Therapeutic (Sub)stance: current practice and therapeutic conduct in preparatory sessions in substance-assisted psychotherapy – a systematized review

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Abstract

Background: Clinical trials are currently investigating the potential of substance-assisted psychotherapy (SAPT) as treatment for several psychiatric conditions. The potential therapeutic effects of SAPT may be influenced by contextual factors including preparation prior to and integration after the substance-assisted therapy sessions.

Aims: This systematized review outlines recommendations for current practice in preparatory sessions in SAPT including safety measures and screening procedures, preparation of set and setting, session contents, methods, and roles, prerequisite, and appropriate conduct of therapists.

Methods: A systematized review of the literature was conducted based on PRISMA guidelines. MEDLINE (OVID), PsycINFO (OVID), and Cochrane Library were searched and clinical trials, treatment manuals, study protocols, case studies, qualitative studies, descriptive studies, theoretical papers, reviews, book chapters, and conference proceedings published until February 1, 2022 were retrieved.

Results: The final synthesis included $k = 83$ sources. Information about safety measures including screening of participants, set and setting, contextual-, physiological-, and psychological preparation, roles, competencies, prerequisites, and characteristics of the therapists, and the establishment of a therapeutic relationship were summarized and discussed.

Conclusion: It is concluded that there is a consensus in the literature about the importance of adequate preparation before the administration of psychoactive substances in substance-assisted psychotherapy. However, the extent and approaches for these sessions vary across different models and there is a need for timelier and more rigorous qualitative and quantitative investigations assessing different approaches and techniques for the optimal preparation for clients in SAPT.

Keywords: Substance-assisted psychotherapy, psychotherapy, psychedelics, therapeutic rationale, therapeutic conduct, preparation

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Therapeutic (Sub)stance: best practice and appropriate therapeutic conduct in preparatory sessions in substance-assisted psychotherapy – a systematized review

Evidence from recent clinical trials using substance-assisted psychotherapy (SAPT) provides preliminary evidence for the safety and efficacy for using some psychoactive substances in combination with psychological support and/or psychotherapeutic interventions for treatment refractory post-traumatic stress disorder (PTSD; Mithoefer *et al.*, 2019), alcohol dependence (Bogenschutz *et al.*, 2015), anxiety and/or depression associated with life-threatening or end stage cancer (Grob *et al.*, 2011; Griffiths *et al.*, 2016; Ross *et al.*, 2016), obsessive-compulsive disorder (Moreno, Wiegand, Keolani Taitano, and Delgado, 2006), treatment-resistant depression (Carhart-Harris *et al.*, 2016), major depressive disorder (Carhart-Harris *et al.*, 2021; Davis *et al.*, 2021), and tobacco dependence (Johnson, Garcia-Romeu, and Griffiths, 2017).

Substances administered in (psycho-)therapeutic contexts include serotonergic psychedelics (e.g., LSD and psilocybin) sharing a primary mechanism of action at the 5-HT_{2A} receptor (Geyer and Vollenweider, 2008; Nichols, 2016; Preller *et al.*, 2018), NMDA antagonists with dissociative properties like ketamine (Krupitsky and Grinenko, 1997; Serafini *et al.*, 2014), serotonergic entactogens like MDMA (Thal and Lommen, 2018), and atypical and pharmacologically complex psychedelics like ibogaine (Alper, 2001).

While there are several theories regarding the mechanism(s) of action of these substances in therapeutic settings (Thal *et al.*, 2021), the mechanisms responsible for therapeutic change across conditions are still not fully understood. It is becoming increasingly apparent that the potential therapeutic effects of SAPT are dependent on several contextual factors including psychological preparation prior to the experience, support during the administration sessions, and psychological integration after the experience (Carhart-Harris, Roseman, *et al.*, 2018; Hartogsohn, 2017).

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The therapeutic effects of SAPT are largely thought to be a combination of the psychopharmacological effects of the substance (see e.g., Carhart-Harris and Friston, 2019; Carhart-Harris et al., 2014; Preller *et al.*, 2019), the client's subjective experience (Carhart-Harris, Erritzoe, *et al.*, 2018; Roseman, Nutt and Carhart-Harris, 2018), the dispositions of the client (Studerus *et al.*, 2012, 2021; Haijen *et al.*, 2018), and to the successful integration (i.e., reflection and meaning making of the evoked material) of the experience (Mithoefer, 2017; Bogenschutz *et al.*, 2018; Malone *et al.*, 2018; Gorman *et al.*, 2021). Acute subjective experiences that may be linked to positive outcome include emotional breakthroughs and psychological insights (Peill *et al.*, 2022), mysticomimetic experiences (Griffiths *et al.*, 2016; Ross *et al.*, 2016; Davis *et al.*, 2021), death transcendence (Schmid and Liechti, 2018), and ego dissolution (Tagliazucchi *et al.*, 2016; Letheby and Gerrans, 2017; Mason *et al.*, 2020). The quality, intensity, and duration of challenging parts of the acute psychedelic experience may be key mediators of the therapeutic outcome (Carbonaro *et al.*, 2016; Roseman, Nutt and Carhart-Harris, 2018; Romeo *et al.*, 2021). Nevertheless, there is an ongoing debate regarding the necessity of the subjective effects of psychedelics for their enduring therapeutic efficacy (Olson, 2020; Yaden and Griffiths, 2020). Those arguing against it (Olson, 2020) stress that associations between subjective effects and positive outcomes do not imply causation and subjective effects may rather be a biomarker for 5-HT_{2A} receptor activation and increased neural plasticity (Vollenweider *et al.*, 1998; Ly *et al.*, 2018) highlighting the potential of non-hallucinogenic psychedelic analogues (Cameron *et al.*, 2020). It is evident that the acute and long-term or persistent effects – which are more relevant for treatment effects – of substances used as adjuncts for therapy differ substantially (Carhart-Harris *et al.*, 2016). Individual experiences might be extremely variable and generalizations based on single sessions or clients could lack validity (Bogenschutz et al., 2018; Grof, 1980).

Different psychotherapeutic approaches like cognitive behavior therapy or motivational enhancement therapy (see Thal *et al.*, 2021 for review) and therapy-related

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variables are thought to contribute to the outcome of the SAPT, including the quality of the therapeutic relationship (Greer and Tolbert, 1998; Garcia-Romeu and Richards, 2018; Watts and Luoma, 2020; Murphy *et al.*, 2022) and the therapist's capacity to be psychologically present or 'hold space' (Geller and Greenberg, 2012; Tai *et al.*, 2021), preparation before administration of the substances, the shared interpersonal experience between client and therapist (Adamson and Metzner, 1988; Cosimano, 2021), and subsequent integration of the experience (Garcia-Romeu and Richards, 2018; Richards, 2017).

Generally, the whole course of SAPT can be divided into three chronological stages (see Van Rhijn, 1967): the pre-administration or preparatory stage (i.e., what happens before the substance-assisted session), the administration stage (i.e., what happens during the substance-assisted session), and the post-administration or integration stage (i.e., what happens after the substance-assisted session). In this article, we review the current evidence for the appropriate therapeutic conduct during the preparatory stage of SAPT – primarily focusing on psychedelics and entactogens as adjuncts to psychotherapy. While we acknowledge that the focus of integration sessions is inextricably linked to the ideas provided to participants during the preparation phase, therapeutic conduct in administration and integration sessions will be discussed in subsequent publications.

We conducted a systematized review of the literature of Western psychotherapeutic paradigms that have been developed and employed since the 1950s to conduct SAPT. The current article is the second in a series of papers. While our first paper (Thal *et al.*, 2021) outlined the appropriate pre-conditions for conducting SAPT, the purpose of the present review is to identify and discuss the evidence currently existing in the extant literature to inform the development of a best practice model for the preparatory stage of SAPTs. Because serotonergic psychedelics and MDMA were (and are still) most prominently used in combination with psychotherapeutic models for the treatment of psychiatric disorders we focused our review on these substances. In particular, we aimed to extract details regarding

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(1) safety measures and screening procedures, (2) preparation of an adequate set and setting, (3) contents and methods of preparatory sessions, and (4) roles, prerequisite, and appropriate conduct of therapists during preparatory sessions.

Method

A systematized review of the literature (Grant and Booth, 2009) was conducted following PRISMA 2020 guidelines (Page *et al.*, 2021) as closely as possible. A meta-analysis was considered inappropriate for this study due to the use of heterogenous interventions, study designs, clinical targets, and instruments. Likewise, a risk of bias analysis was not considered informative since the objective of this review was to extract study details that are not affected by issues with randomization, deviations from intended intervention, missing outcome data, biased outcome measures, or biased selection of reported results. The systematic search included papers that were published until February 1, 2022. The electronic databases MEDLINE (OVID), PsycINFO (OVID), and Cochrane Library were searched. Detailed information about the search strings for the respective databases can be found on the project's *Open Science Framework* (OSF) page (https://osf.io/usgeb/). Results of initial searches were supplemented by scanning the references of retrieved articles and consulting with experts in the field who were contacted via email and telephone. Eventually, the literature was imported into *EndNote 20*.

Eligibility criteria

Since the literature on the topic of preparation for SAPT is rather sparse, we selected broad inclusion criteria, namely: (1) the literature must describe the effects of the use of classic psychedelics or MDMA in SAPT, (2) the literature must outline any type of psychotherapy as part of an intervention involving classic psychedelics or MDMA, (3) the literature must describe the methods and/or theories used for preparation, or safety measures, or screening, and/or to guide the conduct of therapists, and (4) participants in clinical trials

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must be diagnosed with psychiatric disorders according to DSM-4 (American Psychiatric Association, 1994), DSM-5 (American Psychiatric Association, 2013), or ICD-10 (World Health Organization, 1993) criteria. We excluded studies if they (1) involved in vitro research, (2) involved animal research, (3), consisted of anthropological reports of indigenous and ritualistic use, (4) the administered doses were subperceptual (sometimes referred to as 'microdosing'), (5) the full text was unavailable via institutional access or through direct correspondence with the authors, and (6) were written in any language other than English or German. The review included clinical trials and follow-ups, treatment manuals, study protocols, case studies, qualitative studies, descriptive studies, theoretical papers, reviews, book chapters, and conference proceedings.

Since recent research has largely focused on individual sessions, we limited our review to individual therapy but aimed to synthesize applicable and valuable insights from literature regarding group therapy. Likewise, we disregard the discussion of the use of combinations of two or more psychoactive substances (Eisner, 1964), as rigorous clinical research on the therapeutic implications of polydrug administration in this framework was scarce (only one study: Schmid *et al.*, 2021), at the time of our search. Detailed information regarding excluded studies can be found on the project's OSF page (https://osf.io/mu8hp/).

Selection process

For the initial search on July 1, 2019, two independent reviewers (ST and TW) screened the retrieved literature. In a first step, the title and abstract screening was conducted. Good interrater reliability was reached ($\kappa = 0.742$; Cicchetti and Sparrow, 1981). In a second step, a full-text review based on the eligibility criteria was conducted. Good interrater reliability was reached ($\kappa = 0.633$; Cicchetti and Sparrow, 1981). A second search with an identical search string was conducted on February 1, 2022. Two independent reviewers (ST and MW) conducted the title and abstract screening reaching good interrater reliability ($\kappa =$

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0.799; Cicchetti and Sparrow, 1981) and a full-text review reaching excellent interrater reliability (κ = 0.921; Cicchetti and Sparrow, 1981). If consensus was not reached (i.e., sources were identified as suitable for inclusion by one reviewer but not the other) in either search, the suitability of the literature was discussed with the other co-authors until a consensus was reached.

Data collection and analysis

Data from eligible studies including details on the type of the study design, aims of the study, number of participants, eligibility criteria, diagnostic- and screening tools, safety measures, substance administered, dosage administered, number of sessions, therapist team, set and setting, content and method of preparation session, and roles, prerequisite, and appropriate conduct of therapists were extracted and recorded. Subsequently, information pertinent to a current best-practice approach was synthesized. The implication of these findings and future directions for research were discussed, respectively.

Terminology

Several terms may be used to describe those involved in SAPT. The person conducting the session is sometimes referred to as guide (Fadiman, 2011; Pahnke & Richards, 1966), practitioner (Fadiman, 2011), monitor (Johnson, Richards and Griffiths, 2008), sitter (Greer and Tolbert, 1998), or therapist (Cohen and Eisner, 1959; Walsh and Grob, 2006). Phelps (2017) identified the term ‘therapist’ to be the preferred terminology by psychedelic scholars and this expression is used for the purpose of this article. The person receiving SAPT is named client (Gasser *et al.*, 2014), patient (Johnson et al., 2008), or voyager (Fadiman, 2011). We prefer the term ‘client’ to avoid pathological connotations but simultaneously maintain a professional reference. For the purposes of this paper, we have established the term ‘therapeutic stance’ which we defined as the approach of the therapist reflected in their roles, attitude, adaptability, and conduct towards and with the client and towards and themselves.

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This definition encompasses several essential prerequisites and established constructs like therapeutic relationship, responsiveness, and therapeutic presence, and requires particular characteristics of the therapist and the alliance with their client.

Results and Discussion

The initial search resulted in 3,932 hits and 45 records which were identified through other sources. A total of 390 duplicates were removed and after preliminary analysis of the titles and abstracts, 136 sources were identified for further full-text analyses. Through consensus 54 sources were included in the initial version of the paper. The second search resulted in 6,619 hits. A total of 447 duplicates were removed using the *EndNote 20* software. The remaining 6,172 sources were screened by title and abstract resulting in 5,948 exclusions. A total of 224 additional full-text publications were identified for full text analysis by two independent reviewers (ST, MW) and 29 additional articles and book chapters were included with the result that 83 papers and book chapters were included in the final version of the paper (see Figure 1).

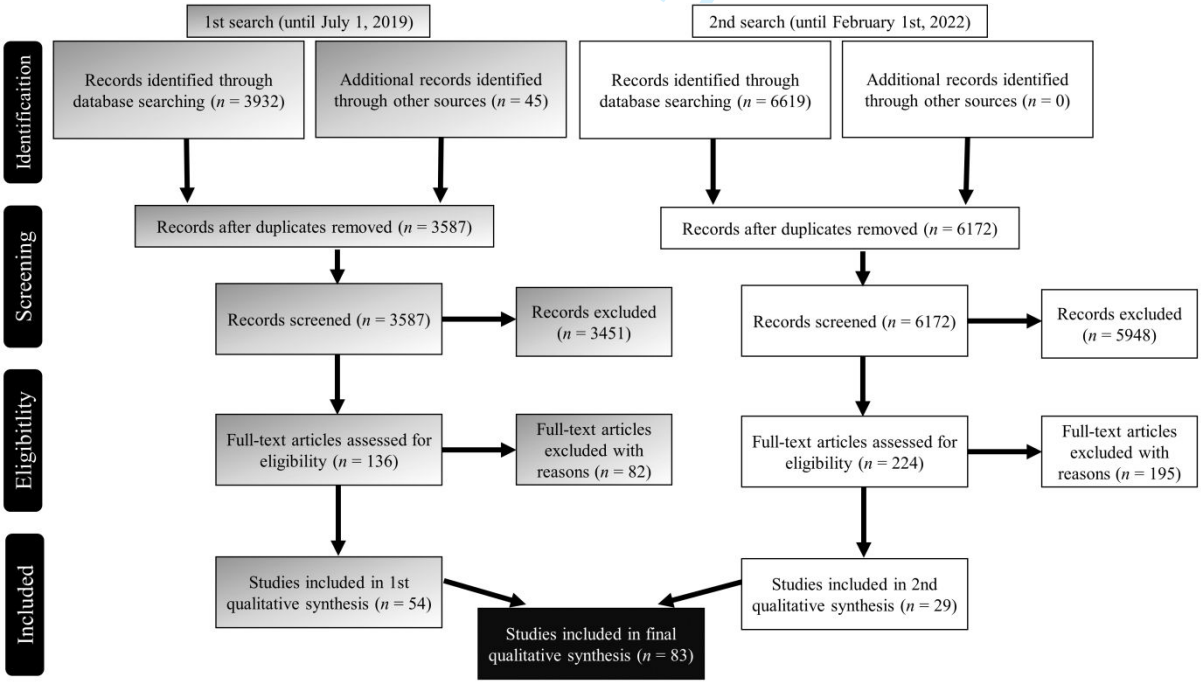

Figure 1. Visualization of the literature search

Characteristics of included studies

The details of all included sources can be found in Appendix A. The 83 sources included in the final qualitative synthesis included 24 clinical trials ($N = 536$), 1 study with preliminary data from a clinical trial, 2 follow-up analyses, 1 pooled analysis, 4 treatment manuals, 1 study protocol, 2 quasi experiments ($N = 108$), 1 case study, 4 qualitative investigations, 3 descriptive studies ($N = 928$), 1 observational study, 1 time-series study, 10 opinion papers, 23 reviews, and 5 book chapters.

Safety

Across the sources included in the final synthesis there was a consensus about the importance of extensive preparation and safety considerations in SAPT, including key factors like set and setting, screening, choice of substance and dose, and subsequent integration (Strassman, 1995; Johnson *et al.,* 2008; Cosimano, 2021). Serotonergic psychedelics (in the doses that are recommended for administration) are physiologically safe (Nichols, 2016), non-addictive (Johnson, Griffiths, Hendricks, and Henningfield, 2018), and long-term adverse effects related to research procedures or substances have not been reported in clinical trials (Ross *et al.*, 2016; Feduccia *et al.*, 2019; Bender and Hellerstein, 2022; Schlag *et al.*, 2022; Zeifman *et al.*, 2022). Likewise, there are no reports of long-term adverse effects of MDMA in clinical trials (Mithoefer *et al.*, 2019) and several trials offer evidence that doses used in clinical trials are safe and tolerable (e.g., Mithoefer *et al.*, 2011, 2018; Sessa *et al.*, 2019). Nevertheless, therapists should be aware that the effects of these substances can induce challenging experiences (Carbonaro *et al.*, 2016) and acute adverse effects including transient anxiety, psychotic thinking, headaches, fatigue, and nausea (Thomas and Malcolm, 2021). Since the therapeutic effects of SAPT may be influenced by the context the therapy is conducted in (Carhart-Harris, Roseman, *et al.*, 2018), certain preparations are required for the experience to be therapeutically valuable.

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In the early stages of first wave research, clients, on occasion, were allowed to take LSD home to self-administer, or were left alone with untrained, disinterested observers and a tape recorder, with traumatic and detrimental effects in a number of cases (Cutner, 1959; Hausner and Dolezal, 1963). Researchers have, however, stressed the importance of a doctor trained in rehabilitation and screening procedures and at least one empathic therapist being present throughout the entire substance-assisted session (Hausner and Dolezal, 1963; Hofmann, 2009). Adverse reactions were sometimes treated with antipsychotic or anxiolytic medications (Strassman, 1984), although some authors advised against pharmacological interruption of the sessions unless absolutely necessary (Hausner and Dolezal, 1963).

These risks of adverse reactions should be minimized by ample preparation (Garcia-Romeu and Richards, 2018). Eligibility criteria vary across studies and clinical targets (see Appendix B and Appendix C) and physiological or psychological contraindications are screened out during pre-assessment (see below). The long-term safety and efficacy of clinical use of these substances has to be investigated by future independent longitudinal studies (Aday *et al.*, 2020).

Screening, diagnostics, and assessment

Screening should include an examination of the client's medical history, a general physical examination, ECG, hematology, blood chemistry profile, alcohol breath test, urinalysis, and, if applicable, a pregnancy test (Johnson *et al.*, 2008; Sessa, 2017). Individuals actively taking medications that alter the effects the substances given as adjuncts to therapy (see e.g., Callaway and Grob, 1998) are usually excluded from treatment (Johnson et al., 2008; Mithoefer, 2017), including tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), lithium (Bonson and Murphy, 1995), selective serotonin reuptake inhibitors (SSRIs; Bonson, Buckholtz, and Murphy, 1996; Fiorella, Helsley, Rabin, and Winter, 1996; Strassman, 1992), antipsychotics (Vollenweider et al., 1998), and supplements affecting

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serotonergic function (Johnson *et al.*, 2008). It is noteworthy, that a recent investigation with healthy subjects into SSRI pretreatment before psilocybin administration has found significant acute reductions in anxiety, adverse cardiovascular effects, and other adverse effects for SSRI pretreatment compared with placebo pretreatment (Becker *et al.*, 2021). Meanwhile, pooled data from four phase 2 trials suggest that recent exposure to SSRIs may reduce the treatment response to MDMA for people suffering from PTSD (Feduccia *et al.*, 2021). However, these effects were not replicated in a recent phase 3 study (Mitchell *et al.*, 2021). Inclusion criteria regarding psychopharmacological pre- or supplementary treatment might thus be extended in the future. Recreational use of psychoactive substances – even if the risk for cross-reactions may be negligible in some cases – is usually discouraged for a certain period before the start of therapy (Mithoefer, 2017). Those at risk of hospitalization, who are significantly under- or overweight, with evidence of a history of cardiac disease or severe liver disease, or signs of hypo- or hypertension are usually excluded from treatment (Johnson *et al.*, 2008; Mithoefer, 2017; Sessa, Higbed, and Nutt, 2019).

It was suggested that the outcome of SAPT may be dependent on the personality structure of the client (Sandison and Whitelaw, 1957; Cohen, 1960; Gucker, 1963). Clients with suicidal ideation, mania, personality disorders, or disorders (or family history of disorders) on the psychotic spectrum (i.e., schizophrenia or bipolar disorder) are usually excluded from treatment (Johnson *et al.*, 2008; Mithoefer, 2017; Sessa, Higbed, and Nutt, 2019). Therefore, psychiatric interviews (First, 2015), commonly the Structured Clinical Interview For DSM-IV (Gorgens, 2011) and the Mini-International Neuropsychiatric Interview (Sheehan *et al.*, 1998), are used during screening (see Appendix B). In the future, personality assessments like the Personality Inventory for DSM-5 (Krueger *et al.*, 2012) may be recommended as additional tools to better predict a client's suitability for SAPT.

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Set and Setting

The consideration of context of the psychedelic experience became popular in the West during the first period of psychedelic research in the 1950s and 1960s. Though not initially termed by Timothy Leary (Zinberg, 1984), but popularized by him (Leary, 1961; Leary, Litwin and Metzner, 1963), psychological and environmental influences on the psychedelic experience were referred to as 'set' and 'setting', respectively (Hartogsohn, 2016, 2017a). The set and setting hypothesis suggests that the effects of psychedelics are mediated by the pre-existing mental *set* of the person taking the substance, including conscious and unconscious parts of the client like their expectations about the experience and the therapist, intentions, beliefs, preparations, motivation, personality, hopes, fears, potential pathologies, attitude towards the therapeutic (or often research) setting, the substance, relationship with the therapists, and potential cultural attributions to the substances, and the environmental *setting*, including cultural, social, constitutional, and actual physical environment surrounding the substance experience (Hartogsohn, 2015; Sloshower, Guss and Krause, 2020). Thereby, Sloshower, Guss and Krause (2020) stress that the relationship between client and therapists is a 'primary aspect of the setting' (p. 14). Each therapist thus contributes a personal and unique combination of perspectives and training to the therapeutic setting. The therapists' roles and prerequisites will be outlined below.

The importance of set and setting for the quality of the psychedelic experience was suggested early on in the first wave of psychedelic research (Hofmann, 2009; Leary, 1961; Leary et al., 1963) and has thus influenced considerations for recent research (Carhart-Harris, Roseman, *et al.*, 2018; Hartogsohn, 2015, 2016, 2017; Roseman *et al.*, 2018). Strassman (1995) argued that the 'set' of the research team should be considered, as well. This includes type and amount of training in psychotherapy and experience in working with respective pathologies, the theoretical model the research is based on and expectations relating to the outcome, mechanism of action, and/or the effect of the substances. Eisner (1997) expanded

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the concept of set and setting to include a third element – the *matrix*: the environment from which an individual comes, the environment the individual is living in during the time of therapy, and the environment the individual returns to. Ideally, these environments are supportive and nurturing. If this is not the case, therapeutic changes may not be integrated well into everyday life or it may lead to an exacerbation of the difficulties that led to the need for treatment in the first instance.

Extra-pharmacological parameters such as, subjects' traits (biological or psychological) and pre-states (e.g., assumptions, expectations, and anxiety) and, dosage, environmental factors, and their interaction with a substance's specific pharmacology, are proposed to be impossible to eliminate from the psychedelic experience (Carhart-Harris and Nutt, 2017). Some of the effects of these substances may even be amplified by or dependent on contextual influences and their therapeutic effects may be more pronounced when taken within a (psychologically) supportive context (Carhart-Harris, Bolstridge, *et al.*, 2018; Carhart-Harris and Nutt, 2017; Haijen *et al.*, 2018; Hartogsohn, 2016; Vizeli and Liechti, 2017). This contextual influence is exemplified within earlier psychotomimetic and psychotherapeutic studies with psychedelics (mostly LSD) in the 1950s, which rendered varying and sometimes contradicting results. Accounts of substance users (see McElrath and McEvoy, 2002; Shewan, Dalgarno, and Reith, 2000) suggest this may be partly explained by the different consideration of contextual factors (Hartogsohn, 2016). Outcomes (i.e., long-term wellbeing; Carhart-Harris, Roseman, *et al.*, 2018) within modern clinical trials may therefore be influenced by whether contextual factors are favorable or whether these factors are intentionally neglected or manipulated in a negative regard (see Ludwig, Levine, Stark, and Lazar, 1969; Oram, 2014). Examples include LSD administration without preparation, psychotherapy or participants knowing which substance was administered to them (Smart *et al.*, 1966; Hollister, Shelton and Krieger, 1969), as well as the infamous MK-Ultra experiments by the CIA investigating LSD's potential for mind control in often uninitiated

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subjects (Linville, 2016).

While the centrality of set and setting to the entirety of the substance experience has long been suggested (Carhart-Harris, Roseman, *et al.*, 2018; Sessa et al., 2019), Haijen et al. (2018) recently found significant associations between set and setting and the quality of the psychedelic experience. Reports of being comfortable in the setting and with the people present during the experience were linked to higher long-term well-being scores (i.e., rating of the setting was positively associated with scores on the Warwick-Edinburgh Mental Wellbeing Scale; Tennant et al., 2007). Clients reported increased feelings of security and safety linked to the controlled setting encountered in MDMA-assisted therapy sessions (Vizeli and Liechti, 2017). Some therapists have stated that, to them, set and setting seem more important for positive therapeutic effects than the psychopharmacological effects of the substances that are given as adjunct to therapy (Greer and Tolbert, 1998; Metzner and Adamson, 2001). Although there is evidence that long-term effects of psychedelics are predicted by the quality of the acute experience (Roseman, Nutt and Carhart-Harris, 2018), the assumed relationship between psychedelics and context has not yet been investigated by means of rigorous research (Carhart-Harris, Roseman, *et al.*, 2018; Hartogsohn, 2016, 2017). Further details regarding preparation of set and setting that have been retrieved from the literature and all recent clinical trials are included below.

Contextual preparation

The preparation of an adequate environment for the administration of substances is essential. Preparation sessions may take place in the same facilities as administration sessions (Johnson *et al.*, 2008; Watts, 2021). An aesthetically pleasant surrounding – often a living room-like, calm, and informal setting with comfortable furniture – may decrease that client's acute psychological distress during the substance-assisted session (Bogenschutz and Forcehimes, 2017; Johnson et al., 2008; Mithoefer, 2017; Twemlow and Bowen, 1979). In

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contrast, clinical-, hospital-, or entirely unprepared and uncontrolled settings may foster anxious and adverse reactions in clients (Strassman, 1984, 2001; Bogenschutz and Ross, 2018). All recent clinical studies ($k = 24$) took place in a controlled clinical setting (see Appendix B). The environment is usually designed to avoid potentially dangerous, sharp, and disruptive objects or events (such as telephone calls), plus providing a separate bathroom, and secure windows and exits so clients may not leave the premises unsupervised (Johnson *et al.*, 2008). Contemporary clinical studies commonly take place in a hospital, where clients are encouraged to lie down on a comfortable sofa or bed that has been prepared for them (Johnson *et al.*, 2008; Mithoefer, 2017), while the therapists are usually seated nearby on comfortable furniture (Garcia-Romeu and Richards, 2018). It is suggested, that therapists actively participate in creating a suitable environment in which they can comfortably conduct therapeutic sessions (Sloshower, Guss and Krause, 2020).

Music – most often delivered through headphones – has been a consistent feature (Barrett, Preller and Kaelen, 2018) and method for guidance and support (Bonny and Pahnke, 1972; Eisner and Cohen, 1958) across different models of SAPT with potential influences on the psychoactive experience itself and the therapeutic outcome (Kaelen *et al.*, 2015; Kaelen *et al.*, 2016, 2018; Preller *et al.*, 2017; Swift *et al.*, 2017; Watts *et al.*, 2017). It was suggested by Kaelen et al. (2018) that optimal music may personalize the experience and foster the expression of meaningful therapeutic content. Some modern investigations use curated playlists (e.g., Palhano-Fontes *et al.*, 2019; Sloshower, Guss and Krause, 2020; Davis *et al.*, 2021) and other encourage participants to adjust the playlist to their likings (e.g., Carhart-Harris *et al.*, 2021; Watts, 2021). Best practice may involve the playlist being composed in collaboration with the client in the preparatory sessions.

In earlier therapeutic research, extra-pharmacological manipulations like mirrors, photographs, flowers, lighting, artworks, and even naturalistic settings, were offered to clients (Bonny and Pahnke, 1972; Eisner, 1997; Eisner, 1964; Fadiman, 2011; Richards, 2017; Walsh

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and Grob, 2006). In most recent clinical trials, these manipulations have been avoided to foster controlled conditions. In recent trials, eyeshades are frequently provided to direct the experience inwards and shield from environmental distractions (Garcia-Romeu and Richards, 2018; Sessa, Higbed and Nutt, 2019).

Recently, it has been proposed to harness potential synergistic effects between psychedelic administration and nature contact and to include natural setting in the preparation for psychedelic experiences. Thereby, horticultural exercises and Shinrin-Yoku (i.e., forest bathing) may be included in the preparation session to foster connectedness (Gandy *et al.*, 2020). This has not been implemented in modern clinical trials thus far.

Future research should aim to investigate the influence of these contextual variations on the psychedelic experience. Adapting contextual variables to individual needs or certain pathologies might produce synergistic therapeutic effects.

Physiological preparation

The physiological effects of various classes of substances that may be used in SAPT are detailed by Garcia-Romeu et al. (2016). Most substances affect pulse and blood pressure, potentially excluding clients with cardiac and other conditions, and those with poor general health (e.g., severely under- or overweight participants) from treatment (Johnson *et al.,* 2008). A physician should be present or close-by to measure vital signals and they should be able to provide Basic Cardiac Life Support (BCLS) and Advanced Cardiac Life Support (ACLS) while antihypertensive, anxiolytic, and antipsychotic medication may be used in cases of extreme anxiety and adverse reactions (Strassman, 1984; Johnson *et al.,* 2008; Bogenschutz and Forcehimes, 2017; Mithoefer, 2017; Sloshower, Guss and Krause, 2020). Clients may be transferred to a close-by emergency department as a last resort or in case of medical emergency (Grinspoon and Bakalar, 1979; Johnson *et al.*, 2008; McCabe, 1977). The

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discussion of precautionary measures with the client during preparatory session(s) is a standard procedure in modern clinical trials.

Psychological preparation

The length of the preparatory stage is dependent on the therapeutic framework that is applied. First-wave research evidenced great variability in the amount of psychological preparation before substance-assisted sessions, ranging from no preparation (Hollister, Shelton and Krieger, 1969) to meticulously structured procedures (Kurland *et al.*, 1967) that show strong similarities to recent protocols (Johnson *et al.,* 2008; Sloshower, Guss and Krause, 2020; Watts, 2021). Across all retrieved sources that offered information about the numbers of sessions ($k = 28$), usually two ($k = 8$) to three ($k = 11$) of the four to 23 total sessions were dedicated to preparation (see Appendix A). Recent models usually include between one to four preparatory therapy sessions (Garcia-Romeu and Richards, 2018). It was suggested that more extensive preparation can contribute to more profound or intense therapeutic processes during the administration stage (Whitfield, 2021). This hypothesis has not been investigated by rigorous studies thus far.

Generally, it is recommended that substances be only used as adjuncts to therapy, after both therapist and client are convinced of the client's capacities and readiness to handle and surrender to the intensity of the experience (Eisner, 1964, 1997; Weinreich, 2006). In modern trials, life events and relationship issues, like death of loved ones, physical illnesses, or break-ups are monitored throughout the preparatory stage. If their impact on the client's mood is sufficiently destabilizing, decisions to postpone a substance-assisted therapy session are made on an individual basis, in the best interest of the client (Garcia-Romeu and Richards, 2018). Clients receive psychoeducation regarding common effects of the respective substance (side-effects, risks, and acute and long-term psychological effects plus potential implications of treatment with these substances), are familiarized with the therapeutic approach (Sloshower,

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Guss and Krause, 2020), and the therapeutic target are usually discussed with the client prior to the substance-assisted session (i.e., intention setting; Garcia-Romeu and Richards, 2018; Johnson *et al.*, 2008). Psychoeducation, in particular, is an important element in nearly all recent clinical investigations and explicitly included in preparation sessions in 15 of the 24 clinical trials (see Appendix B). The opportunity for clients to ask questions is vital to foster a sense of security and ample time is usually spent on that process (Sloshower, Guss and Krause, 2020; Watts, 2021). Some therapists have preferred to use analogies to outline the experience to their clients. An example for this stems from Stolaroff, 2004 p.62:

Imagine that you're on a stage, a very large stage, a round stage, circular. You're standing in the center of the stage. Around this stage is a huge curtain, very, very high and it's closed and where the curtain comes together there's about say three feet of space, of an opening. You're standing in the middle of that stage and you're looking out through that opening. Everything you see is the totality of your experience of yourself. What happens on a trip is by some mysterious means the curtain very gradually is pulled back. Very gradually. It's pulled back until it's pulled all the way around the back and you're given the opportunity to see everything that's been there all the time but you couldn't see it before because there was a curtain. All the different levels of experience that it's possible to have, you have. All the different truths, all the different things, you have. You experience it. Then, as you start to come down, very gradually the curtain gets pulled back around until you're all the way down. When you're all the way down, the difference is that before, you had about three feet of space that was open to look through. You now have about fifteen feet of space. You have really expanded your awareness, which is what they call these materials, awareness-expanders.

Thereby, the potential for heightened suggestibility (Carhart-Harris *et al.*, 2015) induced by some substances should be considered: how the experience is prepared will likely influence the experience itself and subsequent integration (Sessa *et al.*, 2019). The expectations and

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desires of clients regarding the effects of this therapeutic approach should be managed and discussed adequately (see e.g., Danforth, 2009). Expectation management is part of most, but not all modern clinical trials. It should be stressed that the experience itself may not be curative per se but rather be beneficial if it can be properly integrated into everyday life (Eisner, 1997; Sloshower, Guss and Krause, 2020) – encouragement of positive expectancies and intentions may, however, affect the therapeutic outcome positively (Bogenschutz and Forcehimes, 2017). This supports the notion that there is an inextricable connection between the content of preparation, administration, and integration sessions. The content of preparation and administration sessions likely feeds back into integration sessions and vice versa. Therefore, recent models usually include multiple administration sessions separated by respective preparation and integration (Mithoefer, 2017; Sloshower, Guss and Krause, 2020; Watts, 2021). Although, preliminary results seem promising, SAPT may not be beneficial to everyone and it is conceivable that in some people the severity of symptoms may not change, or their condition may even worsen. Therefore, proper psycho-social support can be essential (Sessa *et al.*, 2019) and social support following a dosing session should be prepared beforehand (Sloshower, Guss and Krause, 2020; Spriggs *et al.*, 2021). Despite these reference to the importance of social support, it is not considered a standard in modern trials. Further, the client's expectancy may be assessed using the Stanford Expectations of Treatment Scale (Younger *et al.*, 2012). This data can be helpful for evidence-based expectancy management as well as to control for potential salient effects on the therapeutic outcome in clinical trials (Gukasyan and Nayak, 2021).

Further content of preparation sessions may vary depending on the substance, therapeutic approach, and the therapeutic target(s) (for a review see Thal *et al.*, 2021) and can include, amongst others, motivational-behavioral approaches tailored for substance use treatment (Bogenschutz *et al.*, 2015), third wave cognitive-behavioral approaches like acceptance and commitment therapy tailored for treatment of depression (Sloshower *et al.*,

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2020), and humanistic approaches such as logotherapy (Ross *et al.*, 2016). Preparatory sessions should explore the potential for a positive therapeutic relationship and an intimate connection between client and therapist and might touch on topics like the client's personal history, individual growth, psychological training and workshops they participated in and what readings they have done, their accomplishments, intentions, major life events, interpersonal relationships, worldviews, but also complaints, taboo subjects, and perceptions of inadequacies (Adamson and Metzner, 1988; Greer and Tolbert, 1998; Stolaroff, 2004; Fadiman, 2011; Garcia-Romeu and Richards, 2018; Sloshower, Guss and Krause, 2020; Watts, 2021). Thereby, the establishment of trust and rapport is vital (Bogenschutz and Forcehimes, 2017; Garcia-Romeu and Richards, 2018; Sloshower, Guss and Krause, 2020; Watts, 2021).

Although precautionary measures and procedures for the administration session are usually extensively discussed with the client, it should be emphasized that the content of the experience and the outcome are unpredictable (Watts, 2021). Clients should be given guidance and tools assisting them to handle difficult or challenging experiences and facilitating surrender to and trust into the substances' effects and the subsequent experience. Thereby, clients should be encouraged to approach rather than resist disturbing imagery and thoughts, to actively inquire about the purpose and meaning of these visions by moving toward the problem, and to subjectively allow oneself to give in to extremely convincing sensations (such as melting, exploding, and dissolving) and physical symptoms and psychosomatic discomforts (such as nausea) that may occur (Blewett and Chwelos, 1959; Masters and Houston, 1966; McCabe, 1977; Eisner, 1997; Johnson *et al.,* 2008; Watts and Luoma, 2020; Wolff *et al.*, 2020; Tai *et al.*, 2021; Watts, 2021). While there is evidence to suggest that challenging experiences mediate the therapeutic outcome (Carbonaro *et al.*, 2016; Roseman, Nutt and Carhart-Harris, 2018; Romeo *et al.*, 2021) and people report having benefitted from challenging experiences (Carbonaro *et al.*, 2016), it was proposed that it is not

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the kind of the experience (e.g., challenging or mysticomimetic) but whether or not the client relates to the experience with a continued awareness of self-perspective and function, that may mediate therapeutic outcome (Whitfield, 2021).

Usually, potential support and interventions for difficult parts of the sessions are extensively discussed with clients during preparation sessions. A pre-existing action plan can alleviate anxiety in clients (Garcia-Romeu, Kersgaard and Addy, 2016). Therapists may try to relate to and reveal the healthy core of the client's personality (Grof, 1980). Trust in one's inner healing intelligence (i.e., one's sophisticated and spontaneous innate ability to heal and grow; see Mithoefer, 2017), one's mind, or the deep unconscious and everyone's deep positive potential ~~should be~~is often encouraged in both clients and therapists (Grof, 1980; Eisner, 1997; Greer and Tolbert, 1998; Stolaroff, 2004; Mithoefer, 2017; Watts, 2021). Likewise, clients are reassured that they can trust the therapeutic team (Watts, 2021). Important predictors for the quality of the experience might be clear intentions (Adamson and Metzner, 1988; Haijen *et al.*, 2018), trait anxiety and neuroticism (Haijen *et al.*, 2018; Studerus *et al.*, 2021), openness to novel experiences (Studerus *et al.*, 2021), mood and excitability before the experience (Studerus *et al.*, 2012), and the ability to surrender oneself to the experience (Eisner, 1964). A more in-depth discussion of techniques that may help clients to handle the acute effects of these substances will be outlined in a subsequent article.

In addition, the client's attitude towards psychoactive substances and motivation for SAPT could be assessed to prevent individuals entering treatment to overcome reluctance against regular psychotherapy by chemical means, as has been described by Hausner and Dolezal (1963), or because they idealize SAPT and see it as their last hope (Sloshower, Guss and Krause, 2020). In regular therapy, a lack of motivation for change is negatively associated with treatment outcomes (see e.g., Ryan *et al.*, 2011). Individual reasons for the resistance against regular therapy – and thus resistance in general – may thus be explored as part of the preparation. On the other hand, idealization of substance-assisted treatments from either the

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client or the therapists may obstruct genuine interactions between client and therapists and bias outcome measures (Sloshower, Guss and Krause, 2020).

Therapeutic stance

Most contemporary clinical trials employ a mixed-gender co-therapist team throughout all stages of the therapeutic process (Bogenschutz and Forcehimes, 2017; Garcia-Romeu and Richards, 2018; Johnson *et al.*, 2008; Mithoefer, 2017). There are exceptions with no considerations of gender specifications of the therapists (see Wagner *et al.*, 2019). Roles and responsibilities for different aspects of the therapy can be divided between the therapists and, as was reported in first-wave psychedelic research, some sessions have been conducted by a single highly experienced therapist (Grof and Halifax, 1977; Grof, 1980; Kurland, 1985; Eisner, 1997; Johnson *et al.,* 2008; Bogenschutz and Forcehimes, 2017; Watts, 2021). While the economic feasibility of having both therapists present at all times is yet to be established and tested on a larger scale, there are potential pragmatic and safety advantages to the co-therapist model. Due to the extraordinary length of substance-assisted sessions (between 6-48 hours depending on the substance, dose, and route of administration – with Dimethyltryptamine, a tryptamine regarded as classic psychedelic, ~~DMT~~ being an exception due to the much shorter effect time of this substance), a co-therapist approach can prevent exhaustion in therapists and allows brief breaks without having to leave the client alone (Garcia-Romeu and Richards, 2018; Johnson *et al.*, 2008). A mixed-gender team can enhance feelings of safety, support, rapport, presence and bonding, and, from a psychoanalytical perspective, facilitates the occurrence of parental transference and countertransference (Bogenschutz and Forcehimes, 2017; Garcia-Romeu and Richards, 2018). Further, if responsibilities were divided between two therapists, each therapist would only need to be an expert in their specific domain (Bogenschutz and Forcehimes, 2017).

Other facilitators or substitutes who may be present during the substance-assisted

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session (e.g., nurses, receptionist, or security personal) are usually known to the clients and are introduced to them prior to administration sessions (Johnson *et al.*, 2008) – this contributes to the client's sense of security, as every instance of contact may influence the experience and the early establishment of trusting rapport is vital (Sloshower, Guss and Krause, 2020; Cosimano, 2021). It is generally recommended that all involved should be responsible, supportive, and mature professionals who are familiar with the effects of the substances that are given in therapy, and be attentive to the potential needs of the clients (Bogenschutz, 2013; Bogenschutz and Forcehimes, 2017;; Eisner, 1997; Garcia-Romeu and Richards, 2018).

Therapist's roles and training

The roles of the therapists during the substance-assisted sessions should be adapted to the needs and personality structure of the clients and can change between and also during sessions (Buckman, 1967; Martin, 1964). Generally, a non-critical, supportive, and encouraging role was advised across sources (Spencer, 1963; Mithoefer, 2017; Watts and Luoma, 2020). Therapists may be described as 'trusted supporters' who witness the clients' therapeutic processes and offer unconditional positive regard (Carhart-Harris *et al.*, 2021; Watts, 2021; c. f., Rogers, 1949). In addition, the therapists can take the role of a 'facilitator of self-transcendence', an 'empathetic listener', and/or a 'trustworthy guide' (Sloshower, Guss and Krause, 2020). The therapist can be explicitly or implicitly expected to engage in roles other than those traditionally expected from a counsellor or mental health treatment provider, for instance, as teacher, healer, and spiritual companion. In order to avoid a blending of too many roles, reassessment and clarification of the therapist's role(s) throughout the therapeutic process is vital (Jungaberle, Gasser, Weinhold, and Verres, 2008).

As mentioned above, formal training and perspectives of the therapists, including their identity as a therapist, experience in the treatment of certain disorders, personal history with

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psychological disorders, personal experience with psychedelics, transferences toward and expectations about the outcome of the therapy, transferences between therapists, and transferences between disciplines and the psychedelic community, likely influence their encounters with the clients. Therapists are thus encouraged to be mindful of how their experiences affect their emotional presence during the therapeutic encounters with clients (Sloshower, Guss and Krause, 2020).

Some authors believe that authentic empathy and respect can be more important than formal qualifications and degrees (Johnson *et al.,* 2008). In recent clinical investigations, the majority of lead therapists are fully-trained clinical psychologists, psychiatrists, or clinical social workers while co-therapists may have different (but mental health related) professional backgrounds and might gain their clinical training during their time as a co-therapist (Johnson *et al.,* 2008; Phelps, 2019; Tai *et al.*, 2021; Watts, 2021). Formal training is imperative and various training programs are currently being or have been developed and implemented by multiple organizations (e.g., the Multidisciplinary Association for Psychedelic Studies, Swiss Medical Association for Psycholytic Therapy, the California Institute of Integral Studies, Usona Institute, Innate Path, the MIND Foundation, and COMPASS Pathways). The content of these training programs is beyond the scope of this article (for more information see e.g., Tai *et al.*, 2021).

Therapist's core competencies

While different therapeutic modalities have been outlined elsewhere (Thal *et al.*, 2021), the purpose of this section is to depict therapist competencies described in the literature that go beyond therapeutic orientations. In a recent article, Phelps (2017) outlined six core-competencies for therapists working with substances as adjuncts for therapy: Empathetic abiding presence, trust enhancement, spiritual intelligence, knowledge of the physical and psychological effects of psychedelics, therapist self-awareness and ethical

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integrity, and proficiency in complementary techniques.

Empathetic abiding presence incorporates the concept of empathy introduced into psychotherapy by humanistic scholars (Rogers, 1957) and elements of therapeutic presence (Geller and Greenberg, 2002) outlined below. Thereby, empathy refers to the capability and willingness of the therapist to comprehend the perspective of the client and communicate that to them (Rogers, 1949). Empathetic and present listening, as well as the therapists' natural comfort of being with clients has more impact than other interventions (Stolaroff, 2004; Walsh and Grob, 2006; Richards, 2009; Horton, Morrison and Schmidt, 2021) and therapists should have a sense of how and when to share useful ideas and concepts with the client (Fadiman, 2011).

Trust enhancement comprises of three areas: trust in the client's inner healing capabilities (similar to self-actualizing tendency; Rogers, 1959), the therapist's trustworthiness as a practitioner (also called epistemic trust; Fonagy and Allison, 2014), and trust in the psychotherapeutic process (see the 'predictable process'; Rogers, 1946). Trust in these areas is fostered by the therapist's functioning as a role-model, particularly by embodying trust in the therapeutic process through an open and welcoming attitude for the entire range of potential experiences (Grof, 1980; Lennard and Hewitt, 1960; Richards, Grof, Goodman, and Kurland, 1972). It is important to enhance the client's trust and confidence in their unfolding inner healing process which may be facilitated by optimizing set and setting variables (Phelps, 2017). Möckel Graber (2010) argues that the trust framework can be further enhanced through self-disclosure and self-transparency. In doing so, therapists adopt a role-model function. The therapist's ability to show themselves with their weaknesses, imperfections, and peculiarities creates a more open atmosphere.

Spiritual intelligence is associated with a certain familiarity with altered states of consciousness with mystical- (King and Decicco, 2009) and existential meaning making (Emmons, 2003; Moss and Dobson, 2006) qualities and their implications for therapy

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(Johnson *et al.*, 2008; Passie, 2012; Richards, 2014). Fadiman (2011), in this regard, emphasizes the usefulness of a basic knowledge of various spiritual traditions. This may also extend to indigenous beliefs. Generally, a cultural-sensitive and accepting attitude might be recommended. Future research should further investigate similarities between spiritual beliefs and psychedelic experiences and therapists should be well-informed in this regard.

Knowledge of the physical and psychological effects of psychedelics includes theoretical and experiential knowledge of the global and cross-cultural use of psychoactive substances (Bravo and Grob, 1989; Dobkin de Rios, 2009; Metzner, 1998; Smith *et al.*, 2004), and the physiology, pharmacology, neurobiology, neuropharmacology, and interactions of the substances used as adjuncts for therapy (Bogenschutz, 2013; Fadiman, 2011; Nichols, 2004; Pahnke and Richards, 1966; Walsh and Grob, 2006). In addition, knowledge of the range of effects relative to the dose and substance employed is crucial (Stolaroff, 2004; Fadiman, 2011; Metzner, 2015).

Therapist self-awareness and ethical integrity includes self-awareness of personal motives, self-care, analysis of transference and counter-transference processes, integrity in protecting boundaries, capacities for building and fostering therapeutic relationships, and competences in attachment theories (Hausner and Dolezal, 1963; Phelps, 2017). Reflection on interpersonal processes (Grof, 1968; Sherwood et al., 1968; Strassman, 2001), continuation of the therapist's own inner work or personal therapy, and regular debriefings with the therapeutic team (Mithoefer, 2017), preferably in close collaboration with a clinical supervisor (Bogenschutz, 2013; Phelps, 2017; Tai *et al.*, 2021), are crucial to process the content of the sessions and avoid compassion fatigue (Eisner and Cohen, 1958; Smith, 1988).

Finally, *proficiency in complementary techniques* refers to additional therapeutic skills and techniques that may be applied in SAPT. The literature has identified a range of complementary techniques, including Holotropic Breathwork (Grof and Grof, 2010), therapeutic body work (Eisner and Cohen, 1958; Johnson, Richards and Griffiths, 2008;

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Danforth, 2009; Mithoefer, 2017), eye-gazing (Eisner and Cohen, 1958; Grof, 1968), guided affective imagery (Bonny and Pahnke, 1972), meditation (Griffiths *et al.*, 2018; Smigielski *et al.*, 2019), logotherapy, existential, and narrative therapy (Ross *et al.*, 2016), family-oriented techniques and systemic approaches (Stolaroff, 2004; Mithoefer, 2017), shadow work (Grof, 1980), and hakomi and gestalt (Mithoefer, 2017). In addition, therapists should be knowledgeable in developmental theories as sessions often revolve around regression and current and past biographic and developmental challenges (Phelps, 2017).

Therapist's characteristics and attitude

Since the beginning of research into SAPT various essential qualities of therapists have been highlighted. These include appropriate compassion, congruence, patience, honesty, empathy, authenticity, integrity, transparence, self-love, intuition, sensitivity, patience, presence, open-mindedness and openness for the client, themselves, and the therapeutic process, forgiveness, acceptance, peace, relaxation, and loving-kindness (Eisner, 1997; Fadiman, 2011; Garcia-Romeu and Richards, 2018; Grof, 1980; Holland, 2001; Jungaberle *et al.*, 2008; Möckel Graber, 2010; Spencer, 1964; Tai *et al.,* 2021). Moreover, therapists should use an appropriate amount of responsiveness and sensitivity to whatever spontaneously arises in the substance-assisted therapeutic process, such as swift and sudden shifts in the mental state of the client (Fadiman, 2011). Thus, considerable clinical experience and a demonstrated ability to care for people experiencing severe psychological distress are skills likely to facilitate the maintenance of a calm and reassuring presence during SAPT sessions (Tai *et al.*, 2021).

The substance-assisted therapist is encouraged to foster a sense of safety for the client, so they are able to let go of their usual defenses and surrender to the experience. Yet hostile, aggressive, and overtly sexual reactions of clients are possible, and the therapist must be able to deal with extreme situations (Grof, 1980; Noorani, Garcia-Romeu, Swift, Griffiths, and

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Johnson, 2018). Personal security, the degree of human and professional interest emitted by the therapist, clinical and therapeutic skill, freedom from anxiety (Costello, 1964), the therapist's current mental and physical condition, and the absence of the need to demonstrate power and authority may determine the success of the substance-assisted session. Thereby, it is recommended that the guidance of the therapist be based on their own intrinsic and universal set of values associated with healthy functioning (Grof, 1980). Having clear intentions for the therapy and being mindful of them may be equally important for therapists as for clients (Cosimano, 2021). For therapists, it may thus be helpful to reconsider and examine the motivation, attitude, hopes, and fears for both oneself and the client before the sessions. Even though it may be a natural tendency, it is recommended that therapists avoid (and be trained well to do so) intending or hoping for a specific outcome and for the client to agree with them on certain (often spiritual) issues of the experience (Fadiman, 2011; Grof, 1980). Therapists should be aware of the heightened potential for transference and countertransference situations and this should be discussed with the client (Grof, 1980). With the exception of potentially enhanced focus on spiritual aspects of therapy and increased transference and countertransference, it currently appears that these therapist characteristics do not necessarily differ from important therapist qualities in regular psychotherapy but rather constitute basic indicators of individuals who may be more suited to practicing SAPT.

Support in the initial phase of SAPT may enhance a client's confidence in the therapeutic process, which may translate to future sessions (i.e., during integration; Buckman, 1967). Further, an array of internal factors – such as self-awareness, a non-judgmental attitude towards the emerging processes and the content of the session, acceptance for disordered and delusional thoughts as well as highly emotional states, confidence in the ability to contain the entire continuum of potential reactions – are vital in relating the psychedelic experience into subsequent integration (Eisner, 1997; Nielson and Guss, 2018; Watts, 2021). During all encounters, a perception of excitement, personal commitment, and expectations of positive

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integration may be emanated by the therapist while the client may be viewed as unique and capable being rather than a helpless, incapable, and sick person in need of support (Twemlow and Bowen, 1979).

Adamson and Metzner (1988) recommend therapists adopt an integrative attitude in which they value healing of the body, psychological problem solving, and spiritual awareness as interrelated aspects of a unified process. The therapist should be self-contained while offering support and orientation. They should have healthy access to the feelings and moods of the client while being independent of their approval or rejection. They should be familiar with the topics and challenges potentially emerging in substance-assisted sessions and should have been exposed to these topics and challenges themselves, such as fear of death, insanity, and complete loss of self-control. This may, in turn, illicit emotional or psychosomatic reactions in the therapist and could disrupt their attention and ability to be present (Möckel Graber, 2010). This may be related to the perspective of integral psychotherapy, claiming that sound therapy is not a matter of the manualized application of certain techniques but a question of the development of the therapist's own self-consciousness (Weinreich, 2005). While there ~~is~~ are a variety of recommendations for therapist characteristics in the literature we retrieved, they are largely based on experiences and their influences on therapeutic outcomes have not been assessed in clinical studies to da~~y~~te (see Thal, Engel and Bright, 2022a; Thal, Engel and Bright, 2022b).

Establishment of a therapeutic relationship

As in traditional psychotherapy (Ardito and Rabellino, 2011; Lambert and Barley, 2001; Martin, Garske, and Katherine Davis, 2000), in SAPT (Weiss *et al.*, 1997) the therapeutic relationship, sometimes referred to as therapeutic alliance, has often been described as one of the most important factors for the success and positive treatment effects of SAPT (Savage, 1957; Cohen and Eisner, 1959; Spencer, 1963; Mechaneck *et al.*, 1968; Grof,

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1980; Greer and Tolbert, 1998; Garcia-Romeu and Richards, 2018; Horton, Morrison and Schmidt, 2021). The establishment of a well-functioning therapeutic relationship supporting the honest expressiveness of the client is one of the primary responsibilities of the therapist in the preparation sessions (Sloshower, Guss and Krause, 2020; Tai *et al.*, 2021). This may be extended to the significance of the therapist's readiness for permanent adjustment and development of themselves within the therapeutic relationship (Weinreich, 2005) and, in the case of a two-therapist team, also involve their relationship and mutual growth and development. Indeed, it was noted that by altering the relationship to the therapist, the client may learn to adapt other interpersonal relationships in more satisfying ways (Savage, 1957). Some authors note that instead of being treated, clients treat themselves through the use of substances as catalysts for mystical experiences or ego dissolution and their relationships to the therapists (Greer and Tolbert, 1998; Stolaroff, 2004). Thereby, emphasis can be put on one or the other depending on the client's needs and the therapeutic goals (Mechaneck *et al.*, 1968).

The establishment of a good therapeutic relationship before the first substance-assisted session can be essential (Masters and Houston, 1966; Kurland *et al.*, 1967; Grof, 1980; Johnson *et al.,* 2008; Watts, 2021). This relationship between client and therapists may be more egalitarian (and less top-down) than in traditional psychiatric settings (Carhart-Harris *et al.*, 2021b; Watts, 2021) and during the progression of the therapeutic process, it can be expected to intensify beyond the limits of conventional therapy (Grof, 1980; Hausner and Dolezal, 1963). Clients may be able to accurately tune in to the feelings of the therapist and thus be able to relate to the therapist's true dedication, concentration, or satisfaction with the therapeutic process (Grof, 1980). The preparation stage can last for more than a month and, in the case of the John Hopkins studies, is constituted of four personal meetings (i.e., eight contact hours; see Appendix B; Johnson et al., 2008). The current protocol for psilocybin for depression at Imperial College London, on the other hand, includes one entire day of

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preparation (subsequent to an extensive phone call) right before the day of the first administration session (Watts, 2021).

Some have suggested that the preparation stage should allow for therapist and client to get to know each other through a two-dimensional, mutual sharing of information (Greer and Tolbert, 1998; Grof, 1980). Thereby, therapeutic intention and presence can be initiated and developed while the screening and preparation of the client is conducted (Greer and Tolbert, 1998; Sloshower, Guss and Krause, 2020; Watts, 2021) and mutual trust, comfort, and rapport can be developed (Garcia-Romeu and Richards, 2018; Johnson *et al.*, 2008). Knowledge about the client's biography, worldview, motivation, and beliefs could aid the understanding of the intra- and interpersonal processes during the substance-assisted session(s).

At least one of the meetings may take place in the environment where the substance-assisted session(s) will be conducted and if more than one therapist will conduct the session(s), the client should have met each one before (Johnson *et al.*, 2008; Watts, 2021). As mentioned above, a person-centered approach (Rogers, 1949, 1957; Kirschenbaum, 2004) can be convenient to establish a sound therapeutic relationship in SAPT (Garcia-Romeu and Richards, 2018). By establishing an empathetic, congruent, authentic, and sincere relationship through self-disclosure and mindful interactions, the therapeutic alliance can be fostered (Burks and Robbins, 2012). Rigidity, aloofness, uncertainty, tension, and distraction should be avoided since these factors may have a negative effect on the therapeutic relationship (Ackerman and Hilsenroth, 2001). For trauma therapy it is recommended that the established relationship should differ fundamentally from trauma inducing situations and relationships. These should be replaced by support and acceptance (Spencer, 1963). This may allow for the client to experience the trauma in more favorable conditions allowing for unlearning and decoding (Hausner and Dolezal, 1963; Thal and Lommen, 2018). Ideally, the therapeutic relationship allows for anxiety to be tolerated without the need to establish further psychological defenses (Savage, 1957).

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Some authors have suggested that the therapeutic relationship may be enhanced through the administration of psychedelics (Grinspoon and Bakalar, 1979; Grinspoon and Doblin, 2001) and MDMA (Luoma *et al.*, 2021). On the other hand, the therapeutic relationship could rupture through the work with substances as adjuncts. This may be due to over expectancy on the side of the client, resulting in disappointment and the feeling of loneliness (Hausner and Dolezal, 1963). However, rigorous clinical investigations into expectancy effects and credibility effects is lacking (Garcia-Romeu and Richards, 2018; Gukasyan and Nayak, 2021). It was thus proposed that future research should measure aspects of the therapeutic relationship using instruments like the Working Alliance Inventory (Horvath and Greenberg, 1989; Gukasyan and Nayak, 2021).

Therapist's personal experience with substances

A controversial but, nevertheless, significant topic is the therapist's personal experience with the substances administered in SAPT. Among researchers and those currently working as therapists in SAPT clinical trials, there likely exists a continuum from those without any personal experiences to those with a vast amount of experience across substances and settings. Due to the current legal situation (whereby most of the classic compounds are internationally prohibited), open discussion of these experiences, for fear of personal, professional, and sometimes legal consequences, is constrained (Nielson and Guss, 2018). During the first wave of psychedelic research, researchers and clinicians regarded the personal direct experiences with these substances as valuable in order to function as a successful therapist (Blewett and Chwelos, 1959; Hausner and Dolezal, 1963; Kafka and Gaarder, 1964; Leary, Metzner and Alpert, 1964). A high proportion of the practitioners in the field still regard personal experiences with these substances as essential and advantageous (Metzner, 1998; Möckel Graber, 2010; Bogenschutz, 2013; Bogenschutz and Forcehimes, 2017), and some have even proclaimed it to be imperative in order to empathize with the

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client's experiences and exhibit more tolerance and acceptance towards them (Eisner, 1997; Grof, 1980; Stolaroff, 2004).

In some European countries, such as Switzerland, personal experience with psychedelics is required for therapists to work with clients in substance-assisted settings (Grof, 1980; Strassman, 2001) and in shamanistic and ceremonial settings first-hand experience is a central part of the facilitator training (Fernandez and Fernandez, 2001; Metzner, 1998; Thomas and Humphrey, 1996; Winkelman and Roberts, 2007). On the other hand, it is argued that personal experiences with these substances could impair therapists' and researchers' ethical conduct and scientific objectivity (Langlitz, 2012). For instance, having prior experiences with the substances used in the therapy may lead some therapists to become less curious about the client if they believe that their clients' experience will be similar to their own (Bogenschutz, 2013; Bogenschutz and Forcehimes, 2017). Thus, personal experience may be a potential confound to research and therapy that has not been empirically investigated yet (Nielson and Guss, 2018). First-hand experience with psychoactive substances and medications is of minor importance and an invalid source of information in contemporary psychiatry and pharmacology – even though it has played an essential role in the past (Passie and Brandt, 2018), whereas in psychotherapy self-experience is necessary and a respected and valid source of knowledge, understanding, and improvement (Norcross, Strausser-Kirtland and Missar, 1988; Nielson and Guss, 2018).

Self-experience in SAPT is controversial since it inhabits both pharmacological and psychotherapeutic elements (Nielson and Guss, 2018). There are avenues for therapists to legally partake in substance-induced experiences: for example the Multidisciplinary Association for Psychedelic Studies (MAPS), offers therapists' training in which trainees may take MDMA while being supervised by trained MDMA-therapists (Sessa, 2017). The Ayahuasca Foundation offers 4 – 8 week long training Ayahuasca training programs in locations where the use of the plant-mixture is legal (Ayahuasca Foundation, 2020). However,

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there is currently no legal self-experience provided to facilitators of psilocybin research (Bogenschutz and Forcehimes, 2017). There are several methods to induce comparable psychological states (see Schmidt and Berkemeyer, 2018) without the use of psychoactive substances, such as Holotropic Breathwork (Grof and Grof, 2010).

Conclusion

In this systematized review, we have outlined and critically discussed the therapeutic conduct and therapeutic stance during preparatory sessions in SAPT. While there is a general consensus in the literature that preparing clients before the administration session in SAPT is important, the extent and approaches for these sessions vary across different models (see Thal *et al.*, 2021). Usually, a therapeutic relationship and rapport are first established, during which time clients are educated about the effect of the substances, potential experiences, safety measures, and the therapeutic approach. Logistics, interpersonal boundaries, and intentions are also discussed. Appropriate preparation (and subsequent integration) of the administration session may reduce client's resistance and enhance the therapeutic effects of SAPT (Sloshower *et al.*, 2020; Watts and Luoma, 2020).

Although not necessarily different to important therapist qualities in regular psychotherapy empathy, non-directive support, therapeutic presence, integrity, responsiveness, intuition, knowledge and training, experience, and the ability to establish a sound therapeutic relationship likely constitute salient basic indicators of individuals who may be well-suited to practice SAPT. These therapists' factors should be developed and adapted throughout different stages of the therapeutic process to form a solid therapeutic stance. Their influences on treatment outcomes should be investigated in future studies. It is likely that the therapeutic framework the experience is embedded in, the screening tools that are used to determine eligibility and to assess the efficacy of the treatment, as well as the expectancy of both the client and the therapist team affect the outcome. Future studies should

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consider the influences of these factors, too.

It is worth noting that the majority of the suggestions identified in the review are mainly derived from the various authors' experience and assumptions. Further research that ~~is able to provide empirical grounding~~ empirically examines these assumptions is warranted. Much of the work informing therapeutic approaches today has been conducted in the first wave of psychedelic research. It is evident, that only a limited number of recent clinical investigations with SAPTs have offered ample (qualitative) descriptions about preparatory sessions. While the value of this early evidence is undisputed, the need for timelier and more rigorous qualitative and quantitative investigations assessing different approaches and techniques for the optimal preparation for clients in SAPT is obvious. As of today, it is impossible to make conclusive assumptions about the importance and influence of (different aspects of) ~~of~~ preparation sessions on therapeutic outcomes.

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References

Ackerman, S. J. and Hilsenroth, M. J. (2001) 'A review of therapist characteristics and techniques negatively impacting the therapeutic alliance', *Psychotherapy*. American Psychological Association Inc., pp. 171–185. doi: 10.1037/0033-3204.38.2.171.

Adamson, S. and Metzner, R. (1988) 'The nature of the MDMA experience and its role in healing, psychotherapy and spiritual practice', *ReVision*, 10(4), pp. 59–72.

Aday, J. S. *et al.* (2020) 'Long-term effects of psychedelic drugs: A systematic review', *Neuroscience and Biobehavioral Reviews*, 113(March), pp. 179–189. doi: 10.1016/j.neubiorev.2020.03.017.

Aixalá, M. *et al.* (2020) 'Patterns of use, desired effects, and mental health status of a sample of natural psychoactive drug users', *Drugs: Education, Prevention and Policy*. Taylor and Francis Ltd, 27(3), pp. 191–198. doi: 10.1080/09687637.2019.1611739.

Almond, K. and Allan, R. (2019) 'Incorporating MDMA as an Adjunct in Emotionally Focused Couples Therapy With Clients Impacted by Trauma or PTSD', *Family Journal*, 27(3), pp. 293–299. doi: 10.1177/1066480719852360.

Alper, K. R. (2001) 'Chapter 1 Ibogaine: A review', *Alkaloids: Chemistry and Biology*, pp. 1–38. doi: 10.1016/S0099-9598(01)56005-8.

American Psychiatric Association (1994) *Diagnostic and statistical manual of mental disorders (4th. ed.), DSM-IV*. Washington DC: APA.

American Psychiatric Association (2013) *Diagnostic and statistical manual of mental disorders (5th ed.)*. Washington.

Ardito, R. B. and Rabellino, D. (2011) 'Therapeutic Alliance and Outcome of Psychotherapy:

For Peer Review

Historical Excursus, Measurements, and Prospects for Research', *Frontiers in Psychology*, 2. doi: 10.3389/fpsyg.2011.00270.

Barrett, F. S., Preller, K. H. and Kaelen, M. (2018) 'Psychedelics and music: neuroscience and therapeutic implications', *International Review of Psychiatry*. Taylor and Francis Ltd, pp. 350–362. doi: 10.1080/09540261.2018.1484342.

Becker, A. M. *et al.* (2021) 'Acute Effects of Psilocybin After Escitalopram or Placebo Pretreatment in a Randomized, Double-Blind, Placebo-Controlled, Crossover Study in Healthy Subjects', *Clinical Pharmacology & Therapeutics*. John Wiley & Sons, Ltd. doi: 10.1002/CPT.2487.

Bender, D. and Hellerstein, D. J. (2022) 'Assessing the risk–benefit profile of classical psychedelics: a clinical review of second-wave psychedelic research', *Psychopharmacology*. Springer Science and Business Media Deutschland GmbH, 1, pp. 1–26. doi: 10.1007/S00213-021-06049-6/TABLES/2.

Blewett, D. B. and Chwelos, N. (1959) *Handbook for the Therapeutic Use of Lysergic Acid Diethylamide-25: Individual and Group Procedures*. Available at: https://maps.org/research-archive/ritesofpassage/lsdhandbook.pdf (Accessed: 13 December 2019).

Bogenschutz, M. P. (2013) 'Studying the effects of classic hallucinogens in the treatment of alcoholism: rationale, methodology, and current research with psilocybin.', *Current drug abuse reviews*, 6(1), pp. 17–29. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23627783.

Bogenschutz, M. P. *et al.* (2015) 'Psilocybin-assisted treatment for alcohol dependence: A proof-of-concept study', *Journal of Psychopharmacology*, 29(3), pp. 289–299. doi: 10.1177/0269881114565144.

For Peer Review

Bogenschutz, M. P. *et al.* (2018) 'Clinical Interpretations of Patient Experience in a Trial of Psilocybin-Assisted Psychotherapy for Alcohol Use Disorder', 9(February), pp. 1–7. doi: 10.3389/fphar.2018.00100.

Bogenschutz, M. P. and Forcehimes, A. A. (2017) 'Development of a Psychotherapeutic Model for Psilocybin-Assisted Treatment of Alcoholism', *Journal of Humanistic Psychology*, 57(4), pp. 389–414. doi: 10.1177/0022167816673493.

Bogenschutz, M. P. and Ross, S. (2018) 'Therapeutic applications of classic hallucinogens', in *Current Topics in Behavioral Neurosciences*. Springer Verlag, pp. 361–391. doi: 10.1007/7854_2016_464.

Bonny, H. L. and Pahnke, W. N. (1972) 'The Use of Music in Psychedelic (LSD) Psychotherapy', *Journal of Music Therapy*, 9(2), pp. 64–87. doi: 10.1093/jmt/9.2.64.

Bonson, K. R., Buckholtz, J. W. and Murphy, D. L. (1996) 'Chronic administration of serotonergic antidepressants attenuates the subjective effects of LSD in humans', *Neuropsychopharmacology*. Nature Publishing Group, 14(6), pp. 425–436. doi: 10.1016/0893-133X(95)00145-4.

Bonson, K. R. and Murphy, D. L. (1995) 'Alterations in responses to LSD in humans associated with chronic administration of tricyclic antidepressants, monoamine oxidase inhibitors or lithium', *Behavioural Brain Research*, 73(1–2), pp. 229–233. doi: 10.1016/0166-4328(96)00102-7.

Bravo, G. and Grob, C. (1989) 'Shamans, sacraments, and psychiatrists', *Journal of Psychoactive Drugs*, 21(1), pp. 123–128. doi: 10.1080/02791072.1989.10472149.

Buckman, J. (1967) 'THEORETICAL ASPECTS OF L.S.D. THERAPY', *International Journal of Social Psychiatry*, 13(2), pp. 126–138.

For Peer Review

Burks, D. J. and Robbins, R. (2012) 'Psychologists' authenticity: Implications for work in professional and therapeutic settings', *Journal of Humanistic Psychology*, 52(1), pp. 75–104. doi: 10.1177/0022167810381472.

Callaway, J. C. and Grob, C. S. (1998) 'Ayahuasca preparations and serotonin reuptake inhibitors: A potential combination for severe adverse interactions', *Journal of Psychoactive Drugs*, 30(4), pp. 367–369. doi: 10.1080/02791072.1998.10399712.

Cameron, L. P. *et al.* (2020) 'A non-hallucinogenic psychedelic analogue with therapeutic potential', *Nature 2020 589:7842*. Nature Publishing Group, 589(7842), pp. 474–479. doi: 10.1038/s41586-020-3008-z.

Carbonaro, T. M. *et al.* (2016) 'Survey study of challenging experiences after ingesting psilocybin mushrooms: Acute and enduring positive and negative consequences', *Journal of Psychopharmacology*. SAGE Publications Ltd, 30(12), pp. 1268–1278. doi: 10.1177/0269881116662634.

Carhart-Harris, R. *et al.* (2021a) 'Trial of Psilocybin versus Escitalopram for Depression', *New England Journal of Medicine*, 384(15), pp. 1402–1411. doi: 10.1056/nejmoa2032994.

Carhart-Harris, R. *et al.* (2021b) 'Trial of Psilocybin versus Escitalopram for Depression', *New England Journal of Medicine*. Massachusetts Medical Society, 384(15), pp. 1402–1411. doi: 10.1056/NEJMOA2032994/SUPPL_FILE/NEJMOA2032994_DATA-SHARING.PDF.

Carhart-Harris, R. L. *et al.* (2014) 'The entropic brain: A theory of conscious states informed by neuroimaging research with psychedelic drugs', *Frontiers in Human Neuroscience*. Frontiers Media S. A., 8(1 FEB). doi: 10.3389/fnhum.2014.00020.

Carhart-Harris, R. L. *et al.* (2015) 'LSD enhances suggestibility in healthy volunteers', *Psychopharmacology*. Springer Verlag, 232(4), pp. 785–794. doi: 10.1007/s00213-014-3714-

For Peer Review

z.

Carhart-Harris, Robin L. *et al.* (2016) 'Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study', *The Lancet Psychiatry*. Elsevier Ltd, 3(7), pp. 619–627. doi: 10.1016/S2215-0366(16)30065-7.

Carhart-Harris, R. L. *et al.* (2016) 'The paradoxical psychological effects of lysergic acid diethylamide (LSD)', *Psychological Medicine*. Cambridge University Press, 46(7), pp. 1379–1390. doi: 10.1017/S0033291715002901.

Carhart-Harris, R. L., Bolstridge, M., *et al.* (2018) 'Psilocybin with psychological support for treatment-resistant depression: six-month follow-up', *Psychopharmacology*. Springer Verlag, 235(2), pp. 399–408. doi: 10.1007/s00213-017-4771-x.

Carhart-Harris, R. L., Erritzoe, D., *et al.* (2018) 'Psychedelics and connectedness', *Psychopharmacology*. Springer Verlag, pp. 547–550. doi: 10.1007/s00213-017-4701-y.

Carhart-Harris, Robin L., Roseman, L., *et al.* (2018a) 'Psychedelics and the essential importance of context', *Journal of Psychopharmacology*. SAGE Publications Ltd, 32(7), pp. 725–731. doi: 10.1177/0269881118754710.

Carhart-Harris, Robin L., Roseman, L., *et al.* (2018b) 'Psychedelics and the essential importance of context', *Journal of Psychopharmacology*, 32(7), pp. 725–731. doi: 10.1177/0269881118754710.

Carhart-Harris, R. L. and Friston, K. J. (2019) 'REBUS and the anarchic brain: Toward a unified model of the brain action of psychedelics', *Pharmacological Reviews*. American Society for Pharmacology and Experimental Therapy, 71(3), pp. 316–344. doi: 10.1124/pr.118.017160.

Carhart-Harris, R. L. and Nutt, D. J. (2017) 'Serotonin and brain function: A tale of two

For Peer Review

receptors', *Journal of Psychopharmacology*. SAGE Publications Ltd, pp. 1091–1120. doi: 10.1177/0269881117725915.

Carlin, C. S. *et al.* (2018) 'A Manual for Adherence Ratings of MDMA-Assisted Psychotherapy for Treatment of Posttraumatic Stress Disorder'. Available at: https://mapscontent.s3-us-west-1.amazonaws.com/pdfs/Adherence+Ratings+Manual+Version+4+24+Oct+2018%5B2%5D.pdf (Accessed: 8 February 2022).

Cicchetti, D. V. and Sparrow, S. A. (1981) 'Developing criteria for establishing interrater reliability of specific items: applications to assessment of adaptive behavior', *American journal of mental deficiency.*, 86(2), pp. 127–137.

Cohen, S. (1960) 'Lysergic acid diethylamide: Side effects and complications', *Journal of Nervous and Mental Disease*, 130(1), pp. 30–40. doi: 10.1097/00005053-196001000-00005.

Cohen, S. and Eisner, B. G. (1959) 'Use of Lysergic Acid Diethylamide in a Psychotherapeutic Setting', *AMA Archives of Neurology & Psychiatry*, 81(5), pp. 615–619.

Cosimano, M. P. (2021) 'The Role of the Guide in Psychedelic-Assisted Treatment', in Grob, C. S. and Grigsby, J. (eds) *Handbook of Medical Hallucinogens*. New York: Guilford Press, p. 377.394.

Costello, C. G. (1964) 'Lysergic Acid Diethylamide (LSD 25) and Behavior Therapy', *Behaviour research and therapy*, 2(2–4), pp. 117–129.

Cutner, M. (1959) 'Analytic work with LSD 25', *Psychiatric Quarterly*, 33(4), pp. 715–757.

Danforth, A. (2009) 'Focussing-oriented Psychotherapy as a Supplement to Preparation for Psychedelic Therapy', *The Journal of Transpersonal Psychology*, 41(2), pp. 151–160.

For Peer Review

Davis, A. K. *et al.* (2021a) 'Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial', *JAMA Psychiatry*, 78(5), pp. 481–489. doi: 10.1001/jamapsychiatry.2020.3285.

Davis, A. K. *et al.* (2021b) 'Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial', *JAMA Psychiatry*. American Medical Association, 78(5), pp. 481–489. doi: 10.1001/JAMAPSYCHIATRY.2020.3285.

Dobkin de Rios, M. (2009) *The Psychedelic Journey of Marlene Dobkin de Rios: 45 Years with Shamans, Ayahuasqueros, and Ethnobotanists*. Rochester, VT: Park Street Press.

Eisner, B. (1997) 'Set, setting, and matrix', *Journal of Psychoactive Drugs*, 29(2), pp. 213–216. doi: 10.1080/02791072.1997.10400190.

Eisner, B. G. (1964) 'Notes on the use of drugs to facilitate group psychotherapy', *The Psychiatric Quarterly*, 38(1–4), pp. 310–328. doi: 10.1007/BF01573385.

Eisner, B. G. and Cohen, S. (1958) 'Psychotherapy with lysergic acid diethylamide', *Journal of Nervous and Mental Disease*, 127(6), pp. 528–539. doi: 10.1097/00005053-195812000-00006.

Emmons, R. A. (2003) *The psychology of ultimate concerns : motivation and spirituality in personality*. Guilford Press.

Fadiman, J. (2011) *The psychedelic explorer's guide : safe, therapeutic, and sacred journeys*. Park Street Press.

Feduccia, A. A. *et al.* (2019) 'Breakthrough for Trauma Treatment: Safety and Efficacy of MDMA-Assisted Psychotherapy Compared to Paroxetine and Sertraline', *Frontiers in Psychiatry*. Frontiers Media S.A., 10(SEP), p. 650. doi: 10.3389/fpsyt.2019.00650.

For Peer Review

Feduccia, A. A. *et al.* (2021) 'Discontinuation of medications classified as reuptake inhibitors affects treatment response of MDMA-assisted psychotherapy', *Psychopharmacology*. Springer Science and Business Media Deutschland GmbH, 238(2), pp. 581–588. doi: 10.1007/S00213-020-05710-W/TABLES/3.

Fernandez, J. W. and Fernandez, R. L. (2001) '"Returning to the path": the use of iboga[ine] in an equatorial African ritual context and the binding of time, space, and social relationships.', *The Alkaloids. Chemistry and biology*, 56, pp. 235–47. doi: 10.1016/s0099-9598(01)56017-4.

Fiorella, D. *et al.* (1996) 'Potentiation of LSD-induced stimulus control by fluoxetine in the rat', *Life Sciences*. Elsevier Inc., 59(18). doi: 10.1016/0024-3205(96)00490-0.

First, M. B. (2015) 'Structured Clinical Interview for the DSM (SCID)', in *The Encyclopedia of Clinical Psychology*. Hoboken, NJ, USA: John Wiley & Sons, Inc., pp. 1–6. doi: 10.1002/9781118625392.wbecp351.

Fonagy, P. and Allison, E. (2014) 'The role of mentalizing and epistemic trust in the therapeutic relationship', *Psychotherapy*, 51(3), pp. 372–380.

Foundation, A. (2020) *Learn More About Us | Ayahuasca Foundation*. Available at: https://www.ayahuascafoundation.org/ayahuasca-training-programs/ (Accessed: 12 January 2020).

Gandy, S. *et al.* (2020) 'The potential synergistic effects between psychedelic administration and nature contact for the improvement of mental health.', *Health psychology open*. SAGE PublicationsSage UK: London, England, 7(2), p. 2055102920978123. doi: 10.1177/2055102920978123.

Garcia-Romeu, A., Kersgaard, B. and Addy, P. H. (2016) 'Clinical applications of

For Peer Review

hallucinogens: A review', *Experimental and Clinical Psychopharmacology*, 24(4), pp. 229–268. doi: 10.1037/pha0000084.

Garcia-Romeu, A. and Richards, W. A. (2018) 'Current perspectives on psychedelic therapy: use of serotonergic hallucinogens in clinical interventions', *International Review of Psychiatry*. Taylor & Francis, 30(4), pp. 291–316. doi: 10.1080/09540261.2018.1486289.

Gasser, P. *et al.* (2014) 'Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases', *Journal of Nervous and Mental Disease*. Lippincott Williams and Wilkins, 202(7), pp. 513–520. doi: 10.1097/NMD.0000000000000113.

Geller, S. M. and Greenberg, L. S. (2002) 'Therapeutic Presence: Therapists' experience of presence in the psychotherapy encounter', *Person-Centered and Experiential Psychotherapies*. Routledge, 1(1–2), pp. 71–86. doi: 10.1080/14779757.2002.9688279.

Geller, S. M. and Greenberg, L. S. (2012) *Therapeutic presence: a mindful approach to effective therapy*. American Psychological Association.

Geyer, M. A. and Vollenweider, F. X. (2008) 'Serotonin research: Contributions to understanding psychoses', *Trends in Pharmacological Sciences*. Elsevier Ltd, pp. 445–453. doi: 10.1016/j.tips.2008.06.006.

Gorgens, K. A. (2011) 'Structured Clinical Interview For DSM-IV (SCID-I/SCID-II)', in *Encyclopedia of Clinical Neuropsychology*. Springer New York, pp. 2410–2417. doi: 10.1007/978-0-387-79948-3_2011.

Gorman, I. *et al.* (2021) 'Psychedelic Harm Reduction and Integration: A Transtheoretical Model for Clinical Practice', *Frontiers in Psychology*. Frontiers, 12, p. 645246. doi: 10.3389/fpsyg.2021.645246.

For Peer Review

Grant, M. J. and Booth, A. (2009) 'A typology of reviews: an analysis of 14 review types and associated methodologies', *Health Information & Libraries Journal*. John Wiley & Sons, Ltd, 26(2), pp. 91–108. doi: 10.1111/J.1471-1842.2009.00848.X.

Greer, G. R. and Tolbert, R. (1998) 'A Method of Conducting Therapeutic Sessions with MDMA', *Journal of Psychoactive Drugs*, 30(4), pp. 371–379. doi: 10.1080/02791072.1998.10399713.

Griffiths, R. R. *et al.* (2006) 'Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance', *Psychopharmacology*, 187(3), pp. 268–283. doi: 10.1007/s00213-006-0457-5.

Griffiths, R. R. *et al.* (2016) 'Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial', *Journal of Psychopharmacology*, 30(12), pp. 1181–1197. doi: 10.1177/0269881116675513.

Griffiths, R. R. *et al.* (2018) 'Psilocybin-occasioned mystical-type experience in combination with meditation and other spiritual practices produces enduring positive changes in psychological functioning and in trait measures of prosocial attitudes and behaviors', *Journal of Psychopharmacology*. SAGE Publications Ltd, 32(1), pp. 49–69. doi: 10.1177/0269881117731279.

Grinspoon, L. and Bakalar, J. B. (1979) *Psychedelic Drugs Reconsidered*. New York: Basic Books.

Grinspoon, L. and Doblin, R. (2001) 'Psychedelics as catalysts of insight-oriented psychotherapy', *Social Research*, 68(3), pp. 677–695.

Grob, C. S. *et al.* (2011) 'Pilot study of psilocybin treatment for anxiety in patients with

For Peer Review

advanced-stage cancer', *Archives of General Psychiatry*, 68(1), pp. 71–78. doi: 10.1001/archgenpsychiatry.2010.116.

Grof, S. (1968) 'Tentative theoretical framework for understanding dynamics of lsd psychotherapy.', in Shlien, J. M. (ed.) *Research in psychotherapy.* American Psychological Association, pp. 449–465. doi: 10.1037/10546-021.

Grof, S. (1980) *LSD Psychotherapy*. Pomona: Hunter House.

Grof, S. and Grof, C. (2010) *Holotropic breathwork : a new approach to self-exploration and therapy*. State University of New York Press.

Grof, S. and Halifax, J. (1977) *The human encounter with death*. E.P. Dutton.

Gucker, D. K. (1963) 'Combining External and Internal Symbolization in the LSD Episode', *Journal of Psychology: Interdisciplinary and Applied*, 55(2), pp. 401–408. doi: 10.1080/00223980.1963.9916633.

Gukasyan, N. and Nayak, S. M. (2021) 'Psychedelics, placebo effects, and set and setting: Insights from common factors theory of psychotherapy.', *Transcultural psychiatry*. SAGE PublicationsSage UK: London, England, p. 1363461520983684. doi: 10.1177/1363461520983684.

Haijen, E. C. H. M. *et al.* (2018) 'Predicting responses to psychedelics: A prospective study', *Frontiers in Pharmacology*, 9(NOV), pp. 1–20. doi: 10.3389/fphar.2018.00897.

Hartogsohn, I. (2015) *The psycho-social construction of LSD: How set and setting shaped the American psychedelic experience 1950–1970*. Bar Ilan University, Israel.

Hartogsohn, I. (2016) 'Set and setting, psychedelics and the placebo response: An extra-pharmacological perspective on psychopharmacology', *Journal of Psychopharmacology*,

For Peer Review

30(12), pp. 1259–1267. doi: 10.1177/0269881116677852.

Hartogsohn, I. (2017a) 'Constructing drug effects: A history of set and setting', *Drug Science, Policy and Law*, 3, p. 205032451668332. doi: 10.1177/2050324516683325.

Hartogsohn, I. (2017b) 'Constructing drug effects: A history of set and setting', *Drug Science, Policy and Law*, 3, p. 205032451668332. doi: 10.1177/2050324516683325.

Hausner, M. and Dolezal, V. (1963) 'Group and Individual Psychotherapy Under Lsd.', *Advances in psychosomatic medicine*, 11, pp. 39–59. doi: 10.1159/000285664.

Hofmann, A. (2009) *LSD, my problem child: reflections on sacred drugs, mysticism, and science*.

Holland, J. (2001) *Ecstasy, A Complete Guide: A Comprehensive Look at the Risks and Benefits of MDMA*.

Hollister, L. E., Shelton, J. and Krieger, G. (1969) 'A controlled comparison of lysergic acid diethylamide (LSD) and dextroamphetmine in alcoholics.', *The American journal of psychiatry*, 125(10), pp. 1352–1357. doi: 10.1176/ajp.125.10.1352.

Horton, D. M., Morrison, B. and Schmidt, J. (2021) 'Systematized review of psychotherapeutic components of psilocybin-assisted psychotherapy', *American Journal of Psychotherapy*, 74(4), pp. 140–149. doi: https://doi.org/10.1176/appi.psychotherapy.20200055.

Horvath, A. O. and Greenberg, L. S. (1989) 'Development and Validation of the Working Alliance Inventory', *Journal of Counseling Psychology*, 36(2), pp. 223–233. doi: 10.1037/0022-0167.36.2.223.

Johnson, M. W. *et al.* (2018) 'The abuse potential of medical psilocybin according to the 8

For Peer Review

factors of the Controlled Substances Act', *Neuropharmacology*. Elsevier Ltd, pp. 143–166. doi: 10.1016/j.neuropharm.2018.05.012.

Johnson, M. W. (2021) 'Consciousness, Religion, and Gurus: Pitfalls of Psychedelic Medicine', *ACS Pharmacology and Translational Science*. American Chemical Society, 4(2), pp. 578–581. doi: 10.1021/ACSPTSCI.0C00198/ASSET/IMAGES/ACSPTSCI.0C00198.SOCIAL.JPEG_V03.

Johnson, M. W., Garcia-Romeu, A. and Griffiths, R. R. (2017) 'Long-term follow-up of psilocybin-facilitated smoking cessation', *American Journal of Drug and Alcohol Abuse*. Taylor and Francis Ltd, 43(1), pp. 55–60. doi: 10.3109/00952990.2016.1170135.

Johnson, M. W., Richards, W. A. and Griffiths, R. R. (2008) 'Human hallucinogen research: Guidelines for safety', *Journal of Psychopharmacology*, 22(6), pp. 603–620. doi: 10.1177/0269881108093587.

Jungaberle, H. *et al.* (2008) *Therapie mit psychoaktiven Substanzen : Praxis und Kritik der Psychotherapie mit LSD, Psilocybin und MDMA*. Bern: Huber.

Kaelen, M. *et al.* (2015) 'LSD enhances the emotional response to music', *Psychopharmacology*. Springer Verlag, 232(19), pp. 3607–3614. doi: 10.1007/s00213-015-4014-y.

Kaelen, M. *et al.* (2016) 'LSD modulates music-induced imagery via changes in parahippocampal connectivity', *European Neuropsychopharmacology*. Elsevier B.V., 26(7), pp. 1099–1109. doi: 10.1016/j.euroneuro.2016.03.018.

Kaelen, M. *et al.* (2018) 'The hidden therapist: evidence for a central role of music in psychedelic therapy', *Psychopharmacology*. Springer Berlin Heidelberg, 235(2), pp. 505–519. doi: 10.1007/s00213-017-4820-5.

For Peer Review

Kafka, J. S. and Gaarder, K. R. (1964) 'Some Effects of the Therapist's LSD Experience on his Therapeutic Work', *American journal of psychotherapy*, 18, pp. 236–243. doi: 10.1176/appi.psychotherapy.1964.18.2.236.

King, D. B. and Decicco, T. L. (2009) 'A Viable Model and Self-Report Measure of Spiritual Intelligence', *International Journal of Transpersonal Studies*, 28(1), pp. 68–85. doi: 10.24972/ijts.2009.28.1.68.

Kirschenbaum, H. (2004) 'Carl Rogers's Life and Work: An Assessment on the 100th Anniversary of His Birth', *Journal of Counseling & Development*, 82(1), pp. 116–124. doi: 10.1002/j.1556-6678.2004.tb00293.x.

Krueger, R. F. *et al.* (2012) 'Initial construction of a maladaptive personality trait model and inventory for DSM-5', *Psychological Medicine*. Cambridge University Press, 42(9), pp. 1879–1890. doi: 10.1017/S0033291711002674.

Krupitsky, E. M. and Grinenko, A. Y. (1997) 'Ketamine psychedelic therapy (KPT): A review of the results of ten years of research', *Journal of Psychoactive Drugs*, 29(2), pp. 165–183. doi: 10.1080/02791072.1997.10400185.

Kurland, A. A. *et al.* (1967) 'Psychedelic Therapy Utilizing LSD in the Treatment of the Alcoholic Patient: A Preliminary Report', *American Journal of Psychiatry*. American Psychiatric Publishing, 123(10), pp. 1202–1209. doi: 10.1176/AJP.123.10.1202.

Kurland, A. A. (1985) 'LSD in the supportive care of the terminally ill cancer patient', *Journal of Psychoactive Drugs*, 17(4), pp. 279–290. doi: 10.1080/02791072.1985.10524332.

Lambert, M. J. and Barley, D. E. (2001) 'Research summary on the therapeutic relationship and psychotherapy outcome', in *Psychotherapy*. American Psychological Association Inc., pp. 357–361. doi: 10.1037/0033-3204.38.4.357.

For Peer Review

Langlitz, N. (2012) *Neuropsychedelia : the revival of hallucinogen research since the decade of the brain*. University of California Press.

Leary, T. (1961) 'Drugs, Set & Suggestibility', in *Annual meeting of the American Psychological Association*.

Leary, T., Litwin, G. H. and Metzner, R. (1963) 'Reactions to psilocybin administered in a supportive environment', *The Journal of Nervous and Mental Disease*, 137(6), pp. 561–573. doi: 10.1097/00005053-196312000-00007.

Leary, T., Metzner, R. and Alpert, R. (1964) *The psychedelic experience: a manual based on the Tibetan book of the dead*. Citadel Press.

Lennard, H. and Hewitt, M. (1960) 'The study of communication processes under LSD', in Abramson, H. (ed.) *The use of LSD in psychotherapy*. Princeton: Josiah Macy Jr. Foundation, pp. 199–240.

Letheby, C. and Gerrans, P. (2017) 'Self unbound: ego dissolution in psychedelic experience', *Neuroscience of Consciousness*, 2017(1). doi: 10.1093/nc/nix016.

Linville, T. M. (2016) *Project MKULTRA and the Search for Mind Control: Clandestine Use of LSD Within the CIA*. History Capstone Research Papers. 6.

Ludwig, A. *et al.* (1969) 'A Clinical Study of LSD Treatment in Alcoholism', *American Journal of Psychiatry*. American Psychiatric Publishing, 126(1), pp. 59–69. doi: 10.1176/ajp.126.1.59.

Luoma, J. B. *et al.* (2021) 'Potential processes of change in MDMA-Assisted therapy for social anxiety disorder: Enhanced memory reconsolidation, self-transcendence, and therapeutic relationships', *Human Psychopharmacology: Clinical and Experimental*. John Wiley & Sons, Ltd, p. e2824. doi: 10.1002/HUP.2824.

For Peer Review

Ly, C. *et al.* (2018) 'Psychedelics Promote Structural and Functional Neural Plasticity', *Cell Reports*. Cell Press, 23(11), pp. 3170–3182. doi: 10.1016/J.CELREP.2018.05.022.

Malone, T. C. *et al.* (2018) 'Individual experiences in four cancer patients following psilocybin-assisted psychotherapy', *Frontiers in Pharmacology*, 9(APR), pp. 1–6. doi: 10.3389/fphar.2018.00256.

Martin, A. J. (1964) 'L.S.D. Analysis', *International Journal of Social Psychiatry*, 10(3), pp. 165–169.

Martin, D. J., Garske, J. P. and Katherine Davis, M. (2000) 'Relation of the therapeutic alliance with outcome and other variables: A meta-analytic review', *Journal of Consulting and Clinical Psychology*. American Psychological Association Inc., 68(3), pp. 438–450. doi: 10.1037/0022-006X.68.3.438.

Mason, N. L. *et al.* (2020) 'Me, myself, bye: regional alterations in glutamate and the experience of ego dissolution with psilocybin', *Neuropsychopharmacology 2020 45:12*. Nature Publishing Group, 45(12), pp. 2003–2011. doi: 10.1038/s41386-020-0718-8.

Masters, R. and Houston, J. (1966) *The Varieties of Psychedelic Experience*. New York: Holt, Rinehart & Winston.

McCabe, O. L. (1977) 'Psychedelic Drug Crises: Toxicity and Therapeutics', *Journal of Psychedelic Drugs*, 9(2), pp. 107–121. doi: 10.1080/02791072.1977.10472036.

McElrath, K. and McEvoy, K. (2002) 'Negative experiences on Ecstasy: The role of drug, set and setting', *Journal of Psychoactive Drugs*, 34(2), pp. 199–208. doi: 10.1080/02791072.2002.10399954.

Mechaneck, R. *et al.* (1968) 'Experimental investigation of LSD as a psychotherapeutic adjunct', *Comprehensive Psychiatry*, 9(5), pp. 490–498. doi: 10.1016/S0010-440X(68)80080-

For Peer Review

X.

Metzner, R. (1998) 'Hallucinogenic drugs and plants in psychotherapy and shamanism', *Journal of Psychoactive Drugs*, 30(4), pp. 333–341. doi: 10.1080/02791072.1998.10399709.

Metzner, R. (2015) *Allies for awakening : guidelines for productive and safe experiences with entheogens*. Berkeley: Regent Press.

Metzner, R. and Adamson, S. (2001) 'Using MDMA in healing, psychotherapy and spiritual practice.', in Holland, J. (ed.) *Ecstasy, A Complete Guide: A Comprehensive Look at the Risks and Benefits of MDMA*. Rochester, VT: Park Street Press, pp. 182–207.

Mitchell, J. M. *et al.* (2021) 'MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study', *Nature Medicine*. Springer US, 27(6), pp. 1025–1033. doi: 10.1038/s41591-021-01336-3.

Mithoefer, M. C. *et al.* (2011) 'The safety and efficacy of ±3,4-methylenedioxymethamphetamine- assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: The first randomized controlled pilot study', *Journal of Psychopharmacology*. SAGE Publications Ltd, 25(4), pp. 439–452. doi: 10.1177/0269881110378371.

Mithoefer, M. C. (2017) *A Manual for MDMA-Assisted Psychotherapy in the Treatment of Posttraumatic Stress Disorder*.

Mithoefer, M. C. *et al.* (2018) '3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: a randomised, double-blind, dose-response, phase 2 clinical trial', *The Lancet Psychiatry*. Elsevier Ltd, 5(6), pp. 486–497. doi: 10.1016/S2215-0366(18)30135-4.

Mithoefer, M. C. *et al.* (2019) 'MDMA-assisted psychotherapy for treatment of PTSD: study

For Peer Review

design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials', *Psychopharmacology*. Springer Verlag, 236(9), pp. 2735–2745. doi: 10.1007/s00213-019-05249-5.

Möckel Graber, C. (2010) *Eintritt in heilende Bewusstseinszustände Grundlagen zur psycholytischen Praxis*. Nachtschatten-Verl.

Moreno, F. A. *et al.* (2006) *PRESS, INC. Safety, Tolerability, and Efficacy of Psilocybin in 9 Patients With Obsessive-Compulsive Disorder*, *J Clin Psychiatry*.

Moss, E. L. and Dobson, K. S. (2006) 'Psychology, spirituality, and end-of-life care: An ethical integration?', *Canadian Psychology*. Canadian Psychological Association, 47(4), pp. 284–299. doi: 10.1037/co2006019.

Murphy, R. *et al.* (2022) 'Therapeutic Alliance and Rapport Modulate Responses to Psilocybin Assisted Therapy for Depression', *Frontiers in Pharmacology*. Frontiers, 0, p. 3819. doi: 10.3389/FPHAR.2021.788155.

Muthukumaraswamy, S. D., Forsyth, A. and Lumley, T. (2021) 'Blinding and expectancy confounds in psychedelic randomized controlled trials', *https://doi.org/10.1080/17512433.2021.1933434*. Taylor & Francis, 14(9), pp. 1133–1152. doi: 10.1080/17512433.2021.1933434.

Nichols, D. E. (2004) 'Hallucinogens', *Pharmacology and Therapeutics*. Elsevier Inc., pp. 131–181. doi: 10.1016/j.pharmthera.2003.11.002.

Nichols, D. E. (2016) 'Psychedelics', *Pharmacological Reviews*. American Society for Pharmacology and Experimental Therapy, 68(2), pp. 264–355. doi: 10.1124/pr.115.011478.

Nielson, E. M. and Guss, J. (2018) 'The influence of therapists' first-hand experience with psychedelics on psychedelic-assisted psychotherapy research and therapist training', *Journal*

For Peer Review

of Psychedelic Studies, 2(2), pp. 64–73. doi: 10.1556/2054.2018.009.

Noorani, T. *et al.* (2018) 'Psychedelic therapy for smoking cessation: Qualitative analysis of participant accounts', *Journal of Psychopharmacology*, 32(7), pp. 756–769. doi: 10.1177/0269881118780612.

Norcross, J. C., Strausser-Kirtland, D. and Missar, C. D. (1988) 'The processes and outcomes of psychotherapists' personal treatment experiences', *Psychotherapy*, 25(1), pp. 36–43. doi: 10.1037/h0085321.

Olson, D. E. (2020) 'The Subjective Effects of Psychedelics May Not Be Necessary for Their Enduring Therapeutic Effects', *ACS Pharmacology & Translational Science*. American Chemical Society, 4(2), pp. 563–567. doi: 10.1021/ACSPTSCI.0C00192.

Oram, M. (2014) 'Efficacy and enlightenment: LSD psychotherapy and the drug amendments of 1962', *Journal of the History of Medicine and Allied Sciences*. Oxford University Press, 69(2), pp. 221–250. doi: 10.1093/jhmas/jrs050.

Page, M. J. *et al.* (2021) 'The PRISMA 2020 statement: an updated guideline for reporting systematic reviews', *BMJ*. British Medical Journal Publishing Group, 372. doi: 10.1136/BMJ.N71.

Pahnke, W. N. and Richards, W. A. (1966) 'Implications of LSD and experimental mysticism', *Journal of Religion and Health*. Kluwer Academic Publishers, 5(3), pp. 175–208. doi: 10.1007/BF01532646.

Palhano-Fontes, F. *et al.* (2019) 'Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: A randomized placebo-controlled trial', *Psychological Medicine*. Cambridge University Press, 49(4), pp. 655–663. doi: 10.1017/S0033291718001356.

For Peer Review

Passie, T. (2012) *Healing with entactogens : therapist and patient perspectives on MDMA-assisted group psychotherapy*. Multidisciplinary Association for Psychedelic Studies (MAPS).

Passie, T. and Brandt, S. D. (2018) 'Self-experiments with psychoactive substances: A historical perspective', in *Handbook of Experimental Pharmacology*. Springer New York LLC, pp. 69–110. doi: 10.1007/164_2018_177.

Peill, J. M. *et al.* (2022) 'Validation of the Psychological Insight Scale: A new scale to assess psychological insight following a psychedelic experience.', *Journal of psychopharmacology (Oxford, England)*. SAGE PublicationsSage UK: London, England, 36(1), pp. 31–45. doi: 10.1177/02698811211066709.

Phelps, J. (2017) 'Developing Guidelines and Competencies for the Training of Psychedelic Therapists', *Journal of Humanistic Psychology*, 57(5), pp. 450–487. doi: 10.1177/0022167817711304.

Phelps, J. (2019) 'Training psychedelic therapists', in Sessa, B. and Winkelman, M. (eds) *Advances in psychedelic medicine: State of the art therapeutic applications*. Westport: Praeger Publishers, pp. 274–294.

Preller, K. H. *et al.* (2017) 'The Fabric of Meaning and Subjective Effects in LSD-Induced States Depend on Serotonin 2A Receptor Activation', *Current Biology*. Cell Press, 27(3), pp. 451–457. doi: 10.1016/j.cub.2016.12.030.

Preller, K. H. *et al.* (2018) 'Changes in global and thalamic brain connectivity in LSD-induced altered states of consciousness are attributable to the 5-HT2A receptor', *eLife*. eLife Sciences Publications Ltd, 7. doi: 10.7554/ELIFE.35082.

Preller, K. H. *et al.* (2019) 'Effective connectivity changes in LSD-induced altered states of

For Peer Review

consciousness in humans', *Proceedings of the National Academy of Sciences of the United States of America*. National Academy of Sciences, 116(7), pp. 2743–2748. doi: 10.1073/pnas.1815129116.

Van Rhijn, C. H. (1967) 'Variables in psycholytic treatment', in *Address at the second conference on the use of LSD in psychotherapy*, pp. 208–222.

Richards, W. A. *et al.* (1972) 'LSD-assisted psychotherapy and the human encounter with death', *Journal of Transpersonal Psychology*, 4, pp. 121–150.

Richards, W. A. (2009) 'The rebirth of research with entheogens: Lessons from the past and hypotheses for the future', *Journal of Transpersonal Psychology*, 41, pp. 139–150.

Richards, W. A. (2014) 'Here and now: Discovering the sacred with entheogens', *Zygon: Journal of Religion & Science*, 49(3), pp. 652–665. doi: 10.1111/zygo.12108.

Richards, W. A. (2017) 'Psychedelic Psychotherapy: Insights From 25 Years of Research', *Journal of Humanistic Psychology*, 57(4), pp. 323–337. doi: 10.1177/0022167816670996.

Rodger, J. (2018) 'Understanding the Healing Potential of Ibogaine through a Comparative and Interpretive Phenomenology of the Visionary Experience', *Anthropology of Consciousness*, 29(1), pp. 77–119. doi: 10.1111/anoc.12088.

Rogers, C. R. (1946) 'Significant aspects of client-centered therapy', *American Psychologist*, 1(10), pp. 415–422.

Rogers, C. R. (1949) 'The attitude and orientation of the counselor in client-centered therapy', *Journal of Consulting Psychology*, 13(2), pp. 82–94. doi: 10.1037/h0059730.

Rogers, C. R. (1957) 'The Necessary and Sufficient Conditions of Therapeutic Personality Change', *Journal of Consulting Psychology*, 21(2), pp. 95–103.

For Peer Review

Rogers, C. R. (1959) *A theory of therapy, personality, and interpersonal relationships: As developed in the client-centered framework*. New York: McGraw-Hill.

Romeo, B. *et al.* (2021) 'Clinical and biological predictors of psychedelic response in the treatment of psychiatric and addictive disorders: A systematic review', *Journal of Psychiatric Research*. Pergamon, 137, pp. 273–282. doi: 10.1016/J.JPSYCHIRES.2021.03.002.

Roseman, L., Nutt, D. J. and Carhart-Harris, R. L. (2018) 'Quality of acute psychedelic experience predicts therapeutic efficacy of psilocybin for treatment-resistant depression', *Frontiers in Pharmacology*, 8(JAN). doi: 10.3389/fphar.2017.00974.

Ross, S. *et al.* (2016) 'Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial', *Journal of Psychopharmacology*, 30(12), pp. 1165–1180. doi: 10.1177/0269881116675512.

Ryan, R. M. *et al.* (2011) 'Motivation and Autonomy in Counseling, Psychotherapy, and Behavior Change: A Look at Theory and Practice', *Invited Integrative Review The Counseling Psychologist*, 39(2), pp. 193–260. doi: 10.1177/0011000009359313.

Sanders, J. W. and Zijlmans, J. (2021) 'Moving Past Mysticism in Psychedelic Science', *ACS Pharmacology and Translational Science*. American Chemical Society, 4(3), pp. 1253–1255. doi: 10.1021/ACSPTSCI.1C00097/ASSET/IMAGES/ACSPTSCI.1C00097.SOCIAL.JPEG_V03.

Sandison, R. A. and Whitelaw, J. D. (1957) 'Further studies in the therapeutic value of lysergic acid diethylamide in mental illness.', *The Journal of mental science*, 103(431), pp. 332–343. doi: 10.1192/bjp.103.431.332.

Savage, C. (1957) 'The resolution and subsequent remobilization of resistance by lsd in

For Peer Review

psychotherapy', *Journal of Nervous and Mental Disease*, 125(3), pp. 434–436. doi: 10.1097/00005053-195707000-00015.

Schlag, A. K. *et al.* (2022) 'Adverse effects of psychedelics: From anecdotes and misinformation to systematic science':, *https://doi.org/10.1177/02698811211069100*. SAGE PublicationsSage UK: London, England, p. 026988112110691. doi: 10.1177/02698811211069100.

Schmid, Y. *et al.* (2021) 'Acute subjective effects in LSD- and MDMA-assisted psychotherapy', *Journal of Psychopharmacology*. SAGE Publications Ltd, 35(4), pp. 362–374. doi: 10.1177/0269881120959604.

Schmid, Y. and Liechti, M. E. (2018) 'Long-lasting subjective effects of LSD in normal subjects', *Psychopharmacology*. Springer Verlag, 235(2), pp. 535–545. doi: 10.1007/s00213-017-4733-3.

Schmidt, T. T. and Berkemeyer, H. (2018) 'The altered states database: Psychometric data of altered states of consciousness', *Frontiers in Psychology*. Frontiers Media S.A., 9(JUL), p. 1028. doi: 10.3389/FPSYG.2018.01028/BIBTEX.

Serafini, G. *et al.* (2014) 'The Role of Ketamine in Treatment-Resistant Depression: A Systematic Review', *Current Neuropharmacology*. Bentham Science Publishers, 12(18), pp. 444–461.

Sessa, B. (2017) 'MDMA and PTSD treatment: "PTSD: From novel pathophysiology to innovative therapeutics"', *Neuroscience Letters*. Elsevier Ireland Ltd, 649, pp. 176–180. doi: 10.1016/j.neulet.2016.07.004.

Sessa, B. *et al.* (2019) 'First study of safety and tolerability of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in patients with alcohol

For Peer Review

use disorder: Preliminary data on the first four participants', *BMJ Case Reports*, 12(7), pp. 1–4. doi: 10.1136/bcr-2019-230109.

Sessa, B., Higbed, L. and Nutt, D. (2019) 'A review of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy', *Frontiers in Psychiatry*, 10(MAR), pp. 1–7. doi: 10.3389/fpsyt.2019.00138.

Sheehan, D. V. *et al.* (1998) 'The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10', *Journal of Clinical Psychiatry*, 59(SUPPL. 20), pp. 22–33.

Sherwood, J. N., Stolaroff, M. J. and Harman, W. W. (1968) 'The Psychedelic Experience - A New Concept in Psychotherapy', *Journal of Psychoactive Drugs*, 1(2), pp. 96–111. doi: 10.1080/02791072.1968.10524522.

Shewan, D., Dalgarno, P. and Reith, G. (2000) 'Perceived risk and risk reduction among ecstasy users: The role of drug, set, and setting', *International Journal of Drug Policy*, pp. 431–453. doi: 10.1016/S0955-3959(99)00038-9.

Sloshower, J. *et al.* (2020) 'Psilocybin-assisted therapy of major depressive disorder using Acceptance and Commitment Therapy as a therapeutic frame', *Journal of Contextual Behavioral Science*. Elsevier Inc., pp. 12–19. doi: 10.1016/j.jcbs.2019.11.002.

Sloshower, J., Guss, J. and Krause, R. (2020) 'The Yale Manual for Psilocybin-Assisted Therapy of Depression'. doi: 10.31234/osf.io/u6v9y.

Smart, R. G. *et al.* (1966) 'A controlled study of lysergide in the treatment of alcoholism. I. The effects on drinking behavior.', *Quarterly journal of studies on alcohol*, 27(3), pp. 469–482.

Smigielski, L. *et al.* (2019) 'Psilocybin-assisted mindfulness training modulates self-

For Peer Review

consciousness and brain default mode network connectivity with lasting effects', *NeuroImage*. Elsevier Inc., 196, pp. 207–215. doi: 10.1016/j.neuroimage.2019.04.009.

Smith, E. D. (1988) 'Evolving Ethics in Psychedelic Drug Taking', *Journal of Drug Issues*, 18(2), pp. 201–214. doi: 10.1177/002204268801800207.

Smith, H. *et al.* (2004) 'Do Drugs Have Religious Import? A 40-Year Retrospective', *Journal of Humanistic Psychology*, 44(2), pp. 120–140. doi: 10.1177/0022167804263209.

Spencer, A. M. (1963) 'Permissive group therapy with lysergic acid diethylamide.', *The British journal of psychiatry*, 109, pp. 37–45. doi: 10.1192/bjp.109.458.37.

Spencer, A. M. (1964) 'Modifications in the technique of LSD therapy', *Comprehensive Psychiatry*, 5(4), pp. 232–252. doi: 10.1016/S0010-440X(64)80003-1.

Spriggs, M. J. *et al.* (2021) 'Study Protocol for "Psilocybin as a Treatment for Anorexia Nervosa: A Pilot Study"', *Frontiers in Psychiatry*. Frontiers Media S.A., 12, p. 1770. doi: 10.3389/FPSYT.2021.735523/BIBTEX.

Stolaroff, M. (2004) *The secret chief revealed: Conversations with a pioneer of the underground therapy movement*.

Strassman, R. (2001) *DMT : the spirit molecule : a doctor's revolutionary research into the biology of near-death and mystical experiences*.

Strassman, R. J. (1984) 'Adverse reactions to psychedelic drugs. A review of the literature', *Journal of Nervous and Mental Disease*, pp. 577–595. doi: 10.1097/00005053-198410000-00001.

Strassman, R. J. (1992) 'Human hallucinogen interactions with drugs affecting serotonergic neurotransmission.', *Neuropsychopharmacology : official publication of the American*

For Peer Review

College of Neuropsychopharmacology, 7(3), pp. 241–3. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1388647 (Accessed: 13 December 2019).

Strassman, R. J. *et al.* (1994) 'Dose-Response Study of N,N-Dimethyltryptamine in Humans: II. Subjective Effects and Preliminary Results of a New Rating Scale', *Archives of General Psychiatry*, 51(2), pp. 98–108. doi: 10.1001/archpsyc.1994.03950020022002.

Strassman, R. J. (1995) 'Hallucinogenic drugs in psychiatric research and treatment: Perspectives and prospects', *Journal of Nervous and Mental Disease*, 183(3), pp. 127–138.

Studerus, E. *et al.* (2012) 'Prediction of Psilocybin Response in Healthy Volunteers', *PLOS ONE*. Public Library of Science, 7(2), p. e30800. doi: 10.1371/JOURNAL.PONE.0030800.

Studerus, E. *et al.* (2021) 'Prediction of MDMA response in healthy humans: a pooled analysis of placebo-controlled studies', *Journal of Psychopharmacology*. SAGE Publications Ltd, 35(5), pp. 556–565. doi: 10.1177/0269881121998322.

Swift, T. C. *et al.* (2017) 'Cancer at the Dinner Table: Experiences of Psilocybin-Assisted Psychotherapy for the Treatment of Cancer-Related Distress', *Journal of Humanistic Psychology*. SAGE Publications Inc., 57(5), pp. 488–519. doi: 10.1177/0022167817715966.

Tagliazucchi, E. *et al.* (2016) 'Increased Global Functional Connectivity Correlates with LSD-Induced Ego Dissolution', *Current Biology*. Cell Press, 26(8), pp. 1043–1050. doi: 10.1016/j.cub.2016.02.010.

Tai, S. J. *et al.* (2021) 'Development and Evaluation of a Therapist Training Program for Psilocybin Therapy for Treatment-Resistant Depression in Clinical Research', *Frontiers in Psychiatry*. Frontiers Media S.A., 12, p. 27. doi: 10.3389/FPSYT.2021.586682/BIBTEX.

Tennant, R. *et al.* (2007) 'The Warwick-Dinburgh mental well-being scale (WEMWBS): Development and UK validation', *Health and Quality of Life Outcomes*, 5, pp. 1–13. doi:

For Peer Review

10.1186/1477-7525-5-63.

Thal, S. B. *et al.* (2021) 'Current Perspective on the Therapeutic Preset for Substance-Assisted Psychotherapy', *Frontiers in Psychology*. Frontiers, 0, p. 2501. doi: 10.3389/FPSYG.2021.617224.

Thal, S. B., Engel, L. B. and Bright, S. J. (2022) 'Sober sitter or coconsumer? Psychedelics, online forums and preferences for interpersonal interactions', *https://doi.org/10.1080/16066359.2022.2065268*. Taylor & Francis. doi: 10.1080/16066359.2022.2065268.

Thal, S. B. and Lommen, M. J. J. (2018) 'Current Perspective on MDMA-Assisted Psychotherapy for Posttraumatic Stress Disorder', *Journal of Contemporary Psychotherapy*. Springer New York LLC, 48(2), pp. 99–108. doi: 10.1007/s10879-017-9379-2.

Thal, S., Engel, L. B. and Bright, S. J. (2022) 'Presence, Trust, and Empathy: Preferred Characteristics of Psychedelic Carers':, *https://doi.org/10.1177/00221678221081380*. SAGE PublicationsSage CA: Los Angeles, CA. doi: 10.1177/00221678221081380.

Thomas, K. and Malcolm, B. (2021) 'Adverse Effects', in Grob, C. S. and Grigsby, J. (eds) *Handbook of Medical Hallucinogens*. New York: Guilford Press, pp. 414–443.

Thomas, N. and Humphrey, C. (1996) *Shamanism, history, and the state*. University of Michigan Press.

Twemlow, S. W. and Bowen, W. T. (1979) 'Psychedelic drug-induced psychological crises: Attitudes of the "crisis therapist"', *Journal of Psychoactive Drugs*, 11(4), pp. 331–335. doi: 10.1080/02791072.1979.10471416.

Vizeli, P. and Liechti, M. E. (2017) 'Safety pharmacology of acute MDMA administration in healthy subjects', *Journal of Psychopharmacology*. SAGE Publications Ltd, 31(5), pp. 576–

For Peer Review

588. doi: 10.1177/0269881117691569.

Vollenweider, F. X. *et al.* (1998) 'Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action.', *Neuroreport*. Neuroreport, 9(17), pp. 3897–902.

Wagner, A. C. *et al.* (2019) 'Combining Cognitive-Behavioral Conjoint Therapy for PTSD with 3 , 4- Methylenedioxymethamphetamine (MDMA): A Case Example Combining Cognitive-Behavioral Conjoint Therapy for PTSD with', *Journal of Psychoactive Drugs*. Taylor & Francis, 51(2), pp. 166–173. doi: 10.1080/02791072.2019.1589028.

Walsh, R. and Grob, C. S. (2006) 'Early Psychedelic Investigators Reflect on the Psychological and Social Implications of their Research', *Journal of Humanistic Psychology*, 46(4), pp. 432–448. doi: 10.1177/0022167806286745.

Watts, R. *et al.* (2017) 'Patients' Accounts of Increased "Connectedness" and "Acceptance" After Psilocybin for Treatment-Resistant Depression', *Journal of Humanistic Psychology*, 57(5), pp. 520–564. doi: 10.1177/0022167817709585.

Watts, R. (2021) 'Psilocybin for Depression: The ACE Model Manual'. doi: https://doi.org/10.31234/osf.io/5x2bu.

Watts, R. and Luoma, J. B. (2020) 'The use of the psychological flexibility model to support psychedelic assisted therapy', *Journal of Contextual Behavioral Science*. Elsevier Inc., pp. 92–102. doi: 10.1016/j.jcbs.2019.12.004.

Weinreich, W. M. (2005) *Integrale Psychotherapie : ein umfassendes Therapiemodell auf der Grundlage der integralen Philosophie nach Ken Wilber*. Araki.

Weinreich, W. M. (2006) *Psychoaktive Substanzen aus integraler Sicht*. Available at: http://www.integrale-psychotherapie.de/Resources/Integdrugs.pdf (Accessed: 7 December 2019).

For Peer Review

Weiss, M. *et al.* (1997) 'The role of the alliance in the pharmacologic treatment of depression', *Journal of Clinical Psychiatry*. Physicians Postgraduate Press Inc., 58(5), pp. 196–204. doi: 10.4088/JCP.v58n0504.

Whitfield, H. J. (2021) 'A Spectrum of Selves Reinforced in Multilevel Coherence: A Contextual Behavioural Response to the Challenges of Psychedelic-Assisted Therapy Development', *Frontiers in Psychiatry*. Frontiers Media S.A., 12, p. 2095. doi: 10.3389/FPSYT.2021.727572/BIBTEX.

Winkelman, M. and Roberts, T. B. (2007) *Psychedelic medicine : new evidence for hallucinogenic substances as treatments*. Praeger Publishers.

Wolff, M. *et al.* (2020) 'Learning to Let Go: A Cognitive-Behavioral Model of How Psychedelic Therapy Promotes Acceptance', *Frontiers in Psychiatry*. Frontiers, 11, p. 5. doi: 10.3389/fpsyt.2020.00005.

World Health Organization (1993) *The ICD-10 classification of mental and behavioural disorders*. World Health Organization.

Yaden, D. B. and Griffiths, R. R. (2020) 'The Subjective Effects of Psychedelics Are Necessary for Their Enduring Therapeutic Effects', *ACS Pharmacology & Translational Science*. American Chemical Society, 4(2), pp. 568–572. doi: 10.1021/ACSPTSCI.0C00194.

Younger, J. *et al.* (2012) 'Development of the Stanford Expectations of Treatment Scale (SETS): A tool for measuring patient outcome expectancy in clinical trials', *Clinical Trials*. SAGE PublicationsSage UK: London, England, 9(6), pp. 767–776. doi: 10.1177/1740774512465064.

Zeifman, R. J. *et al.* (2022) 'Decreases in Suicidality Following Psychedelic Therapy: A Meta-Analysis of Individual Patient Data Across Clinical Trials', *The Journal of Clinical*

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Psychiatry. Physicians Postgraduate Press, Inc., 83(2), p. 39235. doi: 10.4088/JCP.21R14057.

Zinberg, N. E. (1984) *Drug, Set, and Setting The Basis for Controlled Intoxicant Use*. London: Yale University Press. Available at: https://www.brianwilliamson.id.au/aod/aodlinks/Drug Set and Setting - Zinberg N.pdf (Accessed: 5 February 2019).

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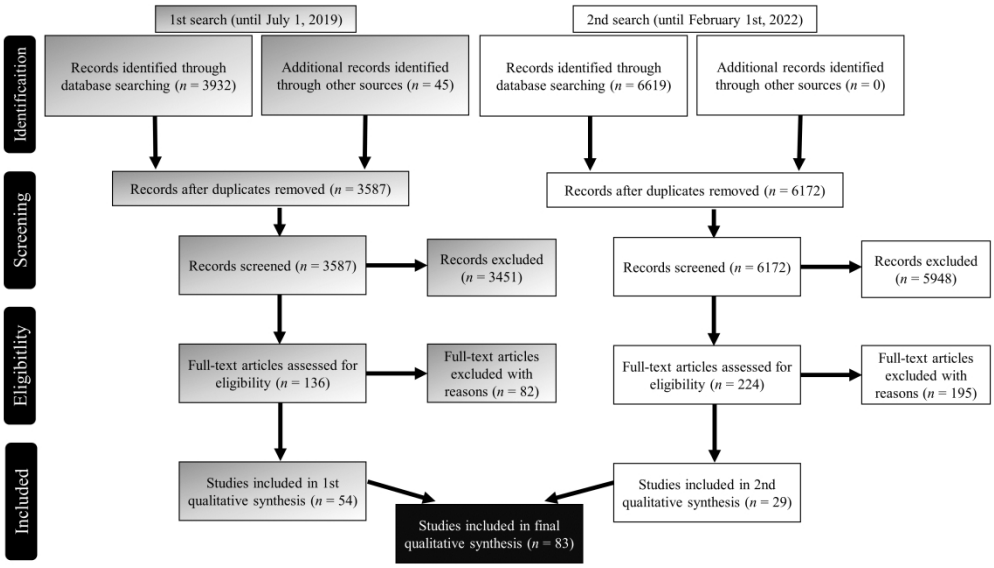

Figure 1. Visualization of the literature search

861x484mm (118 x 118 DPI)

Appendix A

Characteristics of Literature Included

Study	Design	Aims	*N*	Eligibility criteria		Substance	Dosage	Number of sessions	Preparation sessions	Administration sessions	Integration sessions	Therapist team
				Inclusion	Exclusion							
Almond and Allan (2019)	Review	Integrate MDMA-assisted psychotherapy for PTSD with Emotionally Focused Therapy	N/A	N/A	• Below 21 years old • pregnant or nursing women, or plan to become pregnant • eating disorder that includes active purging • history of primary psychotic disorder or bipolar affective disorder type 1 • risk of suicide or self-harm • at risk of hospitalization • below 50 or above 105 kg of body weight • not meeting the appropriate medical criteria (Mithoefer et al., 2017)	MDMA	N/A	N/A	N/A	N/A	N/A	N/A
Anderson et al. (2020)	single-arm, open-label, pilot study	Assess safety and feasibility of psilocybin-assisted group therapy for demoralization in older long-term AIDS survivor men	18	• Gay-identified • English-speaking • cisgender men • at least 50 years old • HIV diagnosis • Self-report of HIV diagnosis prior to the clinical availability of protease inhibitors (~1996) • moderate-to-severe demoralization assessed by a Demoralization Scale-II of at least 8	• Physical, neurological, or cognitive condition that makes participation unsafe or unfeasible • regular psychotropic medication use • personal or family history of serious mental illness • severe depression requiring immediate standard-of-care treatment • exclusion by the clinical judgment of the study investigators	Psilocybin	0.3mg/kg or 0.36mg/kg	11 - 13	5	1	5 - 7	Two, gender not specified

For Peer Review

Study	Design	Aims	*N*	Eligibility criteria		Substance	Dosage	Number of sessions	Preparation sessions	Administration sessions	Integration sessions	Therapist team
				Inclusion	Exclusion							
Barone et al. (2019)	Qualitative investigation	Complement on quantitative findings from phase 2 study to better understand outcomes and participants' experiences	19	N/A	N/A	MDMA	N/A	N/A	N/A	N/A	N/A	N/A
Barrett et al. (2018)	Review	History of contemporary research and future directions regarding the use of music in psychedelic research and therapy	N/A	N/A	N/A	Serotonin 2A, or 5-HT2A receptor agonists	N/A	N/A	N/A	N/A	N/A	N/A
Bogenschutz (2013)	Review	Rationale, Methodology, and Current Research with classic hallucinogens	N/A	• Adequate current severity to detect improvement • relative homogeneity in terms of severity • co-occurring psychiatric disorders, and other substance use disorders • reasonable likelihood of completing the treatment and follow-ups • for outpatient studies: psychosocial support network and interpersonal relationships	• Personal or family history of psychosis • extensive history of psychedelic exposure • medical contraindications	Classic hallucinogens	Prior studies suggest doses of 3 - 6 µg/kg for LSD and 0.29 - 0.43 mg/70 kg for Psilocybin	N/A	N/A	N/A	N/A	N/A

For Peer Review

Study	Design	Aims	*N*	Eligibility criteria		Substance	Dosage	Number of sessions	Preparation sessions	Administration sessions	Integration sessions	Therapist team
				Inclusion	Exclusion							
Bogenschutz and Forcehimes (2016)	Review	Provide a framework for possible psychedelic-assisted treatment models for alcoholism	N/A	• AUD	N/A	Classic hallucinogens (Psilocybin in Treatment model)	Control: medication Experimental: 25 - 40 mg/70 kg of Psilocybin	19 (9 Motivational Enhancement and Taking Action Therapy sessions)	4	3	3	Male and female co-therapy team
Bogenschutz and Ross (2016)	Review	The therapeutic uses of the serotonergic or classic hallucinogens	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Bogenschutz et al. (2015)	single-group proof-of-concept study	Assess psychoactive effects and tolerability of oral psilocybin in alcohol-dependent participants	10	• Diagnosis of current alcohol dependence determined by SCID-IV • at least two heavy drinking days in the past 30 days • concerned about own drinking and not currently in treatment • abstinent and not in alcohol withdrawal during substance sessions	• Medical or psychiatric contraindications • family history of schizophrenia, bipolar disorder, or suicide • cocaine, psychostimulant, or opioid dependence • prior experience with hallucinogens more than 10 times or any use in the past 30 days	Psilocybin	1st session: 0.3 mg/kg 2nd session: 0.4 mg/kg If participant unwilling, experienced adverse effects or strong effects indicating complete mystical experience during 1st session then 0.3 mg/kg	14 (7 Motivational Enhancement Therapy sessions)	3	2	2	Two, gender not specified

For Peer Review

Study	Design	Aims	*N*	Eligibility criteria		Substance	Dosage	Number of sessions	Preparation sessions	Administration sessions	Integration sessions	Therapist team
				Inclusion	Exclusion							
Bouso et al. (2008)	Double-blind, ascending-dose study, randomized and placebo-controlled within each dose condition	Assess safety of single dose of MDMA for women with chronic PTSD secondary to sexual assault	6 Women	• Good physical health • previously failed to respond to at least one standard treatment • free of medications for at least one month prior to enrollment	• Pregnant women • psychiatric disorder other than PTSD and comorbid symptoms	MDMA	Placebo Experimental: 50 mg or 75 mg	7	3	1	3	Male and female co-therapy team
~~Buckman (1967)~~	~~Opinion paper~~	~~The use of LSD 25 as an adjunct to analytic form of psychotherapy~~	~~N/A~~	~~N/A~~	~~N/A~~	~~LSD~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~
Carhart-Harris et al. (2016)	Open-label, single-arm pilot study	Assess safety and efficacy of psilocybin for treatment-resistant MDD	12	• Major depression of a moderate to severe degree indicated by a score of 17 or above on the 21-item Hamilton Depression Rating scale • no improvement despite two courses of antidepressant treatment that lasted at least 6 weeks within the current depressive episode	• Personal or family history of psychotic disorder • medical contraindications • history of serious suicide attempts that required hospitalization • history of mania • blood or needle phobia • pregnant women • current drug or alcohol dependence	Psilocybin	1st session: 10 mg 2nd session: 25 mg	4-5	1	2 (1x low dose, 1x high dose)	3 (after low dose one via telephone, after high dose two in-person sessions one week apart)	Two psychiatrists

For Peer Review

Study	Design	Aims	*N*	Eligibility criteria		Substance	Dosage	Number of sessions	Preparation sessions	Administration sessions	Integration sessions	Therapist team
				Inclusion	Exclusion							
Carhart-Harris et al. (2021)	Double-blind RCT	Compare psilocybin with escitalopram in the treatment of MDD	59	• 18-80 years old • major depressive disorder (DSM-IV) • depression of moderate to severe degree indicated by a score of 17 or above on the 21-item Hamilton Depression Rating scale • no MRI contraindications • no SSRI contraindications • GP or other mental healthcare professional who can confirm diagnosis • sufficiently competent with English language	• Personal or family history of psychotic disorder • medical contraindications • history of serious suicide attempts that required hospitalization • history of mania • psychiatric condition judged to be incompatible with establishment of rapport with therapy team and/or safe exposure to psilocybin • blood or needle phobia • women who are pregnant or nursing, or planning to become pregnant • participants who are not practicing an effective means of contraception • current drug or alcohol dependence • no email access • use of contraindicated medication • patients presenting with abnormal QT interval prolongation at screening or with a history of this (QTc at screening above 440ms for men and above 470ms for women)	Psilcybin and escitalopram	Psilocybin arm: 25 mg psilocybin Escitalopram arm: 1 mg psilocybin, 10-20 mg escitalopram	12	2	2	6	Two, gender not specified
Carlin et al. (2018)	Manual	Describe procedures that establish and maintain congruence to the Treatment Manual for MDMA-Assisted Psychotherapy in	N/A			MDMA	N/A	N/A	N/A	N/A	N/A	N/A

For Peer Review

Study	Design	Aims	*N*	Eligibility criteria		Substance	Dosage	Number of sessions	Preparation sessions	Administration sessions	Integration sessions	Therapist team
				Inclusion	Exclusion							
		the Treatment of PTSD										
Cohen and Eisner (1959)	Opinion paper	Preliminary exploration of LSD-25 as an aid to the uncovering and acceptance of unconscious material and to determine whether the therapeutic process could be accelerated	22	• Neuroticism • anxiety • compulsiveness • depression • passive-aggressive character disorder • borderline schizophrenia • immature hysterical personality	N/A	LSD	Initial dose was 25 µg, subsequently increased by 25 µg until 100 or 150 µg were reached. In two cases, the increments were 50 µg. In five cases 500 µg of ALD-52 or MLD-4T were administered.	N/A	N/A	1 - 16 (M = 4.6)	N/A	Male and female co-therapy team
Cosimano in Grob & Grigsby (2021)	Book chapter	Outline the role of a guide sitting with people during psychedelic-assisted sessions in the Johns Hopkins University Psychedelic Research Program	N/A			Psychedelics	N/A	N/A	6 - 8 hours	≥ 1	≥ 1	Two, gender not specified
~~Costello (1964)~~	~~Case studies~~	~~Use of LSD in treatment of complex neurotic conditions~~	~~3~~	~~N/A~~	~~N/A~~	~~LSD~~	~~400 µg~~	~~N/A~~	~~N/A~~	~~1~~	~~N/A~~	~~N/A~~
~~Cutner (1959)~~	~~Review~~	~~Evaluating the use of LSD 25 as an aid to deep analysis~~	~~N/A~~	~~N/A~~	~~N/A~~	~~LSD~~	~~25 - 400 µg~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~

For Peer Review

Study	Design	Aims	*N*	Eligibility criteria		Substance	Dosage	Number of sessions	Preparation sessions	Administration sessions	Integration sessions	Therapist team
				Inclusion	Exclusion							
Danforth (2009)	Review	Prepare participants for psychedelic-assisted therapy with focusing-oriented psychotherapy	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Danforth et al. (2015)	Placebo-controlled, double-blind	Evaluate MDMA-assisted psychotherapy for the treatment of social anxiety in autistic adults	12	• At least 21 years old • at least two years of college education or the equivalent • autism diagnosis confirmed by an independent rater • moderate to severe social anxiety • able to safely taper off any psychotropic medication • healthy cardiovascular function	• Personal or family history of schizophrenia, bipolar I disorder, borderline personality disorder, dissociative identity disorder, eating disorder, or active suicidal ideation • substance use disorder • prior experience with MDMA	MDMA	75 - 125 mg	12	3	2	7	Male and female co-therapy team

For Peer Review

Study	Design	Aims	*N*	Eligibility criteria		Substance	Dosage	Number of sessions	Preparation sessions	Administration sessions	Integration sessions	Therapist team
				Inclusion	Exclusion							
Danforth et al. (2018)	Blinded, placebo-controlled pilot study	Assess feasibility and safety of MDMA-assisted psychotherapy for social fear and avoidance in autistic adults	12	• Diagnosis of ASD • social anxiety • two years of college education or comparable • willing to refrain from psychiatric medication for at least 5 half-lives plus a week prior to experimental session • global score of 60 or above on Leibowitz Social Anxiety Scale • at least 21 years old • MDMA naïve by self-report • physically healthy • psychologically stable	• Medical or psychiatric past or present history that might be a risk • abusing illegal drugs • pregnant or nursing women	MDMA	75 - 125 mg	11	3	2	6 (2x3 after each experimental session)	Two, gender not specified
Davis et al. (2021)	Waiting list RCT	Investigate the effect of psilocybin therapy in patients with MDD	27	• 21 - 75 years old • no current pharmacotherapy for depression • medically stable with no uncontrolled cardiovascular conditions • agreeing to use contraception	• Medical contraindications, such as diabetes, epilepsy, or cardiovascular conditions • pregnant or nursing women • lifetime or family history of psychotic or bipolar disorders • moderate or severe alcohol or other drug use disorder (including nicotine) in the past year • substantial lifetime use (>10 total) or recent use (past 6 months) of ketamine or classic hallucinogens • MRI contraindications	Psilocybin	20 - 30 mg/70 kg	≥ 9	8 hours (≥ two sessions)	2	5	Two, gender not specified

For Peer Review

Study	Design	Aims	*N*	Eligibility criteria		Substance	Dosage	Number of sessions	Preparation sessions	Administration sessions	Integration sessions	Therapist team
				Inclusion	Exclusion							
Eisner (1964)	Observational study	Effect of different substances on the therapeutic progress in a group setting	42	Sample characteristics: • no records of hospitalization for mental illness • some have had psychotherapy • alcoholics in remission • passive-aggressive character disorder • schizoid personality		Dexedrine, mescaline, amphetamine, LSD	Mescaline: 10 - 22 mg Methedrine: 5 - 10 mg LSD: 10 - 25 µg Dexedrine: 15 mg Spansule: 15 mg	N/A	N/A	3 - 5	N/A	One female therapist (Author)
Eisner (1997)	Review	Review of most important elements in set, setting and matrix	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Gandy et al. (2020)	Review	Outline how nature-based settings and practices could be useful for some stages of psychedelic therapy (mainly preparation and integration)	N/A			Psychedelics	N/A	N/A	N/A	N/A	N/A	N/A
Garcia-Romeu and Richards (2018)	Review	Overview of past and present models of psychedelic therapy	N/A	N/A	N/A	Serotonergic hallucinogens	N/A	N/A	N/A	N/A	N/A	N/A

For Peer Review

Study	Design	Aims	*N*	Eligibility criteria		Substance	Dosage	Number of sessions	Preparation sessions	Administration sessions	Integration sessions	Therapist team
				Inclusion	Exclusion							
Gasser et al. (2014)	Double-blind, randomized, active placebo-controlled pilot study	Test safety and efficacy of LSD-assisted psychotherapy for anxiety related to life-threatening disease	12	• Anxiety associated with life threatening disease • score of 40 or above on STAI	• Current alcohol or drug dependence (except caffeine or nicotine) • primary psychotic, bipolar I affective, or dissociative disorders • neurocognitive impairment • pregnant or nursing women	LSD	Active placebo: 20 µg of LSD Experimental: 200 µg of LSD	10	2	2	6 (2x3 after each experimental session)	Male and female co-therapy team
Greer and Tolbert (1998)	Review and case studies	Method to prepare clients and conduct therapeutic sessions with MDMA	N/A	• Functional, well-adjusted individuals	• Medical contraindications for substance administration including hypertension, cardiovascular disease, hyperthyroidism, epilepsy, pregnancy, • elicits emotional uneasiness in one of the therapists • desire to take part in MDMA session opposes therapists' philosophy	MDMA	Men: 100 - 150 mg Women: 75 - 125 mg Optional 50 mg, if requested later	N/A	N/A	N/A	N/A	Male and female co-therapy team
Griffiths et al. (2016)	Two-session, double-blind cross-over design	Assess the effects of psilocybin on anxiety and depression in patients with life-threatening cancer	51	• 21 - 80 years old • high school level of education • potentially life-threatening cancer diagnosis • ECOG performance status of 0, 1, or 2 • Axis I DSM-IV psychiatric diagnosis determined by the SCID • see Griffiths et al. (2016; Supplementary material) for full eligibility criteria	• Cancer with known CNS involvement • other major CNS disease • pregnant or nursing women • women who are not practicing an effective means of contraception • taking on a regular basis: investigational agents, psychoactive prescription medications; medications having a primary pharmacological effect on serotonin neurons, or medications that are MAO inhibitors • severe depression or anxiety symptoms • current, past or family	Psilocybin	Inactive placebo: 3 mg/70 kg, lowered to 1 mg/70 kg after first three participants Experimental: 30 mg/70 kg, lowered to 22 mg/70 kg after first three participants	N/A	≥ 2	2 (1x inactive placebo, 1x experimental)	≥ 4 (≥ 2 after each administration session)	Two, gender not specified

For Peer Review

Study	Design	Aims	*N*	Eligibility criteria		Substance	Dosage	Number of sessions	Preparation sessions	Administration sessions	Integration sessions	Therapist team
				Inclusion	Exclusion							
					history of meeting DSM-IV criteria for schizophrenia, psychotic disorder, or bipolar I or II disorder • lifetime history within the last 5 year of meeting DSM-IV criteria for alcohol or drug dependence (excluding caffeine and nicotine) • currently meeting DSM-IV criteria for dissociative disorder, anorexia nervosa, bulimia nervosa, or other psychiatric conditions that are incompatible with safe exposure to psilocybin and/or establishment of rapport							
Grob et al. (2011)	Double-blind, placebo-controlled study	Assess safety and efficacy of psilocybin in patients with advanced-stage cancer and reactive anxiety	12	• 18 - 70 years old • advanced-stage cancer • DSM-IV diagnosis of generalized anxiety disorder, acute stress disorder, anxiety disorder due to cancer, or adjustment disorder with anxiety	• Cancer that involves the CNS or brain function • severe cardiovascular illness • untreated hypertension • abnormal hepatic or renal function • diabetes • history of schizophrenia, bipolar disorder, other psychotic illness, and anxiety or affective disorders one year prior to the onset of cancer • active cancer chemotherapy • antiseizure medications, insulin and oral hypoglycemics, and psychotropic medications 2 week prior to enrollment • pregnant women or	Psilocybin	Placebo: Niacin 250 mg Experimental: 0.2 mg/kg	N/A	N/A	2	N/A	N/A

For Peer Review

Study	Design	Aims	*N*	Eligibility criteria		Substance	Dosage	Number of sessions	Preparation sessions	Administration sessions	Integration sessions	Therapist team
				Inclusion	Exclusion							
					women who are not practicing an effective means of contraception							
~~Gucker (1963)~~	~~Case study~~	~~Influence of external and internal symbolization during LSD session~~		~~Patient characteristics:~~ ~~• AUD~~ ~~• depression~~ ~~• suicidal ideation~~ ~~• hostility towards herself and others~~	~~N/A~~	~~LSD~~	~~200 µg~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~
Gukasyan & Nayak (2021)	Review	Review four major contextual factors shared in traditional healing methods	N/A									Two therapists, gender not specified
Haijen et al. (2018)	Time-series study ('prospective study design')	Improve ability to predict acute- and longer-term responses to psychedelics	T1 = 654, T2 = 535 T3 = 379 T4 = 315 T5 = 212	• At least 18 years old • good comprehension of the English language • intention to take a classic psychedelic drug (psilocybin/magic mushrooms /truffles, LSD/1P-LSD, ayahuasca, DMT/5-MeO-DMT, salvia divinorum, mescaline, or iboga/ibogaine)	N/A	Classic psychedelics	N/A	N/A	N/A	N/A	N/A	N/A

For Peer Review

Study	Design	Aims	*N*	Eligibility criteria		Substance	Dosage	Number of sessions	Preparation sessions	Administration sessions	Integration sessions	Therapist team
				Inclusion	Exclusion							
Hausner and Doležal (1963)	Quasi experiment	Therapeutic effects of LSD in conjunction with the psychotherapy of neurotics in individual and group sessions	39 (Control, LSD, Placebo)	• Neurotic	• Contraindications	LSD	50 - 100 µg	N/A	N/A	1	N/A	N/A
Horton et al. (2021)	Review	Discuss the counseling components associated with psilocybin-assisted psychotherapy	N/A			Psilocybin	N/A	N/A	N/A	N/A	N/A	N/A
Jardim et al. (2021)	Open label pilot study	Brazil's first clinical trial employing MDMA-assisted psychotherapy for PTSD	3	• At least 18 years old • DSM-IV PTSD diagnosis for at least 6 months • CAPS-4 score > 60 • at least one previous treatment failure • herbal supplements, any non-prescribed medications, and any illicit drugs • alcohol abstinence for 24 hours prior to the MDMA sessions • nicotine and caffeine abstinence for at least six hours after MDMA administration • refraining from driving or operating machinery for 24 hours after MDMA administration • providing an emergency contact • fluency in Portuguese	• Pregnant women or women who are not practicing an effective means of contraception • history of primary psychotic disorder, type 1 bipolar disorder or personality disorder • evidence or a history of coronary artery disease or peripheral vascular disease; hepatic disease (except asymptomatic Hepatitis C) or any other condition that could increase the risks of administering MDMA • hypertension • weight below 48 kg • history of hyponatremia or hyperthermia • suicide risk or risk to injure others • past use of illegal drugs on more than 10 occasions in the last ten years or once in past six months	MDMA	75 - 125 mg; optional supplemental half-dose after 1.5 - 2 hours	15	3	3	9 (3x3 after each experimental session)	Male and female co-therapy team

For Peer Review

Study	Design	Aims	*N*	Eligibility criteria		Substance	Dosage	Number of sessions	Preparation sessions	Administration sessions	Integration sessions	Therapist team
				Inclusion	Exclusion							
				• having completed middle school • granting permission to record all sessions • agreeing not to enroll in any other concurrent study	• unable to taper off psychiatric medication for the study • DSM-IV diagnosis of substance use or dependence • any medical or psychiatric condition that could potentially interfere with participation							
Johnson et al. (2008)	Review	Reviews the risks of hallucinogen administration and safeguards for minimizing these risks	N/A	• Unless relevant for the research question, psychologically healthy sample • if certain condition is investigated, exclusion criteria might be adjusted accordingly	• Pregnant women or women who are not practicing an effective means of contraception • lifetime or family history of bipolar I or II disorder, schizophrenia or other psychotic disorders • taking certain dietary supplements or over-the-counter medications (e.g., 5-hydroxytryptophan and St John's Wort) • resting blood pressure > 140 systolic, 90 diastolic (mmHg), averaged across four assessments on at least two separate days • taking tricyclic antidepressants, lithium, SRI, or Haloperidol	Classic hallucinogens	N/A	N/A	≥ 8 hours spread over a month	N/A	≥ 1	At least two, if possible male and female co-therapy team

For Peer Review

Study	Design	Aims	*N*	Eligibility criteria		Substance	Dosage	Number of sessions	Preparation sessions	Administration sessions	Integration sessions	Therapist team
				Inclusion	Exclusion							
Johnson et al. (2014)	Open label pilot study	Assess the safety and feasibility of psilocybin as an adjunct to tobacco smoking cessation treatment	15	• Smoking at least 10 cigarettes per day • be healthy determined by medical interview • several unsuccessful quit attempts and still the desire to quit smoking	• Personal or family history of bipolar and/or psychotic disorders • drug dependence including alcohol (excluding nicotine) within the past 5 years	Psilocybin	1st session: 20 mg/70 kg 2nd and 3rd session: 30 mg/70kg (participants were allowed to switch to 20 mg/70 kg)	23 - 25 (15 support sessions)	4	2 - 3	2 - 3	N/A
Kaelen et al. (2018)	Qualitative investigation	Assess the influence of music on the acute experience and clinical outcomes of psychedelic therapy	19	• Score of 17 or above on 21-HAM-D indicating moderate to severe major depression • absence of improvements despite at least two different pharmaceutical antidepressant treatments for a minimum of 6 weeks within the current depressive episode	• Lifetime or family history of psychotic disorder • history of suicide attempts that required hospitalization • history of mania • having a blood or needle phobia • pregnant women • current drug or alcohol dependence	Psilocybin	1st session: 10 mg 2nd session: 25 mg	N/A	1	2	N/A	Two therapists, gender not specified
Kaelen in Grob & Grigsby (2021)	Book chapter	The use of music in psychedelic therapy	N/A			Psychedelics	N/A	N/A	N/A	N/A	N/A	N/A

For Peer Review

Study	Design	Aims	*N*	Eligibility criteria		Substance	Dosage	Number of sessions	Preparation sessions	Administration sessions	Integration sessions	Therapist team
				Inclusion	Exclusion							
~~Kafka and Gaarder (1964)~~	~~Descriptive~~	~~Effect of Therapist's LSD experience on therapeutic work~~	~~5~~	~~• Psychotherapists~~	~~N/A~~	~~LSD~~	~~75-250 µg~~	~~N/A~~	~~N/A~~	~~1 - 2~~	~~N/A~~	~~N/A~~
Kurland et al. (1967)	Quasi experiment	Treatment of alcoholic patients with LSD	69 male patients	N/A	N/A	LSD	450 mg	N/A	12 - 15 hours over approximately two weeks	1	N/A	Therapist and nurse, gender not specified
Luoma et al. (2019)	Opinion paper	Why contextual behavioral science may be uniquely positioned to potentially increase the efficacy of psychedelic-assisted therapy	N/A	N/A	N/A	Psychedelics	N/A	N/A	N/A	N/A	N/A	N/A
Malone et al. (2018)	Qualitative analysis	Outline several thematic similarities and differences across the various sessions	4	• Cancer-related anxiety and depression	N/A	Psilocybin	0.3 mg/kg	N/A	N/A	N/A	N/A	N/A
Martin (1964)	Descriptive	Outline the treatment of neurotic disorders with LSD using an analytical and behavioristic technique	N/A	N/A	N/A	LSD	N/A	20-60	N/A	N/A	N/A	N/A

For Peer Review

Study	Design	Aims	*N*	Eligibility criteria		Substance	Dosage	Number of sessions	Preparation sessions	Administration sessions	Integration sessions	Therapist team
				Inclusion	Exclusion							
Meckel (2019)	Book chapter	Describe personal experiences from more than 10 years of experience in psychedelic therapy	N/A	N/A	N/A	MDMA, LSD, 2C-B	N/A	N/A	N/A	N/A	N/A	N/A
Metzner (1998)	Review	Differences between psychedelic-assisted psychotherapy and shamanic healing	N/A			N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mitchell et al. (2021)	Randomized, double-blind, placebo-controlled phase 3 study	Assess the efficacy and safety of MDMA-assisted therapy in individuals with severe PTSD	90	• At least 18 years old • meeting the DSM-5 criteria for current PTSD with a symptom duration of ≥ 6 months • CAPS-5 total severity score of ≥ 35 • comply to study requirements and procedures during duration of study	• Primary psychotic disorder, bipolar I disorder, dissociative identity disorder, eating disorders with active purging, major depressive disorder with psychotic features, personality disorders • current alcohol and substance use disorders • pregnancy or lactation • any medical condition that could make receiving a sympathomimetic drug harmful	MDMA	80 - 120 mg; optional supplemental dose of 40 - 60 mg	15	3	3	9 (3x3 after each experimental session)	One or more two-person therapy teams, male/female preferred
Mithoefer (2017)	Manual	Manual for MDMA-Assisted Psychotherapy in the Treatment of PTSD	N/A	N/A	N/A	MDMA	N/A	N/A	N/A	N/A	N/A	N/A

For Peer Review

Study	Design	Aims	*N*	Eligibility criteria		Substance	Dosage	Number of sessions	Preparation sessions	Administration sessions	Integration sessions	Therapist team
				Inclusion	Exclusion							
Mithoefer et al. (2011)	Randomized, double-blind, placebo pilot study	Assess efficacy of MDMA-assisted psychotherapy for chronic PTSD	20	• Meet criteria for crime or war-related chronic PTSD • treatment-resistant symptoms defined as a CAPS score of 50 or above despite at least 3 months of prior SSRI or SNRI treatment in addition to at least 6 months of psychotherapy	• Borderline personality disorder or any current Axis I disorder except anxiety disorders, affective disorders other than bipolar disorder type 1, substance abuse or dependence in remission for more than 60 days, and eating disorder without active purging	MDMA	125 mg; optional 62.5 mg after 2 - 2.5 hours	12	2	2	8 (2x4 after each experimental session)	Male and female co-therapy team
Mithoefer et al. (2018)	Randomized, double-blind, dose-response, phase 2 clinical trial	Assess efficacy and safety of MDMA-assisted psychotherapy for chronic PTSD in first responders and military personnel	26	• Veterans, firefighters, or police officers with chronic PTSD • at least 18 years old • at least 6 months or more of PTSD • score of 50 or above on CAPS-4 • previously failed to respond to or tolerate pharmacotherapy or psychotherapy • permitted comorbid disorders: anxiety disorders, affective disorders except bipolar disorder type 1, substance abuse or dependence in remission for at least 60 days or more, and eating disorders without active purging	• Major medical conditions except controlled hypertension or adequately treated hypothyroidism • pregnant or nursing women and/or who are not practicing an effective means of contraception • unable to taper off any psychiatric medication except anxiolytics or sedative hypnotics	MDMA	Low dose/active control: 30 mg; supplemental dose of 15 mg after 1.5 - 2 hours Medium dose: 75 mg; supplemental dose of 37.5 mg after 1.5 - 2 hours Full dose: 125 mg; supplemental dose of 62.5 mg after 1.5 - 2 hours Low and medium dose groups have option to take part in open-label segment	11	3	Low/medium dose: 2 Full dose: 3 Last session is open label	6 (2x3 after each experimental session)	Male and female co-therapy team

For Peer Review

Study	Design	Aims	*N*	Eligibility criteria		Substance	Dosage	Number of sessions	Preparation sessions	Administration sessions	Integration sessions	Therapist team
				Inclusion	Exclusion							
Mithoefer et al. (2019)	Pooled Analysis of six double-blind RCT	Evaluation of six phase 2 trials to determine the study design for phase 3 trials of MDMA-assisted psychotherapy for PTSD	103	• At least 18 years old • chronic PTSD with symptoms lasting longer than 6 months • failure to respond to at least one treatment of pharmacotherapy or psychotherapy • CAPS-4 scores of 50 or above (all studies except MP-4) • CAPS-4 scores of 60 or above (MP-4)	• Lifetime history of psychotic disorder or bipolar disorder I • current borderline personality disorder and/or eating disorder with active purging • medical contraindications for MDMA • pregnant or nursing women • body weight below 48 kg • diagnosis of substance abuse disorders within 60 days of screening for five studies, within 6 months for one study • cardiovascular or cerebrovascular disease, except in one study: controlled hypertension and no other evidence of vascular disease could enroll after additional screening • unable to taper off psychiatric medication	MDMA	Placebo: 0 mg placebo; 25 mg, 30 mg, or 40 mg MDMA Experimental: 75, 100, or 125 mg MDMA	8 - 11	2 - 3	2 - 3	4 - 5	Male and female co-therapy teams, all but one team trained in MAPS Therapy training program

For Peer Review

Study	Design	Aims	*N*	Eligibility criteria		Substance	Dosage	Number of sessions	Preparation sessions	Administration sessions	Integration sessions	Therapist team
				Inclusion	Exclusion							
Monson et al. (2020)	Uncontrolled trial	Assess the safety, tolerability, and efficacy of MDMA-facilitated cognitive-behavioural conjoint therapy for PTSD	12	• One partner has current PTSD diagnosis according to CAPS-5 for at least six months • at least 18 years old • generally healthy • abstinence from psychiatric medication during study period • use of appropriate contraception	• Acute psychosis or mania • substance use disorder • pregnant or nursing women • weighing less than 48 kg	MDMA	75 - 100 mg; optional supplemental half-dose after 1.5 hours	15	3	2	10	
Moreno et al. (2006)	Double-blind proof-of-concept study phase I	Assess safety, tolerability, and clinical effects of psilocybin for individuals with OCD	9	• Current OCD diagnosis determined by SCID-4 • at least one failed treatment defined as at least 12 weeks with SRIs with no significant improvements • symptomatic at time of enrollment • abstinence from anti-depressants for at least two weeks, pharmaceutical and nutritional supplements for at least one week, and other prescription, over-the counter medication and drugs • prior experience	• Other psychiatric disorder than OCD • personal or family history of psychosis	Psilocybin	Very low dose: 25 µg/kg of body weight Low dose: 100 µg/kg of body weight Medium dose: 200 µg/kg of body weight High dose: 300 µg/kg of body weight	N/A	N/A	1 - 4	N/A	Whenever possible, male and female co-therapy team

For Peer Review

Study	Design	Aims	*N*	Eligibility criteria		Substance	Dosage	Number of sessions	Preparation sessions	Administration sessions	Integration sessions	Therapist team
				Inclusion	Exclusion							
				with indole-based psychedelics								
Nichols (2016)	Review	Comprehensive review of psychedelic research from 2004 to 2016	N/A			Psychedelics	N/A	N/A	N/A	N/A	N/A	N/A
Nielson and Guss (2018)	Review	Academic dialogue on the role of researchers' and clinicians' personal experience with psychedelic compounds	N/A			N/A	N/A	N/A	N/A	N/A	N/A	N/A

For Peer Review

Study	Design	Aims	*N*	Eligibility criteria		Substance	Dosage	Number of sessions	Preparation sessions	Administration sessions	Integration sessions	Therapist team
				Inclusion	Exclusion							
Noorani et al. (2018)	Qualitative analysis	Identify perceived mechanisms of change for smoking cessation and identify key themes in participant experiences and long-term outcomes	15	See Johnson et al., 2014	See Johnson et al., 2014	Psilocybin	See Johnson et al., 2014	See Johnson et al., 2014	See Johnson et al., 2014	See Johnson et al., 2014	See Johnson et al., 2014	Two study guides, gender not specified
Oehen et al. (2013)	Double-blind, active placebo RCT	Assess efficacy and safety of MDMA-assisted psychotherapy for treatment-resistant PTSD	12	• Diagnosed with PTSD • failure to respond to at least one treatment of psychotherapy or pharmacotherapy • may meet criteria for a mood disorder	• Significant medical conditions except for hypothyroidism under hormonal replacement • history of psychotic illness, bipolar disorder type I, dissociative identity and/or borderline personality disorder • substance dependence within 60 days of enrollment • prior exposure to MDMA more than five times or less than six months before enrollment • unable to taper off psychotropic medication	MDMA	Active placebo: 25 mg; optional 12.5 mg after 2 - 2.5 hours and option for open-label segment Experimental: 125 mg; optional 62.5 mg after 2 - 2.5 hours	15	2	3	9 (3x3 after each administration session)	Male and female co-therapy team
Oram (2012)	Review	History of LSD research after 1962	N/A			LSD	N/A	N/A	N/A	N/A	N/A	N/A

For Peer Review

Study	Design	Aims	*N*	Eligibility criteria		Substance	Dosage	Number of sessions	Preparation sessions	Administration sessions	Integration sessions	Therapist team
				Inclusion	Exclusion							
Ot'alora et al. (2018)	Randomized double-blind dose response comparison	Assessment of safety and efficacy of different doses of MDMA in MDMA-assisted psychotherapy for women with PTSD secondary to sexual assault	28	• At least 18 years old • PTSD for at least six months • score of 50 or above on CAPS-4 • failure to respond to at least one treatment of psychotherapy and/or psychopharmacotherapy • psychiatric medication needed to be tapered off • no other psychiatric disorder	• Pregnant or nursing women • medical or psychiatric contraindications for receiving MDMA	MDMA	Active comparator: 40 mg of MDMA; optional 20 mg after 1.5 hours and option for open-label segment Experimental: 100 or 125 mg of MDMA; optional 50 or 62.5 mg after 1.5 hours	11	3	2	6 (2x3 after each experimental session)	Male and female co-therapy team
Palhano-Fontes et al. (2019)	Parallel-arm, double-blind placebo RCT	Test the antidepressant effects of ayahuasca while controlling for placebo effect	29	• 18 - 60 years old • DSM-IV diagnosis of MDD • failure to respond to at least two antidepressant medications from different classes • score of 17 or above on HAM-D	• Prior experience with ayahuasca • current medical disease based on history • pregnant women • current or prior history of neurological disorders • personal or family history of schizophrenia, bipolar affective disorder, mania or hypomania • substance dependence • suicidal risk	Ayahuasca	Placebo: 1 ml/kg of liquid similar in taste and color to Ayahuasca Experimental: 0.36 mg/kg of N, N-DMT	N/A	N/A	1	N/A	At least two, gender not specified
Peill et al. (2022)	Descriptive study	Development of a new scale to measure psychological insight after a psychedelic experience: the Psychological Insight Scale	Study 1: 886 Study 2: 279	N/A	• Below 18 years old	Psilocybin/ magic mushrooms/ truffles, Ayahuasca, DMT, LSD or 1P-LSD, San Pedro, ketamine, 5MEO-DMT	N/A	N/A	N/A	N/A	N/A	N/A

For Peer Review

Study	Design	Aims	*N*	Eligibility criteria		Substance	Dosage	Number of sessions	Preparation sessions	Administration sessions	Integration sessions	Therapist team
				Inclusion	Exclusion							
Phelps (2017)	Review	Competencies of psychedelic therapists	N/A			N/A	N/A	N/A	N/A	N/A	N/A	N/A
Phelps (2019)	Book chapter	Training of psychedelic therapists	N/A			N/A	N/A	N/A	N/A	N/A	N/A	N/A
Richards (2016)	Opinion paper	Personal account of 25 years of clinical research experience	N/A			N/A	N/A	N/A	8 hours spread over two weeks	N/A	N/A	N/A
Rosemann et al. (2018)	Follow-up analysis to Carhart-Harris et al., 2016	Whether Oceanic Boundlessness and Dread of Ego Dissolution predict long-term positive outcomes	20	• Major depression of a moderate to severe degree • score of 17 or above on the 21-item HAM-D • no improvement despite two adequate courses of antidepressant treatment of different pharmacological classes lasting at least 6 weeks within the current depressive episode	See Carhart-Harris et al., 2016	Psilocybin	1st session: 10 mg 2nd session: 25 mg	5	1	2	2	Two therapists, gender not specified
Ross et al. (2016)	Double-blind, placebo-	Assess efficacy of psilocybin in reducing anxiety	29	• Lifetime diagnosis of cancer • estimated life	• Score of less than 8 on the HADS at baseline • medical	Psilocybin	Active placebo: 250 mg niacin	11	3	2	6 (2x3 after each	Usually male and female co-therapy team

For Peer Review

Study	Design	Aims	*N*	Eligibility criteria		Substance	Dosage	Number of sessions	Preparation sessions	Administration sessions	Integration sessions	Therapist team
				Inclusion	Exclusion							
	controlled, crossover trial	and depression compared to active control and psychotherapy in patients with life-threatening cancer		expectancy of at least one year • DSM-IV diagnosis of acute stress disorder, generalized anxiety disorder, anxiety disorder due to cancer, adjustment disorder with anxious features • any stage of cancer diagnosis	contraindications, such as epilepsy, renal disease, diabetes, abnormal liver function, severe cardiovascular disease, malignant hypertension • baseline BP > 140/90 • personal history or family history of schizophrenia, bipolar affective disorder, delusional disorder, schizoaffective disorder or other psychotic spectrum illness • current substance use disorder • medication contraindications: anti-seizures medications, insulin, oral hypoglycemics, clonidine, aldomet, cardiovascular medications, anti-psychotics, anti-depressants and mood stabilizers		Experimental: 0.3 mg/kg				administration session)	
Savage (1957)	Opinion paper	Effects of LSD and mescaline on therapeutic relationship	N/A			LSD, Mescaline	LSD: 50 - 150 µg Mescaline: 250 mg	N/A	N/A	N/A	N/A	N/A

For Peer Review

Study	Design	Aims	*N*	Eligibility criteria		Substance	Dosage	Number of sessions	Preparation sessions	Administration sessions	Integration sessions	Therapist team
				Inclusion	Exclusion							
Sessa (2017)	Review	MDMA as PTSD Treatment	N/A			MDMA	N/A	N/A	N/A	N/A	N/A	N/A
Sessa (2019)	Review	Therapeutic applications of MDMA	N/A			MDMA	N/A	N/A	N/A	N/A	N/A	N/A
Sessa et al. (2019)	Preliminary data of proof-of-concept study	Safety and tolerability of first four patients	4	• Primary diagnosis of AUD who have successfully undergone community alcohol detoxification	• History of psychosis • personality disorder • serious suicidal risk • cardiac disease • severe liver disease • unstable hypertension • dependence on drugs other than alcohol • regular user of 'ecstasy' • pregnant or nursing women	MDMA	125 mg; optional 62.5 mg booster dose after 2 hours	10	N/A	2	N/A	Male and female co-therapy team
Sessa et al. (2021)	Open-label safety and tolerability proof-of-	Assess the safety and tolerability of MDMA-assisted psychotherapy	14	• 18 - 65 years old • primary diagnosis of AUD (as defined by DSM-IV) • successful alcohol detoxification	• Lacking capacity • lifetime history of psychotic disorder, bipolar affective disorder type 1 or personality disorder	MDMA	125 mg with a booster dose of 62.5 mg after 2 hours	10	6	2	2	Male and female co-therapy team

For Peer Review

Study	Design	Aims	*N*	Eligibility criteria		Substance	Dosage	Number of sessions	Preparation sessions	Administration sessions	Integration sessions	Therapist team
				Inclusion	Exclusion							
	concept study	for AUD post detoxification		• effective use of contraception	• serious suicide risk as determined by the C-SSRS • relevant abnormal clinical findings that render the subject unsuitable for study • regular user of ecstasy • currently taking or unwilling/unable to stop any medications likely to interact with MDMA • regular use of other drugs, such as benzodiazepines, synthetic cannabinoids, cocaine and heroin • pregnant or nursing women • taken part in a study involving an investigational product in the last three months • patients who might face additional risks from immunosuppression							
Sessa, Higbed, and Nutt (2019)	Review	Potential therapeutic applications for MDMA therapy	N/A			MDMA	N/A	N/A	N/A	N/A	N/A	N/A

For Peer Review

Study	Design	Aims	*N*	Eligibility criteria		Substance	Dosage	Number of sessions	Preparation sessions	Administration sessions	Integration sessions	Therapist team
				Inclusion	Exclusion							
Sloshower et al. (2020)	Opinion paper	Psychedelic-assisted psychotherapy within an ACT framework for depression	N/A			Classic psychedelics	N/A	10	2	2	6	N/A
Sloshower et al. (2020)	Manual	MDD	N/A			Psilocybin	Moderate to high dose	8	2	2	4	Therapist and physician, gender not specified
Spencer (1963)	Opinion paper	Group therapy with LSD		• Female • "bad, if not hopeless, prognosis who had failed to respond to all other treatments."	• Psychotic disorder	LSD	200 - 1500 µg	N/A	N/A	N/A	N/A	Male therapist, female nurse
Spencer (1964)	Opinion paper	N/A	N/A			LSD	N/A	N/A	N/A	N/A	N/A	Ideally female psychiatric nurse and doctor
Spriggs et al. (2021)	Study protocol	Assess the feasibility, brain mechanisms, and preliminary outcomes of psilocybin-assisted psychotherapy for anorexia nervosa	20 female participants	• 21 - 65 years old • DSM-5 diagnosis of anorexia nervosa for more than three years • current or past treatments have been unsuccessful • female at birth • BMI ≥ 15 kg/m2 • medically stable • use of appropriate contraception	• Lifetime history of psychotic disorder, mania, or personality disorder • family history of psychotic disorder • unstable physical condition • medical condition not suitable for psilocybin, MRI, or EEG • history of laxative abuse in the past three months • drug dependence in the past six months • present or past suicide risk or attempts • currently inpatient • pregnant or nursing women • enrolled in another	Psilocybin	Maximum of 25 mg	9	3	3	3	Two therapists, gender not specified

For Peer Review

Study	Design	Aims	*N*	Eligibility criteria		Substance	Dosage	Number of sessions	Preparation sessions	Administration sessions	Integration sessions	Therapist team
				Inclusion	Exclusion							
					clinical trial in the last three months							
Strickland et al. (2021)	Follow-up analysis to Johnson et al. (2014, 2017)	Assess the effects of the musical genre played during sessions of a psilocybin study for tobacco smoking cessation	Subsample of 10	• Smoke at least 10 cigarettes per day • report a current desire to stop smoking cigarettes • be physically healthy as determined by medical screening	• Family history of psychotic or bipolar disorders • history of substance use disorder other than nicotine in the past 5 years	Psilocybin	1st session: 20 mg/70 kg 2nd session: 30 mg/70 kg	See Johnson et al. (2014, 2017)	See Johnson et al. (2014, 2017)	3	See Johnson et al. (2014, 2017)	See Johnson et al. (2014, 2017)
Tai et al. (2021)	Descriptive study	Outline the development and practical implementation of a therapist training program of psychological support within a current RCT of psilocybin therapy for people experiencing treatment-resistant depression	216	• Mental health care practitioner with a professional license in good standing • have clinical experience • minimum master's degree	N/A	Psilocybin	Low: 1 mg Medium: 10 mg High: 25 mg	N/A	N/A	N/A	N/A	Two therapists, gender not specified
Thomas & Malcolm in Grob & Grigsby (2021)	Book chapter	Review the adverse effects of psychedelics	N/A	N/A	MDMA: history of epilepsy, uncontrolled hypertension, stroke, myocardial infarction, heart failure, arrhythmias, or other advanced cardiovascular conditions, unable to discontinue antidepressants at least 2 weeks prior to MDMA Ayahuasca: unable to avoid foods and drugs with interaction potential prior to ayahuasca use,	Psychedelics	N/A	N/A	N/A	N/A	N/A	N/A

For Peer Review

Study	Design	Aims	*N*	Eligibility criteria		Substance	Dosage	Number of sessions	Preparation sessions	Administration sessions	Integration sessions	Therapist team
				Inclusion	Exclusion							
					particularly susceptible to electrolyte abnormalities Ibogaine: cardiac diseases, such as coronary artery disease, history of myocardial infarction, angina, concurrent use with drugs of abuse or medications that inhibit CYP2D6 or prolong the QTc interval Ketamine: unable to avoid drugs that interfere with glutamate or enhance neurotransmission of GABA, or drugs that inhibit or induce CYP3A4, CYP2C9 or CYP2B6 enzyme metabolism of oral ketamine							
Twemlow and Bowen (1979)	Review and case studies	Management of acute psychedelic crises and their after-effects	N/A				N/A	N/A	N/A	N/A	N/A	N/A
Wagner et al. (2019)	Case study	Cognitive Behavioral Conjoint Therapy for PTSD (CBCT) combined with MDMA for PTSD	2	• At least 18 years old • one partner with diagnosis of PTSD	• Current substance use disorder • active suicidal planning or intent • mania and/or psychosis (applies to both partners) • severe partner aggression • both partners have diagnosis of PTSD • unable to taper off any psychiatric medication	MDMA	Case study: 1st session: 75 mg; supplemental half-dose (37.5 mg) after 1.5 hours 2nd session: 100 mg; supplemental half-dose (50 mg) after 1.5 hours	23 (15 modules of CBCT)	4	2	2	Manual: Two therapists, gender not specified Case study: male and female co-therapy team

For Peer Review

Study	Design	Aims	*N*	Eligibility criteria		Substance	Dosage	Number of sessions	Preparation sessions	Administration sessions	Integration sessions	Therapist team
				Inclusion	Exclusion							
Walsh and Thiessen (2018)	Narrative review	Potential for third wave behavior therapies to serve as adjuncts to psychedelic-assisted therapy	N/A				N/A	N/A	N/A	N/A	N/A	N/A
Watts (2021)	Manual	Describe the steps, procedures, and scripts used in the "Psilodep" study and how the ACE model was incorporated into the study protocols	12	See Carhart-Harris et al., 2016	See Carhart-Harris et al., 2016	Psilocybin	1st session: 10 mg 2nd session: 25 mg	4-6	1	2 (1x low dose, 1x high dose)	3 (after low dose one via telephone, after high dose two in-person sessions one week apart)	Two therapists, gender not specified
Watts and Luoma (2020)	Opinion paper	Integration of Accept, Connect, Embody model in psychedelic-assisted psychotherapy	N/A			Psilocybin	N/A	N/A	N/A	N/A	N/A	N/A
Whitfield (2021)	Opinion paper	Outline a coherent theoretical foundation for a CBS-consistent psychedelic-assisted therapy	N/A			Psilocybin	N/A	N/A	N/A	N/A	N/A	N/A
Wolff et al. (2020)	Opinion paper	Outlining how a cognitive-behavioral model of psychedelic therapy promotes acceptance	N/A			N/A	N/A	N/A	N/A	N/A	N/A	N/A

For Peer Review

Study	Design	Aims	*N*	Eligibility criteria		Substance	Dosage	Number of sessions	Preparation sessions	Administration sessions	Integration sessions	Therapist team
				Inclusion	Exclusion							
Wolfson et al. (2020)	Phase 2 double-blinded, randomized, placebo-controlled trial with an open-label crossover	Assess safety and efficacy of MDMA-assisted psychotherapy, for patients with cancer or non-dementing neurological diseases	18	• At least 18 years old • diagnosis of life-threatening cancer or non-dementing neurological illness that was ongoing or in remission with risk of recurrence and had an estimated life expectancy of at least nine months	• Ongoing primary treatment for their illness • medical contraindications • weight less than 48 kg • pregnant or nursing women • diagnosis of psychotic disorders, bipolar disorder I, dissociative identity disorder, or eating disorder with active purging • unable to safely taper off psychiatric medications	MDMA	Placebo: 125 mg lactose Experimental: 125 mg; optional dose of 62.5 mg MDMA	11	3	2	6 (2x3 after each experimental session)	Male and female co-therapy team

For Peer Review

Appendix B

Safety Characteristics Clinical Studies

Study	Clinical Target	Design	Pre-diagnostics	Post-diagnostics	Screening Tools	Setting	Contextual preparation	Physiological preparation	Psychological preparation
Anderson et al. (2020)	Distress, Depression, Grief (Long-term AIDS survivors)	Open-label mixed-methods pilot study	AUDIT, ART Medication Adherence Scale, Concomitant Therapeutics Checklist, Centers for Epidemiologic Studies Depression Scale—Revised, Demoralization Scale—II, DUDIT, Duke UNC Functional Social Support Questionnaire-5, Experiences in Close Relationships scale—Modified 16, International Personality Item Pool—Openness to Experience-20, Inventory of Complicated Grief, MQoL-Revised-Short, Multidimensional Assessment of Interoceptive Awareness, Nature Relatedness Scale Short Form, PCL-5, PTGI-Short Form, Social Connectedness Scale-Revised, Schedule of Attitudes towards Hastened Death, STAI, C-SSRS, Clinical Global Impressions scale	ART Medication Adherence Scale, Centers for Epidemiologic Studies Depression Scale—Revised, Demoralization Scale—II, Duke UNC Functional Social Support Questionnaire-5, Experiences in Close Relationships scale—Modified 16, Inventory of Complicated Grief, MQoL- Revised-Short, Nature Relatedness Scale Short Form, PCL-5, Schedule of Attitudes towards Hastened Death, PTGI-Short Form, Social Connectedness Scale-Revised, STAI, International Personality Item Pool—Openness to Experience-20, Multidimensional Assessment of Interoceptive Awareness, HARSI, Montreal Cognitive Assessment, Clinical Global Impressions scale, Client Satisfaction Scale, HIV and Abuse Related Shame Inventory Concomitant Therapeutics Checklist	General: vital signs, physical exam, mental status exam, medical and psychiatric history Laboratory: blood count, metabolic panel, urinalysis, urine toxicology, HIV viral load, Other: Montreal Cognitive Assessment, ECG. SCID-5, C-SSRS, ART Medication Adherence Scale, Centers for Epidemiologic Studies Depression Scale—Revised, Demoralization Scale—II, Inventory of Complicated Grief, MQoL-Revised-Short, LEC-5, PCL-5, Schedule of Attitudes towards Hastened Death, STAI	Controlled clinical setting: Langley Porter Psychiatric Institute	Room with comfortable furniture	• AE were recorded • vital signs monitored throughout experimental session • study physician was on call • emergency department less than a minute away • anxiolytic medication available (e.g., lorazepam)	• Modified Brief Supportive Expressive Group Therapy by replacing autohypnosis exercises with breathing exercises and guided meditations

For Peer Review

Bogenschutz et al. (2015)	Alcohol dependence	Single-group proof-of-concept study	TLFB, SIP, SOCRATES 8A, AASE, PACS, POMS, Hood Mysticism Scale, PEQ, ASPIRES Spiritual Transcendence Scale, Brief Multidimensional Measure of Religiousness/Spirituality, NEO-PI-3, Schwartz Value Survey	Intensity subscale of the HRS, 5D-ASC, SOCQ, ARCI, TLFB, SIP, SOCRATES 8A, AASE, PACS, POMS, Monitor Session Rating Form (from monitors)	General: physical examination, medical history, BMI Laboratory: liver function tests, complete blood count, blood tests, chemistries, urinalysis, serum pregnancy test Other: SCID-4 Axis I, fertile women completed a menstrual calendar at each assessment visit, and urine pregnancy tests prior to each drug administration session, CIWA-Ar at screening and prior to each drug administration session	Controlled clinical setting	Room with comfortable furniture, pre-selected music, eyeshades, headphones	• Rescue medications were available for hypertension (sublingual nitroglycerin 0.4 mg), anxiety (lorazepam 1–2 mg PO/IM), acute psychosis (ziprasidone 10–20 mg PO/IM) • vital signs were taken at each visit and monitored during experimental sessions • AE were recorded	• Motivational Enhancement Therapy
Bouso et al. (2008)	PTSD	Double-blind, ascending-dose study, randomized and placebo-controlled within each dose condition	Semi-Structured Interview about Sexual Assault, Severity of Symptoms Scale for PTSD, STAI, BDI, HAM-D, Modified Fear Scale, Maladjustment Scale, RSES	Semi-Structured Interview about Sexual Assault, Severity of Symptoms Scale for PTSD, STAI, BDI, HAM-D, Modified Fear Scale, Maladjustment Scale, RSES, HRS, UKU Scale of Secondary Effects, Penn Helping Alliance Questionnaire	General: medical history Laboratory: urinalysis, pregnancy test Other: ECG, SCID-4	Controlled clinical setting: hospital	Patients lied in bed with eyes closed and pre-selected music	• BP and HR monitored throughout experimental session • AE were recorded	• Psychoeducation • specific objectives were developed for each participant • relaxation techniques

For Peer Review

Carhart-Harris et al. (2016)	Treatment-resistant MDD	Open-label, single-arm pilot study	fMRI, QIDS, BDI, STAI-T, HAM-D, SHAPS, MADRS, GAF	fMRI, QIDS, BDI, STAI-T, HAM-D, SHAPS, MADRS, GAF	General: physical and mental health background, BP, HR, physical exam Laboratory: blood tests, urine drug screening Other: MINI, 21-item HAM-D, MADRS, GAF, QIDS, BDI, STAI-T, SHAPS, ECG, breathalyzer test for alcohol use	Controlled clinical setting: The National Institute for Health Research/Wellcome Trust Imperial Clinical Research Facility	Dosing room that was pre-decorated, music (see Kaelen et al. 2016, 2018), Living room-like with music over headphones and/or speakers	• BP, HR, and observer ratings of the intensity of psilocybin's acute psychoactive effects monitored • tranquilizing medications were available (oral lorazepam and risperidone) • AE were recorded	• Psychoeducation • sample of session music
Carhart-Harris et al. (2021)	MDD	Double-blind RCT	fMRI, QIDS-SR-16, QIDS-SR-14, BDI-1A, HAM-D-17, MADRS, FS, STAI, BEAQ, WSAS, SHAPS, WEMWBS, SIDAS	Functional MRI, QIDS-SR-16, QIDS-SR-14, BDI-1A, HAM-D-17, MADRS, FS, STAI, BEAQ, WSAS, SHAPS, WEMWBS, SIDAS Psychotropic-Related Sexual Dysfunction Questionnaire, Laukes Emotional Intensity Scale, Emotional Breakthrough Inventory, Post-Treatment Changes Scale	General: medical, family, and psychiatric history, physical exam Laboratory: urine drug testing, baseline blood tests, pregnancy test Other: HAM-D-17, MINI, ECG	Controlled clinical setting: National Institute for Health Research Imperial Clinical Research Facility	Pre-selected music, headphones, eyeshades, and bed	• AE were recorded	• Psychoeducation • visual exercise following the Accept Connect Embody Model • practice run of the experimental session
Danforth et al. (2015)	Social anxiety in autistic adults	Placebo-controlled, double-blind pilot study	LSAS, TASIT, ERQ, BDI, PSS, IRI, RSES, STAI	LSAS, TASIT, ERQ, BDI, PSS, IRI, RSES, STAI	General: physical exam Laboratory: baseline labs drawn for measurement of plasma OT, vasopressin, and cortisol Other: SCID-I-RV, LSAS, ADOS-2, ECG	Controlled clinical setting: clinical research center	Room with comfortable furniture, pre-selected music, art supplies, journals, silent introspection	• Water intake, BP, body temperature, and HR monitored throughout experimental session • C-SSRS and SUD assessed hourly • AE were recorded	• Psychoeducation • mindfulness training

For Peer Review

Danforth et al. (2018)	Social fear and anxiety in autism	Blinded, placebo-controlled pilot study	LSAS, BDI-II, PSS, IRI, RSES, STAI, TAS-20, TASIT, ERQ	LSAS, BDI, STAI, PSS, IRI, RSES, TAS-20, TASIT, ERQ	General: N/A Laboratory: N/A Other: SCID-4 Axis I Research Version, C-SSRS, LSAS, Autism Diagnostic Observation Schedule	Controlled clinical setting	Room with comfortable furniture, pre-selected music, eyeshades, headphones, objects for self-regulating behavior (e.g., fidgeting, "stimming"), private lavatory	• BP, body temperature, SUD, and HR monitored throughout experimental session • AE and concomitant medications recorded each session • C-SSRS was done before and after each treatment days	• Standardized mindfulness-based therapy adapted from dialectical behavioral therapy • guided progressive muscle relaxation exercise directly before administration
Davis et al. (2021)	Investigate the effect of psilocybin therapy in patients with MDD	Waiting list RCT	GRID-HAMD, C-SSRS, BDI II, PHQ-9, HAM-A, STAI, MRI	GRID-HAMD, C-SSRS, BDI II, PHQ-9, HAM-A, STAI, MEQ30, CEQ26, PEQ, MRI	General: physical exam, medical history Laboratory: blood test, urinalysis, laboratory tests Other: SCID-5, GRID-HAMD, ECG	Controlled clinical setting: Center for Psychedelic and Consciousness Research	Room with comfortable furniture, pre-selected music, eyeshades, headphones	• BP and HR monitored throughout experimental session • AE were recorded	According to Johnson et al. 2008
Gasser et al. (2014)	Anxiety	Double-blind, randomized, active placebo-controlled pilot study	STAI, European Cancer Quality of Life Questionnaire 30-item version, SCL-90-R, HADS, daily visual analog pain scale, Daily Anxiety/Pain Medication Diary	STAI, European Cancer Quality of Life Questionnaire 30-item version, SCL-90-R, HADS, daily visual analog pain scale, Daily Anxiety/Pain Medication Diary	General: N/A Laboratory: urine drug screen Other: SCID-4	Controlled clinical setting: Private practice office	Safe, quiet, and pleasant room, music	• BP and HR monitored • concomitant medications for depression, pain and anxiety were documented • physical examination by physician after the administration sessions • AE were recorded	• Psychoeducation

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Griffiths et al. (2016)	Anxiety and depression in life-threatening cancer patients	Two-session, double-blind cross-over design	HAM-D-17, HAM-A, BDI, HADS, STAI, POMS, BSI, MQoL, LOT-R, LAP-R Death Acceptance, Death Transcendence Scale, Purpose in Life Test, LAP-R Coherence, FACIT-Sp, Spiritual-Religious Outcome Scale, Faith Maturity Scale	HAM-D-17, HAM-A, BDI, HADS, STAI, POMS, BSI, MQoL, LOT-R, LAP-R Death Acceptance, Death Transcendence Scale, Purpose in Life Test, LAP-R Coherence, FACIT-Sp, Spiritual-Religious Outcome Scale, Faith Maturity Scale, HRS, 5D-ASC, Mysticism Scale (Experience-specific 9-point scale), SOCQ, PEQ	General: cardiovascular screening (≥ four blood pressure assessment occasions over at least two separate days), neurological exam: Laboratory: N/A Other: N/A	Controlled clinical setting	Room with comfortable furniture, pre-selected music, eyeshades	• BP and HR monitored throughout experimental session • AE were recorded	According to Johnson et al., 2008
Grob et al. (2011)	Advanced cancer and reactive anxiety	Double-blind, placebo-controlled study	BP, HR, body temperature, BDI, POMS, STAs	BP, HR, body temperature, BDI, POMS, STAI, 5D-ASC, Brief Psychiatric Rating Scale	General: medical and psychiatric screening Laboratory: N/A Other: MRI, communication with treating oncologists, formal psychiatric diagnostic interviews	Controlled clinical setting: hospital clinical research unit	Room with comfortable furniture, pre-selected music, eyeshades	• BP and HR monitored throughout experimental session • AE were recorded	• Psychoeducation
Jardim et al. (2021)	PTSD	Open label pilot study	CAPS-4, PCL-L, PTGI, C-SSRS, BDI-II, DES II, PSQI, DSM-IV GAF	CAPS-4, PCL-L, PTGI, C-SSRS, BDI-II, DES II, PSQI, DSM-IV GAF, MEQ30, SUD	N/A	Controlled clinical setting	N/A	N/A	N/A
Johnson et al. (2014)	Smoking cessation	Open label pilot study	Breath CO, Urine cotinine samples, smoking TLFB assessment, Questionnaire on Smoking Urges, Smoking Abstinence Self-Efficacy scale, Wisconsin Smoking Withdrawal Scale, Visual Effects Questionnaire, Mysticism Scale, Fagerström Test for Cigarette Dependence	Breath CO, Urine cotinine samples, smoking TLFB assessment, Questionnaire on Smoking Urges, Smoking Abstinence Self-Efficacy scale, Wisconsin Smoking Withdrawal Scale, Visual Effects Questionnaire, Mysticism Scale, Post-session headache	General: N/A Laboratory: blood tests, urinalysis Other: SCID-4-TR	Controlled clinical setting: Johns Hopkins Bayview campus	Room with comfortable furniture, pre-selected and personally selected music, eyeshades	• Safety guidelines according to Johnson et al., 2008 • BP and HR monitored throughout session • physician and rescue medication were available • AE were recorded	• Psychoeducation • body-scan meditation • development of brief motivational statement for smoking cessation • guided imagery exercise • scented oil was smelled before each exercise and used when participant experienced cravings

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				interview, SOCQ, PEQ					
Mitchell et al. (2021)	Assess the efficacy and safety of MDMA-assisted therapy in individuals with severe PTSD	Randomized, double-blind, placebo-controlled phase 3 study	CAPS-5, SDS, Dissociative Subtype of PTSD Interview, ACE, BDI-II, Chronic Pain Grade Scale, EQ-5D-5L, Inventory of Altered Self Capacities, IPF, SCS, TAS-20	CAPS-5, SDS, Dissociative Subtype of PTSD Interview, ACE, BDI-II, Chronic Pain Grade Scale, C-SSRS, LEC-5, EQ-5D-5L, Inventory of Altered Self Capacities, IPF, SCS, TAS-20, AUDIT, DUDIT, Self-reported Nicotine Use, Eating Attitudes Test, HPQSF, Utilization of Facility-based and Emergent Care	General: medical history, pre-study medications, physical exam Laboratory: laboratory testing (including pregnancy and drug tests: Other: PCL-5 with LEC-5, MINI for DSM-5, SCID-5-SPQ and –PD, DDIS, Lifetime C-SSRS, ECG	Controlled clinical setting	Room with comfortable furniture, eyeshades, program of music	• If applicable, qualitative urine drug screen and pregnancy screen • BP, body temperature and HR measured pre-substance and at the end of the experimental session • AE were recorded	• Psychoeducation
Mithoefer et al. (2011)	Treatment-resistant PTSD	Blinded, placebo-controlled study	CAPS, Impact of Events Scale-Revised, SCL-90-R, RBANS, Paced Auditory Serial Addition Task, Rey-Osterrieth Complex Figure, Working Alliance Inventory, NEO-PI-R	CAPS, Impact of Events Scale-Revised, SCL-90-R, RBANS, Paced Auditory Serial Addition Task, Rey-Osterrieth Complex Figure, RRPQ	General: medical history, physical exam, Laboratory: serum chemistry profile, complete blood count, thyroid-stimulation hormone, free thyroxine, HIV serology, urinalysis Other: SCID Axis I diagnosis, SCID-II for personality disorders, CAPS, ECG	Controlled clinical setting: outpatient office with facilities	Room with comfortable furniture, pre-selected music, eyeshades, headphones	• BP, pulse, SUD, and temperature monitored throughout experimental sessions • equipment and drugs for treatment of medical emergencies • an emergency physician and nurse were on site • AE were recorded	• Psychoeducation
Mithoefer et al. (2018)	PTSD	Randomized, double-blind, dose-response, phase 2 trial	CAPS-4, BDI-II, PSQI, PTGI, NEO-PI-R, self-reported DES II, GAF, clinician-administered C-SSRS	CAPS-4, BDI-II, PSQI, PTGI, NEO-PI-R, self-reported DES II, GAF, clinician-administered C-SSRS	General: N/A Laboratory: N/A Other: CAPS-4, • SCID-4 Axis I disorders, assessment of non-psychiatric medical criteria by physician	Controlled clinical setting: outpatient psychiatric clinic	Room with comfortable furniture, eyeshades, pre-selected music	• BP, HR, and body temperature monitored throughout sessions • AE were recorded	According to Mithoefer, 2017

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Monson et al. (2020)	Assess the safety, tolerability, and efficacy of MDMA-facilitated cognitive-behavioural conjoint therapy for PTSD	Uncontrolled trial	CAPS-5, PCL-5, BDI-II, ERQ, IRI, PSQI, PTGI, TAS-20, Quality of Relationships Inventory, Significant Others' Responses to Trauma Scale, CTS-2, IPF, Miller Social Intimacy Scale, Trauma and Attachment Beliefs Scale, Multiscale Dissociation Inventory, Interpersonal Closeness Scale, C-SSRS, Somatic Symptoms	CAPS-5. PCL-5, BDI-II, ERQ, IRI, PSQI, PTGI, TAS-20, Quality of Relationships Inventory, Significant Others' Responses to Trauma Scale, CTS-2, IPF, Miller Social Intimacy Scale, Trauma and Attachment Beliefs Scale, CTS-2, IPF, Multiscale Dissociation Inventory, Interpersonal Closeness Scale, RRPQ, LTFU	General: physical exam, medical and psychiatric history Laboratory: laboratory tests, drug, and pregnancy screen, if applicable Other: SCID-RV, ECG	Controlled clinical setting	Room with comfortable furniture, eyeshades, pre-selected music	• BP, HR, SUD, and body temperature monitored throughout experimental sessions • AE were recorded	• CBCT including psychoeducation, relational safety, communication skills, dyadic cognitive intervention, and tools for behavioral approach
Moreno et al. (2006)	OCD	Double-blind proof-of-concept study phase I	Yale-Brown Obsessive Compulsive Scale, visual analog scale	Yale-Brown Obsessive Compulsive Scale, visual analog scale, HRS	General: physical exam Laboratory: blood test, urine and pregnancy, screening, urine drug screen Other: ECG	Controlled clinical setting: outpatient offices at the University of Arizona Health Sciences Center	Eyeshades, pre-selected music	• Vital signs monitored throughout sessions • AE were recorded	• Psychoeducation
Oehen et al. (2013)	Treatment-resistant PTSD	Double-blind, active placebo RCT	CAPS, Posttraumatic Diagnostic Scale, SCID-I substance abuse module	CAPS, Posttraumatic Diagnostic Scale, RRPQ, SCID-I substance abuse module	General: medical history, physical exam Laboratory: metabolic profile, measurement of thyroid hormones, serum electrolytes, HIV test, urine drug screen, pregnancy test Other: CAPS, SCID I and II, stress ECG for subjects > 40 years and family history of coronary heart disease	Controlled clinical setting: group psychotherapy room in clinic	Patients sat reclined on mattress during session, pre-selected music	• BP, HR, body temperature, and SUD monitored throughout session • rescue medication was available • AE were recorded	According to Mithoefer, 2011

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Ot'alora et al. (2018)	Treatment-resistant PTSD	Randomized double-blind dose response comparison	CAPS-4, BDI-II, PSQI, DES II, C-SSRS	CAPS-4, BDI-II, PSQI, DES II, C-SSRS	General: physical exam Laboratory: blood tests, pregnancy test for females Other: SCID-4, CAPS-4, ECG, neuropsychological measures	Controlled clinical setting: outpatient clinic	Room with comfortable furniture, pre-selected music, eyeshades, headphones	• BP, HR, and body temperature monitored throughout experimental sessions • AE were recorded	• Psychoeducation • several relaxation techniques, e.g., breath control respiration • gain realistic purpose and deep knowledge about the impact of the event
Palhano-Fontes et al. (2019)	Treatment-resistant MDD	Parallel-arm, double-blind placebo RCT	MADRS, HAM-D, Clinician-Administered Dissociative States Scale, Brief Psychiatric Rating Scale, Young Mania Rating Scale	MADRS, HAM-D, psychiatric evaluation, debriefing of experience, HRS, MEQ30, Clinician-Administered Dissociative States Scale, Brief Psychiatric Rating Scale, Young Mania Rating Scale	General: medical history, mental health evaluation, screen personal/ family history of mania or bipolar disorder Laboratory: N/A Other: SCID for Axis I	Controlled clinical setting: hospital	Room with comfortable furniture, pre-selected music	N/A	• Psychoeducation
Ross et al. (2016)	Anxiety and depression in cancer patients	Double-blind, placebo-controlled, crossover trial	HADS, STAI, BDI, DEM scale, Hopelessness Assessment and Illness, Death Anxiety Scale, Death Transcendence Scale, World Health Organization Qualify of Life scale - brief version, FACIT-Sp, HR, BP	HADS, STAI, BDI, DEM scale, Hopelessness Assessment and Illness, Death Anxiety Scale, Death Transcendence Scale, World Health Organization Qualify of Life scale - brief version, FACIT-Sp, MEQ30, PEQ	General: cardiovascular screening (≥ four blood pressure assessment occasions over at least two separate days) Laboratory: N/A Other: SCID-4	Controlled clinical setting: specially prepared room at the NYU Bluestone Center for Clinical Research	Room with comfortable furniture, pre-selected music, eyeshades, personal items	• BP and HR monitored throughout session • rescue medication was available (diazepam 5-10 mg, olanzapine 5-15 mg) • AE were recorded	• Psychoeducation
Sessa et al. (2021)	Assess the safety and tolerability of MDMA-assisted psychotherapy for AUD post detoxification	Open-label safety and tolerability proof-of-concept study	CIWA, C-SSRS, PHQ-9, GAD-7,	CIWA, C-SSRS, PHQ-9, GAD-7, POMS, Leeds Sleep Evaluation Questionnaire	General: physical and psychiatric history Laboratory: blood tests Other: SCID-4, MINI, PHQ-9, GAD-7, SADQ, SIP, ECG	Controlled clinical setting: treatment center	Pre-selected music	• Sedative medication was available for acute anxiety (lorazepam) • BP, HR, SUD, and body temperature monitored throughout experimental sessions • AE were recorded	• Motivational interviewing • third-wave cognitive–behavioural approaches

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Wolfson et al. (2020)	Assess the safety and efficacy of MDMA-assisted psychotherapy for patients with cancer or non-dementing neurological diseases	Phase 2 double-blinded, placebo-controlled RCT with an open-label crossover	STAI, MADRS, BDI-II, PSQI, PTGI, GAF, FACIT-Sp, FFMQ, DAP, SCS, C-SSRS	STAI, MADRS, BDI-II, PSQI, PTGI, GAF, FACIT-Sp, FFMQ, DAP, SCS, C-SSRS	General: physical exam Laboratory: blood tests Other: SCID, STAI, ECG, neuropsychological measures	Controlled clinical setting: outpatient psychiatric clinic	Room with comfortable furniture, pre-selected music, eyeshades	• BP, HR, and body temperature monitored throughout experimental sessions • AE were recorded	• Psychoeducation

Note. 5-Dimension Altered States of Consciousness = 5D-ASC; 21-item Hamilton Depression Rating scale = HAM-D; 17-item GRID-Hamilton Depression Rating Scale = GRID-HAMD; 17-item Hamilton Depression Rating Scale = HAM-D-17; 16-item Quick Inventory of Depressive Symptoms = QIDS; 16-item Quick Inventory of Depressive Symptomatology–Self-Report = QIDS-SR-16; 14-item Quick Inventory of Depressive Symptomatology–Self-Report = QIDS-SR-14; Addiction Research Center Inventory = ARCI; Adverse Childhood Experience Questionnaire = ACE; Adverse Events = AE; Alcohol Abstinence Self-Efficacy Scale = AASE; Alcohol Use Disorders Identification Test = AUDIT; Beck Depression Inventory—original version = BDI; Beck Depression Inventory 1A = BDI-1A; Beck Depression Inventory II = BDI-II; Brief Experiential Avoidance Questionnaire = BEAQ; Brief Symptom Inventory = BSI; Columbia-Suicide Severity Rating Scale = C-SSRS; Clinical Institute Withdrawal Assessment for Alcohol = CIWA; Clinical Institute Withdrawal Scale—Alcohol, revised = CIWA-Ar; Clinician-Administered PTSD Scale = CAPS; Death Attitudes Profile = DAP; Demoralization scale = DEM scale; Dissociative Experience Scale = DES II; Drug Use Disorders Identification Test = DUDIT; Electrocardiogram = ECG; Emotion Regulation Questionnaire = ERQ; EuroQol Five Dimensions-Five Levels Questionnaire = EQ-5D-5L; Five-Facet Mindfulness Questionnaire = FFMQ; Flourishing Scale = FS; Functional assessment of chronic illness therapy = FACIT; Functional assessment of chronic illness therapy – Spiritual Well-being Scale = FACIT-Sp; Functional magnetic resonance imaging = fMRI; Global Assessment of Functioning = GAF; Hamilton Anxiety Inventory = HAM-A; Hallucinogen Rating Scale = HRS; Health and Work Performance Absenteeism and Presenteeism Short Form = HPQSF; Hospitalized Anxiety and Depression Scale = HADS; Interpersonal Reactivity Index = IRI; Inventory of Psychosocial Functioning = IPF; Leibowitz Social Anxiety Scale = LSAS; Life Attitude Profile-Revised = LAP-R; Life Event Checklist—5 = LEC-5; Life Orientation Test Revisited = LOT-R; Long-term Follow-up Questionnaire = LTFU; Montgomery-Åsberg Depression Rating Scale = MADRS; Mystical Experience Questionnaire = MEQ; McGill Quality of Life Questionnaire = MQoL; Mini International Neuropsychiatric Interview = MINI; Neuroticism Extroversion Openness Personality Inventory-Revised = NEO-PI-R; Patient Health Questionnaire-9 = PHQ-9; Penn Alcohol Craving Scale = PACS; Perceived Stress Scale = PSS; Persisting Effects Questionnaire = PEQ; Pittsburgh Sleep Quality Index = PSQI; Post Traumatic Growth Inventory = PTGI; PTSD Checklist-Civilian Version = PCL-L; Inventory Profile of Moods States questionnaire = POMS; Repeatable Battery for the Assessment of Neuropsychological Status = RBANS; Reactions to Research Participation- Questionnaire-Short Form (Revised) = RRPQ; Revised Conflict Tactics Scale = CTS-2; Rosenberg Self-Esteem Scale = RSES; Self-Compassion Scale = SCS; Severity of Alcohol Questionnaire = SADQ; Sheehan Disability Scale = SDS; Short Inventory of Problems = SIP; Snaith-Hamilton Pleasure Scale = SHAPS; Spielberger's Trait Anxiety Inventory = STAI; Spielberger's State-Trait Anxiety Inventory - trait version only = STAI-T; Stages of Change Readiness and Treatment Eagerness Scale = SOCRATES 8A; States of Consciousness Questionnaire = SOCQ; Structured Clinical Interview for DSM = SCID; Subjective Units of Distress = SUD; Suicidal Ideation Attributes Scale = SIDAS; Symptom Checklist-90-Revised = SCL-90-R; The Awareness of Social Inference Test = TASIT; Time-line follow-back = TLFB; Toronto Alexithymia Scale = TAS-20; Warwick Edinburgh Mental Wellbeing Scale = WEMWBS; Work and Social Adjustment Scale = WSAS

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Appendix C

Safety Characteristics Remaining Literature

Study	Clinical Target	Design	Pre-diagnostics	Post-diagnostics	Screening Tools	Setting	Contextual preparation	Physiological preparation	Psychological preparation
Almond and Allan (2019)	PTSD/Trauma	Review	N/A	N/A	General: N/A Laboratory: N/A Other: assessments for domestic violence, substance abuse/dependency	N/A	N/A	• Licensed medical professional and nurse should be present	• Psychoeducation
Barone et al. (2019)	PTSD	Qualitative investigation, follow-up to Mithoefer et al. 2018	See Mithoefer et al., 2018	See Mithoefer et al., 2018	N/A	N/A	N/A	N/A	N/A
Barrett et al. (2018)	–	Review	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Bogenschutz (2013)	Alcohol dependence	Review		Self-reports and collateral information on days abstinent, heavy drinking days, drinks per drinking day, time to first drink, time to relapse, longest duration of abstinence; urine drug screening, quality of life, psychological and medical health questionnaires; substance experience and intensity (e.g., 5D-ASC, HRS); changes in mood and affect; anxiety, craving, self-efficacy, personality, and values	N/A	N/A	Music	N/A	• Psychoeducation • encouragement of positive expectancies • psychosocial treatment to heighten motivation (e.g., motivational interviewing) • treatment should be standardized by use of a manual

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Study	Clinical Target	Design	Pre-diagnostics	Post-diagnostics	Screening Tools	Setting	Contextual preparation	Physiological preparation	Psychological preparation
Bogenschutz and Forcehimes (2016)	Alcohol dependence	Study protocol	N/A	N/A	N/A	N/A	Room with comfortable furniture, pre-selected music, eyeshades, headphones	• If one of the therapists is not a physician, a physician should be immediately available • emergency medications available to treat hypertension, severe anxiety, and psychosis • mental status exam at the end of the session • follow-up on any adverse events	• Psychoeducation • Motivational Enhancement and Taking Action manual as therapy model • first four sessions are highly structured; the remaining sessions are individualized sessions adapted to the needs of the patient
Bogenschutz and Ross (2016)	–	Review	N/A	N/A	N/A	N/A	N/A	N/A	N/A
~~Buckman (1967)~~	~~–~~	~~Opinion paper~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~
Carlin et al. (2018)	PTSD	Manual	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Cohen and Eisner (1959)	–	Opinion paper	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Cosimano in Grob & Grigsby (2021)	–	Book chapter	N/A	N/A	General: medical and psychiatric interviews, physical exam, Laboratory: blood tests Other: ECG, completion of questionnaires, interviews	Controlled clinical setting	Room with comfortable furniture, pre-selected music, eyeshades, headphones	• Safety medication and physician available in case of emergency	• Psychoeducation • intention setting • practical information regarding the experimental sessions according to Johnson et al., 2008
~~Costello (1964)~~	~~–~~	~~Case studies~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~
~~Cutner (1959)~~	~~–~~	~~Review~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~

For Peer Review

Study	Clinical Target	Design	Pre-diagnostics	Post-diagnostics	Screening Tools	Setting	Contextual preparation	Physiological preparation	Psychological preparation
Danforth (2009)	–	Review	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Eisner (1964)	–	Observational study	To determine intelligence, Rorschach examinations were given to a random half of the sample	N/A	N/A	Controlled clinical setting	Living room-like with music	• Physician was present during sessions	N/A
Eisner (1997)	–	Review	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Gandy et al. (2020)	-	Review	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Garcia-Romeu and Richards (2018)	–	Review	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Greer and Tolbert (1998)	N/A	Review and case studies	N/A	Follow-up questionnaire that essentially repeated the same questions in the screening questionnaire was given to them to answer after one or two weeks and again after one to two years	General: questionnaire on medical, personal, and psychiatric history and other substance use Laboratory: N/A Other: brief screening via telephone, personal interview enquiring about purpose for session, spiritual orientation, significant losses	Client's or practitioner s' home	Eyeshades and headphones with music were available	N/A	• Activities to optimize the experience, such as fasting, meditation, or keeping a dream journal were encouraged
~~Gucker (1963)~~	~~–~~	~~Case study~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~
Gukasyan & Nayak (2021)	–	Review	N/A	N/A	N/A		Living room-like	• BP and HR monitored	

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Study	Clinical Target	Design	Pre-diagnostics	Post-diagnostics	Screening Tools	Setting	Contextual preparation	Physiological preparation	Psychological preparation
Haijen et al. (2018)	–	Prospective study	WEMWBS, TIPI, MODTAS, STAI-SF, SSS, MISS, SOP	11D-ASC, MEQ30, CEQ, WEMWBS, TIPI, MODTAS, STAI-SF, SSS, MISS, SOP	N/A	N/A	N/A	N/A	N/A
Hausner and Doležal (1963)	–	Quasi experiment	Questionnaire on Neurotic Symptoms "N 5", Lack of Satisfaction in Life, Manifest Anxiety Scale, special questionnaire about the run of the group Session, Test of Sympathy and Antipathy	LSD Sort List, questionnaire on Neurotic Symptoms "N 5", Lack of Satisfaction in Life, Manifest Anxiety Scale, special questionnaire about the run of the group session, Test of Sympathy and Antipathy	N/A	N/A	N/A	N/A	N/A
Horton et al. (2021)	–	Review	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Johnson et al. (2008)	–	Guidelines	N/A	N/A	General: physical exam Laboratory: blood chemistry profile, hematology, urinalysis Other: psychiatric interview (e.g., SCID), 12-lead ECG	Controlled clinical setting	Room with comfortable furniture, pre-selected music, eyeshades, headphones, ideally with private restroom for patient	• Physician should be available • rescue medication for hypertension, severe anxiety, psychosis (except haloperidol), and hallucinogen administration (e.g., ketanserin) were available • follow-up on possible perceptual disturbances (e.g., hallucinogen persisting perception disorder)	• Psychoeducation

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Study	Clinical Target	Design	Pre-diagnostics	Post-diagnostics	Screening Tools	Setting	Contextual preparation	Physiological preparation	Psychological preparation
Kaelen et al. (2018)	Treatment-resistant major depressive disorder	Qualitative investigation	QIDS	11D-ASC, visual analogue scale, QIDS, semi-structured interview	See Carhart-Harris et al., 2016	Controlled clinical setting: specially designed therapy room in Clinical Research Facility at Imperial College London	Living room-like, pre-selected music, headphones, and speakers	N/A	• Psychoeducation • expectations for the sessions
Kaelen in Grob & Grigsby (2021)	–	Book chapter	N/A	N/A	N/A			N/A	N/A
~~Kafka and Gaarder (1964)~~	~~–~~	~~Descriptive~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~	~~N/A~~
Kurland et al. (1967)	Alcohol dependence	Quasi experiment	"Comprehensive battery of intellectual functioning and impairment", MMPI for a few participants	"Comprehensive battery of intellectual functioning and impairment", MMPI for a few participants	N/A	Hospital setting	Room with comfortable furniture, pre-selected music, eyeshades, headphones	N/A	• Psychoeducation
Luoma et al. (2019)	–	Review	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Malone et al. (2018)	Anxiety and depression in cancer patients	Qualitative analysis	HADS, BDI, STAI, DEM scale, Hopelessness Assessment and Illness scale, Death Anxiety Scale, Death Transcendence Scale, WHO Quality of Life scale - brief version, FACIT-Sp	HADS, BDI, STAI, DEM scale, Hopelessness Assessment and Illness scale, Death Anxiety Scale, Death Transcendence Scale, WHO Quality of Life scale - brief version, FACIT-Sp	N/A	N/A	Living room-like with headphones and eyeshades	N/A	• Psychedelic psychotherapy model by Grof • meaning making intervention (Lee, 2008) • practices to spirituality or religion, yoga and meditation history, beliefs in heaven, hell, and surrounding death and afterlife

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Study	Clinical Target	Design	Pre-diagnostics	Post-diagnostics	Screening Tools	Setting	Contextual preparation	Physiological preparation	Psychological preparation
Martin (1964)	–	Descriptive	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Meckel (2019)	–	Descriptive	N/A	N/A	N/A	N/A	Single: Room with comfortable furniture, eyeshades, headphones Group: friendly room, participants lie on mats, music, sounds and noises of other participants audible	N/A	• At least two sessions of Holotropic Breathwork
Metzner (1998)	–	Review	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mithoefer (2017)		Manual	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mithoefer et al. (2019)	PTSD	Pooled Analysis of six double-blind RCT's	N/A	N/A	General: psychological and physical examination Laboratory: laboratory testing Other: SCID-I-RV or SCID-II, ECG	N/A	N/A	• Therapists had Basic Life Support certification • physician was available by telephone	N/A
Nichols (2016)	–	Review	N/A	N/A	N/A	N/A	N/A	N/A	N/A

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Study	Clinical Target	Design	Pre-diagnostics	Post-diagnostics	Screening Tools	Setting	Contextual preparation	Physiological preparation	Psychological preparation
Nielson and Guss (2018)	–	Review	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Noorani et al. (2018)	Smoking	Qualitative analysis	See Johnson et al., 2014	See Johnson et al., 2014	See Johnson et al., 2014	See Johnson et al., 2014	Music	See Johnson et al., 2014	• Short body-scan meditation • mantra/motivational statement for quitting smoking • scented oil and brief guided imagery
Oram (2012)	–	Review	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Peill et al. (2022)	–	Descriptive study	Study 1 and 2: WEMWBS	Study 1 and 2: MEQ30, EBI, CEQ, Psychological Insight Scale, WEMWBS	N/A	N/A	N/A	N/A	N/A
Phelps (2017)	–	Review	N/A	N/A	N/A	N/A	Artful and aesthetic physical environment	N/A	N/A
Phelps (2019)	–	Book chapter	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Richards (2016)	–	Opinion paper	N/A	N/A	N/A	N/A	Couch with closed eyes and headphones, pre-selected classical music	N/A	• Usually, 8 hours of preparation to develop a therapeutic relationship
Rosemann et al. (2018)	Major depression	Follow-up analysis to Carhart-Harris et al., 2016	QIDS, HAM-D, BDI, DAS, STAI, LOT-R, SHAPS	QIDS, HAM-D, BDI, DAS, STAI, LOT-R, SHAPS, ASC, "psychedelic questionnaire"	See Carhart-Harris et al., 2016	N/A	Music selected by research team	N/A	N/A
Savage (1957)	–	Opinion paper	N/A	N/A	N/A	N/A	N/A	N/A	N/A

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Study	Clinical Target	Design	Pre-diagnostics	Post-diagnostics	Screening Tools	Setting	Contextual preparation	Physiological preparation	Psychological preparation
Sessa (2017)	PTSD	Review	N/A	N/A	General: physical health Laboratory: urine drug screen, pregnancy test for females Other: alcohol breath test	Controlled setting	Eyeshades and importance of music	• HR, BP, and temperature were monitored	• Psychoeducation
Sessa (2019)	–	Book chapter	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Sessa et al. (2019)	AUD	Preliminary data of proof-of-concept study	SCS, GAD-7, PHQ-9, SF-36	SCS, GAD-7, PHQ-9, SF-36, POM	General: N/A Laboratory: blood tests Other: SCID, ECG	Preparation sessions in outpatient clinic; administration sessions in treatment facility	N/A	• BP and temperature monitored • follow-up on quality of sleep, suicide risk, and affect for seven days via telephone	• Motivational Enhancement Therapy
Sessa, Higbed, and Nutt (2019)	–	Review	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Sloshower et al. (2020)	MDD	Review		N/A	N/A	N/A	N/A	N/A	• Psychoeducation • grounding techniques • intention setting • mindfulness practice
Sloshower et al. (2020)	MDD	Manual	N/A	N/A	General: N/A Laboratory: urine toxicology, pregnancy test if applicable Other: N/A	Controlled clinical setting	Private room, free from interruption, with minimal external stimuli, speakers and headphones for music, eyeshades	• Vital signs will be monitored • Basic Cardiac Life Support should be immediately available and Advanced Cardiac Life Support should be available reasonably quickly	• Psychoeducation • ACT principles • grounding techniques • intention setting • mindfulness practice
Spencer (1963)	Psychopathy, hysteria, phobic anxiety, recurrent	Opinion paper	N/A	N/A	N/A	Powick Hospital	Similar to Child Guidance Play Therapy Room, patients could leave the room	N/A	N/A

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Study	Clinical Target	Design	Pre-diagnostics	Post-diagnostics	Screening Tools	Setting	Contextual preparation	Physiological preparation	Psychological preparation
	neurotic depression						and walk around hospital grounds, classical music		
Spencer (1964)	–	Opinion paper	N/A	N/A	N/A	LSD Unit at Powick Hospital	As 'homely' as possible, moderately soundproof, doors of rooms should have glass panel, individual rooms should be placed around center for group activities and open directly to it	• For non-specific anxiety 10 mg of methyl-amphetamine hydrochloride • one hour before the LSD for non-specific fear short acting barbiturate, such as 100 mg or 200 mg of pentobarbitone • end of session 100 mg of chlorpromazine and/or 200 mg of pentobarbitone	N/A
Spriggs et al. (2021)	Anorexia nervosa	Study protocol	MRI, EEG, Readiness and motivation questionnaire, EDE, EDE Questionnaire, PHQ-9, BDI-II, WEMWBS, MPFI, b-EAQ, YBC-EDS, CIA, RRS-ED, STAI-T, WCS, SCS, EES, CFS, P-CAN, IDEA, MAIA, Openness, FSCS, CEAS, IUS, self-constructed items, support person questionnaire, ACE, credibility/expectancy, SSS, MODTAS, Scale to assess the therapeutic relationship, TMT, WCST, LO-FPT, HRD	MRI, EEG, Readiness and motivation questionnaire, EDE, EDE Questionnaire, PHQ-9, BDI-II, WEMWBS, MPFI, b-EAQ, YBC-EDS, CIA, RRS-ED, STAI-T, WCS, SCS, EES, CFS, P-CAN, IDEA, MAIA, Openness, FSCS, CEAS, IUS, self-constructed items, support person questionnaire, ASC, CEQ, MEQ43, EBI, PMQ, SM-B, self-constructed acute measures, self-constructed integration measures, COE, MODTAS, STAI-S, PPS, TMT, WCST, LO-FPT, HRD	General: physical exam Laboratory: blood tests Other: MacArthur Competence Assessment Tool for Clinical Research, ECG, MINI	Controlled clinical setting	Patients sit in semi-reclined position with eyeshades, pre-selected selected music over headphones	• Medical professional will be on site during dosing sessions	• Identified support person will be involved in study process • treatment manual will be made available upon completion
Strickland et al. (2021)	Smoking cessation	Follow-up analysis to Johnson et al. (2014, 2017)	See Johnson et al. (2014, 2017)	See Johnson et al. (2014, 2017)	See Johnson et al. (2014, 2017)	Controlled clinical setting	Room with comfortable furniture, pre-selected and personally	See Johnson et al. (2014, 2017)	See Johnson et al. (2014, 2017)

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Study	Clinical Target	Design	Pre-diagnostics	Post-diagnostics	Screening Tools	Setting	Contextual preparation	Physiological preparation	Psychological preparation
							selected music, eyeshades		
Tai et al. (2021)	Treatment-resistant depression	Descriptive study	N/A	N/A	N/A	N/A	N/A	• Psychiatrist needs to be on call during dosing sessions	• Self-directed enquiry and experiential processing
Thomas & Malcolm in Grob & Grigsby (2021)	–	Book chapter	N/A	N/A	Ibogaine: medical history, ECG, electrolyte, and liver function (no greater than 2.5 times the upper limit of normal)	N/A	N/A	Classic hallucinogens: anxiolytics and antipsychotics should be available in case of emergency; benzodiazepine for severe acute distress MDMA: Clonidine or carvedilol potentially useful in the management of MDMA-induced hypertensive crisis Ayahuasca: monitor for aspiration risk due to potential vomiting Ibogaine: continuous ECG monitoring, pulse oximetry, and vital sign monitoring; protocols, personnel, and equipment required for emergent cardiac resuscitation should be in place Ketamine: monitor for development of lower urinary tract symptoms with chronic use	N/A
Twemlow and Bowen (1979)	Psychedelic-induced crisis	Review and case studies	N/A	N/A	N/A	Informal setting	Pre-selected music and music of person's preference, eye shades	N/A	N/A

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Study	Clinical Target	Design	Pre-diagnostics	Post-diagnostics	Screening Tools	Setting	Contextual preparation	Physiological preparation	Psychological preparation
Wagner et al. (2019)	PTSD	Case study	PCL-5, Couples Satisfaction Index, CAPS	PCL-5, Couples Satisfaction Index, CAPS	General medical screening including HR, cardiac functioning, BP, and any major medical condition Laboratory: N/A Other: SCID-5	Private practice facility	Comfortable room with reclining chairs, optional music, eyeshades, and headphones	• SUD, BP, and temperate taken hourly • follow-up on adverse events for seven days via telephone	• Psychoeducation
Walsh and Thiessen (2018)	–	Narrative review	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Watts (2020)	Treatment-resistant MDD	Describe the structure, procedure, and scripts used in the Psilodep studies	See Carhart-Harris et al., 2016	See Carhart-Harris et al., 2016	See Carhart-Harris et al., 2016	See Carhart-Harris et al., 2016	See Carhart-Harris et al., 2016	See Carhart-Harris et al., 2016	• ACE (Accept, Connect and Embody) model as a therapeutic framework
Watts and Luoma (2020)	Treatment-resistant depression	Opinion	N/A	N/A	N/A	N/A	N/A	N/A	• Psychoeducation • experiential visualization exercise (P-ACE) • intention setting • encouragement to welcome the challenge
Whitfield (2021)	–	Opinion	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Wolff et al. (2020)	–	Opinion	N/A	N/A	N/A	N/A	N/A	N/A	N/A

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Note. 5-Dimension Altered States of Consciousness = 5D-ASC; 11-dimensional Altered States of Consciousness Scale = 11D-ASC; 21-item Hamilton Depression Rating scale = HAM-D; 16-item Quick Inventory of Depressive Symptoms = QIDS; Adverse Childhood Experience Questionnaire = ACE; Alcohol Abstinence Self-Efficacy Scale = AASE; Beck Depression Inventory —original version = BDI; brief experiential avoidance questionnaire = b-EAQ; Challenging Experience Questionnaire = CEQ; Clinical Impairment Inventory = CIA; Clinical Institute Withdrawal Scale—Alcohol, revised = CIWA-Ar; Clinician-Administered PTSD Scale = CAPS; Cognitive flexibility scale = CFS; Compassionate Engagement and Action Scale – self compassion and compassion for others subscale = CEAS; Demoralization scale = DEM scale; Dysfunctional Attitudes Scale = DAS; Eating Disorder Examination = EDE; Electrocardiogram = ECG; Emotion Regulation Questionnaire = ERQ; Experience of embodiment scale = EES; Functional assessment of chronic illness therapy – Spiritual Well-being Scale = FACIT-Sp; Function of self-criticism/attacking scale = FSCS; Generalised Health Questionnaire-7 = GAD-7; Hallucinogen Rating Scale = HRS; Heart rate discrimination tasks = HRD; Hospitalized Anxiety and Depression Scale = HADS; Identity in Eating disorders scale = IDEA; Intolerance to Uncertainty Scale = IUS; Leeds Oxford food preference questionnaire = LO-FPQ; Life Changes Inventory - revised = LCI-R; Life Orientation Test Revisited = LOT-R; full Multidimensional Iowa Suggestibility Scale - short version = MISS; Multidimensional Assessment of Interoceptive Awareness = MAIA; Multidimensional Psychological Flexibility Inventory = MPFI; Mystical Experience Questionnaire = MEQ; Neuroticism Extroversion Openness Inventory = NEO; Neuroticism Extroversion Openness Personality Inventory-Revised = NEO-PI-R; Patient Health Questionnaire-9 = PHQ-9; Penn Alcohol Craving Scale = PACS; Profile of Moods States questionnaire = POMS; Pros and Cons of Anorexia Scale = P-CAN; PTSD Checklist = PCL-5; Ruminative response scale for eating disorders = RRS-ED; Self Compassion Scale = SCS; Short Form Health Survey = SF-36; Short Suggestibility Scale = SSS; Snaith-Hamilton Pleasure Scale = SHAPS; Spielberger's Trait Anxiety Inventory = STAI; Spielberger State-Trait Anxiety Inventory - short version = STAI-SF; Stages of Change Readiness and Treatment Eagerness Scale = SOCRATES 8A; States of Consciousness Questionnaire = SOCQ; Structured Clinical Interview for DSM = SCID; Stubborn Opinionatedness scale = SOP; Subjective Units of Distress = SUD; Symptom Checklist-90-Revised = SCL-90-R; Tellegen Absorption Scale - modified version = MODTAS; Ten-Item Personality Inventory = TIPI; Time-line follow-back = TLFB; Trail Making Test = TMT; Warwick-Edinburgh Mental Wellbeing Scale = WEMWBS; Watts connectedness scale (self-constructed) = WCS; Wisconsin Card Sorting Task = WCST; Yale-Brown Cornell Eating Disorder Scale = YBC-EDS

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