [96], and were rated by most participants as one of the five most important events in life, even years later [97]. In both trials mentioned above with tobacco and alcohol use disorder, the intensity of subjective mystical-type effects was related to reduction of substance use [15, 98]. Another phenomenon also associated with long-term positive changes in well-being in the context of acute substance use is the emotional breakthrough experience [99]. This refers to an intense experience of positive feelings that is perceived as cathartic, typically occurring with the successful resolution of emotionally stressful episodes of psychedelic experience, and often accompanied by valuable personal and interpersonal insights. As described, some authors found an increased feeling of connectedness to the self, to others and the world, as a main subjective effect of the experience [78]. Others pointed out the importance of different types of insight during the psychedelic experience for treatment outcome [43, 100]. However, not only the acute substance effect during the psychedelic session seems to be decisive for the success of the therapy but also a phenomenon which is described as the so-called afterglow effect. The term describes a period of 2–4 weeks after the psychedelic experience, which is characterized by increased mindfulness and cognitive flexibility, which can lead to an improvement in the effectiveness of psychosocial or psychotherapeutic intervention [42]. The aspect of heightened cognitive and emotional flexibility might in part be a correlate of increased sub-acute neural plasticity after psychedelic intake. Nonhuman animal studies have shown such neuroplasticity [92], consistent with elevated BDNF levels in humans [101]. However, research has yet to directly tie such effects to subjective afterglow or therapeutic effects. As treatment response in most of the early LSD alcohol trials only lasted for several weeks—the usual length of the afterglow phase—this could be explained by the strong anti-craving properties of the afterglow state [102]. From this perspective, patients might create a permanent afterglow effect by repeated dosing one or several weeks apart,

as performed in traditional religious groups in Northern and Southern America like Native American Church, Santo Daime and Unio do vegetal, whose communities show an exceptionally low rate of substance use disorders [8, 103, 104]. Other explanations of this low rate include the protective function of a religious community, or selection bias of individuals having turned away from unhealthy, addictive behavior towards a personally meaningful lifestyle.

Common Factors of Psychotherapy

Much has been written about the common factors in psychotherapy, and the high context sensitivity and increased suggestibility in the psychedelic state should make this even more important for therapy with psychedelics. Nayak, Johnson, and Gukasyan argue that common factors like therapeutic relationship and alliance, a healing setting, a conceptual scheme, and a healing ritual should play a major role in efficacy of any psychotherapy which is assisted by a psychedelic substance, especially with regard to the capacity of these compounds to enhance the sense of meaning to everything which is being processed [76]. The common factors approach is likely to become even more influential in psychedelic therapy and psychotherapy in general and will help blurring the lines between traditional psychotherapy schools. However, the somewhat dichotomous presentation in this article of the psychodynamic and the cognitive behavioral perspective served the purpose to facilitate understanding and adoption of the described complex interactions in psychedelic therapy from two major therapy schools, keeping in mind that many therapists adhere to specific therapy schools and probably identify with them.

Conclusions

In the history of psychedelic therapy, several variants developed in the twentieth century, which partly show substantial differences with regard to the dose of psychedelic substances, the practical implementation and the psychotherapeutic interpretation model. We have only focused on two classical therapy models, psychodynamic and behavioral therapy, and have not included, for example, humanistic and hypnotherapeutic methods in combination with psychedelic substances [105–107].

The current standard model applied in most recent clinical trials largely eschews specific psychotherapeutic intervention. The psychodynamic approach offers many compelling theoretical and practical arguments for synergies between the psychedelic state and the psychodynamic therapeutic process, while it has shown promising treatment success in the past. Early psychodynamic studies lacked rigorous methodology though, which makes it difficult to draw

solid conclusions about mechanisms of action and efficacy. Similarly, behavioral therapy and its further developments may provide a suitable conceptual framework for psychedelic therapy. Direct (head-to-head) differences in efficacy of psychedelic therapy based on different psychotherapies (e.g., psychodynamic therapy vs. behavioral therapy) have not yet been investigated, but would be informative for dismantling specific psychotherapy effects. However, a substantial part of the suggested psychedelic-related factors like valuable insights in oneself that are described above is neither distinctly classifiable to a psychodynamic approach, nor to a CBT approach.

Independently of certain psychotherapeutic schools of thought, it seems reasonable to view the therapeutic effects of psychedelics not as purely pharmacological, but essentially as a consequence of complex psychological processes that are enabled and triggered by the pharmacological substance effects. From this perspective, psychedelic therapy would always be substance-assisted psychotherapy. Such a view should certainly be applied not only to the understanding of psychedelics, but to that of all psychotropic drugs. However, in the case of psychedelics, the special importance of complex psychological processes is evident both in the strong dependence of therapeutic success on the subjective experience during the psychedelic experience, and in the equally crucial dependence of this experience on internal and external influencing factors referred to as set and setting. The exceptional mechanisms of action compared to other psychiatric drugs, which seem to be more similar to those of intensified psychotherapy, could promote further integration of psychopharmacological and psychotherapeutic approaches within psychiatry in the long term, particularly for the treatment of substance use disorders. To further elucidate the many open questions in the promising field of psychedelic therapy of SUD, particularly about the exact mechanisms of action, predictors and moderating factors, the right amount of psychotherapeutic intervention and relapse prevention, more clinical trials with higher sample size, better blinding and control conditions, and systematic comparison of different psychotherapy interventions are needed.

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