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Psychedelics, placebo effects, and set and setting: Insights from common factors theory of psychotherapy

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Abstract

Psychedelic-assisted treatment is at first glance markedly different in structure and approach from mainstream forms of psychotherapy in the West. A major criticism of clinical psychedelic research rests on the difficulty of executing placebo-controlled studies and distinguishing drug effects from those of the psychotherapeutic container in which psychedelics are typically presented. Detractors also tend to find fault in spiritual or mystical themes that often arise in the context of psychedelic use. Common factors theory of psychotherapy is a useful and extensively studied framework that can help make sense of these issues, and has much to contribute to our understanding of contextual effects that are often discussed in psychedelic literature as "set and setting." In this article, we examine four major contextual "common factors" shared by various healing traditions: 1) the therapeutic relationship; 2) the healing setting; 3) the rationale, conceptual scheme, or myth; and 4) the ritual. We explain how these factors show up in psychedelic-assisted treatment and how they may contribute to therapeutic effects. Lastly, we discuss the implications of these factors for the concept of placebo, and for future research.

Keywords

common factors, placebo, psychedelics, psychotherapy, set and setting

Introduction

The past two decades have seen a remarkable revival in scientific and public interest in psychedelics. As researchers work to understand the mechanisms by which these drugs exert their effects, considerable attention has been paid to the role of "set and setting," i.e., the internal and external contextual factors that accompany drug administration. Thus far, the literature on this subject has ventured a step further to consider the conceptual similarity between set and setting and placebo effects (Hartogsohn, 2016). However, little attention has been paid to the many striking parallels between set and setting and contextual or "common factors" in psychotherapy. In addition to highlighting some relevant points that may help to advance the conversation about how best to understand and study the clinical effects of psychedelics, we hope that this review can help bridge the gaps between psychedelic-assisted treatments, Indigenous healing practices, and present-day mental healthcare in the West.

While there is debate over which drugs are considered psychedelics (and, for that matter, what this class of compounds should be called), for the purposes of this discussion, we will define psychedelics as drugs that exert their effects primarily by serotonin 2A (5-HT_{2A}) receptor agonism or partial agonism. These include the prodrug psilocybin, lysergic acid diethylamide (LSD), and *N,N*-dimethyltryptamine (DMT) (Nichols, 2004). In humans, psychedelics produce profound changes in perception and mood that are often described as highly meaningful (Griffiths et al., 2006).

After a decades-long standstill in human subjects research with psychedelics, researchers across the U.S. and Europe have published promising data suggesting that just one or two doses of a psychedelic administered under supportive conditions can produce impressive and long-lasting improvements in mental health.

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In individuals with advanced cancer, psilocybin-assisted treatment was associated with marked improvements in symptoms of both anxiety and depression (Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016). An open-label study of psilocybin for treatment-resistant depression showed similar decreases in depressive symptoms at 1 week and 3 months (Carhart-Harris et al., 2016). Ayahuasca, a plant brew containing DMT, has also been found to relieve symptoms in individuals with depression (Osório et al., 2015; Sanches et al., 2016). In the realm of addictive disorders, Bogenschutz et al. (2015) found that psilocybin delivered with motivational interviewing resulted in a significant decrease in the number of heavy-drinking days for people with alcohol use disorder. Similarly, 67% of smokers receiving two to three moderate–high doses of psilocybin with cognitive behavioral therapy (CBT) were able to achieve and maintain abstinence from tobacco at 12-month follow up (Johnson et al., 2017). The use of psilocybin in healthy subjects may even be associated with enduring changes in personality traits (MacLean et al., 2011).

Universally positive results over a phenomenologically diverse range of diagnoses have understandably drawn scrutiny and skepticism. A commonly raised concern in the aforementioned studies is a lack of placebo-controlled conditions. Implementation of "gold-standard" randomized double-blind placebo-controlled trials is challenging in part because of the powerful acute subjective effects of psychedelics—both participants and their observers can often recognize whether the verum or sham intervention has been provided. An adjacent concern is the difficulty of distinguishing drug effects from those of adjunctive psychotherapy (Barnby & Mehta, 2018). CBT, motivational interviewing, and supportive psychotherapy have all been shown to be effective on their own for particular psychiatric conditions and likely make independent contributions to symptom improvement in these studies. Researchers have also been criticized for employing non-representative samples composed mostly of highly educated White participants (Michaels et al., 2018). Finally, a pervasive but less overt bias involves the general attitude toward psychedelics in the West. Klerman (1972) coined the term "pharmacologic Calvinism" to describe the societal tendency to mistrust certain drugs, capturing the common sentiment that "if it makes you feel good it must be morally bad." At the time of this writing in the United States, psilocybin and related compounds remain classified as Schedule I under the Controlled Substances Act, suggesting a dangerous potential for abuse with little to no clinical benefit. In light of the ongoing addiction epidemics in Western nations, institutions may be wary of any potential benefits to be gleaned from the use of these compounds.

The concept of "set and setting" frequently turns up in the discussion of the above concerns. This term, coined by Timothy Leary (1961) and colleagues, encompasses psychological, environmental, and social factors that affect the psychedelic experience. Set and setting theory posits that psychedelics might act as non-specific amplifiers of the contents of consciousness. Thus, preparation, expectation, physical environment, and even cultural attitudes can shape acute drug effects. This is often cited as an explanation for varied and contradictory reports of drug effects in early psychedelic research (Hartogsohn, 2017). Some LSD researchers in the 1950s and 1960s recognized these influences and experimented with manipulating non-pharmacologic variables in their studies (Dyck, 2008, pp. 68–69). Eventually a series of common practices was developed, and set and setting continues to be an important consideration in modern clinical psychedelic research design. Apart from ensuring physical comfort, commonly used guidelines stress the importance of rapport and trust, which are built between clinicians and volunteers via extended contact prior to drug administration (Johnson et al., 2008).

More recently, there has been recognition of the significant overlap between set and setting and factors known to augment placebo response, highlighting an issue that has beguiled researchers attempting to design high quality clinical trials using psychedelics (Hartogsohn, 2016). In typical drug studies, the goal is to demonstrate significant benefit compared to placebo, which is why factors known to boost placebo response are actively minimized. This would include a "warm, empathetic, and confident patient-practitioner relationship," the use of touch, and extended discussions of the disease state (Kaptchuk et al., 2008, p. 1000). Standard practices in psychedelic-assisted treatment, as described above, are obviously at odds with the goal of minimizing placebo response, yet are simultaneously touted to be necessary for both safety and efficacy.

A number of striking similarities exist between "set and setting" and contextual factors in the study of psychotherapy. However, the discussion on set and setting has thus far omitted examination of this extensive literature. Both psychotherapy and psychedelic-assisted treatment share substantial reliance on contextual factors, and interestingly, both seem to be able to provide benefit for a wide range of mental health conditions. The concept of placebo, and the development of adequate placebo-controlled trials, has similarly been perplexing in psychotherapy. Some have even gone so far as to suggest that all clinical benefits of psychotherapy can be attributed to placebo effects (Gaab et al., 2016).

Notably, the same claim has been made of psychedelics (Strassman, 2017). Olson et al. (2020) sought to determine whether it was possible for a placebo to induce a psychedelic-like altered state by maximizing expectancy. The authors manipulated environmental cues to deliberately enhance expectancy effects and employed confederates to act out an intoxicated state, resulting in a majority (61%) of their participants reporting some subjective drug effect. In many ways, the average study examining the effects of psychedelics more closely resembles a psychotherapy trial than a standard pharmaceutical trial, regardless of whether an explicitly defined "adjunctive" psychotherapy is used. The use of such hybrid practices—i.e. delivering psychedelics in conjunction with CBT or other circumscribed therapy—only serves to further complicate the picture.

Thus, the conversation about set and setting, expectancy, and placebo effects in the context of psychedelic-assisted treatments stands to benefit from a review of the lessons of many decades of scholarly work on the role of contextual or "common" factors in psychotherapy. In this paper, we seek 1) to explain common factors theory of psychotherapy and how it applies to psychedelic-assisted treatments as they have been described in recent literature, 2) to use common factors theory to clarify the definition and nature of possible "placebo effects" associated with this treatment, and 3) to explain how these insights may inform future research and understanding across cultures.

Common factors theory of psychotherapy

Broadly defined, psychotherapeutic methods have existed from the earliest days of human history, and likely in prehistory. By psychotherapy, we mean the use of psychological methods, such as verbal and nonverbal communication, by a socially sanctioned healer to bring relief to a sufferer. This would include various forms of religiomagical healing for both somatic and psychological ailments, including those still practiced today in Indigenous societies. Western psychotherapy emerged as a distinct form of healing in 18th and 19th century Europe, as greater value was placed on therapies that seemed to demonstrate a logical or rational mechanism, as opposed to being based in faith. Thus, religious-based therapies like "moral treatment" were displaced by more scientific efforts to understand and influence human behavior (Wampold, 2001). The development and adoption of psychotherapy was further catalyzed by Sigmund Freud and his contemporaries and intellectual heirs. Today, the field of psychotherapy is burgeoning with hundreds of distinct theoretical orientations and ongoing debates about the superiority of one or another approach.

Despite conflicting theories about why any given type of psychotherapy should work, it is rare for one form of psychotherapy to be demonstrated as significantly more effective than another (Wampold, 2015). An early effort to make sense of this came from Rosenzweig (1936) who posited that factors common to all forms of psychotherapy, rather than specific characteristics of any such treatment, may be responsible for efficacy. Jerome Frank expanded on this idea in his seminal book, *Persuasion and Healing* (Frank, 1961; Frank & Frank, 1993), which is a survey of shared or "common" factors that he believed to underwrite all forms of effective psychotherapy. Since then, there have been at least two other common factors models proposed—Wampold's "contextual model" and Orlinsky's "process model" (Orlinsky & Howard, 1987; Wampold & Imel, 2015). All three models reach similar conclusions about the importance of these common factors, but we will frame our discussion using Frank's model, given his attention to diverse forms of psychotherapeutic processes, including shamanism and religious healing.

Frank described psychotherapy as a salve for demoralization, which arose in individuals who repeatedly failed to adapt to life circumstances for reasons including personality vulnerabilities, environmental stressors, or psychiatric illness. He hypothesized that the positive clinical effects of psychotherapy were due to the transformation of maladaptive meanings that individuals ascribed to their emotions and life events. Frank suggested that successful psychotherapies exert these effects via four broad features: 1) an emotionally charged, confiding relationship with a helping person, 2) a healing setting, 3) a rationale, conceptual scheme, or myth that provides a plausible explanation for the patient's suffering and a means of alleviation, and 4) a ritual that requires participation of both patient and therapist, which is mutually believed to be the means of succor. Below, we will review key evidence that has accumulated to support the validity of these factors, and examples of how they show up in psychedelic-assisted treatments even in the absence of any circumscribed adjunctive psychotherapy.

The therapeutic relationship

Decades of research have reinforced the importance of the therapeutic relationship in psychotherapy, and in many cases it has been demonstrated to be more impactful than a therapist's adherence to any specialized technique (Lambert & Barley, 2001). The most researched component of the relationship is therapeutic alliance, which refers to agreement between therapist and patient on the purpose and tasks of therapy, as well as the working bond between them.

A meta-analysis covering studies from 1957–2017, which included more than 30,000 participants, revealed that working alliance was highly correlated with outcomes ($r = .28$, equivalent to a Cohen's d of .57) (Flückiger et al., 2018). This result did not differ across therapies, including CBT, psychodynamic, and interpersonal therapy. Interestingly, the connection between alliance and outcome varied by the target disorder—substance use and eating disorders showed a weaker association between alliance and outcome.

Distinct from the alliance is the interpersonal affective bond with the patient. It can be described by the Rogerian factors of therapy, which are empathy, congruence (a therapist's "genuineness"), and positive regard. These elements are thought to promote the trust that is needed to disclose sensitive personal information. Multiple studies have confirmed common sense, showing that perceived therapist empathy was highly predictive of therapeutic benefit (Barrett-Lennard, 1981; Elliott et al., 2011). In two recent meta-analyses, empathy and congruence ratings were positively correlated with outcomes and contributed medium effect sizes (Cohen's $d = .58$ and .46 respectively) (Elliott et al., 2019; Kolden et al., 2019). Similarly, measures of perceived positive regard were positively correlated with outcomes with a small effect size ($g = .28$) (Farber et al., 2019).

Individual characteristics of therapist and patient also fall under the domain of relationship and can affect outcomes. For example, patients who score lower on certain facets of neuroticism and higher in agreeableness are known to have better outcomes following CBT for depression (Bagby et al., 2008). However, there is some evidence to suggest that the relationship between patient personality characteristics and outcomes may actually be mediated via therapeutic alliance, i.e., agreeableness may result in better outcomes because it promotes alliance (Kushner et al., 2016). With respect to therapist characteristics, Heinonen et al. (2012) found that therapists with higher levels of extraversion generated greater short-term effects for mood and anxiety disorders, but that more reserved therapists had better effects in longer term therapy. Both lower clinician confidence and enjoyment in therapeutic work are predictors of poor patient outcomes.

In psychedelic-assisted treatment, participants typically have the support of not one but two clinicians during preparatory, dosing, and follow-up sessions. It is not clear if increasing the number of providers also has an additive effect on relationship-related factors. In any case, this level of support is unusual in traditional Western psychotherapy settings and may boost expectancy. Having two clinicians may also introduce a novel complicating factor which has yet to be studied—that of the rapport and dynamic between the two therapists themselves. It is obvious that elements of the relationship may influence parts of the intervention that are not explicitly defined as psychotherapy—for example, when study staff tactfully obtain a life history from a participant or provide guidance on what to expect during acute drug effects, but are not using specific CBT or motivational interviewing techniques.

There is accumulating evidence that patient characteristics can interact with psychedelic drug effects. Patients reporting depressed or anxious mood immediately prior to drug administration were more likely to report negative experiences during drug administration (Metzner et al., 1965). Barrett et al. (2017) have demonstrated that higher levels of trait neuroticism are associated with higher likelihood of challenging experiences. There is less existing research on the effects of therapist characteristics on outcomes, but one study showed that deliberate manipulation of staff attitudes toward patients (indifferent, cold, or friendly) resulted in differing degrees of negative experiences with LSD (Hyde, 1960).

The healing setting

Frank highlighted the importance of a specialized environment for healing (Frank, 1961; Frank & Frank, 1993). In some societies, this might occur in a temple or other sacred location. In secular forms of healing, clinicians meet patients in clinics and hospitals, places that carry an "aura of science" (Frank & Frank, 1993, p. 41). The importance of location is twofold: 1) to reinforce expectation of help by symbolizing the therapist's role as healer, and 2) to provide safety and confidentiality, which can facilitate acting and speaking in ways that might otherwise be difficult. The role of setting has proven to be more difficult to study on a large scale in psychotherapy, but many smaller studies have been performed on individual characteristics of treatment environment such as décor, furniture, lighting, amount of space, as well as olfactory and sound cues (Pressly & Heesacker, 2001). Manipulation of these factors can, in some cases, produce small changes in patient expectation, but the overall effect is obviously complex and multifactorial. For example, one study found that humanistic décor tended to increase positive perception of credibility for male therapists, but more traditional office décor was associated with higher ratings of credibility for female therapists (Bloom et al., 1977).

In light of "set and setting" concerns, the environment used in clinical psychedelic research is rather idiosyncratic. Though differing somewhat from one institution to the next, treatment rooms tend to bear

more resemblance to a living room than a medical office or research laboratory. One description of a treatment room at Johns Hopkins commented that the décor included such items as "relics from various cultures and faith traditions... a blue and gold mandala, a statue of the Buddha, a brightly beaded mask... an earthenware chalice" (Scharper, 2017). For some studies, a fresh red rose is placed in the room on dosing days in keeping with a tradition established in earlier psychedelic research (Richards, 2015). Such environmental cues might have substantial effects on expectancy, signaling to patients that the procedure that takes place in this setting is particularly powerful or special. In early studies in patients with alcohol use disorders, researchers found that the use of religious images, icons, and music increased rates of spiritual reactions to LSD (Dyck, 2008). Psychedelic-assisted treatment may draw power from both an "aura of science" associated with the affiliate hospital or research institution, and religious or spiritual cues in the immediate environment.

Contemporary research on setting in psychedelics has included a prospective analysis of contextual factors in naturalistic use of psychedelics (Haijen et al., 2018). In this study, 56% of respondents took psychedelics in a retreat or in an otherwise "therapeutic setting." The authors' reported "setting" measure was a composite score that took into account feelings about both the physical environment and about the people that would be present during acute drug effects. Though the latter seems more likely to be related to relationship factors, this composite "setting" measure was positively associated with wellbeing two weeks after drug ingestion.

The rationale, conceptual scheme, or myth

According to Frank, the conceptual scheme or myth behind a given psychotherapy serves a variety of functions in the development of expectation (Frank, 1961; Frank & Frank, 1993). In conjunction with a ritual, the myth inspires expectations of help, arouses strong emotional responses, and enhances a sense of mastery or self-efficacy (Frank & Frank, 1993, p. 44). In Indigenous forms of healing, the myth is drawn from the cosmology of the group. In modern day Western societies, the enduring source of symbolic healing power has been faith in science or connection to a prestigious figure. So long as the patient accepts the myth or rationale, the actual contents or scientific validity seem to be much less important to producing positive outcomes (Wampold & Imel, 2015, p. 59).

Under Wampold's contextual theory of psychotherapy, the contents of rationale and myth would constitute "specific" (as opposed to common) elements. Wampold and others posit that specific clinical techniques, presumed by many to be essential ingredients, contribute little to the overall effectiveness of any given psychotherapy. In two meta-analyses of "dismantling" studies, in which the effects of removing a single specific ingredient are examined, removal of one or more "critical" elements of treatment resulted in no statistically significant change in treatment efficacy (Ahn & Wampold, 2001; Bell et al., 2013). Present-centered therapy, initially designed as a control condition for psychotherapy containing minimal specific ingredients, was shown in a meta-analysis to be equivalent to standard exposure-based therapies (Frost et al., 2014). Frank advises that the content of therapeutic procedures ought not to be confused with their functions, which may be to serve as a support structure for common factors (Frank & Frank, 1993, p. 158). Specific techniques serve an important purpose in providing a reason to establish the therapeutic relationship and for the therapist to demonstrate expertise.

What, then, is the myth or rationale behind psychedelic-assisted treatment? There seem to be two major categories of answers to this question. On the one hand, scientists are uncovering information about the objective neurobiological effects of these drugs. For example, we now know that psilocybin exerts its effects via 5-HT_{2A} receptor agonism, and that changes in brain functional connectivity occur during the period of acute drug effects (Carhart-Harris et al., 2012; Quednow et al., 2012). These effects seem to be associated with acute and long-term behavior and mood change. Explanations like these are readily accepted by Western culture, where science is held in high esteem. However, whether functional connectivity adequately explains the acute or enduring effects of psychedelics is yet to be determined. Nonetheless, images like the diagram produced by Petri et al. (2014) comparing functional connectivity under psilocybin versus placebo conditions are frequently referenced by researchers and in popular media when attempting to explain why this treatment works. Frank offers a germane anecdote about how faith in science can be used to bolster psychotherapeutic theories:

> A symposium of proponents of leading therapeutic schools amusingly demonstrated this point. Each began by invoking symbols of science. One showed anatomical charts, another displayed polygraphic tracings, and a third referred to experimental work with mice. In each case, the introductory material was related only tenuously to the description of therapy which followed. (Frank & Frank, 1993, p. 42)

The other set of explanations about the effects of psychedelics rely on subjective experiences produced by

these drugs, which some people interpret as deeply meaningful, emotionally rich, or even "mystical" (Griffiths et al., 2006, 2008). The labeling of these experiences as mystical has been the cause of some turmoil among psychedelic researchers, with some believing that such language is unscientific and harmful to credibility (Roseman et al., 2018). Alternative, more secular terms such as "peak" have been suggested in its place. Regardless, there seems to be a dose-dependent relationship between psychedelics and measures of "mystical" qualities of the experience, with greater mystical qualities being correlated with better outcomes (Griffiths et al., 2011, 2016). This speaks to a much more mysterious but still quite potent metaphysical or spiritual source of clinical effects. Other subjective experiences are less overtly spiritual in nature, and instead center on forgiveness, compassion for self and others, and catharsis (Bogenschutz et al., 2018).

This closely relates to the concept of the explanatory model (EM), first described by Kleinman (1978), which refers to a patient's or clinician's culturally determined understanding of an illness, its causes, available treatments, and prognosis. Though originally conceptualized for the purpose of comparing medical systems between cultures, the importance of EMs has also become apparent for clinical practice in various fields of medicine. A patient's EM can have consequences for adherence to treatment and outcomes (Galli et al., 2010; Halm et al., 2006; Weinman et al., 2000). Though clinicians have stressed the importance of exploring EMs during clinical encounters, it is unclear how much of the benefit of this practice is mediated by changes in therapeutic alliance, and systematic research on the relationship of EM differences between patients and clinicians to mental health treatment outcomes remains scant (Dinos et al., 2017).

For psychedelic-assisted treatment, the magnitude of a patient's emphasis on scientific, metaphysical, or other rationale for its mechanism likely varies, but psychedelics seem unique in their potential to draw symbolic power from multiple domains. The growing body of evidence on the effects of psychedelics on brain function are of obvious interest to clinicians and a subset of patients, but these drugs also produce profound subjective experiences that are open to the patient's own interpretation. A variety of psychological explanations have been proposed for the immediate and longer term efficacy of psychedelics, including improvements in psychological insight, emotional breakthrough, cognitive flexibility, ego-dissolution, and mystical or peak experiences (Davis et al., 2020; Garcia-Romeu et al., 2019; Griffiths et al., 2016; Letheby & Gerrans, 2017; Roseman et al., 2019). The EM or rationale with which patients identify may relate to personal spiritual/religious practice, personality traits, prior experiences with psychotherapy, or a folk psychological account of how mental suffering operates. This can have important implications for expectation building within and without the study, as well as for treatment outcomes.

The ritual

Ritual is a symbolic extension of the myth or rationale that is usually undertaken together by healer and patient. In addition to bolstering the perception of power of the therapist and/or treatment, ritual provides a key opportunity for practice. Frank notes that one method by which psychotherapy may work is by affording the patient a chance to "survive an emotionally intense experience," thereby strengthening self-confidence and mastery (Frank & Frank 1993, p. 46). This type of experience may also enhance sensitivity to environmental influences. In Western schools of psychotherapy, strong emotions can be aroused by confronting repressed feelings and thoughts, or by purposely exposing oneself to stressful stimuli, as in exposure-response prevention therapy. Frank writes:

> New experiences provided by therapy can enhance morale by showing patients potentially helpful alternative ways of looking at themselves and their problems. The more numerous and more intense the experiential, as opposed to the purely cognitive, components of learning, the more likely they are to produce changes in the patients' attitudes or behavior . . . intense emotional experiences. . . may break up old patterns of personality integration and facilitate the achievement of better ones. (Frank & Frank 1993, p. 46)

Religiomagical rituals in non-industrialized societies may more overtly evoke strong emotional responses. Frank (Frank, 1961; Frank & Frank, 1993) highlights an illustrative 1948 account of a healing ritual taking place in a village in Guatemala (Gillin, 1948). A 63-year-old woman was treated for *espanto*, or "soul loss," which bore phenomenological similarity to a depressive episode. After an initial interview, in which she detailed the events of her life and more recent events leading up to the present illness, the healer voiced confidence in her potential to be cured and prepared for the ceremony. In a process lasting more than 12 hours, he brought together a group of individuals from the village and proceeded to engage in a complex set of activities including prayer, offering gifts to the spirits who were causing the woman's symptoms, rubbing her body with eggs, and dousing her with an alcoholic fluid that left her cold and shivering. At the conclusion of the ritual he broke the eggs into a bowl of water, observed that they sunk to the bottom of the bowl, and declared that his efforts had been successful; the woman agreed and fell into a deep sleep. In the weeks that followed, the anthropologist who documented the

ritual observed that the woman showed marked improvement.

The drug dosing day ritual in psychedelic treatment has been described by Johnson and colleagues (2008) and others. The patient arrives in the morning and is greeted by her session guides. After she settles in to a private and comfortably furnished room, the triad might review intentions or helpful reminders for the day. She is then offered a capsule to take with a glass of water. Soon after, she is guided to lay down on the couch with eyeshades and headphones playing a program of music, and encouraged to draw her focus inward. Music plays an important role in the dosing day and has long been used as a component of psychedelic-assisted treatment (Bonny & Pahnke, 1972). The typical playlist of music used today includes a mix of classical and world music. Though effects of music are complex and vary by personal preference, openness, and other factors, the combination of psychedelics and music has been shown to increase emotional responses, autobiographical memory recall, and mental imagery, possibly via parahippocampal activation (Kaelen et al., 2015, 2016). Throughout the day, blood pressure and heart rate are monitored intermittently. The guides are available throughout the day to monitor for safety, and provide reassurance and physical forms of support as needed (offering a hand to hold, etc.).

Participants are instructed to be open and curious about whatever comes up, which may include intense emotional or somatic experiences, urges to laugh, cry, or move one's body. They are also provided with reassurance that they will ultimately come out of the experience and will also be contained in a setting where they will be physically safe. Participants are also warned of the possibility of ego dissolution or the loss of sense of self as a separate entity. Some participants have dysphoric or "challenging" experiences, but ultimately even a challenging experience can be associated with overall positive outcomes (Carbonaro et al., 2016). This seems to be compatible with Frank's observations about the usefulness of emotionally intense experiences in transforming meanings. It also begs the question of whether what is happening in psychedelic-assisted treatment is all that unique. For someone with depression, is it really the direct effect of the drug that improves mood via physiological changes in the brain, or is it the patient's transformation of meanings secondary to an emotionally powerful experience?

On the troubling concept of placebo in psychotherapy

Although it is beyond the scope of this paper to capture the entirety of the ongoing debate about placebo in psychotherapy (see Wampold & Imel, 2015), we wish to highlight key points that are pertinent to our discussion. Common factors are central to the problem of designing gold-standard randomized, placebo-controlled double-blind clinical research in psychotherapy (Blease, 2018; Kirsch et al., 2016; Locher et al., 2018). Despite any differences that may exist between rationales for two distinct psychotherapies, in most cases, both require common factors, such as the healing relationship and various other cues that affect patient expectation (providing a logical rationale, expressions of hope, confidence in the therapy, etc.). Because these factors may provide the majority of the clinical benefit and may be necessary for any treatment effects to occur at all, it becomes impossible to do away with them. The impasse seems to boil down to a semantic problem: the concept of placebo is straightforward when applied to medicine, but is not coherent when applied to psychotherapy. As summarized by Kirsch et al. (2016):

> The placebo effect in medicine is produced by factors other than the physical properties of the treatment. However, the effect of psychotherapy is—by definition of the term psychotherapy—produced by something other than the physical properties of the treatment. Therefore, using the medical definition of placebo, the effects of psychotherapy are ipso facto placebo effects, and psychotherapy is ipso facto a placebo. (p. 123)

Due to its medical roots, placebo has carried connotations of deception and ineffectiveness, yet we know that psychotherapy is indeed effective for the treatment of many mental health issues. Rather than thinking of common factors as "placebo," Kirsch and colleagues (2016) suggest that we understand them as "active psychological ingredients" that are necessary but not sufficient for adequate treatment.

The problems that this poses for rigorous clinical research involving psychedelics are closely related to those encountered in pure psychotherapy research, which stem from the difficulties of developing an adequate "placebo" condition when the experimental treatment involves a psychological intervention. First, the majority of modern protocols involving psychedelics include a substantial psychotherapy component, which is thought to be necessary for the safe delivery of this treatment (Johnson et al., 2008). Though effect sizes reported for psychedelic-assisted psychotherapy are generally larger than those found in most trials of psychotherapy alone, this has yet to be borne out in larger trials. One method that researchers have used to tease apart direct effects from psychotherapy vs. psychedelic is to include a substantial portion of the psychotherapy intervention prior to drug dosing, and to measure changes in primary outcomes between the

start of psychotherapy and just prior to the drug session (Anderson et al., 2020; Bogenschutz et al., 2015). However, as we have described, common factors are present in psychedelic-assisted treatment even when no explicit adjunctive psychotherapy like CBT or motivational interviewing is specified. If common factors have been shown to be responsible for the majority of treatment effect in psychotherapy, this still raises the question of whether the same is true of psychedelic-assisted psychotherapy.

Second is the issue of participant blinding. The subjective effects of moderate to high dose psychedelics are difficult to mistake for placebo over the course of a 6–8 hour drug dosing session. In a study that compared effects of psilocybin to those of methylphenidate, 77% of drug administrations were correctly identified by the participants (Griffiths et al., 2006). Though Olson et al. (2020) reported being able to induce subjective psychedelic-like effects from a true placebo, they did so under conditions that would not be possible for a placebo-controlled clinical trial with standard informed consent practices. Participants were told to expect a drug with psychoactive properties similar to psilocybin, and the possibility of receiving a placebo was not discussed. They also delivered the drug in a group setting and used confederate actors who feigned intoxication. In a placebo-controlled trial, especially one without a cross-over design where participants would be assured of receiving a dose of active drug at some point during their participation in the study, the benefits of psychedelics may be overestimated due to nocebo effects; i.e., a participant could become further demoralized by the disappointment of believing that they received an inactive compound rather than a promising experimental drug.

A third complication is staff or therapist blinding. The acute effects of psychedelics are often strong enough that the monitoring staff may also accurately deduce whether a placebo or active drug condition is used. This is reflected in the fact that monitor ratings and participant ratings of drug effects are closely correlated (Carbonaro et al., 2018). Drug effects are also discussed extensively in follow-up visits, which could further serve to inform the monitors about the likely drug condition used. Psychotherapy research has highlighted the difficulty of blinding research staff when the treatment being studied involves significant interpersonal interaction (Locher et al., 2018). In "horse-race" trials comparing two or more psychotherapies, clinicians are typically aware of which treatment is being provided. Allegiance, driven by factors like higher confidence or more training in a particular type of therapy, may have substantial effects on patient outcomes in such trials. Cuijpers et al. (2012) found that controlling for allegiance accounted for the differences found between particular psychotherapies when compared to "placebo" treatments. Allegiance may be of consequence in trials with psychedelics in that experienced therapists are likely to have an opinion about the benefits of treatment with a psychedelic vs. placebo condition, and may even contribute to nocebo effects in their interactions with participants. We predict that this may be a driver of differences in outcomes between sites in larger phase 2 and 3 multi-site studies of psychedelics, where some sites may have less experience with this type of intervention.

Some trials have attempted to remedy the problem of participant and researcher blinding by using an active placebo or comparator drug such as niacin, which may produce somatic symptoms like flushing, nausea, and headache, but is devoid of inherent psychological effects (Ross et al., 2016). Given the differences between duration of action and the nature of subjective effects of psychedelics, which are explained at length during preparatory meetings, there is still a strong possibility that a participant would be able to determine which drug condition they received. Comparator drug conditions such as very low dose psychedelic compounds, dextromethorphan, and methylphenidate have been used in other studies (Griffiths et al., 2006, 2016; Carbonaro et al., 2018). Very low or subperceptual doses of psychedelics appear to be comparable to a true placebo condition and remain problematic for the reasons described earlier. Drug conditions with more obvious subjective effects are also problematic in that they appear to produce some independent benefit, which raises the question of whether strong subjective effects are therapeutic regardless of the precipitating drug or its mechanism. For example, in Griffiths and colleagues (2006) study, which compared methylphenidate to high-dose psilocybin, the authors found that a non-negligible number of participants in the methylphenidate condition described those experiences as being highly meaningful. In fact, methylphenidate has previously been used for the purpose of enhancing psychotherapy (Blair et al., 1962; Rogers, 1960). Carbonaro et al. (2018) compared dextromethorphan to placebo and escalating doses of psilocybin. Although dextromethorphan produced a somewhat different profile of subjective effects compared to psilocybin despite equal reports of drug intensity, both compounds were significantly different from placebo in their ability to produce increases in the Altered States of Consciousness questionnaire (5D-ASC), Mystical Experiences Questionnaire (MEQ30), and the Challenging Experience Questionnaire (CEQ). Dextromethorphan is a dissociative anesthetic and works by a different mechanism than psilocybin, yet has also been hypothesized to have some antidepressant effects (Lauterbach, 2011; Murrough et al., 2017).

Can we look to psychotherapy research to help solve these methodological problems with psychedelic-assisted treatment? Unsurprisingly, psychotherapy researchers have not fully resolved the challenges described above, but a number of recommendations have been identified (Locher et al, 2018). Descriptions of psychotherapy procedures, including rationales provided to patients and therapist experience and training should be thoroughly documented (Baskin et al., 2003). Control conditions should be structurally matched to experimental conditions when possible, as passive control conditions (e.g., waitlist-controlled) may contribute to nocebo effects (Furukawa et al., 2014). Dismantling studies, though costly and labor-intensive, could help determine which specific aspects of psychedelic-assisted treatment provide the most benefit (Ahn & Wampold, 2001). A more recently proposed strategy to control for inter-therapist differences, allegiance, and other biases involves delivery of psychotherapy via programmed virtual therapist avatars, though this technology is still in early phases of development and it is not known whether its efficacy would be on par with standard psychotherapy (Blease, 2018).

Conclusions and implications for future research

By looking to existing research in common factors, we have identified several candidate factors that may explain a significant portion of "set and setting" effects in psychedelic-assisted treatment. Others have suggested that we should systematically study the effects of set and setting components on treatment outcome (Carhart-Harris et al., 2018). This is similar to what has been done in psychotherapy research via "dismantling" studies (Ahn & Wampold, 2001; Bell et al., 2013). However, rather than arbitrarily isolating and testing the myriad factors that comprise psychedelic-assisted treatment, we should prioritize investigation of those factors which have been identified as the most salient to producing treatment response in other types of therapy. These would include expectancy and credibility effects, the working alliance, and various other factors of the therapeutic relationship captured by the Rogerian terms of empathy, positive regard, and congruence.

The common factors and placebo literature have produced a number of validated scales that could be readily applied to psychedelic clinical trials. Aspects of the relationship can be measured by the Working Alliance Inventory (WAI) and the Barrett-Lennard Relationship Inventory (BLRI; Barrett-Lennard, 2015). Several questionnaires have been used for expectancy, but the most widely used and applicable measure is the Credibility and Expectancy Questionnaire (CEQ; Devilly & Borkovec, 2000). The CEQ is a 6-item questionnaire that examines credibility (the patient's perception of "rationale") and overall expectations for improvement. The Stanford Expectations of Treatment Scale (SETS) is another more recently created measure that could also be useful for examining expectancy (Younger et al., 2012). It was developed to be broadly applicable to pharmacological, surgical, and psychotherapeutic interventions. No expectancy questionnaire has been developed specifically for use in psychedelic-assisted treatments thus far, but this could be helpful especially in assessing personal knowledge and connotations of psychedelics (1960s counterculture, Indigenous mysticism, or cutting-edge science).

Ideally, common factors would be experimentally manipulated in psychedelic trials. For example, expectancy effects might be altered by systematically providing more or less positive messaging. Alternatively, participants could be offered differing plausible treatment rationales—that the drug experience might bring to the surface unconscious conflicts, or bring about a therapeutic mystical experience, or simply act through a direct effect of the drug. The ritual surrounding drug administration could similarly be altered to have greater or lesser plausibility or connotations of healing. According to common factors theory, the effects of such manipulations would be dependent on the participant's perception of them. However, given the dependence of psychedelic drugs on context and the possibility of extremely distressing experiences, some manipulations of the therapeutic relationship, setting, or ritual may be unethical. Influences driven by cultural norms or media representation may obviously be more difficult to manipulate, but researchers should be vigilant about the effects of increasing media attention on psychedelics as well as their own contributions to the portrayal of psychedelics in media.

While common factors in psychedelic trials may be impossible to completely isolate and manipulate, they should at least be rigorously measured. Along those lines, screening, preparation, and aftercare procedures should be carefully documented and reported in literature. Larger trials would benefit from standardizing procedures throughout the entire study period as much as possible, and fidelity ratings may help to ensure that this goal is met.

We did not discuss the likelihood that the collective nature of many religiomagical healing ceremonies may engage additional group psychotherapeutic factors. It is unclear how psychedelics would affect such group factors as "cohesion," which are related to psychotherapy outcomes (Burlingame et al., 2019). The current psychedelic treatment research model involves running one study participant at a time, and so these factors are not relevant. However, this model may face challenges

in wider adoption due to the sheer number of therapist hours required per patient. As a result, alternative models that involve group preparation, dosing, or integration sessions may begin to look more attractive. For studies of such modalities, we advocate careful measurement of group factors known to be associated with outcome, such as cohesion.

The common factors lens allows us to more clearly see psychedelic treatment in a broader historical and cultural context. Though at face value psychedelics might appear to have exotic qualities, psychedelic-assisted treatment likely has much more in common with established forms of mental healthcare than not. The same is true when we compare Western and non-Western forms of psychotherapy. The specific ingredients can look very different across cultures and treatment modalities, but the majority of effects are driven by shared underlying mechanisms. Regardless of their true mechanism of action, psychedelics show obvious promise as healing agents and may serve as an important tool to help us understand how to harness the "active psychological ingredients" of psychotherapy, set and setting, and placebo effects.

Declaration of Conflicting Interests

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