



Investigator's Brochure

PRODUCT: Psilocybin, [3-[2-(dimethylamino)ethyl]-1H-indol-4-yl] dihydrogen phosphate

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SPONSOR: Usona Institute
2800 Woods Hollow Road, Madison, WI 53711

CONTACT: info@usonainstitute.org
608-278-7662

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Psilocybin Investigator's Brochure Amendments

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Original Psilocybin Investigator's Brochure Version 1.0	07 February 2018
Version 2.0	17 December 2018
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Summary of Changes, Version 2.0

- Section 5.3.1. Introduction: Articulation of number of subjects exposed to psilocybin compared to number of doses administered
- Section 5.3.5.2.1. QTc: University of Wisconsin Study additional analysis of the effect of psilocybin concentration on QTc interval prolongation
- Section 6.5.6. Abuse Potential: Updates around the abuse potential for psilocybin from published literature (Heal, Gosden, & Smith, 2018; Johnson, Griffiths, Hendricks, & Henningfield, 2018)

Summary of Changes, Version 3.0

- Formatting changes
- Tables renumbered
- Table 5.3-8: List of complaints 24 hours post-dose: Corrected unit values in first row (mg to µg)
- Section 4.3, Non-Clinical Toxicology: Added Usona genetic toxicology studies PSIL-GEN-101 and PSIL-GEN-102
- Section 5.3.4, Clinical Trials for Depression and Anxiety: Added Usona clinical studies PSIL201 and PSIL201-LTFU

Summary of Changes, Version 4.0

- Formatting changes
- Tables renumbered
- [Section 1](#), [Section 5.1](#) and [Section 5.2](#): Added Madsen et al., 2012 describing a correlation of plasma psilocin, near-maximal occupancy of neocortical serotonin 5-HT_{2A} receptors and subjective intensity ratings of elements of the psychedelic experience at the 25-mg psilocybin dose.
- [Section 4.3](#): Revised safety margin calculations for 25-mg psilocybin dose and added

clarification that the Sponsor's genotoxicity studies were conducted with drug substance representative of the current manufacturing process.

- [Section 5.3](#): Added Davis et al., 2020 and updated subject exposure counts respectively and added age ranges and Davis et al., 2020 to [Table 5.3-1](#).
- [Section 5.3.2.1](#): Added additional experimental details and subject demographics ([Table 5.3-2](#)); and revised PK data to match data provided by study investigator ([Table 5.3-3](#) and [Figure 5.3-1](#))
- [Section 5.3.2.2](#): New section on retrospective analysis of oral psilocybin on QT interval (Dahmane et al., 2020)
- [Section 5.3.4.2](#): New section on Davis et al., 2020
- [Section 5.3.4.5](#): Added long-term follow-up data (Agin-Liebes et al., 2020)
- [Section 5.3.4.6](#): Updated information about Sponsor Study PSIL201
- [Section 5.3.5.2.1](#): Added discussion of effects on QT interval from Dahmane et al., 2020
- [Section 5.3.5.2.3](#): Added discussion of effects on heart rate from Dahmane et al., 2020

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USONA INSTITUTE

Usona Institute is a non-profit medical research organization founded in 2014. Usona Institute conducts and supports biochemical and clinical research to further the understanding of the therapeutic effects of psilocybin and other consciousness-expanding medicines. Usona is developing psilocybin for oral administration (25 mg, single-dose) in conjunction with a supportive set and setting protocol for major depressive disorder (MDD). Additional information about Usona can be found at www.usonainstitute.org.

ABBREVIATIONS

AE	Adverse event
API	Active Pharmaceutical Ingredient
ASC	Altered State of Consciousness
AUC	Area Under the Curve
BDI	Beck Depression Inventory
BP	Blood Pressure
BPM	Beats Per Minute
BSI	Brief Symptom Inventory
C	Celsius
CI	Confidence Interval
CRU	Clinical Research Unit
CTCAE	Common Terminology Criteria for Adverse Events
<i>d</i>	Cohen's <i>d</i> effect size
DBP	Diastolic Blood Pressure
DEA	Drug Enforcement Agency
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-5	Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition
ECT	electroconvulsive shock
EGR1	early growth response protein 1
FDA	Food and Drug Administration
fMRI	Functional magnetic resonance imaging
GAD	Generalized Anxiety Disorder
GAF	Global Assessment of Functioning
HADS	Hospital Anxiety and Depression Scale
HAM-A	Hamilton Anxiety Scale
HAMD	Hamilton Depression Rating Scale
HED	human equivalency doses
HPMC	hydroxypropyl methyl cellulose
HPPD	Hallucinogen Persisting Perception Disorder
hr	Hour
IND	Investigational New Drug
IB	Investigator's Brochure
LAP-R	Life Attitude Profile-Revised
LD ₅₀ /ED ₅₀	The ratio of the lethal dose in 50% of the population to the effective dose in 50% of the population
LOT-R	Life Orientation Test-Revised
LSD	Lysergic Acid Diethylamide
MADRS	Montgomery-Asberg Depression Rating Scale

MDD	Major Depressive Disorder
MDMA	3,4-methylenedioxy-methamphetamine
min	Minute
mg	Milligram
mg/kg	Milligrams per Kilogram
mm Hg	Millimeters of Mercury
MMRM	Mixed Methods for Repeated Measures
MQOL	McGill Quality of Life
N	Sample Size
ng/mL	Nanograms per Milliliter
NSDUH	National Survey on Drug Use and Health
NYU	New York University
OCD	Obsessive Compulsive Disorder
<i>p</i>	<i>p</i> -value
PEA	Phenethylamine
PET	Positron Emission Tomography
POMS	Profile of Mood States
QIDS	Quick Inventory of Depressive Symptomatology
SAE	Serious Adverse Event
SAMHSA	Substance Abuse and Mental Health Services Administration
SBP	Systolic Blood Pressure
SCID	Structured Clinical Interview for DSM-IV Axis I Disorders
SEM	Standard Error of the Mean
SHAPS	Snaith-Hamilton Pleasure Scale
STAI	State-Trait Anxiety Inventory
SNRI	Serotonin-norepinephrine reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitor
<i>t</i>	Student's <i>t</i> -test
TRD	Treatment-Resistant Depression
vs	Versus
UCLA	University of California at Los Angeles
µg/kg	Microgram per Kilogram
UGTs	UDP-glucuronosyltransferase
US	United States
USP	United States Pharmacopeia
UW	University of Wisconsin-Madison
VAS	visual analog scale
YBOCS	Yale-Brown Obsessive Compulsive Scale
ZPES	Zehe Pharmaceutical Experiment Station

1. SUMMARY

This Investigator's Brochure (IB) describes the physical, chemical, and pharmacological characteristics of psilocybin, its effects in non-clinical and clinical studies, and the safety profile of psilocybin administered under supportive conditions within the clinical research setting. It summarizes relevant information for the investigator to consider regarding the use of psilocybin in an accompanying clinical protocol detailing study design and conduct. Key non-clinical and clinical data from published and unpublished research studies supporting psilocybin's safety and potential efficacy have been provided. This IB will be reviewed annually and amended as further information becomes available.

Psilocybin (3-[2-(dimethylamino)ethyl]-1H-indol-4-yl] dihydrogen phosphate) is a natural product produced by numerous species of *Psilocybe* mushrooms, which is manufactured for clinical use to control potency and purity. It is a tryptamine derivative, and in humans the phosphate group is rapidly enzymatically cleaved in the body to produce psilocin, an agonist at a variety of serotonin receptors, the most important of which in this setting is the 5-HT_{2A} receptor (Carhart-Harris et al., 2014; Nichols, 2004). Oral psilocybin has about a 50% bioavailability and psilocin is detectable in plasma within 20 minutes of administration of the parent compound (Brown et al., 2017; Hasler, Bourquin, Brenneisen, Bär, & Vollenweider, 1997). The half-life of psilocin in blood is 2-3 hours. Onset of noticeable psychoactive effects occurs within one hour, peaks at about two hours after a dose, and loss occurs typically around six hours after the dose. Based on this time course, protocols mandate observation in the clinical trial setting until approximately 8 hours after dosing. Further, exposure following a 25 mg oral dose is associated with both near-maximal occupancy of neocortical serotonin 5-HT_{2A} receptors and subjective intensity ratings of elements of the psychedelic experience that have been repeatedly associated with longer-term therapeutic benefits (Madsen et al., 2019).

Psilocybin reliably induces profound changes in sensory perception, emotion, thought, and sense of self, characterized by marked alterations in all mental functions, including perception, mood, volition, cognition and self-experience (Geyer & Vollenweider, 2008; Studerus, Kometer, Hasler, & Vollenweider, 2011). These profound changes are often referred to as mystical-type experiences. Measures of mystical-type experience occurring during psilocybin treatment have been repeatedly observed to predict later effects on behavior and emotions, including reductions in depressive and anxious symptoms (Griffiths et al., 2016; MacLean, Johnson, & Griffiths, 2011; Ross et al., 2016).

Non-clinical *in vivo* and *in vitro* studies, found via literature searches, demonstrate that, similar to humans, when psilocybin is administered orally to rats it is rapidly dephosphorylated to psilocin in the intestinal mucosa by alkaline phosphatase and a nonspecific esterase, with approximately 50% of the total volume of psilocin absorbed from the digestive tract (Kalberer et al., 1962). Maximum plasma levels are achieved after approximately 90 minutes (Chen et al., 2011). When administered systemically (i.e., bypassing the gut), initial psilocybin metabolism is performed by tissue phosphatases, with *in vitro* studies indicating the kidneys as being among the most active metabolic organs (Horita & Weber, 1961). Across species tested, the highest levels of psilocin were found in the neocortex, hippocampus, and thalamus (Hopf & Eckert, 1974).

Recent clinical studies utilizing pharmaceutical-grade oral psilocybin under controlled conditions have been performed upon healthy participants and various subpopulations to characterize the

safety profile and evaluate clinical efficacy. Though the safety reporting criteria and the level of data verification varied greatly between studies, including many participant-reported outcomes, these data have been utilized to elucidate the expected adverse event (AE) profile of psilocybin. The clinical studies summarized in this IB present similar safety profiles, with both psychological and physical adverse events reported. The most common adverse psychological events included anxiety, negative emotional states and paranoid/delusional thinking during dosing sessions, and the most common physical effects were increased blood pressure (BP) and heart rate, mild nausea, and mild headache.

Preliminary efficacy of psilocybin in clinical studies showed a decrease in symptomatic response in indications including obsessive compulsive disorder (OCD), substance use disorder, depression, and anxiety. Overall, psilocybin has been well tolerated at the doses examined in the clinic. Due to the psychoactive nature of the compound, it should only be administered in a controlled setting and per the accompanying clinical protocol.

Please note that this IB was written to support Usona-sponsored studies under IND 129532 as governed by U.S. law and regulations. Other investigators referencing this document may need to adjust certain details as appropriate to their own studies or local regulations.

2. INTRODUCTION

2.1. Psilocybin Background

Psilocybin 3-[2-(dimethylamino) ethyl]-1H-indol-4-yl] dihydrogen phosphate is a natural product produced by numerous species of *Psilocybe* mushrooms. The phosphate group is enzymatically cleaved in the body to produce psilocin, an agonist at a variety of serotonin receptors, the most important of which, for its behavioral effects, is the 5-HT_{2A} receptor (Carhart-Harris et al., 2014; Nichols, 2004). Psilocybin was first isolated from *Psilocybe* mushrooms in 1957, followed by *de novo* synthesis in 1958 (Passie, Seifert, Schneider, & Emrich, 2002). It was marketed worldwide in the 1960s as *Indocybin*[™] for experimental and psychotherapeutic purposes. Although it was well tolerated and demonstrated potentially useful effects, it was classified as a controlled substance in the U.S., placed in Schedule I in 1970, and effectively removed from clinical use or scientific study. Psilocybin, and similar drugs such as lysergic acid diethylamide (LSD) and mescaline, fall into a pharmacological class that are referred to in this application as “classic psychedelics” to differentiate them from other psychoactive substances (ex. 3,4-methylenedioxy-methamphetamine; MDMA) that have different psychological/behavioral effects and different adverse effect profiles and risk/benefit ratios than psilocybin (Carhart-Harris & Nutt, 2013; Nutt, King, Phillips, & Independent Scientific Committee on, 2010).

Several lines of evidence suggest that serotonergic hallucinogens, such as psilocybin, have clinical potential for inducing therapeutically beneficial behavior change in subjects with a variety of psychiatric conditions. Results of completed and published studies are reported.

2.2. Importance of a Supportive Set and Setting Protocol

Due to the psychoactive nature of psilocybin, the safety of participants in clinical trials can be enhanced by testing psilocybin within a “set and setting” protocol (Lyons & Carhart-Harris, 2018). By addressing the *set* (the emotional/cognitive/behavioral state/mindset and expectations of study participants just prior to psilocybin exposure) and *setting* (the physical environment in which the exposure occurs) of the experience, the risk of the subject reporting an event which was distressing or injuring themselves can be reduced. This approach generally incorporates three components: 1) preparation, 2) drug session, and 3) post session meetings to integrate the classic hallucinogen experience.

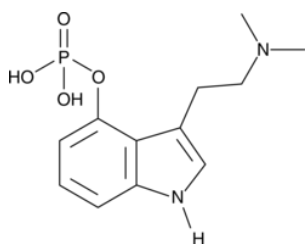
In the first phase, participants undergo pre-exposure preparation sessions designed to build rapport with the facilitators who would be present during the drug exposure session and to identify personal themes and struggles that might be especially likely to impact the session experience. In the second phase, the drug session itself is conducted by two facilitators (typically a male and female) who are present throughout the session. Sessions are typically conducted in a room designed to be quiet, comfortable, and aesthetically pleasing, and participants are encouraged to wear eyeshades and listen to a program of music through headphones during the drug exposure to aid them in focusing their attention inward. In the third phase, participants are engaged in a series of drug-free interview meetings of variable frequency, sometimes over a period of several weeks, to discuss their session experience thoroughly with the goal of maximizing its therapeutic benefit.

3. PHYSICAL, CHEMICAL AND PHARMACEUTICAL PROPERTIES AND FORMULATION

3.1. Chemical Name and Structure of Investigational Substance

[3-[2-(dimethylamino)ethyl]-1H-indol-4-yl] dihydrogen phosphate

Figure 3.1-1: Molecular structure of psilocybin.



3.2. Description of Investigational Substance

Psilocybin is a tryptamine derivative presenting as a white crystalline solid with a melting point of 220-228°C. It is stable over extended periods in dark storage at controlled room temperature. Psilocybin is soluble in 20 parts boiling water or 120 parts boiling methanol.

3.3. Description of Investigational Product

For use in Usona sponsored clinical studies, psilocybin is provided as 25 mg capsules (size 2, hydroxypropyl methyl cellulose (HPMC), white).

3.4. Description of the Placebo

For use in Usona sponsored clinical studies, the placebo niacin, also known as vitamin B3, is provided as 100 mg capsules (size 2, HPMC, white). Niacin is United States Pharmacopeia (USP)-grade and sourced from a commercial nutritional supplement vendor.

3.5. Storage and Handling

Both placebo and psilocybin capsules are packaged individually into high-density polyethylene bottles (30 cc) and labelled in a double-blind fashion with appropriate randomized codes. Bottles must be maintained at room temperature in a locked, secure location within the research pharmacy at the site and in accordance with Drug Enforcement Agency (DEA) regulations. Study staff with access to the psilocybin inventory will be pre-defined.

3.6. Administration of Investigational Product

Capsules should be administered orally, with water, per the associated clinical protocol. Capsules should not be opened or chewed.

4. NON-CLINICAL STUDIES

Non-clinical studies summarized in this section were conducted by the Sponsor or pooled from literature searches and include *in vitro* analyses, as well as *in vivo* studies involving rats, mice, cats and rhesus macaques. Psilocybin doses utilized in the studies varied, some within the range of the 25-mg oral dose (0.36 mg/kg in a 70-kg individual) proposed for clinical use, based on standard animal-to-human dose equivalency.

4.1. Non-Clinical Pharmacology

When administered acutely, psilocybin has been shown to induce new behaviors in animals. These behaviors were subsequently tested following attenuation or inactivation of associated serotonin receptors to test for interaction with psilocin. Head twitching behavior, exhibited by rodents and similar to psychedelic effects in humans, was found to be blocked by pharmacologic inactivation of the 5HT_{2A} receptor (Willins & Meltzer, 1997). Most, but not all, of the other behaviors induced by psilocybin in animals (Table 4.1-1) are similarly blocked or significantly attenuated by inactivation of the 5HT_{2A} receptor, either pharmacologically or via gene knock-out. However, *in vitro* psilocybin binds to a wide range of receptors in addition to 5HT_{2A}, including (ordered by increasing binding affinity): 5HT_{2B}, 5HT_{1D}, dopamine D₁, 5HT_{1E}, 5HT_{1A}, 5HT_{5A}, 5HT₇, 5HT₆, D₃, 5HT_{2C}, and 5HT_{1B} (Ray, 2010). In rodents, behaviors not impacted by 5HT_{2A} inactivation include locomotor inhibition, which appears to be mediated by 5HT_{1A} and 5HT_{2B/C} receptors, based on antagonist studies.

Table 4.1-1: Behaviors exhibited by animal species upon psilocybin administration

Animal Species	Behaviors Exhibited
Rodent	Head-twitching, discrimination of psilocybin from non-psychedelic psychoactive compounds, inhibition of locomotion, disruption of short interstimulus interval (ISI), prepulse inhibition of startle (PPI), enhancement of long ISI PPI, reductions in aggression/dominance, enhancement/impairment of memory consolidation and retrieval (task dependent)
Cat	Head shaking, staring, clonic muscle activity, investigatory or play behavior
Monkey	Increased transient self-administration of psilocybin

In the rat brain, electroencephalographic changes induced by psilocybin were partly normalized by antagonists of 5-HT_{1A}, 5HT_{2A/C} as well as dopamine D₂ receptors (Tylš et al., 2014). Agonism at 5HT_{1A} autoreceptors also appeared to account for psilocybin-induced inhibition of dorsal raphe nucleus activity (Aghajanian & Hailgler, 1975), although no association was observed between dorsal raphe inhibition and any measure of behavior in freely moving cats (Trulson et al., 1981). Autoradiographic evidence shows that after systemic administration in the rat, psilocin concentrates in the neocortex, the hippocampus, and the thalamus, while showing much lower values in the hypothalamus and striatal regions (Hopf & Eckert, 1969). A single study found that doses of psilocybin within range of a 25 mg oral dose in humans (based on standard animal-to-human dose delivery) reduced neurogenesis in the rat dentate gyrus of the hippocampus, as did the 5HT_{2A} antagonist ketanserin (Catlow et al., 2013). An *in vitro* study of rat hippocampus reported that application of psilocybin reduced neuronal spike activity in hippocampal CA1 pyramidal neurons, consistent with a suppression of glutamate transmission in that brain structure (Moldavan et al., 2001).

In addition to effects on serotonin neurotransmission, non-clinical studies suggest that psilocybin also has effects on other brain systems/chemicals that may be of behavioral relevance. A microdialysis study in awake rats found that systemically administered psilocin significantly increased extracellular dopamine, but not serotonin, levels in the nucleus accumbens ([Sakashita et al., 2015](#)). Conversely, systemic administration of psilocin significantly increased extracellular serotonin levels in the rat medial prefrontal cortex, but dopamine was decreased in this region. Neither extracellular dopamine nor serotonin levels in the ventral tegmental area were altered by administration of psilocin. Psilocybin has also been reported to reduce norepinephrine levels in the rat hypothalamus, although this effect was not associated with behavioral alterations induced by the drug ([Sugrue, 1969](#)). Psilocybin increased plasma prolactin levels in a serotonergically-dependent fashion ([Meltzer et al., 1978](#)).

4.2. Non-Clinical Pharmacokinetics

Similar to human pharmacokinetics ([Section 5.1](#)) studies in rats demonstrate that upon ingestion psilocybin is rapidly dephosphorylated to psilocin in the intestinal mucosa by alkaline phosphatase and a nonspecific esterase, with approximately 50% of the total volume of psilocin absorbed from the digestive tract ([Kalberer et al., 1962](#)). When administered systemically (i.e., bypassing the gut), initial psilocybin metabolism is performed by tissue phosphatases, with *in vitro* studies indicating the kidneys as the most active metabolic organs ([Horita & Weber, 1961](#)). Psilocin metabolism occurs primarily via endoplasmic enzymes UDP-glucuronosyltransferase (UGTs), which produce psilocin-*O*-glucuronide ([Manevski et al., 2010](#)). Of 19 recombinant UGTs that have been evaluated, UGT1A10 in the small intestine and UGT1A9 in the liver have been shown to have the greatest activity ([Manevski et al., 2010](#)).

Following oral administration of psilocybin in rats, maximum plasma levels are achieved after approximately 90 minutes ([Chen et al., 2011](#)). Psilocin is distributed to all tissues, including the brain (maximum concentration at one hour post dose), and is excreted within 24 hours, with the majority excreted within the first eight hours (65% in the urine, and 15–20% in the bile and feces) ([Kalberer et al., 1962](#); [Hofmann, 1968](#)). Across species, the highest levels of psilocin were found in the neocortex, hippocampus and thalamus ([Hopf & Eckert, 1974](#)). In mice, psilocin accumulates in the kidneys and the liver prior to appearing in the brain ([Hopf & Eckert, 1974](#); [Horita & Weber, 1962](#)).

4.3. Non-Clinical Toxicology

Non-clinical studies to date suggest that psilocybin has very low toxicity, consistent with its repeated safe administration in clinical studies in humans ([Nichols et al., 2016](#)). Early studies examining isolated organs (e.g., intestine, heart) from guinea pigs and rats exposed to high doses of psilocybin (i.e., equivalent to > 25 mg in humans using standard animal-to-human dose conversion) ([Cerletti, 1958](#)). Non-clinical studies of the neurotoxicity of psilocybin have not been conducted, per literature review.

The LD50 for psilocybin is reported to be between 280-285 mg/kg in rats ([Tylš et al., 2014](#)), which is far higher than the proposed 25-mg dose for evaluation in humans (0.36 mg/kg in a 70-kg individual). Based on standard human equivalency doses (HED), the LD50 in rats is approximately 125 times the dose that a 70-kg human would receive in the current IND. The LD50 of psilocin,

the active first metabolite of psilocybin, is significantly lower for rodents than the LD50 of psilocybin itself, being 75 mg/kg. The ratio between the LD50 and ED50 is 641 per the National Institute for Occupational Safety and Health Registry of Toxic Effects (Tylš et al., 2014), which compares favorably with many drugs approved for human use (e.g., aspirin has an LD50/ED50 of 199). When administered to awake animals (including rats, mice, rabbits, cats and dogs) at a dose of 10 mg/kg (HEDs higher in all species than the 0.36 mg/kg clinical dose in humans) autonomic effects were induced that included mydriasis, piloerection, irregularities in heart and breathing rate and hyperglycemia (Cerletti, 1958; Steiner & Sulman, 1963) that were time limited and completely resolved following exposure. Similar autonomic effects were observed when psilocybin at a dose of 1-4 mg/kg was administered to baboons (Meldrum & Naquet, 1971).

Although the mutagenicity risk of psilocybin has not been definitively established, a study that utilized the micronucleus test in mice and administered psilocybin dosages of 4-16 mg/kg (0.9 to 3.6 times the proposed clinical dose of 25 mg) found no evidence of genetic abnormalities, based on an absence of chromosome breakage (Van Went, 1977).

Two GLP-compliant genotoxicity studies with psilocybin have been conducted by Usona Institute: a bacterial reverse mutation assay and an *in vitro* micronucleus assay. These two studies are summarized in Table 4.3-1 and further described below. Both studies evaluated psilocybin drug substance prepared using the Sponsor's current manufacturing process; thus the material is representative of the drug substance evaluated in clinical studies.

Table 4.3-1: Completed genotoxicity studies with psilocybin

Study Description	Test Formulation	Test Organisms/ Species	Dose/ Concentration (µg/mL)	Result	GLP
Bacterial Reverse Mutation Test	Psilocybin in purified water	<i>Salmonella typhimurium</i> TA98, TA100, TA1535, TA1537 and TA102	0, 5, 16, 50, 160, 500, 1600, 5000	Negative	Yes
<i>In Vitro</i> Micronucleus	Psilocybin in purified water	Human peripheral blood lymphocytes	200, 240, 284.1	Negative	Yes

GLP: Good Laboratory Practice

Bacterial reverse mutation test (PSIL-GEN-101): Seven concentrations of psilocybin were assayed for mutation in five histidine-requiring strains (TA98, TA100, TA1535, TA1537 and TA102) of *Salmonella typhimurium*, both in the absence and in the presence of metabolic activation by an Aroclor 1254-induced rat liver post-mitochondrial fraction (S-9). No evidence of mutagenic activity was seen at any concentration of the drug substance with or without the S9 metabolizing system. Psilocybin was not mutagenic in the bacterial reverse mutation tests at concentrations up to 5,000 µg/plate.

***In Vitro* Micronucleus test in Human Lymphocytes (PSIL-GEN-102):** This study tested psilocybin drug substance at concentrations of 200, 240 and 284.1 µg/mL in cultures of human peripheral blood lymphocytes from pooled blood of two male donors. The highest concentration

tested, 284.1 µg/mL (equivalent to 1 mM), was determined from a preliminary cytotoxicity range-finding experiment.

Treatment of cells with psilocybin for 3+21 hours in the absence and presence of S-9 and for 24+24 hours in the absence of S-9 resulted in frequencies of micronucleated binucleate (MNB) cells that were similar to and not significantly higher (at the $p \leq 0.05$ level), compared to those observed in the concurrent vehicle controls, at all test article concentrations analyzed under each treatment condition and there were no statistically significant linear trends (Table 4.3-2). It was concluded that psilocybin did not induce micronuclei in cultured human peripheral blood lymphocytes when tested up to a concentration equivalent to 1 mM in this *in vitro* cytogenetic test system.

Table 4.3-2: Frequency of Micronucleated Binucleate Cells in *In Vitro* Micronucleus Assay with Psilocybin

Treatment	Concentration (µg/mL)	Cytotoxicity (%) ^a	Mean MN Cell Frequency (%)	Historical Control Range (%) ^b	Statistical Significance
3+21 –S-9	Vehicle ^c	-	0.45	0.00 to 0.70	-
	200.0	0	0.60		NS
	240.0	0	0.50		NS
	284.1	0	0.40		NS
	MMC, 0.30 ^d	38	7.15		$p \leq 0.001$
3+21 +S-9	Vehicle ^c	-	0.40	0.10 to 0.90	-
	200.0	0	0.50		NS
	240.0	0	0.25		NS
	284.1	0	0.40		NS
	CPA, 5.00 ^d	52	3.20		$p \leq 0.001$
24+24 –S-9	Vehicle ^c	-	0.25	0.00 to 0.80	-
	200.0	3	0.50		NS
	240.0	7	0.35		NS
	284.1	6	0.30		NS
	VIN, 0.04 ^d	49	5.00		$p \leq 0.001$

CPA: Cyclophosphamide; MN: Micronucleated; MMC: Mitomycin C; NS: Not significant; VIN: Vinblastine

^a Based on replication index

^b 95th percentile of the observed range

^c Vehicle control was purified water

^d Positive control

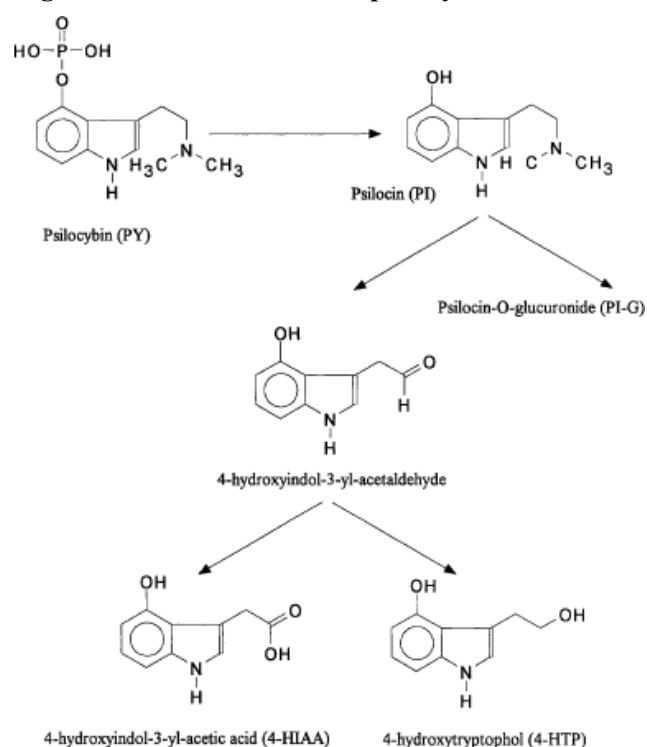
5. EFFECTS IN HUMANS

5.1. Pharmacokinetics and Metabolism in Humans

Following oral administration of 0.224 mg/kg psilocybin (10 to 20 mg), average blood concentration of the active metabolite psilocin was calculated to be 8.2 ± 2.8 ng/mL after 105 ± 37 minutes, yielding an estimated dose-normalized bioavailability of psilocybin of $52.7 \pm 20\%$ (N = 3) (Hasler, Bourquin, Brenneisen, Bar, & Vollenweider, 1997). Psilocin typically appears in plasma within 15 minutes after oral administration. Psilocin half-life following oral administration of psilocybin was found to be approximately 3 ± 1.1 hours, and is detectable for up to 24 hours after administration (Brown et al., 2017). The levels of psilocin peaked at approximately 80 minutes, but the peak psilocin concentration was more gradually attained in some subjects than in others, suggesting metabolism rates can vary between individuals (Brown et al., 2017). Plasma psilocin concentrations are directly correlated with neocortical 5-HT_{2A} occupancy and subjective assessment of its psychoactive effects (Madsen et al., 2019).

Psilocin is metabolized to 4-hydroxyindole-3-acetic acid by deamination and demethylation via liver enzymes such as monoamine oxidase, and aldehyde dehydrogenase (Figure 5.1-1) (Hasler, Bourquin, Brenneisen, Bär, et al., 1997). Psilocin is also extensively glucuronidated by the UDP-glucuronosyltransferase (UGT) family of enzymes, with the highest glucuronidation activity demonstrated by UGT1A10 (Manevski et al., 2010). The amount of psilocin glucuronide-excreted renally has been shown to exceed that of psilocin over a 24-hr time period, and analysis of psilocin in urine over 24 hours after a single dose has shown that less than 4% of the overall clearance of psilocin occurs through renal excretion (Hasler, Bourquin, Brenneisen, & Vollenweider, 2002). The pharmacokinetics of psilocybin (as psilocin) are linear over the dose range of 0.3 – 0.6 mg/kg (Brown et al., 2017; Hasler et al., 2002).

Figure 5.1-1: Metabolism of psilocybin.



5.2. Human Pharmacology

Studies using positron emission tomography (PET) showed that psilocybin ingestion (15 or 20 mg orally) increased absolute metabolic rate of glucose in frontal, and to a lesser extent in other, cortical regions as well as in striatal and limbic subcortical structures in healthy participants, suggesting that some of the key behavioral effects of psilocybin involve the frontal cortex ([Gouzoulis-Mayfrank, Schreckenberger, et al., 1999](#); [Vollenweider & Geyer, 2001](#); [Vollenweider et al., 1997](#)). Although classic psychedelics, including psilocybin, vary in their specific repertoires of receptor binding affinities across a range of receptor sites, these agents share in common agonism at the serotonin 5HT_{2A} receptor site ([Carhart-Harris et al., 2014](#); [Nichols, 2016](#); [Vollenweider & Kometer, 2010](#)). Pre-treatment with the serotonin 5HT_{2A} receptor antagonist ketanserin was found to block most of the experiential/emotional/psychedelic effects of psychedelic compounds in humans (including acute increases in positive mood) ([Kometer et al., 2012](#); [Vollenweider, Vollenweider-Scherpenhuyzen, Babler, Vogel, & Hell, 1998](#)). 5HT_{2A} receptor stimulation depolarizes layer 5 pyramidal neurons leading to an increased firing rate ([Aghajanian & Marek, 1997](#); [Andrade, 2011](#)). This increased firing in prefrontal cortex results in increased glutamatergic recurrent network activity, which can be abolished not only by 5HT_{2A} receptor antagonists, but by also antagonists of several glutamate receptors, including the AMPA (alpha-amino-3-hydroxyl-5-methyl-4-isoxazole-propionic acid) receptor, that are increasingly implicated in the pathophysiology of depression ([Maeng & Zarate, 2007](#)).

Recent evidence suggests that psychedelic agonists have distinct biological effects not found in non-psychedelic 5HT_{2A} agonists. Psychedelic, but not non-psychedelic, 5HT_{2A} agonists have been shown via receptor-receptor interactions to enhance signaling through the dopamine D₂ receptor in ventral striatum, which is of significant interest given that increased dopamine activity in this

area correlates with euphoria in response to psilocybin (Vollenweider, Vontobel, Hell, & Leenders, 1999), and given that abnormalities in the D2 receptor have been reported in the same brain area in patients with major depression (Pei et al., 2010). Recent studies indicate that psychedelic and non-psychedelic 5HT2A agonists also differentially regulate intracellular signaling pathways in pyramidal neurons, with resultant differences in the expression of downstream signaling proteins, such as beta-arrestin 2 and early growth response protein 1 (EGR1) (Gonzalez-Maeso et al., 2007; Schmid, Raehal, & Bohn, 2008). Although 5HT2A agonism is widely recognized as the primary action of classic psychedelic agents, psilocybin has lesser affinity for a wide range of other pre- and post-synaptic serotonin and dopamine receptors, as well as the serotonin reuptake transporter (Tylš, Palenicek, & Horacek, 2014). Psilocybin activates 5HT1A receptors, which may contribute to antidepressant/anti-anxiety effects.

Plasma psilocin concentrations have been shown to be directly correlated with neocortical 5-HT2A occupancy as well as subjective assessment of its psychoactive effects (Madsen et al., 2019). A single oral dose of psilocybin (3 to 30 mg) resulted in dose-related 5-HT2A receptor occupancies up to 72%. Further, subjective intensity was correlated with both 5-HT2A receptor occupancy and psilocin levels.

5.3. Clinical Trial Summaries

5.3.1. Introduction

Clinical trials examining the safety and preliminary efficacy of oral psilocybin administration in conjunction with cognitive enhancement therapy have been completed in the academic setting and are summarized in this section. These trials, enrolling 302 adult participants, include open-label, dose-escalating studies, as well as randomized, double-blind trials, and enrolled both healthy volunteers and various subpopulations with differing indications (Table 5.3-1).

Of the 302 participants enrolled across these studies, 290 received at least one dose of oral psilocybin, 204 participants received two doses, 71 participants received three doses, and 14 participants received four doses (study dosing schedules varied and are described in the sections below). In total, 579 oral psilocybin doses were administered. Doses administered in the studies in the clinical setting have ranged from a “very low dose” (45 µg/kg) to a “high dose” (600 µg/kg; 0.6 mg/kg), corresponding to doses of 3.15 mg to 42 mg in a 70-kg human.

Table 5.3-1: Summary of completed clinical trials studying oral psilocybin

Study	Reference	Study Design	Description	Enrollment	Population (Age)	Dose
<i>Clinical Studies in Healthy Subjects</i>						
University of Wisconsin	Brown et al; <i>Clinical Pharmacokinetics</i>, 2017	Open-label, dose-escalating	PK of an oral formulation of psilocybin in normal, healthy adults	12	Healthy adults	0.3, 0.45, 0.6 mg/kg (oral, dose escalating, every four weeks)
University of Zurich	Studerus et al; <i>J Psychopharmacol</i>, 2011	Retrospective analysis	Acute, short- and long-term subjective effects from previously conducted double-blind, placebo- controlled experimental studies	110	Healthy adults	1-4 doses of oral psilocybin (45-315 µg/kg)
<i>Clinical Studies in Subjects with Depression and Anxiety, Obsessive Compulsive Disorder (OCD) and Substance Abuse/Dependence</i>						
Johns Hopkins-MDD	Davis et al.; <i>JAMA Psych</i> 2020	Randomized, wait list controlled, with wait list receiving psilocybin approximately 4 weeks after the immediate treatment group	Efficacy of two psilocybin doses	27	Adults with MDD, (40 ± 12 yr)	20 mg/70 kg, 30 mg/70 kg; 1.6 weeks apart
University of Arizona	Moreno et al; <i>J Clin Psychiatry</i>, 2006	Open-label, dose-escalating, proof of concept	Safety and clinical effects of 4 doses of psilocybin in symptomatic OCD subjects	9	Adults with OCD (26-62 yr)	Oral psilocybin, 1x 100 µg/kg (low dose), 1x 200 µg/kg (medium dose) and 1x 300 µg/kg (high dose) sequentially, with 1x 25 µg/kg (very low dose) inserted randomly
University of New Mexico	Bogenschutz et al; <i>J Psychopharmacol</i>, 2015	Single-group, dose-escalating proof of concept study	Acute effects in alcohol-dependent subjects	10	Adults with active alcohol dependence (25-65 yr)	Oral psilocybin, 1x 0.3 mg/kg, and 1x 0.3 or 0.4 mg/kg four weeks apart
Johns Hopkins (Tobacco)	Johnson et al; <i>J Psychopharmacol</i>, 2014	Open-label, dose-escalating	Safety and feasibility as an adjunct to tobacco smoking cessation treatment	15	Nicotine-dependent adult smokers (26-65 yr)	Oral psilocybin, 1x 20 mg/70 kg (low dose), 1x 30 mg/70 kg (high dose), and 1x optional dosing (low or high)
Imperial College of London	Carhart-Harris et al; <i>Lancet Psych</i>, 2016 and Carhart-Harris et al; <i>Psychopharmacol</i>, 2018	Open-label, dose-escalating feasibility study	Safety and efficacy outcomes for up to 6 months	20	Adults with moderate or severe TRD depression (30-64 yr)	Oral psilocybin, 1x 10 mg (low dose), 1x 25 mg (high dose) one week apart

Study	Reference	Study Design	Description	Enrollment	Population (Age)	Dose
Harbor-UCLA	Grob et al; <i>Arch Gen Psychiatry</i> , 2011	Randomized, double-blind, placebo-controlled, crossover	Safety and efficacy in advanced-stage cancer patients with anxiety	12	Adults with advanced cancer and reactive anxiety (26-58 yr)	0.2 mg/kg (1x oral psilocybin, 1x oral placebo)
Johns Hopkins	Griffiths et al; <i>J Psychopharmacol</i> , 2016	Randomized, double-blind, crossover	Effects of psilocybin dose (low vs high dose) on anxiety or depressive disorders exacerbated by cancer diagnosis	56 ^a	Adult cancer patients (56 yr ^b)	Oral psilocybin, 1x 0.014 mg/kg or 0.042 mg/kg (low dose) / 1x 0.31 mg/kg or 0.43 mg/kg (high dose) ^c
NYU	Ross et al; <i>J Psychopharmacol</i> , 2016 (LTFU by Agin-Liebes et al., 2020)	Randomized, double-blind, placebo-controlled, crossover	Efficacy of a single dose on clinically significant anxiety or depression	29 ^d	Adults with cancer diagnosis (22-75 yr)	0.3 mg/kg oral psilocybin or 250 mg oral placebo

LTFU: Long-term follow-up; MDD: Major depressive disease; NYU: New York University; OCD: Obsessive-compulsive disorder; PK: Pharmacokinetics; TRD: Treatment-resistant depression; UCLA: University of California at Los Angeles

^a Fifty-six (56) subjects were randomized but 51 completed at least one session

^b Mean age for N=51 participants

^c The initial high dose of 0.43 mg/kg was reduced to 0.31 mg/kg (22 mg/70 kg) after two of the first three participants who received 0.43 mg/kg were discontinued from the study (one from vomiting shortly after capsule administration and one for personal reasons). The low dose/placebo was decreased from 0.043 mg/kg to 0.014 mg/kg after 12 participants for concern that the 0.43 mg/kg dose (3 mg/70 kg) may not serve as an inactive placebo

^d Thirty-one (31) subjects were randomized but 29 completed at least one session

5.3.2. Safety and Pharmacokinetics Clinical Trials

5.3.2.1. University of Wisconsin Study

This single-site, open-label, dose-escalating clinical trial evaluated the pharmacokinetics of an oral formulation of psilocybin in normal, healthy adults (Brown et al., 2017). This study was performed to describe the pharmacokinetics and safety profile of psilocybin in sequential, escalating oral doses of 0.3, 0.45, and 0.6 mg/kg in 12 healthy adults. These participants had a mean weight of 78.1 kg, with a range of 60.9-119.8 kg. The mean doses for each dosing level, as defined by the average participant weight, would be 23.4 mg (0.3 mg/kg), 35.1 mg (0.45 mg/kg), and 46.9 mg oral psilocybin (0.6 mg/kg). The mean dose at the 0.3 mg/kg level, which was the lowest dose tested in this study, would be similar to a 25 mg oral psilocybin dose. Dosing was administered a minimum of four weeks apart, and subjects were monitored and observed for a 24-hour period with the time of dosing as the starting point. Subjects were allowed a standardized breakfast and ingested the psilocybin with 360 mL of water. Assessments included blood pressure, heart rate and temperature measurements at pre-dose, 15, 30, 45, 60, 90, 120 minutes, and three, four, six, eight, 12, 18, and 24 hours post-dose. Standard 12-lead ECGs were obtained pre-dose, and at 2, 4, and 8 hours post-dose.

Blood samples for PK assessment were collected pre-dose, and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 18 and 24 hours post dose and urine was collected for 24 hours after the dose. Blood and urine samples were assayed by a validated LC–MS/MS assay for psilocybin and psilocin with a lower limit of quantitation (LLOQ) for psilocin in plasma and urine of 0.5 and 5.0 ng/mL, respectively.

5.3.2.1.1. Results

Twelve subjects who met the inclusion/exclusion criteria were enrolled in this study. One subject was removed from the study and replaced because no blood samples could be obtained from the indwelling catheter or venipuncture at any time-point after the first dose. One subject received only one of the three planned doses due to hypertension unrelated to the investigational product. A third subject received only two doses of psilocybin due to an inability to continue participation unrelated to the investigational product. A total of 33 of 36 planned doses were administered.

Subject dosing and demographics by dose group are provided in [Table 5.3-2](#)

Table 5.3-2: Subject demographics in Phase 1 pharmacokinetic study at University of Wisconsin

Psilocybin Dose (mg/kg)	Number of Subjects (M/F)	Median Body Weight (kg) (Range)	Individual Psilocybin Dose Range (mg)
0.30	12 (10/2)	71.2 (62.8 – 122)	19 – 37
0.45	11 (9/2)	69.2 (60.2 – 119.9)	27 – 54
0.60	10 (8/2)	71.7 60.4 – 98.6	36 – 59

F: Female; M: Male

5.3.2.1.2. Pharmacokinetics

Following a single dose administration of psilocybin at a dose of 0.3, 0.45 and 0.6 mg/kg, no parent psilocybin was found in plasma or urine, confirming the rapid metabolism of psilocybin to psilocin, probably by luminal and first-pass dephosphorylation ([Dinis-Oliveira 2017](#)). The kinetics of downstream metabolites from psilocin were not determined.

Psilocin demonstrated linear pharmacokinetics over the dosing range of 0.3 – 0.6 mg/kg. This dose range covers the proposed clinical dose of 25 mg, which for a 70-kg individual is almost equivalent to a weight-based dose of 0.30 mg/kg. The elimination half-life of psilocin was approximately 2.5 to 3 hours and the apparent volume of distribution (V_c/F) was 298 L. Median psilocin PK parameters for all 12 subjects are presented in [Table 5.3-3](#), and the plasma psilocin concentration versus time curves are presented in [Figure 5.3-1](#).

The 24-hour collection of urine after the administration of psilocybin allowed the renal clearance of psilocin to be determined from the amount of psilocin in the aggregate 24-hour urine collection and the plasma psilocin AUC_{0-24h} . Renal clearance of psilocin was less than 2% of total clearance, which is similar to the 3.4% renal excretion previously reported by Hasler ([2002](#)). Further, the renal clearance of psilocin was 58% that of measured creatinine clearance.

While the sample size from the study is limited, there were no apparent effects of intrinsic factors on the kinetics of psilocin; no effects of sex or age were observed on psilocin exposure.

Table 5.3-3: Plasma psilocin pharmacokinetic parameters (Mean±SEM [range])

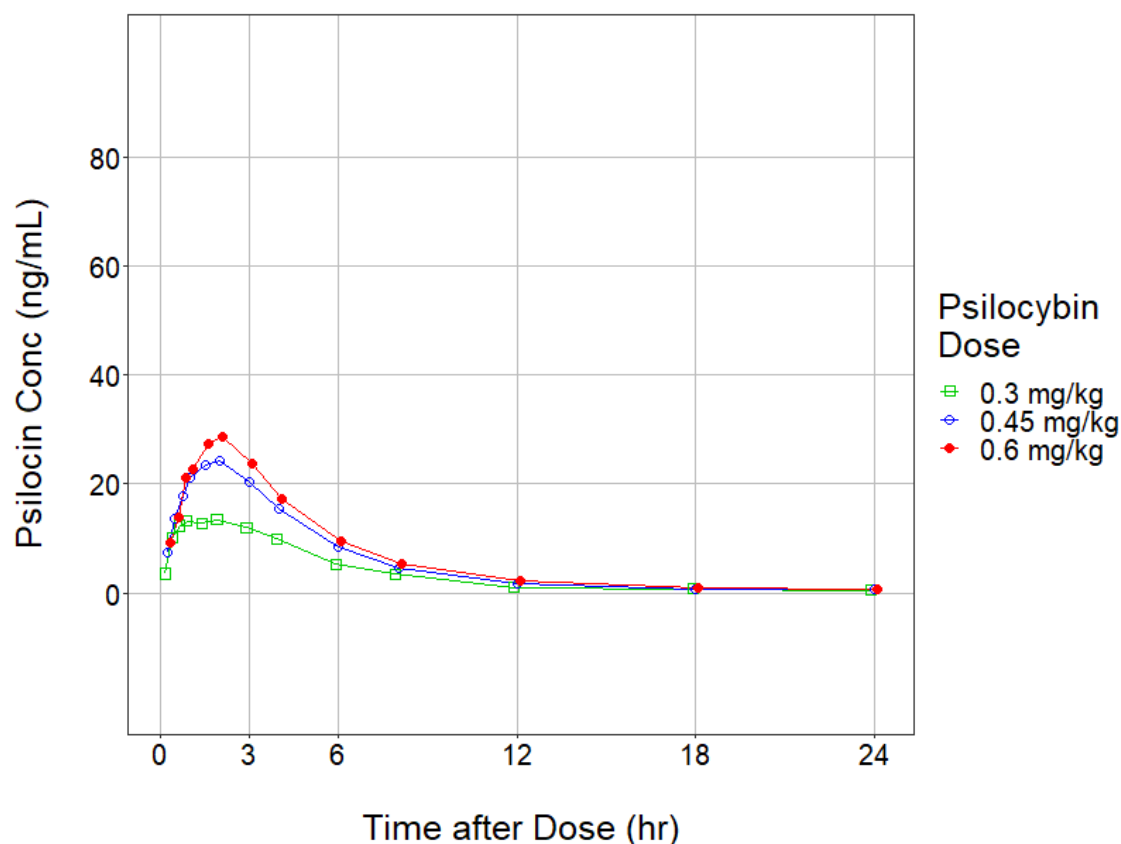
Psilocybin Dose (mg/kg)	N	AUC _{0-24h} (ng·h/mL)	AUC _{0-inf} (ng·h/mL)	C _{max} (ng/mL)	T _{max} (h)	t _{1/2} (h)
0.30	12	79.1 ± 8 (432.6-147)	83 ± 8 (44-151)	16.9 ± 1.4 (11.0-30.6)	2.14 (0.97-7.65)	2.69 (1.52-5.49)
0.45	11	130 ± 13.5 (823-228)	135 ± 13 (876.6-232)	27.8 ± 2.5 (15.8-43.3)	2.15 (0.93-4.17)	2.86 (2.13-18.6)
0.60	10	151 ± 15 (74-223)	156 ± 15 (78-227)	35.3 ± 3.8 (16.4-54.1)	2.22 (0.73-3.43)	3.67 (2.42-7.71)

AUC: Area under the concentration versus time curve; C_{max}: Maximum plasma psilocin concentration; N: Total number of subjects; SEM: Standard error of mean; T_{max}: Time when maximum psilocin concentration was reached; t_{1/2}: Terminal half-life.

Data are presented as mean ± SEM (range), except for T_{max} and t_{1/2}, where the median (range) is presented. T_{max} range values (in parentheses) reflect the elapsed time from dosing, in hours.

Source: Paul Hutson - Personal Communication

Figure 5.3-1: Mean plasma psilocin concentrations in normal subjects after a single oral dose of psilocybin



5.3.2.1.3. Adverse Events

In general, all three dose strengths were physically and psychologically well tolerated, and no serious physical or psychological adverse events (AEs) occurring during or within 30 days of any dose were reported. The most frequently occurring AEs related to IP were mild hypertension (22 instances, 83% of participants), mild bradycardia (22 instances, 58%), mild headache (14 instances, 75%), and mild tachycardia (12 instances, 50%) (Table 5.3-4). Five moderate episodes of hypertension (33% of participants) were reported. Dose strength was not found to correlate to adverse event frequency. Elevations in blood pressure were transient and typically resolved within 8 hours. Ten of 14 (71%) headache AEs were resolved with acetaminophen (650 mg). Other available medications were not used (lorazepam, diazepam, nitroglycerin, carvedilol and IM haloperidol) (*Personal communication, Paul Hutson, PharmD*).

All expected and unexpected adverse events occurring from the time of enrollment into the study through the 30-day visit following the last dose were recorded. Severity of the AEs was graded by the Common Terminology Criteria for Adverse Events (CTCAE) version 4 criteria.

Table 5.3-4: Summary of adverse events related to psilocybin dosing*

Adverse Event Description†	Total No. of Episodes	No. of Participants	No. Subjects Reporting Event		
			0.3 mg/kg	0.45 mg/kg	0.60 mg/kg
hypertension (mild)	22	10/12 (83%)	8	8	6
hypertension (moderate)	5	4/12 (33%)	2	2	1
hypotension (mild)	1	1/12 (8%)	0	0	1
bradycardia (mild)	22	7/12 (58%)	8	7	7
tachycardia (mild)	12	6/12 (50%)	5	1	4
headache (mild)	14	9/12 (75%)	5	5	4
fever (mild)	6	5/12 (42%)	0	1	5
fatigue (mild)	5	4/12 (33%)	1	1	3
nausea (mild)	4	3/12 (25%)	2	2	0
diarrhea (mild)	1	1/12 (8%)	0	0	1
dizziness (mild)	1	1/12 (8%)	0	0	1

* Data are unpublished and were obtained via personal communication from the study investigators.

† AEs were reported within 24 hrs of dosing. Mild hypertension was defined as SBP 140 to 159 mm Hg or DBP 90 to 99 mm Hg; moderate hypertension was defined as SBP \geq 160 mmHg or DBP \geq 100 mm Hg; mild hypotension was defined as SBP <90 mm Hg over DBP <60 mm Hg, bradycardia was defined as <60 BPM; tachycardia was defined as > 100 BPM, mild fever was defined as <39.0°C.

5.3.2.1.4. Conclusion

Psilocybin was well tolerated in this study, and the PK parameters were found to be linear across a series of escalating doses.

5.3.2.2. Assessment of the Impact of Psilocybin on QT Interval (Retrospective Analysis from University of Wisconsin Pharmacokinetic Study)

The potential for psilocin proarrhythmic effect was assessed using a concentration-QTc interval analysis from the open-label single ascending dose study of psilocybin described in [Section 5.3.2.1 \(Dahmane et al., 2020\)](#). In this study, 12-lead ECGs were collected prior to psilocybin administration (Baseline) and 2, 4 and 8 hours post dose and the data correlated with plasma psilocin concentration. ECGs were overread by an electrophysiologist, and QT corrections for heart rate (HR) were performed using Bazett's (QTcB) and Fridericia's (QTcF) formula. During the analysis, QTcF was determined to be a better correction method for the QT interval and thus only QTcF was further considered.

Plasma concentrations of psilocin were re-explored using binned individual fixed doses of psilocybin in mg instead of the body weight-standardized doses (mg/kg) utilized in the study. This provided dose ranges that were representative of an intended therapeutic dose of 25 mg, or as sub- and supra-therapeutic doses:

19 – 22 mg (N=8)
26 – 31 mg (N=9)
32 – 41 mg (N=7)
42 – 59 mg (N=9)

The relationship between psilocin concentration and the change from baseline in QTc interval (Δ QTc) was modeled using a population mixed-effects approach. Exploratory analyses for psilocin mean PK profiles and the time-matched mean change from baseline in heart rate (Δ HR) and in QTc interval (Δ QTc) were performed using nominal time points and the aforementioned binned individual fixed dose groups.

5.3.2.2.1. Results

Oral psilocybin resulted in an increased heart rate, with slightly higher mean change from baseline in heart rate (Δ HR) at higher psilocybin doses and corresponding higher psilocin exposures ([Table 5.3-5](#)). The maximum mean Δ HR was observed at the time of psilocin C_{max} (i.e., at 2 hours post dose) in nearly all psilocybin dose groups, and mean Δ HR decreased with decreasing psilocin concentration at subsequent time points. Mean Δ HR (upper bound of the 2-sided 90% confidence interval [CI] for mean Δ HR) is shown in [Table 5.3-5](#).

Table 5.3-5: Δ HR and psilocin exposure by dose quartile

Psilocybin Dose Range (mg)	N	Time (h)	Mean Psilocin Concentration (ng/mL) (90% CI)	Mean Δ HR (bpm) (90% CI)
19 – 22	8	2	13.2 (8.5 – 17.9)	1.0 (-8.4 – 10.4)
26 – 31	8	2	18.0 (12 – 24)	5.8 (-3.4 – 14.9)
32 – 41	7	2	23.1 (3.1 – 43.1)	6.0 (-0.4 – 12.4)
42 – 59	8	2	31.8 (14.7 – 48.8)	8.0 (1.0 – 15.0)

Data are unpublished and were obtained via the study investigators.

Δ HR: Change from baseline in heart rate; CI: Confidence interval; N: Number of subjects/observations at 2-hour post dose time point

This trial showed a significant but shallow C-QTc relationship for oral psilocybin doses ranging from 0.3 to 0.6 mg/kg (corresponding to absolute doses of 19 to 59 mg); psilocybin had a positive effect on QTcF prolongation, with a linear relationship between psilocin C_{max} and $\Delta QTcF$. There was no delay in the time course of psilocin PK and the change in $\Delta QTcF$, with maximum $\Delta QTcF$ occurring at the time of peak psilocin concentration. No subject had a QTcF interval above 450 msec during the study, only 4% to 8% of subjects had $\Delta QTcF$ between 30 msec and 60 msec, and no subject experienced a $\Delta QTcF$ above 60 msec. At the highest psilocybin dose quartile (42 to 59 mg), the mean change in $\Delta QTcF$ at the time of psilocin C_{max} (2 hours post dose) was 15 msec; this was observed at a mean plasma psilocin concentration of ~32 ng/mL. The upper bound of the 90% CI of the model-predicted that the mean $\Delta QTcF$ crossed 10 msec at a psilocin concentration of 31.1 ng/mL. This threshold concentration is well above the expected range of maximum psilocin concentrations for the psilocybin therapeutic dose of 25 mg.

For the proposed therapeutic dose of 25 mg psilocybin, the anticipated mean psilocin C_{max} is approximately 18.7 ng/mL. The associated upper bound of the 90% CI of the predicted mean $\Delta QTcF$ at this exposure is 6.6 msec.

The mean predicted $\Delta QTcF$ versus psilocin concentrations and distribution of psilocin maximum concentrations in each dose quartile are shown in [Figure 5.3-2](#) (upper and lower panels, respectively).

Table 5.3-6: $\Delta QTcF$ and psilocin exposure by dose quartile

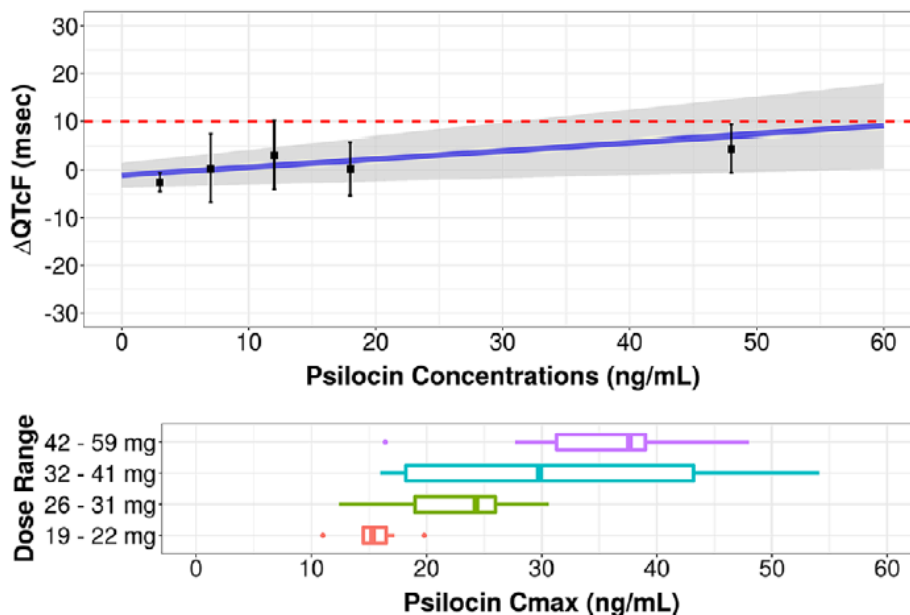
Psilocybin Dose Range (mg)	N	Time (h)	Mean Psilocin Concentration (ng/mL) (90% CI)	Mean $\Delta QTcF$ (msec) (90% CI)
19 – 22	8	2	13.2 (8.5 – 17.9)	-1.1 (-11.5 – 9.2)
	8	4	9.4 (1.2 – 17.6)	2.9 (-4.7 – 10.4)
	8	8	2.5 (0.6 – 4.5)	-6.2 (-17.4 – 4.9)
26 – 31	8	2	18.0 (12 – 24)	-3.9 (-7.7 – 0.0)
	8	4	13.4 (3.2 – 23.7)	-5.1 (-11.6 – 1.4)
	6	8	3.8 (0 – 9)	-9.7 (-20.1 – 0.8)
32 – 41	7	2	23.1 (3.1 – 43.1)	0.1 (-3.8 – 4.1)
	7	4	13.7 (6.5 – 20.8)	3.4 (-9.9 – 16.8)
	7	8	6.0 (0 – 14.7)	1.0 (-10.9 – 12.9)
42 – 59	8	2	31.8 (14.7 – 48.8)	15.0 (3.1 – 26.9)
	9	4	19.5 (4.6 – 34.4)	6.9 (-3.1 – 16.8)
	9	8	5.3 (1 – 9.6)	1.3 (-10.6 – 13.3)

Data are unpublished and were obtained via the study investigators.

ΔHR : Change from baseline in heart rate; CI: Confidence interval; N: Number of subjects/observations

Figure 5.3-2: Mean predicted Δ QTcF versus psilocin concentrations (upper panel) and distribution of psilocin maximum concentrations in each dose quartile (lower panel).

In the upper panel, the shaded gray area represents the 90% confidence interval around the mean predicted Δ QTcF (solid blue line). The squared dots with error bars represent the mean and 90% confidence interval of Δ QTcF in each quantile of psilocin concentrations.



5.3.2.3. University of Zurich

This was a retrospective analysis to analyze acute, short- and long-term subjective effects of psilocybin in healthy humans from eight previously conducted double-blind, placebo-controlled experimental trials (Table 5.3-7) (Studerus et al., 2011). Oral psilocybin was provided in either a single dose, or a range of up to four doses per participant, with dose strength varying from 45 to 315 μ g/kg. All studies were performed in a single laboratory over the course of 10 years, and analyzed the acute and persisting effects of 228 psilocybin sessions in 110 healthy volunteers. For dose escalation studies, doses were randomized and separated by at least 14 days, and each volunteer received placebo in addition to oral psilocybin.

Table 5.3-7: Studies involving oral psilocybin dosing included in [Studerus et al., 2011](#)

Study description	Psilocybin dose conditions	Number of subjects receiving at least one dose of psilocybin	Very low dose (45 µg/kg)	Low dose (115–125 µg/kg)	Medium dose (115–260 µg/kg)	High dose (315 µg/kg)
1. Dose–effect study on acute psychological and physiological effects of psilocybin	1) 45 µg/kg 2) 115 µg/kg 3) 215 µg/kg 4) 315 µg/kg	8	8	8	8	8
2. Acute effects of psilocybin on cognitive functions and subjective experience	1) 115 µg/kg 2) 215 µg/kg 3) 315 µg/kg	16	-	16	16	16
3. Effects of psilocybin on brain activity using H2O-PET	260 µg/kg	12	-	-	12	-
4. Effects of psilocybin on prepulse inhibition of startle in healthy human volunteers	1) 115 µg/kg 2) 215 µg/kg 3) 315 µg/kg	20	-	17	17	18
5. Effects of psilocybin on the rate and rhythmicity of perceptual rivalry alternations	1) 115 µg/kg 2) 250 µg/kg	12	-	12	12	-
6. Investigation on the relationship between attention, working memory, and the serotonin 1A and 2A receptors using psilocybin and ketanserin	1) 215 µg/kg 2) 215 µg/kg after ketanserin pretreatment	10	-	-	10	-
7. Effects of psilocybin on visual processing: An EEG study	1) 125 µg/kg 2) 250 µg/kg	21	-	21	18	-
8. Serotonin 5-HT _{2A} receptor dynamics in the human brain following psilocybin stimulation: A PET study	250 µg/kg	11	-	-	11	-
<i>Total number of subjects</i>	-	110	8	74	104	42

5.3.2.3.1. Adverse Events

Psilocybin was generally well tolerated. There were no serious adverse events (SAEs) reported. The most frequent self-reported adverse experiences were mild headache and mild lethargy (fatigue, exhaustion, or lack of energy) immediately after psilocybin administration. For these events, normal function was largely restored after 24 hours. Complaints were reported 24 hours post-dose as per by the List of Complaints questionnaire. [Table 5.3-8](#) shows the complete list of participant complaints, differentiated by dose effect relation versus placebo, and medium dose comparison to placebo.

Table 5.3-8: List of complaints 24 hours post-dose in healthy human subjects (Studerus et al., 2011)

Complaints	Dose effect relation (N = 40)						Medium Dose Comparison (N = 72)			
	Placebo	115 µg/kg	215 µg/kg	315 µg/kg	p-value	Signif.	Placebo	215-250 µg/kg	p-value	Signif.
Fatigue	12.5% (5)	40.0% (16)	35.0% (14)	60.0% (24)	<0.001	***	19.4% (14)	40.3% (29)	0.009	**
Exhaustion	7.5% (3)	22.5% (9)	22.5% (9)	22.5% (9)	0.090		9.7% (7)	27.8% (20)	0.009	**
Headaches, head pressure or face pain	2.5% (1)	12.5% (5)	22.5% (9)	37.5% (15)	<0.001	***	8.3% (6)	19.4% (14)	0.099	
Lack of energy	0.0% (0)	15.0% (6)	7.5% (3)	22.5% (9)	0.002	**	4.2% (3)	16.7% (12)	0.027	*
Excessive sleep requirement	2.5% (1)	10.0% (4)	10.0% (4)	15.0% (6)	0.177		6.9% (5)	12.5% (9)	0.386	
Difficulty concentrating	5.0% (2)	7.5% (3)	7.5% (3)	17.5% (7)	0.015	*	4.2% (3)	13.9% (10)	0.046	*
Gone feeling	2.5% (1)	10.0% (4)	5.0% (2)	22.5% (9)	0.005	**	2.8% (2)	12.5% (9)	0.023	*
Fast exhaustibility	2.5% (1)	12.5% (5)	10.0% (4)	17.5% (7)	0.064		4.2% (3)	8.3% (6)	0.371	
Brooding	5.0% (2)	5.0% (2)	0.0% (0)	12.5% (5)	0.106		4.2% (3)	12.5% (9)	0.114	
Lack of appetite	0.0% (0)	7.5% (3)	5.0% (2)	17.5% (7)	0.015	*	1.4% (1)	9.7% (7)	0.077	
Neck or shoulder pain	7.5% (3)	7.5% (3)	2.5% (1)	5.0% (2)	0.629		4.2% (3)	8.3% (6)	0.450	
Irritability	5.0% (2)	10.0% (4)	5.0% (2)	7.5% (3)	0.768		2.8% (2)	5.6% (4)	0.683	
Sexually stimulating fantasies	5.0% (2)	2.5% (1)	5.0% (2)	5.0% (2)	0.801		6.9% (5)	5.6% (4)	1.000	
Strong thirst	2.5% (1)	5.0% (2)	5.0% (2)	0.0% (0)	0.468		1.4% (1)	9.7% (7)	0.077	
Heavy or tired legs	2.5% (1)	0.0% (0)	2.5% (1)	12.5% (5)	0.008	**	2.8% (2)	4.2% (3)	1.000	
Sleeplessness	2.5% (1)	0.0% (0)	7.5% (3)	5.0% (2)	0.290		1.4% (1)	6.9% (5)	0.221	
Bloated feeling	5.0% (2)	0.0% (0)	5.0% (2)	2.5% (1)	0.300		2.8% (2)	5.6% (4)	0.617	
Backache	2.5% (1)	5.0% (2)	2.5% (1)	2.5% (1)	0.896		2.8% (2)	5.6% (4)	0.683	
Worries about professional or private affairs	0.0% (0)	5.0% (2)	2.5% (1)	5.0% (2)	0.532		4.2% (3)	4.2% (3)	1.000	
Dark thoughts	5.0% (2)	5.0% (2)	2.5% (1)	2.5% (1)	0.801		4.2% (3)	2.8% (2)	1.000	
Inner tension	2.5% (1)	7.5% (3)	0.0% (0)	7.5% (3)	0.234		1.4% (1)	2.8% (2)	1.000	
Abdominal pain or stomach ache	2.5% (1)	2.5% (1)	2.5% (1)	7.5% (3)	0.392		1.4% (1)	2.8% (2)	1.000	

	Dose effect relation (N = 40)						Medium Dose Comparison (N = 72)			
Complaints	Placebo	115 µg/kg	215 µg/kg	315 µg/kg	p-value	Signif.	Placebo	215-250 µg/kg	p-value	Signif.
Intolerances to certain smells	0.0% (0)	2.5% (1)	2.5% (1)	5.0% (2)	0.494		1.4% (1)	5.6% (4)	0.371	
Nausea	0.0% (0)	7.5% (3)	5.0% (2)	2.5% (1)	0.232		0.0% (0)	4.2% (3)	0.248	
Uneasiness	2.5% (1)	2.5% (1)	2.5% (1)	5.0% (2)	0.875		1.4% (1)	2.8% (2)	1.000	
Tendency of crying	2.5% (1)	0.0% (0)	2.5% (1)	0.0% (0)	0.572		1.4% (1)	5.6% (4)	0.371	
Joint aches	2.5% (1)	2.5% (1)	2.5% (1)	0.0% (0)	0.733		1.4% (1)	4.2% (3)	0.617	
Cold feet	2.5% (1)	0.0% (0)	2.5% (1)	2.5% (1)	0.801		1.4% (1)	4.2% (3)	0.617	
Freezing	0.0% (0)	2.5% (1)	5.0% (2)	0.0% (0)	0.300		1.4% (1)	4.2% (3)	0.617	
Ravenous appetite	5.0% (2)	2.5% (1)	2.5% (1)	0.0% (0)	0.494		2.8% (2)	1.4% (1)	1.000	
Throat pain or irritated throat	5.0% (2)	0.0% (0)	0.0% (0)	7.5% (3)	0.101		2.8% (2)	0.0% (0)	0.480	
Easy rubescence	2.5% (1)	7.5% (3)	0.0% (0)	0.0% (0)	0.066		2.8% (2)	0.0% (0)	0.480	
Lump in throat or throat tightness	2.5% (1)	2.5% (1)	2.5% (1)	0.0% (0)	0.733		1.4% (1)	1.4% (1)	1.000	
Diarrhea	2.5% (1)	0.0% (0)	0.0% (0)	7.5% (3)	0.112		1.4% (1)	0.0% (0)	1.000	
Restless legs	5.0% (2)	2.5% (1)	0.0% (0)	0.0% (0)	0.300		2.8% (2)	0.0% (0)	0.480	
Cold intolerance	0.0% (0)	2.5% (1)	2.5% (1)	0.0% (0)	0.392		0.0% (0)	4.2% (3)	0.248	
Vertigo	2.5% (1)	0.0% (0)	0.0% (0)	2.5% (1)	0.392		2.8% (2)	1.4% (1)	1.000	
Forgetfulness	0.0% (0)	0.0% (0)	2.5% (1)	5.0% (2)	0.194		0.0% (0)	2.8% (2)	0.480	
Difficulty swallowing	2.5% (1)	0.0% (0)	0.0% (0)	5.0% (2)	0.300		1.4% (1)	0.0% (0)	1.000	
Frequent urges to urinate	2.5% (1)	0.0% (0)	2.5% (1)	0.0% (0)	0.572		1.4% (1)	1.4% (1)	1.000	
Strong perspiration	2.5% (1)	2.5% (1)	0.0% (0)	0.0% (0)	0.572		1.4% (1)	1.4% (1)	1.000	

Numbers in parentheses indicate absolute frequencies. Dose effect relation population data is pooled from studies 1, 2 and 4 in [Table 5.3-7](#). Medium dose comparison population data is pooled from studies 1, 2, 4, 5, 6 and 8.

Five participants terminated their studies early. Three were withdrawn from their respective studies due to adverse events caused by psilocybin (two were removed by the investigator following an unusually intense reaction to low-dose psilocybin, and one subject was removed by the investigator after experiencing a transient hypotonic reaction with dizziness, fainting and vomiting after receiving low-dose psilocybin), and two voluntarily withdrew following administration of high-dose psilocybin due to symptoms of anxiety. In each case, symptoms were completely resolved by the end of the dosing day.

5.3.2.3.2. Abuse Potential

The large majority of participants (approximately 90%) reported “no change” in their psilocybin use following their laboratory sessions, as well as “no change” in their overall drug consumption habits (e.g., use of alcohol, nicotine, cannabis, MDMA). Those who did report changes often described decreased consumption. Specifically, in terms of psilocybin use, more participants reported using it less often after their laboratory sessions (5.6% of all participants) than more often (3.3% of all participants).

5.3.2.3.3. Conclusion

Collected data from the eight studies listed in [Table 5.3-7](#) demonstrated that psilocybin was safe and well tolerated under the conditions tested. Adverse events were generally classified as mild and resolved within 24 hours.

5.3.2.4. Additional Safety Results in Studies with Healthy Participants

The below studies present additional data related to monitoring of cardiovascular and psychological events. The first study not did actively monitor for participant-reported physical adverse outcomes, and the second checked only for a pre-determined subset of physical adverse events (yawning, nausea, spontaneous motor activity, and restlessness), as graded on a participant-reported scale from 0-4. The results are included for their relevance to acute cardiovascular and psychological outcomes.

5.3.2.4.1. Adverse Events

In a first study in 36 medically and psychiatrically healthy adults, a single dose of psilocybin (0.43 mg/kg) was compared to a methylphenidate placebo ([Griffiths, Richards, McCann, & Jesse, 2006](#)). In the group as a whole, psilocybin increased systolic BP by an average of 20 mm Hg and diastolic BP by an average of 12 mm Hg. Average heart rate increased by 10 beats per minute (BPM). No participants required pharmacological intervention for these cardiovascular effects. Eleven participants (31%) experienced significant anxiety and/or dysphoria during their psilocybin sessions, and six of these subjects (17% of the total) experienced transient episodes of paranoid ideation/ideas of reference, but none required pharmacological intervention. All acute effects resolved by the end of the psilocybin sessions.

In a second study, 18 medically- and psychiatrically-healthy adults were exposed to five sessions with dosages of 0 (placebo), 5, 10, 20, or 30 mg/kg, respectively, randomized to either an ascending or descending dose order ([Griffiths et al., 2011](#)). All physiological and psychological AEs showed a strong dose-response relationship, escalating as dosage increased. Mean peak systolic BP for the

escalating dosages was 132.6, 143.3, 145.7, 145.7, and 153.1 mm Hg, respectively. Mean peak diastolic BP were 77.5, 83.4, 83.9, 84.3, and 88.8 mm Hg respectively. The four maximal BP readings in the highest dose (0.43 mg/kg) condition were 187/84, 166/64, 182/88, and 178/95 mm Hg respectively. Mean maximal heart rate by dose was 74.8, 78.7, 77.9, 82.1, and 83.0 beats per minute, respectively. No pharmacological interventions were required for BP or heart rate elevations. Feelings of anxiety and fear, as well as paranoid ideation or ideas of reference also increased in frequency during the sessions as a function of increasing dose, being significantly more prominent at the highest dose (0.43 mg/kg) than the other doses. Overall, 39% of participants indicated they experienced extreme anxiety/fear at some time during the session.

Both of these studies included a 14-month follow-up, at which point no cases of hallucinogen persisting perception disorder (HPPD) were reported. No long-term AEs were identified in either study population. Follow-up interviews have found no evidence that participating in the study precipitated any abuse of psychoactive drugs, including alcohol ([Garcia-Romeu, Griffiths, & Johnson, 2014](#)).

5.3.3. Clinical Trials for Alternative Indications (OCD and Addiction)

5.3.3.1. University of Arizona Study

This open-label, dose-escalating proof-of-concept study explored safety of four doses of oral psilocybin in nine adult participants with symptomatic obsessive compulsive disorder (OCD) ([Moreno, Wiegand, Taitano, & Delgado, 2006](#)). Escalation occurred sequentially with 100 µg/kg (low), 200 µg/kg (mid), and 300 µg/kg (high) oral doses, with a 25 µg/kg (very low) dose inserted randomly and in double-blind fashion any time after the first dose; all doses were administered at least one week apart. Assessments included the Yale-Brown Obsessive Compulsive Scale (YBOCS) and visual analog scale (VAS) for OCD symptom severity, which were administered immediately before dosing, and at four, eight, and 24 hours post-dose.

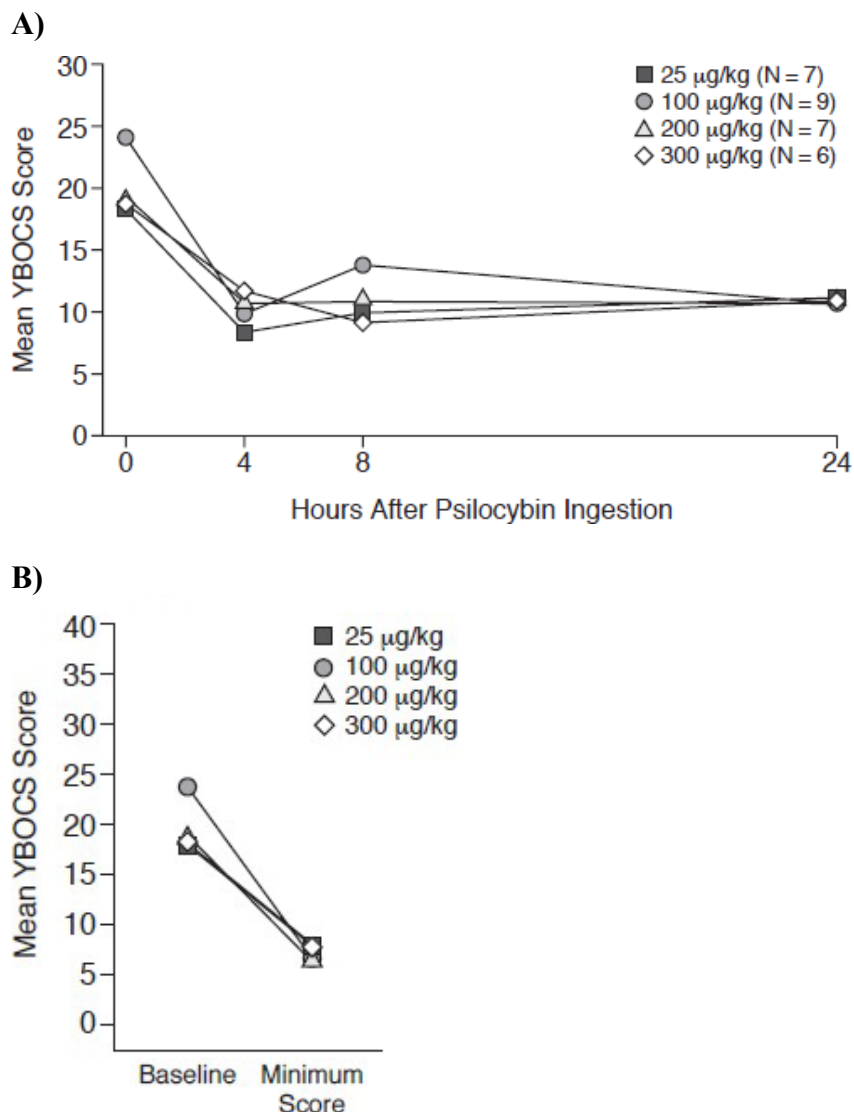
5.3.3.1.1. Results

Nine participants (seven male, two female) meeting the inclusion criteria were administered a total of 29 oral psilocybin doses. All nine subjects received the low dose of psilocybin, seven also received the mid and very low doses, and six received all four doses. Two participants declined further participation unrelated to the study product following the low dose.

5.3.3.1.2. Clinical Efficacy

Decreases in OCD symptoms of a variable degree (23%-100%) were observed in all subjects during at least one dosing session per the YBOCS ([Figure 5.3-3](#)). Dose dependency on symptom reduction was not observed, with a decrease in average YBOCS score occurring after administration of each dose level ([Figure 5.3-3](#)).

Figure 5.3-3: Decreases in OCD scores as assessed by YBOCS. A) Mean YBOCS scores immediately prior to ingesting psilocybin through 24 hours after ingestion, and B) Average YBOCS scores prior to psilocybin ingestion as compared to the average of the lowest scores obtained (4, 8, or 24 hours) after ingestion, per dose.



5.3.3.1.3. Adverse Events

One participant experienced hypertension which was not associated with psychic anxiety or somatic symptoms. No other adverse reactions were observed.

5.3.3.1.4. Conclusion

Psilocybin was reported to be safe and well tolerated at all four dose levels and was associated with acute reductions in core OCD symptoms in a small population of adults with symptomatic OCD.

5.3.3.2. University of New Mexico Study

This was a single-group, dose-escalating proof of concept study to quantify the acute effects of oral psilocybin in 10 alcohol-dependent adult participants (four females), and provide preliminary outcome and safety data (Bogenschutz et al., 2015). Participants received a 12-week, 14-session manualized intervention including two open-label oral psilocybin sessions, the first after four weeks of psychosocial treatment (0.3 mg/kg), and the second after eight weeks (0.3 mg/kg or 0.4 mg/kg). Participants' vital signs were monitored at each visit at 30, 60, 90 and 120 minutes post-dose, and then hourly for an additional four hours. Psychological assessments were performed at subsequent follow-up visits, and cessation of drinking was monitored through 36 weeks.

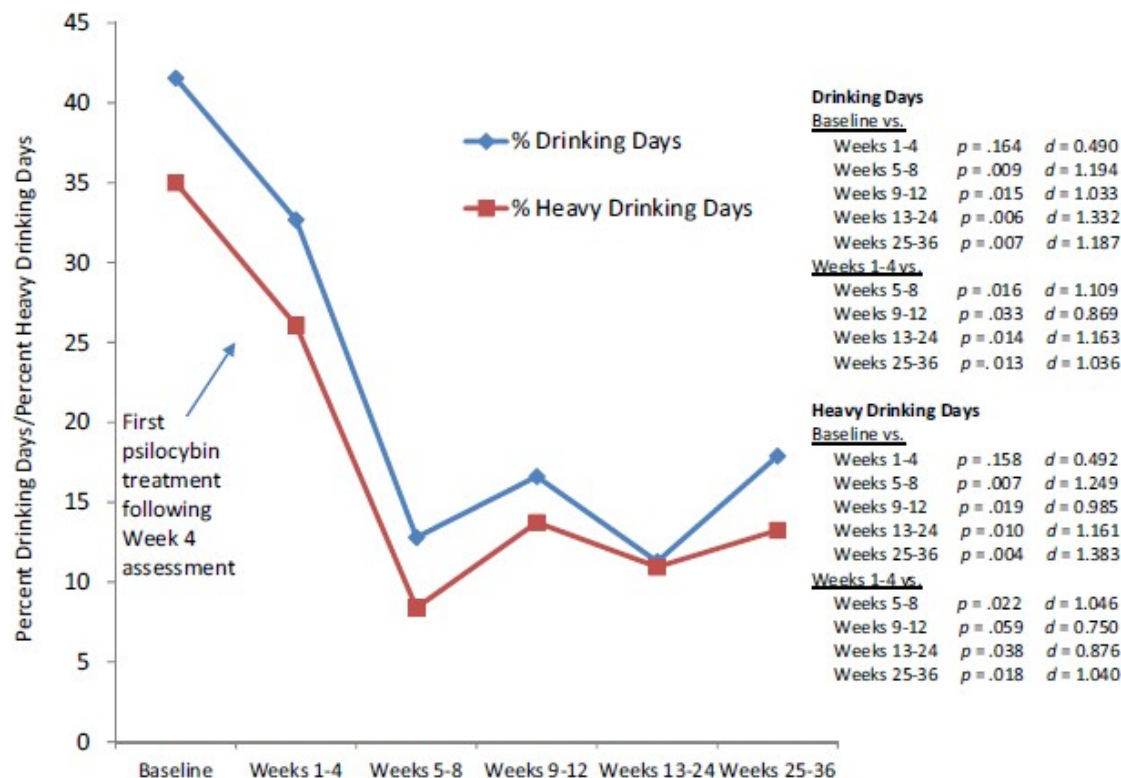
5.3.3.2.1. Results

All ten participants enrolled in the study completed the first oral psilocybin dosing at week 4 (0.3 mg/kg). Seven participants received the second psilocybin dose at week 8, with six receiving the increased dose (0.4 mg/kg). Three participants did not receive the second psilocybin dose. One withdrew participation, and two others did not receive treatment but completed all follow-up assessments. A total of 17 of 20 planned doses were administered.

5.3.3.2.2. Clinical Efficacy

Participants exhibited improvement in alcohol reliance after psilocybin dosing, and maintenance through 36 weeks (Figure 5.3-4). Mean percent of drinking days (days with any consumption of alcohol) decreased during weeks 5-12 relative to baseline ($27.2 \pm 23.7\%$; 95% CI 9.0-45.4, $p = 0.009$), and relative to weeks 1-4 ($21.9 \pm 21.8\%$; 95% CI 5.1-38.6, $p = 0.017$) prior to psilocybin administration. Mean percent of heavy drinking days (days where male participants consumed five or more drinks containing 14 g of alcohol, or female participants consumed four or more drinks containing 14 g of alcohol) also decreased during weeks 5-12 relative to baseline (26.0 ± 22.4 ; 95% CI 8.7-43.2, $p = 0.008$) and weeks 1-4 ($18.2 \pm 20.0\%$; 95% CI 2.8-33.5, $p = 0.026$).

Figure 5.3-4: Improvement in alcohol reliance following psilocybin treatment. Means shown for all available data (N=10 at baseline, N = 9 at all other time points).



5.3.3.2.3. Adverse Events

Adverse events were collected following psilocybin administration and at all subsequent visits. The most common adverse event was mild headache (5 of 10 participants, 50%), which resolved within 24 hours following psilocybin administration. One participant (10%) reported nausea with one episode of emesis. One participant (10%) experienced diarrhea after psilocybin administration, though the participant had pre-existing irritable bowel syndrome. One participant (10%) reported insomnia on the night following psilocybin administration. Treatment or other intervention was not required for blood pressure, anxiety, or other psychiatric symptoms. No serious adverse events were reported.

5.3.3.2.4. Conclusion

Psilocybin administration was well tolerated at the two dosing levels examined, and in conjunction with motivational enhancement therapy, an increased alcohol abstinence relative to baseline was observed in a population of participants with alcohol dependence.

5.3.3.3. Johns Hopkins (Tobacco) Study

This was an open-label, dose-escalating study to determine the safety and feasibility of oral psilocybin as an adjunct to tobacco smoking cessation treatment in 15 psychiatrically healthy, nicotine-dependent adult smokers (five females) (M. W. Johnson, Garcia-Romeu, Cosimano, &

Griffiths, 2014). Oral psilocybin was administered at a low dose (20 mg/70 kg body weight) and a high dose (30 mg/70 kg body weight), with an option for a third dose (low or high), during a 15-week period coinciding with a structured smoking cessation cognitive behavioral therapy treatment protocol. Dosing occurred at weeks 5, 7, and 13 (optional). Participants were monitored through week 15, and then again during a six-month follow-up. Assessments included questionnaires, self-efficacy determinations, biomarker (breath carbon monoxide, urine cotinine) and safety data.

5.3.3.3.1. Results

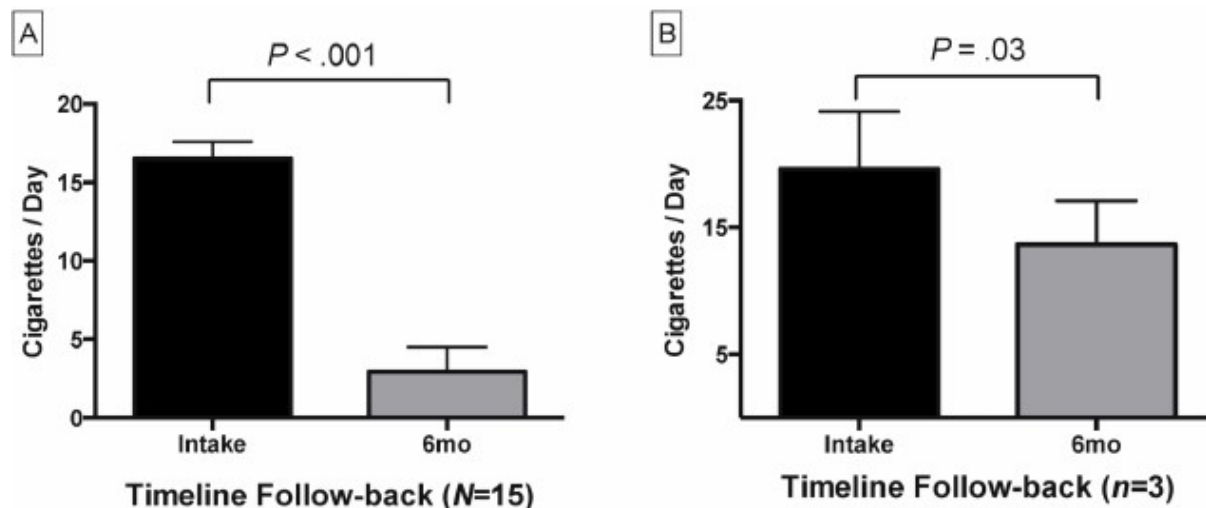
Fifteen participants completed the study, and 12 participants (80%) completed three doses of psilocybin. Three of 15 participants (20%) did not receive the third, optional dose. Amongst participants who received the optional dose, 11 of 12 (92%) opted for the high dose. Thirty (30) of 30 (100%) planned doses were administered, and 42 of 45 (93%) possible psilocybin sessions occurred under supportive conditions.

5.3.3.3.2. Clinical Efficacy

Twelve of 15 participants (80%) reported seven-day point prevalence abstinence at the six-month follow-up, and 11 (73%) were biologically confirmed to have quit smoking. Three participants (20%) tested positive for smoking at the six-month follow-up. On average, daily cigarette intake was reduced following psilocybin administration across the study population, as well as in the subpopulation (3 of 15) who tested positive for smoking at the six-month follow-up (Figure 5.3-5).

Figure 5.3-5: Timeline follow-back data for smoking cessation following psilocybin treatment.

Timeline follow-back data at the six-month time point for A) the entire study population, and B) the three participants who tested positive for smoking at the six-month follow-up.



5.3.3.3.3. Adverse Events

No serious adverse events were reported during the study. The most frequently reported adverse events included increases in blood pressure (BP) and heart rate (HR), post-treatment headache and in-session episodes of anxiety. The number of increases in blood pressure was not explicitly

reported, but across all sessions baseline values for mean maximal systolic BP increased from 125 ± 10 mm Hg to 153 ± 11 mm Hg, mean maximal diastolic BP increased from 71 ± 8 mm Hg to 87 ± 11 mm Hg, and mean maximal HR increased from 68 ± 9 to 87 ± 11 beats per minute following psilocybin administration. Ten of 15 subjects were assessed for headache following dosing (the initial five study participants did not receive post-session headache interviews), and eight (80%) reported headaches of mild severity on average (individual assessments not provided). Five of 10 (50%) reported use of over-the-counter medication to resolve the headache. Six participants (40%) had at least one episode (5 total episodes during low dose administration and 5 during high dose administration) of significant fear/anxiety during psilocybin sessions, with one (7%) self-reporting the event as extreme and five (33%) self-reporting the events as strong. With the exception of headaches, all acute adverse events had resolved by the end of the psilocybin sessions, and no pharmacological interventions were required.

5.3.3.3.4. Conclusion

Oral psilocybin was well tolerated under the conditions tested, and the authors considered the results of the study to support the feasibility of psilocybin with behavioral therapy as treatment for cessation of smoking.

5.3.4. Clinical Trials for Depression and Anxiety

5.3.4.1. Imperial College of London Study

This was an open-label, dose-escalating feasibility study to determine the safety and efficacy outcomes for up to six months post-dose of oral psilocybin in 20 adults (six females) with moderate ($N = 2$) or severe depression ($N = 18$) ([Carhart-Harris et al., 2016](#)). Participants received a low (10 mg) and high (25 mg) dose of oral psilocybin one week apart, with monitoring for six hours after dosing, and long-term follow-up through six months. Assessments included blood pressure, heart rate, and observer ratings of psilocybin's psychoactive effects at pre-dose, and 30, 60, 120, 180, 240, 300, and 360 minutes post-dose time points. Functional magnetic resonance imaging (fMRI) scanning also occurred the day after the second dose, and interim questionnaires were presented at Day 1, Week 1, Week 2, Week 3, Week 5, Month 3, and Month 6 after the second dose.

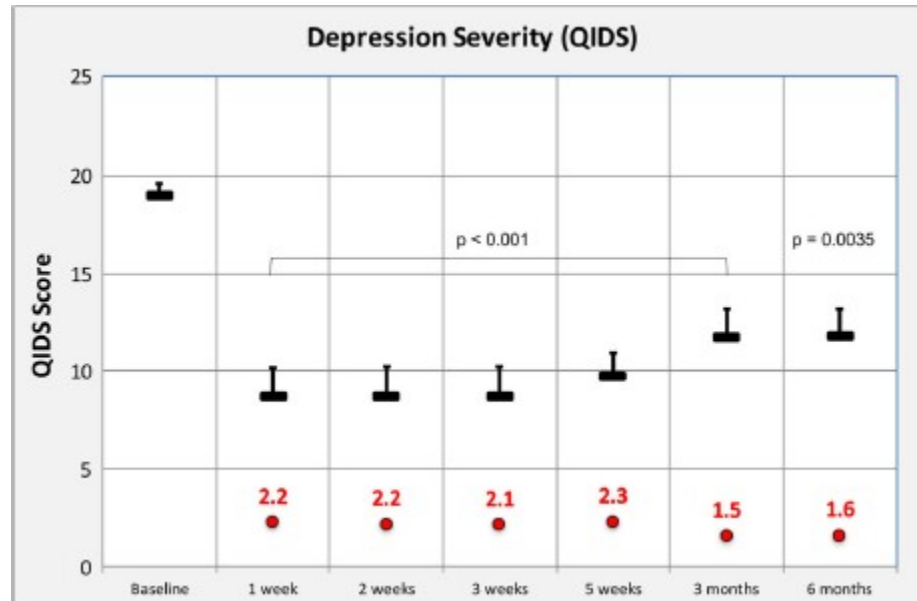
5.3.4.1.1. Results

Nineteen of 20 participants completed assessments at all time points, and all participants completed both doses of oral psilocybin. One participant did not complete follow-up measures following his second dose.

5.3.4.1.2. Clinical Efficacy

The primary outcome measure of self-reported depression severity as gauged by the Quick Inventory of Depressive Symptomatology (QIDS) showed reductions relative to baseline QIDS scores, from one week to six months after high-dose psilocybin administration for the 19 participants who completed all assessments. Mean QIDS values were found to be below the threshold for reflection of severe depression for each post-dose time point ([Figure 5.3-6](#)) ([Carhart-Harris et al., 2016](#)).

Figure 5.3-6: Mean QIDS values to assess self-reported depression. Mean values (black horizontal bars) as calculated for the 19 study completers, with error bars included. QIDS scores of 16-20 are considered to reflect severe depression. Cohen's d values vs baseline are shown in red, all contrasts vs baseline yielded p values of < 0.001 with the exception of the 6 month contrast which was $p = 0.0035$.



Score results relative to baseline for the additional study questionnaires are summarized in [Table 5.3-9](#). Self-reported questionnaires gauged depression (Beck Depression Inventory; BDI), anxiety (State- Trait Anxiety Inventory; STAI), and anhedonia (Snaith-Hamilton Pleasure Scale; SHAPS). Clinician-administered ratings were collected to assess depression (Hamilton Depression Scale; HAM-D), and global functioning (Global Assessment of Functioning; GAF). Nine and four participants respectively met the criteria for response and remission at the week five time point, and reductions in depressive symptoms were observed through six months.

Table 5.3-9: Individual patient clinical rating results

	BDI				STAI				SHAPS			HAM-D		GAF	
	Baseline	1 Week	3 Mos	6 Mos	Baseline	1 Week	3 Mos	6 Mos	Baseline	1 Week	3 Mos	Baseline	1 Week	Baseline	1 Week
Mean (SD)	34.5 7.3	11.8 11.1	19.2 13.9	19.5 13.9	68.6 6.1	44.8 15.7	56.5 13.3	53.8 13.3	6.6 4.1	1.9 2.7	3.3 4.2	24.1 5.4	9.3 7.6	48.9 10.3	74.2 16.05
Difference vs base-line (SD)	-	- 22.7 10.6	- 15.3 13.7	- 14.9 12.0	-	- 23.8 15.2	- 12.2 12.7	- 14.8 14	-	- 4.6 4.1	- 3.3 4.6	-	- 14.8 7.8	-	+ 25.3 17.1
Cohen's d value	-	2.5	1.4	1.4	-	2.2	1.2	1.5	-	1.3	0.8	-	2.3	-	1.9
p value	-	$p < 0.001$	$p < 0.001$	$p < 0.001$	-	$p < 0.001$	$p < 0.001$	$p < 0.001$	-	$p < 0.001$	$p = 0.005$	-	$p < 0.001$	-	$p < 0.001$

Clinician administered ratings (HAM-D and GAF) were completed at baseline and one week post-dosing only.

5.3.4.1.3. *Adverse Events*

The most common side effects reported were mild to moderate transient anxiety (N = 15; 79%), and mild to moderate headache (N = 8; 42%). Five participants (26%) reported transient nausea, but there were no cases of vomiting. Three participants (16%) reported transient paranoia within the duration of the acute drug experience. There were no serious adverse events reported.

5.3.4.1.4. *Conclusion*

Oral psilocybin was well tolerated under the conditions tested, and the depressive symptoms measured were seen to improve and remain improved for six months following the final study dose.

5.3.4.2. Johns Hopkins University – Major Depressive Disorder (MDD) Study

This was a randomized waitlist-controlled study in 24 patients with major depressive disorder (MDD) with a minimum HAMD (Hamilton Depression Rating Scale) score of 17 ([Davis et al., 2020](#)). Subjects received two psilocybin administrations (dose 1: 20 mg/70 kg body weight; and dose 2: 30 mg/70 kg) with doses separated by an average of 1.6 weeks. Clinical response was assessed by the HAMD (at 1 week and 4 weeks post dose 2) and QIDS (at 1 day and 1 week post dose 1, and 1 day, 1, 2 and 4 weeks post dose 2). One week after completion of the immediate treatment cohort, subjects randomized to the waitlist condition entered an identical treatment and assessment protocol, allowing scores from both groups to be collapsed to examine the absolute impact of psilocybin on depressive scores and on rates of response and remission.

5.3.4.2.1. *Results*

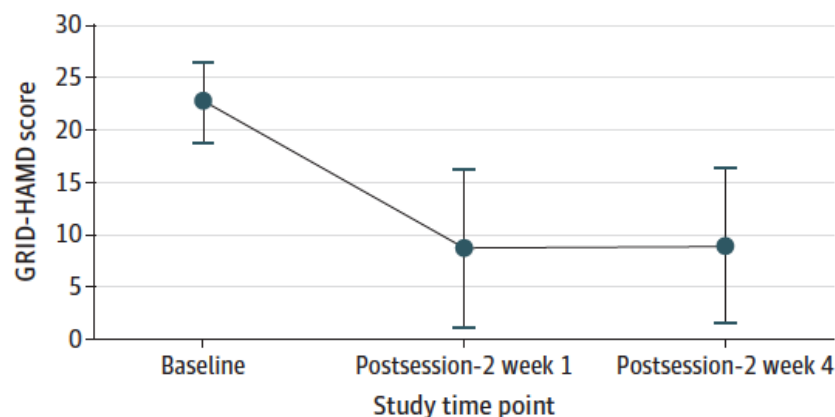
Of the 27 randomized participants, 24 (89%) completed the intervention and the week 1 and week 4 post-session assessments and were included in the modified intent-to-treat (ITT) analysis. This ITT population had a mean (SD) age of 39.8 (12.2) years, was composed of 16 women (67%), and was 92% Caucasian. The ITT population had a mean (SD) baseline HAMD score of 22.8 (3.9), the mean depressive illness length was 21.5 (12.2) years and mean length of the current depressive episode was 24.4 (22.0) months. Fifty-eight (58) percent of subjects had failed at least one antidepressant agent in the current episode. Fifteen (15) were randomized to the immediate treatment group and 12 to the delayed treatment group; thirteen (13) completed both sessions in the immediate treatment group and 11 completed both sessions in the delayed treatment group.

5.3.4.2.2. *Clinical Efficacy*

The primary outcome, depression severity was assessed with the GRID-HAMD scores at weeks 5 and 8 after enrollment for the delayed treatment group, which corresponded to weeks 1 and 4 after the intervention for the immediate treatment group. The GRID-HAM is a version of the 17-item Hamilton Depression Rating Scale that has high reliability and validity ([Williams JBW, et al., 2008](#)). Secondary outcomes included the Quick Inventory of Depressive Symptomatology-Self Rated (QIDS-SR), the Beck Depression Inventory II and the 9-item Patient Health Questionnaire.

After the psilocybin session, 16 participants (67%) at week 1 and 17 participants (71%) at week 4 had a clinically significant response to the intervention ($\geq 50\%$ reduction in GRID-HAMD score), and 14 participants (58%) at week 1 and 13 participants (54%) at week 4 met the criteria for remission of depression (≤ 7 GRID-HAMD score). Specifically, compared with the waitlist condition, two doses of psilocybin significantly reduced GRID-HAMD scores at 1- and 4-weeks post-dosing session 2. GRID-HAMD scores in the psilocybin-treated group were 22.9 (3.6) at baseline, 8.0 (7.1) at week 1, and 8.5 (5.7) at week 4 post-dosing. In the delayed treatment group, the mean (SD) GRID-HAMD scores were 22.5 (4.4) at baseline, 23.8 (5.4) at 1 week and 23.5 (6.0) at 4 weeks post-baseline assessment (Week 1: Cohen $d = 2.2$; 95% CI, 1.4-3.0; $P < .001$; Week 4: Cohen $d = 2.6$; 95% CI, 1.7-3.6; $P < .001$) In addition, within-participant t tests showed statistically significant decreases in GRID-HAMD scores among 14 participants from baseline to week 1 (Figure 5.3-7) post psilocybin dosing.

Figure 5.3-7: Decrease in the GRID Hamilton Depression Rating Scale (GRID-HAMD) Scores at Week 1 and Week 4 Postsession-2 Follow-up in the Overall Treatment Sample. The mean (SD) GRID-HAMD score was 22.8 (3.9) at baseline, 8.7 (7.6) at week 1, and 8.9 (7.4) at week 4. Effect sizes (Cohen d with 95%CI) and P values reflect the results of a paired sample t test that compared scores between baseline and week 1 (Cohen $d = 3.6$; 95%CI, 2.2-5.0; $p < .001$) and week 4 postsession-2 follow-up (Cohen $d = 3.6$; 95%CI, 2.2-4.9; $p < .001$).



All secondary depression and anxiety outcomes showed a similar pattern of results as the primary depression outcomes, with statistically significant differences between conditions and across both conditions after entry into the active intervention period. For example, statistically significant treatment condition effects were found on self-reported depression (Beck Depression Inventory II and Patient Health Questionnaire–9) and clinician-administered anxiety (Hamilton Anxiety Rating Scale) measures.

5.3.4.2.3. Adverse Events

No serious adverse events occurred. A transient increase in blood pressure (diastolic blood pressure >100 mm Hg) occurred during 1 session, but no medical intervention was needed, and the blood pressure level remained within predetermined safety parameters and resolved spontaneously during the session. Other nonserious adverse effects which occurred included challenging emotional (e.g., fear and sadness) and physical (e.g., feeling body shake or tremble) experiences. Mild to moderate transient headache was reported during 33% of sessions.

5.3.4.2.4. Conclusion

Two oral doses of psilocybin were well tolerated under the conditions tested, and treatment with psilocybin produced statistically significant antidepressant effects in this study of patients with MDD.

5.3.4.3. Harbor-UCLA Study

This was a randomized, double-blind, placebo-controlled crossover design study (NCT00302744) to evaluate the efficacy of psilocybin in 12 adults (11 females) with advanced-stage cancer (various types) and reactive anxiety ([Grob et al., 2011](#)). The dosing sessions were spaced several weeks apart, and participants would receive either oral psilocybin (0.2 mg/kg) or oral placebo (niacin, 250 mg) in a randomized order. Assessments included monitoring for temperature, heart rate and blood pressure, and dosing sessions concluded with self-reported participant outcomes. The duration of follow-up was six months following the second dosing session.

5.3.4.3.1. Results

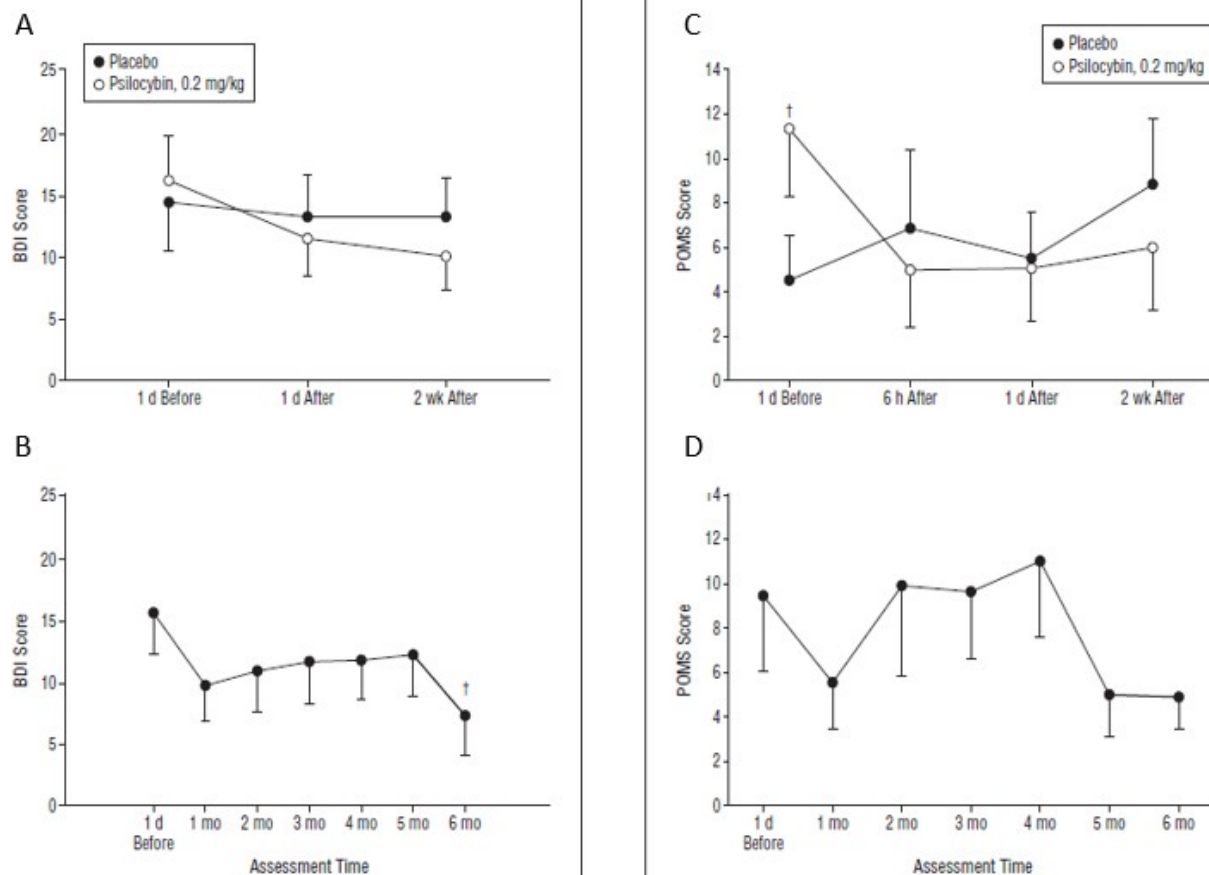
All 24 planned doses (12 psilocybin, and 12 placebo) were administered. Eight of 12 participants (67%) completed the 6-month follow-up assessment, 11 (92%) completed at least the first four months of assessment, and all 12 (100%) completed at least the first 3 months of follow-up. Two subjects died due to their underlying cancer during the follow-up period, and two others became too ill to continue participating.

5.3.4.3.2. Clinical Efficacy

As per the self-reported Beck Depression Inventory (BDI) scores for psilocybin through two weeks post-dose, there was an overall reaction that approached but did not attain statistical significance. There was no appreciable change in BDI scores for the placebo control ([Figure 5.3-8A](#)). Long-term follow-up through six months were sustained, dropping nearly 30% from pre-administration to month one, and achieving statistical significance at month six ($P = 0.03$).

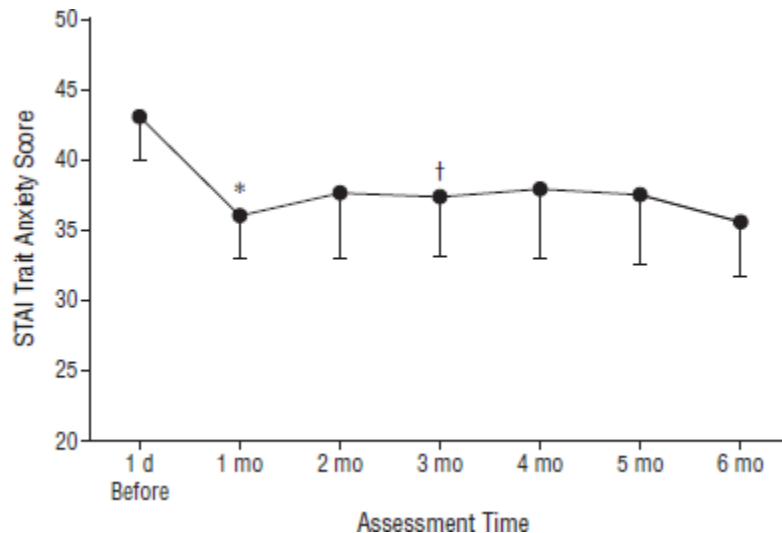
Self-reported Profile of Mood States (POMS) scores also revealed a trend for reduced adverse mood relative to placebo, with improvement of mood shown by 11 of 12 (92%) of participants after psilocybin dosing. It was noted though that mean POMS scores prior to dosing were elevated for psilocybin relative to placebo. There was no pattern observed for POMS scores during the six-month follow-up period ([Figure 5.3-8](#)).

Figure 5.3-8: BDI and POMS scores between placebo and psilocybin for assessment of clinical efficacy. A) Mean BDI scores between placebo and psilocybin for up to two weeks after administration. B) Mean BDI scores reported during the 6-month follow-up following the second dosing event. C) Mean POMS scores between placebo and psilocybin for up to two weeks after administration. D) Mean POMS scores during the 6-month follow-up following the second dosing event. N = 12 for all time points up to three months, N = 11 for the 4-month time point, and N = 8 for the Months 5 and 6 time points. † $p < 0.05$ for psilocybin vs the value from 1 day before the first treatment session (t tests were used to compare individual monthly follow-up values with values on the day before the first session).



Self-reported scores from the State-Trait Anxiety Index (STAI) did not yield significant change for the state anxiety subscale. A sustained decrease for the STAI trait anxiety subscore was shown through the duration of follow-up, achieving statistical significance at Months 1 and 3 ([Figure 5.3-9](#)).

Figure 5.3-9: STAI trait anxiety subscores through long-term follow-up. N = 12 for all time points up to three months, N = 11 for the 4-month time point, and N = 8 for the Months 5 and 6 time points. * $p < 0.01$, † $p < 0.05$ for psilocybin vs the value from 1 day before the first treatment session (t tests were used to compare individual monthly follow-up values with values on the day before the first session).



5.3.4.3.3. Adverse Events

No serious adverse events were reported during the study, and no adverse psychological effects arose from treatment (Grob et al., 2011). Adverse events were collected during study administration and solicited during monthly follow-up phone calls. No untoward cardiovascular sequelae was observed, though treatment with psilocybin produced transient increases in blood pressure (BP) and heart rate as compared to placebo. In response to psilocybin, mean maximum systolic BP increased from 117 ± 4.3 mm Hg to 138.9 ± 6.4 mm Hg, mean maximal diastolic BP increased from 69.6 ± 2.7 mm Hg to 75.9 ± 3.4 mm Hg, and mean maximal heart rate increased from 70.4 ± 4.3 beats per minute to $81.5 \pm (5.8)$ beats per minute. No additional information on adverse event reporting was available.

5.3.4.3.4. Conclusion

The study demonstrated that controlled use of psilocybin in advanced-stage cancer patients could provide an alternative model for treatment of anxiety and despair. Psilocybin was found to be well-tolerated, and no clinically significant adverse events were reported.

5.3.4.4. Johns Hopkins University – Cancer-related Depression Symptoms Study

This was a randomized, double-blind, crossover study (NCT00465595) to investigate the effects of psilocybin dose (low vs high dose) on a variety of outcome measures relevant to anxiety or depressive disorders exacerbated by cancer diagnosis (Griffiths et al., 2016). Participants were initially randomized to either the low dose oral psilocybin (0.014 mg/kg or 0.042 mg/kg), meant to act as placebo, or high dose oral psilocybin (0.31 mg/kg or 0.43 mg/kg), followed by crossover approximately five weeks later. The low dose was permanently adjusted to 0.014 mg/kg due to concern that a 0.042 mg/kg dose might not serve effectively as an inactive placebo, and the high

dose was similarly adjusted from 0.43 mg/kg to 0.31 mg/kg after two of the first three participants to receive the 0.43 mg/kg dose were discontinued from the study. Monitoring for adverse events occurred during dosing days up to six hours post-dose, and participant reported outcomes were solicited for up to six months following the second dose.

5.3.4.4.1. Results

Fifty-six participants meeting the inclusion and exclusion criteria were initially randomized to receive either the low dose (N = 27) or high dose (N = 29) oral psilocybin. Five subjects were removed from the study following randomization, with data not obtained for the first dosing session, including two in the low dose arm (one for pre-treatment anxiety and one for cancer progression), and three in the high dose arm (one for anxiety, one for vomiting shortly after capsule administration, and one for family reasons). Data were not obtained for an additional two participants, one in each randomization group, following crossover, due to progression of disease. Data following the initial dosing session were obtained from 51 participants (91%), 49 participants (88%) following the second dosing session, and six-month follow-up data was obtained for 46 participants (82%).

5.3.4.4.2. Clinical Efficacy

Therapeutically relevant measures describing mood, attitude, disposition and behavior were collected at baseline, approximately five weeks after each dosing session, and at six months following the second dosing session. Primary therapeutic outcomes included two clinician-rated measures: the GRID-HAMD for depression, and the Hamilton Anxiety Rating Scale (HAM-A) for anxiety. Secondary measures included self-rated questionnaires to examine depression, anxiety, mood, quality of life, and other psychosocial measures.

Both primary outcome measures, as well as most secondary measures, showed sustained effects following high-dose psilocybin treatment (either an effect from baseline to the first dose for the study arm starting with high-dose psilocybin, or an effect after the second dose for the study arm starting with low-dose psilocybin). Data for GRID-HAMD and HAM-A from baseline through the six-month follow-up time point, as well as the other statistically significant secondary measures, are provided in [Table 5.3-10](#) and [Figure 5.3-10](#). Numerical data in [Table 5.3-10](#) show means (and standard error) for outcome measures in the two dose sequence groups: (1) those that received a low dose on the first session and a high dose on the second (N = 25, 25, 24, and 22 at Baseline, Post-session one, Post-session two, and six months, respectively), and (2) those that received a high dose on first session and a low dose on the second (N = 26, 25 or 26, 25, and 24 at Baseline, Post-session one, Post-session two, and six months, respectively). Data are shown for the 11 measures that fulfilled the most conservative criteria for demonstrating psilocybin effects.

Table 5.3-10: Effects of psilocybin on primary and select secondary outcome measure scores

Measure	Group	Assessment time-point			
		Baseline ^a	Post-session 1 ^b	Post-session 2 ^c	6 months ^d
GRID-HAMD-17 (Depression)	Low-Dose-1st (High-Dose-2nd)	22.32 (0.88)	14.80 (1.45)	6.50 (0.86)***	6.95 (1.24)
	High-Dose-1st (Low-Dose-2nd)	22.84 (0.97)	6.64 (1.04)***	6.52 (1.44)	6.23 (1.30)
Beck Depression Inventory	Low-Dose-1st (High-Dose-2nd)	18.40 (1.09)	12.92 (1.58)	8.17 (1.24)***	8.00 (1.50)
	High-Dose-1st (Low-Dose-2nd)	17.77 (1.61)	7.00 (1.39)**	5.80 (1.41)	6.17 (1.26)
HADS Depression	Low-Dose-1st (High-Dose-2nd)	9.48 (0.71)	6.04 (0.79)	4.57 (0.73)*	4.64 (0.72)
	High-Dose-1st (Low-Dose-2nd)	9.81 (0.69)	3.92 (0.74)*	4.28 (0.89)	3.46 (0.66)
HAM-A (Anxiety)	Low-Dose-1st (High-Dose-2nd)	25.68 (0.89)	16.64 (1.53)	8.92 (1.14)***	7.95 (1.19)
	High-Dose-1st (Low-Dose-2nd)	25.73 (1.11)	8.48 (1.16)***	7.52 (1.27)	7.04 (1.17)
STAI-Trait Anxiety	Low-Dose-1st (High-Dose-2nd)	47.46 (1.62)	40.48 (2.11)	35.48 (2.05)**	36.83 (2.08)
	High-Dose-1st (Low-Dose-2nd)	47.73 (1.91)	34.64 (1.84)*	34.28 (2.25)	35.32 (2.18)
POMS Total Mood	Low-Dose-1st (High-Dose-2nd)	51.72 (6.35)	42.48 (7.72)	21.09 (5.81)***	23.50 (6.57)
	High-Dose-1st (Low-Dose-2nd)	56.93 (5.33)	18.96 (5.78)**	17.14 (6.35)	12.52 (5.36)
Brief Symptom Inventory	Low-Dose-1st (High-Dose-2nd)	41.76 (4.40)	33.74 (4.47)	26.08 (4.53)*	23.50 (3.85)
	High-Dose-1st (Low-Dose-2nd)	40.19 (3.71)	18.08 (3.62)**	16.48 (3.77)	14.35 (3.35)
MQOL (Overall Quality of)	Low-Dose-1st (High-Dose-2nd)	5.69 (0.24)	6.17 (0.32)	6.90 (0.34)**	6.88 (0.37)
	High-Dose-1st (Low-Dose-2nd)	5.32 (0.29)	7.14 (0.29)*	7.46 (0.34)	7.65 (0.36)
MQOL (Meaningful Existence)	Low-Dose-1st (High-Dose-2nd)	6.03 (0.30)	6.10 (0.39)	7.30 (0.35)***	7.29 (0.31)
	High-Dose-1st (Low-Dose-2nd)	5.43 (0.29)	7.23 (0.33)*	7.30 (0.38)	7.62 (0.35)
LAP-R Death Acceptance	Low-Dose-1st (High-Dose-2nd)	28.05 (2.04)	29.14 (2.25)	34.95 (1.92)***	34.95 (1.52)
	High-Dose-1st (Low-Dose-2nd)	29.09 (2.07)	36.17 (1.59)*	35.13 (1.90)	36.25 (1.59)
LOT-R (Optimism)	Low-Dose-1st (High-Dose-2nd)	13.56 (0.97)	13.60 (1.23)	15.96 (1.12)**	16.68 (1.14)
	High-Dose-1st (Low-Dose-2nd)	14.15 (0.97)	17.23 (0.67)*	17.16 (0.99)	17.43 (0.92)

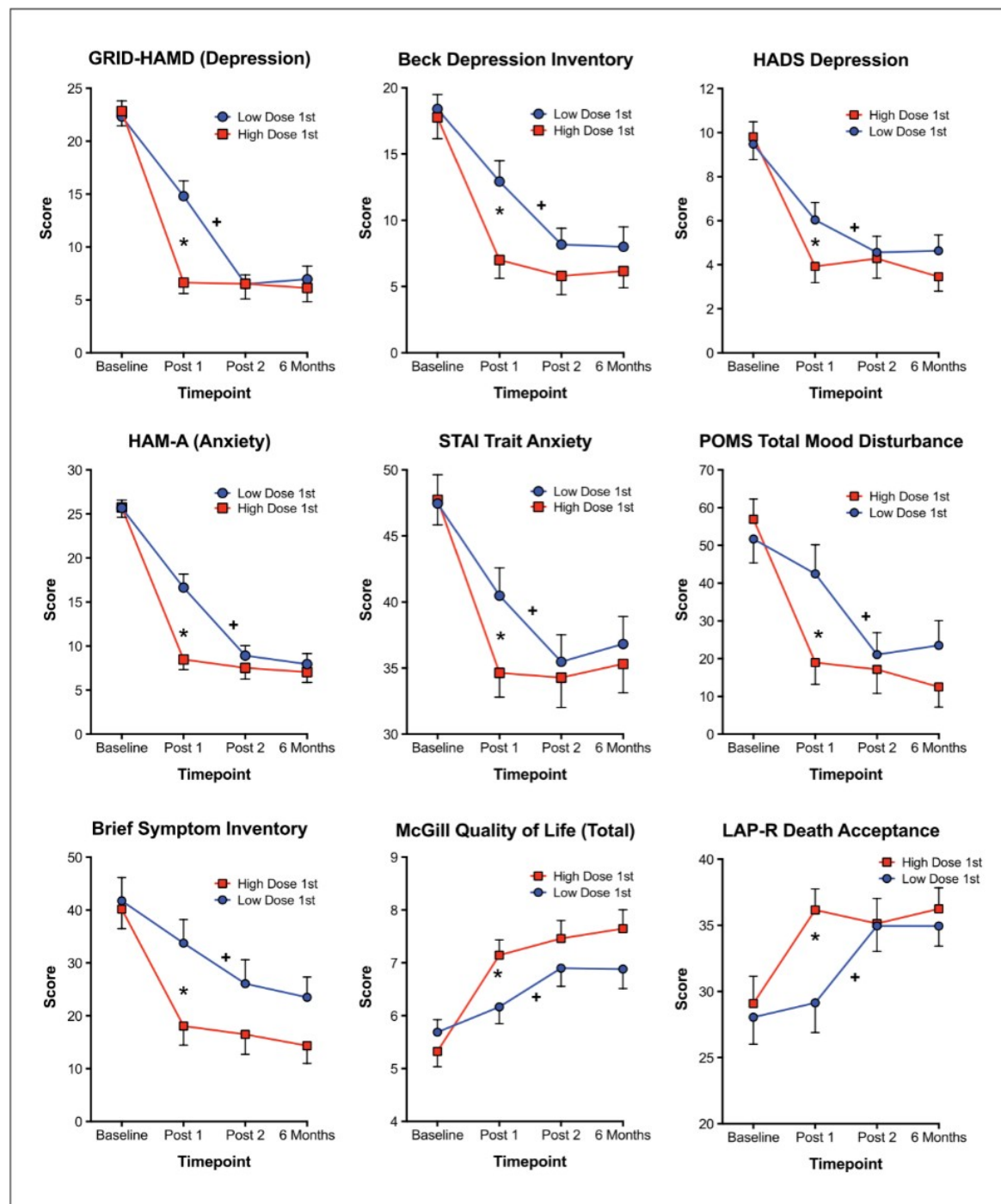
^a In this column (Baseline), there were no significant differences between groups.

^b In this column, italic font indicates a within-group significant difference from Baseline ($p < .05$, planned comparison); asterisks indicate significant differences between groups (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, planned comparisons); between groups effect size (Cohen's d as absolute values) for the 11 measures from top to bottom were: 1.30, 0.81, 0.56, 1.23, 0.60, 0.70, 0.78, 0.65, 0.65, 0.97, and 0.75.

^c In this column, there were no significant differences between groups; asterisks indicate significant differences between the Post-session 1 and Post-session 2 assessments in the Low-Dose-1st (High-Dose-2nd) Group (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, planned comparisons); effect size (Cohen's d as absolute values) for the 11 measures from top to bottom were: 1.33, 0.69, 0.40, 1.10, 0.50, 0.64, 0.35, 0.46, 0.66, 0.68, and 0.41.

^d The difference between Baseline and 6 months, collapsed across groups, was significant for all 11 measures ($p < 0.001$, planned comparison); effect size (Cohen's d as to bottom were: 2.98, 1.63, 1.65, 3.40, 1.20, 1.26, 1.17, 1.14, 1.12, 0.84, and 0.66.

Figure 5.3-10: Outcome measures to assess clinical efficacy in the Johns Hopkins study. Data points show means; brackets indicate one standard error of the mean; circles represent the group that received a low dose on the first session and a high dose on the second session (N = 25, 25, 24, and 22 at Baseline, Post-session one, Post-session two, and six months, respectively); squares represent the group that received a high dose on first session and a low dose on the second session (N = 26, 26, 25, and 24 at Baseline, Post-session one, Post-session two, and six months, respectively). *Indicates a significant difference between the two groups at the Post-session one time-point ($p < 0.05$, planned comparison). +Indicates a significant difference between the Post-session one and Post-session two time-points in the Low-Dose-first (High-Dose-second) Group ($p < 0.05$, planned comparison).



Following the first post-dose assessment 92% of participants in the high-dose first group met standard criteria for depressive symptom clinical response and 60% met criteria for symptom remission as per the GRID-HAMD measure ($p < 0.001$ and $p = < 0.01$, respectively), compared with 32% and 16% respectively in the low-dose first group. In the high-dose first group 76% met criteria for anxiety symptom clinical response and 52% met criteria for symptom remission at first post-dose assessment as per the HAM-A measure ($p < 0.001$ and $p = < 0.01$, respectively), compared with 24% and 12% respectively in the low-dose first group. At the six-month assessment, by which time all participants were at least six months out from receiving a high-dose intervention, rates of response and remission remained high in both groups (high-dose first: depressive clinical response was 79% and symptom remission was 71%, and anxiety clinical response was 83% and symptom remission was 63%; low-dose first: depressive clinical response was 77% and symptom remission was 59%, and anxiety clinical response was 82% and symptom remission was 50%).

In addition to large-effect size reductions in depression and anxiety, high-dose psilocybin produced significantly greater ratings than low-dose psilocybin of positive persisting effects on attitudes about life and self, social effects, and spirituality. These effects were generally sustained at the six-month follow-up. Consistent with the positive changes, high-dose experiences (whether received at the first or second intervention) were also rated as producing significantly greater personal meaning, spiritual significance and increased well-being or life satisfaction than the low-dose experiences, with these improvements sustained at six months.

5.3.4.4.3. Adverse Events

No serious adverse events were attributed to psilocybin. The most frequent adverse events occurring during psilocybin dosing sessions (both low dose and high dose) are shown in [Table 5.3-11](#). With the exception of headache, all adverse events had resolved fully by the end of the sessions. The most frequent adverse events were transient moderate increases in systolic and/or diastolic blood pressure (DBP) after psilocybin, psychological discomfort, anxiety, and physical discomfort. Episodes of elevated systolic blood pressure (> 160 mm Hg) occurred in 18 of 53 (34%) high dose sessions, as compared to 17% ($N = 9$) of the low dose “placebo” sessions. Episodes of elevated diastolic blood pressure (> 100 mm Hg) occurred in 7 of 53 (13%) high dose sessions, and 1 of 52 (2%) of the low dose sessions. One participant experienced a transient peak blood pressure (214/114 mm Hg) during the high dose session that met severity criteria, but not the duration (15 minutes) criteria for pharmacologic intervention, and therefore no intervention was delivered.

Psychological discomfort was reported in 17 of 53 (32%) of high dose sessions and 6 of 52 (12%) low dose sessions. Anxiety was reported in 14 of 53 (20%) of high dose sessions, and 8 of 52 (15%) low dose sessions. Episodes of physical discomfort (any type) occurred in 21% of high dose sessions and 8% of low dose sessions.

One instance of mild headache was reported during a high dose session. Toward the end of this study, the study team became interested in documenting the occurrence of delayed headache after psilocybin sessions. Of the 11 (of 53) participants queried, two (18%) reported moderate headache following their high dose sessions.

Table 5.3-11: Adverse events reported during dosing sessions

Adverse Event Description*	Low Dose (N = 52)	High Dose (N = 53)
Elevated Diastolic Blood Pressure (> 100)**	1 (2%)	7 (13%)
Elevated Systolic Blood Pressure (> 160)**	9 (17%)	18 (34%)
Elevated Systolic (> 160) and/or Diastolic Blood (> 100)	10 (19%)	18 (34%)
Elevated Heart Rate (> 110)**	1 (2%)	3 (6%)
Mild Headache	0	1 (2%)
Nausea/vomiting	0	8 (15%)
Paranoia	0	1 (2%)
Psychological Discomfort	6 (12%)	17 (32%)
Physical Discomfort	4 (8%)	11 (21%)
Anxiety during session	8 (15%)	14 (20%)

* AE during sessions refer to one or more instance(s) of the AE that occurred on session days after capsule administration; in all cases, the AE had resolved by the end of the session day.

** In one participant, the peak blood pressure magnitude (214/114 mmHg) met the protocol criterion for pharmacological treatment, however the protocol criterion for duration of elevation for pharmacological treatment was not met as the event lasted less than 15 minutes. In all cases blood pressure returned to normal levels by the end of the session.

Spontaneously reported adverse events that occurred following psilocybin sessions that were judged to be possibly related to drug administration were rare, with four occurring following the low dose session and one occurring following the high dose session (Table 5.3-12). The reported adverse events judged to be possibly related to drug administration following lower-dose sessions included instances of a feeling of fullness in the chest (n=1), anxiety (n=1), insomnia (n=1) and decreased appetite (n=1). One instance of leg pain occurred following a higher-dose session. There were no cases of hallucinogen persisting perception disorder (HPPD) or prolonged psychosis.

Table 5.3-12: Adverse events reported after the psilocybin dosing session

Adverse Event Description*	Number of Instances	Causality
Death due to disease progression	2	Unrelated
Fullness in chest (post low-dose session)	1	Possible
Anxiety (post low-dose session)	1	Possible
Insomnia (post low-dose session)	1	Possible
Decreased appetite (post low-dose session)	1	Unrelated
Suicide after dropping out of study (did not receive high dose)	1	Unlikely
Eye infection (post low-dose session)	1	Unrelated
Coronary Artery blockage	1	Possible
Leg pain (post high-dose session)	1	Possible
Breast biopsy	1	Unrelated

* AE not during sessions refer to any AE that occurred outside of sessions but after drug exposure during study participation until study termination, dropout, or completion of the six month follow-up; detailed event reports are appended

5.3.4.4.4. Conclusion

When administered in conjunction with psychological support, psilocybin was found to produce substantial and enduring (six-month follow-up) decreases in depressed mood and anxiety in participants with cancer diagnosis versus the comparator (0.014 mg/kg psilocybin) in this setting. The psilocybin treatment was safe and well-tolerated up to 0.31 mg/kg dosing.

5.3.4.5. New York University (NYU) Study

This was a randomized, double-blind, placebo-controlled crossover study (NCT00957359) to investigate the efficacy of a single psilocybin dosing session versus placebo (in conjunction with psychotherapy) to treat clinically significant anxiety or depression in adults who received a cancer diagnosis (Ross et al., 2016). Participants were initially assigned to receive oral psilocybin (0.3mg/kg) or placebo (niacin, 250 mg), administered during an 8-hour treatment session. Crossover to the other arm occurred seven weeks after the first administration. Adverse events were monitored throughout the trial, including during and after dosing sessions. Primary outcomes of potential improvement of participant anxiety and depression were measured through 26 weeks after the second dosing session.

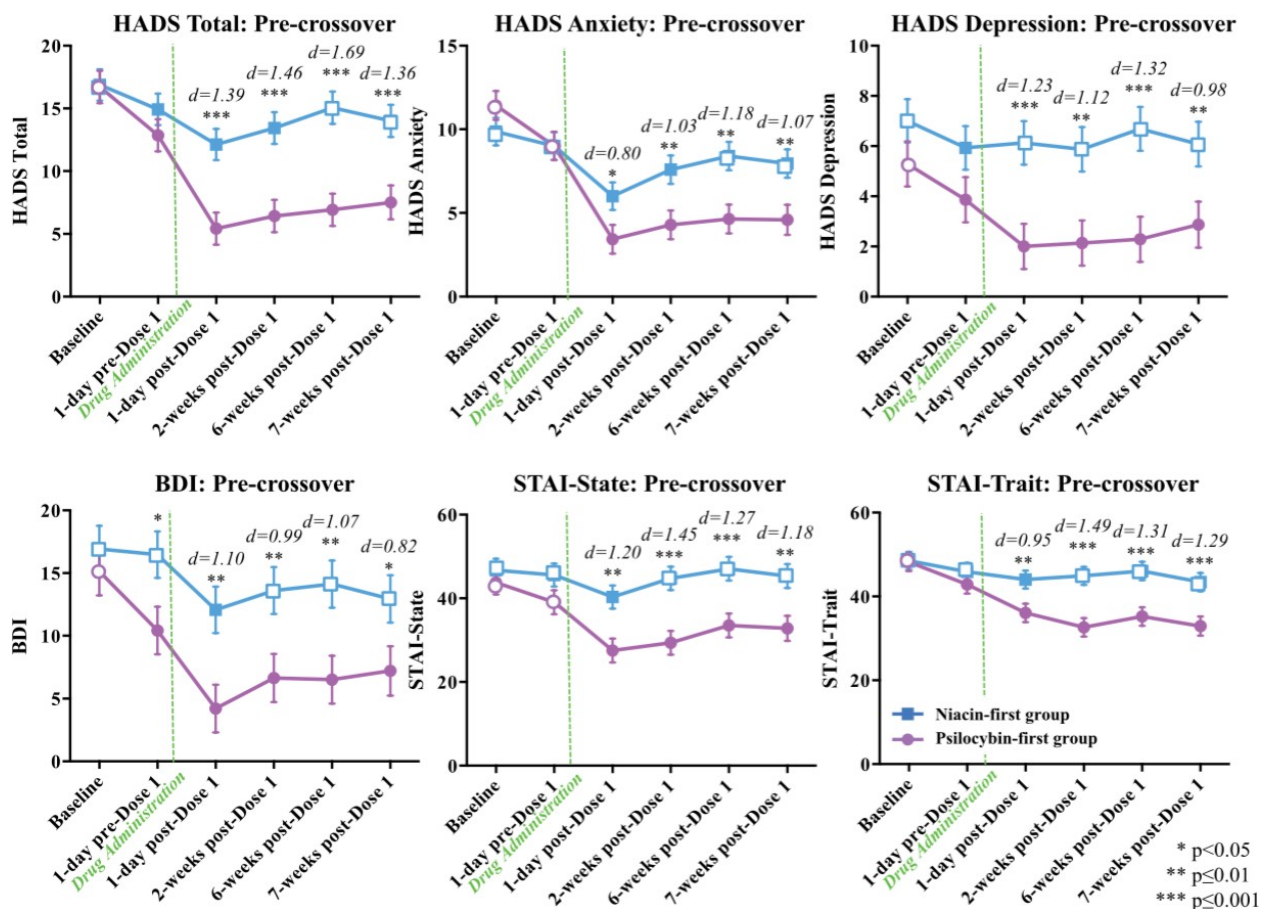
5.3.4.5.1. Results

Thirty-one participants with significant distress due to a cancer diagnosis were initially randomized to receive oral psilocybin (N = 16) or placebo (N = 15). Two participants were removed from the psilocybin arm prior to dosing due to the development of a secondary illness prior to receiving a study intervention. Of the 29 remaining participants who completed the first dosing session, 28 (97%) completed the six-week post-dose follow-up assessments, and 26 (90%) completed the second dose after crossover. Twenty-four participants (83%) completed the second six-week post-dose follow-up, and 23 (79%) completed the six-month follow-up assessments (including one participant who missed the six-week assessment after the second dosing session). Of the 29 participants who completed the first dosing session, four (14%) withdrew due to disease progression, one (3%) passed away, and one (3%) withdrew due to resumption of prohibited concomitant medication.

5.3.4.5.2. Clinical Efficacy

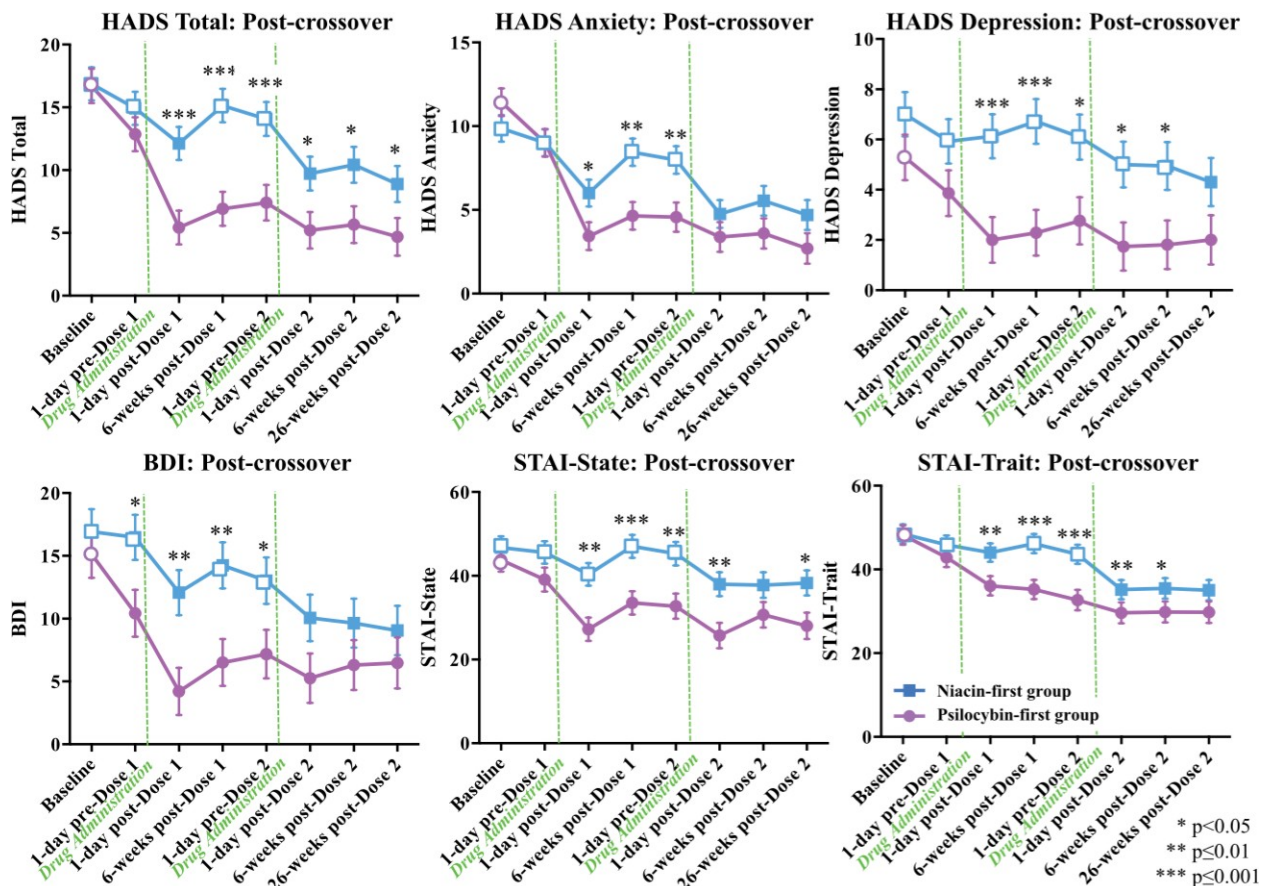
When compared to placebo, a single dose of psilocybin produced a significant acute and sustained reduction in combined anxiety and depressive symptoms as measured by the total Hospital Anxiety and Depression Scale (HADS) score. Compared to baseline and pre-dose results, statistically significant psilocybin efficacy was seen one day following treatment (with persistence through the two-week post-treatment assessment (Figure 5.3-11). Psilocybin showed large effect size advantages for both the depression and anxiety subscales of the HADS based on between-group differences prior to the crossover, as measured by Cohen's d. Convergent support for these effects was provided by similar results on the BDI and trait and state subscales of the STAI (Figure 5.3-11).

Figure 5.3-11: Psilocybin as a method of sustainment for reduction of anxiety and depression in the NYU study. Means (\pm SE) for primary outcome measures are shown in the two treatment groups at the following time points: baseline (psilocybin first $n=14$, niacin first $n=15$), 1 day pre-dose 1 (psilocybin first $n=14$, niacin first $n=15$), 1 day post-dose 1 (psilocybin first $n=14$, niacin first $n=15$), 2 weeks post-dose 1 (psilocybin first $n=14$, niacin first $n=14$), 6 weeks post-dose 1 (psilocybin first $n=14$, niacin first $n=14$), 7 weeks post-dose 1 (psilocybin first $n=12$, niacin first $n=14$). Asterisks indicate significance level of between-group t -tests. Effect sizes, represented as Cohen's d , are shown above time points at which the treatment groups differ. Closed points represent significant within-group differences relative to scores at baseline.



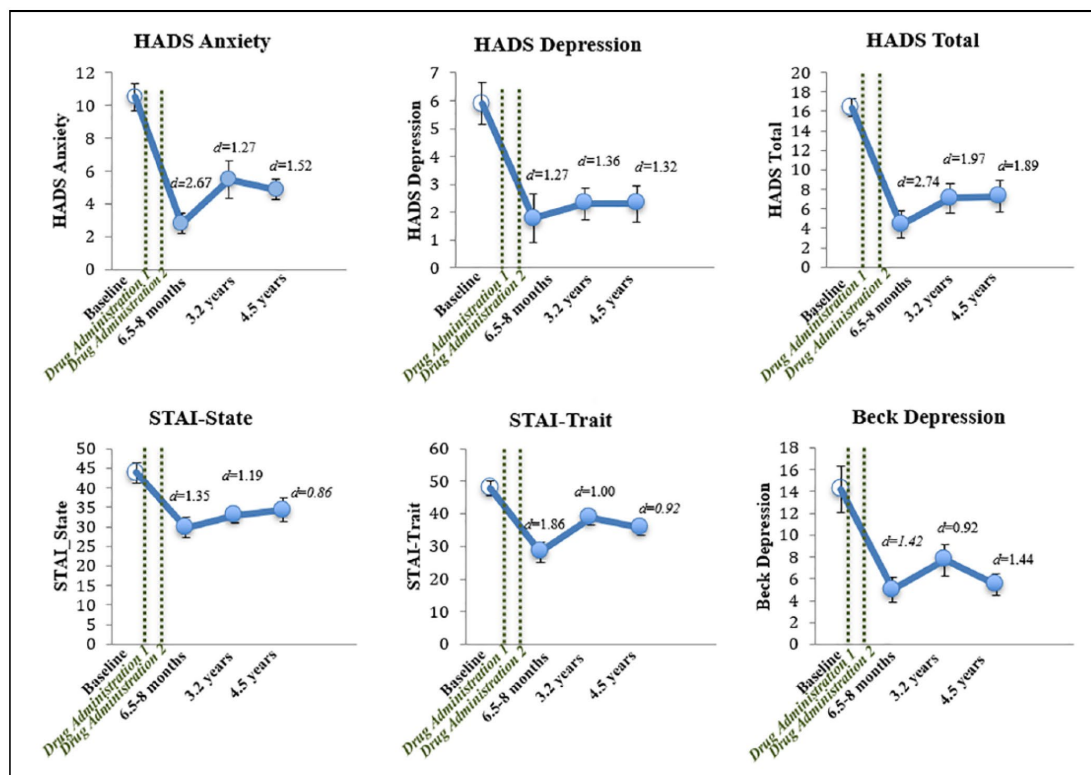
The psilocybin-first group demonstrated significant within-group reductions in all distress measures one day after receiving psilocybin, that endured following the crossover dosing session. Similarly, when the niacin-first group received psilocybin in the crossover, there were significant within-group differences from the day before dosing to the day after and for at least the subsequent 6 months as demonstrated by the following measures: HADS total, HADS anxiety subscale, STAI trait subscale and BDI (Figure 5.3-12). Taken together, these data suggest that the effects of psilocybin persist longer than six weeks post dosing (as represented by the between group comparisons before the crossover) and may be as long as six to nine months in duration from a single dose. In addition to these effects on anxiety and depression, secondary outcomes showed psilocybin significantly impacted related constructs linked to emotional well-being, including quality of life, fear of death, and spiritual well-being.

Figure 5.3-12: Acute and Durable Depression Efficacy Outcomes in the NYU study. Means (\pm SE) for primary outcome measures are shown in the two treatment groups at the following time points: baseline (psilocybin first $n=14$, niacin first $n=15$), 1-day pre dose-1 (psilocybin first $n=14$, niacin first $n=15$), 1 day post-dose 1 (psilocybin first $n=14$, niacin first $n=15$), 6 weeks post-dose 1 (psilocybin first $n=14$, niacin first $n=14$), 7 weeks post-dose 1 (1 day pre-dose 2) (psilocybin first $n=12$, niacin first $n=14$), 1 day post-dose 2, 6 weeks post-dose 2 (psilocybin first $n=12$, niacin first $n=11$), 26 weeks post-dose 2 (psilocybin first $n=11$, niacin first $n=12$). Asterisks indicate significance level of between-group t -tests. Closed points represent significant within-group differences relative to scores at baseline.



Further, a remarkable longevity of benefit of psilocybin from this study was reported up to 5 years post dose (Agin-Liebes et al., 2020). At an average follow-up time of 3.2 years (1st long-term follow up) and 4.5 years (2nd follow up) post-dosing, all 15 of 16 still living subjects were assessed for depressive and anxious symptoms. Reductions in anxiety, depression, hopelessness, demoralization, and death anxiety observed at the six-month assessment were sustained at 3.2 and 4.5 years post-dosing (Figure 5.3-13). At the second follow-up (4.5 years) approximately 60-80% of participants met the criteria for clinically significant antidepressant or anxiolytic responses. Participants overwhelmingly (71-100%) attributed positive life changes to the psilocybin-assisted therapy experience and rated it among the most personally meaningful and spiritually significant experiences of their lives.

Figure 5.3-13: Long-term follow-up in the NYU study. Means (\pm SE) for primary outcome measures for both dose-sequence groups combined shown at the following time points: baseline (N=16), 6.5 months (parent study endpoint; N=16), mean 3.2 years (first follow-up; N=15); and mean 4.5 years (second follow-up; N=14). Closed points represent significant within-subject differences relative to scores at baseline. Longitudinal within-subject effect sizes, presented as Cohen's d, are shown above time points. HADS: Hospital Anxiety and Depression Scale; STAI: State-Trait Anxiety Inventory.



5.3.4.5.3. Adverse Events

The most common adverse events that occurred during the psilocybin dosing sessions (before and after crossover, N = 28) included elevated systolic (>160 mm Hg) and diastolic BP (>100 mm Hg), headache and migraine, anxiety, and nausea. None of the elevated BP episodes required pharmacological intervention.

One participant died as a result of cancer disease progression. Four subjects were withdrawn from the study due to disease progression and passed away shortly after withdrawal from the study. These serious adverse events were not attributed to psilocybin.

Adverse events that occurred outside the dosing sections were collected, and causality from psilocybin was assessed (Table 5.3-13). Three of 11 events (27%) were determined to be possibly related to psilocybin administration.

After the long-term follow up, none of the participants reported lasting negative or adverse effects from the psilocybin-assisted therapy experiences.

Table 5.3-13: Adverse events occurring outside the psilocybin dosing sessions

Adverse Event Description*	Number of Instances	Causality
Community Acquired Pneumonia	1	Unrelated
Death due to disease progression	1	Unrelated
Hypotension	1	Unrelated
Lumbar Spinal Surgery	1	Unrelated
Migraine	1	Unrelated
Ocular Migraine	1	Unrelated
Experience of Thought Disorder	1	Possible
Neurosurgery	1	Unrelated
Visual Field Impairment	1	Possible
Vasovagal Syncopal Event	1	Possible
Vomiting	1	Unrelated

* AE not during sessions refer to any AE that occurred outside of sessions but after drug exposure during study participation until study termination, dropout, or completion of the six month follow-up.

5.3.4.5.4. Conclusion

In this setting, psilocybin was found to produce rapid and sustained effects against anxiety and depression in a population of adults who were diagnosed with cancer. Further, reductions in anxiety, depression, hopelessness, demoralization, and death anxiety were sustained at three to four and a half years post dosing. Single-dose psilocybin was well tolerated at a 0.3 mg/kg dose.

5.3.4.6. Usona Institute PSIL201 Study

[Study PSIL201](#) (NCT03866174), sponsored by Usona, is a randomized, double-blind, active comparator-controlled study of single-dose psilocybin in subjects with MDD. One hundred participants (males and females) ages 21 to 65 who, at Screening, meet DSM-5 criteria for MDD and meet all other inclusion/exclusion criteria are stratified by study site and randomized with a 1-to-1 allocation under double-blind conditions to receive a single 25 mg oral dose of psilocybin or a single 100 mg oral dose of niacin. Both formulations are visually consistent, excipient-free, and consist of the drug substance encapsulated in an immediate release, hard, white, opaque, size 2, hydroxypropyl methylcellulose capsule. Niacin serves as an active comparator that provides an acute physiological response (flushing) that is intended to aid in blinding of intervention allocation. Participants deemed eligible following successful completion of all screening assessments complete central rater, on-site rater and self-report measures at Baseline for a final eligibility determination. Eligible participants at Baseline undergo preparation sessions and are eligible for randomization on Dosing Day to receive either psilocybin or niacin active-comparator; they complete follow-up visits and assessments on study Day 2, 8, 15, 29 and 43 (within corresponding visit windows). Study outcome measures assess depressive symptoms, clinical global functioning, functional disability, anxiety symptoms and health-related quality of life. Safety outcome measures are collected at all assessment time points from the time of consent through the end of study.

To enhance participant safety, Study PSIL201 utilizes a “set and setting” (SaS) approach similar to the protocol that has been used in modern studies of psilocybin in both diseased and normal healthy populations. The SaS protocol for this study includes: 1) a period of preparation with session Facilitators prior to dosing; 2) administration of study medications in an aesthetically pleasing room under the supervision of two Facilitators who are present throughout the session (with the exception of short, temporary allowances for facilitator breaks; e.g. bathroom breaks); and 3) three post-dose integration sessions during which participants are encouraged to discuss their intervention experience with the Facilitators.

Participant enrollment for Study PSIL201 began in December 2019. As of the drafting of the current version of this Investigator's Brochure, no unexpected TEAEs and no post-randomization SAEs have occurred.

Table 5.3-14: Usona Institute PSIL201 study overview

Planned Enrollment	Design	Duration of Treatment/ Dosing Regimen	Study Population	FSFV ^a	Subject Exposure per Treatment Arm (psilocybin/control)
n=100	Randomized, double-blind, active placebo-controlled safety and efficacy study	Single dose	Adults (age 21-65) with MDD	19DEC2019	Planned: 50:50

FSFV: First subject first visit; MDD: Major Depressive Disorder

^a FSFV date is considered the first date on which a subject signed the informed consent form

5.3.4.7. Usona Institute PSIL201 Long-Term Follow-Up Study (PSIL201-LTFU)

[Study PSIL201-LTFU](#) is a double-blind, long-term observational follow-up study open to all randomized subjects in Study PSIL201. Participants providing informed consent will be enrolled into the study and will complete web surveys and telephone interviews conducted by one central site. Site personnel and participants will remain blinded to any information that might directly reveal the treatment assignment from Study PSIL201. Observational assessments will include self-reported outcomes conducted via web or paper survey and the following measures conducted by the central site via telephone: 1) a record of concomitant medication/therapy use, 2) the Montgomery-Åsberg Depression Rating Scale [MADRS], 3) a review of DSM-5 diagnostic criteria for Major Depressive Disorder, 4) the Sheehan Disability Scale [SDS], 5) a review of solicited adverse events, and 6) the Columbia-Suicide Severity Rating Scale [C-SSRS].

5.3.5. Summary of the Clinical Safety of Psilocybin in Clinical Trials

Thousands of participants have received psilocybin under controlled conditions in a clinical setting for various indications, with subsequent results published in peer-reviewed journals ([J. Rucker, Iliff, & Nutt, 2017](#); [Metzner, 2005](#)). As these studies were predominantly performed in an academic setting, safety reporting criteria and the level of data verification varied greatly between studies, but these data can be utilized to elucidate the expected adverse event profile of psilocybin.

Overall, the most commonly reported adverse events associated with psilocybin administration are psychological in nature and include anxiety, the induction of negative emotional states and paranoid/delusional thinking during psilocybin sessions, as well as far less frequent reports of Hallucinogen Persisting Perception Disorder (HPPD) (M. Johnson, Richards, & Griffiths, 2008; Tylš et al., 2014). Rates of prolonged psychiatric symptoms of any kind following psilocybin exposure in healthy study participants are estimated to be 0.08-0.09%. Cardiovascular changes including increased BP and heart rate, nausea, and headaches are also commonly reported with psilocybin administration. These events are therefore examined further in this section.

5.3.5.1. Hallucinogen Persisting Perception Disorder (HPPD)

Some people who have used serotonergic hallucinogens, such as psilocybin, experience persistent, distressing alterations in mostly visual perception that last from weeks to years after use (Espiard, Lecardeur, Abadie, Halbecq, & Dollfus, 2005). This condition is now diagnosed as hallucinogen persistent perception disorder (HPPD). To date, however, no cases of HPPD have occurred in volunteers given psilocybin in current research studies (Studerus et al., 2011). In studies involving cancer patients examining cancer related anxiety and depression, no cases of HPPD were identified and no participants developed any symptoms of paranoia or anxiety that required pharmacological intervention or anything more than reassurance from session facilitators. The risk of HPPD occurring after psilocybin administration can be reduced by screening participants for potential risk factors such as substance dependence and by excluding people reporting HPPD or other significant adverse events after prior use of hallucinogens.

5.3.5.2. Cardiovascular

5.3.5.2.1. QTc

Psilocybin doses ranging from 0.3 to 0.6 mg/kg (corresponding to absolute doses of 19 to 59 mg) resulted in a positive effect on QTc prolongation with a linear relationship between maximum plasma psilocin concentration and Δ QTcF (Dahmane et al., 2020). No delay between the time course of psilocin PK and the change in Δ QTcF was observed; i.e., the maximum Δ QTcF was observed at the time of psilocin C_{max} . At the therapeutic dose of 25 mg, the expected mean psilocin C_{max} is about 18.7 ng/mL and the associated upper bound of the 90% CI of the predicted mean Δ QTcF is 6.6 msec, below the threshold of 10 msec. The concentration-QTc analysis by Dahmane et al. demonstrated that at a psilocin C_{max} of 60 ng/mL, which is approximately 3 times higher than the expected C_{max} following an oral psilocybin dose of 25 mg, Δ QTcF remains below 10 msec, with a mean predicted Δ QTcF of 9.1 msec and a 90% upper CI limit for mean Δ QTcF of 17.9 msec. These observations suggest that there is a limited potential of QTc prolongation under psilocybin at the intended investigational dose of 25 mg but that this should followed during clinical evaluations.

5.3.5.2.2. Blood Pressure

Higher doses of psilocybin (>0.3 mg/kg) also may transiently lead to elevated mean blood pressure, peaking 30-60 min following psilocybin administration and returning to baseline levels after 90-180 min without necessitating further interventions (Griffiths et al., 2006; Hasler, Grimberg, Benz, Huber, & Vollenweider, 2004). The severity of elevations in blood pressure were usually asymptomatic, and were graded as mild or moderate (CTCAE Grade 1 or 2, respectively). Although several subjects in the University of Wisconsin dose escalation study reached blood pressure elevations that were graded as moderate, they remained asymptomatic. It is not clear whether the changes in blood pressure and heart rate are due to the elevated psilocin concentration directly or to the psychedelic effect caused by this active metabolite. Psilocybin appears to produce only slight sympathetic system activation. Psilocybin may elevate prolactin, but not cortisol or ACTH (Gouzoulis-Mayfrank, Thelen, et al., 1999) with prolactin elevation no longer detectable 300 minutes post-drug (Hasler et al., 2004).

5.3.5.2.3. Heart Rate

Transient elevations of heart rate are common in subjects receiving doses of psilocybin at doses of 0.3 mg/kg or more. The time course of these elevations in heart rate are similar to those seen for the elevations in blood pressure, peaking between 60-120 minutes after the dose. This is similar to the time of peak psilocin concentrations and peak psychedelic effect. Again, it is not clear whether the changes in blood pressure and heart rate are directly due to the elevated psilocin concentration or caused indirectly by the psychedelic effect.

In a Phase 1 dose-escalation study in healthy volunteers, there were several instances in which mild bradycardia and tachycardia was noted. In a retrospective analysis, it was demonstrated that psilocybin resulted in an increased heart rate, with slightly higher mean change from baseline in heart rate (Δ HR) at higher psilocybin doses and corresponding higher psilocin exposures (Table 5.3-5; Dahmane et al., 2020). The maximum mean Δ HR was observed at the time of psilocin C_{max} (i.e., at 2 hours post dose) in nearly all psilocybin dose groups, and mean Δ HR decreased with decreasing psilocin concentration at subsequent time points. Instances of bradycardia or tachycardia were unimodal, with no swing between bradycardia and tachycardia after a given dose. The episodes of bradycardia and tachycardia reported in current studies at NYU, Johns Hopkins, and Wisconsin were asymptomatic ("mild" or CTCAE Grade 1) and did not require treatment.

5.3.5.2.4. Headache

Mild headaches are common within the 24 hours after a dose of psilocybin. No auras or photo/phonophobia are associated with these headaches, which respond well to a single dose of acetaminophen. The headaches did not appear to be dose-related in the University of Wisconsin study, with no higher incidence after doses of 0.6 mg/kg vs 0.3 mg/kg.

6. SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR

6.1. Summary of Data

Psilocybin is a tryptamine derivative that can be enzymatically cleaved in the body to produce psilocin, an agonist at a variety of serotonin receptors. The pharmacokinetics, pharmacology and human metabolism of psilocybin are well known and well characterized. In conjunction with psychotherapy, psilocybin has been utilized broadly in Phase 2 clinical trials conducted in the academic setting, which have demonstrated an improvement in symptoms of anxiety, depression, and substance use disorder.

The clinical safety of psilocybin has been extensively studied, both as a single agent and as adjunctive treatment in adult populations. Psilocybin is administered orally, and has been studied in open-label and double-blind, controlled trials. Dosing regimens have ranged from 0.014 mg/kg to 0.6 mg/kg, administered as either a single dose, or multiple doses weeks apart.

The most common adverse experiences are psychological, including anxiety, and the induction of negative emotional states and paranoid/delusional thinking during psilocybin sessions. The most common physical adverse events are cardiovascular (increased blood pressure and heart rate), as well as nausea and headache.

Psilocybin capsules should be stored in a secure location at room temperature.

6.2. Method of Administration

A capsule of psilocybin is administered orally with a full glass of water, as per the study protocol. As described under Special Warnings and Special Precautions for Use, the study drug must be administered to participants who have been screened for psychiatric and other risk factors for an adverse psychedelic experience, per protocol. The participant must have adequate counselling and preparation ahead of dosing, and after ingesting the dose must be attended by at least one Facilitator, but preferably two, for the subsequent 6-8 hours.

6.3. Dose Response

A meta-analysis of 8 double-blind placebo-controlled studies including 110 healthy subjects who had received 1–4 oral doses of psilocybin (45–315 µg/kg body weight) showed that effects of psilocybin are dose-dependent, although other factors such as personality structure and the setting (e.g. environment) appear to modulate its overall effects ([Preller et al., 2016](#); [Studerus, Gamma, Kometer, & Vollenweider, 2012](#)). Although psilocybin dose-dependently induced profound changes in mood, perception, thought, and self-experience, most subjects described the experience as pleasurable, enriching, and non-threatening. Acute adverse drug reactions, characterized by strong dysphoria and/or anxiety/panic, occurred transiently only in the two highest dose conditions in a relatively small proportion of subjects (5 and 8% respectively). All acute adverse drug reactions were successfully managed by providing interpersonal support and did not require psychopharmacological intervention. In fact, individual reactions to serotonergic hallucinogens

can vary, even when the experimental conditions are consistently maintained ([Dittrich, 1994](#); [Nichols & Chemel, 2006](#)).

A meta-analysis of psilocybin effects (dose range from 0.115–0.315 mg/kg) in a sample of 261 healthy volunteers found that drug dose, the personality trait absorption, a positron emission tomography (PET) scanning environment, and age were significant factors predicting response to psilocybin ([Studerus et al., 2012](#)). Specifically, higher dose predicted greater overall drug effects. Greater personality absorption predicted higher “oceanic boundlessness” scores on the five dimensional Altered State of Consciousness (ASC) — a scale that measures the positively experienced loss of self/ego boundaries associated with heightened mood, bliss and derealisation phenomena. Lower age and conducting the study in the PET scanner environment predicted greater anxiety ([Studerus et al., 2012](#)). Participant gender was not found to have any significant effects on psilocybin response, ([Studerus et al., 2012](#)) consistent with the limited human data examining sex differences in classic psychedelics' effects ([Leary, Litwin, & Metzner, 1963](#)).

Psilocybin intake resulted in dose-related 5-HT_{2A} receptor occupancies up to 72%, with subjective intensity strongly correlated with both receptor occupancy and psilocin levels ([Madsen et al., 2019](#)).

6.3.1. Dose Modification

Dose modification is not applicable. Psilocybin is administered as a single, fixed dose.

6.4. Contraindications

Psilocybin is contraindicated in participants who are on monoamine oxidase inhibitors or who have a known sensitivity to the drug or its metabolites. It is contraindicated in medications that are known uridine diphosphate glucuronosyltransferase enzyme modulators. It is contraindicated in patients with schizophrenia or bipolar disease, or in those with first degree relatives with these disorders. The concurrent use of selective serotonin reuptake inhibitor/serotonin-norepinephrine reuptake inhibitors (SSRI/SNRI) medications is assumed to be contraindicated due to the potential to increase the risk of serotonin syndrome and/or to attenuate the binding of psilocin to the HT_{2A} receptor.

6.5. Special Warnings and Special Precautions for Use

Prior to enrollment participants must first be screened per the clinical protocol for contraindicated psychologic conditions or interacting medications. Appropriate counselling and preparation for the session typically requires approximately 6-8 hours ([M. Johnson et al., 2008](#)).

Dosing with psilocybin must be also performed per the clinical protocol. This is typically in a setting that minimizes distraction and interruption, and the patient is attended following the dose by a therapist trained in providing reassurance and a safe environment until the effects of the single dose have dissipated. Upon discharge from the study setting, the patient should be delivered to the care of a responsible individual who can observe the patient for the remainder of 24 hours after the dose was administered.

Although there have been no reports of their use in well reported clinical trials with oral psilocybin,

medications should be available for the treatment of causal symptomatic hypertension, agitation, or severe psychosis. Typically, these supplies are two dosage units of labetalol, nitroglycerin, lorazepam and/or diazepam, and risperidone or similar orally-disintegrating antipsychotic.

6.5.1. Undesirable Effects

6.5.1.1. Physical Adverse Effects

Previous studies in healthy participants have shown oral psilocybin to be well tolerated. No drug-related serious adverse events were reported.

The Phase 1 **University of Wisconsin Study**, an open-label, dose-escalating (0.3 - 0.6 mg/kg oral psilocybin) trial described safety events in 12 healthy participants. Ten (10) of 12 participants (83%) reported mild hypertension, 9 of 12 (75%) reported mild headache, 7 of 12 (58%) reported mild bradycardia, and 6 of 12 (50%) reported mild tachycardia. Other mild events affecting fewer than 50% of the study participants included hypotension, fever, fatigue, nausea, diarrhea, and dizziness. Four of 12 (33%) of participants reported moderate hypertension. Dose strength was not found to correlate to adverse event frequency.

The retrospective **University of Zurich** study described subjective, participant-reported events in a population of 110 healthy volunteers across eight clinical trials. The most frequent self-reported adverse experiences reported were mild headache ([M. W. Johnson, Sewell, & Griffiths, 2012](#)), and mild lethargy (fatigue, exhaustion, or lack of energy) immediately after psilocybin administration. For these events, normal function was largely restored after 24 hours. Three participants were withdrawn from their respective studies due to adverse events caused by psilocybin (two had unusually intense reaction to low-dose psilocybin, and one experienced a transient hypotonic reaction with dizziness, fainting and vomiting after receiving low-dose psilocybin). In each case, symptoms were completely resolved by the end of the dosing day.

Additional studies detailed the most common physical adverse events as cardiovascular (increased BP and heart rate), as well as nausea and headache.

Within Study PSIL201, no unexpected TEAEs have been reported, and no SAEs have been reported following participant randomization (study medical monitors remain blinded to participant treatment).

6.5.1.2. Behavioral and Psychologic Adverse Effects

The most likely potential acute adverse effects of psilocybin were shown to be anxiety, as well as panic, delusion, and cognitive impairments, particularly at higher doses (> 25 mg oral psilocybin) during the period of acute drug action. Such transient episodes of fear or anxiety respond well to reassurance and have not required pharmacological intervention. In previous clinical experience, acute psychological events were resolved by the end of the dosing day.

Rates of prolonged psychiatric symptoms of any kind following psilocybin exposure in healthy study participants are estimated to be 0.08-0.09%. These include the possibility of prolonged adverse psychological reactions, such as psychosis and depression.

The low rate of enduring psychological symptoms is consistent with a summary of such effects from the **University of Zurich** study. In that retrospective analysis, seven participants endorsed negative changes in psychological well-being, but only one participant (0.9%) reported a level of distress sufficient for him to contact the researchers. Those symptoms were resolved after a few sessions with an experienced psychotherapist.

6.5.2. Interactions

After administration psilocybin is rapidly metabolized (via dephosphorylation) to psilocin, the active molecule. This is further glucuronidated by the uridine diphosphate glucuronosyltransferase UGT1A9 and 1A10, and deaminated to 4-hydroxyindoles by monoamine oxidase, and aldehyde and alcohol dehydrogenase. The pharmacologic activity of the metabolites of psilocin are not known and no controlled studies of the effect of other drugs upon psilocybin metabolism / pharmacokinetics or effect have been performed. Inhibitors of UGT1A9 and 1A10 would be expected to increase the C_{max} and Area Under the Curve (AUC) of psilocin, and should be discontinued at least five half-lives prior to the administration of psilocybin. Similarly, monoamine oxidase and aldehyde or alcohol dehydrogenase inhibitors should be discontinued at least 5 half-lives prior to the dose of psilocybin.

6.5.3. Use During Pregnancy and Lactation

There have been no human case reports or studies involving the effects of psilocybin on pregnancy. It is recommended that women who are pregnant avoid using psilocybin. Women of childbearing potential who have a negative pregnancy test at screening will undergo repeated pregnancy testing prior to treatment administration, and only if the results are negative the morning of treatment will psilocybin or placebo be administered. Any pregnancy occurring after study enrollment should be followed until an outcome is known. (i.e., spontaneous miscarriage, elective termination, normal birth). All live births must be followed for a minimum of 30 days or to the first well-baby visit.

Non-clinical and clinical data describing the effects of oral psilocybin on lactation, sperm, and teratogenicity are not available.

6.5.4. Carcinogenesis and Mutagenesis

Non-clinical and clinical data describing carcinogenic and metagenetic effects of oral psilocybin are not available.

6.5.5. Overdose

There are no confirmed reports of an overdose of pharmaceutical psilocybin. Previous clinical trials involved single or multiple doses of oral psilocybin in predefined quantities, administered in a controlled environment. Oral psilocybin, 25 mg capsules, are within the dosing range previously shown to be safe and well-tolerated. Should an accidental overdose occur, appropriate symptomatic measures should be initiated, followed by monitoring any adverse events to resolution.

6.5.6. Abuse Potential

Currently, psilocybin is placed in Schedule 1, defined as having no medical use, possessing high abuse liability, and no safety when used under medical supervision. However, in preclinical studies, psilocybin, mescaline and NN-DMT did not serve as positive reinforcers in MDMA-experienced rhesus monkeys argues strongly that monkeys at least do not find the psychoactive effects of the 5-HT_{2A} receptor agonists rewarding ([Heal, Gosden, & Smith, 2018](#)).

In previous clinical studies with psilocybin, exposing individuals with either no history of hallucinogen use or a history of minimal use (e.g. less than 10 times total and not within the last five years) in the context of a supervised and controlled research setting has not resulted in reported instances of subsequent illicit hallucinogen abuse ([Griffiths et al., 2011](#); [Griffiths et al., 2006](#)). Additionally, these recent studies have shown side effects including acute elevations in fear and anxiety, aspects that are potentially predictive of low abuse potential ([M. W. Johnson, Griffiths, Hendricks, & Henningfield, 2018](#)). Based on available literature, it is not expected that either psilocybin-naïve or experienced individuals will develop dependence after exposure.

Additional survey research within the United States suggests hallucinogens were selected as a primary substance of abuse in only a fraction of a percentage of responders ([M. W. Johnson et al., 2018](#)). Continuing, in the University of Zurich study the large majority of participants reported “no change” in their psilocybin use following their laboratory sessions, as well as “no change” in their overall drug consumption habits (e.g., use of alcohol, nicotine, cannabis, MDMA). Those who did report changes often described decreased consumption, specifically in terms of psilocybin use.

6.5.7. Ability to Drive and Use Machines

Participants must agree to be driven home following dosing with psilocybin. The clinical protocol must be followed regarding patient discharge after dosing.

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