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Long-term effects of psychedelic drugs: A systematic review

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ABSTRACT

Research into the basic effects and therapeutic applications of psychedelic drugs has grown considerably in recent years. Yet, pressing questions remain regarding the substances' lasting effects. Although individual studies have begun monitoring sustained changes, no study to-date has synthesized this information. Therefore, this systematic review aims to fill this important gap in the literature by synthesizing results from 34 contemporary experimental studies which included classic psychedelics, human subjects, and follow-up latencies of at least two weeks. The bulk of this work was published in the last five years, with psilocybin being the most frequently administered drug. Enduring changes in personality/attitudes, depression, spirituality, anxiety, wellbeing, substance misuse, meditative practices, and mindfulness were documented. Mystical experiences, connectedness, emotional breakthrough, and increased neural entropy were related to these long-term changes in psychological functioning. Finally, with proper screening, preparation, supervision, and integration, limited aversive side effects were noted by study participants. Future researchers should focus on including larger and more diverse samples, lengthier longitudinal designs, stronger control conditions, and standardized dosages.

1. Introduction

Psychedelic drugs have been used by humans for hundreds—if not thousands—of years for recreational, spiritual, and healing purposes (Jay, 2019). These substances have the capacity to induce intense shifts in consciousness and cognition through transient changes in emotions (Roseman et al., 2019), perceptual processing (Kometer and Vollenweider, 2016), one's sense of self (Lebedev et al., 2015), and feelings of connectedness (Carhart-Harris et al., 2018c). Scientific interest into their effects grew slowly throughout the early 20th century and boomed during the 1950s and 60s (Aday et al., 2019a; Grinspoon and Bakalar, 1997) before a tightening of pharmaceutical regulations restricted research (Oram, 2016; Strassman, 1991). Clinical psychedelic science remained relatively dormant until the early-1990s and has since seen a resurgence (Aday et al., 2019c).

There is emerging evidence that, in carefully screened and monitored volunteers, psychedelic-assisted psychotherapy can be a potent treatment option for depression (Carhart-Harris et al., 2016a), anxiety (Gasser et al., 2014), obsessive-compulsive disorder (OCD; Moreno et al., 2006), substance misuse (Bogenschutz et al., 2018; Johnson et al., 2014), and end-of-life distress (Griffiths et al., 2016). However, one of the most pressing questions from patients, regulatory bodies, the general public, and the broader scientific and psychiatric communities, regards the long-term effects of psychedelic drug administration—specifically, how long do the positive outcomes last? Although several individual studies in recent years monitored sustained effects, findings have yet to be systematically aggregated. To remedy this gap, this review synthesized the contemporary psychedelic experimental studies examining long-term changes in human subjects. Results from earlier research as well as recent correlational and naturalistic studies are first summarized but were excluded from our systematic search in order to narrow our scope and strengthen confidence in our conclusions. We use 1994 as our cutoff year for the new era of psychedelic research because Strassman et al.'s (1994) study was the first to administer classic psychedelic compounds after several decades of prohibition in the US. Although, it should be acknowledged that psychedelic studies began to reemerge in other parts of the world around the same time (Hermle et al., 1992).

1.1. Early research (pre-1994)

To begin, it may be useful to review the long-term experiments conducted during the first era of psychedelic research. However, the utility of historical studies is an area of contention among researchers, primarily because of the primitive methodological standards of the period (e.g., lack of blinding, lack of independent raters, undetailed reporting of methodology). Nevertheless, results have much to offer in terms

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of generating hypotheses and corroborating contemporary findings (Bonson, 2018). McGlothlin et al. (1967) utilized methodology generally comparable to today when evaluating the effects of 200 *ug* of d-lysergic acid diethylamide (LSD) against amphetamine or a low-dose of LSD (25 *ug*) in healthy participants. At the 6-month follow-up, 33% of participants in the high-dose LSD group experienced less anxiety compared to 13% and 9% for the amphetamine and low-dose LSD groups, respectively. Further, 50% in the 200 *ug* LSD group reported "enhanced understanding of self and others" compared to 11% across the two control groups. Interestingly, the most common changes in the high-dose LSD group at the 6-month follow-up were enhanced appreciation of music (62%) and art (46%). Validating these subjective reports, the researchers found that 6 months post-drug administration, the high-dose group had significantly higher number of records bought, time spent in museums, and number of musical events attended.

Adverse reactions and case reports of symptoms resembling hallucinogen persisting perception disorder (HPPD) began to appear in the literature during this period as well (Sandison and Whitelaw, 1957; Horowitz, 1969; Rosenthal, 1964). There is considerable variability in symptoms experienced by those with HPPD, but the most common effects include afterimages of color, "floaters" in field of vision, difficulty concentrating, and tinnitus, persisting after using a psychoactive drug. Type I HPPD involves transient flashbacks, whereas Type II is more chronic and invasive. To the best of our knowledge, there are no reliable and direct prevalence estimates of Type I nor Type II HPPD from the first era of research, although Cohen (1960) surveyed researchers working with LSD or mescaline and reported no lasting adverse side effects across roughly five thousand participants. Strassman (1984) reviewed the adverse effects attributed to psychedelic drug administration across recreational and early experimental settings, and found that use was occasionally associated with reports of suicide and prolonged psychotic reactions. Additionally, research suggesting that LSD may cause chromosomal damage generated considerable publicity during the 1960s (Cohen, Hirschhorn, & Frosch, 1967). While these studies were ultimately refuted for methodological confounds (Dishotsky, Loughman, Mogar, & Lipscomb, 1971; Long, 1972), retraction of the findings did not draw the same media attention as the original work. In their evaluation of adverse reactions, McWilliams and Tuttle (1973) concluded there was a low risk of long-lasting negative psychological side effects when LSD is used by healthy individuals in controlled settings compared to those with unstable psychiatric disorders or in crisis situations.

1.2. Contemporary correlational studies (1994–present)

Correlational research assessing differences between psychedelic users and non-users can also provide insight into long-term differences associated with psychedelic use. However, it is important to keep in mind the inherent methodological limitations associated with correlational studies (i.e., inconclusive causality, selection bias, recall bias, etc.). Despite these limitations, this research has documented that lifetime history of psychedelic use—but not other illicit drug taking—was related to reduced past month psychological distress and suicidality (Hendricks et al., 2015), and not linked to mental illness (Johansen and Krebs, 2015). Forstmann and Sagioglou (2017) found that lifetime experience with psychedelics predicted increases in pro-environmental behavior, and these changes were explained through heightened nature relatedness. A neuroimaging study compared ayahuasca users with controls matched for sex, age, years of education, as well as verbal and fluid IQ (Bouso et al., 2015). Users had reduced cortical thickness in the posterior cingulate cortex (PCC), a main hub of the default mode network (DMN), and this was related to greater intensity and duration of ayahuasca use. These results indicate that, in addition to the psychological differences between psychedelic users and non-users, there may be structural differences in the brain as well. Pisano et al. (2017) found that psychedelic users were at a 40% reduced risk of abusing opiates in the year prior to the study. Psychedelic users also have lower rates of prison recidivism than non-users (Hendricks et al., 2014), and male users are less likely to perpetrate intimate partner violence (Thiessen et al., 2018). Finally, Type II HPPD seems to be relatively rare, with an estimated 1/50,000 psychedelic users meeting criteria (Halpern et al., 2016). Although limited, correlational research supports the notion that there are long-term differences in various aspects of neuropsychological functioning between psychedelic users and non-users.

1.3. Contemporary naturalistic research (1994–present)

The majority of funding for experimental studies administering psychedelics has been limited to private donors and non-profit foundations, and there are immense regulatory hurdles in administering Schedule I drugs to humans, both of which have restricted the number of recent investigations in psychedelic research. Therefore, some researchers have used naturalistic survey study designs to circumvent these hurdles (Mason et al., 2019; Sampedro et al., 2017). For others (e.g., anthropologists), naturalistic designs are preferred to enhance ecological validity. This research has predominantly recruited participants visiting psychedelic retreats in countries where the practice is legal or unregulated. Although this can increase the methodological rigor compared to correlational research, naturalistic studies can also be limited by a number of factors including potentially unstandardized dosages, unknown drug purity, self-selection biases, lack of control groups, and expectancy effects. Yet, they can be a viable low-cost option for testing research hypotheses, yielding results that are useful for a still growing field like psychedelic science.

One such naturalistic study followed-up on first-time ayahuasca users six months after taking the drug in an urban Brazilian religious setting. Participants exhibited decreases in intensity of minor psychiatric symptoms and bodily pain, as well as heightened wellbeing, confidence, optimism, and independence (Barbosa et al., 2009). Uthaug et al. (2018) reported that ayahuasca ceremony attendees exhibited decreased stress and depression four weeks after consumption. Level of "ego dissolution" (i.e., a loss of a sense of self; Lebedev et al., 2015), experienced during the ceremony seemed to be an important factor as it predicted changes in affect, life satisfaction, and mindfulness. Similarly, Uthaug and colleagues (2019) examined the long-term effects of a single inhalation of 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT), a potent hallucinogen secreted by the Sonoran desert toad and produced synthetically. At the one-month follow-up, participants reported increased life satisfaction, mindfulness (non-judgement and awareness), and convergent creativity as well decreased measures of depression, stress, and anxiety (Uthaug et al., 2019); consistent with previous research, ratings of ego dissolution were associated with positive long-term changes in affect.

Other naturalistic studies have utilized large-scale survey methods to examine the outcomes of psychedelics used in the natural environment. For example, Davis et al. (2019) found that use of 5-MeO-DMT in a naturalistic group setting was associated with improvements in depression and anxiety, and a large survey of 5-MeO-DMT users in the general population found that use of the drug was associated with improvements in substance use problems, post-traumatic stress disorder, depression, and anxiety (Davis et al., 2018a). Additionally, several studies have documented the effect of psychedelic use on substance use problems, indicating that these drugs could show promise for people with alcohol and other substance use problems (Garcia-Romeu et al., 2019). For example, surveys conducted among people with an opioid use disorder who sought ibogaine treatment at a clinic in Mexico have documented the effectiveness of this treatment, wherein approxi-

mately 80% of respondents reported that ibogaine eliminated or drastically reduced their withdrawal symptoms in the short-term, and 41% reported sustained abstinence from opioids at the time of the survey (Davis et al., 2017, 2018b). Collectively, these results offer further evidence of long-term psychological changes attributed to experience with psychedelics and preliminary insight into their mechanisms.

1.4. The current review

The growing pace of psychedelic research necessitates a review of the field's current understanding of the long-term effects of psychedelic drugs. The limitations associated with historical, correlational, and naturalistic research make them less-ideal candidates for this analysis. Our systematic review filled this crucial gap in the literature by searching for articles which utilized psychedelic drugs, human samples, experimental designs, follow-up measures of at least two weeks latency, and were published within the contemporary era of psychedelic research. This analysis of the literature can coalesce the field's current understanding of the long-term effects of psychedelic drugs—a pressing scientific and public question.

2. Material and methods

2.1. Objectives and search strategy

This review synthesized the contemporary experimental research on the long-lasting effects of psychedelic drugs in human subjects. To this end, we wrote summaries and methodological critiques for each study retrieved from a search conducted in accordance with PRISMA guidelines (Moher et al., 2009). Our protocol required searchers to document the sample type, drug, drug dosage, latency of follow-up measures, and type of long-term measures collected. To ensure that our investigation was exhaustive, two of the authors (JSA & CMM) each conducted the search twice using two different search engines, PubMed and ProQuest (Fig. 1). Discrepancies regarding inclusion were resolved with consultation among the research team.

2.1.1. PubMed

Established in 1997, PubMed is a premiere search engine for researchers and clinicians and has been utilized in previous systematic reviews of psychedelic science (e.g., Bouso et al., 2018; dos Santos et al., 2016). Six psychedelic-related (e.g., "ayahuasca," "LSD," "lysergic acid diethylamide," "mescaline," "n, n-dimethyltryptamine," and "psilocybin") and fifteen long-term-related (e.g., "chronic," "continuing," "durable," enduring," "follow-up," "lasting," "lingering," "long-lasting," "long-term," "longitudinal," "non-acute," "ongoing," "persisting," "prolonged," and "residual") search terms were systematically cross-referenced into PubMed's search engine for a total of 90 distinct searches (e.g., "ayahuasca chronic," "ayahuasca continuing," etc.). Articles were initially filtered for language (English), species (human), and year (1994–2019). While Strassman et al. (1994) motivated this cutoff date for the new era of psychedelic research, this study was excluded from our results because no long-term measures were collected.

2.1.2. ProQuest

ProQuest is an online search engine with an extensive archive of scientific research articles. Our ProQuest search used the same 90 search combinations as the PubMed search and included the same filters.

2.2. Selection criteria

In addition to our initial filters for year, language, and species, articles returned from our search were examined for those that also met the criteria: they were experimental studies, published in peer-reviewed journals, administered classic psychedelic drugs (e.g., LSD, psilocybin, mescaline, or ayahuasca/DMT), measured psychological or neurological outcomes, and used follow-up latencies that were at least two weeks. Naturalistic studies as well as correlational research, book chapters, reviews, and case reports were excluded. Studies were also required to provide unique datasets, even if they had overlapping samples with other articles. For clarity, we explicitly identify when studies used overlapping samples.

3. Results

3.1. Study selection

Our 90 PubMed and ProQuest searches yielded 984 and 892 articles, respectively. From these results, we utilized our selection criteria to reduce the list to 26 articles and added 8 others which were found outside of our systematic search (4 of which were published after our search was conducted), resulting in 34 articles which were included in the review. Given the relatively high number of studies which met

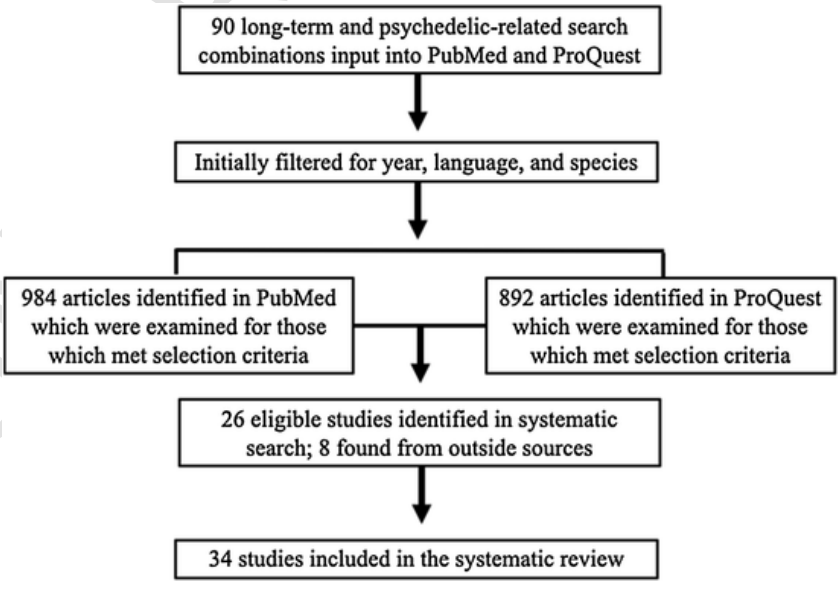

Fig. 1. Flow Diagram. Flow diagram depicting the search process for the systematic review.

our selection criteria, we do not provide individualized sections for each study as recommended by PRISMA guidelines; instead, this general information is encapsulated by Table 1.

3.2. Descriptives

We begin with a descriptive analysis of our findings to broadly characterize the long-term sequelae examined in contemporary psychedelic studies (Table 2). First, although our search filters included the years 1994–2019, the year range of the 34 articles was 2006–2020, and the majority of this work was published in the last five years. Indeed, the mean and median year of the included studies was 2016, indicating that this is a growing area of research. The most common sample that was studied and included a long-term assessment was depressed individuals (10 studies), followed by healthy volunteers (9 studies), those with end-of-life distress (7 studies; many of which were also depressed/anxious), tobacco use disorder (4 studies), spiritually active individuals (2 studies), alcohol use disorder (1 study), and meditators (1 study). Psilocybin was the most common drug administered in these studies (28 studies), followed by LSD (5 studies) and ayahuasca (1 study). Samples were generally small, with a range of 6–75 participants (M = 16.81, SD = 9.80), and roughly half included control conditions (i.e., 15/34 studies). The most prevalent long-term follow-up measures assessed personality/attitudes (14 studies), depression (11 studies), spirituality (10 studies), wellbeing/quality of life (9 studies), anxiety (8 studies), affect/mood (7 studies), qualitative analyses (4 studies), tobacco use (3 studies), alcohol consumption (1 study), mindfulness (1 study), and meditative practices (1 study).

3.3. Changes by outcome measure

Next, it may be useful to review how many studies showed change across each individual outcome measure. Our search returned 12 studies examining long-term changes in depression (see Supplementary Material for effect sizes). However, two of these articles used depression datasets overlapping with other studies (Lyons and Carhart-Harris, 2018; Roseman et al., 2018a), leaving ten unique samples. Since these two articles also provided unique long-term data (e.g., personality and neuroimaging measures, respectively), they were still included in the overall review. Of the ten distinct studies which indexed long-term changes in depression (nine psilocybin and one ayahuasca), nine demonstrated short-term reductions in symptoms (i.e., at least two weeks), and the five studies which monitored changes for at least six months demonstrated that these reductions were sustained (Griffiths et al., 2016; Grob et al., 2011; Lyons and Carhart-Harris, 2018; Ross et al., 2016; Stroud et al., 2018). Starkly, Carhart-Harris et al. (2017) found that 19/20 participants with treatment-resistant depression showed reduced depressive symptoms for at least one week, with over one-half qualifying for complete remission. Seven of the eight studies examining long-term changes in anxiety found that psychedelic treatment led to significant reductions in symptoms (Barrett et al., 2020; Carhart-Harris et al., 2016a; Carhart-Harris et al., 2018, a; Gasser et al., 2014; Grob et al., 2011; Griffiths et al., 2016; Ross et al., 2016). Of the seven distinct studies examining lasting changes in openness to experience, participants reported increases in four (Carhart-Harris et al., 2016b; Erritzoe et al., 2018; Griffiths et al., 2018; Madsen et al., 2020). The increases in openness documented in Lebedev et al. (2016) utilized the same personality dataset as Carhart-Harris et al. (2016b), but this study was still included in the review because it provided additional data as well. All nine studies assessing changes in wellbeing/quality of life showed increases. Of the ten studies assessing long-term changes in spirituality after psychedelic use, nine found increased ratings. All four studies examining psilocybin-assisted psychotherapy for substance use disorders (three tobacco use disorder and one alcohol use disorder) demonstrated positive abstinent effects at the group-level (Bogenschutz et al., 2015; Garcia-Romeu et al., 2015; Johnson et al., 2014; Johnson et al., , 2017). The only studies assessing changes in meditation frequency (Griffiths et al., 2018) or mindfulness (Madsen et al., 2020) showed increases. Finally, only one study collected neuroimaging measures at a long-term follow-up: Barrett et al. (2020) found that the number of significant resting-state functional connections across the brain increased one month after healthy volunteers received psilocybin.

3.4. Safety

In addition to examining efficacy, understanding the long-term safety of psychedelic use is a pressing question facing researchers and clinicians. Case reports of HPPD resulting from recreational use have appeared in the literature (e.g., Hermle et al., 2012) but are rare. In our search, few subjects reported lasting negative side effects. Ross and colleagues (2016) commented that no long-term adverse effects had been reported across over 2000 participants that had been run through contemporary psychedelic trials as of 2016. This should not, however, be taken as evidence that the drugs are risk-free as they can lead to experiences that are markedly psychologically challenging, particularly when used in the absence of proper preparation, support, and integration (Carbonaro et al., 2016). Psychedelics seem to be unique drugs in that their immediate and long-term effects can vary dramatically as a function of the context they are taken in (Carhart-Harris et al., 2018b). Even in tightly controlled research settings with robust therapeutic support, some experiments have noted up to almost a third of participants reporting acute anxiety or fear at some point during high dose sessions (Griffiths et al., 2006). Although these episodes have been transient and manageable, it is not hard to imagine how the same situation could escalate or potentially become dangerous in an uncontrolled recreational environment. Studerus et al. (2011) noted that 1/110 participants who received psilocybin reported experiences of anxiety and depression in the weeks following administration which warranted treatment. Additionally, "a few" noted less severe emotional instability—but all adverse effects were resolved within a month. All in all, limited harm has been reported in the new era of research which utilizes extensive safety protocols (see Johnson et al., 2008 for safety guidelines), and the drugs' potential for dependency is low (Aixalá et al., 2019; Johnson et al., 2018). In subjective accounts, samples with depression (Watts et al., 2017) and addiction (Noorani et al., 2018) have noted the lack of long-term adverse side effects as being a considerable benefit over previous treatments they had attempted (e.g., antidepressants).

4. Discussion

Our systematic review of the current psychedelic literature revealed that psychedelic experiences can lead to myriad long-lasting psychological changes and research into these effects is a growing area of study. The long-term alterations have been examined across a variety of psychiatric (e.g., depression, anxiety, substance use disorder) and healthy (e.g., meditators, spiritually active) samples. Psilocybin has received the most research interest of the classic psychedelic drugs. In this section, we will explore the long-term findings by outcome measure and provide a critical analysis of the methodological rigor of these studies.

4.1. Depression/anxiety

Treatment for depression and anxiety is among the fastest growing areas of psychedelic research (Schenberg, 2018). Indeed, in late 2018, psilocybin was designated by the United States Food and Drug Administration as a "breakthrough therapy" for treatment-resistant depres-

Table 1
Our systematic review identified 34 studies examining long-term effects of psychedelics.

Authors	Year	Population/Diagnosis	Drug	Dosage (ROA)	Sample Size	Control	Follow-up Latency	Primary Follow-up Measures
Agin-Liebes et al.	2020	End-of-life Distress	Psilocybin	0.3 mg/kg (Oral)	15	No*	3.2–4.5 years	Depression, Anxiety, Spirituality, QoL
Barrett et al.	2020	Healthy	Psilocybin	25 mg/70 kg (Oral)	12	No	1 month	Depression, Anxiety, Affect, Neuroimaging, Personality
Belser et al.	2017	End-of-life Distress	Psilocybin	0.3 mg/kg (Oral)	13	No	1 week or 1 year	Interpretative Phenomenological Analysis
Bogenschutz et al.	2015	Alcoholism	Psilocybin	0.3 mg/kg, 0.4 mg/kg (Oral)	10	No	1–36 weeks	% Drinking Days, % Heavy Drinking Days
Carhart-Harris et al.	2012	Healthy	Psilocybin	2 mg (Oral)	10	Yes	2 weeks	Wellbeing
Carhart-Harris et al.	2016a	Depression	Psilocybin	10, 25 mg (Oral)	12	No	1–12 weeks	Depression & Anxiety
Carhart-Harris et al.	2016b	Healthy	LSD	75 ug (IV)	20	Yes	2 weeks	Personality, Optimism, & Delusions
Carhart-Harris et al.	2017	Depression	Psilocybin	10, 25 mg (Oral)	19	Yes	5 weeks	Depression
Carhart-Harris et al.	2018a	Depression	Psilocybin	10, 25 mg (Oral)	20	No	1–24 weeks	Depression & Anxiety
Erritzoe et al.	2018	Depression	Psilocybin	10, 25 mg (Oral)	20	No	12 weeks	Personality
Garcia-Romeu et al.	2015	Tobacco Addiction	Psilocybin	20 mg/70 kg, 30 mg/70 kg (Oral)	15	No	6 months	Tobacco Cessation
Gasser et al.	2014	End-of-life Distress	LSD	20 ug or 200 ug (Oral)	12	Yes	8 weeks, 1 year	Anxiety
Gasser et al.	2015	End-of-life Distress	LSD	200 ug (Oral)	9	No*	1 year	Qualitative Content Analysis
Griffiths et al.	2006	Spiritually Active	Psilocybin	30 mg/70 kg (Oral)	30	Yes	2 months	Personality, Affect, Wellbeing, & Spirituality
Griffiths et al.	2008	Spiritually Active	Psilocybin	30 mg/70 kg (Oral)	36	No*	14 or 16 months	Personality, Affect, Wellbeing, & Spirituality
Griffiths et al.	2011	Healthy	Psilocybin	0, 5, 10, 20, 30 mg/70 kg (Oral)	18	Yes	1, 14 months	Attitude, Mood, Behavior, & Spirituality
Griffiths et al.	2016	End-of-life Distress	Psilocybin	1 or 3 mg/70 kg, 22 or 30 mg/70 kg (Oral)	51	Yes	5 weeks, 6 months	Depression, Anxiety, Spirituality, & QoL
Griffiths et al.	2018	Healthy	Psilocybin	1 mg/70 kg or 20 mg, 30 mg/kg (Oral)	75	Yes	6 months	Mysticism, Meditative, Personality & Spiritual Practices
Grob et al.	2011	End-of-life Distress	Psilocybin	0.2 mg/kg (Oral)	12	Yes	2 weeks–6 months	Depression & Anxiety
Johnson et al.	2014	Tobacco Addiction	Psilocybin	20 mg/70 kg, 30 mg/70 kg (Oral)	15	No	1 week–6 months	Tobacco Cessation
Johnson et al.	2017	Tobacco Addiction	Psilocybin	20 mg/70 kg, 30 mg/70 kg (Oral)	15	No	1 year, 16–57 months	Tobacco Cessation, Affect
Lebedev et al.	2016	Healthy	LSD	75 ug (IV)	19	Yes	2 weeks	Personality
Lyons & Carhart-Harris	2018	Depression	Psilocybin	10, 25 mg (Oral)	14	Yes	7–12 Months	Depression, Authoritarianism, Nature Relatedness
Madsen	2020	Healthy	Psilocybin	0.2–0.3 mg/kg	10	No	3 months	Personality, Mindfulness
Nicholas et al.	2018	Healthy	Psilocybin	18.8–36.6 mg, 27.1–54.0 mg, and 36.3–59.2 mg (Oral)	12	No	1 month	Attitude, Mood, Behavior, & Spirituality
Noorani et al.	2018	Tobacco Addiction	Psilocybin	20 mg/70 kg, 30 mg/70 kg (Oral)	12	No	16–57 months	Qualitative Interview Analysis
Osorio et al.	2015	Depression	Ayahuasca	2.2 mL/kg, 0.8 mg/mL DMT (Oral)	6	No	3 weeks	Depression, Mood, & Attitudes
Roseman et al.	2018a	Depression	Psilocybin	10, 25 mg (Oral)	20	No	1–5 weeks	Depression, Neuroimaging
Roseman et al.	2018b	Depression	Psilocybin	10, 25 mg (Oral)	20	No	5 weeks, 3 months, & 6 months	Depression
Ross et al.	2016	End-of-life Distress	Psilocybin	0.3 mg/kg (Oral)	29	Yes	2 weeks–6 months	Depression, Anxiety, Spirituality, & QoL
Schmid & Liechti	2018	Healthy	LSD	200 ug (Oral)	16	Yes	1 month, 1 year	Personality, Anxiety, Spirituality, & QoL
Smigielski et al.	2019	Meditators	Psilocybin	315 μg/kg (Oral)	38	Yes	4 months	Attitude, Mood, Behavior, & Spirituality
Stroud et al.	2018	Depression	Psilocybin	10, 25 mg (Oral)	33	Yes	1 month	Depression & Emotional Face Recognition
Watts et al.	2017	Depression	Psilocybin	10, 25 mg (Oral)	19	No	6 months	Qualitative Thematic Analysis

* These studies included an initial control condition, but long-term measures did not have a control.

Table 2
Cumulative and descriptive statistics of studies on the long-term effects of psychedelic drugs.

Cumulative & Descriptive Statistics of Long-term Psychedelic Studies										
Year		Population		Drug		Sample Size		Control		Long-term Follow-up Measures	
Mean	2016	Depression	10	Psilocybin	28	Mean	16.81	Yes	15	Personality/Attitude	14
Median	2016	Healthy	9	LSD	5			No	19	Depression	10
		End-of-life Distress	7	Ayahuasca	1					Spirituality	10
		Tobacco Addiction	4							Wellbeing/QoL	9
		Spiritually Active	2							Anxiety	8
		Alcoholism	1							Affect/Mood	7
		Meditators	1							Qualitative Analysis	4
										Tobacco Consumption	3
										Alcohol Consumption	1
										Mindfulness	1
										Neuroimaging	1
										Meditative Practices	1

sion. This designation should streamline future studies and indicated tentative regulatory acknowledgement of the efficacy of psychedelic-assisted psychotherapy. However, it is still important to determine whether these anti-depressive effects are maintained over the long-term given that many current antidepressant options have been shown to have diminishing results over time (Uher and Pavlova, 2016). Our search documented robust positive and enduring effects of psychedelic treatment on measures of depression across several studies and research groups. An important note is that some studies required patients to abstain from their typical antidepressant treatments, whereas others did not, and many did not report this information. Also, although reductions in depressive symptoms are generally maintained at the group-level, there is evidence that some individuals are prone to relapse and that depression levels may rebound over time—albeit to levels that are still below pre-treatment levels (Carhart-Harris et al., 2016a). Barrett et al. (2020) administered psilocybin to healthy participants and found that depression scores decreased at the one-week follow-up, but returned to baseline when assessed a month after their session. Psychedelic therapy appeared to have similar effects on anxiety, which is unsurprising given the high comorbidity between anxiety and depression as well as the overlap in their treatments and neural mechanisms (Aday et al., 2017; Risal et al., 2016). The study which did not find changes in anxiety used a healthy sample, suggesting potential floor effects (Schmid and Liechti, 2018), and no psychotherapy was applied. It is also possible that anxiolytic effects are drug dependent, as this study utilized LSD instead of psilocybin.

Given the reliability of these therapeutic effects in recent studies, researchers have begun to elucidate predictors and mechanisms of long-term changes. The degree to which one has a "mystical" experience has emerged as one factor related to a variety of affective changes (Griffiths et al., 2008, 2011, 2018; Maclean et al., 2011), including depression. Mystical experiences are characterized by deep feelings of meaning/sacredness, interconnectedness, transcendence of time and space, ineffability, and a strong positive mood (Grob et al., 2013; Kelmendi et al., 2016). Grob and colleagues (2011) argued that existential self-narratives can be "recalibrated" during this period of transcendence and altered perspective. Ross et al. (2016) and Griffiths et al. (2016) concurrently found that the more mystical one's psilocybin session was rated, the greater the reductions in depression at the 6-month follow-up. When combining psilocybin with a meditation regimen, Griffiths and colleagues (2018) found that scores on the Mystical Experiences Questionnaire (MEQ-30) were associated with positive outcomes on 18/19 of their measures. Similarly, Carhart-Harris et al. (2016a) noted that the degree to which one experienced a unitive, spiritual, and blissful (USB) state during the psychedelic session predicted improvements in depression. Watts et al. (2017) conducted structured interviews with depressed patients and identified three main themes for remission. These themes include moving from a state of disconnection to reconnection, confronting painful memories, thoughts, and feelings, and, finally, the treatment promoted acceptance of previously avoided emotions. In another qualitative analysis, depressed individuals suggested that the therapeutic changes stem from a sense of empowerment and acceptance lasting after the session (Belser et al., 2017).

Researchers have also begun to monitor neural markers accompanying long-term changes in depression. Roseman and colleagues (2018a) found that decreases in depressive symptoms could be predicted by increased amygdala reactivity to emotional stimuli, with those higher in amygdala activation to fearful stimuli post-psilocybin treatment also showing the greatest clinical improvements. The relationship between psychedelic-assisted psychotherapy-mediated changes in depressive symptoms and amygdala activity appears to be dynamic though, as Carhart-Harris et al. (2017) found that decreases in amygdala activity at rest the day after psilocybin therapy predicted improvements in symptoms. These apparently discrepant results can perhaps be explained through changes in emotional blunting to affective stimuli. When emotional stimuli are presented post-treatment, increased amygdala activation is consistent with reduced emotional blunting. On the other hand, attenuated amygdala activity at rest may relate to reduced chronic distress—both outcomes would be expected in successful depression treatment. Carhart-Harris and colleagues (2017) also found that increased resting-state functional connectivity (RSFC) between the ventromedial prefrontal cortex (vmPFC) and bilateral inferior-lateral parietal cortex (ilPC) after treatment predicted decreases in depression five weeks later. The authors contended that their results could be representative of a commonality in the antidepressant mechanisms of electroconvulsive therapy (ECT) and psilocybin, where connectivity of the DMN is acutely disintegrated and then normalized post-treatment in a "reset" that facilitates subsequent changes. Finally, researchers have found that, in non-human models, psychedelics can stimulate neuroplasticity (Ly et al., 2018) and neurogenesis (Catlow et al., 2013; Lima da Cruz et al., 2018), both of which have been long-theorized to interact with depression (Brunoni et al., 2008; Jacobs et al., 2000); however, these two neural mechanisms remain speculative until further elucidated in humans.

4.2. Personality/attitudes

Changes in personality and attitudes are among the most commonly studied long-term changes related to psychedelic use. In particular, increased openness to experience has been commonly linked to experience with psychedelics (Bouso et al., 2018; Maclean et al., 2011). Although 4 of the 7 unique studies assessing openness reported increases, participants in one of the null samples (Griffiths et al., 2006) were already particularly high in openness prior to the experiment, potentially leading to ceiling effects. It should perhaps be unsurprising that these individuals were high in openness to experience given that they were the first participants administered psilocybin in the modern era of psychedelic research. Predictors of changes in openness include the degree to which one has a mystical experience (Maclean et al., 2011) as well as increases in global measures of neural entropy (Lebedev et al., 2016). Neural entropy is thought to reflect uncertainty or randomness in neural signaling. Carhart-Harris et al. (2014) argue that psychedelics increase entropy past the point of "criticality", such that there is a wider repertoire of functional connectivity, allowing for individuals to think in new ways. In addition to increased openness, heightened extraversion and decreased neuroticism have been documented, both of which correlated with ratings of insightfulness during the psilocybin session (Erritzoe et al., 2018). Measures of conscientiousness and absorption have also been shown to increase one month after administration of psilocybin (Barrett et al., 2020).

Other studies examined broader long-term changes in attitudes about life, one's self, others, and nature. Lasting improvements in mood and positive attitudes were common themes extrapolated from the review (Griffiths et al., 2006, 2008, 2011, 2018; Ross et al., 2016; Smigielski et al., 2019), and increased optimism and mindfulness may be driving some of the positive psychological changes (Carhart-Harris et al., 2016b; Madsen et al., 2020). Lyons and Carhart-Harris (2018) found decreased authoritarianism and strengthened nature relatedness after psilocybin (Lyons and Carhart-Harris, 2018), supporting previous correlational findings between psychedelic use and nature connectedness (Forstmann and Sagioglou, 2017). These increases in connection seem to be broad and generalizable as studies also noted sustained improvements in social relations and altruism (Griffiths et al., 2006, 2008, 2011, 2018; Noorani et al., 2018; Ross et al., 2016). Psychedelic-induced ego dissolution and declines in DMN activity (Lebedev et al., 2015) are consistent with these changes in connection and selflessness, offering speculative underlying mechanisms.

4.3. Wellbeing/quality of life

Long-term changes in wellbeing and quality of life have been studied primarily in healthy, spiritually active (i.e., those with at least intermittent participation in religious or spiritual activities), or end-of-life distress participants. In healthy/spiritually active samples, psilocybin (Carhart-Harris et al., 2012; Griffiths et al., 2006, 2008) and LSD (Schmid and Liechti, 2018) have been shown to induce lasting improvements in wellbeing. Notably, Griffiths et al. (2006) found that 79% of participants rated that the experience increased their wellbeing or sense of life satisfaction "moderately" (50%) or "very much" (29%) two months after their psilocybin session. This effect seemed to be generally enduring as 64% responded the same at the 14-month follow-up (Griffiths et al., 2008). However, further research is needed to identify what factors led to a subset of participants tempering their reaction. In a follow-up psilocybin study, 94% noted improved wellbeing or life satisfaction at the one-month assessment (Griffiths et al., 2011).

Improvements in quality of life may be even more important among those approaching death. In their simultaneous trials, Ross et al. (2016) and Griffiths et al. (2016) respectively found that 87% and 82% of patients with life-threatening cancer reported increased life satisfaction or wellbeing six months post-psilocybin treatment. Many indicated that the experience was cathartic, led to a greater appreciation of life, and helped them come to terms with their own mortality. Psychedelic treatment's unique capacity to assuage distress related to dying has been demonstrated in several studies as researchers have found increased sense of continuity after death (Griffiths et al., 2011) and death acceptance (Griffiths et al., 2016), as well as 77% of participants reporting less fear of death in another study (Gasser et al., 2015). These changes may be contributing to decreases in cancer-related demoralization and hopelessness which have been documented with psilocybin (Ross et al., 2016).

More direct inquiries into participant accounts have identified several factors which seem to be related to increased wellbeing, particularly in those with end-of-life distress. In their qualitative analysis of participant reports, Gasser and colleagues (2015) found that patients with life-threatening diseases consistently reported that their LSD experience was insightful, cathartic, and fundamentally restructuring. They generally felt more relaxed with themselves and others. One representative patient account summarized "Quality of life changed extremely insofar as I became calmer, that I take things easier. It makes a difference if I look upon death with stress or with equanimity. I believe that is an enormous difference in quality of life." Finally, Carhart-Harris et al. (2012) noted there was a strong correlation ($r = .72$) between memory vividness under psilocybin and long-term increases in wellbeing, suggesting that an assortment of factors can play into these changes.

4.4. Meaningful and spiritual experiences

Given the robustness of the affective changes discussed so far, it should be unsurprising that, long after their sessions, many participants report their psychedelic experiences as being incredibly personally meaningful, and sometimes spiritually significant. In a seminal study, Griffiths et al. (2006) found that two-thirds of participants rated their psilocybin session as being among the top five most meaningful experiences of their entire lives two months after the experiment; 58% responded similarly at the 14-month follow-up (Griffiths et al., 2008). In a subsequent experiment, this research group once again found that two-thirds of a new sample of participants included the experience as being among their five most meaningful experiences five months later (Griffiths et al., 2018). Likewise, Johnson et al. (2017) evaluated the efficacy of psilocybin treatment for smoking cessation and found that 86% put it in their five most meaningful experiences, and 58% reported similarly in another study one month after their psilocybin session (Nicholas et al., 2018). Schmid and Liechti (2018) noted that 71% of healthy participants administered LSD included the session in their ten most meaningful events. The fluctuation across studies likely relates to small sample sizes, but in-general, psychedelic treatment appears to reliably induce meaningful experiences—experiences which have been reported to be comparable in importance to events such as childbirth or losing a parent (Griffiths et al., 2006).

In addition to being personally meaningful, in some cases, psychedelic experiences have been described as being spiritually significant and can lead to long-lasting changes in spirituality (Griffiths et al., 2019). These findings are in line with anthropological evidence noting the substances' traditional use in religious ceremonies, which has continued for centuries (Jay, 2019). In our search, changes in spirituality were shown to be dose-dependent (Griffiths et al., 2011) and corroborated by community ratings (i.e., close family members and friends; Griffiths et al., 2016). The one study which did not find increased spirituality utilized a sample of exclusively spiritually active participants (Griffiths et al., 2008), suggesting potential ceiling ef-

fects; however, because these participants reported increased spirituality at an earlier follow-up (i.e., two months; Griffiths et al., 2006), it is unclear why this effect attenuated at the 14-month follow-up. In addition to lasting trait-level changes in spirituality, some individuals rate their psychedelic session itself as being a spiritually significant experience long after the experiment. For example, 83% of participants in two studies included their psilocybin session as one of their five most spiritually significant experiences at the long-term follow-up (Griffiths et al., 2011; Nicholas et al., 2018) and 67% responded similarly in another trial (Griffiths et al., 2008). In this study, the degree to which one had a mystical experience predicted enduring increases in spirituality (Griffiths et al., 2008).

It should be noted, however, that it is currently unclear how the extent to which one is primed to explore their spiritual convictions on the drugs, as well as their intention to have a spiritual experience, influences their likelihood of having spiritual insights and/or reinforced spiritual beliefs. This is an important area of study given that psychedelics have been shown to enhance suggestibility (Carhart-Harris et al., 2014) and meaning (Hartogsohn, 2016). That is, while under the influence of the drugs, suggestions and insights can feel more convincing and meaningful than they otherwise would (Hartogsohn, 2018). In the presence of a skilled therapist or shaman, this state can be utilized to positively alter self-narratives and attitudes, or reinforce spiritual convictions. Some, however, have attempted to exploit this state to convince individuals to commit acts they otherwise may not have done, as was seen with Charles Manson. Baseline measures of conscientiousness are one factor which correlate with enhanced suggestibility (Carhart-Harris et al., 2015).

4.5. Substance use disorder

A reemerging application of psychedelic therapy, which dates back to the first era of research (Abramson, 1966; Dyck, 2006; see Krebs and Johansen, 2012 for a meta-analysis), is in their treatment for substance use disorders. Our search returned one proof-of-concept study examining the effects of psilocybin on alcohol use disorder (Bogenschutz et al., 2015), three studies with tobacco use disorder (Garcia-Romeu et al., 2015; Johnson et al., 2014; Johnson et al., 2017), and one qualitative analysis of participants' accounts taken several years after the smoking cessation intervention (Noorani et al., 2018). Bogenschutz et al. (2015) conducted the only study examining the effects of psilocybin treatment on alcohol use disorder. They found that, relative to baseline, percentage of drinking days and percentage of heavy drinking days immediately decreased, and these changes were sustained at least 36 weeks after treatment. Intensity of acute effects and the degree to which one had a mystical experience predicted long-term changes in abstinence and cravings. Although changes in abstinence and cravings were maintained, measures of mood and motivation were unchanged; currents trials are ongoing to follow-up these preliminary findings.

More work has been published examining psilocybin therapy for tobacco use disorder, but all four of the articles we identified used the same sample of participants. The pilot study found that 6 months after psilocybin treatment, 12/15 participants (i.e., 80%) were abstinent and this was verified with nicotine biomarkers (Johnson et al., 2014); cravings and temptation to smoke were attenuated as well. At the 12-month follow-up, 10/15 (67%) remained abstinent as did 9/15 (60%) at the long-term (i.e., avg. 30 months) assessment (Johnson et al., 2017). Mean ratings of the sessions' personal meaning, spiritual significance, and mystical experience predicted positive changes in cravings, self-reported abstinence, and smoking biomarkers (Garcia-Romeu et al., 2014). A long-term qualitative analysis of 12 patient accounts found many reported that the overpowering sense of awe, and subsequent lingering curiosity about life's mysteries, evoked by the session diminished the relative importance of smoking in their lives (Noorani et al., 2018). Preparatory counselling, secure rapport with the research team, and a sense of momentum once treatment began were additional variables perceived as integral in maintaining abstinence. Decreased intensity and frequency of withdrawal symptoms compared to previous attempts to quit smoking were noted in 11 out of 12 patients. Beyond achieving abstinence, participants subjectively reported various other enduring positive effects including heightened aesthetic appreciation, altruism, prosocial behavior, and interconnectedness—leading some to identify quitting smoking as one of the least important outcomes of the study.

4.6. Methodological critique

Although the findings reported to-date have been promising and stimulated interest within the recreational and scientific psychedelic communities, it is important to critically assess the methodological rigor of these studies. Doing so can advance future experimental methodology in psychedelic science and, thus, improve subsequent treatment. To begin, although roughly half of the studies in our review included control conditions, there is still much debate within the research community about what constitutes an adequate control for a psychoactive drug (Hendy, 2018). Some experiments have used amphetamines (Griffiths et al., 2006), whereas others have opted to use low doses of hallucinogens (Griffiths et al., 2016), niacin (Ross et al., 2016), or Benadryl (Bogenschutz et al., 2018). This is among the most important methodological concerns in psychedelic research, given the potential self-selection biases inherent to the field. These effects can be magnified in studies which include participants with history of previous psychedelic use. That is, ostensibly only those with positive previous experiences with the drugs would choose to take them again in a study, and those with adverse reactions would want to avoid them and would be less apt to enroll. Another considerable limitation for the field regards the generalizability of the findings; the samples used to date have been largely homogenous: white, educated, and generally middle-aged. There has been a call in recent years to consider individual differences, such as age and race, by incorporating more diverse participants (Aday et al., 2019b; George et al., 2019; Michaels et al., 2018; Williams and Leins, 2016). Screening procedures which commonly exclude those with cardiovascular conditions as well as those with personal or family histories of schizophrenia, Psychotic Disorder, or Bipolar Disorder also limit the generalizability of findings. Typically small sample sizes and, as of yet, variable dosages across studies are additional limitations to the field. Future studies should consistently report if participants used other medications during and after treatment. Researchers should also provide clearer operational definitions for psychospiritual terms and more explicitly detail what changes in spirituality encompass. That being said, some studies have employed a high level of methodological rigor. For example, Griffiths et al. (2016) and Ross et al.'s (2016) simultaneous dual-site, double-blind, placebo-controlled, crossover psilocybin trials for cancer patients experiencing end-of-life distress conducted at Johns Hopkins University and New York University, respectively, are of particular note, demonstrating that a high level of control is possible in psychedelic research.

4.7. Future directions

Several themes emerged from this review that can guide forthcoming studies. First, future researchers should mitigate the previously discussed limitations by including larger and more diverse samples, stronger blinding procedures/control groups, stronger methods to reduce expectancies, and standardized dosages. More direct comparisons between individual psychedelics drugs and further research into

the long-lasting effects of psychedelics beyond psilocybin are also important future areas of study. Lengthier longitudinal designs are required to identify the extent to which the aforementioned changes are maintained beyond the long-term latencies studied so far (Agin-Liebes et al., 2020). A notable finding from our review was the paucity of research on how structural and functional neuroimaging measures relate to long-term changes. Four studies related acute neural effects to long-term psychological changes (Carhart-Harris et al., 2017; Lebedev et al., 2016; Roseman et al., 2018a; Smigielski et al., 2019), but only one assessed long-term neural measures (Barrett et al., 2020). Despite the growing number of psychedelic studies utilizing neuroimaging (see dos Santos et al., 2016 for a review), it seems the drugs' effects on long-term neural measures is an open area of research. Future researchers should also delineate psychedelics' effects on suggestibility, meaning, and enhancement of placebo effects, which could coalesce some of their transdiagnostic applications. Finally, although the role of music in psychedelic therapy sessions is another growing area of research (e.g., Barrett et al., 2018; Kaelen et al., 2015, 2018), future studies assessing long-term behavioral outcomes related to interest in music, or art more broadly, are warranted given findings from historical research (McGlothlin et al., 1967) and subjective reports (Noorani et al., 2018).

5. Conclusion

This systematic review filled a critical gap in the literature regarding the long-term outcomes of psychedelic drugs. Our search identified 34 human-sample, long-term studies in the contemporary era of research with classic psychedelics. Most of this work utilized psilocybin and was published in the last five years. Sustained changes in personality/attitudes, depression, spirituality, affect/mood, anxiety, well-being, substance use, meditative practices, and mindfulness were documented. Mystical experiences, connectedness, emotional breakthrough, and increased neural entropy were among the most commonly theorized mechanisms leading to long-term change. Psychedelics have been shown to be relatively safe when used with the proper preparation, supervision, and integration, but it is unclear the extent to which this generalizes to recreational use. Future research can improve upon current experimental limitations by utilizing larger and more diverse samples, refining control conditions, and delineating dosage effects. Nonetheless, the weight of the evidence collected to-date suggests that, in carefully screened and monitored individuals, psychedelic treatment can mediate changes in psychological functioning that are generally positive and enduring.

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Uncitedreferences

Liechti (2017); Millière et al. (2018); Mueller et al. (2016); Osório et al. (2015); Roseman et al. (2018b) and Stolaroff (1999).

Declaration of Competing Interest

Dr. Davis is a board member of Source Research Foundation. This organization was not involved in the design/execution of this study or the interpretation or communication of findings.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2020.03.017.

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