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Review Article

Pharmaceutical Development Considerations of Psilocin and Its Prodrug Psilocybin: A Comprehensive Review of Published Pharmacokinetic Data

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Abstract

Psilocybin and its active metabolite, psilocin, are potent psychoactive tryptamines naturally prevalent in Psilocybin mushrooms. They are being investigated for possible therapeutic applications in the treatment of several neurological disorders, depression, post traumatic stress disorder, obsessive-compulsive disorder, anxiety, addiction, and cluster headaches. Recent reports have broadened these investigations to include treatments as anti-inflammatory agents that cross the blood-brain barrier. Although promising as therapeutics, their development faces significant pharmaceutical challenges.

This report provides a thorough examination of the pharmacokinetics of psilocybin and its active metabolite, psilocin. Data from five varied laboratories are analysed and presented in a consistent format, underscoring the necessity for further research to enhance understanding of psilocybin's bioavailability, impact of food, and ultimately, its usefulness as a pharmaceutical active ingredient.

The findings of this article cast doubt on the current paths being pursued by researchers and underscore the necessity for a systematic approach to develop a suitable dosage and frequency of administration to maximize efficacy in each therapeutic application.

Keywords: Psilocybin; Psilocin; Pharmacokinetics; Tryptamines; Indole-alkylamine therapy; Psychedelic Treatment; Mental health disorders

Abbreviations

5HT: 5 Hydroxytryptamine; Adm: Administration; AUC: Area Under Curve; C_{max}: Maximum Plasma Concentration; FDA: Food and Drug Administration; IV: Intravenous; MDD: Major Depressive Disorder; N: Number; OCD: Obsessive-Compulsive Disorder; PET: Positron Emission Tomography; T_{max}: Time to peak drug concentration; TRD: Treatment-Resistant Depression

Introduction

The therapeutic potential of naturally occurring hallucinogenic compounds has intrigued both researchers and clinicians, presenting novel opportunities for treating mental health disorders that are resistant to traditional treatments. Compounds like psilocybin (4-phosphoryloxy-N, N-dimethyltryptamine) and psilocin (4-hydroxy-N, N-dimethyltryptamine), are present in Psilocybe mushrooms, and have attracted significant interest due to their powerful psychoactive properties and potential therapeutic benefits. These mushrooms are found in regions such as Mexico, South America, and certain areas of the United States [1,2]. More recently, both have shown promise as potent psychoactive and anti-inflammatory agents that rapidly penetrate the blood brain barrier [3]. Psilocin is a naturally existing psychedelic tryptamine. Its presence in psychedelic mushrooms is in minor amounts. However, its phosphorylated counterpart, psilocybin, which undergoes enzymatic conversion after ingestion to psilocin, is more abundant. The ceremonial use of hallucinogenic mushrooms, due to its psilocybin content, occurred before millennia in indigenous cultures [4]. However it was not until the mid-20th century that Western science began to unravel their pharmacological benefits for treating a host of mental illnesses. Following its introduction to the scientific community by Robert G. Wasson in the 1950s, psilocybin was systematically studied, leading to the isolation, identification, and synthesis of it by pioneering researchers such as Roger Heim and Albert Hofmann. However, the early promise of psychedelic research was overshadowed by misuse, regulatory crackdowns, and societal stigma, leading to psilocybin and consequently, psilocin being classified as a Schedule 1 substance in the United States, significantly limiting further research [5].

Recent research has sparked renewed interest in the therapeutic prospects of psilocybin and psilocin for addressing a wide array of medical conditions and health issues. Clinical trials show promising results for ailments like anxiety, post-traumatic stress disorder, addiction, treatment-resistant depression and obsessive-compulsive disorder. Although it would be preferable to formulate therapeutics

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with psilocin and not its prodrug psilocybin, psilocin's inherent rapid degradation has limited its use in most applications. Hence most of the research in this area has focused on psilocybin, which must convert to psilocin in a predictable and reproducible fashion to be considered approvable under today's US FDA regulations [6]. The Food and Drug Administration (FDA) emphasizes that creating clinical trials to assess the safety and efficacy of these compounds poses several challenges that necessitate careful deliberation. Tiffany Farchione, M.D. Director of the Division of Psychiatry in the FDA's Center for Drug Evaluation and Research, commented, "Psychedelic substances display early potential as prospective cure for anxiety, mood and substance use disorders. Nevertheless, sponsors investigating the therapeutic potential of these substances should take into account their experimental nature and distinctive attributes when outlining clinical trials." The considerations outlined in the FDA's draft proposal encompass trial execution, data gathering, participant safety, and requirements for new drug applications. For instance, the FDA has highlighted the importance of researchers implementing adequate safety measures to prevent misuse during all stages of clinical development. Other considerations include requiring the pharmacokinetics and pharmacodynamics of psychedelic drugs to be adequately characterized both *in vitro* and *in vivo* - such as evaluating the impact of high-fat meals on the pharmacokinetics of an oral psychedelic drug early in development to inform clinical study design. The FDA guidance recommends that two professionals closely monitor each clinical trial patient for several hours after dosing with psychedelic drugs. They say that this monitoring period is required to assess any potential adverse effects, psychological reactions, or other safety concerns that may arise following dosing. FDA suggests that having two professionals on hand enables the trial team to quickly tackle any problems and safeguard patient health in the aftermath of dosing. According to the authors' understanding, this marks the initial instance of the FDA issuing a directive likely to escalate clinical trial expenses to such an extent that conducting research in this domain will become almost unfeasible [7].

Psilocin serves as a partial agonist at serotonin receptors, particularly the 5-HT2A receptor, producing psychedelic effects at high concentrations. The similarity in chemical structure to serotonin, a neurotransmitter involved in regulating mood, appetite, and sleep, may also categorizes psilocin and psilocybin's bioactivity. At high concentrations, these compounds are known for their hallucinogenic and euphoric effects, known as "trips" which result from their action on serotonin receptors in the central nervous system [4]. At doses ranging up to 35 mg, psilocybin can trigger hallucinations lasting six hours or more. Recreational consumption, such as in tea or food, can also lead to negative experiences or "bad trips." These experiences can vary greatly depending on factors like the type of mushroom, preparation method, and individual sensitivity, making recreational use highly unpredictable and potentially dangerous [8]. Even with the popularity of these substances, there's a dearth of formal probe on the dose-response relationship. Notably, the therapeutic effects of psilocin and psilocybin may not directly correlate with their hallucinogenic properties, leading to current investigations into the benefits of micro dosing, or the use of sub-hallucinogenic levels.

The psychedelic or hallucinogenic effects of these compounds, such as altered perception, mood, and cognition, May not be essential to their therapeutic use but may simply be side effects that occur at improper dosages. Through rigorous drug development and clinical research, it's possible to identify dosages at which therapeutic benefits are achieved without significant or any psychedelic effects. The key lies in the dosage and method of administration, and knowledge of their pharmacokinetics which are critical in balancing therapeutic outcomes with unwanted side effects. This approach enables researchers to isolate the beneficial medicinal properties of this class of compounds from adverse events, paving the way for their use in treating a range of unmet medical needs with dosages and frequencies that resemble other pharmaceutical products [8].

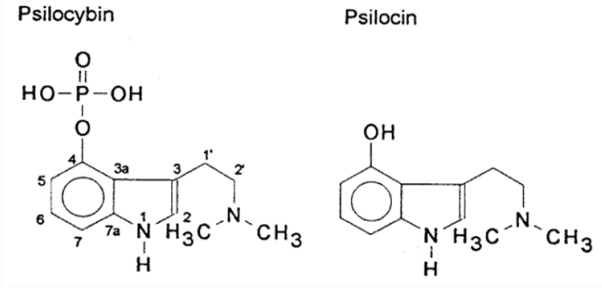
This article provides a basic understanding of the pharmacology of psilocybin, and then focuses on the current available literature concerning the pharmacokinetics of psilocybin and psilocin. We present the published data, reformatted to allow direct comparisons of the results of each of five diverse pharmacokinetic studies conducted over a span of 30 years. It provides researchers a detailed analysis of data for this transformative drug class and seeks to suggest that the hallucinogenic experience reported in most clinical settings may be a side effect of the dose and frequency of dosing rather than a mode of action necessary for efficacy. It also suggests that by limiting the dose to a sub-hallucinogenic level, the efficacy may be maintained for many of the indications and the negative aspects of the drug eliminated.

Soon, these compounds must enter into standard pharmaceutical development protocols as suggested by the FDA. These pharmaceutical development programs must rely on a thorough and accurate knowledge of pharmacokinetics of the drug and its metabolite. In the case of the prodrug psilocybin, which has been investigated extensively, key assumptions regarding its conversion rate to the active metabolite psilocin, as well as its absorption characteristics, tissue distribution, and rate of elimination, must be confirmed. The primary aim of this article is to offer developers a comprehensive source of available data and highlight aspects of pharmacokinetics that may contradict current thinking.

Materials and Methods

Pharmacology of psilocybin

Psilocybin ingestion administered orally at doses of 15 mg or 20 mg, increases glucose metabolic rates in the frontal cortical regions of healthy participants, suggesting the frontal cortex may be involved in some of its behavioral effects. This is supported by Positron Emission Tomography (PET) investigations. Classic indole-alkylamines, like psilocin, share agonism at the serotonin 5HT2A receptor site. The antagonist ketanserin blocks most cognitive impact of psychedelic compounds in humans, such as acute positive mood increases. Stimulation of the 5HT2A receptor depolarizes pyramidal neurons, leading to higher firing rates in the prefrontal cortex. This heightened firing induced an increase in recurrent glutamatergic network function, which can be nullified by 5HT2A receptor antagonists and certain glutamate receptor antagonists [9,10].



Molecular structures of Psilocybin and Psilocin.

A recent study reveals that indole-alkylamine agonists have unique effects that are not found in non-indole-alkylamine 5HT2A agonists. These agonists can increase signaling *via* the D2 dopamine receptor in the ventral striatum, which is linked to psilocybin-induced euphoria and abnormalities in the D2 receptor in depression patients. The modulation of intracellular signaling pathways in pyramidal neurons by psychedelic and non-psychedelic 5HT2A agonists varies, leading to variations in downstream signaling proteins. Psilocin has a weaker affinity for the serotonin reuptake transporter and many dopamine receptors. Plasma concentrations of psilocin are positively linked with subjective evaluations of the drug's psychoactive effects and neocortical 5-HT2A occupancy. PET tracer research determined that 1.95 µg psilocin/L was the plasma concentration that resulted in 50% availability of the 5 HT2A receptor. Subjective intensity scores and plasma psilocin showed a favourable correlation. Relying on brain 5-HT2A receptor engagement, doses that produced occupancy levels below 20% were not recognized by cognitive or physiological assessments, indicating that this concentration might serve as a baseline for micro dosing [10,11].

Pharmacokinetics

Psilocybin is not active and it has not been seen in plasma in any of the studies reviewed. It is a prodrug, and is converted into its active metabolite; psilocin, which has been studied in numerous clinical applications. Some of these studies are listed in Table 1 [12-18].

When psilocybin is taken orally, specific enzymes, such as alkaline phosphatase, transforms it into psilocin, which is then absorbed and circulates, then distributes into various tissues [19,20]. Post oral administration, psilocybin itself has not been found in circulation or in faeces or urine. Absorption of the psilocin is slow and typically in the 2-3-hour range as noted in Table 2 and Figure 3. When an IV dosage of psilocybin is used, the conversion to psilocin is reported to be rapid with no residual prodrug found in circulation. The studies in Table 2 on psilocybin's pharmacokinetics were run under various conditions. Only one of the listed studies was reported to be conducted under fasted conditions. The remaining studies were conducted with food but did not follow a standard "fed" protocol. However, with only limited data, there is no indication that a food effect impacts all pharmacokinetic parameters of psilocin derived from psilocybin. Figure 1 and 2 graphically presents C_{max} and AUC data across all the studies listed in Table 2. The data extracted from each publication was converted to equimolar psilocin concentrations and a body weight of 70 Kg was used to adjust the data to the same scale. The rescaled data is presented with (*) in Table 2. A standard body weight of 70 kg was assumed and each data point was recalculated and reported in the same units to allow a direct comparison.

Generally, both C_{max} and AUC seem dose proportional over a wide range of concentrations and laboratory conditions. Figure 3 and 4 show similar graphs of T_{max} and $T_{½}$ for the 5 studies reported in Table 2. Aside from data collected in the Hasler et al. [21] Study which involved participants in a fasted state, the T_{max} values ranged from 2 to 3 hours. Notably, the Hasler et al. [21] study, which is unique in its maintenance of fasted conditions, reported the shortest time to peak compared to all other studies. One explanation of this data could be that while C_{max} and AUC appear to be unaffected by a food, the time to maximum concentration in the blood (T_{max}) is considerably faster under fasted conditions. Note also that the elimination rate appears to be almost random across studies. As previously noted, unrestricted food consumption during the trial period could lead to unpredictable metabolism rates of the psilocybin or increased retention in the gut.

Also of note is the IV study of a 1 mg psilocybin solution. While

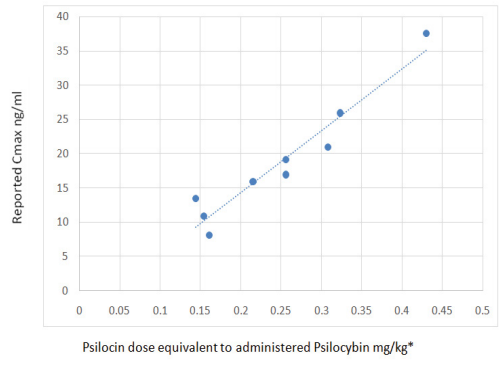


Figure 1: C_{max} *vs.* Psilocin Dose Reported in 5 studies Listed in Table 2.

Table 1: Completed Psilocybin Administered Clinical Trials Summary.

Reference and year	Study Design	Description	Enrollment	Population (age)	Dose
Studerus et al. [12]	Retrospective investigation	Subjective effects, both immediate and long-term, from previous double-blind, placebo-controlled experimental trials	110	Healthy adults	1-4 oral of psilocybin dose (45-315 µg/kg)
Davis et al. [13]	Randomized trial psilocybin is supplied to the four weeks post initial treatment	Efficacy of two psilocybin doses in patients with MDD	27	Adults with MDD (40 ± 12 years old)	20 mg/70 kg, and 30 mg/70 kg oral dose of psilocybin; 1.6 weeks apart
Moreno et al. [14]	Open label, escalating dose, proof of concept	Safety and clinical effects of four psilocybin doses in subjects with OCD	9	Adults with OCD (26-62 years old)	Psilocybin oral 100 µg/kg, 200 µg/kg, 300 µg/kg, and 25 µg/kg added random
Bogenschutz, et al. [15]	Single-group proof of concept study with dosage escalation	Effects in alcohol-dependent subjects	10	Adults with active alcohol dependence (25-65 years old)	Oral psilocybin, 1 × 0.3 mg/kg, and 1 × 0.3 or 0.4 mg/kg four weeks apart
Johnson et al. [16]	Open-label, escalating dose	Safety and feasibility testing as adjunctive treatment for chronic tobacco smoking	15	Nicotine- dependent adult smokers (26-65 years old)	One oral dose of psilocybin (20 mg/70 kg), 30 mg/70 kg and 1 × low or high dose optional medication
Carhart-Harris et al. [17,18]	Open-label. escalating dose study of feasibility	Safety and effectiveness for individuals with TRD (six months)	20	individuals aged 30 to 64 who suffer from mild to severe TRD depression	Oral psilocybin administered once a week, at a dose of 10 mg and 25 mg

MDD: Major depressive disease; OCD: Obsessive- compulsive disorder; PK: Pharmacokinetics; TRD: Treatment-resistant depression.

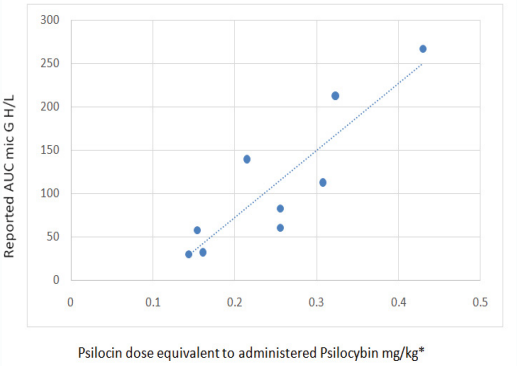


Figure 2: AUC *vs.* Psilocin Dose Reported in 5 Clinical Studies Reported in Table 2.

comparison of T_{max} and C_{max} are related to the dosage form, the comparison of the AUC of the IV to the oral studies is interesting. The reported AUC, corrected for psilocin concentration and assuming a 70 kg* weight of subjects is 4 µG H/L. Assuming a quasi-linear relationship with the oral AUC observed, it would appear that Hasler's IV injection of 0.01 mg/kg per dose (corrected for body weight and based on molar psilocin) has nearly twice the bioavailability of the oral doses across all 5 trials, leading to a possible conclusion that oral psilocybin has less than 50% overall bioavailability [21]. This would be of considerable importance when pharmaceutical formulation development is initiated for this drug. High quality, well controlled pharmacokinetic trials are needed for psilocybin where absolute bioavailability is established, and food effect determined.

It is also noteworthy to consider the comparative analysis of the elimination half-life ($T_{½}$) for Intravenous (IV) dosage, relative to the significantly prolonged elimination half-life observed with oral administration as reported by other studies [21]. For every instance analysed, the half-life for oral administration was markedly longer than that for IV administration. Brown et al. findings suggest the elongation of $T_{½}$ could be due to the potential formation and subsequent hydrolysis of psilocin glucuronide back to psilocin, a hypothesis that finds discord with the IV data presented by Hasler et al. [19-21]. We propose that the extended C_{max} and increased $T_{½}$ following oral intake is probably due to either the slow absorption rate of psilocin from the gastrointestinal tract or the decelerated conversion rate of psilocybin to psilocin within the same. Further, given the observed bioavailability of approximately 50% and the prolonged transit time through the gastrointestinal tract, it is plausible to consider a more extended interaction with gut serotonin receptors, including 5 HT2A among others. This interaction could be pertinent and directly linked to the hallucinogenic properties. This phenomenon should be investigated to ascertain the actual pharmacokinetics of psilocybin. Studies with the direct dosing of psilocin should be conducted to determine its pharmacokinetics and absolute bioavailability and compared with data for psilocybin to better understand its properties and provide pharmaceutical development scientists with information critical to product development activities.

Figure 1 and 2 graphically presents C_{max} and AUC data across all the studies listed in Table 2. The data extracted from each publication was converted to equimolar psilocin concentrations and a body weight of 70 Kg was used to adjust the data to the same scale. The rescaled data is presented with (*) in Table 2. A standard body weight of 70 kg was assumed, and each data point was recalculated and reported in the same units to allow a direct comparison.

Clinical trial investigations without pharmacokinetics

Figure 3 and 4 show similar graphs of T_{max} and $T_{½}$ for the 5 studies reported in Table 2. Except for data generated in the Hasler et al. [21] study which was fasted, the T_{max} data are in a range of 2-3 hours. However, the Hasler et al. [21] study was the only study where fasted conditions were maintained and it reported the quickest time to peak when compared to all other studies. One explanation of this data could be that while C_{max} and AUC appear to be unaffected by a food, the time to maximum concentration in the blood (T_{max}) is considerably faster under fasted conditions. Note also that the elimination rate appears to be almost random across studies. As previously noted, unrestricted food consumption during the trial period could lead to unpredictable metabolism rates of the psilocybin or increased retention in the gut.

Table 1 summarizes several clinical programs examining the safety and efficacy of psilocybin, and its active metabolite, psilocin. One additional evaluation, Hasler et al. [21] listed in Table 2 also presents pharmacodynamic data of consequence. These studies administered doses of psilocybin expected to show psychedelic effect. Only one of these trials included a sub-psychedelic concentration and as a result, little is known of the activity of psilocybin or psilocin at such levels. These trials, covering over 200 adult volunteers, involve open-label, escalating dosage studies and randomized, double-blind trials. The studies were conducted in medical healthcare facilities along with psychotherapy, with over 300 participants ranging from healthy volunteers to those with various illnesses. The results indicate that, of the 302 participants, 290 received at least one oral psilocybin dose, 204 were given two doses, 71 and 14 acquired three and four doses respectively. A total of 579 oral dosages were administered. These studies used a range of dosages, from "very low" (45 µg/kg; 0.045 mg/kg) to "high" (600 µg/kg; 0.6 mg/kg) that is, doses ranging from 3.15 mg to 42 mg in an individual weighing 70 kg. Aside from the expected psychedelic effect, few significant side effects were reported leading to a conclusion that psilocybin and its metabolite, psilocin, are safe and possibly effective over a wide range of indications.

These studies demonstrate the range of psilocin and psilocybin's pharmacological properties, potential applications, and safety profile. Studies included conditions such as MDD, OCD, and substance dependence. Additional research will be imperative in the future to elucidate the optimal dosing methods for psilocybin, alongside assessing its long-term effects and safety implications. These investigations will ultimately shape the utilization of psilocybin therapy in clinical contexts. The research conducted on these active moieties clearly demonstrates the absence of a systematic drug development program employing conventional, stepwise evaluation. There is no indication that any of the formulations utilized in these studies have not been optimized, nor is there evidence suggesting a comprehensive understanding of psilocybin's pharmacokinetics.

Hasler et al. [21] research underscores essential data regarding the plasma concentrations at which psychopathological modifications begin. They observed that these alterations occurred when psilocin plasma levels were within a range of 4 ng/ml to 6 ng/ml. In their study, individuals reached this concentration as early as 20 minutes after administration, while some showed no effects until 90 minutes later, indicating significant variability in psilocybin's bioavailability [21]. In a distinct study, Griffiths et al. [22] investigated the use of both

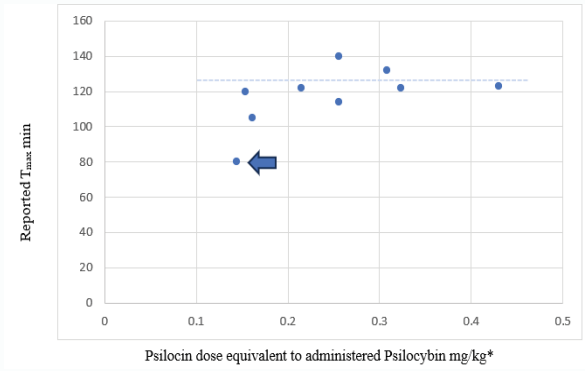


Figure 3: T_{max} for Studies listed in Table 2 (Note: Hasler fasted data at 80 minutes).

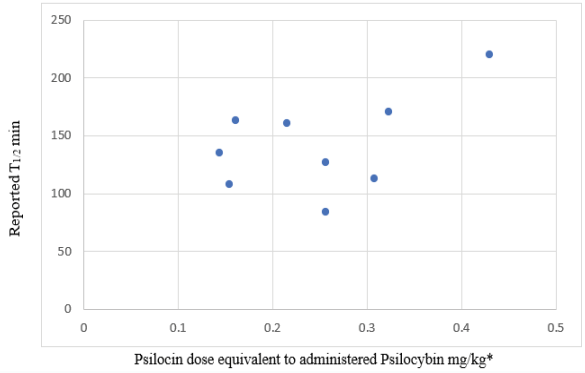


Figure 4: Elimination half-life associated with Table 2.

high and low doses of psilocybin in treating depression and anxiety in patients confronting life-threatening cancer. This randomized double-blind study utilized a placebo that was inactive, comprising 1 mg of psilocybin, equivalent to 0.01 mg per 70 kg patient. This dosage aligns with the IV dosage examined by Hasler et al. [21] However, in Griffiths et al. [22] research; the equivalent oral dosage did not elicit psychopathological changes and was considered a suitable placebo. This indicates a significant difference in bioavailability and effects based on the route of administration, with oral intake demonstrating reduced bioavailability.

Metabolism

After being taken orally, psilocybin is dephosphorylated by the enzyme alkaline phosphatase in the stomach or intestines, to create psilocin. It undergoes substantial first-pass Phase I metabolism in the liver, resulting in the formation of 4 hydroxyindole-3-acetaldehyde, 4-hydroxytryptophol, and 4-hydroxyindole-3-acetic acid (4 HIAA). The UDP-glucuronosyltransferase enzyme family catalyses phase II metabolism, with UGT1A10 being the main metabolic pathway. Psilocin-O-glucuronide is the primary urine metabolite, eliminated unaltered in 2% to 4% of cases. Following oral treatment, plasma has significantly higher quantities of 4-HIAA and psilocin glucuronide than psilocin itself. Psilocin plasma concentrations are directly correlated with subjective psychedelic effects and neocortical 5-HT2A receptor activity. Up to 72% of 5-HT2A receptors were dose-dependently occupied by single doses of psilocybin ranging from 3 mg to 30 mg. Psilocin's receptor occupancy EC50 was 1.97µg/L [9].

Pharmacodynamics review

Psilocin engages with numerous receptor subclasses as demonstrated through the use of radioligand binding studies. An early preclinical investigation in two species demonstrated a sequence of affinity of binding for psilocin is 5HT2A>5HT1A>5HT2B [23]. Subsequent research revealed that psilocin also binds to a wide range of additional receptors, involving dopamine D1, 5HT1E, 5HT1A, 5HT5A, 5HT7, 5HT6, D3, 5HT2C, and 5HT1B. With a 40% effectiveness rate, psilocin is a partial agonist at the 5HT2A receptor. It is thought that the partial agonist actions at the 5HT1A auto receptors are the source of its psychedelic effects. Using certain antagonists, the evidence supporting the 5HT2A receptor's role in mediating psilocybin effects has been investigated. Psilocybin-induced perceptual disruption and hallucinations were dose-dependently inhibited by ketanserin, a selective 5HT2 receptor antagonist (0.25 mg/kg) [24]. The findings that suggested a particular activity at the 5HT2A receptor were likewise suppressed by risperidone, an atypical antipsychotic. Wet dog shakes and head twitches are caused by psilocybin's psychedelic nature in dogs and mice, according to preclinical research, however, 5HT2A antagonists prevent these effects. Antagonisms to 5HT1A, 5HT2B/2C, and D2 receptors can block some of the behavioral effects of psilocybin. Several signaling pathways have been used to connect psilocin to alterations in neuroplasticity, such as neuritogenesis [25]. This implies that non-hallucinogenic effects of this class of drugs can contribute to their therapeutic impact. Potential psilocybin derivatives might target the 5HT2A signalling complex to provide psychotropic effects devoid of hallucinogenic ones, meaning they could have antidepressant benefits without causing behavioral toxicities. Systemic psilocin treatment in rats causes alterations in the serotonin and dopamine concentration in particular brain regions. Both 5HT1A and 5HT2A activation in the accumbens as well as the stimulation of mesocortical 5HT2A receptors may account for these effects. The mood-elevating and psychotomimetic effects of psilocybin treatment may be explained by the correlation found between dopamine increases and depersonalization and bliss. The way that hallucinogens work is associated with alterations in neurochemistry and receptors. The injection of psilocybin alters the characteristics of 5HT2A agonists by increasing BDNF synthesis in the hippocampal region [9-26]. This leads to increased neurogenesis and the eradication of conditioned fear-related behaviours.

Drug safety review

Psilocybin and its metabolite psilocin have a favourable safety profile due to their large therapeutic index and nearly unattainable lethal dose. It has a reduced rate of seizures, hospital stays, and other major side effects and lacks addictive or bolstering properties when compared to other drugs in the class. Results from studies at supra-therapeutic levels have been good with little to no safety issues. Psychological safety, not physiological safety, is the main danger associated with psilocybin. Nonetheless, there is still a chance that the acute psychotomimetic effects of psilocybin might cause psychological suffering and, in extreme circumstances, even psychosis. Adverse effects, both psychological and physical, have been documented; many of them are temporary and connected to the therapeutic aspect of processing emotions during sessions. Clinical study data show no significant adverse effects when appropriate screening is carried out and consumption is well monitored [9,10].

Table 2: Comparison of Five Published Pharmacokinetics Studies*

Parameter		Hasler et al. [21]		Lindenblatt et al. [30]	Brown etal. [19]			Kolaczynska etal. [31]	Holze etal. [32]		
		1	2		1	2	3		1	2	3
No of Subjects		6	6	7	12	11	10	3	28	22	28
Dose and Route of Adm	Actual dose of study drug Administered Psilocybin	1 mg i.v.	0.224 mg/kg p.o.	0.2 mg/kg p.o.	0.3 mg/kg p.o.	0.45 mg/kg p.o.	0.6 mg/kg p.o.	25 mg p.o.	15 mg p.o.	25 mg p.o.	30 mg p.o.
	Equivalent Psilocin dose	0.718 mg	0.161 mg/kg	0.144 mg/kg	0.215 mg/kg	0.323 mg/kg	0.43 mg/kg	17.95 mg	10.77 mg	17.95 mg	21.54 mg
	Equivalent Psilocin Per Kg dose* (mg/kg)	0.01	0.161	0.144	0.215	0.323	0.43	0.256	0.154	0.256	0.308
C_{max}		12.9 ng/ml	8.2 ng/ml	6-21 µg/L	16(14.5-17.2) µg/L	26(22.7-35.1) g/L	37.6(27.7-43.2) µg/L	19.2 ± 4 ng/ml	11 ng/ml	17 ng/ml	21 ng/ml
C_{max}(µg/L)*		12.9	8.2	13.5	16	26	37.6	19.2	11	17	21
T_{max}		1.9 min	105 min	70-90 min	2.03 hr (1.15-2.07)	2.03 hr (1.3-3)	2.05 hr (1.55-2.08)	140 ± 46 min	2.0 hr	1.9 hr	2.2 hr
T_{max}(min)*		1.9	105	80	121.8	121.8	123	140	120	114	132
AUC		240 ng.min/ml	1963 ng.min/ml	20.2-40.8	140 µGH/L	213 µGH/L	267 µGH/L	3670 ± 780 ng.min/ml	58 ng.hr/ml	83 ng.hr/ml	113 ng.hr/ml
AUC (µG H/L)*		4	32.71	30.5	140	213	267	61.16	58	83	113
T½ (min)		74.1	163.3	135	161.4	171.6	220.2	127 ±18	108	84	113
F Value **		100	50.8	52.9	162.8	164.8	155.2	59.7	94.1	81.05	91.7

*Elements have been recalculated to use a standard 70 kg body weight, units of measure and molarity based on psilocin content.

**F (Bioavailability) from these studies shows variability from 50 to 150% and highlights the issue being described in this publication.

Microdosing review

Microdosing is the use of small to moderate amounts of psychedelic drugs like psilocybin to improve mood and daily functioning without causing intense hallucinations, typically administered orally in a single dose of 0.2 mg/kg-0.42 mg/kg with medication-assisted psychotherapy program under medical supervision [27]. The recommended dosage typically falls within a range of three to five times per week. The observational study of 900 participants reported micro dosing of psilocybin for 30 days showed small to moderate improvements in the anxiety, depression and stress compared to the non-micro dosing comparators [28]. Cavana et al. examined the impact of 0.5 g dried mushrooms on personal experience, behaviour, creativity, perception, thinking, and neural activity. Results indicated that active dosages had more potent acute effects than placebo, but only for those who properly recognized the circumstances of the experiment. For this reason, even little quantities of psilocybin mushrooms can result in notable subjective effects and abnormalities in EEG rhythm [29-31]. More extensive study is needed to determine if psychedelic microdosing might be helpful in treating mental health concerns, even though the area of psychedelic research is expanding and the results seem promising.

Discussion

Psilocybin and its active metabolite, psilocin are potentially game changers for the treatment of several neurological disorders. In recent years, dozens of research programs have investigated their use in the treatment of these unmet medical needs. However, only five peer reviewed publications report pharmacokinetic data from relatively small studies and most of these studies were focused on presenting analytical methods. Of the five studies reviewed in this article, only one study (Holze) provides data in more than 15 subjects. The remaining four studies utilized only three to twelve subjects [32]. Food effects and erratic elimination rates have not been accounted for and an oral bioavailability of less than 50% is indicated but must be confirmed through appropriately designed trials.

In general, psilocybin dosed orally tends to reach its maximum concentration in blood after 2 hours. The elimination rate shows considerable variability with half-lives ranging from about one hour for the IV formulation to nearly 4 hours for oral administration. Brown et al. suggests that this slower than expected absorption and elimination rate may be related to the reversible glucuronidation of psilocin [19]. However, he also suggests further investigation to confirm this theory. We suggest that the issue is related to either a slow conversion to the active metabolite or retention of the psilocin in the gut which may contribute to its hallucinogenic effect and reduced bioavailability suggested to be 50% at best.

Conclusion

Overall, psilocybin and psilocin are important new drug candidates that have attracted dozens of researchers to investigate their use to treat a wide range of neurological disorders. However, current studies do not provide the needed data to successfully deal with hurdles posed by normal pharmaceutical development practices. There is a dire need for well controlled pharmacokinetic studies to evaluate the appropriate route of administration for these drugs. Data evaluating the food effect, patient variability, possible retention in the gut, and an almost random elimination rate must be determined. Because of this lack of well controlled pharmacokinetic trials, formulation research may not lead to optimized drug products at this time. Since psilocin and not psilocybin is the active moiety, efforts to develop stable and bio available psilocin formulations may be the route to rapid deployment of this new class of therapeutic.

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