Investigator's Brochure

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

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Psilocybin Investigator's Brochure Amendments

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Original Psilocybin Investigator's Brochure Version 1.0	07 February 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)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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 has developed 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
d	Cohen's d 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
HMPC	hydroxypropyl methyl cellulose
Hopkins	Johns Hopkins University
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
p	*p*-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
t	Student's t-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	Zeeh 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. All relevant 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-HT2A 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, in the clinical trial setting, protocols mandate observation until approximately 8 hours after dosing.

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 in order to gauge safety events and preliminary 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 presented 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 these studies showed a decrease in symptomatic response in indications including obsessive compulsive disorder (OCD), substance use disorder, depression, and anxiety. Overall, psilocybin was 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.

2. INTRODUCTION

2.1. Interventional Approach

2.1.1. 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-HT2A 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, 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 we refer 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 suggested that serotonergic hallucinogens, such as psilocybin, have clinical potential for inducing therapeutically-beneficial behavior change in a variety of psychiatric conditions. Results of completed and published studies are reported.

2.1.2. 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
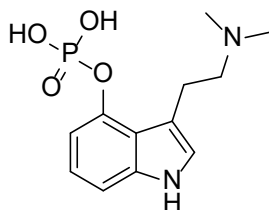
psilocybin
Chemical Formula: $C_{12}H_{17}N_2O_4P$
Molecular Weight: 284.3

Figure 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 (HMPC), blue).

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, HMPC, blue). 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 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, and do include some within range of a 25-mg oral dose (0.36 mg/kg in a 70-kg individual) 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 5HT2A receptor (Willins & Meltzer, 1997). Most, but not all, of the other behaviors induced by psilocybin in animals (**Table 1**) are similarly blocked or significantly attenuated by inactivation of the 5HT2A receptor, either pharmacologically or via gene knock-out. However, *in vitro* psilocybin binds to a wide range of receptors in addition to 5HT2A, including (ordered by increasing binding affinity): 5HT2B, 5HT1D, dopamine D1, 5HT1E, 5HT1A, 5HT5A, 5HT7, 5HT6, D3, 5HT2C, and 5HT1B (Ray, 2010). In rodents, behaviors not impacted by 5HT2A inactivation include locomotor inhibition, which appears to be mediated by 5HT1A and 5HT2B/C receptors, based on antagonist studies.

Table 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-HT1A, 5HT2A/C as well as dopamine D2 receptors (Tylš et al., 2014). Agonism at 5HT1A 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 5HT2A 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. In awake rats a microdialysis study 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 being among 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. > 25 mg for humans, using standard animal-to-human dose equivalency) (Cerletti, 1958). Non-clinical studies of the neurotoxicity of psilocybin have not been conducted, per literature review. A study of rats found the LD50 for psilocybin to be between 280-285 mg/kg, which is far higher than a 25-mg dose in humans (0.36 mg/kg in a 70-kg individual). Based on standard human equivalency doses (HED), the LD50 in rodents is approximately 5,000 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 (significantly higher in all species than a 25 mg 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 (all doses higher than dose for this Investigational New Drug (IND)) 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 (significantly higher than a 25 mg dose in humans) found no evidence of genetic abnormalities, based on an absence of chromosome breakage (Van Went, 1977).

5. EFFECTS IN HUMANS

5.1. Pharmacokinetics and Metabolism in Humans

Following oral administration (0.224 mg/kg) of psilocybin, 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 to be $52.7 \pm 20\%$ ($N = 3$). 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; Hasler, Bourquin, Brenneisen, Bar, & Vollenweider, 1997). 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).

Psilocin is metabolized to 4-hydroxyindole-3-acetic acid by deamination and demethylation via liver enzymes such as monoamine oxidase, and aldehyde dehydrogenase (**Figure 2**) (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).
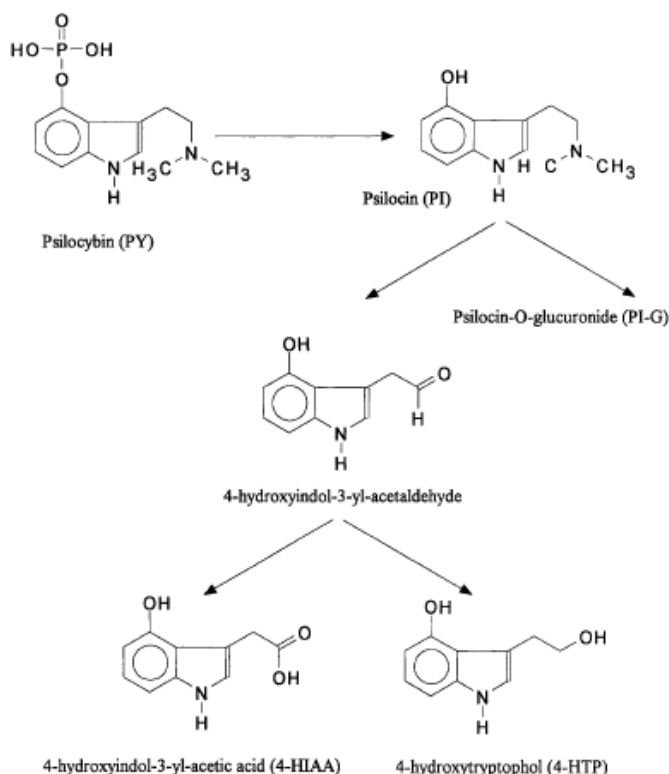
Figure 2: Metabolism of psilocybin

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 5HT2A receptor site (Carhart-Harris et al., 2014; Nichols, 2016; Vollenweider & Kometer, 2010). Pre-treatment with the serotonin 5HT2A 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). 5HT2A 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 5HT2A 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 5HT2A agonists. Psychedelic, but not non-psychedelic, 5HT2A 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 (Tyls, Palenicek, & Horacek, 2014). Psilocybin activates 5HT1A receptors, which may contribute to antidepressant/anti-anxiety effects.

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 275 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 2**).

Of the 275 participants enrolled across these studies, 264 received at least one dose of oral psilocybin, 180 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, 529 oral psilocybin doses were administered. Doses ranged from "very low dose" (45 µg/kg) through "high dose" (600 µg/kg; 0.6 mg/kg).

One study (Imperial College of London) utilized a 25 mg dose. Six other studies and one retrospective analysis used within a range of 300 µg/kg – 315 µg/kg, which by body weight of participants closely resembles a 25 mg dose on average. Of these studies using either a 25 mg dose or 300-315 µg/kg range dose, 182 oral psilocybin doses were administered. Of these eight studies, six were dose-escalating studies and two were placebo-controlled studies. Of the dose-escalating studies, the 25 mg or 300-315 µg/kg dose was the highest dose in three, and the lowest dose in three.

Table 2: Summary of completed clinical trials studying oral psilocybin

Study	Reference	Study Design	Objective	Enrollment	Population	Dose
University of Wisconsin	Brown et al; *Clinical Pharmacokinetics*, 2017	Open-label, dose-escalating	Determine 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; *J Psychopharmacol*, 2011	Retrospective analysis	Analyze acute, short- and long-term subjective effects of psilocybin in healthy humans from previously conducted double-blind, placebo-controlled experimental studies	110	Healthy adults	1-4 doses of oral psilocybin (45-315 µg/kg)
University of Arizona	Moreno et al; *J Clin Psychiatry*, 2006	Open-label, dose-escalating, proof of concept	Explore safety for human consumption of 4 doses of psilocybin in a small sample of symptomatic Obsessive Compulsive Disorder patients	9	Adults with Obsessive Compulsive Disorder	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; *J Psychopharmacol*, 2015	Single-group, dose-escalating proof of concept study	Quantify acute effects of psilocybin in alcohol-dependent participants and provide preliminary outcome and safety data	10	Adults with active alcohol dependence	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; *J Psychopharmacol*, 2014	Open-label, dose-escalating	Determine the safety and feasibility of psilocybin as an adjunct to tobacco smoking cessation treatment.	15	Psychiatrically healthy, nicotine-dependent adult smokers	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; *Lancet Psych*, 2016 and Carhart-Harris et al; *Psychopharmacol*, 2018	Open-label, dose-escalating feasibility study	Determine safety and efficacy outcomes for up to 6 months in an open-label trial of psilocybin for treatment-resistant depression	20	Adults with moderate or severe depression	Oral psilocybin, 1x 10 mg (low dose), 1x 25 mg (high dose) one week apart
Harbor-UCLA	Grob et al; *Arch Gen Psychiatry*, 2011	Randomized, double-blind, placebo-controlled, crossover	Evaluate efficacy of psilocybin for advanced-stage cancer patients	12	Adults with advanced cancer (various types)	0.2 mg/kg (1x oral psilocybin, 1x oral placebo)
Johns Hopkins	Griffiths et al; *J Psychopharmacol*, 2016	Randomized, double-blind, crossover	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	56	Adult cancer patients	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)
NYU	Ross et al; *J Psychopharmacol*, 2016	Randomized, double-blind, placebo-controlled, crossover	Investigate the efficacy of a single psilocybin dosing session versus placebo (in conjunction with psychotherapy) to treat clinically significant anxiety or depression	31	Adults with cancer diagnosis	0.3 mg/kg oral psilocybin or 250 mg oral placebo

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. 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.

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.

5.3.2.1.2. Pharmacokinetics

Anticoagulated blood samples were collected at the time points mentioned above, and urine was collected for 24 hours after each dose. Psilocybin, as its active metabolite psilocin, demonstrated linear pharmacokinetics over the dose range tested, as indicated by the noncompartmental evaluation of dose-normalized area under the curve and C_{max}. The mean maximal concentration of psilocin increased in a dose proportional manner from 0.3 mg/kg psilocybin (16 µg/L), to 0.45 mg/kg (26 µg/L), to 0.6 mg/kg (37.6 µg/L). The dose-adjusted maximum concentration changed from 0.7 µg/L (0.3 mg/kg), to 0.838 µg/L (0.45 mg/kg), to 0.799 µg/L (0.6 mg/kg), and the time to reach C_{max} was between 2.03-2.05 hours for each dose level (**Figure 3**). Less than 5% of the oral psilocybin dose was excreted in urine as psilocin.
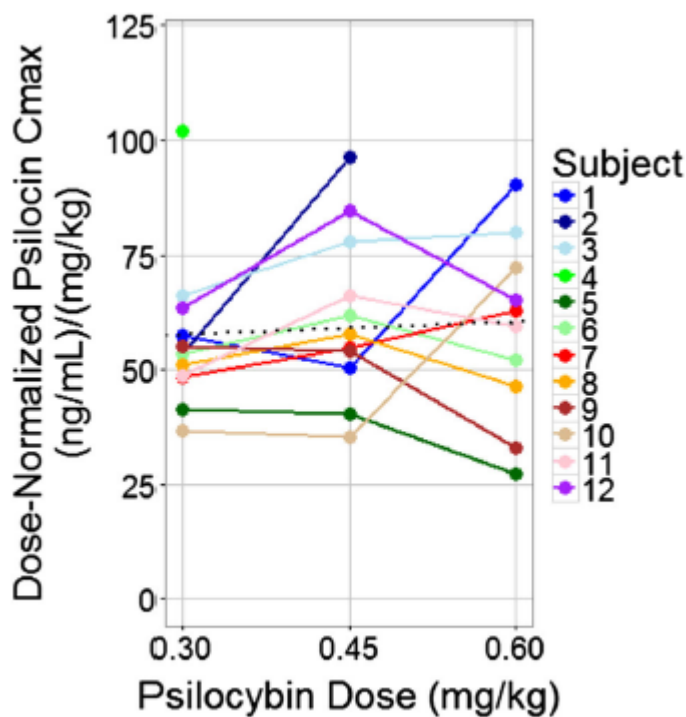
Figure 3: Dose-normalized plasma psilocin C_{max}.
The dotted black line represents the least squares regression.

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 (N = 22, 83% of participants), mild bradycardia (N = 22, 58%), mild headache (N = 14, 75%), and mild tachycardia (N = 12, 50%) (**Table 3**). 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 3: Summary of adverse events related to psilocybin dosing*

Adverse Event Description†	Total No. of episodes	# of participants	# per dose		
			0.3mg/kg	0.45mg/kg	0.60mg/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 is unpublished, and was 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 ≥160 mmHg or DBP ≥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 <39.0^0 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. 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 4**) (Studerus et al., 2011). Oral psilocybin was provided in either a single dose, or a range of up to four doses per participant, with dosing strength varying from 45 to 315 µg/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 4: Studies involving oral psilocybin dosing

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-HT2A receptor dynamics in the human brain following psilocybin stimulation: A PET study.	250 μg/kg	11	-	-	11	-
Total number of subjects	-	*110*	*8*	*74*	*104*	*42*

5.3.2.2.1. *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** shows the complete list of participant complaints, differentiated by dose effect relation versus placebo, and medium dose comparison to placebo.

Table 5: List of complaints 24 hours post-dose

Complaints	Dose effect relation (N = 40)						Medium Dose Comparison (N = 72)			
	Placebo	115 mg/kg	215 mg/kg	315 mg/kg	*p*-value	Signif.	Placebo	215–250 mg/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	
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	

Complaints	Dose effect relation (N = 40)						Medium Dose Comparison (N = 72)			
	Placebo	115 mg/kg	215 mg/kg	315 mg/kg	*p*-value	Signif.	Placebo	215–250 mg/kg	*p*-value	Signif.
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 4. 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.

5.3.2.2.2. *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).

5.3.2.2.3. *Conclusion*

Collected data from the eight studies listed in **Table 4** demonstrated that psilocybin was safe and well-tolerated under the conditions tested. Adverse events were generally classified as mild and resolved within 24 hours.

5.3.2.3. **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.

5.3.2.3.1. *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 for human consumption 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 (medium), 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, with all doses occurring 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 medium 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 4**). Dose dependency on symptom reduction

was not observed, with a decrease in average YBOCS score occurring after administration of each dose level (**Figure 4**).

A. YBOCS score over time

B. Average YBOCS score by dose
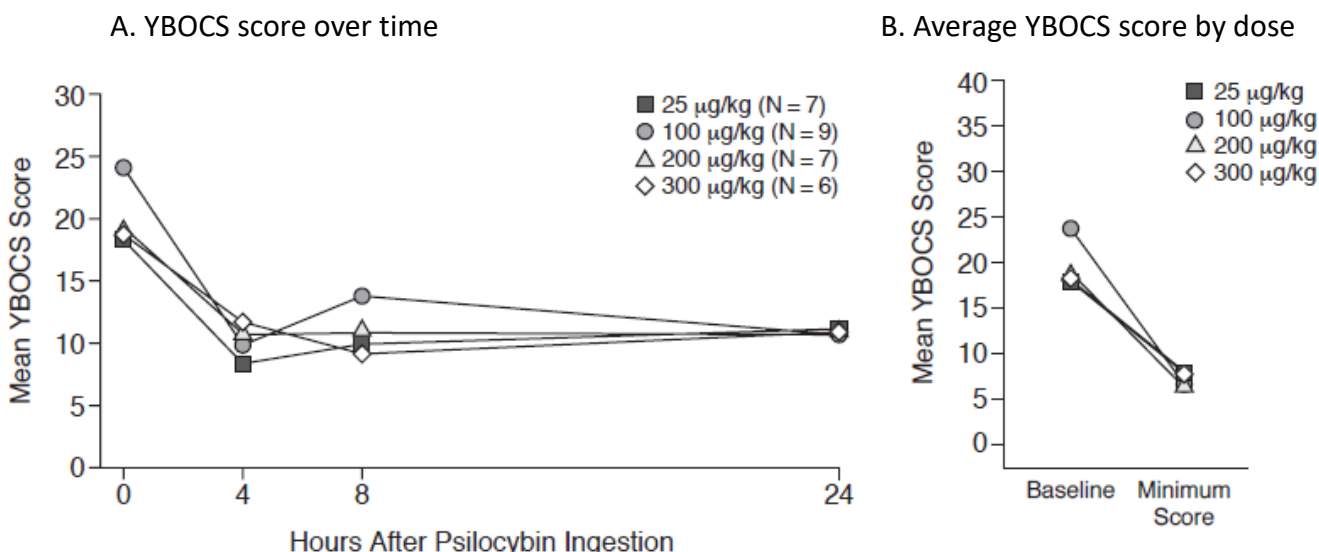
Figure 4: Decreases in OCD scores as assessed by YBOCS
A. Mean YBOCS scores immediately prior to ingesting psilocybin through 24 hours after ingestion, and B. Average YBOCS scores prior to psilocybin ingestion as compared to the average of the lowest scores obtained (4, 8, or 24 hours) after ingestion, 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 under the conditions tested at a series of four dosing levels, and was associated with acute reductions in core OCD symptoms in a 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**). 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: Improvement in alcohol reliance following psilocybin treatment
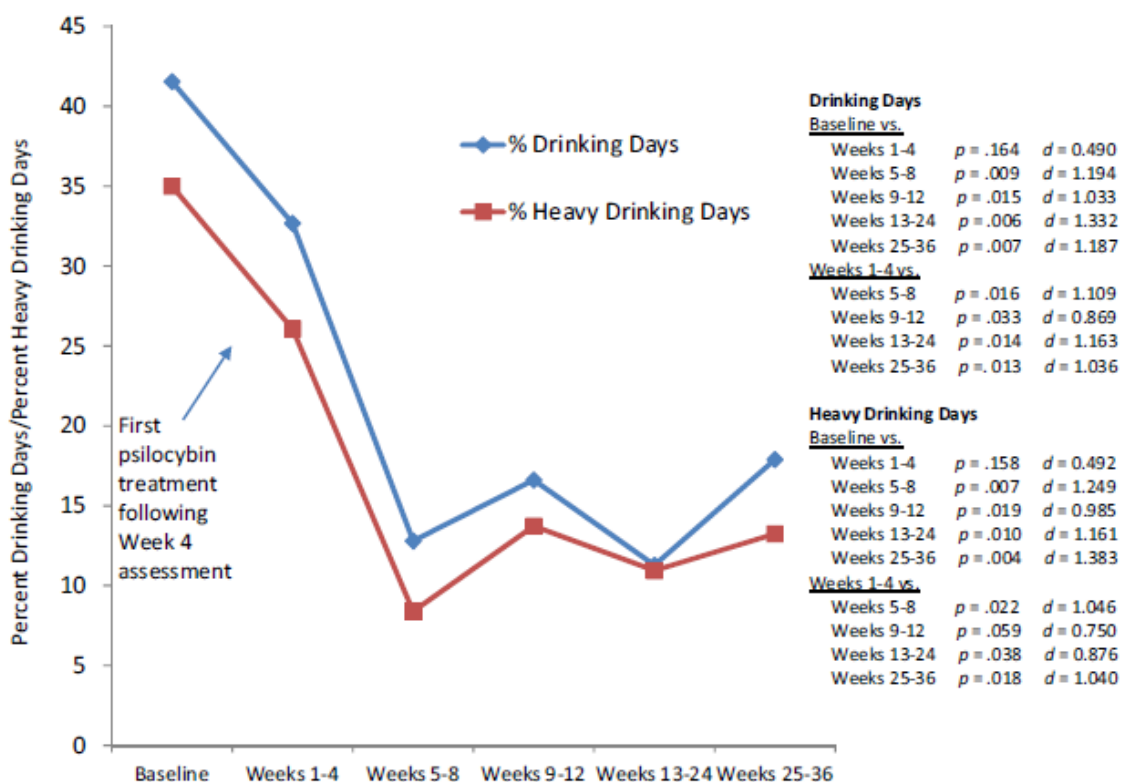   Means shown for all available data (N=10 at baseline, N = 9 at all other time points)

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, increased alcohol abstinence in a population of participants with alcohol dependence when compared to baseline.

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) and a high dose (30 mg/70 kg), 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. 30 of 30 (100%) planned doses were administered, and 42 of 45 possible psilocybin sessions (93%) 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 6**).
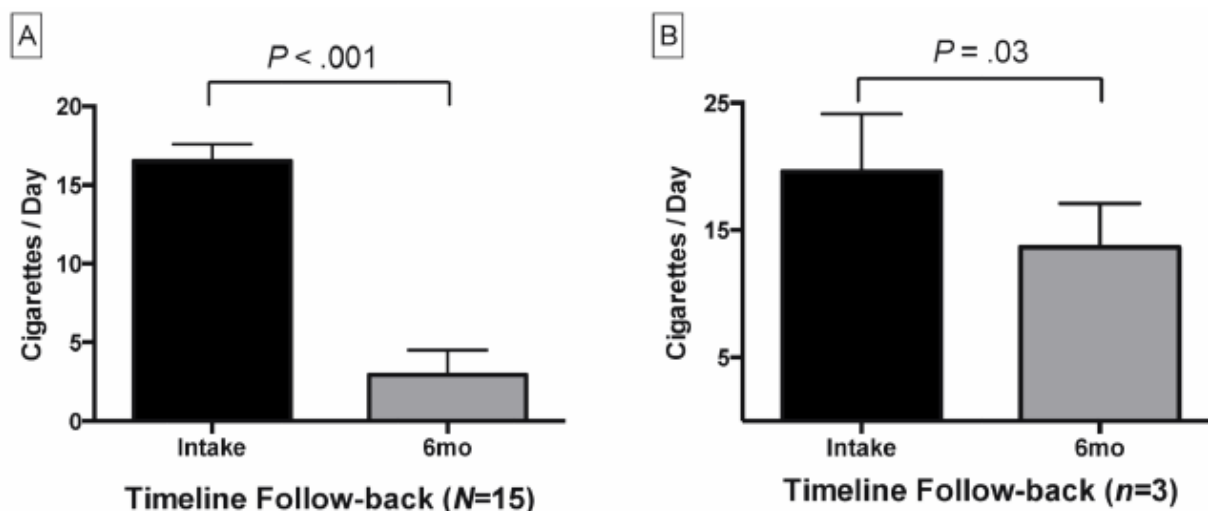
Figure 6: Timeline follow-back data for smoking cessation following psilocybin treatment
Timeline follow-back data at the six-month time point for A) the entire study population, and B) the three participants who tested positive for smoking at the six-month follow-up.

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 7**) (Carhart-Harris et al., 2016).
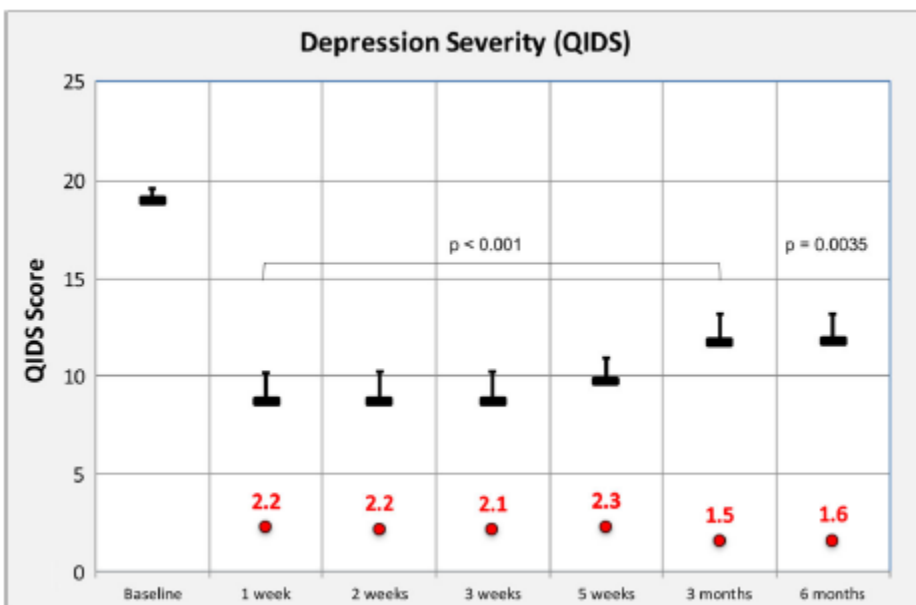
Figure 7: Mean QIDS values to assess self-reported depression
Mean values (black horizontal bars) as calculated for the 19 study completers, with error bars included. QIDS scores of 16-20 are considered to reflect severe depression. Cohen's d values vs baseline are shown in red, all contrasts vs baseline 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 6**. 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 6: Individual patient clinical rating results

	BDI				STAI				SHAPS			HAM-D		GAF	
	Baseline	1 Week	3 Months	6 Months	Baseline	1 Week	3 Months	6 Months	Baseline	1 Week	3 Months	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 baseline (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.   **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.

5.3.4.2.1.   *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.

5.3.4.2.2.   *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 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 8**).
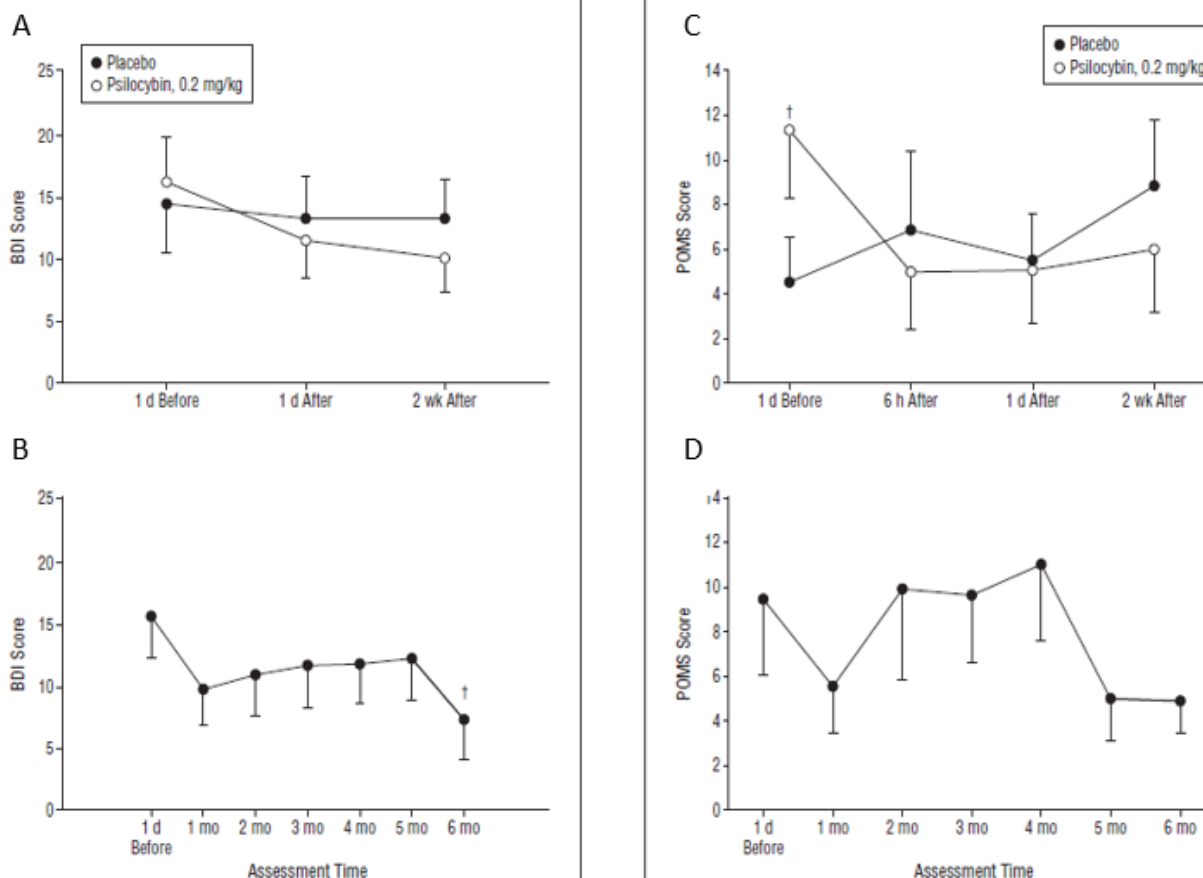
Figure 8: BDI and POMS scores between placebo and psilocybin for assessment of clinical efficacy
A) Mean BDI scores between placebo and psilocybin for up to two weeks after administration.
B) Mean BDI scores reported during the 6-month follow-up following the second dosing event.
C) Mean POMS scores 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 9**).
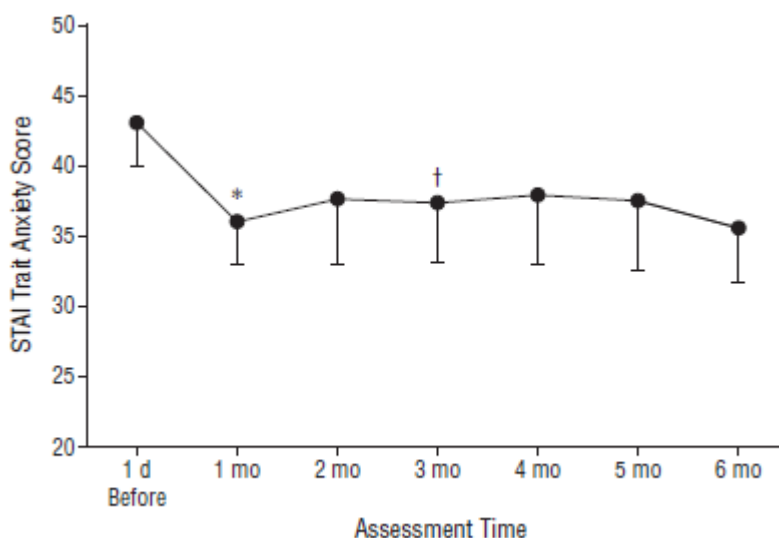
Figure 9: STAI trait anxiety subscores through long-term follow-up.
N = 12 for all time points up to three months, N = 11 for the 4-month time point, and N = 8 for the Months 5 and 6 time points.
*P_<0.01, †P_<0.05 for psilocybin vs the value from 1 day before the first treatment session (t tests were used to compare individual monthly follow-up values with values on the day before the first session).

5.3.4.2.3.   *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 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.

5.3.4.2.4.   *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.

5.3.4.3.   **Johns Hopkins 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.

5.3.4.3.1. 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%).

5.3.4.3.2. 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-Hamilton Depression Rating Scale (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 7** and **Figure 10**.

Numerical data in **Table 7** 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 7: 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.
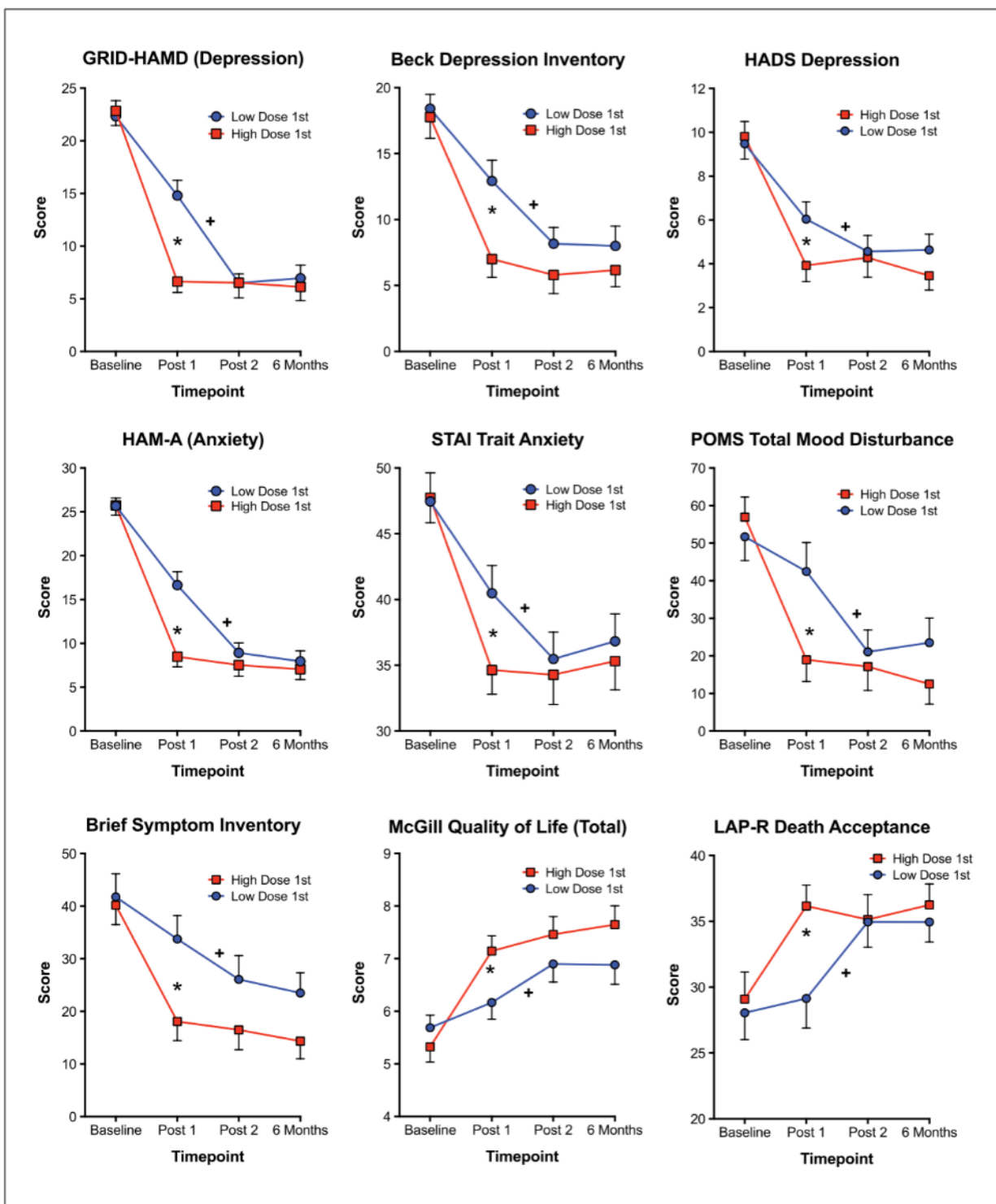
Figure 10: Outcome measures to assess clinical efficacy in the Johns Hopkins study

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.

5.3.4.3.3.   *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 8**. 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 8: 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 9**). 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 9: 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

5.3.4.3.4.   *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.

5.3.4.4. 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 (0.3 mg/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.

5.3.4.4.1. 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.

5.3.4.4.2. 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 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 11**).
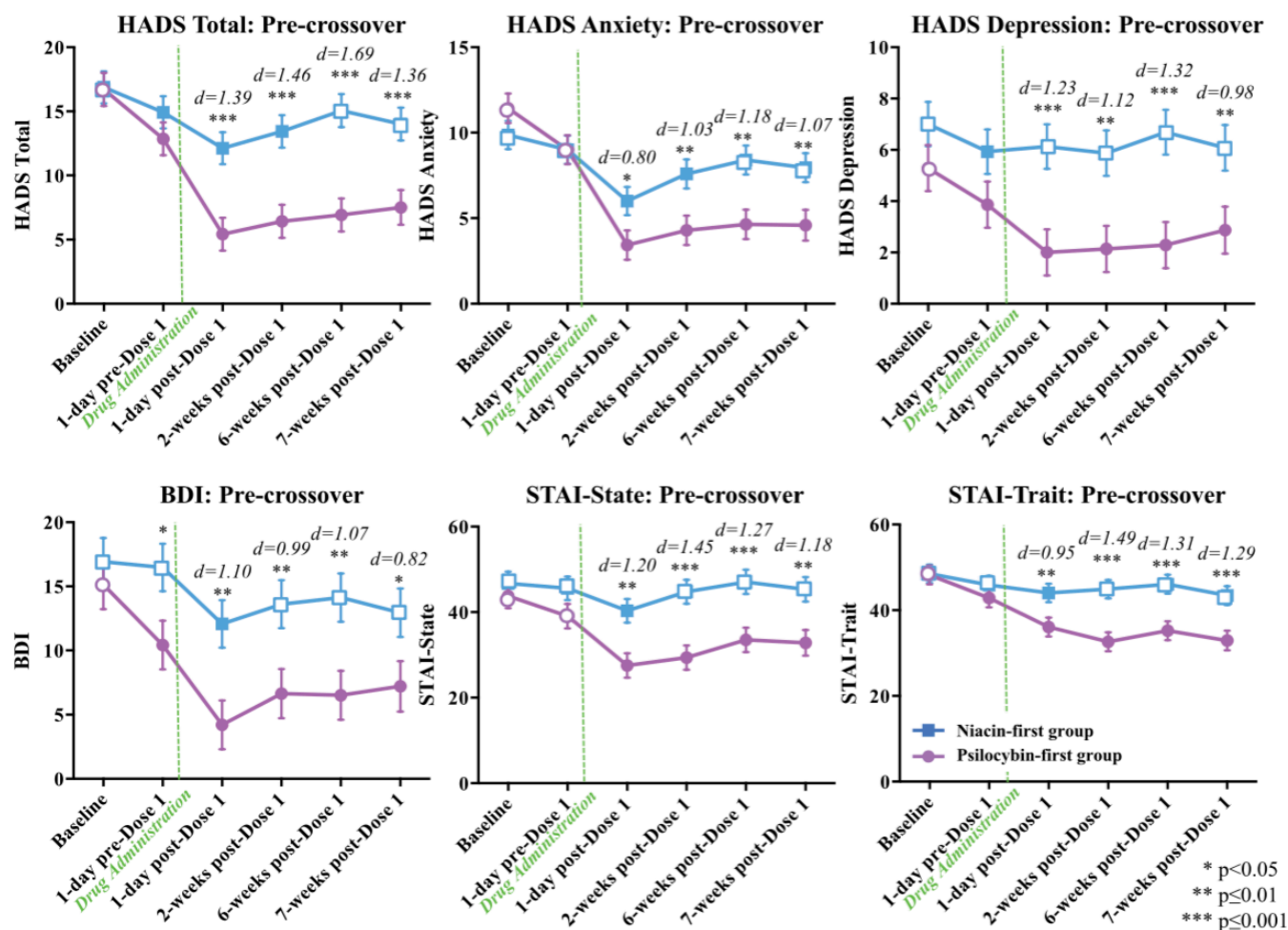
Figure 11: Psilocybin as a method of sustainment for reduction of anxiety and depression in the NYU study
Means (±SE) for primary outcome measures are shown in the two treatment groups at the following time points: baseline (psilocybin first $n=14$, niacin first $n=15$), 1 day pre-dose 1 (psilocybin 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 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.
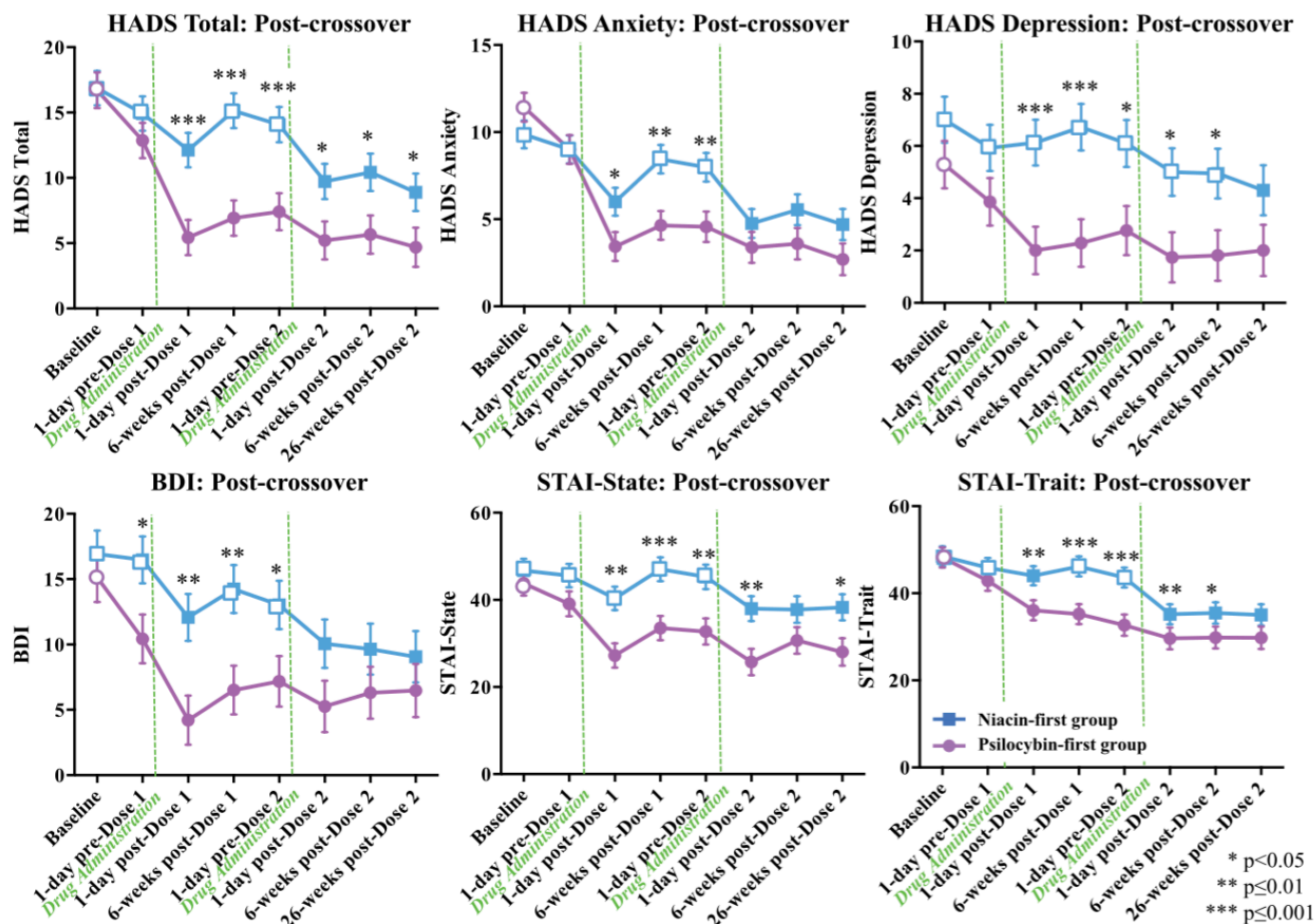
Figure 12: Long-term follow-up in the NYU study

Means (±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.

5.3.4.4.3. *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 10**). Three of 11 events (27%) were determined to be possibly related to psilocybin administration.

Table 10: Adverse events not occurring during 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.

5.3.4.4.4.   *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. Single-dose psilocybin was well-tolerated at a 0.3 mg/kg dose.

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

Over the course of its clinical development phase, 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; Meltzner, 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; Tyls 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

In the **University of Wisconsin Study** (Phase 1 dose escalation of oral psilocybin in healthy participants), additional analysis was performed in order to ascertain the effect of psilocin concentration on QTc interval prolongation. Blood samples for PK assessment were collected at predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 18 and 24 hours post dose. 12-lead ECG were obtained predose, 2, 4 and 8 hours post-dose. The ECGs, including QTcB and QTcF durations, were overread by an electrophysiologist. The study did not include a placebo arm or a positive control arm.

The studied psilocybin doses ranged from 19 to 59 mg (0.3 to 0.6 mg/kg) and psilocin C_{max} ranged from 11 to 54 ng/mL. No delay between the time course of psilocin PK and the change in ΔQTcF was observed, with maximum ΔQTcF occurring at the time of psilocin C_{max}. The concentration-QTc analysis showed a positive effect of psilocybin on QTcF prolongation with a linear relationship between psilocin Cmax and ΔQTcF, under the studied psilocybin doses. The upper bound of the 90%CI of the model-predicted mean ΔQTcF crosses the threshold of regulatory concern of 10 msec at a psilocin concentration of 31.1 ng/mL. 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 ΔQTcF is 6.6 msec, below the threshold of 10 msec.

The values for the median C_{max}, model-predicted mean ΔQTcF, and upper and lower 90% confidence interval (CI) limits for the change in QTcF at any of the ECG samplings are shown below (**Table 11**).

Data is unpublished, information was obtained from final draft of QTc specific technical report generated by Joga Gobburu, PhD and his team at University of Maryland.

Table 11: Model-predicted mean ΔQTcF at the observed median Cmax of each dose quartile

Dose / Dose range	Median Cmax (ng/mL)	Model-predicted mean ΔQTcF (msec)	Lower 90% CI of mean ΔQTcF (msec)	Upper 90% CI of mean ΔQTcF (msec)
19 - 22 mg	15.3	1.5	-2.7	5.7

25 mg	18.7	2.1	-2.4	6.6
26 - 31 mg	24.3	3.0	-2.1	8.1
32 - 41 mg	29.8	3.9	-1.7	9.6
42 - 59 mg	37.6	5.3	-1.2	11.8

The psilocin concentrations as compared with QTcF are shown over time for dose group in Figure 13.
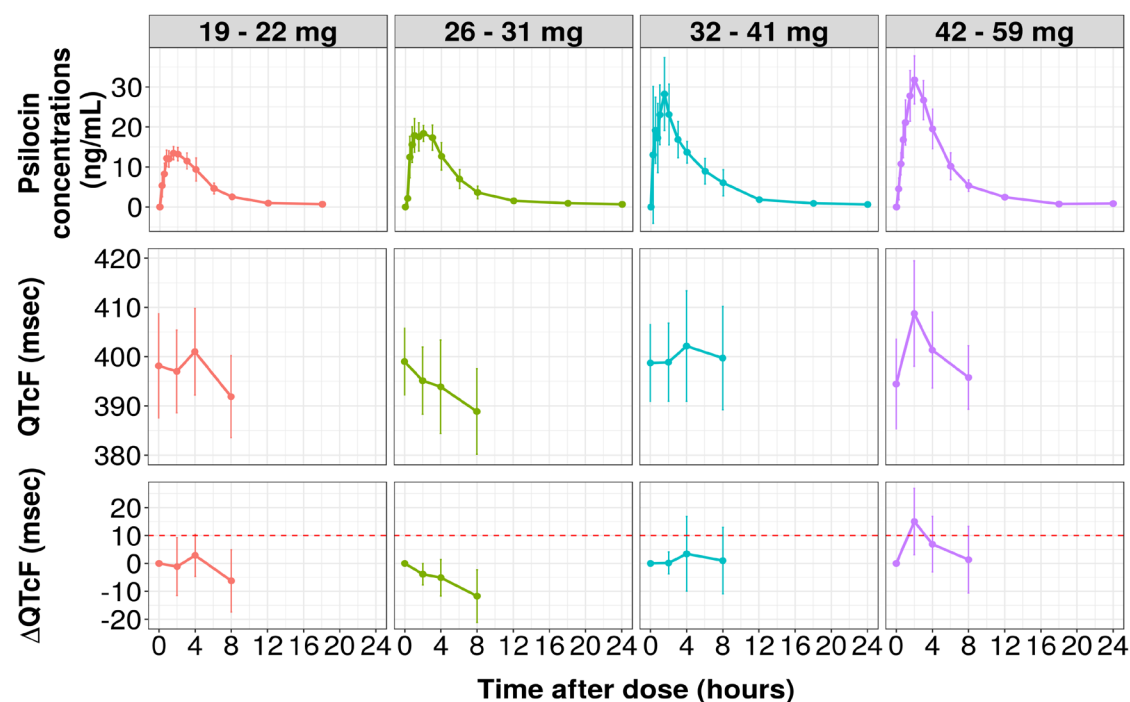
Figure 13: Time course of mean (± 90%CI) psilocin concentrations, QTcF and baseline-adjusted QTcF (ΔQTcF) intervals in each psilocybin dose quartile

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 the Wisconsin Phase I dose-escalation study, there were several instances in which mild bradycardia was noted. 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, including in improving 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 eight 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).

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 HT2A 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**, a completed, open-label, dose-escalating (0.3 – 0.6 mg/kg oral psilocybin) trial described safety events in 12 healthy participants. 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.

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-HT2A 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 Unites 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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