Review

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Can psilocybin be safely administered under medical supervision? A systematic review of adverse event reporting in clinical trials

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Abstract

This systematic review investigates whether clinical trials of psilocybin support criterion number three of the drug's schedule I designation: *There is a lack of accepted safety for use of the drug or other substance under medical supervision*. Data were collected by using the PubMed database and conducting a search on November 24, 2021, with the search term *psilocybin* and applying the clinical trial filter. Only primary reports on the sole administration of psilocybin by a medical professional were included for analysis, excluding trials wherein psilocybin was not administered, trials wherein psilocybin was exclusively co-administered with other drugs, articles that were not clinical trials, and articles that were repeat analyses of already included trials. 52 included publications were closely examined for reports of adverse events, drug tolerability, and drug safety. Zero of these articles reported psilocybin to be unsafe, while 27 of the included trials suggested that psilocybin is safe to administer under proper medical supervision.

Keywords

psilocybin, safety, adverse event, schedule I

Intro

Psilocybin is a naturally occurring psychoactive chemical produced by various species of mushroom, mainly in the *psilocybe* genus. Human consumption of psilocybin, primarily for its psychoactive properties, dates back thousands of years (Tylš et al., 2013). It was first isolated in 1958 by Albert Hoffmann, who was later the first to synthesize it (Hofmann et al., 1958). Soon thereafter, the United States passed the Controlled Substance Act of 1971. This legislation classified psilocybin as a schedule I drug, a category for substances which meet the following three criteria (21 U.S.C. § 812, 2021):

1. The drug or other substance has a high potential for abuse.
2. The drug or other substance has no currently accepted medical use in treatment in the United States.
3. **There is a lack of accepted safety for use of the drug or other substance under medical supervision**.

In the time between the isolation of psilocybin and its Schedule I designation, a myriad of studies were published investigating the efficacy of psilocybin for the treatment of various psychiatric disorders (Grinspoon and Bakalar, 1981). As the United States faces a growing behavioral health crisis (Belouin and Henningfield, 2018), it is becoming paramount that all applicable, scientifically supported treatment options are considered. Numerous clinical trials have investigated psilocybin in the decades since its legal designation. This paper seeks to systematically review these trials for reports of adverse events, drug tolerability, and drug safety, in order to evaluate the scientific support for psilocybin's classification under criterion number three of the schedule I designation: *There is a lack of accepted safety for use of the drug or other substance under medical supervision*.

An adverse event, the measure of safety in the present review, is defined as "any untoward medical occurrence associated with the use of a drug in humans, whether or

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not considered drug related." An adverse event is considered serious if, "it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition" (21 C.F.R. § 312.32, 2021).

Methods

Documentation of clinical trials of psilocybin was collected by using the PubMed database. The search was conducted on November 24, 2021, using the search term *psilocybin* and applying the clinical trial filter. The search yielded 88 results from 1965–2021, with a gap in publications from 1972–1996. Of these articles, only primary reports on the sole administration of psilocybin by a medical professional were included.

12 publications wherein psilocybin was not administered were excluded (Dolder et al., 2017; Gouzoulis-Mayfrank et al., 2005; Heekeren et al., 2008; Heekeren et al., 2007; Jan et al., 2010; Liechti et al., 2017; Maqueda et al., 2016; Olson et al., 2020; Riba et al., 2002, Rocha et al., 2021; Snyder et al., 1967, Vojtěchovský et al., 1966), one was excluded for exclusively co-administering other drugs alongside psilocybin (Pokorny et al., 2016), seven were excluded for not being clinical trials (Doblin, 1991; Gross et al., 2002; Hallock et al., 2013; Heimann, 1969; Studerus et al., 2012; Studerus et al., 2010; Studerus et al., 2011), and 15 were excluded for being repeat analyses of already included trials (Carhart-Harris et al., 2018; Carhart-Harris et al., 2017; Carrillo et al., 2018; Garcia-Romeu et al., 2014; Gouzoulis-Mayfrank et al., 1998; Gouzoulis-Mayfrank et al., 1999a; Gouzoulis-Mayfrank et al., 2002; Johnson et al., 2017; Johnson et al., 2012; Kometer et al., 2013; Mertens et al., 2020; Mason et al., 2021; Petri et al., 2014; Smigielski et al., 2019b; Turton et al., 2014), leaving a final total of 52 publications.

Publications were carefully reviewed for specific reports of adverse events, drug tolerability, and drug safety. While nearly all the publications reported behavioral and biological effects of the drug, these findings were not included in this review unless it was clearly stated to be an adverse event or safety risk.

Table 1. Articles that did not contain mention of adverse events, drug tolerability, or drug safety.

Authors	Year
Barnett et al.	2020
Barrett et al.	2018
Barrett et al.	2020
Bernasconi et al.	2014
Carhart-Harris et al.	2012a
Carter et al.	2005a
Carter et al.	2005b
Duke et al.	1968
Fischer et al.	1969
Gabay et al.	2018
Hill et al.	1971
Kometer et al.	2015
Kometer et al.	2012
Kraehenmann et al.	2015
Lewis et al.	2017
Lindenblatt et al.	1998
Mason et al.	2020
Pokorny et al.	2017
Preller et al.	2016
Schmidt et al.	2012
Spitzer et al.	1996
Vojtěchovský	1968
Vollenweider et al.	1998
Vollenweider et al.	1999
Wittmann et al.	2007

Results

25 of the 52 publications did not contain any reference to adverse events, drug safety, or drug tolerability (Table 1). The remaining 27 publications documented the administration of psilocybin on over 800 occasions to 550 individuals, and reported no serious and/or significant adverse events, positive drug tolerability, and/or overall safe administration of psilocybin (Table 2). Information on number of participants, route of administration (ROA), and dosing for the included studies can be found in Table 3.

All adverse events were reported to be transient and mild, the most common being headaches (Bogenschutz et al., 2015; Brown et al., 2017; Carhart-Harris et al., 2016; Carhart-Harris et al., 2021; Davis et al., 2021; Griffiths et al., 2016; Johnson et al., 2014; Preller et al., 2020; Ross et al., 2016; Schindler et al., 2021), elevated blood pressure (Brown et al., 2017; Davis et al., 2021; Griffiths et al., 2016; Griffiths et al., 2018; Hasler et al., 2004; Johnson et al., 2014; Moreno et al., 2006; Ross et al., 2016), nausea (Bogenschutz et al., 2015; Carhart-Harris et al., 2016; Griffiths et al., 2016; Hasler et al., 2002; Ross et al., 2016), and anxiety (Carhart-Harris et al., 2016; Carhart-Harris et al., 2021, Gouzoulis-Mayfrank et al., 1999b; Griffiths et al., 2016; Hasler et al., 2004; Ross et al., 2016).

Table 2. Selected quotes regarding adverse events, drug tolerability, or drug safety.

Authors	Year	Quotes
Abramson, et al.	1965	"The weight of the evidence is that **all of the compounds in this study are safe to use in the hands of qualified physicians**."
Bogenschutz, et al.	2015	"**There were no significant treatment-related adverse events…** Five participants reported mild headaches which resolved within 24 h following psilocybin administration, consistent with prior reports (Johnson et al., 2012). One participant had nausea with one episode of emesis during one psilocybin session. One participant with irritable bowel syndrome experienced diarrhea during one psilocybin session. One participant reported insomnia on the night following a psilocybin session. No participant required medication or other intervention for blood pressure, anxiety, or other psychiatric symptoms. There was no report of illicit hallucinogen use by any participant during study participation."
Bravermanová et al.	2018	"Regarding the safety profile, psilocybin possessed only mild sympathomimetic activation and **did not cause any serious adverse events in our sample group**"
Brown et al.	2017	"**No serious AEs[1] were reported**. The side effects of the doses reflected previously reported findings, and included mild, transient hypertension and tachycardia [34, 35]. As previously reported, mild headaches were common in the second 12 h of the 24-h study periods, and were successfully treated with acetaminophen [36]. No reports of hallucinogen persisting perception disorder (HPPD) were reported during study or at follow-up."
Carhart-Harris et al.	2016	"The most common adverse events were transient anxiety (mostly mild) during drug onset (n = 12), transient confusion or thought disorder (n = 9), mild and transient nausea (n = 4), and transient headache (n = 4; table 2). These adverse events were expected psychological effects of psilocybin. Subacute headache typically presented 1 day after the psilocybin session, and subsided after 1–2 days. Paranoia presented in only one patient, but this was mild and transient. No prolonged psychotic symptoms were observed in any of the patients. One patient contacted the study psychiatrists during the 3 months of follow-up due to deterioration of their depression, and was referred to their general practitioner."
Carhart-Harris et al.	2021	"**No serious adverse events were observed in either trial group.** The percentage of patients reporting adverse events was similar in the two groups: 26 (87%) in the psilocybin group and 24 (83%) in the escitalopram group (Table 3, and Fig. S6). The percentage of patients who had increased anxiety and dry mouth was higher in the escitalopram group than in the psilocybin group. Adverse events in the psilocybin group typically occurred within 24 h after the dosing day; the most common adverse event was headache."
Carhart-Harris et al.	2012b	"… **the experience was well tolerated by all of the participants"**
Carhart-Harris et al.	2011	"**No significant acute or persistent adverse phenomena were reported**. This work supports the view that, if careful consideration is given to screening and subject care, **psilocybin can be safely administered** to healthy human volunteers in a controlled fMRI setting."
Davis et al.	2021	"**There were no serious adverse events in the study**." "…more than half the participants endorsed experiencing a variety of potentially unpleasant or challenging emotions and physical sensations during psilocybin sessions, however other studies have shown that such experiences after psilocybin are not uncommon. Increases in blood pressure and heart rate (HR) above criteria levels were rare and resolved spontaneously. Headache occurred during 33% of sessions and after 29% of sessions."
Gouzoulis-Mayfrank et al.	1999b	"… in four cases, there were transient paranoid thoughts and/or anxious experiences of loss of control, **which could always be managed by merely talking down"**
Griffiths et al.	2016	"**No serious adverse events attributed to psilocybin administration occurred.** A number of adverse events occurred during psilocybin sessions, none of which were deemed to be serious. Except as noted below, all of these adverse events had resolved fully by the end of the sessions. Consistent with previous research (Griffiths et al., 2006, 2011), there were transient moderate increases in systolic and/or diastolic blood pressure after psilocybin. In this study, an episode of elevated systolic blood pressure (>160 mm Hg at one or more time-point) occurred in 34% of participants in the high-dose session and 17% of participants in the low-dose session. An episode of elevated diastolic blood pressure (>100 mm Hg at one or more time-point) occurred in 13% of participants in the high-dose session and 2% of participants in the low dose session. None of these episodes met criteria for medical intervention. Nausea or vomiting occurred in 15% of participants in the high-dose session and none in the low-dose session. An episode of physical discomfort (any type) occurred in 21% of participants in the high-dose session and 8% in the low-dose session. Also consistent with previous research (Griffiths et al., 2006, 2011), transient episodes of psychological distress during psilocybin sessions (as rated by session monitors) were more common after the high dose than the low dose. Psychological discomfort (any type) occurred in 32% of

(continued)

Table 2. (continued)

Authors	Year	Quotes
		participants in the high-dose session and 12% in the low-dose session. An episode of anxiety occurred in 26% of participants in the high-dose session and 15% in the low-dose session. One participant had a transient episode of paranoid ideation (2% of high-dose sessions). There were no cases of HPPD or prolonged psychosis. One participant reported a mild headache starting toward the end of the high-dose session and lasting until 9 p.m. that evening. Of the 11 participants for whom headache was assessed on the day after sessions, two reported a delayed moderate headache after the high-dose session."
Griffiths et al.	2018	"**No serious adverse events attributed to psilocybin administration** or the study procedures occurred. A number of adverse events occurred during psilocybin sessions, none of which was deemed to be serious. Consistent with previous research (Griffiths et al., 2006, 2011, 2016), there were transient moderate increases in systolic and/or diastolic blood pressure after psilocybin. In one participant, diastolic blood pressure was elevated (126 mmHg) about an hour after psilocybin administration in the first session. The increase met protocol criteria for administration of sublingual nitroglycerin. The session was completed uneventfully. Although this participant reported that the session experience was positively meaningful and expressed a desire to continue with the study, the participant was discontinued from further participation."
Griffiths et al.	2011	"**The present study provided no evidence of adverse effects of high dose psilocybin exposure other than the episodes of psychological struggle during some portion of the time of psilocybin action**. This should not be interpreted to suggest that casual use of high dose psilocybin is safe. **It is important to recognize that the present study was conducted in carefully screened volunteers who received ample preparation before sessions, were closely monitored during sessions, and had some continuing contact with study staff after sessions**"
Griffiths et al.	2006	"An important finding of the present study is that, with careful volunteer screening and preparation and when sessions are conducted in a comfortable, well-supervised setting, a high dose of 30 mg/70 kg **psilocybin can be administered safely**."
Grob et al.	2011	"**There were no clinically significant adverse events with psilocybin**… This study established the feasibility and safety of administering moderate doses of psilocybin…"
Hasler et al.	1997	"Throughout the clinical study with intravenous PY, the chosen threshold dosage of 1 mg PY^2 was found to be **well tolerated by all subjects**." - Note: this refers to 6 subjects, as there were 3 subjects who only received oral psilocybin.
Hasler et al.	2002	"**The PY^2 dose employed in our study was well tolerated**, with all subjects unequivocally reporting a positive experience. Only slight and short-term physical adverse reactions such as nausea and dizziness were observed during onset of PY effects in some subjects. None of our volunteers reported negative delayed effects in the follow-up Lists of Complaints. In accordance with previous reports, when applied under controlled clinical conditions, **PY^2 was found to be safe for experimental use in healthy subjects**."
Hasler et al.	2004	"Our investigations provided **no cause for concern that administration of PY to healthy subjects is hazardous with respect to somatic health**. However, as our data revealed tendencies of PY to temporarily increase blood pressure, we advise subjects suffering from cardiovascular conditions, especially untreated hypertension, to abstain from using PY or PY-containing mushrooms. Furthermore, **our results indicate that PY^2-induced ASC^3 are generally well tolerated and integrated by healthy subjects.** However, a controlled clinical setting is needful, since also mentally stable personalities may, following ingestion of higher doses of PY, transiently experience anxiety as a consequence of loosening of ego-boundaries"
Johnson et al.	2014	"**During the 42 psilocybin sessions (16 moderate, 26 high dose) conducted in the course of this study, no clinically significant adverse events requiring physician or pharmacologic intervention occurred**. As expected from previous research (Griffiths et al., 2011), States of Consciousness Questionnaire data showed that one participant (7%) reported extreme ratings, and five others (33%) reported strong ratings of fear, fear of insanity, or feeling trapped at some time during a session. These episodes occurred in six participants (40%), and occurred during five moderate and five high dose sessions. They were readily managed by interpersonal support, and had resolved by the end of the sessions. Consistent with previous findings (Griffiths et al., 2006; Grob et al., 2011), blood pressure (BP) and heart rate (HR) were elevated during drug effects with peak values occurring on average between 1.5 and 2.5 h post-psilocybin administration. Systolic BP showed a mean (SD;

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Table 2. (continued)

Authors	Year	Quotes
		range) peak of 153 (11; 134–173) mmHg (compared with baseline: 125 [10; 105–153] mmHg). Diastolic BP showed a mean (SD; range) peak of 87 (11; 72–105) mmHg (compared with baseline: 71 [8; 55–89] mmHg). HR showed a mean (SD; range) peak of 87 (11; 66–120) beats/min (compared with baseline: 68 [9; 51–89] beats/min)…. Of the ten participants assessed for headache, eight reported at least one post-psilocybin headache with a mean (SD; range) duration of 5.8 (2.4; 2.0–9.5) hours, onset at a mean of 6.2 (2.1; 3.5–11.5) hours after psilocybin administration and mean severity rating of mild, or 2.6 (1.3; 1–5) on a scale from = minimal, to 6 = excruciating. Five reported use of over-the-counter headache medication the evening following the session to alleviate symptoms."
Moreno et al.	2006	"One subject experienced **transient hypertension without relation to anxiety or somatic symptoms, but no other significant adverse effects were observed**."
Preller et al.	2020	**"No substantial side effects were recorded during the study. Seven participants reported mild transient headaches and one participant reported transient sleep disturbances for one night after drug administration. Participants were contacted again three months after the last drug administration. No further side effects were recorded."**
Quednow et al.	2012	**"Psilocybin was well tolerated physically and mentally by all subjects, with none of our subjects reporting persisting residual psychotropic effects in systematic follow-up investigations"**
Roseman et al.	2018	"Psilocybin represents a novel intervention for major depression that **appears to be safe**…"
Ross et al.	2016	"**There were no serious AEs[1], either medical or psychiatric**, in the trial that were attributed to either psilocybin or niacin. Regarding psychiatric AEs, no pharmacological interventions (e.g. benzodiazepines, anti-psychotics) were needed during dosing sessions, no participants abused or became addicted to psilocybin, there were no cases of prolonged psychosis or hallucinogen persisting perceptual disorder (HPPD), and no participants required psychiatric hospitalization. In terms of AEs[1] attributable to psilocybin, the most common medical AEs[1] were non-clinically significant elevations in BP and HR (76%), headaches/migraines (28%), and nausea (14%); the most common psychiatric AEs[1] were transient anxiety (17%) and transient psychotic-like symptoms (7%: one case of transient paranoid ideation and one case of transient thought disorder). The medical AEs[1] (non-clinically significant elevations in BP and HR, headaches, nausea), and psychiatric AEs[1] (transient anxiety, transient near-psychotic symptoms) attributable to psilocybin are all known AEs[1] of psilocybin, were transient, tolerable, and consistent with prior trials of psilocybin administration in normal volunteers (Griffiths et al., 2006, 2011), and patients with terminal cancer (Grob et al., 2011)."
Schindler et al.	2021	"**There were no serious or unexpected AEs[1] in this study.** During experimental sessions, lightheadedness and tension/sore muscles were reported with both placebo and psilocybin administration. In the 24 h after experimental sessions, both placebo and psilocybin administration were followed by tension/sore muscles, general headache attack, and migraine attack. There were no significant differences between placebo and psilocybin in the incidences of AEs[1], except that there was a significant drug × time interaction for MAP[4] over the experimental test day ($F(10, 186) = 2.52$, $p = 0.007$). Post hoc analysis revealed a significant increase in MAP[4] with psilocybin administration starting at 45 min until 4 h after ingestion. The maximum acute increase in MAP[4] over placebo was 12.2 (4.61 to 19.73) mmHg at 1.5 h after ingestion. All AEs[1] were transient and self-limiting (i.e. no rescue medications required), and no subjects withdrew from the study due to an AE[1]. During follow-up with subjects, there were no AEs[1] warranting professional intervention. At 3 months follow-up, all subjects denied any lasting physical, psychological, or cognitive changes."
Smigielski et al.	2019a	"At the dose tested, **psilocybin produced no adverse events** (including physical discomfort, disorientation, severe anxiety, panic, or psychotic-like reactions) neither acutely during the trial session nor post-acutely during the retreat"
Vollenweider et al.	2007	"…the present dose regimen was **well tolerated by our subjects** in this as well as in previous studies with psilocybin with healthy volunteers…"

[1] Adverse Events.
[2] Psilocybin.
[3] Altered States of Consciousness.
[4] Mean Arterial Pressure.

Table 3. Information on study size, route of administration (ROA), and dosing.

Authors	Year	N (total)	# of groups	ROA	N (1)	Dose (1)	N (2)	Dose (2)	N (3)	Dose (3)	N (4)	Dose (4)
Abramson et al.	1965	6	4	Oral	3	3mg	6	4mg	6	6mg	6	8mg
Bogenschutz et al.	2015	10	2	Oral	10	0.3mg/kg	10	0.4mg/kg				
Bravermanová et al.	2018	20	1	Oral	20	0.26mg/kg						
Brown et al.	2017	12	3	Oral	12	0.3mg/kg	12	0.45mg/kg	12	0.6mg/kg		
Carhart-Harris et al.	2016	12	2	Oral	12	10mg	12	25mg				
Carhart-Harris et al.	2021	59	2	Oral	29	1mg	30	25mg				
Carhart-Harris et al.	2012b	10	1	IV	10	2mg						
Carhart-Harris et al.	2011	9	2	IV	3	1.5mg	6	2mg				
Davis et al.	2021	27	2	Oral	27	0.286mg/kg	27	0.429mg/kg				
Gouzoulis-Mayfrank et al.	1999b	8	1	Oral	8	0.2mg/kg						
Griffiths et al.	2016	51	4	Oral	39	0.014mg/kg	12	0.043mg/kg	48	0.314mg/kg	3	0.429mg/kg
Griffiths et al.	2018	75	3	Oral	25	0.014mg/kg	25	0.286mg/kg	25	0.429mg/kg		
Griffiths et al.	2011	18	4	Oral	18	0.071mg/kg	18	0.143mg/kg	18	0.286mg/kg	18	0.429mg/kg
Griffiths et al.	2006	36	1	Oral	36	0.429mg/kg						
Grob et al.	2011	12	1	Oral	12	0.2mg/kg						
Hasler et al.	1997	9	2	Oral & IV [1]	6	1mg [2]	6	10mg - 20mg [3]				
Hasler et al.	2002	8	1	Oral	8	.212 ± .025 mg/kg						
Hasler et al.	2004	8	4	Oral	8	0.045mg/kg	8	0.115mg/kg	8	0.215mg/kg	8	0.315mg/kg
Johnson et al.	2014	15	2	Oral	15	0.286mg/kg	15	0.429mg/kg				
Moreno et al.	2006	9	4	Oral	9	0.025mg/kg	9	0.1mg/kg	9	0.2mg/kg	9	0.3mg/kg
Preller et al.	2020	23	1	Oral	23	0.2mg/kg						
Quednow et al.	2012	16	1	Oral	16	0.26mg/kg						
Roseman et al.	2018	20	2	Oral	20	10mg	20	25mg				
Ross et al.	2016	29	1	Oral	29	0.3mg/kg						
Schindler et al.	2021	12	1	Oral	12	0.143mg/kg						
Smigielski L et al.	2019a	20	1	Oral	20	0.315mg/kg						
Vollenweider et al.	2007	16	3	Oral	16	0.115mg/kg	16	0.215mg/kg	16	0.315mg/kg		

[1] Three of the participants received exclusively oral doses, three received exclusively IV, and three participants received both an oral and IV dose.
[2] IV dose.
[3] Oral doses (each participant received a different dose within range).

Discussion

Review of clinical trials investigating psilocybin from 1965 to 2021 suggests that psilocybin does not meet the Controlled Substance Act's third criterion for a schedule I drug: *There is a lack of accepted safety for use of the drug or other substance under medical supervision*. Zero of the 52 publications reviewed reported psilocybin as unsafe to administer. Clinical trials that included reports on safety universally considered psilocybin as safe to administer under proper medical conditions. Notably, 25 of the 52 publications did not report on safety. While it cannot be assumed that these studies did not encounter safety concerns, it is likely that serious adverse events would have been included had they been present.

The reviewed clinical trials demonstrated rigorous medical and psychological screening processes prior to

participant enrollment. All studies excluded participants of vulnerable populations (e.g. history of psychosis), in order to avoid serious adverse events. This practice is utilized for medications across all levels of scheduling, in the event that a drug may be safe and effective for certain populations, while having increased rates of adverse effects for others (e.g. one would not administer a beta-blocker to a hypotensive patient). The participant selection criteria for many of the reviewed trials required prior experience with psychedelics, further screening out individuals who may be prone to psychedelic-related adverse events.

The commonly reported adverse events (headache, elevated blood pressure, and anxiety) were not only transient and mild, but were also anticipated by the researchers, having been widely documented as possible outcomes for psilocybin. Moving forward, it may be better to conceptualize these as side effects rather than adverse effects.

It is important to note that psilocybin dosage varied across all of these studies. Several trials administered double the dose of others, and some utilized weight-corrected doses while others administered a flat dosing regimen. The ROA, either oral consumption or intravenous injection, also differed across trials. The presence of adverse events may have been related to increased doses, the lack of weight correction, or the chosen ROA.

An additional limitation is the role of set and setting. It is now understood that these factors have a crucial function in safe administration of a psychedelic drug such as psilocybin (Noorani, 2021). There is evidence that researchers in the 1960s and 1970s did not properly address set and setting in trial designs (Strassman, 1984); however, the earliest clinical trial included in this review did specifically mention the importance of environment (Abramson, et al., 1965). Nonetheless, Abramson and colleagues distributed as much as 103 mg orally administered psilocybin for participants to consume at home over the course of seven to 12 days, and there is little reason to assume that researchers controlled for set and setting during these instances. Despite the probable lack of control for these factors in early trials, only one of five early publications included in this review included a report on safety, claiming psilocybin as safe to administer (Abramson and Rolo, 1965).

As evidenced by Table 2, all reported adverse events were described as transient and mild by the researchers; however, during the course of the review, some adverse events were uncovered that one could view as serious. One participant in Griffiths and colleagues 2016 study withdrew from participation and later committed suicide, as explained here:

> "There was a death by suicide of a study participant 11 days after the first session, which involved the administration of the placebo-like very low dose of psilocybin (1 mg/70 kg). This volunteer reported feeling bored and was discontinued from the study after insisting upon leaving this study session early. There was no behavioral impairment and no adverse sequelae on follow-up later that day and over the subsequent several days. Our conclusion, which was reported to the Johns Hopkins IRB and to the FDA, was that the suicide was not related to the research procedures or to psilocybin."

Considering both the extremely low dose and that this study was investigating end of life distress with terminally ill patients, their conclusion that psilocybin was not responsible for this case seems apposite. In this same study, the mean blood pressure of participants after receiving the high dose of psilocybin (0.429mg/kg, oral) elevated to a severe level, but was resolved without any medical intervention (Table 2). Also, as shown in Table 2, one participant in Carhart-Harris and colleagues (2016), "contacted the study psychiatrists during the 3 months of follow-up due to deterioration of their depression, and was referred to their general practitioner." It is unclear how severe this was and how it was resolved, but despite this occurrence, the authors of this study concluded that the psilocybin treatment was generally well-tolerated among study participants.

There were notable adverse events in two of the articles that did not meet our inclusion criteria. Doblin (1991), which was excluded from analysis as it is not a clinical trial, was a follow-up methodological critique of Walter Pahnke's 'Good Friday Experiment' (1962), wherein Doblin noted that a participant in Pahnke's study experienced a psychotic episode and required administration of injected thorazine. Similarly, Studerus and colleagues 2011 paper, which was excluded due to its pooled analysis design rather than being a clinical trial, documented the instance of a healthy participant seeking professional help for psychological instability following a high-dose psilocybin study session. Nonetheless, Studerus and colleagues indicate that adverse reactions were successfully managed by providing interpersonal support alone.

These aforementioned examples demonstrate the possibility for potentially serious adverse effects, albeit rare and in most cases transient. However, these are often overshadowed by significant and pronounced increases in psychological wellbeing. Participants from psychedelic trials have described the experience as "pleasurable", "enriching", and "non-threatening" (Studerus et. al., 2011). Despite Griffiths and colleagues (2016) reporting transient episodes of psychological distress, cancer patients in the study sustained significant improvements in self-rated measures of anxiety, depressed mood, quality of life, well-being, optimism, and life satisfaction six months after psilocybin consumption. Comparably, Kometer and colleagues (2015) identify a relationship between psilocybin and neural mechanisms associated with enhanced insight to life and existence, a potential pathway for the cultivation of psychological resilience. Considerable evidence suggests

that psilocybin is generally well-tolerated when administered in a controlled setting. Federally and socially accepted selective serotonin reuptake inhibitors also pose a considerable level of risk (Carhart-Harris et al., 2021), and the acceptable level of risk associated with psilocybin should not serve as a barrier to those whom it could provide positively life-altering outcomes.

The results of this analysis strongly attest to psilocybin's safety and point towards a need for the revision of psilocybin's drug scheduling. In this analysis, out of 550 individuals, no one suffered from a serious adverse event; however, sparse reports from studies not included in this analysis point to the potential of psychiatric side effects arising after administration, which warrants further research into the safety profile and abuse potential of psilocybin to extend the findings of this systematic analysis.

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21 C.F.R. § 312.32: Subchapter D - Drugs for Human Use (2021).

21 U.S.C. § 812: Schedules of controlled substances (2021).