INTERNATIONAL REVIEW OF PSYCHIATRY
https://doi.org/10.1080/09540261.2018.1486289

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REVIEW ARTICLE

Current perspectives on psychedelic therapy: use of serotonergic hallucinogens in clinical interventions

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ABSTRACT

Humans have used serotonergic hallucinogens (i.e. psychedelics) for spiritual, ceremonial, and recreational purposes for thousands of years, but their administration as part of a structured therapeutic intervention is still a relatively novel practice within Western medical and psychological frameworks. In the mid-20th century, considerable advances were made in developing therapeutic approaches integrating administration of low (*psycholytic*) and high (*psychedelic*) doses of serotonergic hallucinogens for treatment of a variety of conditions, often incorporating psychoanalytic concepts prevalent at that time. This work contributed seminal insights regarding how these substances may be employed with efficacy and safety in targeted therapeutic interventions, including the importance of optimizing set (frame of mind) and setting (therapeutic environment). More recently, clinical and pharmacological research has revisited the effects and therapeutic potential of psychedelics utilizing a variety of approaches. The current article provides an overview of past and present models of psychedelic therapy, and discusses important considerations for future interventions incorporating the use of psychedelics in research and clinical practice.

ARTICLE HISTORY
Received 23 April 2018
Accepted 4 June 2018

KEYWORDS
Psychedelic therapy; hallucinogens; psilocybin; LSD

Introduction

Evidence of human hallucinogen use dates back to prehistoric times and spans the globe, with artifacts suggesting a sacred status of these substances among early civilizations (Guerra-Doce, 2015; Harner, 1973; Rudgley, 1995; Schultes, 1969, 1998; Schultes & Hofmann, 1992; Wasson, 1961; Wasson, Hofmann, & Ruck, 2008). While archaeological findings cannot always elucidate the specific roles of hallucinogenic substances in ancient cultures, traditional uses among extant indigenous populations and syncretic religions provide insights into ritual hallucinogen use for healing, divinatory, spiritual, and sacramental purposes (Jones, 2005; Luna, 2011; Lyttle, 1988; Metzner, 1998). Psilocybin mushrooms, peyote, ayahuasca, and other hallucinogens still maintain a central role in numerous spiritual and religious practices, and have been afforded legal protections, even today, in countries where these substances are otherwise outlawed (Bullis, 1990; De Verges, 1974; Labate, 2012). However, use of hallucinogens in modern medicine has been considerably shorter lived, and fraught with cultural and legal complications almost since the outset (Bonson, 2018; Carhart-Harris & Goodwin, 2017; Dyck, 2005; Rucker, Iliff & Nutt, 2017; Sessa, 2016). The purpose of the present paper is to provide a brief overview of the ways in which serotonin 2A (5-HT2A) receptor agonist hallucinogens (i.e. psychedelics) have been used for clinical or research purposes as part of targeted therapeutic interventions, highlighting important considerations for working safely and effectively with these substances, and discussing future directions for research and clinical applications of hallucinogens.

Psychopharmacology of hallucinogens

The term hallucinogen is applied broadly to many different naturally occurring and synthetic drugs with various mechanisms of action and profiles of subjective effects (Garcia-Romeu, Kersgard, & Addy, 2016; Nichols, 2004). These may include the psychedelics such as lysergic acid diethylamide (LSD), psilocybin, mescaline, and dimethyltryptamine (DMT), whose primary psychoactive effects are largely mediated by their activity at serotonin, and particularly serotonin 2A (5-HT2A), receptors (Glennon, Titeler, &

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McKenney, 1984; Nichols, 2016; Vollenweider, Vollenweider-Scherpenhuyzen, Bäbler, Vogel, & Hell, 1998); the entactogens such as 3,4-Methylenedioxymethamphetamine (MDMA), which stimulate release of serotonin, dopamine, and norepinephrine, and inhibit their reuptake (Nichols, 1986; Nichols & Oberlender, 1990); the dissociative anaesthetics that exert their main effects via glutamatergic *N*-Methyl-*D*-Aspartate (NMDA) receptor antagonism (Krystal et al., 1999; Morris & Wallach, 2014); and atypical hallucinogens such as ibogaine (Popik, Layer, & Skolnick, 1995), the kappa opioid receptor agonist salvinorin A (Addy, 2012; Johnson, MacLean, Reissig, Prisinzano, & Griffiths, 2011), anticholinergic deliriants such as Datura (Forrester, 2006), and cannabinoids (Keeler, Ewing, & Rouse, 1971). The focus of this article is on psychedelic therapy involving administration of 5-HT2A agonist psychedelics, as opposed to other hallucinogens, whose pharmacological and potential therapeutic mechanisms differ sufficiently to distinguish them from the current topic.[1]

History and effects of psychedelics

The intersection of psychedelics and modern medicine essentially began with the synthesis of lysergic acid diethylamide (LSD) in 1938, and subsequent discovery of its psychoactive effects in 1943, by Swiss chemist Albert Hofmann (1979, 2013). Prior explorations of related drugs emerged in the 19th and early 20th centuries (e.g. Havelock Ellis, 1897; Klüver, 1928; Mitchell, 1896), including the isolation of mescaline from the peyote cactus (Heffter, 1896, 1898), and the early conceptualization of these substances as *phantastica* by the German toxicologist Louis Lewin, who described them as, 'evoking sense-illusions in a great variety of forms, of giving rise in the human soul, as if by magic to apparitions whose brilliant, seductive, perpetually changing aspects produce a rapture which is incessantly renewed and in comparison with which the perceptions of consciousness are but pale shadows' (Lewin, 1931/1998, p. 80).

Nevertheless, the discovery of LSD represented the dawn of relatively widespread scientific awareness of and interest in psychedelics. LSD is a potent, semisynthetic hallucinogen amenable to pharmaceutical production, and its manufacturer Sandoz made it freely available to physicians and scientists. Thus, research on LSD grew rapidly through the 1950s, contributing to our early understanding of the neurochemistry of serotonin, and its role in mental functioning (Aghajanian & Marek, 1999; Brodie & Shore, 1957; Gaddum, 1953; Woolley & Shaw, 1954). Prior to the passage of the Controlled Substances Act in the US, and the United Nations Convention on Psychotropic Substances (1971) when the psychedelics were effectively outlawed, a robust body of research was conducted with psychedelics, including some 40,000 individuals who were administered LSD as part of research studies during this time (Grinspoon & Bakalar, 1979). Clinical studies of the pre-prohibition era generally found good safety and therapeutic potential for psychedelics in treating conditions such as alcoholism, end-of-life anxiety, and even pain (Kast, 1967; Kast & Collins, 1964; Krebs & Johansen, 2012; Mangini, 1998; Richards, Grof, Goodman, & Kurland, 1972; Rucker et al., 2017; Savage, Hughes, & Mogar, 1967), but, overall, results remained inconclusive due to methodological inconsistencies, and study designs that, from the perspective of current standards, often lacked proper controls, blinding, follow-up, statistical analyses, and use of validated assessments (Rucker et al., 2017).

Set, setting, and expectancy

Early on, LSD and related compounds, such as mescaline and psilocybin, were labelled psychotomimetics, meaning they were thought to produce effects mimicking a temporary, experimental psychosis (Leuner, 1962). However, this view was soon recognized as limited and inadequate to fully describe these drugs' effects, leading to alternative characterizations. Along these lines, Cohen (1967) observed,

> the pharmacology of psychotomimetics is, at present, extensive and somewhat confusing. No well-supported explanation of the actions of these drugs (also called hallucinogens, psychedelics, fantastica) exists, although many have been proposed. It is evident that no simple, single effect will be found to explain all of the complex changes that are observed … they are capable of producing marked changes in perception, emotion, ego function, and thought (p. 301).

Thus, terms like hallucinogenic (producing hallucinations), psychedelic (mind-manifesting or soul-revealing; Osmond, 1957), and entheogenic (evoking the divine within; Ruck, Bigwood, Staples, Ott, & Wasson, 1979) were also proposed.

These disparate conceptualizations reflect the unique and highly variable effects of these substances. They also reveal an important principle for understanding psychedelic effects that was not explicitly formulated until the early 1960s: namely, that an individual's state of mind and expectations when taking

the drug, and the context in which the drug is taken, strongly influence the nature of the drug experience (Hartogsohn, 2017). These elements were dubbed *set* and *setting*, respectively (Leary, Litwin, & Metzner, 1963), and have since become well-established as key factors in research and clinical work with psychedelics (Fadiman, 2011; Johnson, Richards, & Griffiths, 2008). Although optimal parameters for set and setting have not been systematically studied, data suggest that highly clinical settings involving Positron Emission Tomography (PET) scanning are associated with greater anxiety during psilocybin administration than aesthetically furnished laboratory session rooms (Studerus, Gamma, Kometer, & Vollenweider, 2012), thus informing the design of many current psychedelic-therapy research settings.

Conversely, early research that neglected to take elements of set and setting into account may have inadvertently influenced or confounded results. Therefore, some of the initial uncertainty about how to classify these substances may in part have been related to the varied methods, populations, and conditions in which they were administered. However, over time, modern paradigms for administering psychedelics therapeutically developed their own structures and methods to optimize the likelihood of desired clinical outcomes, an evolution that is still ongoing today.

The substantial role of set and setting in influencing drug effects highlights a distinctive feature of psychedelics, setting them apart from many drugs that are generally thought to exert pharmacological effects independent of an individual's mindset or situation, such as antibiotics or sedatives for example. This does, however, raise the consideration of expectancy effects in influencing outcomes of psychedelic treatments, whereby a psychological component may be part and parcel of therapeutic efficacy (Carhart-Harris et al., 2015; Hartogsohn, 2016). Such expectancy effects have been shown to mediate therapeutic efficacy of other drug classes, such as analgesic and antidepressant medications (Carvalho et al., 2016; Khan, Bhat, Kolts, Thase, & Brown, 2010; Price, Finniss, & Benedetti, 2008; Rief et al., 2009; Walach, Sadaghiani, Dehm, & Bierman, 2005), although, due to the powerful subjective effects of psychedelics, expectancy may be even more important to take into account in research and clinical work.

Relatedly, the issue of maintaining strict double-blinding in placebo-controlled clinical trials of psychedelics has remained a methodological concern due to their pronounced effects, which are more often than not notable by both participants and observers (Metzner, Litwin, & Weil, 1965; Smart, Storm, Baker, & Solursh, 1966). A variety of methods have been used to address blinding in research with psychedelics, including enrollment of hallucinogen-naïve volunteers who would not necessarily recognize psychedelic drug effects due to a lack of previous experience, and use of active placebos such as niacin, ephedrine, methylphenidate, or very low doses of psychedelics to obscure drug conditions (Griffiths, Richards, McCann, & Jesse, 2006; Griffiths et al., 2016; Pahnke, 1963; Ross et al., 2016). Controlled trials of psychedelics implementing strict double-blinding procedures find that trained session monitors are often able to accurately identify sessions with LSD or psilocybin from active placebos in 77–95% of drug sessions (Griffiths et al., 2006; Smart et al., 1966). Blinding and expectancy effects will continue to be important considerations in the design and implementation of future clinical trials examining therapeutic efficacy of hallucinogens, which will necessitate adequate sample sizes, appropriate control conditions, and careful data collection and analytic methods to avoid the shortcomings of previous research (Carhart-Harris & Goodwin, 2017; Rucker, Iliff, & Nutt, 2017).

Early models of hallucinogen-facilitated therapy

Among the earliest formal models of hallucinogen-facilitated psychotherapy to emerge were the psycholytic and psychedelic approaches (Bravo & Grob, 1996; Passie, 1997). The psycholytic model was closely related to the psychoanalytic tradition that predominated at the time of LSD's emergence into the research arena. As such, psycholytic treatment took the form of extended talk therapy over multiple sessions, with numerous administrations of low-to-moderate doses of psychedelics (primarily LSD in the range of 30–200 mcg) during therapy, that were thought to be 'ego-loosening'. The psycholytic model proposed hallucinogens to facilitate the psychotherapeutic process by allowing greater access to the unconscious, regression to earlier stages of development, re-experiencing of past traumas, lowering of defense mechanisms, cathartic abreaction of emotionally charged material, and archetypal experiences (Leuner, 1963; Sandison, 1954, 1963).

Psycholytic treatment sometimes included use of guided imagery (Leuner, 1969), and was explored for a variety of conditions including neuroses, character disorders, and psychoses (Leuner, 1963; Passie, 1997; Sandison, 1954, 1963). From the 1950–1970s,

psycholytic therapy was developed and practiced most actively in Europe, often with promising results (Passie, 1997). Other models that emerged during this era included the psychedelytic approach, incorporating multiple low dose sessions that eventually culminated in a high dose session, or an initial high dose administration along with intermittent low dose sessions with psychotherapy to integrate material (e.g. Alnaes, 1964; Grof, 1967), and hypnodelic therapy that included use of hypnosis in conjunction with moderate doses of psychedelics during psychotherapy (Levine & Ludwig, 1966; Ludwig, Levine, Stark, & Lazar, 1969). However, these approaches have not been widely implemented or studied since, likely due to their time intensive nature, and the relatively diminished influence of psychoanalytic theory and hypnosis today.

Concurrently during the 1950s and 1960s, as the existential and humanistic schools of psychology were beginning to take shape (Frankl, 1954/1992; Maslow, 1964, 1968; May, 1961), another form of hallucinogen-facilitated treatment was emerging in North America, under the mantle of psychedelic therapy (Osmond, 1957; Pahnke, Kurland, Unger, Savage, & Grof, 1970). The psychedelic therapy model favoured use of one or a few high doses (e.g. > 250 mcg LSD) of psychedelics to create an overwhelming and transcendent experience, that was thought to catalyse the therapeutic process and serve as a basis for subsequent symptom resolution and behaviour change (Chwelos, Blewett, Smith, & Hoffer, 1959; Grof, Soskin, Richards, & Kurland, 1973; Kurland, Savage, Pahnke, Grof, & Olsson, 1971; Osmond, 1957; Pahnke et al., 1970; Richards et al., 1972; Savage et al., 1967; Savage & McCabe, 1973). During the drug sessions, therapists would largely take a non-directive approach to allow the patient's experience to unfold in a safe and unimpeded manner. The goal of this model varied according to the therapeutic target, but overall the drug sessions were meant to work in conjunction with preparatory therapy before drug administration and integrative therapy afterwards. The combination of drug administration embedded within talk therapy was meant to help process the psychedelic experience and achieve novel insights into the patient's condition, and accompanying improvements in mood, mental functioning, and behavior (Pahnke et al., 1970). This approach showed promise in treating alcoholism and opioid dependence, as well as mood and anxiety issues (Chwelos et al., 1959; Grof et al., 1973; Kurland et al., 1971; Pahnke et al., 1970; Richards et al., 1972; Savage et al., 1967; Savage & McCabe, 1973), all areas that are currently being revisited in contemporary research (Bogenschutz et al., 2015; Bogenschutz & Johnson, 2016; Garcia-Romeu et al., 2016; Griffiths et al., 2016; Grob et al., 2011; Johnson, Garcia-Romeu, Cosimano, & Griffiths, 2014; Ross et al., 2016).

Other work during the 1960s also explored psychedelics' ability not only to help alleviate clinical syndromes such as addiction and depression, but to enhance creativity, spirituality, and optimal functioning in healthy individuals (Harman, McKim, Mogar, Fadiman, & Stolaroff, 1966; Pahnke, 1963; Pahnke & Richards, 1966), in line with the human potential movement that gained popularity at that time (Friedman, 1976). Work on these topics has seen renewed interest in the 21st century, representing an important direction for future non-clinical research with psychedelics (Frecska, Móré, Vargha, & Luna, 2012; Griffiths et al., 2006, 2018).

Contemporary models of psychedelic therapy

After a decades-long lull, human research with psychedelics was gradually reinitiated in the 1990s, with laboratory studies on dimethyltryptamine (DMT; Strassman & Qualls, 1994; Strassman, Qualls, Uhlenhuth, & Kellner, 1994; Strassman, Qualls, & Berg, 1996), mescaline (Hermle et al., 1992; Hermle, Gouzoulis-Mayfrank, & Spitzer, 1998), and psilocybin (Gouzoulis-Mayfrank et al., 1998a, 1999a,b; Spitzer et al., 1996; Vollenweider et al., 1997), examining basic biological and psychological effects in healthy normal volunteers. Over time, potential therapeutic applications of psychedelics once again became the focus of novel research, including pilot studies of psilocybin for obsessive compulsive disorder (OCD; Moreno, Wiegand, Taitano, & Delgado, 2006), and anxiety in patients with advanced stage cancer (Grob et al., 2011). Beginning in the 21st century, clinical trials involving administration of psychedelics have largely mirrored the psychedelic therapy approach using a brief intervention model, generally lasting 1–3 months total, including anywhere from one-to-three moderate and high dose administrations of psychedelics such as psilocybin, with preparatory and integrative counselling occurring before and after drug administration, respectively. Modern day therapeutic research with psychedelics has focused on psilocybin and ayahuasca, and in some cases incorporated evidence-based therapeutic models such as cognitive behavioural therapy (CBT; Johnson et al., 2014), or Motivational Enhancement Therapy (MET; Bogenschutz et al., 2015).

In these cases, use of CBT, for instance in preparatory counselling prior to drug administration, is thought to allow for preliminary examination of maladaptive thought and behaviour patterns, and generation of potential alternative cognitions and behaviours that are more in line with the patient's stated goals (Wright, 2006). The administration of a psychedelic such as psilocybin within a structured CBT intervention provides the opportunity to directly experience altered cognitive and emotional states, which can then be leveraged in ongoing counselling to ultimately challenge and replace maladaptive thought and behaviour patterns such as tobacco craving and cigarette smoking (Johnson et al., 2014). Thus, psychedelic effects in this model can facilitate cognitive reframing of detrimental schemas and self-identity constructs, such as compulsive negative self-talk, towards healthier mental patterns. Similarly, use of psychedelics in conjunction with Motivational Enhancement Therapy (MET) can help patients to examine their current motivations to make changes in problematic behaviours such as chronic alcohol abuse, and the concurrent drug session can ideally help to further enhance motivation to change, and decrease any potential ambivalence about changing their behaviour (Bogenschutz & Pommy, 2012; Bogenschutz et al., 2015; Ross, 2012). This is often achieved through a revaluation of self-concept and reconnection with core beliefs and values that can occur within psychedelic drug sessions (Swift et al., 2017; Watts, Day, Krzanowski, Nutt, & Carhart-Harris, 2017).

Other, less structured therapeutic models incorporating psychedelic administration have also been forthcoming, such as administration of psilocybin or ayahuasca with psychological support in treating depression or anxiety (Carhart-Harris et al., 2016a; Griffiths et al., 2016; Palhano-Fontes et al., 2018; Ross et al., 2016). In such interventions, patients are briefed on potential drug effects, work to set an overall intention for their treatment, and build trust and therapeutic rapport with session monitors who possess varying degrees of psychotherapeutic training prior to drug sessions (Johnson et al., 2008). Then, during drug sessions, acute alterations in consciousness and brain function brought on by the psychedelic agent can be seen as interrupting usual cognitive, emotional, and behavioural patterns. During acute drug effects, and likely directly afterwards within a hypothesized 'afterglow' period lasting ~2–4 weeks, patients may experience a window of plasticity in which their usual patterns of thinking and behaving may be more amenable to novel insights and focused modifications (Majić, Schmidt, & Gallinat, 2015).

It is in this integration period following drug administration that the content of the psychedelic session is unpacked and further explored with the therapeutic team. A session report or narrative is often generated by the participant, and any positive changes in mood or behavioural symptoms can be supported and monitored through ongoing aftercare. Interestingly, this afterglow has also been linked to post-acute changes in brain connectivity and metabolism 24 h after ayahuasca administration (Sampedro et al., 2017). These changes were also associated with enduring increases in the mindfulness-related capacity of non-judging, defined as taking a non-evaluative stance towards one's inner experiences (Sampedro et al., 2017). These and related findings on interactions between psychedelic administration and mindfulness-related capacities (e.g. Soler et al., 2016) suggest further integration of mindfulness-based interventions such as Acceptance and Commitment Therapy (Hayes & Wilson, 1994) or Mindfulness-Based Relapse Prevention (Witkiewitz, Marlatt, & Walker, 2005), concurrent with psychedelic administration, may be a potential avenue for developing novel and effective models of psychedelic therapy. As much of the current clinical research on hallucinogen-facilitated treatment has used some form of the psychedelic therapy model described above, the remainder of the present article will focus on considerations germane to implementing this model in future research and clinical work.

Considerations for clinical work with psychedelics

Psychedelics as pharmacotherapies

Should psychedelics be considered medications in their own right? Neuroimaging and pre-clinical data indicate robust biological and central nervous system effects of psychedelics. A growing body of human neuroimaging research has found psilocybin to significantly alter cerebral blood flow and functional connectivity acutely (Carhart-Harris et al., 2012, 2014; Tagliazucchi, Carhart-Harris, Leech, Nutt, & Chialvo, 2014), as well as 24 h after administration (Carhart-Harris et al., 2017). Similar decreases in default mode network (DMN) integrity have also been observed acutely during LSD (Carhart-Harris et al., 2016b; Tagliazucchi et al., 2016), and ayahuasca administration (Palhano-Fontes et al., 2015), with significant correlations between subjective drug effects and

changes in resting state functional connectivity (Carhart-Harris et al., 2012, 2016b). Interestingly, Carhart-Harris et al. (2017) found increased DMN integrity 1 day after psilocybin administration in a sample of patients with treatment-resistant depression in contrast to acute drug effects. Furthermore, changes in functional connectivity the day following psilocybin predicted antidepressant response 5 weeks post-treatment. These findings suggest that, while psychedelics acutely disrupt and decouple usual patterns of connectivity within the DMN, post-acute effects show trends in the opposite direction, exhibiting greater integration and functional connectivity within the DMN the day after drug administration. Such effects have been proposed as a possible '"reset" mechanism in which acute modular disintegration (e.g. in the DMN) enables a subsequent re-integration and resumption of normal functioning' (Carhart-Harris et al., 2017, p. 5).

Additionally, some psychedelics have exhibited potent anti-inflammatory properties in cellular and animal models at sub-behavioural levels, suggesting potential novel pathways for clinical development (Nau, Yu, Martin, & Nichols, 2013; Nau et al., 2015; Yu et al., 2008). While it is still unknown if therapeutic effects of psychedelics may occur independently of their psychoactive effects in humans, these findings suggest that sub-threshold doses of psychedelics might exert observable and potentially therapeutic biological effects. Others have suggested regular, sub-threshold psychedelic administration in humans, also known as 'microdosing', can confer mental health benefits (Fadiman, 2011; Johnstad, 2018; Waldman, 2018). However, this model remains to be examined under controlled conditions, representing an important area for future research. Finally, congruent with clinical trials on therapeutic effects of psychedelics (Bogenschutz et al., 2015; Carhart-Harris et al., 2016a, 2017; Griffiths et al., 2016; Johnson et al., 2014; Palhano-Fontes et al., 2018; Ross et al., 2016; Rucker, Jelen, Flynn, Frowde, & Young, 2016), recent epidemiological and survey studies have also offered some notable insights about the therapeutic potentials of psychedelic use independent of therapy, finding associations between psychedelic use and reduced recidivism in individuals under correctional supervision (Hendricks, Clark, Johnson, Fontaine, & Cropsey, 2014), reduced suicidality and psychological distress in a nationwide sample (Hendricks, Thorne, Clark, Coombs, & Johnson, 2015), and reports of tobacco smoking cessation attributed to psychedelic use in non-laboratory settings (Johnson, Garcia-Romeu, Johnson, & Griffiths, 2017b). Together these findings suggest that psychedelics likely have therapeutic value as pharmacotherapies, independent of structured treatment interventions. However, based on currently available information, it seems clear that, at least for certain conditions and when using moderate-to-high doses, therapeutic benefits of psychedelics can be maximized by incorporating their use within structured, evidence-based psychotherapeutic interventions delivered by specially trained therapists.

Substance and therapeutic target

Safe and effective use of psychedelics as an adjunct to therapy requires careful attention to a number of key factors including substance, therapeutic target, dose, screening, preparation, set, setting, and integration (Johnson et al., 2008). Regarding substance, most contemporary research with psychedelics has focused specifically on use of psilocybin and ayahuasca, whereas clinical research with LSD, mescaline, and pure DMT, for instance, have remained limited (Gasser et al., 2014). Additionally, a large number of other psychedelic and hallucinogenic compounds have been characterized, such as 5-methoxy-N, N-dimethyltryptamine (5-MeO-DMT; Ott, 2001) and 4-bromo-2,5-dimethoxyphenethylamine (2C-B; De Boer, Gijzels, Bosman, & Maes, 1999; Shulgin & Shulgin, 1991, 1997), all of which are considered Schedule I substances, and are, therefore, difficult to legitimately acquire and study in humans (Nutt, King, & Nichols, 2013). Others, like N, N-dipropyltryptamine (DPT), have been used in preliminary studies showing therapeutic potential (Grof et al., 1973; Richards, 1978; Richards, Rhead, DiLeo, Yensen, & Kurland, 1977; Richards et al., 1980), but have not been examined since.

It is conceivable that each of these substances may have differential benefits for distinct conditions, opening up a large array of pharmacological possibilities for research and treatment. However, due to current regulatory restrictions that limit work with these substances, high costs associated with medication development and clinical trials, and lack of financial incentives for developing psychedelic medications due to their largely off-patent status, it is unlikely that such research will proceed rapidly in the foreseeable future (Rucker et al., 2017; Sellers & Leiderman, 2018). Currently, the most well-supported therapeutic targets for psychedelic therapy include depressive disorders (Carhart-Harris et al., 2017; Palhano-Fontes et al., 2018; Rucker et al., 2016), substance use disorders (Bogenschutz et al., 2015; Bogenschutz &

Pommy, 2012; Johnson et al., 2014; Krebs & Johansen, 2012; Ross, 2012; Thomas, Lucas, Capler, Tupper, & Martin, 2013), and anxiety and psychosocial distress related to cancer or other serious illness (Gasser et al., 2014; Griffiths et al., 2016; Grob et al., 2011; Richards et al., 1972, 1977, 1980; Ross et al., 2016). Additional targets with preliminary evidence for therapeutic efficacy of psychedelic treatments include obsessive-compulsive disorder (Moreno et al., 2006), pain (Kast, 1967; Kast & Collins, 1964), and cluster headaches (Sewell, Halpern, & Pope, 2006). Still other conditions such as post-traumatic stress disorder (PTSD), eating disorders, hoarding disorder, gambling disorder, somatic disorders, sexual dysfunctions, criminal recidivism, and neurodegenerative and inflammatory diseases may all represent potential novel targets for tailored psychedelic-assisted treatments to be examined in future research.

Dosage

Regarding dosage, laboratory research has found, for instance with psilocybin, that doses of 20–30 mg/70 kg can confer enduring improvements in life satisfaction and well-being, and that, furthermore, use of ascending as opposed to descending doses may be preferable in mediating these long-term benefits (Griffiths et al., 2011), a principle that is likely generalizable to clinical work with other psychedelics. Research with LSD has found the lowest detectable dose to be 20 mcg (Greiner, Burch, & Edelberg, 1958), and doses up to 1500 mcg have been safely administered to patients undergoing treatment for alcoholism (MacLean, MacDonald, Byrne, & Hubbard, 1961), although the optimal therapeutic window for LSD has been estimated to be between 100–200 mcg (Passie, Halpern, Stichtenoth, Emrich, & Hintzen, 2008). Human studies with mescaline have used doses in the range of 200–750 mg (Merlis, 1957; Savage et al., 1967), with 500 mg being a commonly researched dose that may serve as a useful starting point for modern clinical research with mescaline that has yet to be initiated (Hermle et al., 1992). Ayahuasca contains a number of active ingredients including ß-carbolines and DMT (McKenna, Towers, & Abbott, 1984), and can be prepared in a variety of ways, making standardized dosing somewhat complex (McKenna, 2004). Contemporary studies have attempted to resolve this issue by using uniform freeze-dried ayahuasca capsules with DMT doses in the range of 0.6–0.85 mg/kg, for example (Riba et al., 2003), or administering specially prepared batches of the liquid brew containing roughly 0.36 mg/kg DMT (Palhano-Fontes et al., 2018), or ∼96–160 mg DMT total (Sanches et al., 2016). Although a great deal of recent human research with psychedelics has utilized weight-adjusted dosing, it is unclear whether this is necessary for optimizing safety and therapeutic efficacy, or if use of flat dosing across a range of body weights would be equally appropriate, an issue that will need to be informed further by future research (Brown et al., 2017; Dolder, Schmid, Haschke, Rentsch, & Liechti, 2016; Garcia-Romeu, Barrett, Johnson, & Griffiths, 2017a; Joyce, 2017).[2]

Screening

Most research in the 21st century has taken a more conservative stance in excluding individuals with potentially problematic physical or mental health conditions than earlier research of the 1950s and 1960s. Thus, individuals with personal or family history of schizophrenia, psychosis, or mania, or those exhibiting potentially severe personality disorders have largely been ruled out from recent studies with psychedelics. Other issues, such as recent suicidality, drug or alcohol use disorders, dissociative disorders, and past history of trauma should be taken into account depending on the therapeutic target, as these may be exacerbated by high-dose psychedelic administration or increase risk for adverse events. Individuals with neurological illness, poor liver or kidney function, and cardiovascular conditions such as uncontrolled hypertension are generally excluded from psychedelic treatments, as are women who are pregnant or nursing. Concurrent use of some medications with serotonergic action, such as selective serotonin reuptake inhibitors (SSRIs; Bonson, Buckholtz, & Murphy, 1996), tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs; Bonson & Murphy, 1995), and some antipsychotics (Vollenweider et al., 1998) can interact with psychedelics, with potential for increased or decreased sensitivity, or possibly serotonin syndrome (Callaway & Grob, 1998), and should, therefore, be carefully monitored as part of screening, well before potential psychedelic administration. As we learn more about the safety and clinical potential of psychedelics for particular indications or populations, it is likely that screening criteria will become less restrictive, allowing access to a greater number of individuals on the basis of empirical findings.

Preparation and set

Beyond careful screening, structured preparation for psychedelic therapy can help to minimize the risk of

adverse events. As a caveat, it is important to note that best practices for psychedelic therapy as presented here are based on clinical observation and direct experience in research settings, but has not been well-validated by prospective studies, representing an important area for future research (Carhart-Harris et al., 2018). Current models of psychedelic therapy typically involve anywhere from two to four dedicated preparation meetings prior to drug session(s) with the same therapist(s) or session monitor(s) who will be present throughout the drug administration session(s) and post-session integration.[3] During these meetings, content can be variable, depending on the drug, therapeutic target, and dosage being employed. However, a general life review of the patient is often conducted as a means of building therapeutic rapport, and learning about major life events, potential traumatic experiences, current and past relationships, and worldview. Additionally, other specific topics and techniques can be integrated as appropriate for the therapeutic target. For instance, in psilocybin-facilitated smoking cessation treatment, there is dedicated time spent discussing the individual's relationship to smoking, how and when the habit was initiated, previous quit attempts, obstacles to remaining abstinent, and major reasons for wanting to quit. Use of homework between meetings, such as keeping a smoking journal to track daily smoking, and thoughts and feelings associated with smoking or quitting, can also be implemented to encourage connections between therapeutic goals and day-to-day life activities. These outside exercises and reflections can in turn be used in therapy to generate further targeted dialogue regarding relevant points of interest that may emerge between meetings. Furthermore, a detailed discussion of potential drug effects is essential for good preparation, including time spent examining any concerns, questions, or fears the individual may have regarding the session, and describing in-depth the possibility of a challenging experience, and best methods to manage such an experience. Potential drug effects and challenging experiences will be elaborated upon further below.

To the extent that individuals undergoing psychedelic therapy feel safe and comfortable with their therapist(s), and well-prepared for the upcoming drug session, set has been optimized. Other life events and relationship issues of import may occur around drug administration sessions and should be monitored closely by therapists in order to minimize the potential negative impact on the patient's state of mind and possible adverse effects in drug sessions. For instance, death of a loved one, breakup of a relationship, loss of home or employment, or physical illness may all be sufficiently upsetting or destabilizing to raise the possibility of postponing drug sessions or otherwise altering treatment in accordance with the patient's preference and therapist's best clinical judgement. Such decisions must be made in the best interest of the patient and his/her safety on a case-by-case basis. It should be noted that, in some circumstances, drug sessions may actually be useful to help process the events in question.

Drug sessions and setting

While ideal procedures and setting considerations for psychedelic therapy have yet to be empirically tested, the current description represents a model that has been used safely in more than 600 psilocybin sessions at Johns Hopkins University since 2000. Drug administration sessions should only occur after ample preparation has been completed, and good rapport has been established between the therapist(s) and patient. It should be noted here that it is often the case that a team of two therapists or session monitors will be on hand throughout preparation, drug sessions, and integration. This has both pragmatic and clinical ramifications for psychedelic therapy. Regarding the former, drug sessions can last from 6–12 h depending on the drug, dose, and route of administration employed. Therefore, having two therapists present makes it possible to conduct full sessions without having to leave the patient alone for any duration, so that one therapist is always available for safety monitoring and reassurance, even if the other should have to leave briefly, as necessary for restroom or meal breaks. Clinically, it has been suggested that a team of two co-therapists consisting of a male-female dyad may be an ideal milieu for eliciting maximal therapeutic bonding, feelings of safety, and support. While this may originally be attributable to psychoanalytic conceptions of transference and counter-transference with therapists as internalized parental figures, for example, this convention has been the norm in much of the recent clinical research and appears to work well. Additionally, from a safety standpoint, it is prudent to assure that at least one therapist is of similar gender to the individual undergoing psychedelic therapy (Bhati, 2014), considering a history of (usually male) therapists and shamans taking advantage of (typically female) clients in therapy (Jehu, 1994), or while under the influence of psychedelics (Kavenská & Simonová, 2015; Ross, 2017).

Drug sessions are conducted in a comfortable, living-room like setting intended to feel warm and inviting, decorated with evocative artwork, and furnished with a sofa on which the patient typically reclines during the session (Johnson et al., 2008). Accommodations should be available for therapists to be seated comfortably nearby throughout the duration of the drug session. Ideally, drug sessions are conducted in a private area, where only the patient and therapists will be present, with access to a dedicated restroom facility. For IRB approved research studies administering psychedelics, a physician is generally nearby and on-call during sessions until peak drug effects have subsided, and antihypertensive, anxiolytic, and antipsychotic rescue medications are available in case of adverse reactions, although use of these is exceedingly rare (Johnson et al., 2008). Another medical precaution that is frequently implemented in clinical research is regular blood pressure monitoring (e.g. at 1-h intervals) during drug sessions, as psychedelics and the emotions they often elicit are known to increase heart rate and blood pressure modestly (Griffiths et al., 2006, 2011; Schmid et al., 2015). These measures were not always taken in research prior to 1970, and risk of cardiac adverse events is seemingly low in controlled settings with physically healthy individuals (Nichols & Grob, 2018; Smart & Bateman, 1967; Strassman, 1984); therefore, regular, repeated monitoring throughout sessions may be considered unwarranted when administering psychedelics to healthy patients without histories of hypertension.

In the psychedelic therapy model as commonly practiced in contemporary research, patients are usually encouraged to lie on a sofa with eyes covered by eyeshades, and headphones playing a programme of pre-selected music throughout the drug session (Bonny & Pahnke, 1972). The eyeshades and headphones are meant to help the patient focus on his/her inner experience, thoughts, emotions, and body sensations, as opposed to being distracted by external events such as perceptual stimuli and distortions or interactions with the therapists. The psychedelic therapy model prescribes a largely non-directive approach by therapists during moderate- or high-dose drug sessions, allowing the session to unfold inwardly, without explicit talk therapy during acute drug effects. Patients are typically instructed to 'go inside', and to 'trust, let go, and be open' during the experience (Pahnke, 1969). Nevertheless, because patients can sometimes feel too overwhelmed by drug effects to communicate articulately, and because disorientation, fear, anxiety, and dysphoria are possible, it is important to continuously monitor patients' facial expressions and body language and maintain adequate contact throughout drug sessions so that patients feel sufficiently safe and supported. In the case of challenging experiences, therapists often initiate physical contact such as hand holding, to the degree that patients are comfortable with this, and therapists may talk patients through the challenging portion of the experience by assessing and acknowledging the patient's emotions, providing reassurances of safety, or use of guided imagery or breathing exercises as appropriate. Contingencies for these situations are also discussed extensively during preparation to assure a pre-established plan of action is in place for managing challenging experiences, and alleviating any potential anticipatory anxiety surrounding such reactions.

During sessions music is played through headphones worn by the patient, and ideally through external speakers in the session room to provide an overarching non-verbal structure for the experience, and to help evoke and support powerful emotions that can enhance therapeutic response and insight. Music has long been thought to hold a central role in psychedelic therapy as well as indigenous psychedelic use (Bonny & Pahnke, 1972; De Rios, 2003; Labate & Pacheco, 2010), and recent research has begun to shed further light on interactions between psychedelics and music (Barrett, Robbins, Smooke, Brown, & Griffiths 2017b; Kaelen et al., 2015, 2018). LSD, for example, has been shown to increase feelings of wonder, power, tenderness, and transcendence in response to music compared to placebo, with important implications for psychedelic therapy (Kaelen et al., 2015, 2018). Music employed in psychedelic therapy varies, but is often instrumental, and has generally been prescribed based on musical dynamics such as pitch, tempo, and mood, in an attempt to facilitate movement through various states of consciousness and support the psychedelic experience through phases of pre-peak, peak, and post-peak drug effects (Barrett et al., 2017b; Bonny & Pahnke, 1972). Judicious use of music in psychedelic therapy is a fairly ubiquitous practice that appears to confer unique benefits over silence (Gaston & Eagle, 1970), yet represents an under-studied area that could aid in the refinement of psychedelic-assisted treatments with further empirical research (Barrett et al., 2017b; Kaelen et al., 2015, 2018).

Integration

Integration, comprised of ongoing aftercare following drug sessions, is considered a vital part of psychedelic therapy (Richards, 2015, 2017). This typically begins 1–2 days after the drug session in a follow-up meeting

between patient and therapist(s) to discuss the patient's experience and reflect upon its content in more depth. Although precise quantity or frequency of integration meetings for best outcomes has not been validated, the integration process can continue in weekly or bi-weekly meetings lasting 1–3 months or longer after the initial drug session, depending on the nature of the treatment and therapeutic target. These meetings are intended to provide ongoing clinical and emotional support in the wake of psychedelic sessions, and monitoring of treatment progress, and can be especially important after challenging experiences. During integration, patients are encouraged to expand and elaborate upon their psychedelic session experiences, describing them in as much detail as possible, interpreting and unpacking their contents with therapists. As part of this process, it is usual to invite patients to generate a written narrative or produce artwork detailing their recollection of the drug session, sometimes replaying relevant music from the session to help aid recall. This in turn is meant to help solidify insights gained during the temporary alternative state of consciousness brought on by the drug into positive and enduring trait changes in personality, attitudes, and behaviours (e.g. Bouso, Santos Dos, Alcázar-Córcoles, & Hallak, 2018; Lebedev et al., 2016; MacLean, Johnson, & Griffiths, 2011). Because acute drug effects are transient, lasting no more than a day, integration serves as a crucial means to bridge the session experience with everyday life. In particular, the days and weeks directly following high-dose drug sessions can be an especially fertile period in which patients may experience an 'afterglow' effect, consisting of features such as elevated mood, decreased anxiety, and increased emotional awareness (Majić et al., 2015). These short-term changes in thought, mood, or behaviour can be leveraged in therapy to foster the development of novel long-term habits and patterns congruent with the therapeutic intent of the treatment. In this way, successful integration can help to maximize the possibility of realizing persisting benefits from one or a few psychedelic drug administrations.

The therapeutic alliance

Psychotherapy research has consistently found the therapeutic alliance, defined as the quality of the bond and working relationship between therapist and client, to be among the most important factors influencing treatment outcomes (Ardito & Rabellino, 2011; Horvath & Luborsky, 1993; Martin, Garske & Davis, 2000). Studies have also shown that the therapeutic response to pharmacotherapy, for instance in the treatment of depression, is significantly affected by the quality of the therapeutic alliance (Krupnick et al., 1996; Weiss, Gaston, Propst, Wisebord, & Zicherman, 1997). This factor may be even more pronounced in the context of psychedelic therapy. Because of the profound, intimate, and intense nature of the material that may emerge during psychedelic drug sessions, a strong bond between patient and therapist can help to ensure maximal safety and potential therapeutic efficacy. Skillful preparation is an important part of establishing this rapport, and carries over into drug sessions and integration. The vulnerability inherent in participating in a high-dose psychedelic session, with the often unpredictable emotions and lack of control this can entail, requires a high degree of trust, security, and confidence in the therapists who will be monitoring the session.

The person-centred approach expounded by Rogers (1949, 1951, 1957) is well-suited to help instill this trust and establish a proper therapeutic alliance in psychedelic therapy, regardless of therapeutic orientation. The primary principles of this approach are unconditional positive regard, empathy, and congruence (Kirschenbaum, 2004; Rogers, 1951, 1957). Unconditional positive regard encompasses a recognition of the inherent value of the patient as a human being, and an acceptance of all aspects of that person without judgement (Rogers, 1951, 1957). This principle is particularly applicable to psychedelic therapy as it can aid patients in adopting a similar attitude of unconditional acceptance toward the contents of their own psychedelic experiences, rather than rejecting, resisting, or avoiding any uncomfortable or unpleasant material that may arise during drug sessions (Richards, 2008). Empathy refers to the therapist's willingness and ability to understand the patient's thoughts and feelings, and to see things from the patient's perspective (Rogers, 1949). To the extent that the therapist exhibits empathy, patients will be able to feel acknowledged, seen, and understood, helping them to feel more comfortable confronting the unknown in drug sessions with the support of the therapist. Finally, congruence refers to the therapists' genuineness and authenticity in their interactions with patients. This requires a realness and honesty on the therapists' part that demonstrates that the therapeutic alliance is based on a sincere relationship, not a façade or deception. By modelling this authenticity through appropriate self-disclosure and mindful awareness of therapeutic interactions, the therapist

encourages the patient to do the same, thereby facilitating more authenticity and congruence on the patient's part and enhancing the therapeutic alliance (Bugental, 1981; Burks & Robbins, 2012). Adoption of a person-centred approach, while not compulsory in psychedelic therapy, is attractive due to its flexibility for use across therapeutic targets, and the ability to be adapted to work harmoniously with other therapeutic models and orientations.

Conversely, certain interpersonal styles and behaviours do not lend themselves to effective psychedelic therapy. In their review on the impact of therapist attributes on the therapeutic alliance, Ackerman and Hilsenroth (2001, p. 171) found that, 'being rigid, uncertain, critical, distant, tense, and distracted were found to contribute negatively to the alliance'. These principles appear highly relevant and applicable to psychedelic therapy as well, and serve as a useful guidepost of conduct to avoid. It has been suggested that administration of hallucinogens can help enhance the therapeutic alliance (Grinspoon & Bakalar, 1986; Grinspoon & Doblin, 2001). However, to our knowledge recent clinical research with serotonergic psychedelics has not explicitly assessed therapeutic alliance with validated measures as a mediator of outcome. One study of MDMA-assisted therapy for PTSD did assess the therapeutic alliance between placebo and low-dose MDMA groups finding no significant differences, but these findings are inconclusive, as the study was ended preemptively by local authorities and, therefore, included only six individuals (Bouso, Doblin, Farré, Alcázar, & Gómez-Jarabo, 2008). Considering the potentially substantial influence that the therapeutic alliance may have in psychedelic therapy, it is evident this element should be assessed more carefully in future research using appropriate existing measures (Elvins & Green, 2008).

Types of psychedelic experiences

A number of types or classes of psychedelic drug experiences have been designated and conceptualized in the literature. Such typologies are largely observational and descriptive in nature, and do not necessarily represent empirically validated classes of experiences. While by no means exhaustive, these may include sensory-aesthetic, psychodynamic-autobiographical, cognitive-intellectual, symbolic-archetypal, challenging, and mystical experiences (Grof, 1994; Masters & Houston, 2000; Pahnke & Richards, 1966; Pahnke et al., 1970; Richards, 2008). Some key caveats to note in any attempt at classification of psychedelic drug effects are that: (1) the map is not the territory (Korzybski, 1958), and (2) the proposal of such typologies can also have important clinical ramifications. Regarding the first point, these descriptions encompass certain qualitative aspects or phenomenological features common to many psychedelic drug experiences, which make them a useful shorthand for discussing the ways such experiences may unfold. However, the therapist should guard against over-generalization, or allowing preconceptions to cloud the clinical picture. In this sense, each drug session should be approached as a unique and reverent experience, similar to the way that every patient should be treated as a unique individual with his/her own personality and life experience. Second, because of the strong role of expectancy in influencing the responses to psychedelic drug administration (although not necessarily the phenomenological content encountered), it is critical not to conceptualize these types of experiences as hierarchical rungs on a ladder, with some being regarded more highly than others. This style of classification raises the potential for both patients and therapists to feel that an experience missed the mark or was otherwise a failure because it did not meet particular criteria. A preferable metaphor would be to think of different classes of experiences, as many shores surrounding a common ocean, with each of them possessing their own significance and intrinsic value (Ferrer, 2002). This conception allows the ability to maximize the potential therapeutic value of a wide range of experiences that may come to pass.

Sensory-aesthetic experiences

The sensory-aesthetic experience is characterized by perceptual changes such as increased vividness of colours, appearance of movement of static objects, fractal and kaleidoscopic imagery, enhanced sensitivity to music, altered sense of touch and texture, altered body awareness, and synesthesia (Pahnke et al., 1970; Richards, 2008; Sinke et al., 2012). These types of effects can occur at lower doses and are common in recreational use where structured psychedelic administration as described here is unusual. From a clinical standpoint, such experiences can be seen as somewhat superficial and auxiliary to therapeutic efficacy. Hence, the use of eyeshades and music, limited movement and interpersonal interaction, and emphasis on inward attention, are meant to minimize these potentially distracting perceptual effects to instead focus on the underlying internal experience. It is noteworthy, however, that data on psychedelic use in naturalistic

settings has shown associations with diverse benefits including tobacco smoking cessation (Johnson et al., 2017b), lower psychological distress and suicidality (Hendricks et al., 2015), and reduced criminal behaviour (Hendricks et al., 2014, 2018; Walsh et al., 2016). These findings suggest psychedelics, in general, and sensory-aesthetic experiences in particular, may hold intrinsic therapeutic value, perhaps in facilitating the experience of awe or natural beauty (e.g., Rudd, Vohs, & Aaker, 2012).

Psychodynamic-autobiographical experiences

Psychodynamic-autobiographical experiences are predominated by emotional recollections and reflections on significant previous or current life events and relationships. This can take many forms, but often involves re-emergence of past transgressions for which the patient may harbour ongoing guilt or sorrow, grief for deceased loved ones or lost relationships, anger or forgiveness regarding unresolved traumas, and insights into one's ways of being and relating throughout one's life. These types of experiences can come about at lower doses in supportive settings, and were the principal aim of psycholytic therapy, which focused on eliciting such reflections as a catalyst for psychotherapy (Sandison, 1954). Psychodynamic-autobiographical experiences may also occur during moderate- or high-dose psychedelic therapy, particularly before and after peak drug effects, and represent an important avenue for revisiting and resolving such personal conflicts, both in drug sessions and during subsequent integration.

Cognitive-intellectual experiences

Cognitive-intellectual experiences entail changes in normal patterns of thinking, in which usual constraints and blockages in abstract processes can be transcended or overcome (Hunt, 1984). These types of experiences have been linked to creativity enhancement, novel perspective-taking, and generation of conceptual insights useful for problem-solving or solution-oriented reasoning (Baggott, 2015; Harman et al., 1966; Sessa, 2008). Cognitive-intellectual experiences can happen in low dose psychedelic sessions, as well as before or after peak effects during moderate- and high-dose administration. Although this kind of problem-solving may not always be the explicit aim in conducting psychedelic therapy, such changes in thinking can be useful in providing new perspectives to aid in cognitive reframing of relevant issues, and challenging maladaptive schemas that can be associated with a variety of conditions such as depression or addiction (Clark & Beck, 2010; McCusker, 2001). During high-dose sessions, research volunteers are usually encouraged to simply 'collect experiences' without trying to think about them with usual cognition and language, as such rational activity can easily manifest as an attempt to control and resist the emerging experiences, constituting the defense mechanism of intellectualization. The insights that emerge in such sessions tend to be more intuitive than rational, as James (1902) noted with his term 'the noetic quality'.

Symbolic-archetypal experiences

Symbolic-archetypal experiences, sometimes called 'visionary', are those that involve the emergence of mythical or symbolic content such as deities (e.g. gods, goddesses, angels, demons), gemstones, imagery associated with other civilizations or historical periods, as well as encounters with universal qualities such as truth, beauty, or love (Richards, 1978, 2002). Whereas psychodynamic-autobiographical experiences revolve around content of a personal nature, symbolic-archetypal experiences have been conceptualized as relating to a larger sphere, or collective unconscious, that transcends time and cultures (Jung, 1936). These experiences are more likely to occur during moderate- and high-dose sessions and are often marked by vivid realizations and profound emotions. From a clinical standpoint, symbolic-archetypal experiences can provide potent material for ongoing integration, often described as visionary imagery, and may be associated with lasting therapeutic benefits such as reductions in existential anxiety in patients with terminal illness (Richards, 1978).

Challenging experiences

Challenging experiences with psychedelics have colloquially been referred to as 'bad trips' and have also been likened to psychotomimetic reactions (Carbonaro et al., 2016; Pahnke et al., 1970).[4] These can involve intense feelings of anxiety, panic, grief, fear, paranoia, disorientation, confusion, isolation, or physical discomfort. In addition, people sometimes describe a strong fear that they are dying or going insane (Barrett et al., 2016). Anonymous online survey data on recreational users' ($N = 1993$) most psychologically challenging experience with psilocybin found the majority (56%) of the acutely challenging portions of these experiences to last less than 2 h in total, with 84% of participants reporting some benefit

of the experience in retrospect (Carbonaro et al., 2016). Intensity of challenging experiences with psilocybin in uncontrolled settings showed significant associations with the personality domain neuroticism, suggesting this personality trait may be a contributing factor to such reactions (Barrett et al., 2017a). Importantly, survey data indicated that positive emotional state prior to the drug experience, comfort of the environment, and the presence of social support during the experience were negatively correlated with intensity and duration of challenging experiences (Carbonaro et al., 2016). Thus, careful screening, adequate preparation, a well-designed therapeutic setting, and a strong therapeutic alliance are among the most valuable preventive measures to minimize the risk of challenging experiences. However, these experiences should not be devalued or avoided out of hand, as they can also lead to insight and lasting therapeutic benefits when skillfully managed and properly integrated.

While these experiences can be difficult acutely, managing challenging experiences during sessions requires that the therapist maintain a calm, reassuring presence and a high degree of emotional responsiveness in the moment. To the degree that the patient is comfortable with physical contact, hand-holding or providing some other expression of physical support can help the patient to feel more grounded and secure. Use of calming guided imagery and breathing exercises can be implemented to provide a sense of structure and containment for the experience. In some cases, changing a musical selection, or lowering the volume if the patient is feeling overwhelmed, can be beneficial. Again, a contingency plan for managing challenging experiences should be discussed thoroughly during preparation, so that therapists and patients have a frame of reference for what might be most effective in successfully resolving the difficulty acutely.

Above all, it is important when helping patients through such experiences to communicate that they are safe, that the experience is related to the drug effect, which is temporary and will pass, that what they are feeling is not abnormal, and that they are going to be alright. These types of reassurances can help the patient to relinquish control, and ultimately accept the experience, as opposed to resisting or rejecting it, which can lead to further distress. Medications such as anxiolytics and antipsychotics may be an option in extreme circumstances, but this measure has been taken exceptionally rarely in modern clinical trials with psychedelics, as interpersonal support of the kind described above is customarily sufficient and effective in ameliorating the situation (Johnson et al., 2008). As acute dysphoric reactions resolve and drug effects begin to subside, it is imperative for therapists to monitor the emotional state of the patient, and to begin the integration process in an appropriate and timely manner, typically the following day. Integration is imperative in all psychedelic therapy, but is especially important following challenging experiences, as intensive integration can help contextualize and ground the difficulties encountered during the drug session through subsequent recapitulation and reflection. This structured examination can help facilitate the meaning-making process around challenging experiences and ensure that the maximum possible value and insight are gleaned from these sessions in the long-run.

Mystical experiences

Mystical experiences, also called transcendent or peak experiences, are characterized by a sense of unity, transcendence of time and space, deeply felt positive mood, sacredness, ineffability, and a sense of ultimate truth or reality, also known as a noetic quality (Pahnke, 1963; Pahnke & Richards, 1966; Stace, 1960). These experiences have been found to be reliably occasioned in well-prepared individuals receiving moderate-to-high doses of psychedelics such as psilocybin, LSD, and ayahuasca in a supportive environment (Bogenschutz et al., 2015; Griffiths et al., 2006, 2011, 2016, 2018; Johnson et al., 2014; Liechti, Dolder & Schmid, 2017; Lyvers & Meester, 2012; Palhano-Fontes et al., 2018; Ross et al., 2016). Mystical experiences have been found to be associated with persisting benefits and personality change more than a year after drug administration in healthy normal volunteers (Griffiths, Richards, Johnson, McCann, & Jesse, 2008; MacLean et al., 2011; Schmid & Liechti, 2018), as well as anxiolytic and antidepressant effects in cancer patients (Griffiths et al., 2016; Pahnke, 1969; Richards, 1978; Richards et al., 1977; Ross et al., 2016), antidepressant effects and post-acute alterations in brain function in patients with treatment-resistant depression (Carhart-Harris et al., 2017), and therapeutic outcomes in psilocybin-assisted smoking cessation (Garcia-Romeu et al., 2014) and alcoholism treatments (Bogenschutz et al., 2015). Although the precise mechanisms underlying these experiences are still being elucidated, psychedelic-occasioned mystical experiences have long been proposed as a major factor mediating the efficacy of psychedelic therapy, seemingly facilitating a recalibration of mood, behaviour,

and attitudes that can be reinforced through subsequent integration (Garcia-Romeu et al., 2014; Pahnke, 1969; Pahnke & Richards, 1966; Richards, 2008).

Psychedelic therapy as a meaning-modulating process

One of the most consistent findings from modern research with psychedelics is their ability to elicit experiences considered to be profoundly meaningful (Griffiths et al., 2006, 2011, 2018; Preller et al., 2017; Schmid & Liechti, 2018). One recent study found that neutral and meaningless musical excerpts were rated as significantly more meaningful after administration of 100 mcg of LSD ($N = 22$) compared to placebo (Preller et al., 2017). Importantly, such attributions of meaning are not only reported during acute drug effects, but are typically sustained for months or even years after the drug experience (Doblin, 1991; Griffiths et al., 2008, 2011). Laboratory studies administering a moderate- or high-dose (20 or 30 mg/70 kg) of psilocybin to healthy volunteers in a supportive setting (total $N = 54$) found that 58–94% of individuals considered their drug session to be among the five most meaningful experiences of their lives 14 months after drug administration (Griffiths et al., 2008, 2011). Similarly, 71% of individuals administered 200 mcg of LSD in a laboratory setting ($N = 14$) reported their drug session to be among the top 10 most meaningful experiences of their lives at 12 months after drug administration (Schmid & Liechti, 2018). Personal meaning of drug experiences has also shown significant associations with long-term therapeutic outcomes in the context of psilocybin-facilitated interventions for smoking cessation (Garcia-Romeu et al., 2014; Johnson, Garcia-Romeu, & Griffiths, 2017a), and cancer-related anxiety and depression (Griffiths et al., 2016), suggesting an important role for meaningfulness in mediating efficacy of psychedelic therapy.

Based on these and related findings, psychedelics have recently been described as 'meaning-enhancers' (Hartogsohn, 2018), echoing earlier conceptions of psychedelics as, 'non-specific catalysts and amplifiers of the psyche' (Grof, 1994, p. 11). Both assertions appear to be an apt portrayal of a basic and essential pharmacological property of psychedelics, which may in large part underlie their clinical potential. In addition, we suggest that the process of psychedelic therapy can tap into and make use of this property as part of a purposeful meaning-modulating process. From this standpoint, psychedelic drug experiences may not only confer a profound and enduring sense of meaning, and enhance the meaning of neutral or meaningless stimuli, but can also be actively employed in altering or diminishing the relative meaning of particular mental contents by focused intervention. For instance, through examination in psychedelic therapy of specific therapeutic targets, such as obsessions, compulsions, existential distress, negative thinking, or substances of abuse, it is seemingly possible to change their perceived meaning for the patient, thereby altering the manner in which they relate to and engage that content. These processes of change likely correspond to those occurring in traditional psychotherapy. However, use of psychedelics can serve as a powerful catalyst to accelerate and amplify such changes. While these shifts certainly have neurological correlates, they simultaneously maintain an inherently psychological dimension related to meaning-making, which can be intentionally modulated via skillful psychedelic therapy. As Frankl (1954/1992, p. 51) noted, 'in some ways, suffering ceases to be suffering at the moment it finds a meaning'.

Psychedelic therapy as a (quasi-) novel paradigm in psychiatry

Considering the long lull in clinical research, promising results from contemporary studies, and largely positive treatment in modern popular media, it is both tempting and exciting to hail the re-emergence of psychedelics in psychiatry as part of a still-evolving novel paradigm entering the 21st century. From a historical perspective, however, it is important to acknowledge and understand the lessons gleaned from centuries of indigenous spiritual use of psychedelics, and decades of psychedelic use in recreational and research contexts. For clinical work with psychedelics to move forward successfully at this time, it will necessitate a cautious and meticulous approach to avoid potential pitfalls (old and new) that could re-stigmatize these substances and render them unusable for another several decades.

A major lesson offered by indigenous psychedelic use for contemporary clinical research is a general attitude of respect and reverence toward these substances and the experiences they can occasion (Frecska, Bokor, & Winkelman, 2016; Harner, 1973; Krippner, 2000; Metzner, 1998). This need not imply an explicitly spiritual or unscientific understanding of psychedelic drugs or their effects. On the contrary, from a strictly humanistic standpoint, if a person regards an experience as among the most meaningful of their lives, then therapists should treat it as such in

the preparation, administration, and integration of drug sessions. Additionally, the widespread recreational use of psychedelics that emerged in the 1960s serves as a useful reminder that media, clinicians, and researchers will need to be responsible and honest in their portrayals of these substances, and not fall prey to sensationalism or otherwise overstate the safety and potential benefits of psychedelics, particularly when taken by individuals in uncontrolled settings. Finally, in order for this work to move forward from a scientific standpoint, current research should be mindful to avoid any missteps that undermined results from earlier research. This will require careful study design and data reporting in adequately powered and conscientiously executed clinical trials.

The current lack of federal funding for research with psychedelics in the US, and generally restrictive regulations for working with psychedelics internationally, remain as barriers to conducting such research (Nutt et al., 2013). Additionally, the lack of profit motive for developing psychedelics as pharmaceutical medications due to their off-patent and illegal status pose further challenges to their eventual implementation in clinical practice (Sellers & Leiderman, 2018). Fortunately, progressive non-profit organizations such as the Heffter Research Institute, the Beckley Foundation, and the Multidisciplinary Association for Psychedelic Studies (MAPS), have helped fund a great deal of encouraging, contemporary research. (Mithoefer, Grob, & Brewerton, 2016; Mithoefer, Wagner, Mithoefer, Jerome, & Doblin, 2011; Mithoefer et al., 2013; Nichols, Johnson, & Nichols, 2017). So much so that Phase 3 clinical trials of MDMA-assisted therapy for post-traumatic stress disorder (PTSD) are currently being initiated, representing an important step towards establishing the therapeutic efficacy necessary to receive formal approval for MDMA-assisted treatment from the US Food and Drug Administration (FDA). As work with psilocybin begins to move in a similar direction, it will also be critical to ensure that hallucinogen-facilitated treatment studies meet the highest standards of clinical care and scientific rigor, including employment of well-trained psychedelic therapists to guide judiciously conceived interventions (Phelps, 2017). This raises questions around who should conduct psychedelic therapy, and what type of training and mentorship is appropriate for these individuals. At the moment, there exists no clear consensus on this issue, although therapists in recent trials with psychedelics have included psychiatrists, clinical psychologists, as well as non-clinically oriented psychologists, and master's level counsellors and therapists. It is useful for psychedelic therapists to have first-hand knowledge of altered states of consciousness, whether through exposure to psychedelics, or practices such as breathwork, meditation, or sensory deprivation, as well as specialized training and mentorship in the pharmacology of psychedelics and best clinical practices for managing their effects (Phelps, 2017).

Moreover, the incorporation of these potent drugs and the powerful experiences they entail within a structured intervention might be the crux of the novel paradigm represented by hallucinogen-facilitated treatments in psychiatry, allowing them to go beyond symptom management to achieve more comprehensive and far-reaching outcomes. Likewise, regarding MDMA-assisted treatment, Bedi (2018, p. E1) observed:

> All currently approved psychiatric medications treat symptoms rather than the disease, with relapse common after treatment cessation. Conversely, the MDMA-assisted psychotherapy model involves limited dosing of MDMA during two or three 8- to 10-hour sessions, with the aim of facilitating the therapeutic process to produce long-lasting changes … To the extent that such an approach proves to be efficacious, it would be a fundamental shift in treatment paradigms, representing (for some, at least) the first evidence-based pharmacologically mediated cure in psychiatry.

In this way, psychedelic therapy and hallucinogen-facilitated treatments can be seen as a novel paradigm in psychiatry, due to their integrative approach and potentially enduring effects. We use the term 'quasi-novel' as an acknowledgement that the approach laid out here in many ways hearkens back to indigenous psychedelic use, and the foundational work of earlier researchers and clinicians. Furthermore, we propose this paradigm serves as an invitation for psychiatry overall to return to a more holistic, humanistic-existential, or biopsychosocial framing of the person and his/her issues as a whole within a larger social matrix and fabric of meaning, as opposed to approaches that reduce the person to mere neurochemistry, symptoms, and disorders.

Future directions

Although widespread clinical implementation of psychedelic-assisted treatment is still on the horizon, the present article is intended to serve as a primer for those who may become involved in the growing research efforts necessary to make this a reality. In order to gain acceptance as a validated treatment, therapeutic efficacy of psychedelic-assisted

interventions will need to be established through Phase 3 clinical trials. In addition to the focused research this will require, there are a plethora of questions surrounding psychedelics and their effects that remain to be examined in future investigations. Further research on the role and optimization of parameters such as preparation, dose, set, setting, music, therapeutic alliance, and best practices for training psychedelic therapists will be needed, as will studies exploring hallucinogen-assisted treatments for novel indications, and developing new models of psychedelic-assisted therapy such as microdosing (Fadiman, 2011; Johnstad, 2018; Waldman, 2018), or psychedelic-assisted group therapy (Passie, 2012; Preller et al., 2016).

With access to technologies such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), modern neuroscience research on psychedelics has progressed rapidly, expanding our knowledge of the biological bases of psychedelic drug effects, an area that will no doubt continue to grow in the years ahead (Carhart-Harris et al., 2012, 2014, 2016b, 2017; Dos Santos, Osório, Crippa, & Hallak, 2016; Hermle et al., 1992, 1998; Kraehenmann et al., 2015, 2016; Lebedev et al., 2016; Palhano-Fontes et al., 2015; Preller et al., 2016, 2017; Roseman, Leech, Feilding, Nutt, & Carhart-Harris, 2014; Roseman, Nutt, & Carhart-Harris, 2017; Tagliazucchi et al., 2014, 2016; Vollenweider et al., 1997). Additionally, the advent of new non-invasive methods of brain stimulation such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) provide fascinating possibilities for new directions in research combining pharmacological interventions, such as psychedelics, and brain stimulation technologies (e.g. Kuo et al., 2017; Weise, Mann, Rumpf, Hallermann, & Classen, 2016). Similarly, the emergence of virtual reality (VR) technology and related therapeutic interventions represent another area that may be well augmented by administration of psychedelics (Chirico, Yaden, Riva, & Gaggioli, 2016; Riva, 2005; Riva, Baños, Botella, Mantovani, & Gaggioli, 2016; Rizzo & Koenig, 2017; Rothbaum et al., 2014).

Ultimately, new and evolving technologies including neuroimaging and brain stimulation tools, VR, machine learning, and Internet will open up new horizons for research on psychedelics. Already, these have begun reinvigorating earlier understandings such as the view of psychedelics as opening the reducing valve of the mind (Carhart-Harris et al., 2014; Huxley, 2009; Swanson, 2018; Tagliazucchi et al., 2014, 2016), or shamanic and psychoanalytic conceptualizations of the psychedelic state as dreamlike in nature (Kraehenmann et al., 2017; Krippner, 2000; Mogar, 1965; Sanz, Zamberlan, Erowid, & Tagliazucchi, 2018). They have also allowed for the rapid collection and dissemination of information online regarding patterns of use and subjective effects of various hallucinogens old and new through sites such as Erowid.org and Globaldrugsurvey.com (Baggott, Coyle, Erowid, Erowid, & Robertson, 2011; Winstock, Kaar, & Borschmann, 2014). These represent but a few of the vast number of possibilities for potential areas that we hope to see investigated in future research with psychedelics.

Conclusion

Despite a long history of traditional use and a robust body of psychiatric and pharmacological research in the mid-20th century, psychedelic drugs such as LSD, psilocybin, mescaline, and DMT were placed in the most restrictive category of drugs in 1971 and became largely taboo in academic research afterwards. Results from prior clinical research found that, when administered under supportive conditions, psychedelics could serve as useful therapeutic adjuncts with profound transformative potential in the treatment of a variety of mental health conditions including mood and substance use disorders, and existential distress. Furthermore, their unique profile of subjective effects set them apart as remarkable tools for understanding the nature of mind and consciousness, leading to widespread use outside the laboratory in the 1960s. Legitimate human research with psychedelics was not reinitiated until the 1990s, with a number of small, but promising clinical trials following in the early 21st century.

Interest in neuroscience and clinical research on psychedelics has since seen an encouraging revival, and progressed towards establishing therapeutic efficacy in large-scale, controlled trials, which would be necessary for medically accepted use of psychedelic-assisted treatments. Among psychedelics' distinctive pharmacological properties are their ability to evoke highly meaningful experiences that lend themselves to structured interventions aimed at altering or modulating an individual's thought, mood, or behaviour patterns through skillful therapy. Unlike the majority of psychiatric medications, these effects seem ill-suited to a standalone pharmacotherapy model, and more amenable to focused work within a strong therapeutic relationship. The present manuscript provides a brief

outline and contemporary overview on the principal considerations essential for safely conducting clinical work with psychedelics.

Notes

1. For useful discussions of MDMA-assisted therapy see Danforth, Struble, Yazar-Klosinski, and Grob (2016); Greer and Tolbert (1998); Johansen and Krebs (2009); and Sessa (2017). Regarding ketamine-assisted treatment, see Krupitsky et al. (1992, 2007, 291) and Krupitsky and Grinenko (1997).
2. Route of administration is another consideration for working with psychedelics. This generally occurs orally for most, which is convenient for clinical administration, but can also employ alternative routes such as intramuscular or intravenous (e.g. Carhart-Harris et al., 2012; Denber & Merlis, 1955; Strassman & Qualls, 1994), which can affect time of onset and intensity of drug effects.
3. While an in-depth discussion of appropriate preparation, set, setting, and integration for psychedelic therapy is outside the scope of the current manuscript, see Johnson et al. (2008), Carhart-Harris et al. (2018), Erritzoe and Richards (2017), and Hartogsohn (2017) for more detailed considerations.
4. It is important to note that the term 'challenging experience' entails acute drug effects of a distressing nature, which largely resolve within a few hours to days. Instances in which individuals develop prolonged reactions involving ongoing psychiatric sequelae are far more severe and unusual than a typical challenging experience, but have been reported in the literature (Strassman, 1984), hence the need for extensive screening and preparation to minimize such risks.

Acknowledgements

The authors would like to thank Mary Cosimano, MSW, Matthew W. Johnson, PhD, and Katherine MacLean, PhD, for their meticulous work in helping train the first author (AGR) in good clinical practice administering psychedelics. The authors would also like to thank August Holtyn, PhD, and Nora Belblidia, MPS, for their helpful comments and support on the manuscript.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Funding

This work was supported by the Heffter Research Institute and Council on Spiritual Practices.

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