Psychedelics and Psychotherapy

Authors
Sandeep Nayak, Matthew W. Johnson

Affiliation
Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Key words
Psychotherapies, Depression treatment, Anxiety disorders

received 09.09.2020
revised 02.11.2020
accepted 12.11.2020
published online 2020

Bibliography
Pharmacopsychiatry
DOI 10.1055/a-1312-7297
ISSN 0176-3679

Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence
Sandeep Nayak MD
Postdoctoral Fellow
Center for Psychedelic and Consciousness Research
Department of Psychiatry and Behavioral Sciences
Johns Hopkins University School of Medicine
5510 Nathan Shock Drive
Baltimore 21224 MD
USA
smn@jhmi.edu

ABSTRACT

Psychedelics have shown great promise in modern clinical trials for treating various psychiatric conditions. As a transdiagnostic treatment that exerts its effects through subjective experiences that leave enduring effects, it is akin to psychotherapy. To date, there has been insufficient discussion of how psychedelic therapy is similar to and different from conventional psychotherapy. In this article, we review the shared features of effective conventional psychotherapies and situate therapeutic psychedelic effects within those. We then discuss how psychedelic drug effects might amplify conventional psychotherapeutic processes—particularly via effects on meaning and relationship—as well as features that make psychedelic treatment unique. Taking into account shared features of conventional psychotherapies and unique psychedelic drug effects, we create a framework for understanding why psychedelics are likely to be effective with very diverse types of psychotherapies. We also review the formal psychotherapies that have been adjunctively included in modern psychedelic trials and extend the understanding of psychedelics as psychotherapy towards implications for clinical ethics and trial design. We aim to provide some common conceptual vocabulary that can be used to frame therapeutic psychedelic effects beyond the confines of any one specific modality.

Introduction

The history of therapeutic psychedelic research, like that of psychotherapy, is marked by a panoply of frameworks, structures, and guiding rationales that include secular traditions such as psychodynamic and cognitive-behavioral, as well as religious and mystical traditions. Yet there is structure within this diversity. Jerome Frank, one of the major contributors to common factors theory of psychotherapy, defined psychotherapy as any process that has 4 cardinal features. These include 1) an emotionally charged, confiding relationship with an expert who is believed to have jurisdiction over psychological healing, 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 that is believed by both to be effective [1].

It is hard to imagine a modern psychedelic clinical trial that does not satisfy these conditions. While psychedelic therapy is often described in preternatural terms that set it apart from more prosaic forms of mental healing, we argue that it exerts its effects through means shared with more conventional psychotherapies. It is unlikely that the long-lasting changes to personality, behavior, and mood occasioned by psychedelics can be attributed to simple drug effects. Rather, durable changes wrought by psychedelics result from qualities of the subjective experience and learning that takes place after the experience. In this way, psilocybin clinical trials are psychotherapy trials.

An assumption of this paper is that the subjective effects of psychedelic experiences matter immensely for their therapeutic value, and that direct drug effects are not sufficient to explain the gamut of therapeutic effects of psychedelics. We take the evidence that acute

effects measures are associated with therapeutic and other persisting effects [2–7], and that psychedelics preliminarily show efficacy across a range of disparate diagnoses to indicate this [3, 4, 8–12].

In this review, we aim to approach psychedelic therapy as psychotherapy and explore the clinical, ethical, and methodological implications therein. We will emphasize the unique psychotherapeutic effects of psychedelics, how these dovetail with more conventional forms of psychotherapy, and explore aspects of psychotherapy trial design relevant to psychedelic trials with an aim toward specific prescriptions for trial design. We hope to provide concepts and vocabulary to better understand psychedelics as psychotherapy.

What is Psychotherapy?

With few exceptions, no bona fide psychotherapy has been shown to consistently outperform another [14, 15]. It is the common factors that psychotherapies share, rather than their distinct components, that consistently demonstrate the bulk of therapeutic benefit [14, 16–18]. Here, we will briefly review these common factors. For a more in-depth discussion of common factors and their relevance to psychedelics, see Gukasyan (in press) [19].

The phenomenon that various psychotherapies are largely equivalent in their effects is famously called the Dodo Bird Verdict [20], referencing Alice in Wonderland ("Everybody has won, so all shall have prizes"). It is surprisingly well-evidenced across a broad range of therapies and conditions. Luborsky et al. [21] examined 17 meta-analyses of trials comparing 2 active psychotherapies in adults with depressive and anxiety disorders. They found statistically insignificant differences, with an average difference among psychotherapies showing a Cohen's d effect size of .20. While specific ingredients of psychotherapies may be of clinical benefit, they simply do not explain the bulk of the effect of psychotherapy.

Meta-analyses of dismantling studies, in which psychotherapies are compared with and without a putative active component, find minimal effect of the supposed active components [16, 17]. There is much active debate about likely exceptions to the Dodo Bird Verdict, including trauma-focused approaches to PTSD, and exposure therapies for obsessive-compulsive disorder (OCD), social phobia, and panic disorder [14, 15, 22–30]. Nonetheless, the validity of the Dodo Bird Verdict across many disorders suggests the critical importance of common factors, even for conditions in which specific therapeutic ingredients are shown to be effective over and above the common factors.

These findings do not imply that all psychotherapies are useful for all patients. Nor do they imply that specific methods of therapy are not required. Some caution is warranted against overinterpreting the Dodo Bird Verdict. Similar effects, on average, do not necessarily mean identical mechanisms. Other factors, such as heterogeneity of control conditions, publication bias, and allegiance bias may complicate a straightforward understanding of similar effects across therapies [31].

Nonetheless, this body of evidence does highlight that a variety of therapies can be effective for a given condition. Moreover, it may suggest that there are core common factors to psychotherapy that may, as in psychedelic trials, operate even without a specifically defined therapy. Below we briefly review some of the common psychotherapeutic factors of psychotherapy pertinent to psychedelic trials, including the construction of meaning, facets of the therapeutic relationship, and skill building.

Per Frank, the overall method of psychotherapeutic change is the rescripting of "pathogenic meanings" [1]. A successful psychotherapy must provide a plausible explanation of the patient's problem that is consistent with emotional well-being and suggest a means to improve. Furthermore, it is important that psychotherapy be emotionally arousing. The 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" [1]. Notably, there are other common factors models, including Wampold's "contextual model" [14] and Orlinsky's "generic model" [32] that reach similar conclusions.

Common factors related to the creation of new meaning include the development of new self-narratives, a plausible explanatory scheme of ongoing problems, cognitive restructuring, and enhanced expectations of self-efficacy [33]. General expectations for improvement also form a critical common factor [14], which overlaps with set and setting and the placebo effect [34].

Psychotherapy is fundamentally a social endeavor, and modern common factors research especially emphasizes the role of the therapeutic relationship [14, 35–40]. Social connectedness has been described as a basic human need [41–43] and is strongly related to physical and mental wellbeing and even mortality [43–45]. Thus, it is perhaps unsurprising that facets of the relationship comprise the most powerful common factors. One such facet is the therapeutic alliance, which is the agreement between therapist and patient on the goals and tasks of therapy. Therapeutic alliance is significantly associated with therapeutic outcomes (Cohen's d = 0.57) according to a large meta-analysis [46]. Similarly, meta-analyses of the quality of affective bond between patient and therapist demonstrate a correlation with therapeutic outcomes with medium effect sizes [38, 39].

Aside from therapeutic alliance, other relational common factors include cathartic and corrective emotional experiences, improving mentalization, mobilizing hope, and decreasing isolation [14, 33]. Meaning and relationship are linked in psychotherapy—a strong rapport may be necessary for a patient to absorb difficult or new interpretations. Similarly, successful psychotherapy may import to a patient a newfound sense of being understood and valued.

Psychotherapies also involve the provision of specific skills and learning experiences that lead to better coping. These include self-mastery experiences, learning to regulate affect, emotional acceptance, mindfulness, etc. [1, 33, 47].

How Do Psychedelics Facilitate Psychotherapy?

We argue that not only does psychedelic therapy rely upon common psychotherapeutic factors, it is uniquely suited to facilitating them through its effects on meaning, relationship, and emotional skills.

Meaning

Rescripting meaning is fundamental to psychotherapy. It is important that the meaning not just feel plausibly constructed, but true. Per Irvin Yalom, the task of psychotherapy is "to invent a meaning

sturdy enough to support a life and to perform the tricky maneuver of denying our personal authorship of this meaning," [48].

An enhanced sense of meaning is perhaps the overriding hallmark of the psychedelic experience, even above mystical phenomena and visual alteration [49–53]. This is best exemplified by the "noetic quality" of psychedelic mystical experiences. Study participants receiving moderate to high dose psilocybin (> 20mg/70kg) often rank such experiences among the top 5 most meaningful experiences of their lives [5, 54, 55], even 14 months later [2].

The primacy of meaning in the therapeutic psychedelic experience is apparent in a variety of settings. Aberle's account of sacramental peyote use among the Navajo notes:

"Cult members do not take peyote to watch or listen to hallucinatory experiences for their own sake: they search for meanings in the visions, and it is the meanings that make them important…Peyote is not taken for simple, pleasurable kicks… It is taken because it supplies a feeling of personal significance which vastly heightens religious experience in the peyote meeting, because it supplies evident proof that something is being done to and for the human organism." [56].

Psychedelics may also facilitate psychotherapeutic meaning by enhancing suggestibility [57–59]. Under the influence of a psychedelic, a person may be more open to new meanings about self and situation that explain their troubles and give them a new path forward.

The Relationship

As in standard psychotherapy, the affective bond, the agreement on goals/procedures, and a general rapport are essential in the therapeutic dyad. Highly arousing emotional experiences, such as those occasioned by high dose psychedelics, may accentuate the formation of affective bonds. A qualitative study of psilocybin for depression found that "after the dose, many reported feeling bonded to their guides, saying they had been through something substantial together" [60].

Another way psychedelics can facilitate the relational factor of psychotherapy is through what David Yaden calls social and spatial unity [61]. Put simply, this entails forming a social connection with the world. Granted, this is speculative, but there are a few ways this could happen. One is an animistic experience in which surroundings take on a quality of being alive and intentional.

In *Antipodes of the Mind*, the psychologist Benny Shanon describes the animistic qualities of ayahuasca administered in a ceremonial context:

"Inanimate objects are invested with personality… It seems that a tremendous force permeates and animates everything around… Typically, people feel a direct tie to this energy and come to appreciate that their very own livelihood comes into being and is nourished by it. Coupled with this is the recognition of the abundant bounty that impregnates all Existence. The feeling is that the world is rich with plenty and that in essence, it is so good and wonderful" [62].

While these are not social relationships in a conventional sense, they are affective connections with an "other" that are experienced as intentional and good. In this respect, psychedelic phenomenology maps onto a broader category of self-transcendent-experiences (STEs) that are characterized by less self-focus and greater feelings of connection to others and the surroundings [61].

Indeed, psychedelic experiences are associated with social connectedness in a prospective internet survey [63] and a retrospective survey among festival goers [64]. A qualitative study of participants in a study of psilocybin for depression revealed connectedness to be a prominent theme. This was not restricted to connection to others, but included connection to the self and the world. Patients emphasized the valuable interplay of meaning and relationship in the psychedelic therapy process, highlighting that support from guides helped them "weave a story of what happened" [60].

Another experience that might forge a type of social connection with the world is the subjective union of self and other—the apotheosis of the mystical experience. In this, the typical conception of a social relation as existing between an "I" and an "other" breaks down. This is described best by Huxley: "I was now a Not-self, simultaneously perceiving and being the Not-self of the things around me. To this new-born Not-self, the behavior, the appearance, the very thought of the self it had momentarily ceased to be… seemed… enormously irrelevant" [65].

Skills

Psychedelic therapy may also be therapeutically effective by promoting psychological skills, including emotional acceptance and mindfulness.

The skills necessary for (and exercised by) navigating a psychedelic state may proffer more general therapeutic benefits [66]. Such skills might include experiential acceptance and mindfulness. Open-label psilocybin and ayahuasca increase trait mindfulness even with no specific mindfulness training [67, 68]. Qualitative reports suggest greater emotional acceptance [60]. It is mechanistically unclear how psychedelic therapy would increase mindfulness and emotional acceptance, though it's noteworthy that participants in psychedelic trials are typically enjoined to "trust, to let go, and to be open to whatever comes" [69]. Wolff et al. [70] argue that psychedelic therapy may shift experiential avoidance to acceptance in part by "relaxing" avoidance-related beliefs, promoting acceptance by way of instruction and by facilitating exposure through intensifying and broadening emotional range. Additionally, overcoming difficult experiences, as in the psychedelic state, can lead to a therapeutic sense of self-mastery [1].

More Than Mystical

Mystical experiences are associated with therapeutic outcomes after psychedelic experiences, and much is made of this [4, 8, 9, 71, 72]. But why should mystical experiences lead to positive outcomes? We argue that mystical experiences are a potent example of a more general therapeutic process.

Not all participants in psychedelic trials who benefit greatly have mystical experiences. Participant's in Bogenschutz's [73] qualitative study of 3 participants from a psilocybin trial for alcohol use disorder described processes of change that may not be adequately captured by existing measures. Bogenschutz et al. note that "while some experiences prominently feature elements of the classic mystical or peak-psychedelic experience, others instead center on feelings of forgiveness, self-compassion, and love, as well as catharsis and acceptance of past behavior," which were "at least as salient as classic mystical content" [73]. The shared feature of these experiences and

mystical experiences is a heightened sense of meaning that allows new narratives, corrective emotional experiences, and connectedness—factors not unique to psychedelic experiences. Finally, Gasser et al. [74] emphasize the ability of psychedelics to "alter the usual frame of reference, especially in respect to cognitive concepts and habits." This "deschematizing" quality likely facilitates the adoption of more adaptive perspectives and less pathogenic meanings.

Other measures of the acute experience, such as psychological insight and emotional breakthrough have been prospectively associated with improvements in wellbeing and depression [75, 76]. It is likely that other acute subjective measures may be associated with benefits, and there is a need to identify them.

Thus, this brief overview suggests many ways that psychedelics may facilitate normal psychotherapeutic processes.

The Psychedelic Framework of Healing

Psychedelics have been used in a variety of psychotherapeutic frameworks. These include the psycholytic, the traditional sacramental, the chemotherapeutic, and the psychedelic therapy framework. The psychedelic framework is the basis of all modern trials and is the focus of this paper [77]. The goal of this framework is to produce an intensely meaningful, transformative experience that has been variously characterized with such terms as mystical, oceanic boundlessness, or peak experience. These are by and large overlapping constructs. The Oceanic Boundlessness subscale of the 5D-ASC correlates very strongly with the MEQ30 ($r = 0.93$) [78].

Pahnke used the term "peak experience" to describe certain acute effects with psychedelics, drawing from the concept of peak experience that Maslow developed aside from drug experiences [79]. This modality is essentially identical to the current psychedelic therapy model used in most modern trials. It involves several cumulative hours of preparative sessions, with a focus on rapport building, gaining a deep understanding of the patient's history, and conveying some sense of how to approach the psychedelic experience to minimize harms and maximize benefits [80]. A key aspect of this modality is post-dosing integration [81–83]. This occurs in the weeks after a psychedelic session and to create meaning from the experience in a way that can be integrated within day-to-day life in the form of actions.

Co-construction of Meaning and the Multiplicity of Psychedelic Therapies

Various schools of formal psychotherapy have been applied to therapeutic psychedelic use including psychoanalytic, Jungian, existential, and so on. Cohen notes, "It is curious how under LSD the fondest theories of the therapist are confirmed by his patient. Freudian symbols come out of the mouths of patients with Freudian analysts. Those who have Jungian therapists deal with the collective unconscious and with archetypal images. The patient senses the frame of reference to be employed, and his associations and dreams are molded to it. Therefore, the validity of any school of healing should not be based upon productions of the patient—especially LSD patients" [84]. This flexibility of meaning in psychedelic therapy follows directly from an understanding of psychedelic therapy as psychotherapy.

Meaning is co-constructed in psychotherapy, and there are many plausible meanings appropriate for any given psychotherapeutic situation. A common factors definition of psychotherapy is broad and allows for a huge breadth of effective modalities including religiomagical healing rituals and psychotherapies with bizarre rationales, such as Mesmerism or past life regression therapy. Per Cohen, "Any explanation of the patient's problems, if firmly believed by both the therapist and the patient, constitutes insight or is as useful as insight. It is the faith, not the validity that counts" [84]. We posit that suggestibility enhancing effects of psychedelics broaden the range of plausibility and possibility, such that very different psychotherapies could work well. However, this may be a double-edged sword.

A relevant example is the recovered memory scandal of the 1980's and '90s, in which zealous psychotherapists implanted, by way of aggressive suggestion, lurid false memories, including of fantastical satanic rituals or alien abductions [85, 86]. These memories were often recovered with suggestibility enhancing techniques, such as hypnosis or guided imagery. Yet one can imagine equally bizarre but therapeutic beliefs arising through psychedelic therapy.

Stanislav Grof developed a highly wrought system of LSD psychotherapy in which the lasting impact of perinatal experiences on individual and society figures prominently. This is not mere metaphor. In his paper, Perinatal Roots of Wars, Totalitarianism, and Revolutions, he states, "The described association could be due to the fact that perinatal matrices represent deep motivational structures that are actually responsible for deviant behavior of individuals and for social psychopathology" [87].

Here is a patient of his, describing a guided LSD experience:

I relived my own conception and various stages of my embryological development. While I was experiencing all the complexities of the embryogenesis, with details that surpassed the best medical handbooks, I was flashing back to an even more remote past, visualizing some phylogenetic vestiges from the life of my animal ancestors. The scientist in me was struck by another riddle: can the genetic code, under certain circumstances, be translated into a conscious experience?... I felt, however, that something of utmost relevance had happened to me on this session day and that I would never be the same. I reached a new feeling of harmony and self-acceptance, and a global understanding of existence that is difficult to define [88].

Under the very reasonable assumption that intrauterine episodic memories are not possible, these are false memories. Perhaps this is a kind of harm. Or perhaps psychotherapeutic meaning is always a kind of skilled pareidolia—satisfying, useful, but ultimately constructed. William James, discussing beliefs, advises us "by their fruits ye shall know them, not by their roots" [89]. Similarly, Krupitsky, in describing ketamine-assisted psychotherapy, calls the "individually tailored psychotherapeutic myth... the most important therapeutic factor" in this modality [90].

At a minimum, the possibility of significant belief changes should perhaps be addressed as part of informed consent. Perhaps, given the wide potential scope for belief change, the individual therapeutic frame alone is insufficient for evaluating these experiences. Psychedelics have the potential to cause epistemic harm by facilitating non-scientific beliefs. This may be of societal concern in an era of widespread scientific disbelief, for example with the

benefit of vaccination or the reality of anthropogenic climate change. How such epistemic harms should be evaluated, predicted, and minimized is unclear, and a greater understanding of what sorts of belief changes are most likely under psychedelic therapy would be useful. Also, much more research is needed on the relative contributions of personality, prior beliefs, guide characteristics, setting, and attitudes toward psychedelics to belief changes. This is ethically ambiguous territory that will likely be debated for years to come.

Formal Psychotherapies Used in Psychedelic Trials

In the modern era, there have been only a handful of formal psychotherapies used in psychedelic trials.

In an open-label trial of psilocybin for DSM-IV Alcohol Dependence, Bogenschutz et al. [9] used Motivational Enhancement Therapy (MET). This is a kind of therapy heavily based in the principles of motivational interviewing, which are commonly used to work with ambivalence and facilitate change in substance use disorders. Their group is currently running a double-blind study of psilocybin for alcohol use disorder using a modified version of MET, called Motivational Enhancement and Taking Action (META) (NCT02061293). Our own group has published a single-group, open-label pilot study [8] and is currently conducting a comparative effectiveness trial of open label psilocybin versus nicotine replacement for smoking cessation with both groups receiving CBT.

Walsh and Thiessen made the case that third wave behavioral therapies could be useful adjuncts to psychedelic therapy. Third wave therapies include Dialectical Behavior Therapy, Mindfulness Based Cognitive Therapy, and Acceptance and Commitment Therapy (ACT) [91]. They are called third wave because, in addition to basic environmental contingencies (first wave) and the integration of cognition (second wave), these therapies include additional emphases on concepts such as mindfulness, metacognition, and emotional regulation. Sloshower et al. proposed ACT as an ideal therapeutic frame for psychedelic psychotherapy for major depressive disorder [92]. ACT is a kind of behavioral therapy with strong existential and mindfulness influences that focuses on cultivating psychological flexibility through 6 core elements. These are acceptance of thoughts and emotions, present awareness, distillation of values and committed action towards those values, as well as "self-as-context" and "defusion."

Defusion refers to separating oneself from overattachment to thought contents, viewing them as events or interpretations rather than truths. Self-as-context is a related idea that can be understood as defusion from a reified or conceptual self. It refers to a self that is more interconnected and processual. Importantly, in ACT, these processes are viewed as skills to cultivate not simply traits. Relatedly, Watts proposes a similar model specific to psychedelic therapy: accept, connect, embody (ACE), reordered under the themes of acceptance and connection [93]. Relatedly, Zeifman et al. [94] suggest incorporating psychedelic therapy with third wave behavioral therapies for borderline personality disorder such as Dialectical Behavioral Therapy.

Regardless of the formal school of psychotherapy, we argue that the majority of modern psychedelic clinical trials effectively include bona fide psychotherapy. Whether or not this is made fully explicit, the set and setting procedures, psychological support with skilled healers, various plausible rationales for efficacy, opportunities to learn and practice emotional skills, and a dramatic ritual include all the common factors of psychotherapy.

Psychedelic Trials as Psychotherapy Plus Drug Trials

The idea that psychedelic therapy is in many respects more like psychotherapy than traditional psychiatric pharmacology has profound implications for methodology. In a standard drug trial, the intervention effect under investigation is the physiological effect of the drug shorn of contextual effects by placebo comparison. This is an assumption about the nature of the intervention effect—that it can be separated from contextual effects. Psychedelic trials, however, emphasize contextual effects. These are thought to interact with the physiological effects of the drug to produce experiences that are themselves therapeutic.

Psychotherapy is also thought to exert therapeutic effects through experiences, and psychotherapy trials and psychedelic trials share similar methodological hurdles. Here we suggest that the intersection of problems facing psychedelic trial methodology may be unique, but their individual components are not. We explore aspects of psychotherapy trials relevant to psychedelic trials with suggestions for trial design.

Psychotherapy trials are nearly impossible to blind and often use non-inert control conditions. Psychedelic trials have the added complication of drug effects and their interactions with psychotherapy. These both create problems for drawing causal inferences from psychedelic trials. Modern double-blind, controlled psychedelic trials purport to compare direct drug effects plus the effect of psychotherapy (in a common factors sense) versus the effect of psychotherapy. However, what is actually compared is direct drug effects plus the effect of psychotherapy plus their interaction plus placebo expectancies generated by a (likely at least partially) broken blind versus the effect of psychotherapy minus nocebo expectancies of a broken blind.

Blinding and its relation to expectancy effects are particularly important given the amount of enthusiasm for psychedelic research and the dramatic subjective effects of these drugs. The data on blind efficacy in psychedelic studies is scant but clear. Therapists could distinguish LSD from ephedrine placebo in 19/20 cases (95 %) and LSD from placebo in 24/28 cases (86 %) [95, 96]. In Ross et al. [4], therapists correctly distinguished psilocybin from niacin in 28/29 cases (97 %). Blind integrity was more encouraging in Griffiths et al. [54]. Psychedelic naïve participants received either a dose of psilocybin and methylphenidate as an active control in random order, or 2 doses of methylphenidate with subsequent open-label psilocybin. An instructional set including the possibility of 2 initial psilocybin sessions was intended to reduce unblinding by process of elimination. These measures appear to have been successful in improving blinding—both therapists misidentified the drug administered in 23 % of cases. Notably, participant guesses were not recorded in these studies, but they are likely to be similar or even more accurate than guesses of the therapists.

Palhano-Fontes et al. performed a randomized, placebo-controlled trial of ayahuasca for treatment-resistant depression [13]. Remarkably, a third of the placebo group believed they had received ayahuasca. Their patient population was clinician referred and psychedelic naïve, 2 factors that may have improved blinding. Furthermore, the placebo compound generated nausea and even vomiting. Perhaps unsurprisingly, none of the ayahuasca group doubted they had received ayahuasca.

Psychedelic trials are surrounded by a cloud of conceptual confusion arising from the fact that they are simultaneously drug trials and psychotherapy trials. A single phenomenon may be viewed as a placebo effect in a drug trial or an active therapeutic effect in a psychotherapy trial. There are a few strategies to guide us through this morass.

One is to measure and control for factors that in a typical drug trial would be considered placebo mediators but in a psychotherapy trial would be considered psychotherapeutic process variables—namely the common factors.

Gukasyan (in press) discusses in depth how common factor measures predictive of outcome in psychotherapy trials could be fruitfully translated to psychedelic trials [19]. The working alliance can easily be assessed with the WAI-SR, a brief 12-item scale completed by the participant [97]. Another process measure predictive of psychotherapy outcome is the affective relationship, operationalized by the Barrett-Lennard Relationship Inventory (BLRI) [98]. Patient expectations, a mechanism of the placebo effect aroused by unblinding, comprise a common psychotherapeutic factor that is consistently shown to be predictive of improvement when measured before or early in psychotherapy [99–101]. This can be assessed with the 6-item Credibility and Expectancy Questionnaire (CEQ) [102]. Gukasyan (in press) also suggested the development of a treatment expectancy questionnaire specific for psychedelics given the broad range of subcultural expectations they carry [19].

Blinding

Psychedelic trials share the blinding conundra of psychotherapy trials because they are psychotherapy trials**.** Without effective blinding, psychedelic trials are open to the critique of being "theatrical placebos" whose apparent effects are bolstered by a de facto nocebo group [103]. The plausibility of this critique does depend on a priori likelihood of clinical improvement and subsequent magnitude of effect, but if successful blinding is viewed to be essential for a methodologically sound psychedelic trial, perhaps it should be systematically assessed. If blind integrity consistently fails, then we must either make greater efforts to improve blinding or acknowledge that the emperor has no clothes and pivot towards trial designs that honestly address this. Ultimately, however, the effects of these inadequacies are a matter of degree.

Let us imagine a trial design that disentangles direct psilocybin drug effects from the effects of psychotherapy while potentially better preserving blind to minimize expectancy effects. There are 3 arms. One group would get high-dose psilocybin and psychological support in a psychedelic framework. This would capture direct drug effects, psychotherapy effects, the interaction between the 2, and expectancy effects related to belief in having received the active drug. A second group would get a psychoactive drug with impressive subjective effects of similar duration to psilocybin, such as THC, with similar psychological support. Facilitators and participants would be told a range of possible control drugs could be administered including DXM, methylphenidate, ketamine, and many others, in the style of Carbonaro et al. [104] and Griffiths et al. [54]. This would capture psychotherapy effects, and possibly expectancy effects if enough participants mistake the placebo for active drug. However, this also introduces drug effects of THC, which may be therapeutic or anti-therapeutic rather than therapeutically neutral. For this reason, a third group would get placebo and psychological support. This group would capture the effect of psychotherapy alone and potentially negative expectancy effects for not having received the active drug. These 2 groups together would allow assessment of psychedelic-assisted therapy while controlling for the effects of receiving a potent psychoactive drug administered in an intensely psychologically supportive setting and positive expectancy effects as well. A fourth group receiving psilocybin alone with minimal psychological support (but judged to meet a sufficient ethical standard as in the standard support group in Griffiths et al. would be useful for illuminating direct drug effects of psilocybin while accounting for positive expectancy effects [5]. Ideally, functional unblinding in one session would not allow prediction of drug in subsequent sessions if the instructional set did not allow for process of elimination, as in Griffiths et al. [54]. Expectations would be directly assessed. Participants would need to be psychedelic naïve, and blind integrity would be assessed directly. Another feature that may reduce expectancy effects is to accept only clinician-referred (as opposed to self-referred) participants.

Even this design may fail if blinding is not successful. The true rate of functional unblinding in psychedelic trials is unknown but likely at least 80 % per the studies above. If we assume that blinding fails 100 % of the time, then blinded controls are nonsensical and possibly nocebo conditions. Under this assumption, non-blinded designs such as comparative effectiveness trials may be more useful, such as our aforementioned smoking cessation trial, or Imperial College's psilocybin versus escitalopram study for depression (NCT03429075). These would side-step negative expectancy confounds and allow clinically meaningful comparisons to existing treatments. Comparative effectiveness trials more realistically model clinical treatment with psychedelics. Clinical practice will not involve patients wondering during the beginning of sessions whether any drug effect will be felt, as is the case when psychedelics are compared to true placebos in blinded trials. This is an especially challenging unknown given that the person has been told that the experience may be extremely intense and potentially frightening.

Conclusion

In this review, we have argued a couple of different points. Firstly, we argued that diverse psychotherapies have more shared features than differentiating ones; that psychotherapies may be understood as vehicles of meaning and new behavioral approaches to life, rather than simply through their specific contents. Secondly, we argued that psychedelics draw on and amplify these psychotherapeutic elements and proffer unique enhancement of meaning, relationships, and connection broadly. We attempted to emphasize the flexibility of psychedelics, as well as their usefulness for diverse and

even contradictory therapeutic approaches. We touched on potential ethical questions of this therapeutic flexibility and believe more active conversation on this topic would be beneficial. Like many, we believe there is much to be gained in combining explicit psychotherapy with psychedelics. However, we are skeptical that there is any one psychotherapeutic approach that is uniquely suited to this endeavor. These drugs have a perhaps unparalleled ability to reflect researchers' and therapists' assumptions. They can produce terrifying psychoses or timeless mystical states. They can elicit castration anxiety or recall of "ancestral memories." Diversity is the watchword. The proclivities of the therapist, the patient, the cultural set and setting, and other contextual factors may be most important in determining the ideal psychotherapeutic approach to an individual psychedelic therapy patient. We explored some of the implications of understanding psychedelic therapy as psychotherapy on trial design with some modest suggestions for improvement. Ultimately, we hope to goad more explicit discussion of psychedelics as psychotherapy, with some concepts and language that may be useful for framing therapeutic psychedelic effects beyond the confines of any one specific modality.

Disclaimers

The views expressed in this article are the authors' own and do not reflect the views of institution or funders.

Sources of Support

Heffter Research Institute, The Steven and Alexandra Cohen Foundation, Tim Ferriss, Matt Mullenweg, Craig Nerenberg, and Blake Mycoskie.

Conflict of Interest

Matthew W. Johnson has advisory relationships with the following organizations AWAKN Life Sciences Inc., Beckley Psychedelic Ltd., Entheogen Biomedical Corp., Field Trip Psychedelics Inc., Mind Medicine Inc., Otsuka Pharmaceutical Development & Commercialization Inc., Silo Pharma, Inc.

References

[1] Frank JD, Frank JB. Persuasion and Healing: A Comparative Study of Psychotherapy. Baltimore: JHU Press; 1993

[2] Griffiths RR, Richards WA, Johnson MW et al. Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. J Psychopharmacol 2008; 22: 621–632

[3] Griffiths RR, Johnson MW, Carducci MA et al. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. J Psychopharmacol 2016; 30: 1181–1197

[4] Ross S, Bossis A, Guss J et al. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. J Psychopharmacol 2016; 30: 1165–1180

[5] Griffiths RR, Johnson MW, Richards WA et al. 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. J Psychopharmacol 2018; 32: 49–69

[6] Roseman L, Nutt DJ, Carhart-Harris RL. Quality of acute psychedelic experience predicts therapeutic efficacy of psilocybin for treatment-resistant depression. Front Pharmacol 2018; 8: 974

[7] Garcia-Romeu A, Griffiths R, Johnson WM. Psilocybin-occasioned mystical experiences in the treatment of tobacco addiction. Curr Drug Abuse Rev 2014; 7: 157–164

[8] Johnson MW, Garcia-Romeu A, Cosimano MP et al. Pilot study of the 5-HT 2A R agonist psilocybin in the treatment of tobacco addiction. J Psychopharmacol 2014; 28: 983–992

[9] Bogenschutz MP, Forcehimes AA, Pommy JA et al. Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. J Psychopharmacol 2015; 29: 289–299

[10] Carhart-Harris RL, Bolstridge M, Rucker J et al. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. Lancet Psychiatry 2016; 3: 619–627

[11] Gasser P, Holstein D, Michel Y et al. Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. J Nerv Ment Dis 2014; 202: 513–520

[12] Moreno FA, Wiegand CB, Taitano EK et al. Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. J Clin Psychiatry 2006; 67: 1735–1740

[13] Palhano-Fontes F, Barreto D, Onias H et al. Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomized placebo-controlled trial. Psychol Med 2019; 49: 655–663

[14] Wampold B, Imel Z. The great psychotherapy debate: The evidence for what makes psychotherapy work. New York: Routledge; 2015

[15] Benish SG, Imel ZE, Wampold BE. The relative efficacy of bona fide psychotherapies for treating post-traumatic stress disorder: A meta-analysis of direct comparisons. Clin Psychol Rev 2008; 28: 746–758

[16] H-n Ahn, Wampold BE. Where oh where are the specific ingredients? A meta-analysis of component studies in counseling and psychotherapy. J Couns Psychol 2001; 48: 251

[17] Bell EC, Marcus DK, Goodlad JK. A meta-analysis of component treatment studies: Are the parts as good as the whole? J Consult Clin Psychol 2013; 81: 722

[18] Ougrin D. Efficacy of exposure versus cognitive therapy in anxiety disorders: systematic review and meta-analysis. BMC Psychiatry 2011; 11: 1–13

[19] Gukasyan N, Nayak S Psychedelics, placebo effects, and set and setting: Insights from common factors theory of psychotherapy. Transcult Psychiatry (in press). Available at https://www.researchgate.net/publication/338776147_Psychedelics_placebo_effects_and_set_and_setting_insights_from_common_factors_theory_of_psychotherapy

[20] Rosenzweig S. Some implicit common factors in diverse methods of psychotherapy. Am J Orthopsychiat 1936; 6: 412

[21] Luborsky L, Rosenthal R, Diguer L et al. The Dodo bird verdict is alive and well—mostly. Clin Psychol 2002; 9: 2–12

[22] Ehlers A, Bisson J, Clark DM et al. Do all psychological treatments really work the same in posttraumatic stress disorder? Clin Psychol Rev 2010; 30: 269–276

[23] Wampold BE, Imel ZE, Laska KM et al. Determining what works in the treatment of PTSD. Clin Psychol Rev 2010; 30: 923–933

[24] DeRubeis RJ, Brotman MA, Gibbons CJ. A conceptual and methodological analysis of the nonspecifics argument. Clin Psychol 2005; 12: 174–183

[25] Laska KM, Gurman AS, Wampold BE. Expanding the lens of evidence-based practice in psychotherapy: A common factors perspective. Psychother 2014; 51: 467

[26] Frost ND, Laska KM, Wampold BE. The evidence for present-centered therapy as a treatment for posttraumatic stress disorder. J Trauma Stress 2014; 27: 1–8

[27] Baardseth TP, Goldberg SB, Pace BT et al. Cognitive-behavioral therapy versus other therapies: redux. Clin Psychol Rev 2013; 33: 395–405

[28] Mayo-Wilson E, Dias S, Mavranezouli I et al. Psychological and pharmacological interventions for social anxiety disorder in adults: a systematic review and network meta-analysis. Lancet Psychiatry 2014; 1: 368–376

[29] Chen L, Zhang G, Hu M et al. Eye movement desensitization and reprocessing versus cognitive-behavioral therapy for adult posttraumatic stress disorder: systematic review and meta-analysis. J Nerv Ment Dis 2015; 203: 443–451

[30] Strauss AY, Huppert JD, Simpson HB et al. What matters more? Common or specific factors in cognitive behavioral therapy for OCD: Therapeutic alliance and expectations as predictors of treatment outcome. Behav Res Ther 2018; 105: 43–51

[31] Cuijpers P, Karyotaki E, Wit L de et al. The effects of fifteen evidence-supported therapies for adult depression: A meta-analytic review. Psychother Research 2020; 30: 279–293

[32] Orlinsky DE. The "Generic Model of Psychotherapy" after 25 years: Evolution of a research-based metatheory. J Psychother Integr 2009; 19: 319

[33] Tschacher W, Haken H, Kyselo M. Alliance: A common factor of psychotherapy modeled by structural theory. Front Psychol 2015; 6: 421

[34] Hartogsohn I. Set and setting, psychedelics and the placebo response: an extra-pharmacological perspective on psychopharmacology. J Psychopharmacol 2016; 30: 1259–1267

[35] Lambert MJ, Barley DE. Research summary on the therapeutic relationship and psychotherapy outcome. Psychother: Theory, Research, Practice. Training 2001; 38: 357

[36] Elliott R, Bohart AC, Watson JC et al. Empathy. Psychother 2011; 48: 43

[37] Elliott R, Bohart AC, Watson JC et al. Therapist empathy and client outcome: an updated meta-analysis. Psychother 2018; 55: 399–410

[38] Elliot R. Empathy., In: Norcross J, Lambert M. Eds. Psychotherapy Relationships that Work. New York: Oxford University Press; 2019: 245–287

[39] Kolden GG, Wang CC, Austin SB et al. Congruence/genuineness: A meta-analysis. Psychother 2018; 55: 424–433

[40] Farber BA, Suzuki JY, Lynch DA. Positive regard and affirmation. In: Norcross JC, Lambert MJ. Eds. Psychotherapy Relationships that Work: Volume 1: Evidence-Based Therapist Contributions. New York: Oxford University Press; 2019: 288–322

[41] Baumeister RF, Leary MR. The need to belong: desire for interpersonal attachments as a fundamental human motivation. Psychol Bull 1995; 117: 497

[42] Deci EL, Ryan RM. The "what" and "why" of goal pursuits: Human needs and the self-determination of behavior. Psychol Inq 2000; 11: 227–268

[43] Cacioppo JT, Cacioppo S. Social relationships and health: The toxic effects of perceived social isolation. Soc Personal Psychol 2014; 8: 58–72

[44] Luo Y, Hawkley LC, Waite LJ et al. Loneliness, health, and mortality in old age: A national longitudinal study. Soc Sci Med 2012; 74: 907–914

[45] Holt-Lunstad J, Smith TB, Layton JB. Social relationships and mortality risk: a meta-analytic review. PLoS Med 2010; 7: 7

[46] Fluckiger C, Del Re AC, Wampold BE et al. The alliance in adult psychotherapy: a meta-analytic synthesis. Psychother 2018; 55: 316

[47] Brown J. Specific techniques vs. common factors? Psychotherapy integration and its role in ethical practice. Am J Psychother 2015; 69: 301–316

[48] Yalom ID. The Gift of Therapy: An Open Letter to a New Generation of Therapists and Their Patients. (p. 133).New York: HarperCollins Publishers; 2002

[49] Hartogsohn I. The meaning-enhancing properties of psychedelics and their mediator role in psychedelic therapy, spirituality, and creativity. Front Neurosci 2018; 12

[50] Preller KH, Herdener M, Pokorny T et al. The fabric of meaning and subjective effects in LSD-induced states depend on serotonin 2A receptor activation. Curr Biol 2017; 27: 451–457

[51] Fischman LG. Seeing without self: discovering new meaning with psychedelic-assisted psychotherapy. Neuropsychoanalysis 2019; 21: 53–78

[52] Metzner R, Litwin GH, Weil GM. The relation of expectation and mood to psilocybin reactions: A questionnaire study. Psychedelic Review 1965; 1: 3–39

[53] James E, Robertshaw TL, Hoskins M et al. Psilocybin occasioned mystical-type experiences. Hum Psychopharm Clin 2020; 2742

[54] Griffiths R, Richards WA, McCann U et al. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. Psychopharmacology (Berl) 2006; 187: 268–283

[55] Griffiths RR, Johnson MW, Richards WA et al. Psilocybin occasioned mystical-type experiences: immediate and persisting dose-related effects. Psychopharmacology (Berl) 2011; 218: 649–665

[56] Aberle DF. The Peyote Religion among the Navaho. Viking Fund Publications in Anthropology 1966; 42

[57] Carhart-Harris RL, Kaelen M, Whalley MG et al. LSD enhances suggestibility in healthy volunteers. Psychopharmacology (Berl) 2015; 232: 785–794

[58] Middlefell R. The effects of LSD on body sway suggestibility in a group of hospital patients. Br J Psychiatry 1967; 113: 277–280

[59] Sjoberg BM, Hollister LE. The effects of psychotomimetic drugs on primary suggestibility. Psychopharmacologia 1965; 8: 251–262

[60] Watts R, Day C, Krzanowski J et al. Patients' accounts of increased "connectedness" and "acceptance" after psilocybin for treatment-resistant depression. J Humanist Psychol 2017; 57: 520–564

[61] Yaden DB, Haidt JH Jr et al. The varieties of self-transcendent experience. Rev Gen Psychol 2017; 21: 143–160

[62] Shanon B. The Antipodes of the Mind: Charting the Phenomenology of the Ayahuasca Experience. Oxford: Oxford University Press; 2002

[63] Carhart-Harris RL, Erritzoe D, Haijen E et al. Psychedelics and connectedness. Psychopharmacology (Berl) 2018; 235: 547–550

[64] Forstmann M, Yudkin DA, Prosser AM et al. Transformative experience and social connectedness mediate the mood-enhancing effects of psychedelic use in naturalistic settings. Proc Natl Acad Sci 2020; 117: 2338–2346

[65] Huxley A. The Doors of Perception. New York: Harper & Row; 1954

[66] Letheby C The varieties of psychedelic epistemology. In: Psychedelicacies: More Food for Thought from Breaking Convention. Strange Attractor Press, 2019

[67] Madsen MK, Fisher PM, Stenbaek DS et al. A single psilocybin dose is associated with long-term increased mindfulness, preceded by a proportional change in neocortical 5-Ht2A receptor binding. Eur Neuropsychopharm 2020; 5

[68] Soler J, Elices M, Franquesa A et al. Exploring the therapeutic potential of Ayahuasca: acute intake increases mindfulness-related capacities. Psychopharmacology (Berl) 2016; 233: 823–829

[69] Pahnke WN. The psychedelic mystical experience in the human encounter with death. Harv Theol R 1969; 62: 1–21

[70] Wolff M, Evens R, Mertens LJ et al. Learning to let go: A cognitive-behavioral model of how psychedelic therapy promotes acceptance. Front Psychiatry 2020; 11: 5

[71] Barrett FS, Johnson MW, Griffiths RR. Validation of the revised Mystical Experience Questionnaire in experimental sessions with psilocybin. J Psychopharmacol 2015; 29: 1182–1190

[72] Garcia-Romeu A, Griffiths RR, Johnson MW. Psilocybin-occasioned mystical experiences in the treatment of tobacco addiction. Curr Drug Abuse Rev 2014; 7: 157–164

[73] Bogenschutz MP, Podrebarac SK, Duane JH et al. Clinical interpretations of patient experience in a trial of psilocybin-assisted psychotherapy for alcohol use disorder. Front Pharmacol 2018; 9: 1–7

[74] Gasser P, Kirchner K, Passie T. LSD-assisted psychotherapy for anxiety associated with a life-threatening disease: A qualitative study of acute and sustained subjective effects. J Psychopharmacol 2015; 29: 57–68

[75] Davis AK, Barrett FS, May DG, et al. Effects of psilocybin-assisted therapy for major depressive disorder: A randomized clinical trial. JAMA Psychiatry 2020

[76] Roseman L, Haijen E, Idialu-Ikato K et al. Emotional breakthrough and psychedelics: validation of the emotional breakthrough inventory. J Psychopharmacol 2019; 33: 1076–1087

[77] Chwelos N, Blewett DB, Smith CM et al. Use of d-lysergic acid diethylamide in the treatment of alcoholism. Q J Stud Alcohol 1959; 20: 577–590

[78] Liechti ME, Dolder PC, Schmid Y. Alterations of consciousness and mystical-type experiences after acute LSD in humans. Psychopharmacology (Berl) 2017; 234: 1499–1510

[79] Maslow AH. Toward a Psychology of Being. Princeton, NJ: D. Van Nostrad Company; 1962

[80] Pahnke WN, Kurland AA, Goodman LE et al. LSD-assisted psychotherapy with terminal cancer patients. Curr Psychiatr Ther 1969; 9: 144

[81] Pahnke WN. The experimental use of psychedelic (LSD) psychotherapy. JAMA 1970; 212: 1856

[82] Savage C, McCabe OL, Kurland AA et al. LSD-assisted psychotherapy in the treatment of severe chronic neurosis. J Alter St Conscious 1973; 1: 31–47

[83] Bogenschutz MP, Forcehimes AA. Development of a psychotherapeutic model for psilocybin-assisted treatment of alcoholism. J Humanist Psychol 2017; 57: 389–414

[84] Cohen S. Psychotherapy with LSD: pro and con., In: Abramson HA, Eds. The Use of LSD in Psychotherapy and Alcoholism. Indianapolis, IN: The Bobbs-Merrill Company; 1967

[85] McHugh PR. Try To Remember: Psychiatry's Clash over Meaning, Memory and Mind. New York: Dana Press; 2008

[86] McNally RJ, Clancy SA. Sleep paralysis, sexual abuse, and space alien abduction. Transcult Psychiatry 2005; 42: 113–122

[87] Grof S. Perinatal roots of wars, totalitarianism, and revolutions: observations from LSD research. J Psychohist 1977; 4: 269

[88] Grof S. Realms of the Human Unconsciousness: Observations from LSD Research. New York: The Viking Press,; 1975

[89] James W. The Varieties of Religious Experience. London: Longmans; Green and Co. 1917

[90] Krupitsky EM, Grinenko AY. Ketamine psychedelic therapy (KPT): A review of the results of ten years of research. J Psychoact Drugs 1997; 29: 165–183

[91] Walsh Z, Thiessen MS. Psychedelics and the new behaviourism: considering the integration of third-wave behaviour therapies with psychedelic-assisted therapy. Int Rev Psychiatry 2018; 30: 343–349

[92] Sloshower J, Guss J, Krause R et al. Psilocybin-assisted therapy of major depressive disorder using Acceptance and Commitment Therapy as a therapeutic frame. J Contextual Behav Sci 2020; 15: 12–19

[93] Watts R, Luoma JB. The use of the psychological flexibility model to support psychedelic assisted therapy. J Contextual. Behav Sci 2020; 15: 92–102

[94] Zeifman RJ, Wagner AC. Exploring the case for research on incorporating psychedelics within interventions for borderline personality disorder. J Contextual Behav Sci 2020; 15: 1–11

[95] Smart RG, Storm T, Baker FW et al. A controlled study of lysergide in the treatment of alcoholism. Q J Stud Alcohol 1966; 27: 469–482

[96] Soskin R. The use of LSD in time limited psychotherapy. J Nerv Ment Dis 1973; 157: 410–419

[97] Hatcher RL, Gillaspy JA. Development and validation of a revised short version of the Working Alliance Inventory. Psychother. Research 2006; 16: 12–25

[98] Barrett-Lennard GT. The Relationship Inventory: A Complete Resource and Guide. Hoboken, NJ: Wiley; 2015

[99] Constantino MJ, Arnkoff DB, Glass CR et al. Expectations. J Clin Psychol 2011; 67: 184–192

[100] Goldstein AP. Patient's expectancies and non-specific therapy as a basis for (un)spontaneous remission. J Clin Psychol 1960; 16: 399–403

[101] Snippe E, Schroevers MJ, Tovote KA et al. Patients' outcome expectations matter in psychological interventions for patients with diabetes and comorbid depressive symptoms. Cognitive Ther Res 2015; 39: 307–317

[102] Devilly GJ, Borkovec TD. Psychometric properties of the credibility/expectancy questionnaire. J Behav Ther Exp Psy 2000; 31: 73–86

[103] Godlee F. Acupuncture: theatrical placebo or caring approach to pain? BMJ 2018; 360

[104] Carbonaro TM, Johnson MW, Hurwitz E et al. Double-blind comparison of the two hallucinogens psilocybin and dextromethorphan: Similarities and differences in subjective experiences. Psychopharmacology (Berl) 2018; 235: 521–534