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Classic psychedelics: An integrative review of epidemiology, therapeutics, mystical experience, and brain network function

Matthew W. Johnson [a,*], Peter S. Hendricks [b], Frederick S. Barrett [a], Roland R. Griffiths [a,c]

[a] Johns Hopkins University School of Medicine, Department of Psychiatry and Behavioral Sciences, Baltimore, MD, United States
[b] University of Alabama, Birmingham, Department of Health Behavior, School of Public Health, Birmingham, AL, United States
[c] Johns Hopkins University School of Medicine, Department of Neuroscience, Baltimore, MD, United States

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ABSTRACT

The purpose of this paper is to provide an integrative review and offer novel insights regarding human research with classic psychedelics (classic hallucinogens), which are serotonin 2A receptor (5-HT_{2A}R) agonists such as lysergic acid diethylamide (LSD), mescaline, and psilocybin. Classic psychedelics have been administered as sacraments since ancient times. They were of prominent interest within psychiatry and neuroscience in the 1950s to 1960s, and during this time contributed to the emergence of the field of molecular neuroscience. Promising results were reported for treatment of both end-of-life psychological distress and addiction, and classic psychedelics served as tools for studying the neurobiological bases of psychological disorders. Moreover, classic psychedelics were shown to occasion mystical experiences, which are subjective experiences reported throughout different cultures and religions involving a strong sense of unity, among other characteristics. However, the recreational use of classic psychedelics and their association with the counterculture prompted an end to human research with classic psychedelics in the early 1970s. We provide the most comprehensive review of epidemiological studies of classic psychedelics to date. Notable among these are a number of studies that have suggested the possibility that nonmedical naturalistic (non-laboratory) use of classic psychedelics is associated with positive mental health and prosocial outcomes, although it is clear that some individuals are harmed by classic psychedelics in non-supervised settings. We then review recent therapeutic studies suggesting efficacy in treating psychological distress associated with life-threatening diseases, treating depression, and treating nicotine and alcohol addictions. We also describe the construct of mystical experience, and provide a comprehensive review of modern studies investigating classic psychedelic-occasioned mystical experiences and their consequences. These studies have shown classic psychedelics to fairly reliably occasion mystical experiences. Moreover, classic-psychedelic-occasioned mystical experiences are associated with improved psychological outcomes in both healthy volunteer and patient populations. Finally, we review neuroimaging studies that suggest neurobiological mechanisms of classic psychedelics. These studies have also broadened our understanding of the brain, the serotonin system, and the neurobiological basis of consciousness. Overall, these various lines of research suggest that classic psychedelics might hold strong potential as therapeutics, and as tools for experimentally investigating mystical experiences and behavioral-brain function more generally.

Abbreviations: 25I-NBOMe, 4-Iodo-2,5-dimethoxy-N-[(2-methoxyphenyl)methyl]-benzeneethanamine; 2C-B, 2,5-Dimethoxy-4-bromophenethylamine; 5-HT_{2A}R, Serotonin 2A receptor; 5-MEO-AMT, 5-Methoxy-α-methyltryptamine; 5-MEO-DPT, 5-Methoxy-N,N-dipropyltryptamine; 5-MEO-DMT, 5-Methoxy-N,N-dimethyltryptamine; ACC, Anterior cingulate cortex; AIRFA, American Indian Religious Freedom Act; AMT, α-Methyltryptamine; BC, Before Christ; BOLD, Blood oxygenation level dependent; DAWN, Drug Abuse Warning Network; DEA, Drug Enforcement Administration; DMN, Default mode network; DMT, Dimethyltryptamine; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; DXM, Dextromethorphan; ED, Emergency department; EEG, Electroencephalography; EMCDDA, European Monitoring Centre for Drugs and Drug Addiction; fMRI, functional magnetic resonance imaging; HD-SS, High-dose with standard support for spiritual-practice; HD-HS, High-dose with high support for spiritual-practice; kg, Kilogram; LD-SS, Low-dose with standard support for spiritual-practice; LPC, Lateral parietal cortex; LSA, Lysergic acid amide; LSD, Lysergic acid diethylamide; MDMA, 3,4-Methylenedioxymethamphetamine; MEG, Magnetoencephalography; MEQ30, 30-item Mystical Experience Questionnaire; MEQ43, 43-item Mystical Experience Questionnaire; mg, Milligram; MPFC, Medial prefrontal cortex; MRS, Magnetic resonance spectroscopy; MTF, Monitoring the Future; NAC, Native American Church; NMDA, N-Methyl-D-aspartate; NSDUH, National Survey on Drug Use and Health; PCC, Posterior cingulate cortex; PET, Positron emission tomography; sgACC, Subgenual anterior cingulate; SPECT, Single photon emission computed tomography; TAAR1, Trace amine-associated receptor 1; UDV, União do Vegetal; USDHHS, United States Department of Health and Human Services.

* Corresponding author.
E-mail address: mwj@jhu.edu (M.W. Johnson).

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Contents

1. Introduction . . . 84
2. Epidemiology of classic psychedelic use. . . . 85
3. Therapeutic effects . . . 90
4. Mystical experiences . . . 92
5. Brain network changes as mechanisms underlying classic psychedelic effects. . . . 95
6. Conclusions . . . 97
Conflict of interest statement . . . 98
Acknowledgments. . . . 98
References . . . 98

1. Introduction

1.1. Classic psychedelics defined

Classic psychedelics (or classic hallucinogens) are psychoactive compounds that exert effects through agonist (including partial agonist) activity at the serotonin 2A receptor (5-HT_{2A}R). Substantial evidence suggests that 5-HT_{2A}R, which is a G-protein-coupled receptor, is the most important receptor underlying classic psychedelic effects (Nichols, 2016). For example, rat studies have shown for a variety of classic psychedelics that 5-HT_{2A}R antagonists block the ability of classic psychedelics to serve as discriminative stimuli (Glennon, Young, & Rosecrans, 1983; Glennon, Titeler, & McKenney, 1984). Human studies have also shown that 5-HT_{2A}R antagonism blocks the subjective and other effects of the classic psychedelic psilocybin (Kometer et al., 2012; Quednow, Kometer, Geyer, & Vollenweider, 2012; Kometer, Schmidt, Jancke, & Vollenweider, 2013; Vollenweider, Vollenweider-Scherpenhuyzen, Bäbler, Vogel, & Hell, 1998). Consistent with these findings, 5-HT_{2A}R knockout mice do not exhibit the head-twitch response, a characteristic rodent response to classic psychedelics (Halberstadt, Koedood, Powell, & Geyer, 2011).

Despite the primary role of 5-HT_{2A}R agonism, other receptor-level mechanisms also contribute to classic psychedelic effects. For example, 5-HT_{2C} receptors, and for certain classic psychedelics, 5-HT_{1A} receptors, play a role in classic psychedelic effects (Nichols, 2016; Halberstadt & Geyer, 2011). The effects of particular classic psychedelics also involve non-5-HT receptors, for example, at high doses LSD has dopaminergic and adrenergic effects (Kyzar, Nichols, Gainetdinov, Nichols, & Kalueff, 2017; Nichols, 2016). Multiple classic psychedelics activate trace amine-associated receptor 1 (TAAR1) (Bunzow et al., 2001; De Gregorio et al., 2016), suggesting the possibility that this receptor may contribute to classic psychedelic effects (Kyzar et al., 2017). However, the behavioral and subjective consequences of classic psychedelic activation of TAAR1 need to be investigated, and multiple drugs other than classic psychedelics (e.g., amphetamine) also activate TAAR1, suggesting TAAR1 activation may not underlie effects that are quintessential to classic psychedelics. Beyond receptor activation, classic psychedelics, but not a nonpsychoactive agonist of the 5-HT_{2A}R, have been shown to upregulate immediate early genes that encode for transcription factors, which in turn regulate multiple genes (González-Maeso et al., 2003). Many of the immediate early genes upregulated by classic psychedelics code for proteins with involvement at the synapse, likely with effects on synaptic structure in addition to neurotransmission, providing potential mechanisms underlying persisting as well as acute classic psychedelic effects (Kyzar et al., 2017).

Classic psychedelics fall within one of two general structural categories. One category includes variations on the structure of *tryptamine*. Examples include LSD, psilocybin, and dimethyltryptamine (DMT), a psychoactive compound present in the South American sacramental beverage *ayahuasca*. The second category includes variations on the structure of *phenethylamine*. One example is mescaline, the main psychoactive agent in the peyote (*Lophophora williamsii*), San Pedro (*Echinopsis pachanoi*) and Peruvian torch (*Echinopsis peruvianus*) cacti (Nichols, 2016). A variety of synthetic compounds not known to occur in nature also fall in the phenethylamine category (e.g., 2C-B, 25I-NBOMe). Indigenous cultures in the Western Hemisphere have used compounds from both structural classes in the sacramental use of ayahuasca, psilocybin-containing mushrooms, and mescaline-containing cacti. One analog of phenethylamine is methylenedioxymethamphetamine (MDMA), which causes psychoactive effects with only partial overlap with classic psychedelics, and which works primarily via serotonin release rather than 5-HT_{2A}R agonism (Nichols, Lloyd, Hoffman, Nichols, & Yim, 1982). Like MDMA, other drugs sometimes labelled as psychedelic (e.g., NMDA antagonists, anticholinergics, cannabinoids, salvinorin A, ibogaine) which are not classic psychedelics, will not be reviewed here because of their substantially differing mechanisms and effects. Although reviews with some overlap to the present manuscript have been published (e.g., Barrett & Griffiths, 2017; dos Santos et al., 2016; Johnson & Griffiths, 2017; Mahapatra & Gupta, 2017; Nichols et al., 1982; Patra, 2016), none of these provide detailed coverage of each domain of the present review (epidemiology, therapeutics, mystical experience, and brain network function).

1.2. Classic psychedelic effects

Perhaps the best description of a classic psychedelic is found in Grinspoon and Bakalar (1979, page 9) who define it as "A drug which, without causing physical addiction, craving, major physiological disturbances, delirium, disorientation, or amnesia, more or less reliably produces thought, mood, and perceptual changes otherwise rarely experienced except in dreams, contemplative and religious exaltation, flashes of vivid involuntary memory, and acute psychosis." Classic psychedelics often cause extreme changes in subjective experience during acute drug action (Passie, Seifert, Schneider, & Emrich, 2002), encompassing complex changes in affective, cognitive, and perceptual domains (Griffiths, Richards, McCann, & Jesse, 2006; Griffiths et al., 2011; Preller & Vollenweider, 2016). One type of subjective experience referred to as mystical-type experience can be occasioned by administration of relatively high doses of classic psychedelics in optimal settings (Gasser et al., 2014; Griffiths et al., 2006, 2011; Pahnke, 1963; Pahnke, 1969; Pahnke & Richards, 1966; Richards, Rhead, Dileo, Yensen, & Kurland, 1977), and will be discussed in detail in a subsequent section.

The term "hallucinogen," which has been widely applied to classic psychedelics in scientific circles, is not ideal because these substances do not typically produce frank hallucinations, and this term, which connotes only perceptual effects, is an insufficient description of the often radical effects these drugs have on human consciousness and one's sense of self. Therefore, the term "hallucinogen" has fallen out of favor, with a re-emergence of the scientific use of the term "psychedelic" to refer to these substances (Nichols, 2016). The term "psychedelic," which means "mind-manifesting," was coined by the pioneering classic-psychedelic researcher Humphrey Osmond in 1957 (Dyck, 2006). As summarized later in this review, recent psychological and biological

research indicates the accuracy of this term by suggesting this class of drugs to cause a non-ordinary and more variable form of consciousness that is less centered on one's normal sense of self, and that involves enhanced autobiographical recollection (Carhart-Harris et al., 2012a; Carhart-Harris et al., 2012b).

Classic psychedelic administration entails risks. These fall into three major categories. One that is relevant to any individual taking a sufficiently high dose of a classic psychedelic is an anxious, dysphoric, confusing, and, less commonly, delusional acute reaction, often referred to as a "bad trip" in colloquial language. Although these can be safely managed with safeguards in place within clinical research, these challenging experiences can potentially lead to accidents or other dangerous behavior in unsupervised settings (Carbonaro et al., 2016). Another risk is the exacerbation of psychotic disorders or instigation of a prolonged psychotic reaction. For cases in which initial psychotic reactions within the lifetime occur after taking a classic psychedelic, psychotic vulnerability is suspected, but it is not possible to determine if that individual would have eventually had a psychotic reaction or not if he/she had not been exposed to the drug (Grinspoon & Bakalar, 1979). Early survey research of investigators who had administered classic psychedelics to humans suggest that prolonged psychiatric reactions (>48 h) are limited to such vulnerable individuals, with only 1 case occurring among 1200 non-patient participants, and that single patient was an identical twin of a patient with schizophrenia. The same report found prolonged psychiatric reactions occurred at a rate of 1.8 per 1000 individuals for psychiatric patients. It also reported no suicide attempts for the 1200 non-patient participants, with suicide attempts and completed suicides occurring at respective rates of 1.2 and 0.4 per 1000 patients (Cohen, 1960). Drawing from multiple previous reports of studies conducted in the 1960s and 1970s, Abraham, Aldridge, and Gogia (1996) reported that rates of developing psychoses following the administration of LSD range from .08% to 4.6%, with higher rates among psychiatric patients. Screening of psychotic disorders and vulnerability is therefore an important safeguard against such psychiatric reactions (Johnson, Richards, & Griffiths, 2008). It should be noted that the acute anxious, dysphoric, confusing, and/or delusional reactions discussed above have sometimes been studied as psychosis symptoms, and therefore classic psychedelics have sometimes been considered to model psychotic symptoms (e.g., Gouzoulis-Mayfrank et al., 1998; Gouzoulis-Mayfrank et al., 2005; Heekeren et al., 2007; Hoch, 1951; Hoffer, Osmond, & Smythies, 1954; Vollenweider et al., 1998; Halberstadt & Geyer, 2013; Murray, Paparelli, Morrison, Marconi, & Di Forti, 2013). However, important differences have been demonstrated. For example, in healthy participants, classic psychedelic effects show some similarity to, or model, the positive (e.g., thought disorder, inappropriate affect) but not negative symptoms (e.g., flat affect, lack of motivation) of psychotic disorders (Gouzoulis-Mayfrank et al., 2005; Heekeren et al., 2007). Perhaps more importantly, these drug-occasioned adverse subjective experiences differ from psychotic disorders in that they have a clear cause (i.e., acute drug effects), and they resolve at the resolution of drug effects in the overwhelming majority of psychiatrically screened populations under appropriate safeguards as discussed above (e.g., Cohen, 1960; Johnson et al., 2008). However, such adverse subjective experiences in unscreened and unsupervised individuals appear to precipitate enduring psychotic reactions among some individuals (e.g., 3 among 1993 individuals who endorsed adverse subjective experiences in a survey focused on such experiences; Carbonaro et al., 2016).

Another category of risk involves short-term physiological effects. Classic psychedelics modestly raise blood pressure and heart rate during their acute course of effects (Griffiths et al., 2006; Griffiths et al., 2011; Hasler, Grimberg, Benz, Huber, & Vollenweider, 2004; Isbell, 1959; Strassman & Qualls, 1994; Gouzoulis-Mayfrank et al., 1999; Passie et al., 2002; Wolbach, Isbell, & Miner, 1962; Wolbach, Miner, & Isbell, 1962). Therefore, those with severe cardiac disease should be excluded (Johnson et al., 2008). Adverse events that can be caused by the administration of classic psychedelics, but that do not pose substantial obstacles for their clinical administration to most individuals, are dose-related headaches (Johnson, Sewell, & Griffiths, 2012), relatively low ratings of nausea (Griffiths et al., 2011; Carbonaro, Johnson, Hurwitz, & Griffiths, 2018), and relatively infrequent vomiting (e.g., 2 of 20 participants vomited after receiving a high dose of 30 mg/70 kg psilocybin, although no participants vomited after 10 or 20 mg/70 kg; Carbonaro et al., 2018). A review of the risks of human classic psychedelic administration research and guidelines for minimizing these risks (Johnson et al., 2008), as well as a review of public health harms associated with psilocybin and other classic psychedelics (Johnson, Griffiths, Hendricks, & Henningfield, 2018), are available elsewhere.

1.3. Pre-historical and historical use of classic psychedelics

Classic psychedelic use by humans appears to be ancient (e.g., Akers, Ruiz, Piper, & Ruck, 2011; Bruhn, De Smet, El-Seedi, & Beck, 2002; Carod-Artal & Vázquez-Cabrera, 2006). Among the varied indigenous societies that have used them, classic psychedelics are widely considered sacraments for use in religious and/or healing contexts (Johnson et al., 2008; Schultes, 1969; Schultes, Hofmann, & Rätsch, 2001). Although mescaline was isolated and identified as the main psychoactive compound in peyote around the turn of the century (Heffter, 1898), it was not until after nearly a half century later, when the psychoactive effects of the synthetic compound LSD were discovered using astonishingly low sub-milligram human doses (Hofmann & Ott, 1980), that clinical interest in classic psychedelics began in earnest (Grinspoon & Bakalar, 1979). Classic psychedelics attracted great interest within psychiatry and the emergent fields of molecular neuroscience and the neuroscience of serotonin in the 1950s to 1960s (Grinspoon, 1981). Promising results were reported for both end-of-life psychological distress and addiction, and classic psychedelics served as tools for studying the biological bases of psychological disorders. The most promising indications examined for classic psychedelic treatment were cancer-related psychological distress (Cohen, 1965; Kast, 1967; Kast & Collins, 1964; Kurland, 1985; Kurland, Pahnke, Unger, Savage, & Goodman, 1969; Kurland, Grof, Pahnke, & Goodman, 1973; Pahnke, Kurland, Goodman, & Richards, 1969; Richards, 1979; Richards, Grof, Goodman, & Kurland, 1972; Richards et al., 1979) and addiction (Bowen, Soskin, & Chotlos, 1970; Chwlos, Blewett, Smith, & Hoffer, 1959; Hollister, Shelton, & Krieger, 1969; Kurland, Savage, Pahnke, Grof, & Olsson, 1971; Ludwig, Levine, Stark, & Lazar, 1969; Savage & McCabe, 1973; Tomsovic & Edwards, 1970). Despite promising findings, this earlier era of human research with classic psychedelics came to a stop in the early 1970s because use of the compounds outside of controlled research settings had become popular and associated with the counterculture movement of the time (Stevens, 1987; Nutt, King, & Nichols, 2013). After decades of dormancy, classic psychedelic research re-emerged in the 1990s (e.g., Spitzer et al., 1996; Strassman & Qualls, 1994; Vollenweider et al., 1997).

2. Epidemiology of classic psychedelic use

2.1. Historical background

Several lines of archaeological evidence suggest that humans have used classic psychedelics in sacramental healing contexts since prehistoric times (Guerra-Doce, 2015; Schultes, 1969). For instance, paintings and sculptures depict stylized humanoids with mushroom features (Froese, Guzmn, & Guzmn-Dvalos, 2016), peyote bulbs stored in southwestern Texas caves have been radiocarbon dated to 3780–3660 BC (El-Seedi, De Smet, Beck, Possnert, & Bruhn, 2005), and classic psychedelic alkaloids have been found in both artifacts and human skeletal remains (Guerra-Doce, 2015). It also has been speculated that the ritualistic sacrament soma, mentioned in the ancient Indian Rig-Veda texts, contained psilocybin mushrooms, fly agaric, and/or other psychoactive plants (Levitt, 2011; McKenna, 1993), and the ancient Greek drink

kykeon, used as a ceremonial rite for millennia in Eleusis, may have contained ergoline alkaloids, including lysergic acid amides (Webster, 2000). Nevertheless, the prevalence of classic psychedelic use prior to the 20th century is unknown.

Scientists investigated the psychoactive effects of the peyote cactus in the late 19th and early 20th centuries, isolating its psychoactive component, mescaline (Bruhn & Holmstedt, 1974; Schultes, 1969). In 1943 Albert Hofmann serendipitously discovered the psychedelic effects of LSD, which was followed by widespread interest in the psychiatric applications of this novel compound (Hofmann et al., 2013; Osmond, 1957). Shortly thereafter in 1955, banker and amateur mycologist R. Gordon Wasson traveled to the Sierra Mazateca of southern Mexico to document the traditional indigenous use of psilocybin mushrooms. The widely circulated American weekly news magazine *Life* published Wasson's experiences in 1957 ("Seeking the Magic Mushroom," 1957), thrusting psilocybin mushrooms into the public eye. Aided by several high profile advocates (e.g., Cary Grant, Ken Kesey, Timothy Leary, and Paul McCartney; Lee & Slain, 1992; Stevens, 1987) classic psychedelics were soon part of both the Western cultural vernacular and the scientific and clinical pharmacopeia.

2.2. Early epidemiological surveys

Among the first epidemiological surveys on classic psychedelic use was *Life Styles and Campus Communities: A Report of a Survey of American Colleges and Universities*, funded by the National Institutes of Mental Health and conducted by Johns Hopkins University. First published in 1972 and later included in the 1974 *Recent Surveys of Nonmedical Drug Use: A Compendium of Abstracts*, this study of 7948 United States college students found that 8.6% reported having ever used a classic psychedelic in 1970 and 12.6% reported having ever used a classic psychedelic in 1971. Of the sample, 1.5% reported "regular use" of classic psychedelics, defined as using at least once every one to two weeks during the academic year (Rossi, Groves, & Grafstein, 1972; Glenn & Richards, 1974).

Drug Experience, Attitudes, and Related Behavior among Adolescents and Adults: Detailed Tabulation, conducted by the Response Analysis Corporation (Response Analysis Corporation, 1973), reported on a national cross-section of 2411 United States adults surveyed in 1972. This report found that 4.6% of all respondents reported having ever used LSD, with men (7.2%) reporting a higher prevalence than women (2.2%). Furthermore, 22% of 18 to 21 year-olds and 18.2% of 18 to 25 year-olds reported having ever used LSD. The Response Analysis Corporation also surveyed 880 United States youth aged 12 to 17. Of these respondents, 4.8% reported having ever used LSD, with girls (5.4%) reporting a slightly higher prevalence than boys (4.4%).

Two additional early surveys included a study of 5050 United States college students (Gergen, Gergen, & Morse, 1972; Glenn & Richards, 1974) and a study of 1517 boys starting tenth grade in public high schools in the fall of 1966 (Johnston, 1973). Of the United States college student respondents, 11.7% reported having ever used LSD or mescaline. Moreover, of the tenth grade boys, 6.8% reported having ever used classic psychedelics in some manner.

In sum, early epidemiological surveys were limited in scope (e.g., consisting of only youth or only college students) and limited in size (880 to 7948 volunteers), but suggest that classic psychedelic use and LSD use in particular was not uncommon among adolescents and young adults in the late 1960s and early 1970s.

2.3. The "Monitoring the Future" survey

Among the first systematic and rigorous epidemiological surveys to assess classic psychedelic use was Monitoring the Future (MTF). Funded by the National Institute on Drug Abuse, MTF has surveyed approximately 50,000 12th graders every year since 1975 and a similar number of 8th graders, 10th graders, college students, and young adults every year since 1991 (Miech et al., 2017).

Fig. 1 displays past 12 months prevalence of LSD use among 8th graders, 10th graders, 12th graders, college students, and young adults from 1975 to 2016 and Fig. 2 presents past 12 months prevalence of "hallucinogens other than LSD" use among these groups across the same time period. Although the aggregated non-LSD hallucinogens include, per MTF methods, the dissociative anesthetic phencyclidine, concentrated tetrahydrocannabinol, and unknown hallucinogens, it also includes the classic psychedelics mescaline, peyote, and psilocybin. According to MTF, the majority of hallucinogens other than LSD use is accounted for by psilocybin. As seen in the Fig. 1, past 12 months prevalence of LSD use peaked in the mid-1990s for all groups before declining and remaining somewhat constant since the early 2000s. As shown in Fig. 2, past 12 months prevalence of hallucinogens other than LSD use was at its highest point among 12th graders in the first year of the MTF survey in 1975, declined until 1992, then increased before reaching another high among all groups in the early 2000s. Past 12 months prevalence of hallucinogens other than LSD use has steadily declined since this time. The prevalence of lifetime use and past 30 days use, also estimated by MTF but not reported here, exhibit similar time trends, though as expected the prevalence of lifetime use is greater and the prevalence of past 30 days use is smaller than the prevalence of past 12 months use. It is noted that in Fig. 2 the uniform spike in prevalence among 8th, 10th, and 12th graders between 2000 and 2001 is likely due a change in methods in which the term "shrooms" was added to the query assessing psilocybin use (Miech et al., 2017).

2.4. National Survey on Drug Use and Health

The National Survey on Drug Use and Health (NSDUH) of the Substance Abuse and Mental Health Services Administration of the United States Department of Health and Human Services (USDHHS) has been conducted since 1979 to estimate the prevalence of substance use and mental illness in the general United States civilian non-institutionalized population (aged 12 and older; Center for Behavioral Health Statistics and Quality, 2016). Initially the NSDUH queried respondents as to how many times they had used a "hallucinogen" (including the dissociative anesthetic phencyclidine) in their lifetime, making it difficult to determine the prevalence of classic psychedelic use. In 1985, the NSDUH began to query respondents with regard to specific substances used, allowing for estimates of the lifetime prevalence of LSD, peyote, mescaline, and psilocybin use. These data are presented in Fig. 3 below.

As seen in this figure, whereas the lifetime prevalence of peyote and mescaline use has remained relatively constant since 1985, the lifetime prevalence of LSD and psilocybin use increased between 1985 and the early 2000s. Whereas the lifetime prevalence of LSD use has slightly decreased since the early 2000s, the lifetime prevalence of psilocybin use has slightly increased since this time. It is noted that differences in time trends between the NSDUH and MTF are likely attributable to the younger demographic captured by MTF.

2.5. Drug Abuse Warning Network

Another important source of information with regard to prevalence of classic psychedelic use is number of emergency department (ED) visits, or "cases," related to these substances. The Drug Abuse Warning Network (DAWN) was established in 1972 by the Drug Enforcement Administration (DEA) to monitor drug-related ED cases. Data pertaining to ED cases associated with classic psychedelic use are available from 2004 to 2011 (Center for Behavioral Health Statistics and Quality, 2012; Center for Behavioral Health Statistics and Quality, 2013). These data are presented in Fig. 4 below. As shown in this figure, ED cases associated with classic psychedelic use rose slightly from 2004 to 2011, increasing by approximately one case over this time. "Miscellaneous hallucinogens" (defined as novel 2C-X compounds, *Datura stramonium*, mescaline, morning glory seeds, psilocybin, *Salvia divinorum*, and "Hallucinogens Not Otherwise Specified") account for the highest

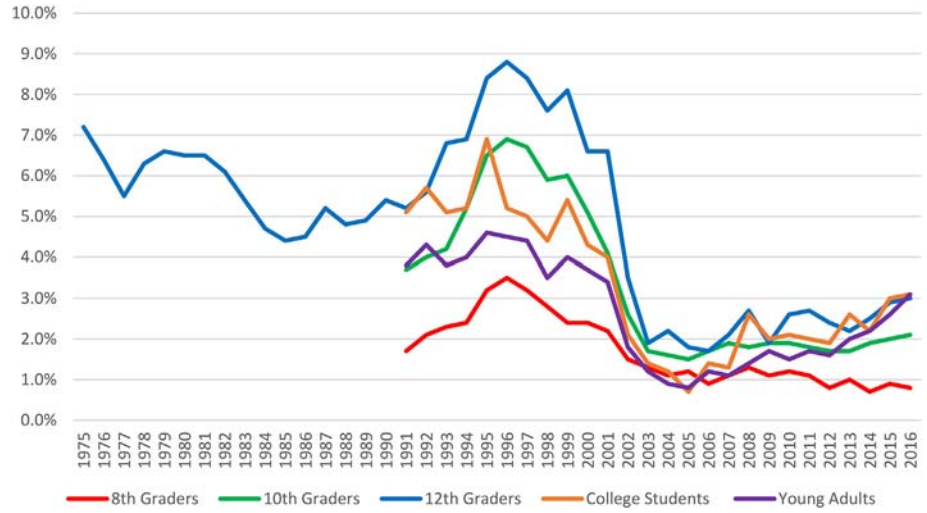

Fig. 1. Past 12 months prevalence of LSD use among United States high school students, college students, and young adults by year from 1975–2016 (Monitoring the Future)

percentage of ED cases among all psychedelic-associated categories, and some of these substances are not considered classic psychedelics (e.g., *Salvia divinorum*). The "Hallucinogens Not Otherwise Specified" category includes 5-MEO-AMT, 5-MEO-DPT, 5-MEO-DMT, AMT, ayahuasca, DMT, LSA, nutmeg, and other purportedly hallucinogenic plants and seeds. Some of these substances also are not considered classic psychedelics. Thus, classic psychedelics appear to account for a very small number of drug-related ED visits. Indeed, to place these findings in context, cocaine was associated an average of 163.8 cases per 100,000 ED visits and opioids were associated with an average of 69.2 cases per 100,000 ED visits over the same seven year period. Of course, these reports may in part reflect the relative prevalence of classic psychedelic use as compared to cocaine and opioid use.

2.6. DEA seizures

The DEA provides drug seizure statistics by year on its website starting in 1986. The DEA reports "hallucinogen" seizures in dosage units, which vary among these compounds. Furthermore, the "hallucinogen" category appears to encompass LSD and psilocybin mushrooms as well as the dissociative anesthetics phencyclidine and ketamine and the empathogen/entactogen MDMA. The DEA drug seizure data are therefore weak indicators of the prevalence of classic psychedelic use, but are nonetheless presented here as they reflect trends in the illicit drug market. Fig. 5 displays DEA hallucinogen doses seized since 1985. As shown in this figure, there has been a decrease in seizures since the early 2000s. In the year 2000, a large LSD manufacturing operation was uncovered by the DEA, which likely explains the spike in seizures that year (DEA Website, 2016; DEA News Release, 2003). The data for 2014 are cited as, "preliminary and subject to updating" although through 2018 they have not changed.

2.7. Epidemiological surveys outside the United States

Although the most comprehensive epidemiological surveys have originated in the United States, a number of surveys outside of the United States inform the global prevalence of classic psychedelic use. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) has been pooling data intermittently from European Union countries since 1990. Among young adults aged 15 to 34, national surveys report past 12 months prevalence rates of less than 1% for LSD and psilocybin combined, though respondents from Finland, the United Kingdom, the Netherlands, and the Czech Republic report slightly higher rates of use (1% to 2.3%; European Monitoring Centre for Drugs and Drug Addiction, 2016). England and Wales independently monitor lifetime, past 12 months, and past 30 days prevalence of LSD use.

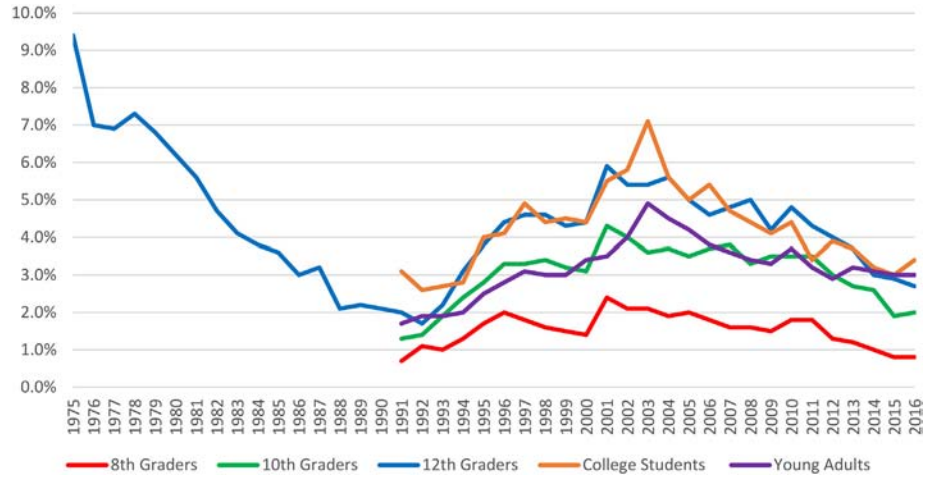

Fig. 2. Past 12 months prevalence of hallucinogens other than LSD use among United States high school students, college students, and young adults by year from 1975–2016 (Monitoring the Future)

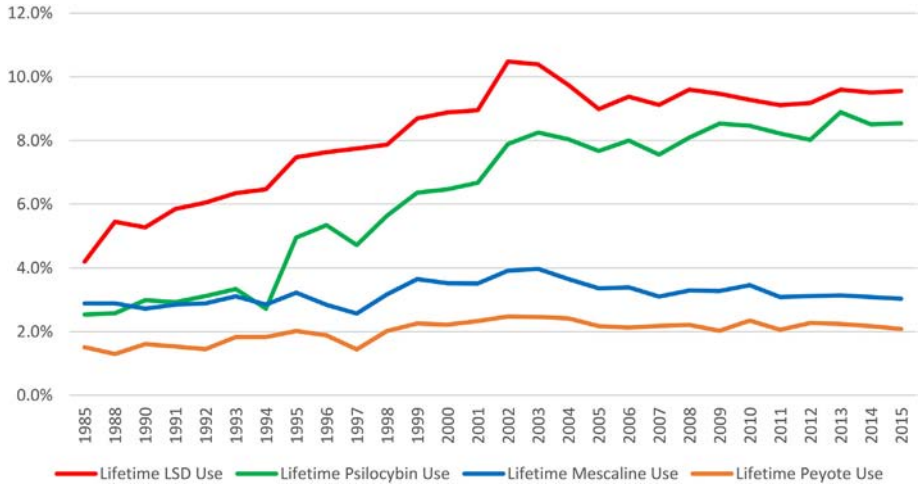

Fig. 3. Weighted lifetime prevalence of LSD, peyote, mescaline, and psilocybin use in the United States population by year from 1985-2015 (National Survey on Drug Use and Health)

Lifetime prevalence rates of LSD use peaked in England and Wales in the late 1990s and early 2000s at approximately 6%. As of 2015, lifetime prevalence of LSD use was 4.4%, past 12 months prevalence of LSD use was 0.2%, and past 30 days prevalence of LSD use approached 0% in England and Wales (European Monitoring Centre for Drugs and Drug Addiction, 2016).

The Global Drug Survey is an online self-selected survey of individuals sampled from the United Kingdom (33.9%), Australia (35.9%), the United States (17.3%), the Eurozone (10%), and Canada (2.9%) initiated in 2012 (Lawn et al., 2014). In total, the Global Drug Survey queried 22,289 individuals, 68.6% of whom were male with an average age of 31.4 years. Fig. 6 summarizes findings from the Global Drug Survey. Of note, 6.2% of Global Drug Survey respondents reported microdosing, or using sub-perceptual doses of classic psychedelics with the intent to improve mood, productivity, and creativity (Linstock et al., 2017). It is noted that because Global Drug Survey participants were self-selected, these statistics are not representative of the general population, and in all likelihood overestimate the prevalence of classic psychedelic use.

The Australian Institute of Health and Welfare has collected data on illicit substance use since 1993. Survey methods are similar to the NSDUH, capturing use prevalence rates of variance substances including "hallucinogens." Though ketamine and MDMA are not included in the hallucinogen category, those substances comprising hallucinogens are not specified. Nevertheless, in 1993 7.3% of respondents (aged 14 and older) reported having ever used a hallucinogen. This figure rose to 9.9% in 1998 and fluctuated around 7% in the early 2000s until peaking again in 2013 at 9.4%. Furthermore, in 1993 1.3% of respondents reported using a hallucinogen in the past 12 months. This peaked in 1998 at 3.0% and then steadily declined to 1.3% in 2013. With regard to frequency of use, 70.2% of respondents who endorsed having ever used a hallucinogen reported using hallucinogens once or twice per year (Australian Institute of Health and Welfare, 2014).

2.8. Special populations

The Native American Church (NAC), Sainto Daime Church, and União do Vegetal (UDV) use classic psychedelic compounds as part of their religious observances in the United States and elsewhere. Prior to the passage of the American Indian Religious Freedom Act (AIRFA) in 1994, which granted the NAC a religious use exemption for peyote, between 1% and 2% of American Indians reported having ever used this substance. Following the passage of the AIRFA, approximately 10% of American Indians reported having ever used peyote. NAC membership is estimated at approximately 600,000 individuals (Prue, 2014). The Santo Daime Church reports that approximately 100,000 people participate in their ayahuasca ceremonies (santodaime.com/en/asks/#28), and the UDV claims over 17,000 members in Brazil in addition to 270 members in the United States (udvusa.org). A number of studies indicate no harm associated with participation in these religious

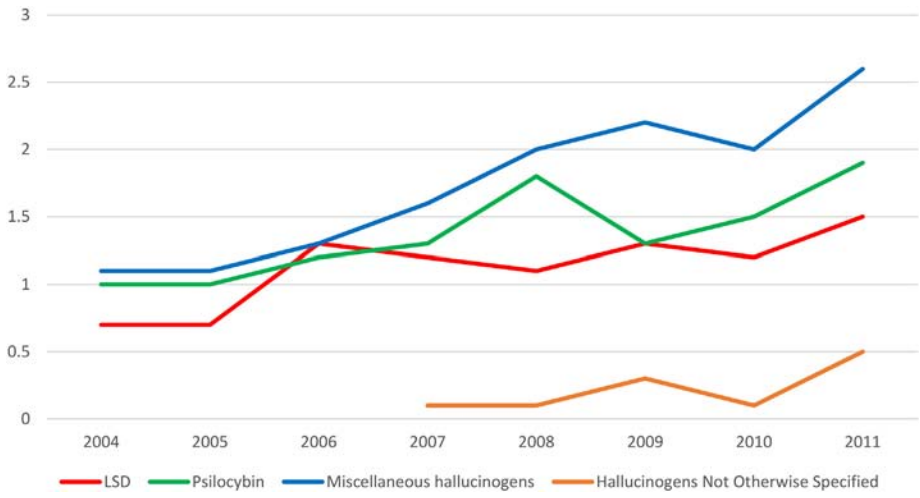

Fig. 4. Classic psychedelic-associated emergency department visits per 100,000 drug-related visits in United States hospitals by year from 2004-2011 (Drug Abuse Warning Network)

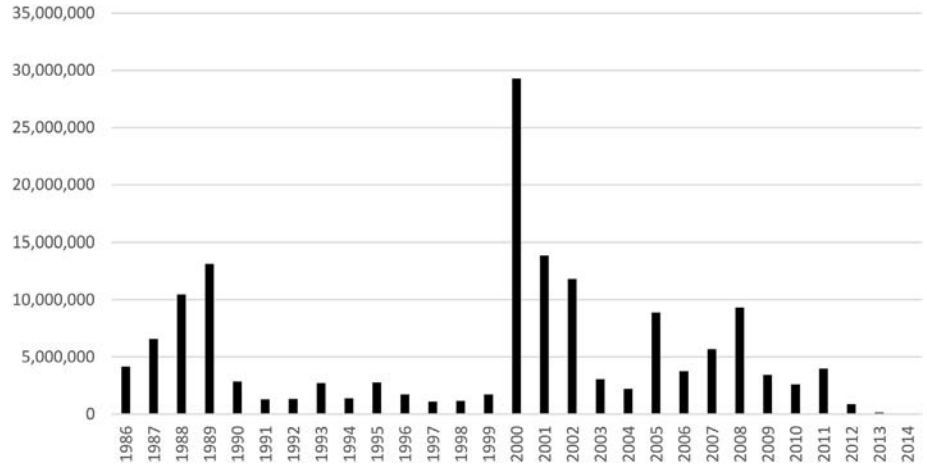

Fig. 5. United States Drug Enforcement Administration hallucinogen dose seizures by year from 1986-2014

observances, and in fact several findings suggest a protective effect with regard to mental health (e.g., Barbosa et al., 2009; Bouso et al., 2012; Doering-Silveira et al., 2005; Fbregas et al., 2010; Halpern et al., 2005, 2008; Miranda et al., 1995).

The United States military has a unique history with LSD, having tested the drug as a potential incapacitating agent, without success, after its discovery by Albert Hofmann in 1943 (Lee and Slain, 1992). Dr. James Ketchum, who was involved in testing LSD at the Army Chemical Center in the 1960s, reported a reduced rate of later death (assessed between 1980 and 1981) among individuals who had previously received LSD (between 1955 and 1975). Specifically, among over 100 individuals who received LSD, only one eventual death was recorded whereas 7.1 were expected to occur (Ketchum, 2006).

2.9. Population-level associations

A number of recent studies have examined population-level associations of classic psychedelic use. Drawing data from multiple years of the NSDUH, Krebs and Johansen (2013) and Johansen and Krebs (2015) found positive trends but no statistically significant associations between lifetime use of classic psychedelics and mental health outcomes, and in fact found some evidence that lifetime use of classic psychedelics was associated with a reduced likelihood of mental health problems. Drawing from a larger number of years of the NSDUH data than the Krebs and Johansen (2013) study but showing similarly sized odds ratios, Hendricks et al. (2015a, 2015b) found that having ever used a classic psychedelic and having ever used psilocybin in particular were both significantly associated with a decreased likelihood of psychological distress and suicidality. Argento et al. (2017) replicated and extended these findings by showing that having ever used a psychedelic, broadly defined (e.g., including MDMA), predicted a decreased likelihood of suicidality among 766 female sex workers in British Columbia. Consistent with recent pilot trials on psilocybin-assisted treatment of addiction (Bogenschutz et al., 2015; Johnson et al., 2014; Johnson et al. 2017), Pisano et al. (2017) found that having ever used a classic psychedelic was associated with a decreased risk of opioid abuse and dependence across multiple NSDUH years. Addressing a line of work that garnered research attention during the first wave of classic psychedelic science (Andersen-Hein, 1963; Leary, 1969; Tenenbaum, 1961), Hendricks et al. (2014) found that naturalistic hallucinogen use predicted a reduced likelihood of supervision failure (i.e., criminal recidivism) among more than 25,000 individuals under community corrections supervision with a history of substance involvement. Walsh et al. (2016) also found that naturalistic hallucinogen use predicted reduced arrest for intimate partner violence among 302 jail inmates, and Hendricks et al. (2018) found that having ever used a

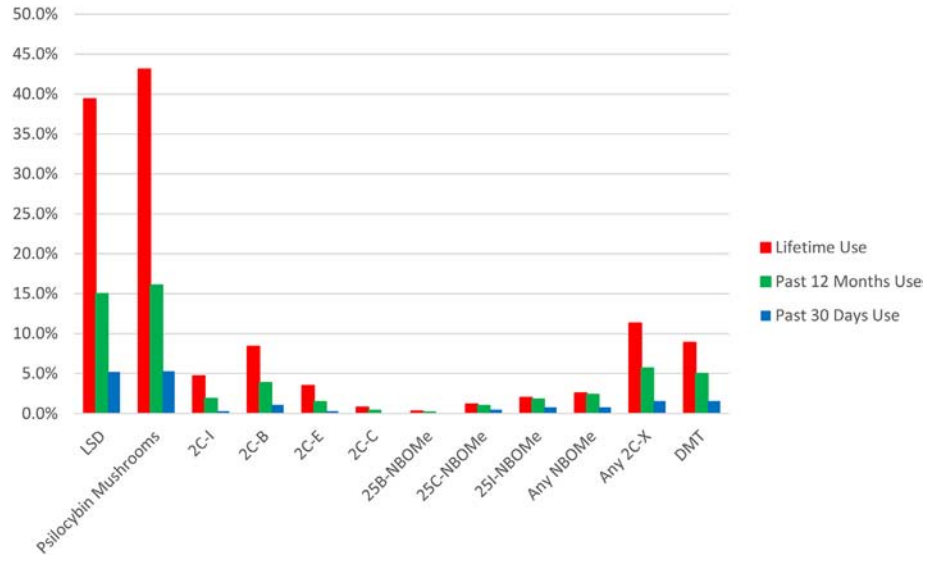

Fig. 6. Self-reported Prevalence of Lifetime Classic and Novel Psychedelic Use, 2013 (Global Drug Survey)

classic psychedelic was associated with a reduced likelihood of larceny/theft and assault using multiple years of NSDUH data. It bears repeating, however, that unsupervised classic psychedelic use can potentially result in dangerous behavior, and prompt or exacerbate psychotic disorders among those predisposed to such disorders (Johnson et al., 2008). Although no contemporary studies have reported psychoses following the administration of a classic psychedelic, rates for developing psychoses following the administration of LSD in studies conducted in the 1960s and 1970s range from .08% to 4.6%, with higher rates among psychiatric patients (Abraham et al., 1996). Clearly then, despite these population-level associations, classic psychedelics are not without risk, and use outside of approved clinical settings is strongly discouraged.

3. Therapeutic effects

Here we review contemporary clinical research examining classic psychedelics in the treatment of cancer-related psychological distress, and the treatment of addictions. One study examined the dose-related effects of psilocybin in the treatment of obsessive-compulsive disorder (Moreno et al., 2006). Although symptoms were reduced temporarily after psilocybin administration, the similar efficacy observed for the high dose and very low dose administered in the study suggests the considerable possibility that results may have been driven by expectancy. Other case-series research has suggested potential efficacy of classic psychedelics in the treatment of cluster headaches, which are notoriously painful and resistant to treatment (Sewell et al., 2006). These patient self-reports suggest that even very low, sub-psychedelic doses of classic psychedelics may effectively abort and prevent cluster headaches. However, because the potential mechanisms at play are likely distinct from the treatment of psychological disorders reviewed herein, this research is not reviewed here. The laboratory clinical trials and pilot studies discussed below have routinely reported the more common adverse events to be expected among classic psychedelic administration studies, specifically, elevated blood pressure and heart rate, psychological discomfort (e.g., anxious or dysphoric reactions), and physical distress (e.g., nausea, vomiting, and headache). While such adverse events are common, they can be managed with appropriate safeguards (Johnson et al., 2008), and do not appear to preclude the possibility of therapeutic benefit.

3.1. Cancer-related psychological distress

All of the studies reviewed in this section and the following *Depression* and *Addiction* sections used a particular treatment approach which was first reported in the scientific literature in 1959 (Chwlos et al., 1959; Majic et al., 2015), and which has come to be known as "psychedelic" psychotherapy. In contrast to the "psycholytic" approach which used lower doses of classic psychedelics, the goal of the psychedelic approach was to administer a high dose in order to occasion a mystical-type experience (sometimes referred to with related terms such as "peak experience" or "ego dissolution") and subsequent behavior change. In addition to the administration of a high dose of a classic psychedelic compound, "psychedelic" psychotherapy includes preparation and rapport building with session facilitators before sessions occur, a comforting physical and interpersonal environment, the use of eyeshades to block visual stimuli, playing carefully selected music during sessions, and follow-up discussion of the session experience.

Following up on the promising findings from trials conducted from the 1950s to 1970s using the psychedelics LSD and dipropyltryptamine (DPT) (Cohen, 1965; Kast, 1967; Kast and Collins, 1964; Kurland, 1985; Kurland et al., 1969; Kurland et al., 1973; Pahnke et al., 1969; Richards, 1979; Richards et al., 1972; Richards et al., 1979), a small pilot study in 2011 compared the effects of a moderate dose of oral psilocybin (0.2 mg/kg) and niacin as a comparator compound within 12 participants with advanced-stage cancer and clinically significant cancer-related anxiety meeting criteria for a DSM-IV anxiety-related disorder (Grob et al., 2011). Importantly, there were no clinically significant adverse events attributable to psilocybin. In a two-week follow-up after drug administration, psilocybin relative to placebo showed a trend toward decreasing depression severity as measured by the Beck Depression Inventory, and anxiety severity as measured by the State-Trait Anxiety Inventory. Relative to scores assessed at study screening, mean depression scores were consistently reduced at each monthly follow-up session, up to the last follow-up at 6 months, when this reduction was statistically significant. Similarly, mean trait anxiety scores were consistently reduced compared to baseline at each monthly follow-up, and this reduction was significant at the 3-month follow-up. This study played an important role in suggesting that the effects reported for LSD and DPT in cancer patients in the earlier era of research are likely relevant to psilocybin as well. Moreover, the study demonstrated safety of psilocybin in this population.

Two larger studies, both using a substantially higher dose of oral psilocybin, were recently published (Griffiths et al., 2016; Ross et al., 2016). One study was conducted in 51 patients with a life-threatening cancer diagnosis who met criteria for at least one DSM-IV mood- or anxiety-related disorder in relation to their cancer (Griffiths et al., 2016). Specifically, these disorders included chronic adjustment disorder with anxiety, chronic adjustment disorder with mixed anxiety and depressed mood, dysthymic disorder, generalized anxiety disorder, and major depressive disorder. Each participant had two drug administration sessions: one in which a high oral dose of psilocybin (22 or 30 mg/70 kg) was administered; and one in which a very low dose of psilocybin (1 or 3 mg/70 kg) was administered as a comparator condition, with the order of the two conditions counterbalanced across participants. Volunteers and session monitors were informed that psilocybin would be administered in both sessions, that the possible dose could range from negligible to high in both sessions, and that at least one session would be at least a moderately-high dose. This instructional set, combined with the use of an inactive or minimally active dose of psilocybin for the comparator condition, maximized expectancy effects for both sessions, thereby increasing the likelihood of positive effects from the low dose and further eliminating the expectancy that an active first session would necessarily be followed by a relatively inactive second session. The high psilocybin dose, compared to the very low dose, significantly improved a variety outcomes measures when measured 5 weeks after each session and before experiencing the other session (if it was still forthcoming). Most astonishingly, results on a number of measures, including the primary clinical outcome measures (Depression: Hamilton Depression Rating Scale, Beck Depression Inventory; Anxiety: Hamilton Anxiety Rating Scale, State-Trait Anxiety Inventory) remained significantly and substantially reduced at the final 6-month follow-up compared to screening scores, with approximately 60% of participants showing scores within the clinically normal range, constituting remission. As discussed in more detail in a later section, ratings of mystical experience occasioned by sessions mediated the effect of psilocybin condition on a number of clinical outcomes. A statistical mediator is a variable that underlies or explains the causal relationship between two other variables. In this case, analysis suggested that the ability of psilocybin to cause positive therapeutic change was due to psilocybin's role in producing mystical-type experience (Baron and Kenny, 1986). No serious adverse effects attributable to psilocybin were observed.

The other study was conducted in 29 patients with a life-threatening cancer diagnosis who met criteria for a DSM-IV anxiety-related disorder in relation to their cancer (Ross et al., 2016). Specifically, these disorders included adjustment disorder and generalized anxiety disorder. Each participant participated in two drug administration sessions. A high oral dose of psilocybin (0.3 mg/kg) was administered in one session, and niacin was administered as a comparator compound in the other. The order of the two conditions was randomized for each participant. Consistent with the results of the larger high-dose study (Griffiths et

al., 2016), the high dose psilocybin condition produced significant improvements on a variety of outcome measures regardless of order of treatment conditions. At approximately 6 months after treatment, anxiety and depression symptoms remained significantly and substantially reduced compared to screening scores, with an approximately 60% remission rate for key anxiety and depression outcome measures. Ratings of mystical experience were shown to be a mediator of the relation between psilocybin administration and therapeutic effect of psilocybin on anxiety and depression. The different designs used by this study (Ross et al., 2016) and the previously described high-dose psilocybin study (Griffiths et al., 2016) both resulted in surprisingly large and lasting antidepressant and anxiolytic effects, providing complementary support for the efficacy of high-dose psilocybin for cancer-related psychological distress. Like the previous studies, no serious adverse effects attributable to psilocybin were observed.

Another recent study more directly replicated and extended the previous research examining classic psychedelics in the treatment of cancer-related psychological distress by examining the effects of LSD (Gasser et al., 2014). Participants were individuals with anxiety associated with one of several life-threatening diseases. Six of these participants had cancer diagnoses, as did participants in the previously described studies (Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016). Participants received two LSD sessions that were separated by 2 to 3 weeks. Each qualifying participant was randomly assigned to receive either 200 (n = 8) or 20 micrograms (n = 3) of LSD in the context of psychedelic psychotherapy (as in the psilocybin cancer studies), with the same dose delivered in each of the two sessions. The 20 microgram dose was considered an active placebo because it was expected to result in mild, detectable effects but to not generally enhance therapeutic process. At a 2-month follow-up, significant reductions in state anxiety as measured by the State-Trait Anxiety Inventory were observed for the experimental group receiving 200 micrograms of LSD in their sessions, and these approximate levels of improvement were also observed at a 12-month follow-up. In contrast, the active placebo group that received 20 micrograms of LSD in their sessions showed a trend for increased state anxiety at the 2-month follow-up. A similar reduction was observed for trait anxiety in the 200 microgram group, but this did not reach statistical significance. The 20 microgram group showed a trend for increased trait anxiety at the 2-month follow-up. After the 2-month follow-up, participants in the 20 microgram active placebo group underwent a "crossover" to receive the experimental dose of 200 micrograms in two sessions. This resulted in trend decreases in state and trait anxiety 2 months later, and 12-month follow-up anxiety scores similar to those in the experimental group. Like the studies described above examining psilocybin, no serious adverse drug effects were reported.

3.2. Depression

A small open-label pilot study of 12 patients recently examined psilocybin in treatment-resistant major depression (Carhart-Harris et al., 2016a). This study involved two sessions separated by one week. In the first session, patients were orally administered 10 mg of psilocybin. In the second session, 25 mg of psilocybin was orally administered. A number of outcomes, including depression as measured by the Quick Inventory of Depressive Symptoms, and anxiety as measured by the State-Trait Anxiety Inventory, showed statistically significant improvements as compared to screening measures, when assessed both one week and three months after psilocybin treatment. No serious adverse events were attributable to psilocybin administration. A follow-up study reported results for an additional number of participants (for a total N = 20) at 6 months post-treatment. Substantial reductions in depressive symptoms were significant at all time points observed post-treatment, including the 6-month follow-up. Greater ratings of mystical-type experience (measured by factors of unity, spiritual experience, and blissful state on the 11-Dimension Altered States of Consciousness Questionnaire) and ratings of insight for the sessions were significantly related to lower depression scores 5 weeks post-treatment (Carhart-Harris et al., 2018). From this same open-label study, an analysis of 16 patients undergoing fMRI found that increased resting state connectivity within the default mode network (DMN) and between DMN (parahippocampal cortex) and prefrontal cortices observed 1 day after the second of two psilocybin treatments was predictive of clinical response 5 weeks post-treatment (Carhart-Harris et al., 2017). Also from the same open-label study, an analysis of 19 participants undergoing fMRI showed increased amygdala response to emotional faces 1 day after the second of two psilocybin treatments, a finding opposite in direction to previous findings with SSRI treatment of depression (Roseman et al., 2017). These findings suggest potential biological mechanisms for therapeutic efficacy in depression treatment that should be confirmed in randomized controlled treatment trials.

Consistent with the preliminary observations for psilocybin, several studies suggest ayahuasca may hold promise for the treatment of depression. One observational study of 57 non-patient individuals attending ayahuasca ceremonies found significantly decreased ratings of depression and stress (and small, non-significant reductions in anxiety) on the 21-item Depression, Anxiety, and Stress Scale when assessed 1 day and 4 weeks after, compared to before, the ayahuasca ceremonies (Uthaug et al., 2018). Ratings of depression and stress 1 day after the ceremonies were significantly related to the extent of "ego dissolution" in regard to the ayahuasca experiences as rated on the Ego Dissolution Inventory. An open label study of ayahuasca administration (2.2 mL/kg body weight, with 0.8 mg/mL DMT content), was conducted in six patients with recurrent major depressive disorder in an inpatient psychiatric unit (Osório et al., 2015). Ayahuasca administration was followed by statistically significant and substantial reductions in symptom ratings in the Hamilton Depression Rating Scale, the Montgomery-Åsberg Depression Rating Scale, and the Brief Psychiatric Rating Scale anxious-depression subscale at 1, 7, and 21 days post-administration compared to baseline. Using similar methods, the same group replicated these findings in a larger sample of 17 patients with recurrent major depressive disorder (Sanches et al., 2016). Using SPECT imaging, the study also found increased blood perfusion in areas involved in mood regulation (left nucleus accumbens, right insula, and left subgenual area) after ayahuasca administration.

The only randomized controlled trial of a classic psychedelic for treatment-resistant depression examined ayahuasca (Palhano-Fontes et al., 2018). Patients (N = 29 who received intervention) were randomized to receive either ayahuasca (containing 0.36 mg/kg DMT; n = 14) or placebo (n = 15). Although the ayahuasca group showed a trend for higher depressive symptom scores on the Montgomery-Åsberg Depression Rating Scale and the Hamilton Depression Rating Scale before the intervention compared to the placebo group, both scales showed significantly and substantially lower depressive symptoms in the ayahausca group compared to the placebo group 7 days after treatment.

In response to promising results in the treatment of depression with classic psychedelics (both within and outside of cancer contexts), a number of reviews and commentaries have been published. A commonality is acknowledgement of promising findings but recognition of the early stages of this research and the need for larger studies investigating methodological variations, in particular the need for randomized research in non-cancer related treatment-resistant depression, continued research on potential risks, and additional research on potential mechanisms (e.g., dos Santos et al., 2016; Mahapatra and Gupta, 2017; Patra, 2016; Cowen, 2016; McCorvy et al., 2016). A challenge not typically recognized in commentaries is that, despite widespread agreement that systematic and rigorous following is essential, substantial funding is required for large trials and mechanistic studies, and to date, federal funding for such follow-up research has not been provided.

Hopefully, recent research on depression and other disorders has set the stage for a transition in which public funding for needed follow-up research may be forthcoming (Johnson, in press).

3.3. Addiction

Until recently, reviews of the older literature examining classic psychedelics in the treatment of addictions have concluded mixed results (Abuzzahab and Anderson, 1971; McGlothlin and Arnold, 1971; Halpern, 1996; Mangini, 1998). However, a meta-analysis published in 2012 quantitatively analyzed the effect sizes observed for all six of the studies that randomized alcohol dependent participants to LSD treatment or comparator conditions and found robust support for the efficacy of LSD, showing, for example, that LSD approximately doubled the odds of improved outcomes at the first follow-up (Krebs and Johansen, 2012). In addition to this rigorous quantitative re-analysis of the previous era of research, multiple recent clinical pilot studies have reinitiated interest in the use of classic psychedelics in the treatment of addiction.

One small open-label pilot study of smoking cessation treatment administered psilocybin to 15 treatment-resistant, biologically confirmed smokers, along with cognitive behavioral therapy for tobacco dependence (Johnson et al., 2014). On the target quit date, the timing of which was determined several weeks beforehand, participants were orally administered 20 mg/70 kg psilocybin. Two weeks later, a second oral dose of psilocybin (30 mg/70 kg) was administered. Eight weeks after the target quite date, a third dose (30 mg/70 kg) was administered. The study included the option to administer the 20 mg/70 kg dose during the second and/or third psilocybin sessions dependent on participant response. The treatment program included weekly cognitive behavioral therapy sessions that occurred until 10 weeks after the target quit date (except when a psilocybin session was scheduled). Results showed that 80% of participants were biologically confirmed as abstinent at 6-months post-target quit date, and 60% of participants biologically confirmed as abstinent at 2.5 years post-target quit date (Johnson et al., 2014; Johnson et al., 2017). Although this pilot study contained no comparison group, the abstinence rates were substantially higher than those typically observed in medication and/or behavioral smoking cessation therapies (e.g., typically ≤35% abstinence at 6 months; Johnson et al., 2014). Those participants who had stronger mystical experiences in psilocybin sessions were more likely to be successful in quitting smoking (Garcia-Romeu et al., 2014). Although spirituality is often an aspect of addiction recovery (e.g., Miller, 2004), we are aware of no data to indicate if classic psychedelic-occasioned experiences are identical to those reported in addiction recovery (e.g., 12 step programs) using either validated self-report instruments or at the neurobiological level. No serious adverse events were attributed to psilocybin. A recent survey study examined individuals claiming to have quit or reduced smoking due to a classic psychedelic experience and found that participants typically judged negative affect withdrawal symptoms (e.g., depression, irritability, craving) to be much less severe compared to previous occasions in which they quit smoking (Johnson et al., 2017).

Another small open-label study tested psilocybin in the treatment of addiction, in this case, alcohol dependence (Bogenschutz et al., 2015). Ten participants who met DSM-IV criteria for alcohol dependence participated in up to two oral psilocybin sessions as part of a motivational enhancement therapy program lasting 12 weeks. Upon at least 24 hours of alcohol abstinence, the first psilocybin session occurred, in which 0.3 mg/kg psilocybin was administered. A second dose of 0.4 mg/kg (or 0.3 mg/kg depending on response in first session) was administered four weeks later for a subset of volunteers. Percentage of drinking days and percentage of heavy drinking days significantly decreased following the first psilocybin session. At 36 weeks after treatment, these self-reported drinking indices were still substantially lower than at screening. More specifically, mean percentage of drinking days dropped from approximately 32.5% in the 4 weeks of treatment preceding the psilocybin session, to approximately 12.5% in the 4 weeks following the psilocybin session, and approximately 17.5% at the final follow-up period 21 to 32 weeks after the psilocybin session. Mean percentage of heavy drinking days (i.e., ≥5 drinks for men, ≥4 drinks for women) dropped from approximately 26% in the 4 weeks of treatment preceding the psilocybin session, to approximately 8% in the 4 weeks following the psilocybin session, and approximately 13% at the final follow-up period 21 to 32 weeks after the psilocybin session. A significant relation was found between higher mystical-type experience scores in the first psilocybin session and decreased alcohol use. Importantly, there were no clinically significant adverse events attributable to psilocybin.

4. Mystical experiences

Mystical-type or quantum change experiences are sometimes occasioned by classic psychedelics. Mystical experiences refer to a class of experiences having a primary feature of a sense of the unity of all people and things accompanied by a sense of reverence, and the authoritative truth value of the experience (e.g., Stace, 1960a). Descriptions of spontaneously occurring mystical experiences date back millennia to the early Indian Upanishads and the Greek philosopher Plotinus. Many reports of such experiences have been catalogued and classified by theologians, psychologists, and philosophers (James, 1902; Stace, 1960a,b). Quantum change is a more recently introduced concept that has significant overlap with mystical experience, but in addition to the phenomenology of the experience itself, quantum change emphasizes the persisting consequences caused by the experience. More specifically, quantum change experiences refer to sudden, distinctive, benevolent, and often profoundly meaningful experiences that are said to result in personal transformations that affect a broad range of personal emotions, cognitions, and behaviors (Baka and Miller, 2001; Miller, 2004). The phenomenon of quantum change is differentiated from the usual process of behavioral change, which occurs in small incremental steps (James, 1902). Two subtypes of quantum change experiences have been proposed: the mystical-type (which overlap with classic mystical experiences) and the insightful-type, which emphasize the importance of sudden and compelling personal insight into life problems or circumstances. These overlapping constructs of mystical experience and quantum change experiences have also been variously labeled as conversion experiences, religious experiences, peak experiences, transcendental experiences, transforming moments, or epiphanies (e.g., James, 1902; Stace, 1960; Maslow, 1968; Baka and Miller, 2001). These experiences are scientifically interesting and important to study because they are sometimes associated with abrupt, substantial, and sustained changes in behavior and perception. Furthermore, the authoritative sense of interconnectedness that is a key feature of mystical-type experiences has been proposed by some to be foundational to the world's ethical and moral systems (Huxley, 1947; Stace, 1960a; Jones, 2016). Despite their apparent importance, the unpredictability and low probability of "naturally occurring" mystical-type and insightful-type experiences, whether they occur in religious or nonreligious contexts, has made them inherently difficult to study in controlled empirical research.

Because much more research has focused on mystical experiences than quantum change experiences and relatively little research has assessed insightful-type experiences per se, our emphasis will be primarily on mystical-type experiences. Our summary below draws heavily on a detailed recent review of classic psychedelics and mystical experience (Barrett and Griffiths, 2017).

The most definitive review of mystical experience was compiled by Stace (1960a) who identified and distilled descriptions of mystical experiences from a variety of sources. Stace hypothesized that mystical experiences have a common core of phenomenological features that are independent from the interpretation of those experiences. He proposed that a defining feature of the mystical experience is a sense of unity, or

the experience of becoming one with all that exists. He distinguished between introvertive (internal) and extrovertive (external) variants of unity experiences. In addition to internal unity and external unity, Stace described several other dimensions of mystical experience: sacredness - a sense that what is encountered is holy or sacred; noetic quality – the experience is imbued with an aspect of meaning and a sense of encountering ultimate reality that is more real than usual everyday reality; positive mood – joy, ecstasy, blessedness, peace, tenderness, gentleness, tranquility, awe; transcendence of time and space – notions of time and space have no meaning during the experience; and ineffability – the experience is difficult to put into words. Stace also cited paradoxicality (the coexistence of mutually exclusive states or concepts) as a dimension of mystical experience, however the validity of that dimension has been questioned in subsequent empirical studies of mystical experience (Hood, 1975; MacLean et al., 2012).

Mystical experiences have been an active area of investigation in the experimental psychology literature, particularly within the psychology of religion (Hood 2009). The Mysticism Scale, a psychometric instrument that codifies the descriptive definition of mystical experience provided by Stace (Hood 1975; Hood et al. 2001) has been used extensively in this research.

4.1. Psilocybin and mystical experiences in healthy volunteers

The long historical use of naturally-occurring classic psychedelics by indigenous populations in ceremonial contexts is well documented (Westermeyer 1988; Wasson et al. 1978; Schultes et al. 2001). Psychoactive plants and fungi for which there is substantive knowledge of ceremonial use include peyote, ayahuasca, and psilocybin mushrooms. The reasons for such ceremonial use included medicinal and divination purposes, but a prominent goal of ceremonial consumption of classic psychedelics has also likely been to occasion mystical-type experiences (Roberts 2001).

The first experimental study to investigate the effects of a classic psychedelic on mystical experience was the so-called Good Friday experiment conducted by Walter Pahnke in 1962. The study involved administration of either 30 mg psilocybin (n = 10) or 200 mg nicotinic acid (n = 10) to seminary students in a private chapel on Good Friday during the broadcast of the traditional Good Friday religious service (Pahnke, 1963). After the experience, and at a 6-month follow-up, participants completed a questionnaire that assessed dimensions of mystical experience that were based on the model of mystical experience developed by Stace (1960a). The mean percentage of maximal possible score for the first 6 Stace dimensions of mystical experience (unity, sacredness, noetic quality, positive mood, transcendence of time and space, and ineffability) was 64.1% among subjects who received psilocybin (Pahnke, 1967b). Pahnke's criteria for a "complete" mystical experience are somewhat unclear, but it appears he considered such experiences as being defined by ratings of at least 60% of the total possible score (Pahnke, 1969) or at least 60% to 70% for each of 9 dimensions (unity, sacredness, positive mood, transcendence of time and space, noetic quality, ineffability, and paradoxicality, transiency, and persisting positive changes in attitudes and behaviors; Pahnke, 1967a). By this criterion, "3 or 4 of the ten psilocybin subjects reached the 60% to 70% level of completeness, whereas none of the control subjects did" (Pahnke, 1967a). In a 25-year follow-up to the Good Friday experiment, Doblin (1991) was able to contact 16 of the 20 original participants and collect additional retrospective ratings. That study found little change between the 6-month retrospective ratings and the 25-year retrospective ratings of mystical experience.

While groundbreaking, the Good Friday experiment had significant limitations, including limited generality due to the highly selective demographics of the participants (seminary students), conduct of the study in a group setting that allowed interactions among participants (thus resulting in nonindependence of individual subject data), explicit instructions to participants that some would and some would not receive psilocybin (thus creating powerful expectancy effects), and the fact that half of the researchers present during the study also received psilocybin. Not surprisingly, under these conditions, the blind was broken shortly after drug administration, which likely contributed to the assessed differences between groups (Doblin 1991; Wulff 1991; Smith 2000).

In a replication and extension of the Good Friday experiment, a double-blind crossover comparative pharmacology study was conducted of psilocybin (30 mg/70 kg) and methylphenidate (40 mg/70 kg) administered in separate sessions to each of 36 participants individually, with at least two months between sessions (Griffiths et al. 2006, 2008). Participants in this study were well educated, psychiatrically and medically healthy, had no prior psychedelic use, and represented a more general sample of the population than those used in the Good Friday experiment. The study reduced expectancy and group confounding effects by studying participants without personal histories of classic psychedelic use, by studying only a single participant at a time, and by using an experimental design and instructions that obscured the range of drug conditions that would be administered as well as the total possible number of sessions. The study also utilized a better control condition (methylphenidate) than the Good Friday experiment (nicotinic acid). Methylphenidate and psilocybin can both induce strong subjective effects with some similarities, and with a reasonably similar time course. Nicotinic acid, in contrast, has a relatively short time course and a profile of subjective effects that is very different from psilocybin. Finally, in addition to using a revised and updated version of the mystical experience questionnaire used in the Good Friday experiment, this study used two psychometrically validated questionnaires that assessed mystical and spiritual effects (the Hood Mysticism Scale and the Spiritual Transcendence Scale) as well as ratings of changes in participants' attitudes and behavior by community observers (family members and friends of participants).

In this and most subsequent studies from the Johns Hopkins laboratory, a 4-scale, 30-item Mystical Experience Questionnaire (MEQ30) was used. The factor structure of the MEQ30 is described in the text box. The MEQ30 is a shortened and psychometrically refined version of the original 43-item Mystical Experience Questionnaire (MEQ43) presented in the appendix to Griffiths et al., 2006. The MEQ30 was validated in both retrospective accounts of mystical experiences with psilocybin (MacLean et al. 2012) and in prospective, experimental laboratory studies with psilocybin (Barrett et al. 2015). The mean percentage of maximum total possible score for the Griffiths et al., 2006 study was 78% and 33% immediately after psilocybin and methylphenidate, respectively, and 76% 14 months after psilocybin (Barrett et al. 2015, appendix 3). Using scoring criteria for having a "complete" mystical experiences that were analogous but more precise than those used in the Good Friday study (i.e. ≥60 percent of the total possible score on each of four factors of the MEQ30), 61% of participants were scored as having had "complete" mystical experiences both at the end of the psilocybin session and at the 14-month follow-up (Barrett et al., 2015, appendix 3). In contrast, 7% of participants met criteria for a "complete" mystical experience at the end of the methylphenidate session. Two months after the session, most participants (71%) rated their psilocybin session as among the top five or single most spiritually significant experience of their lives, compared to 8% of participants after methylphenidate (Griffiths et al., 2006). Ratings of positive attitudes about life and self, positive mood, positive behaviors, and positive social effects 2 months after psilocybin sessions were significantly greater than those provided 2 months after methylphenidate sessions. Further, community observer ratings showed small but significant changes in participants' positive attitudes and behaviors 2 months after the psilocybin sessions, but no changes were found 2 months after methylphenidate sessions. In a 14-month follow-up report, 67% of participants rated their psilocybin session as among the top five most spiritually significant experiences of their lives, and 58% of participants rated their psilocybin session as among the top five most personally meaningful experiences of their

lives (Griffiths et al. 2008). Ratings of positive behavior, mood, attitude, and social changes associated with the psilocybin session at the 14-month follow-up were not significantly different from those provided 2 months post session. Correlation and regression analyses indicated a central role of mystical experience assessed on the session day, but not intensity of psilocybin experience, in predicting the high ratings of spiritual significance and personal meaning assessed at 14 months (Griffiths et al. 2008).

Four Factors in the Mystical Experience Questionnaire (MEQ30)

Factor 1: Mystical

Internal Unity

Experience of pure being and pure awareness (beyond the world of sense impressions).

External Unity

Experience of oneness or unity with objects and/or persons perceived in your surroundings.

Noetic Quality

Certainty of encounter with ultimate reality (in the sense of being able to "know" and "see" what is really real at some point during your experience.

Sacredness

Sense of being at a spiritual height.

Factor 2: Positive Mood

Experience of amazement.

Factor 3: Transcendence of Time and Space

Loss of your usual sense of time or space.

Factor 4: Ineffability

Sense that the experience cannot be described adequately in words.

The MEQ30 is a psychometrically validated retrospective measure of acute mystical experience (MacLean et al. 2012; Barrett et al. 2015). The four factors of the questionnaire are derived from a total of 30 items that probe seven dimensions (designated by underlines) of mystical experience that were identified by Stace (1960b). The Mystical factor is composed of 15 items probing four dimensions of the Stace model (internal unity, external unity, noetic quality, and sacredness). Positive Mood (6 items), Transcendence of Time and Space (6 items) and Ineffability (3 items) factors correspond to three separate dimensions of the Stace model. The psychometrically validated MEQ30 consists of a subset of items from the older MEQ43. Illustrative items are shown in italics. [Adapted from Barrett and Griffiths (2018)]

An extension of this line of research utilized a double-blind placebo-controlled design that assessed the effects of placebo and a range of psilocybin doses (Griffiths et al., 2011). Eighteen volunteers, with demographics generally similar to those in the previous study, participated. Volunteers received 5, 10, 20, and 30 mg/70 kg of psilocybin in separate sessions with at least one month between each session and a placebo session randomly placed within the sequence. Mystical experience was an increasing function of psilocybin dose (Griffiths et al., 2011; Barrett et al., 2015, appendix 3). The mean percentage of maximum total possible score on the MEQ30 on session days was 23%, 47%, 52%, 70%, and 77% after placebo and 5, 10, 20, and 30 mg/70 kg psilocybin. This score for 30 mg/70 kg at 14 months was 81%. The percentage of participants meeting criteria for a "complete" mystical experience on session days was 6%, 11%, 17%, 61%, and 67%, for placebo and the four doses of psilocybin, respectively. This percentage for 30 mg/70 kg at 14 months was 78%. Ratings 1 month after sessions of the spiritual significance of the experience and positive behavior change attributed to the experience also increased with dose. Eighty-three percent of participants rated the session experiences after 20 and/or 30 mg/70 kg as among the five most spiritually significant experiences of their life; 61% also rated at least one of these as the single most spiritually significant experience of their life. Likewise, 1 month follow-up ratings of positive attitudes about life and self, positive behavior, positive social effects, and increased spirituality generally increased as a function of psilocybin dose. One month follow-up ratings after the 20 or 30 mg/70 kg sessions did not differ from follow-up ratings 14 months after study completion. Finally, compared to pre-study ratings, community observers rated significant positive change in the attitudes and behaviors of participants 3 to 4 weeks after the final session and 14 months after the final session.

A further extension of this research explored the role of psilocybin-occasioned mystical experience in combination with meditation and other spiritual practices to produce enduring changes in trait measures of prosocial attitudes and behaviors (Griffiths et al., 2018). Participants were medically healthy and had relatively low rates of meditation and spiritual practices (e.g., 31% reported some level of current meditation; mean frequency of meditation for all participants was 1.1 times per month). Participants were randomized to one of three groups ($n = 25$ each): 1. very-low-dose (1 mg/70 kg on sessions 1 and 2) with moderate-level ("standard") support for spiritual-practice (LD-SS); 2. high-dose (20 and 30 mg/70 kg on sessions 1 and 2, respectively) with standard support (HD-SS); and 3. high-dose psilocybin (20 and 30 mg/70 kg on sessions 1 and 2, respectively) with high support for spiritual-practice (HD-HS). The standard spiritual support conditions consisted of 7 hours of individual meetings over the study, while the high support condition consisted of 35 hours of individual and group meetings. Meetings consisted of discussion and encouragement for daily meditation, spiritual awareness, and journaling practices. Psilocybin was administered double-blind and instructions to participants/staff minimized expectancy confounds. The proportion of participants who met criteria for having had a "complete" mystical experience on the MEQ30 immediately after sessions 1 and 2, respectively, were 0% and 4% (LD-SS), 48% and 50% (HD-SS), and 44% and 52% (HD-HS). Overall, 4%, 61%, and 64% of participants in the LD-SS, HD-SS, and HD-HS groups had "complete" mystical experiences at either or both sessions 1 and 2. The mean percentage of maximum total possible score on the MEQ30 collapsed across both sessions was 19%, 66%, and 74%, respectively for the LD-SS, HD-SS, and HD-HS groups. At 6 months, compared to LD-SS, both high-dose groups showed large significant positive changes on longitudinal measures of interpersonal closeness, gratitude, life meaning/purpose, forgiveness, death transcendence, daily spiritual experiences, religious faith and coping, and community-observer ratings. Hierarchical regression analysis was used to examine the relationship of mystical experience (MEQ30 scores) and specific spiritual practices to the various outcome measures that showed between-group differences at 6 months. This analysis indicated that both mystical experience and spiritual practices contribute to positive outcomes, with mystical experience making a substantially greater contribution. The fact that the measure of mystical experience preceded the assessment of outcome measures by 4-5 months strengthens the interpretation that mystical experience and/or its neurophysiological or other correlates are likely determinants of the enduring positive attitudinal, dispositional, and behavioral effects of psilocybin when administered under spiritually supported conditions.

Although the foregoing study of psilocybin combined with spiritual practices showed robust enduring changes in various trait measures suggesting healthy psychological functioning, the study showed equivocal effects on the personality domain of Openness. Specifically, the study showed that Openness increased from screening to 6 months in the HD-HS group but not in the HD-SS or LD-SS groups. However, there were no between-group differences in Openness at 6 months. Further analyses of these data did not show significant relationships between several measures of mystical-type experience and changes in

Openness. These findings contrast with the results from a previous analysis that showed that psilocybin-occasioned mystical experience was associated with increases in Openness from screening to 1–2 months and to 14 months after psilocybin (MacLean et al., 2011). Increases in Openness have been shown 2 weeks after administration of LSD in healthy individuals (Lebedev et al., 2016). The failure to observe significant increases in Openness in the most recent study might be attributable to engagement in the program of spiritual practices or to some other aspect of the study design.

In a recent study of psilocybin and mystical experience from Johns Hopkins University, Carbonaro et al. (2018) examined single, acute oral doses of psilocybin (10, 20, 30 mg/70 kg), dextromethorphan (DXM; 400 mg/70 kg), and placebo under double-blind conditions to 20 participants with histories of psychedelic use. DXM, an N-methyl-D-aspartate (NMDA) receptor antagonist, was used as a comparator in this study because it is sometimes used at high doses (e.g., ≥300 mg) as an atypical hallucinogen or psychedelic (Banken and Foster, 2008; Morris and Wallach, 2014). Volunteer preparation and session support were similar to previous studies. The mean percentage of maximum total possible score on the MEQ30 at the end of sessions increased with psilocybin dose and was significantly higher after 10, 20, and 30 mg/70 kg psilocybin (39%, 53% and 63%, respectively) than after placebo (8%). Furthermore, the mean percentage of maximum total possible score on the MEQ30 at the end of sessions was significantly higher after 20 and 30 mg/70 kg psilocybin (53% and 63%, respectively) than after DXM (40%). The proportion of volunteers who met a priori criteria for having had a "complete" mystical experience on the MEQ30 was: 0%, 0%, 20%, 40%, and 0% after placebo, 10, 20, and 30 mg/70 kg psilocybin, and DXM, respectively. The incidence of "complete" mystical experience after the 30 mg/70 kg psilocybin dose was significantly greater than after both placebo and DXM.

Barrett and Griffiths (2017) conducted a further analysis of psilocybin-occasioned mystical experience in 119 healthy volunteers by collapsing data at 30 mg/70 kg psilocybin across three studies (Griffiths et al., 2006, 2011, 2018). On the MEQ30 completed on session days, 57% of participants met criteria for a "complete" mystical experience, with the mean percentage of maximum total possible score being 73%. In retrospective follow-up ratings, most participants rated this session experience in the top five most personally meaningful (66%) or spiritually significant (68%) in their lives, with 70% rating moderate or greater positive behavior change that they attributed to the session experience.

4.2. Psilocybin and mystical experiences in therapeutic trials

As previously detailed in Sections 2.1 and 2.3, four studies have assessed psilocybin-occasioned mystical experience in the context of therapeutic trials. All four of these studies showed that psilocybin produced significant increases in mystical experience scores and, consistent with the previous studies showing associations between mystical experience and enduring positive outcomes (Griffiths et al., 2008, 2011), these therapeutic studies suggest similar associations with therapeutic outcomes.

As described in Section 2.1, two studies showed that psilocybin produces substantial and enduring decreases in symptoms of anxiety and depression among patients with a life-threatening cancer diagnosis (Griffiths et al., 2016; Ross et al., 2016). For the Griffiths et al. (2016) study, mean percentage of maximum total possible score on the MEQ30 was significantly higher immediately after the high dose (64%) than after the lower dose (27%). These scores after the first session were significantly correlated with most of the enduring changes in therapeutic outcome measures 5 weeks later. For most measures, this relationship continued to be significant when the intensity of overall psilocybin effect was controlled for in a partial correlation analysis, suggesting that mystical-type experience per se has an important role apart from overall intensity of drug effect. Furthermore, analysis suggested that mystical-type experience was a mediator in positive therapeutic response. Similar to these results, the Ross et al. (2016) study found that the mean percentage of maximum possible total score on the MEQ30 was higher immediately after psilocybin than after niacin (estimated from figures as approximately 66% and 10%, respectively), and correlation analysis controlling for intensity of drug effect and a mediation analysis suggested that mystical experience was a mediator of the therapeutic effects.

As described in Section 2.3, two open-label pilot studies of psilocybin in the treatment of substance dependence have reported data consistent with these findings. In the smoking cessation study (Johnson et al., 2014), mystical experience was assessed with the MEQ43. Nine of 15 participants (60%) had a "complete" mystical experience during one or more of her/his multiple psilocybin sessions (Garcia-Romeu et al., 2014). In 10 of the 13 (77%) sessions in which a "complete" mystical experience occured, it occurred during a high dose (30 mg/70 kg) rather than a moderate dose (20 mg/70 kg) session. Across all psilocybin sessions the mean percentage of maximum total possible score on the MEQ43 was 63%. Significant correlations between mean MEQ43 total scores and smoking craving change scores ($r = -.65$) and urine cotinine ($r = -.56$) were found at the 6-month follow-up. Finally, those participants who showed stronger mystical experiences on psilocybin session were more likely to be successful in quitting smoking (Garcia-Romeu et al., 2014). In the pilot study of alcohol dependence (Bogenschutz et al., 2015), the mean percentage of maximum total possible score on the MEQ43 was 47% ($n = 10$) and 39% ($n = 6$) on session 1 (21 mg/70 kg) and 2 (28 mg/70 kg) respectively. Positive change in drinking was significantly correlated with MEQ43 as well as with other measures of intensity of psilocybin effect.

4.3. Lysergic acid diethylamide (LSD) and mystical experiences

The effects of LSD on mystical experience are of particular interest, as LSD is another classic serotonergically mediated psychedelic. Liechti et al. (2017) present results on the effects of LSD in two studies: 1. a double-blind cross-over study in 16 healthy volunteers comparing placebo and 200 micrograms of LSD; and 2. a double-blind cross-over study in 12 anxious patients with life-threatening diseases comparing 200 micrograms of LSD to a low, placebo-like LSD dose (20 micrograms; Gasser et al., 2014). Estimated mean percentage of maximum total possible score on the MEQ30 was 61% and 2% for LSD and placebo respectively in the healthy volunteers, and 50% and < 5% for 200 micrograms of LSD and 20 micrograms of LSD respectively in the patients. The percentage of participants meeting criteria for a "complete" mystical experience after 200 micrograms of LSD was 12.5% in the healthy volunteers and 17% in the patients. Whether this seemingly lower rate of mystical experience after LSD than psilocybin reflects pharmacodynamic differences between these drugs, the use of a relatively lower dose of LSD than psilocybin, and/or differences between the studies in set, setting, or participant characteristics is unknown. Future research should directly compare LSD and psilocybin within subjects, ideally using procedures to minimize expectancy effects.

5. Brain network changes as mechanisms underlying classic psychedelic effects

The brain is composed of many levels of embedded complex systems. These systems have modularity, in the sense that individual nodes or brain regions that subserve certain individual functions (such as representing line orientation, brightness, and hue of a visual stimulus) are segregated from nodes that serve other functions (such as nodes that represent sounds or bodily sensations, or nodes that represent tactile sensation or motor movement). The embedded complex systems of the brain also require integration (i.e.,connection and communication) between nodes in order to support efficient communication between modules that underlie complex processes (such as hand-eye coordination). A balance of modularity

and efficient integration is necessary to support normal waking consciousness.

Resting-state fMRI connectivity analyses have shown that, under normal conditions, communication between areas of the brain is organized into stable networks (Yeo et al., 2011; Power et al., 2011; Doucet et al., 2011) that demonstrate both modularity and integration (Sporns, 2011). Commonly identified networks underlie sensory, motor, and cognitive processes (Smith et al., 2009, Shirer et al., 2012) and have features that are unique between individuals and stable enough within-individuals that separate scans from the same individual can be identified with very high accuracy (99% or greater) in a large database of scans ("connectome fingerprinting"; Finn et al., 2015; Airan et al., 2016). In such fingerprinting analyses, connectivity among higher-order brain regions involved in self-referential processing and attention show the greatest inter-individual differences and typically contribute most to identifying an individual's connectivity pattern within a large database of connectivity patterns (Finn et al., 2015; Airan et al., 2016). Individual differences in the connectivity of these networks may in a sense constitute an individual's "neural identity."

While typically observed brain networks are reliably found under normal circumstances in resting-state functional connectivity data, activity and correlation within (modularity) and between (integration) these networks has been shown to decrease during the acute effects of psilocybin (Carhart-Harris et al., 2012a; Muthukumaraswamy et al., 2013), ayahuasca (Palhano-Fontes et al., 2015), and LSD (Carhart-Harris et al., 2016b, Speth et al., 2016). In particular, activity and connectivity of brain regions crucial to self-referential processing (including regions of the DMN such as the posterior cingulate cortex) are most strongly impacted by classic psychedelics (Carhart-Harris et al., 2012a, 2016b; Palhano-Fontes et al., 2015). Decoupling and decreased modularity of typically observed large-scale/long-range brain networks has been shown (Lebedev et al., 2015), and during acute drug effects, the brain reorganizes into new, local range networks (Petri et al., 2014). An increased number of distinct patterns in the brain compared to normal waking consciousness has been demonstrated with both psilocybin (Tagliazucchi et al., 2014) and LSD (Schartner et al., 2017), and the overall connectivity and global integration of the brain was shown to increase in a manner that was correlated with subjective reports of "ego dissolution" during LSD[1] (Tagliazucchi et al., 2016). Changes in the brain during the acute effects of classic psychedelics have more generally been associated with subjective effects including "dissolution of the self or ego" (Carhart-Harris et al., 2014) and mystical-type (Barrett and Griffiths, 2017) or spiritual (Kometer et al., 2015) experiences that may have therapeutic value (Garcia-Romeu et al., 2014; Griffiths et al., 2016; Ross et al., 2016; Barrett and Griffiths, 2017).

Overall, the acute effects of classic psychedelics on measures of systems-level neural functioning have included a decrease in both modularity and integration of commonly identified brain networks, and a reconfiguration of communication in the brain. Increased brain entropy[2], which is a physical measure of increased randomness or uncertainty within a system, has been proposed as a mechanism of acute altered states of consciousness with psilocybin (Carhart-Harris et al., 2014) and LSD (Lebedev et al., 2016; Schartner et al., 2017). While this large-scale principle may be at work in the brain during an experience with a classic psychedelic, it does not explain the formation of new, local networks in the brain (Petri et al., 2014) or the observed increases in the number of distinct patterns in the brain compared to normal waking consciousness (Tagliazucchi et al., 2014). An account of temporary and structured reconfiguration of the brain, rather than only increased randomness in the system (entropy), is more consistent with reported data.

Electro- and magneto-cortical studies have demonstrated a broadband reduction of oscillatory power (i.e., decreased brainwave amplitude), and especially low-frequency oscillations (alpha band), by psilocybin (Kometer et al., 2013, 2015, Muthukumaraswamy et al., 2013) and ayahuasca (Riba et al., 2002, 2004, Valle et al., 2016). While oscillations in the same frequency band can serve different functions in different regions of the brain (e.g., theta band oscillations in the hippocampus may not serve the same function as theta band oscillations in the thalamus), lower-frequency oscillations are generally known to modulate information in higher frequencies (Buzsaki et al., 2013). In particular, alpha band synchrony modulates attention and information selection processes that are subserved in higher frequency bands (e.g., gamma; Klimesch, 2012), and serves a specific role in modulating top-down cortical control, which allows for maintenance of integration and modularity of brain networks through altering the transient coupling between and among networks of brain areas (Bazanova and Vernon, 2014). Synchronization of alpha oscillations between parahippocampus, retrosplenial (near posterior cingulate cortex or PCC), and lateral orbitofrontal cortices (regions associated with the DMN) is associated with psilocybin-induced spiritual experience (Kometer et al., 2015), and decreases in alpha power in the PCC are associated with psilocybin-induced "disintegration of the self or ego" (Carhart-Harris et al., 2014). Thus, decreased alpha synchrony in the brain may be an electrocortical mechanism resulting in decreased integration and modularity of typically observed brain networks, and may be critical to the formation of temporary, new, local and stable networks (Petri et al., 2014) and distinct patterns of activity (Tagliazucchi et al., 2014) that are observed during acute classic psychedelic drug effects.

While fMRI, EEG, and MEG measures have primarily shown classic psychedelics to produce an overall reduction in activity and connectivity in the brain, early molecular imaging studies, including PET and SPECT demonstrated various signs of increased brain activity during acute effects of psilocybin (Vollenweider et al., 1997, 1999, Gouzoulis-Mayfrank et al., 1999) and mescaline (Hermle et al., 1992). Along with reports of decreased measures of metabolic activity in subcortical (e.g., thalamus) and posterior (e.g., parietal, occipital, temporal) regions, these molecular imaging studies found a relative increase in activity of frontal brain regions in particular to be a prominent acute neural effect of classic psychedelic drugs. Evidence suggesting a resolution of this discrepancy in the literature was recently provided (Lewis et al., 2017), showing that an overall decrease in brain activity is found when assessing the effects of classic psychedelics on global or absolute cerebral blood flow, and findings of hyperfrontality are recovered when calculating relative cerebral blood flow, which controls for global changes in blood flow. The implication of this finding is that, while overall blood flow may decrease in the brain during the effects of classic psychedelics, these blood flow decreases are not as substantial in prefrontal brain regions in that some frontal regions may be partially spared in relation to posterior brain regions. However, it has yet to be determined whether these relative differences in activity observed in early PET studies relate to increases or decreases in modularity or integration of brain networks. Also, it is as yet unclear whether overall decreases in blood flow, or the relative balance of frontal activity relative to activity in other brain regions, is more directly responsible for the acute effects of classic psychedelics. It is likely that both processes contribute to the unique character of experiences occasioned by the administration of classic psychedelics.

[1] These reports were collected by asking volunteers to respond to questionnaire items such as "I experienced a dissolving of my self or ego" though it is not clear that any further definition was given to volunteers for the terms "self" or "ego."

[2] Entropy as utilized by Carhart-Harris et al. (2014) was formally calculated as the Shannon entropy of intra-brain-network synchrony – more specifically, the negative logarithm of the probability distribution of the variance in the synchrony between nine canonical brain networks. To the degree that only a single event within a probability distribution of a function occurs with high probability, the probability distribution will not be flat, and the frequency of events generated from that distribution will be far less random (or far more predictable) than a probability distribution in which all events occur with equal probability and from which any given event will be nearly unpredictable (or generated from a stochastic process). The former case is a case with very low entropy, and the latter case is a case with very high entropy. Thus, entropy can be used as a formal measure of the randomness or uncertainty within a system.

5.1. Relation of neural effects to therapeutic effects

The DMN consists primarily of the posterior cingulate cortex (PCC), medial prefrontal cortex (MPFC), and lateral parietal cortex (LPC). The PCC is involved with internally-directed cognition (Leech and Sharp, 2014), the MPFC (and adjacent region of the subgenual anterior cingulate, or sgACC) is implicated in rumination (Cooney et al., 2010; Berman et al., 2011; Kucyi et al., 2014), autobiographical memory recall (Svoboda et al., 2006), self-related judgements and theory of mind processes (Gilbert et al., 2006; Denny et al., 2012), and the LPC has been implicated in a number of processes, including empathy (Kubit and Jack, 2013) and coding a sense of self in spatial cognition (Amorapanth et al., 2010). Impaired connectivity of DMN brain regions to non-DMN brain regions in major depression is associated with greater disorder severity (Seminowicz et al., 2004), and abnormally high connectivity among regions of the DMN and abnormally low connectivity between DMN and executive networks have been implicated in the pathophysiology of major depression (Leibenluft and Pine, 2013). Lower connectivity within the DMN, greater connectivity of sgACC to DMN regions, greater connectivity of sgACC to executive network regions, and greater connectivity within the executive network predict better medication treatment response (Dichter et al., 2015). Neuropathological, molecular imaging, and targeted brain stimulation treatment studies demonstrate that dysregulation of an extended network of brain regions in major depression may originate in abnormalities in medial frontal regions of the DMN (Price and Drevets, 2012). DMN connectivity is normalized along with depressive symptoms after transcranial magnetic stimulation (TMS) of the dorsolateral prefrontal cortex, deep brain stimulation of the subgenual anterior cingulate (Mayberg et al., 2005; Lozano et al., 2012), and electroconvulsive therapy (Cano et al., 2016). This demonstrates a functional relationship between DMN and frontal cortex function and depression. It may be that acute reconfiguration of brain networks during the effects of classic psychedelics, which strongly impact DMN and frontal brain activity and connectivity, lead to lasting alterations in these networks that represent a systems-level mechanism by which classic psychedelics may have efficacy in treating depression. However, the enduring effects of classic psychedelics on the brain have not yet been demonstrated.

A growing body of evidence suggests that traditional antidepressants, as well as novel medications effective in treatment-resistant depression, exert their therapeutic efficacy via the indirect, downstream action of glutamate (Cryan and O'Leary, 2010; Deutschenbaur et al., 2016; Duman et al., 2012; Duman and Voleti, 2012; Dutta et al., 2015; Sanacora et al., 2008; Skolnick et al., 2009, Krystal et al., 2013). Depressed patients have lower glutamate/glutamine levels at baseline (Hasler and Northoff, 2011) and reduced baseline glutamate levels are positively correlated with subsequent antidepressant response to ketamine (Salvadore et al., 2012). Biophysical computational models have implicated specific dysfunction of the glutamatergic activity in medial frontal regions of the DMN as the mechanism that underlies impairments in functional connectivity of this region in major depressive disorder (Ramirez-Mahaluf et al., 2017). Recent magnetic resonance spectroscopy (MRS) studies demonstrate that psilocybin decreased blood oxygenation level dependent (BOLD) activity and increased glutamate concentration in healthy individuals in the anterior cingulate cortex (ACC; Preller et al., 2016), in a manner consistent with therapeutic response in the ACC in patients who are being treated for depression. Thus, a molecular mechanism of action of classic psychedelics may be to alter the connectivity and activity of brain regions implicated in the pathophysiology of depression by altering glutamatergic functioning in these regions (Vollenweider and Kometer, 2010).

If a hyperactive and hyperconnected DMN underlies depression, a hypoactive and hypoconnected DMN may underlie addiction. The cycle of addiction is now understood to relate to a disruption of the balance between reward and limbic brain circuitry and top-down cortical control (including control from prefrontal/executive networks and the DMN) (Volkow et al., 2016). DMN and prefrontal/executive network connectivity is decreased in chronic cocaine (Gu et al., 2010), nicotine (Cole et al., 2010), and heroin (Jiang et al., 2011) users. The typically observed balance between activity and connectivity of DMN and prefrontal/executive networks is also altered during craving in volunteers with substance use disorders (Lerman et al., 2014, Sutherland et al., 2012, Lu et al., 2014). Reduction of craving and withdrawal symptoms may result from normalization of these abnormal connectivity patterns (Cole et al., 2010). Similar to depression, acute and/or lasting reconfiguration of brain networks, in particular prefrontal and DMN regions, by classic psychedelics may represent systems-level mechanisms supporting therapeutic effects of classic psychedelics.

5.2. Insights into the biological basis of consciousness

Neurobiological studies of the effects of classic psychedelics have yielded insights that may be relevant to understanding the biological basis of consciousness. It is notable that conscious awareness can be maintained during classic-psychedelic experiences (i.e., experiences resulting from the administration of a classic psychedelic), yet this conscious awareness appears to be vastly different than normal waking consciousness. During classic-psychedelic experiences, the underlying functional connectivity of the brain is also vastly altered. This suggests that there may be a relationship between the changes in functional brain connectivity during classic-psychedelic experiences and the changes in consciousness that are encountered during classic-psychedelic experiences. Communication within and between networks of brain regions may constitute a biological carrier signal on which awareness and a sense of self emerges, but conscious awareness need not be constrained by the typical patterns of communication between and within brain networks. Thus, not only does the brain show plasticity, but we are learning clearly that discrete interventions that vastly alter brain communication can be achieved with classic psychedelics, and these alterations may be the neurobiological basis of quantum change sometimes observed behaviorally after the administration of classic psychedelics.

6. Conclusions

Contemporary therapeutic research with classic psychedelics has shown promising effects for both cancer-related psychological distress, and addiction to both tobacco and alcohol. In addition, basic scientific studies using classic psychedelics have led to numerous advances in the experimental study of mystical experiences and the study of classic psychedelic mechanisms of action. Perhaps most importantly, neurobiological studies of the effects of classic psychedelics have yielded insights into the biological basis of consciousness. Specifically, these studies collectively suggest the possibility that the pattern and structure of communication between brain networks constitutes the neurobiological basis of consciousness, such that alterations of consciousness are driven by alterations of communication between brain regions. Interestingly, large-scale epidemiological studies of naturalistic classic psychedelic use are consistent with contemporary clinical research, and point to intriguing future trends, namely the application of classic psychedelics in forensic settings.

Promising recent results have been published for cancer-related psychological distress, using both psilocybin and LSD, replicating one major focus of the earlier era of classic psychedelic research. Many of these studies have shown such findings using rigorous double-blind procedures that vary in methods. Consistent signals of efficacy in the face of such variations suggest a robust clinical response. In the United States, if future phase 3 research supports these preliminary findings showing the safety and efficacy of psilocybin in the treatment of cancer-related psychological distress, non-research therapeutic use of psilocybin, under appropriately restricted safeguards adhering to strict

safety standards (Johnson et al., 2008), may eventually warrant regulatory approval. Additionally, pilot research on treatment-resistant depression also shows preliminary promise in response to classic psychedelic treatment outside of the context of cancer. If such findings are demonstrated in randomized studies, classic psychedelics may be poised as breakthrough medications for the leading cause of worldwide disability, affecting over 300 million human beings (World Health Organization, 2017). Although the clinical research agenda on addictions is at a lesser stage of development in comparison to cancer-related psychological distress, with only open-label pilot studies having been completed thus far in contemporary research (Bogenschutz et al., 2015; Johnson et al., 2014), if randomized clinical trials continue to suggest safety and efficacy, clinical approval of the use of psilocybin for the treatment of specific addiction may also be on the horizon.

If safety and efficacy are sufficiently demonstrated to warrant approved therapeutic use of one classic psychedelic (e.g., psilocybin, LSD), this would suggest the potential therapeutic potential of additional compounds of the same class. In the typical clinical development of other drug classes (e.g., benzodiazepines), a seminal compound of the class is identified and developed for therapeutic use (e.g., chlordiazepoxide), followed by the discovery and therapeutic development of additional compounds of the class over the subsequent decades. However, the clinical development of classic psychedelics may be unique, in that hundreds of psychoactive compounds related to this class have already been identified (e.g., Shulgin and Shulgin, 1991; Shulgin and Shulgin, 1997). Therefore, the broad array of classic and novel psychedelic compounds that have been universally ignored in pharmaceutical drug development may soon constitute a library of potential therapeutics. They may also help to inform the biological mechanisms of human consciousness.

Conflict of interest statement

Roland R. Griffiths is on the Board of Directors of the Heffter Research Institute. The authors declare that there are no other conflicts of interest.

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