Psilocybin

Investigator's Brochure

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1. Drug Substance and Formulation

Psilocybin (4-phosphoryloxy-N,N-dimethyltrypatmine, also referred to as 3-[2-(Dimethylamino)ethyl]-1H-indol-4-ol dihydrogen phosphate ester has the chemical formula $C_{12}H_{17}N_2O_4P$. It is a tryptamine, and is one of the major psychoactive constituents in mushrooms of the Psilocybe genus, as Psilocybe cubensis and Psilocybe mexicanus. Native peoples in Mexico have used the mushrooms in religious ceremonies and in healing ((Hofmann 2005)), Artifacts and historical documents suggest that ritual use of psilocybin-containing mushrooms occurred as early as 3000 years ago, with documented use occurring in the 16th Century, prior to Spanish prohibition on their use. Psilocybin was first isolated from psilocybe mushrooms by Hofmann in 1957, and later synthesized by him in 1958 (Passie et al. 2002). Psilocybin was used in psychiatric and psychological research and in psychotherapy during the early to mid-1960s up until its scheduling in 1970 in the US, and up until the 1980s in Germany (Passie 2005; Passie et al. 2002). Research into the effects of psilocybin resumed in the mid-1990s, and it is currently the preferred compound for use in studies of the effects of serotonergic hallucinogens (see for example (Carter et al. 2005a; Gouzoulis-Mayfrank et al. 1999b; Hasler et al. 2004), likely because it has a shorter duration of action and suffers from less notoriety than LSD. However, despite frequent non-medical use in humans, few or no in vitro or nonhuman animal studies with psilocybin have occurred.

Psilocybin belongs to a class of drugs referred to as hallucinogens or psychedelics. Specifically it is a serotonergic hallucinogen, along with other tryptamines such as dimethyltryptamine (DMT), ergolines, such as LSD and phenethylamines, such as mescaline. Currently, research in human and nonhuman animals suggests that serotonergic hallucinogens produce most of their effects as a result of $5HT_{2A}$ agonism, with contributions also from agonism at $5HT_{2C}$ and $5HT_{1A}$ receptors (Nichols 2004). Like other members of this class, psilocybin induces sometimes profound changes in perception, cognition and emotion, including emotional lability.

In humans as well as other mammals, psilocybin is transformed into the active metabolite psilocin, or 4-hydroxy-N,N-dimethyltryptamine ($C_{12}H_{16}N_2O$.) It is likely that psilocin partially or wholly produces most of the subjective and physiological effects of psilocybin in humans and nonhuman animals.

2. Pharmacological and toxicological effects

Psilocybin and Psilocin Actions on Neurotransmitter Systems

Overview

Psilocybin and its metabolite psilocin directly affect a number of serotonin receptors without directly affecting other neurotransmitter systems. While there have been fewer studies of the pharmacological profile of psilocybin than of the ergoline LSD, studies conducted with psilocybin and psilocin indicate that like LSD, these tryptamines are

$5HT_{2A}$, $5HT_{2C}$ and $5HT_{1A}$ agonists*. Unlike LSD, they have little affinity for dopamine receptors, and only very high doses affect norepinephrine receptors. Human psilocybin research confirms the $5HT_{2A}$ activity of psilocybin and psilocin, and provides some support for indirect effects on dopamine through $5HT_{2A}$ activity and possible activity at $5HT_{1A}$ receptors.

Psilocybin or psilocin and 5HT2A and 5HT2C Receptors

A majority of known $5HT_{2A}$ agonists produce hallucinogenic effects in humans, and rodents generalize from one $5HT_{2A}$ agonist to others, as between psilocybin and LSD (Aghajanian and Marek 1999; Nichols and Sanders-Bush 2004). Like lysergic acid diethylamide (LSD) and other serotonergic hallucinogens, psilocybin acts as a serotonin $5HT_{2A}$ receptor agonist (McKenna et al. 1990; Nichols 2004). Psilocybin has a stronger affinity for the human $5HT_{2A}$ receptor than for the rat receptor (Gallaher et al. 1993), and it has a lower $K_{(i)}$ for both $5HT_{2A}$ and $5HT_{2C}$ receptors than LSD (Nichols 2004). Results from a series of drug-discrimination (DD) studies in rats found that $5HT_{2A}$ antagonists, and not $5HT_{1A}$ antagonists, prevented rats from recognizing psilocybin (Winter et al. 2007).

Daily doses of LSD and psilocybin reduced numbers of $5HT_2$ receptors in rat brain (Buckholtz et al. 1990). Research examining compound-specific effects on secondary messenger systems found that both psilocybin and LSD stimulate arachidonic acid when activating the rat $5HT_{2A}$ receptor, but psilocybin did not stimulate the phosphoinositide (PI) pathway as strongly as LSD (Kurrasch-Orbaugh et al. 2003). However, psilocin stimulated more PI turnover than a ring-fluorinated version of psilocin that rats in DD trials did not consider LSD-like, suggesting that secondary messenger systems might play a role in producing at least some subjective effects (Blair et al. 2000). Since investigations of compound-specific or "allosteric" trafficking are new, the functional significance of this difference remains unclear.

Researchers examining psilocybin analogs report that a potential metabolite, 4-methylpsilocin, was a potent $5HT_{2C}$ agonist (Sard et al. 2005), but whether or not this compound is produced after psilocybin metabolism is not certain. The development of relatively selective $5HT_{2C}$ antagonists is recent, and to date no studies have examined the contribution of 5-HT_{2C} receptors to the physiological or behavioral effects of psilocybin in human or nonhuman animals.

Psilocybin or Psilocin and other Serotonin Receptors

Direct application of psilocybin to dorsal raphe nucleus (DRN) cells is associated with a decline in firing, a property it shares with LSD (Aghajanian et al. 1968; 1970; Aghajanian and Hailgler 1975) that is likely the result of action at $5HT_{1A}$ autoreceptors (Williams et al. 1988). In contrast, it appears that $5HT_{1A}$ receptor activity contributes little to the psilocybin stimulus in rats (Winter et al. 2007). Though no behavioral studies in humans have determined what role, if any, is played by $5HT_{1A}$ receptors in producing the subjective effects of psilocybin, it is notable that some effects, such as difficulty

concentrating, still occur when psilocybin was co-administered along with a $5HT_{2A}$ antagonist (Carter et al. 2005a; Carter et al. 2005b).

There are no reports describing psilocybin or psilocin actions on $5\text{-}HT_{2B}$ receptors, though the putative psilocybin metabolite *N*-methylpsilocybin was found to act as an inverse agonist at this receptor (Sard et al. 2005). However, no studies have as yet detected this metabolite (Hasler 1997; Hasler et al. 1997).

McKenna and colleagues reported that psilocybin had an affinity for $5\text{-}HT_{1D}$ receptors as well, possibly explaining its ability to abort cluster headaches (Sewell and Halpern 2006). Beyond this finding, however, there is no published literature that examines the actions of psilocybin or psilocin on $5\text{-}HT_3$ receptors or on any of the more recently discovered receptor families. The ergoline LSD affects a number of these receptors, including $5\text{-}HT_{5A}$ (Nichols et al. 2002b), $5\text{-}HT_6$ (Hirst et al. 2003) and $5\text{-}HT_7$ (Nichols et al. 2002b). However, this does not mean that psilocybin or psilocin possess similar profiles.

Psilocybin or Psilocin and other Receptor Systems

Psilocybin does not act directly on dopamine D_1 or D_2 receptors (Creese et al. 1975) or on histamine H_2 receptors (Green et al. 1978). Very high doses of psilocybin (25 mg/kg) increased levels of the norepinephrine metabolite 3H-normetanephrine (Stolk et al. 1974), but it is unlikely that typical doses of psilocybin used in human research will affect norepinephrine. Because interest in the pharmacology of psilocybin and psilocin declined prior to the development of modern neuropharmacology, the complete pharmacological profile of either compound is not as well-known as that of LSD. It is possible that psilocybin, like LSD, acts on one or more of the more recently discovered serotonin receptors, such as $5ht_{5a}$ or $5HT_7$, but currently there is no information on the actions of psilocybin at these receptors. It is likely that psilocybin itself, or its metabolite psilocin, aborts cluster attacks through its effects on $5HT_{1D}$ receptors.

Table 1
Psilocybin Binding Data

Receptor	Ki (nM)	Hot Ligand	Species	Source	Reference
5HT1A	190	3H-8-OH-DPAT			
5HT2A	6	3H-DOI	Rat/cow	Brain	(McKenna et al. 1990)
5HT2C	410	3H-Ketanserin	Rat/cow	Brain	(McKenna et al. 1990)

Table 2
Psilocin binding Data

Receptor	Ki (nM)	Hot Ligand	Species	Source	Reference
5-HT1A	49	3H-8-OH-DPAT	Human	Cloned	(Blair et al. 2000)
5-HT2A	25	125I-DOI	Rat or bovine	Cloned	(Blair et al. 2000)
5-HT2C	10	1251-DOI	Rat	Cloned	(Blair et al. 2000)

One team of researchers performed a series of experiments, many comparing LSD with the non-hallucinogenic compound lisuride and using a mouse model of hallucinogen-associated behavior (head twitch), suggesting that stimulating different secondary

messenger systems may play a role in hallucinogenic effects (Gonzalez-Maeso et al. 2007). Instead of activating only phosopholipase C (PLC) when stimulating $5HT_{2A}$ receptors, LSD and the phenethylamine DOI stimulated pertussis-toxin sensitive $G_{i/o}$ proteins. It is not yet known whether psilocybin shares this feature with LSD and DOI.

Human Neuropharmacological Studies

In studies in humans, researchers found that administering psilocybin along with a 5HT2A receptor antagonist, such as ketanserin or risperidone, attenuated or completely abolished the subjective and perceptual effects of psilocybin (Carter et al. 2004; Vollenweider et al. 1998). Ketanserin did not attenuate reduced visual attention or psilocybin-associated changes in binocular rivalry (oscillation in dominance of one eye over another in visual perception) (Carter et al. 2005a; Carter et al. 2004). Co-administration of the dopamine D2 receptor antagonist haloperidol only reduced positive mood and positively viewed changes in cognition and perception Vollenweider et al. 1998. A human imaging study using radiolabeled raclopride, a D2 receptor antagonist found reduced binding in caudate and putamen after psilocybin administration, suggesting that psilocybin indirectly increased brain dopamine levels, (Vollenweider et al. 1999) probably through $5HT_{2A}$ activity. Taken together, these findings suggest that psilocybin produces its effects in humans chiefly but not wholly through $5HT_{2A}$ receptors, while the compound may produce different effects through other serotonin receptors, such as $5HT_{1A}$ or $5HT_{2C}$. Psilocybin may exert indirect influence over the dopamine system without having any direct effects on dopamine receptors.

Psilocybin and Gene Expression

When activating $5HT_{2A}$ receptors, psilocybin and LSD both increase expression of a number of genes, including *egr-1*, *egr-2*, *period1*, *Nor1* and *l-KappaBetaAlpha* (Gonzalez-Maeso et al. 2003; Nichols and Sanders-Bush 2002). Psilocybin may be associated with a greater increase in egr-1. The significance of psilocybin effects on gene expression is uncertain. However, changes in gene expression may play a role in the ability of psilocybin-containing mushrooms to interrupt cycles of cluster headache, or cluster headache period, as discussed below in "Safety and Toxicity" (Sewell et al. 2006).

Physiological and Psychological (Subjective) Effects

Studies in humans and nonhuman animals indicate that(Winter et al. 2007) psilocybin has extremely low toxicity (Nichols et al. 2002a; Passie et al. 2002). LD_{50} ranged from 285 mg/kg in rats and mice to 12.5 mg/kg in rabbits (Usdin and Efron 1972). It is likely that the lethal dose in humans far exceeds doses that produce profound alterations in consciousness. All ongoing and proposed research will use doses of approximately 0.4 mg/kg, which is at least 20 times smaller than the LD_{50} in rabbits.

Psilocybin Effects in Nonhuman Animals

Rats trained to distinguish between LSD and saline injections treated psilocybin as if it were LSD (Koerner and Appel 1982; Schechter and Rosecrans 1972), suggesting that the two drugs possess similar stimulus characteristics, a finding supported in early human studies comparing the two compounds (Hollister and Hartman 1962; Hollister and Sjoberg 1964; Isbell 1959; Wolbach et al. 1962). Rats trained to recognize psilocybin identified psilocin as psilocybin-like, indicating that psilocybin and its metabolite produce similar cues in these animals. As described later on in this document, most psilocybin is converted into psilocin, and it is likely that most of the physiological and subjective effects of psilocybin are in fact due to psilocin.

Researchers examined the effects of psilocybin in rats, cats, dogs and rabbits found that psilocybin produced piloerection, slight increases in breathing, indications of sympathetic system stimulation, but no increase in locomotor activity (Maxwell et al. 1962; Passie et al. 2002), Psilocybin increased prolactin levels in rats (Meltzer et al. 1978). As described above, behavioral reports of the effects of psilocybin demonstrated that psilocybin produced effects similar to LSD or other tryptamines. As with the ergoline LSD, psilocybin reduced and altered rat exploratory patterns (Geyer et al. 1978). Monkeys self-administering psilocybin exhibited behavior suggestive of visual distortions or alterations in consciousness that included grasping at unseen objects and fixed staring (Fantegrossi et al. 2004), behaviors also seen when the animals self-administered DMT or mescaline. There is no indication that psilocybin produced unique physiological or behavioral effects in rodents or nonhuman primates.

Psilocybin Effects Assessed in Humans

Hasler and colleagues report that the first or onset effects of orally administered psilocybin appeared approximately 20 to 30 minutes post-administration (Hasler et al. 1997; Hasler et al. 2004), and peak effects appeared 60 to 90 minutes post-drug. The effects of orally administered psilocybin subsided four to six hours after drug administration (Hasler et al. 2004). Changes in perception and cognition were no longer detectable seven days later (Gouzoulis-Mayfrank et al. 1999b). Onset of 1 mg intravenous psilocybin effects appeared 2 minutes after administration, with subjective and physiological effects lasting for up to 20 minutes afterwards (Hasler et al. 1997).

Isbell detected increased pupillary diameter after approximately 4, 6 and 8 mg psilocybin and elevated systolic blood pressure after approximately 6 mg psilocybin (Isbell 1959), and later reports also detected elevations in blood pressure and heart rate after higher doses of psilocybin (Griffiths et al. 2006; Hasler et al. 2004), though sometimes changes were only detected at one point in time, as 60 minutes post drug (Hasler et al. 2004). Hence psilocybin produces only slight sympathetic system activation. It is notable, however, that a 26-year old man with obsessive compulsive disorder (OCD) exhibited an elevation in diastolic blood pressure from 91 to 104 mm Hg after receiving 0.2 mg/kg psilocybin in the absence of self-reported anxiety (Moreno et al. 2006). Psilocybin elevated prolactin, but not cortisol or ACTH (Gouzoulis-Mayfrank et al. 1999b; Hasler et al. 2004), with prolactin elevation no longer detectable 300 minutes (5 hours) post-drug (Hasler et al. 2004). In general, physiological effects are similar to those of the ergoline

hallucinogen LSD. To date, there are no findings that either support or disconfirm the existence of menstrual variations in the effects of psilocybin in women.

Psychological and Subjective Effects

Early studies of psilocybin in humans reported changes in perception, as increased perception of visual after-image (Keeler 1965), peculiar thoughts, anxiety, and unusual experiences of the body (as parasthesias) and the environment (Fischer et al. 1966; Hebbard and Fischer 1966; Hofmann et al. 1958; Hollister and Sjoberg 1964; Isbell 1959; Keeler 1963), and side effects of dizziness, impaired concentration and nervousness (Hollister and Sjoberg 1964). Some early reports also found increased difficulty in performing some tasks, such as simple arithmetic problems (Hollister 1961). Psilocybin elicited spiritual or mystical experiences in divinity students during a religions service (Pahnke 1963). This study employed a placebo, but the researchers administered psilocybin or placebo to groups of participants, and retrospective reports suggest that participants could accurately guess their condition from observing themselves or others (Doblin 1991). Recent studies confirmed initial findings (Carter et al. 2005a; Carter et al. 2004; Gouzoulis-Mayfrank et al. 1999b; Griffiths et al. 2006; Hasler et al. 2004; Vollenweider et al. 1997). Participants reported alterations in perception (Gouzoulis-Mayfrank et al. 1999b; Griffiths et al. 2006; Hasler et al. 2004; Vollenweider et al. 1997), and assessments of visual perception detected changes in motion perception, binocular rivalry and time perception (Carter et al. 2004; Carter et al. 2005b; Wittmann et al. 2006). A study of the effects of psilocybin in pre-pulse inhibition (PPI), the reduction in startle response to an intense stimulus if preceded by a less intense stimulus, reported enhanced PPI after a long interval between pre-pulse and pulse, and attenuated PPI when the interval was short (Vollenweider et al. 2007). Participants experienced both increased positive mood and positively experienced derealization (feeling as if they were "in a dream" or as if the external world were unreal) and depersonalization (sense of "being unreal," or of the self belonging to someone else) and negative mood and negatively experienced derealization and depersonalization. Mood could change rapidly over time from very positive to very negative (Vollenweider et al. 1997). Psilocybin was far more likely than methylphenidate to produce mystical or peak experiences in people with existing religious or spiritual practices (Griffiths et al. 2006). People receiving psilocybin in these studies maintained insight concerning the source of their alterations in perception. Observers' descriptions of participant behavior were consistent with the participants' accounts, noting mood lability, changes in sense of self, and unusual or paranoid thoughts (Gouzoulis-Mayfrank et al. 1999b; Griffiths et al. 2006; Vollenweider et al. 1997).

Table 3

Acute observed and self-reported effects and side effects of 0.114-0.4 mg/kg psilocybin

Gouzoulis-Mayfrank et al. 1999 **U-test, p < 0.05** Increased positive psychosis-like symptoms (e.g. hallucinations, unusual thoughts) Increased negative psychosis-like symptoms (feeling withdrawn or apathetic) Increased positive affect/mania Increased negative affect/melancholy	**Griffiths et al. 2006** Difference **p. < 0.001** Anxiety Distance from ordinary reality Dysphoria* Joy/intense happiness Peace/harmony Positive mood Somatization* Tearing/crying Visual alteration and distortion Yawning **p. < 0.01** Anxiety/fearfulness Nausea **p. < 0.05** Sleepiness/sedation Spontaneous motor activity Stimulation Reduced mental efficiency**	**Hasler et al. 1997** **Reported, not quantified** depersonalization derealization "virtual" hallucinations changes in affect, thought disorders (undefined)	**Hollister & Sjoberg 1964** **p. < 0.05** Increased aggressive Depressed Jittery Less clear thinking **Reported, not quantified** Dizziness Nausea Shaking hands Weakness	(Quetin 1960) **adapted in Passie et al. 2002** Midriasis 93% Heart frequency Accelerated 56% Slowed 13% Variable 31% No change 0% Arterial blood pressure Hypotension 34% Hypertension 28% Instability 22% No change 16% Nausea 44% Reflexes tendineae Increased 80% Decreased 6% No change 13% Dysmetry 16% Tremor 25%	**Wittmann et al. 2007** Altered time perception – objective assessment **p. < 0.01** Impaired long interval estimation Impaired tone estimation (trend for 250 mcg/kg) Tiredness Dazed state Introversion Dreaminess Increased positive mood Increased anxiety (250 mcg/kg) p. < 0.05 Impaired spatial working memory (250 mcg/kg)
Compared with placebo	Compared with methylphenidate	Compared with placebo	Pre-drug/post-drug (2nd hour)	Percentage observed/ Self-reported	Compared against placebo, 115 v 250 mcg/kg
N = 8	N = 30 (of 36)	N = 6	N = 24	N = 30	N = 12
Dose = 0.2 mg/kg	Dose = 30 mg/70 kg (approx. 0.4 mg/kg	Dose = 0.224 mg/kg	Dose = 225 mcg/kg	Dose = 8-12 mg i.m. and p.o.	Dose = placebo, 115 mcg/kg, 250 mcg/kg
Between-subjects	Within-subjects	Within-subjects	Within-subjects	Not known	Within-subjects

*ARCI LSD scale, loosely assesses dysphoria, jitteriness and somatic sensations

**ARCI BG = mental efficiency, separate from activation or feeling stimulated

Factors influencing psychological reactions to psilocybin

The variable subjective effects of psilocybin are due at least in part to differences in pre-existing mental state and personality, or "set" and to features of the immediate environment, or "setting" (Nichols 2004). In an early investigation summarizing findings from uncontrolled studies of psilocybin, Leary and colleagues reported that people reporting previous experience with psychoactives, greater feelings of flexibility and lower apprehension about taking psilocybin had more pleasant experiences with psilocybin (Leary et al. 1963). The same report also indicates that features of setting, such as administration in small groups, were associated with more pleasant experiences than when administered in larger groups. Therapists describing their use of LSD or other psychedelics in therapy (Grof 2000: 1980) favored comfortable settings. Patients remain within the confines of the setting during therapy, and sometimes use eyeshades and listen to music to foster introspection and reduce distraction. There has been little formal investigation into the impact of set and setting, but there is at least informal evidence that both may play a role in response to psilocybin.

Long-Term Effects of Psilocybin

To date, only Griffiths and colleagues have assessed potential long-term changes after psilocybin in the context of a double-blind, active placebo controlled study, finding that two months after drug administration, participants were more likely to report positive attitudes toward life and the world and increased satisfaction and well-being after psilocybin than after methylphenidate, and friends noticed small positive life changes after psilocybin (Griffiths et al. 2006). Neither psilocybin nor methylphenidate produced negative changes in attitudes or life changes. Interviews and questionnaires occurring approximately 25 years after the study of the effects of psilocybin in divinity students observing a religious service found that participants who had received psilocybin continued to report a greater number of positive life changes than controls, and very few negative life changes (Doblin 1991). As described earlier, groups of participants underwent the study and the blind was poorly maintained, but follow-up interviews suggest that the lasting effects of psilocybin are positive.

Psilocybin/Psilocin Effects on Brain Activity

Positron emission tomography (PET) studies of psilocybin in humans have detected increased glucose metabolism in frontal areas and anterior cingulate, with possibly greater right hemisphere activity (Gouzoulis-Mayfrank et al. 1999a; Vollenweider et al. 1997). However, an imaging study using radiolabeled raclopride (a D2 antagonist), described above, did not find lateral effects in changes in D2 binding (Vollenweider et al. 1999). Since changes in glucose metabolism can arise from direct and indirect brain activity, and can be indicative of inhibitory or excitatory actions, it is difficult to draw conclusions from these studies alone. However, they suggest that at least some of the effects of psilocybin result from changes in frontal or cingulate activity.

3. Pharmacokinetics and biological disposition of the drug

Psilocybin is detectable in plasma 20 to 40 minutes after oral administration (Hasler 1997) reviewed in (Passie et al. 2002). Psilocybin is metabolized in the liver, where it is chiefly transformed into the active metabolite psilocin, detectable in plasma 30 minutes after administration (Hasler 1997; Hasler et al. 1997; Lindenblatt et al. 1998; Passie et al. 2002), with psilocin first appearing in plasma 15 to 50 minutes after oral administration of 0.2 mg/kg psilocybin. Psilocin half-life ranges between 2 and 3 hours, and is detectable 6 hours after oral administration (Hasler et al. 1997; Lindenblatt et al. 1998). These two studies reported similar but not identical findings, with peak levels of psilocin appearing between 80 and 105 minutes and psilocin half-life ranging between 2.25 h for 0.2 mg/kg and 2.7 h for 0.22 mg/kg.

Hasler and colleagues have detected three additional psilocybin metabolites; 4-hydroxy-3-yl-acetaldehyde (4HIA), 4-hydroxy-3-yl-acetic acid (4HIAA), and 4-hydroxytryptophol (4I-IT) (Hasler 1997).

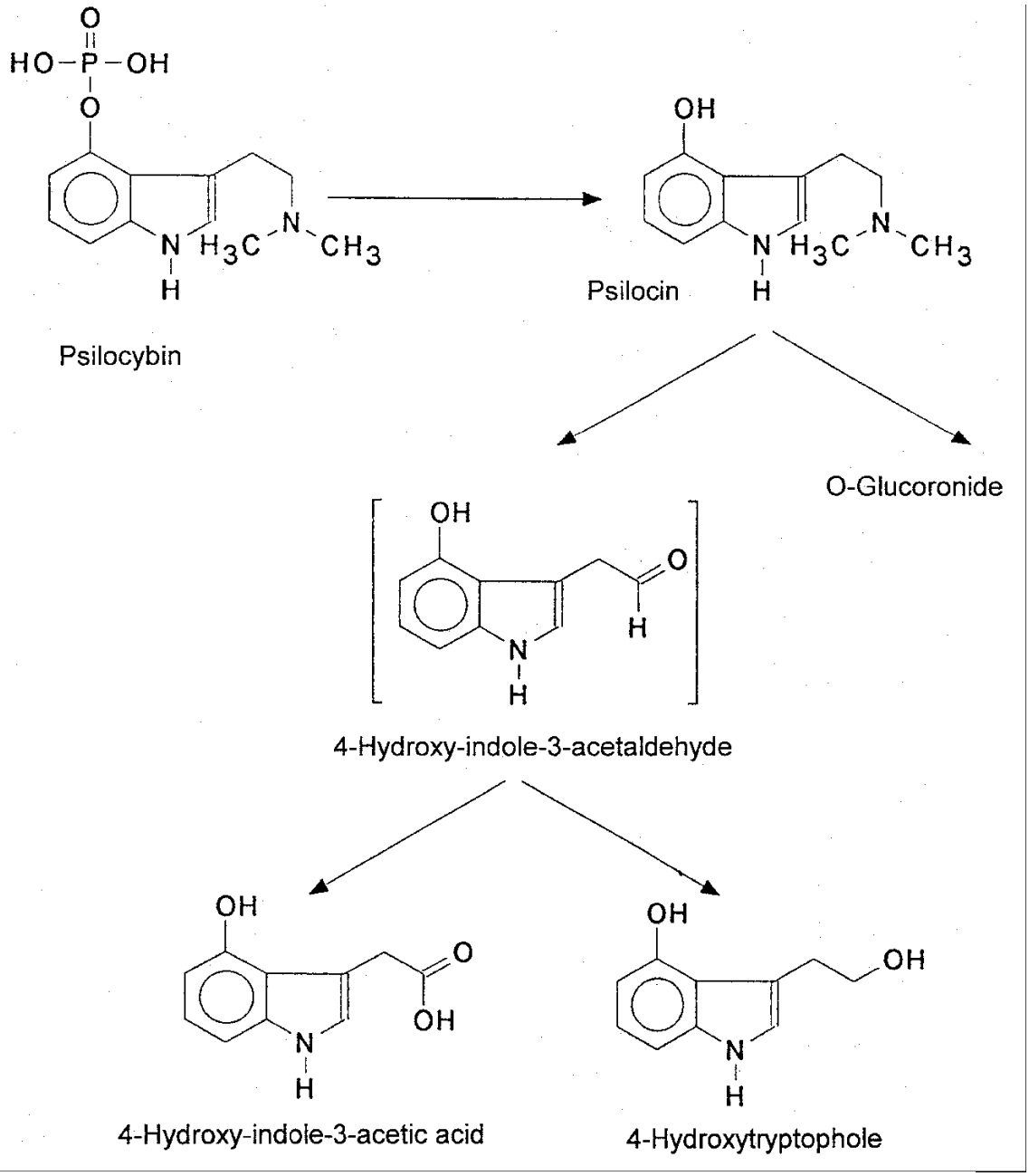

Figure 1: Metabolism of psilocybin; from Hasler 1997 and reproduced in Passie et al. 2002.

Previous research in non-human animals found that the phosphoric ester group of psilocybin is cleaved by alkaline phosphatase (Horita and Weber 1961; 1962). Rat intestinal tissue readily took up psilocin, but not psilocybin, and the tissue transferred psilocin into blood side solutions (Eivindvik et al. 1989), suggesting that psilocin is also more readily distributed around the body than any unmetabolized psilocybin. While there are currently no studies of psilocin metabolism, psilocin is likely metabolized by deamination and demethylation via liver enzymes such as monoamine oxidase and aldehyde dehydrogenase (Hasler et al. 1997).

Psilocin and psilocybin are eliminated through the kidneys, both as unaltered drug and conjugated with glucuronides (Hasler et al. 2002), with most psilocin and psilocybin excreted three hours after oral administration. Researchers detected inter-individual variation in urinary excretion of psilocin and psilocybin. Most detectable psilocin appeared between two and four hours after drug administration. On the basis of urinary psilocin levels 12 to 24 hours after approximately 0.21 mg/kg psilocybin, it is likely that most or all psilocybin and psilocin is excreted from the body at or within 24 hours after administration (Hasler et al. 2002).

4. Safety and effectiveness in humans obtained from prior clinical studies.

History of Psychiatric Research with Psilocybin

At least 19 studies have described the psychotherapeutic potential of psilocybin in approximately 1960 participants (as summarized in (Passie 2005). These studies employed an average minimum dose of 8.24 mg (0.118 mg/kg) and an average maximum dose of 17.19 mg (0.246 mg/kg). Most psychotherapists and psychiatric researchers who performed psilocybin-assisted psychotherapy wished to activate an individual's unconscious memories and conflicts, and chose doses that produced this effect (see for example (Hausner and Dolezal 1963; Leary et al. 1963; Leuner 1963). The researchers probably used processes similar to those described for LSD-assisted psychotherapy (Grof 2000: 1980; Grof et al. 1973; Kurland et al. 1967). Psilocybin-assisted therapy either followed the psycholytic model or the psychedelic model. Psycholytic psychotherapy involved lower doses of a psychedelic compound and more interpretation and analysis during the session, while psychedelic psychotherapy employed higher doses, with interpretation occurring after the experience (Passie 2005). Previous research has also examined the capacity of psilocybin to induce mystical or spiritual experiences in people during a structured religious service (Pahnke 1963; Pahnke and Richards 1966), a finding followed by recent studies of spiritual or peak effects in people with religious or spiritual practices (Griffiths et al. 2006).

Recently, several investigators have examined or are in the process of examining psilocybin as a treatment for specific mental and neurological disorders. These include anxiety arising from diagnosis with advanced stage cancer, interruption of cluster headache cycles or periods, and treatment of obsessive-compulsive disorder (OCD). Results for the investigation of psilocybin in people with OCD are now published, while studies of advanced-stage cancer are still underway. A study of psilocybin in people with cluster headaches is planned and has not yet occurred.

Psilocybin in People with Advanced Stage Cancer

Following previous research indicating that LSD-assisted psychotherapy reduced anxiety and improved quality of life in people with advanced stage illness (Grof et al. 1973), Grob and colleagues decided to investigate the effects of psilocybin-assisted psychotherapy in this population. Research is currently underway looking into the effects

of psilocybin-assisted psychotherapy in people with anxiety related to diagnosis with advanced stage cancer and a projected life expectancy of less than a year (Grob 2005). This study intends to enroll twelve participants. Ten participants have been enrolled in this study. Psilocybin has so far been well-tolerated in this sample and there have been no reports of drug-related serious adverse events.

Psilocybin as Potential Treatment of Cluster Headaches

Cluster headache (CH) is a debilitating illness affecting approximately 250,000 people in the United States. CH attacks are characterized by periods of excruciating pain in the temple, eye, or jaw that can last for up to 90 minutes. Cluster attacks tend to occur during specific times of day, and they can occur during specific times of year. While medications exist that abort cluster headaches, there are no medications that interrupt cluster headache cycles, or periods. Recently, Sewell and colleagues published a case series of 53 people who had self-administered psilocybin-containing mushrooms ("magic mushrooms") or LSD as a means to treat cluster headache (Sewell et al. 2006). Twenty-five of 48 respondents who used psilocybin-containing mushrooms reported that they had terminated their cluster period, and 18 respondents (37%) reported that psilocybin was partially effective in reducing attacks during cluster periods. Subsequent to these reports, at least one team of researchers plans to conduct a controlled study of the safety and efficacy of psilocybin in the treatment of CH, focusing on interruption of cluster headache period.

Psilocybin in People with OCD

Several published case reports have suggested that people could gain symptomatic relief from OCD through ingesting psilocybin-containing mushrooms or LSD (Hanes 1996; Leonard and Rapoport 1987; Moreno and Delgado 1997). On the basis of these accounts, Moreno and colleagues conducted a randomized, double-blind dose-response investigation of psilocybin in nine participants with OCD. They reported that up to 300 mcg/kg psilocybin was well-tolerated and that all participants exhibited at least transient reduction in symptoms, assessed via Yale-Brown Obsessive Compulsive Scale (Y-BOCS). Psilocybin attenuated OCD symptoms even after doses as low as 25 mcg/kg (Moreno et al. 2006), raising questions as to interpreting results with respect to whether the lowest dose served as a placebo and whether it was in fact devoid of therapeutic effects. One participant in this study remained symptom-free five months later.

5. Possible risks and side effects

Overview

Psilocybin is not associated with disease to any organ or system (Nichols 2004 see also IND # 56,530, submitted by Francisco Moreno). Searches of publicly available databases of medical publications have failed to find any cases of psilocybin causing any serious illness to any organ or system.) A recent extensive search conducted on the PubMed database in September, 2005 using the words "psilocybin" and various organs or medical

terms ("heart," "cardiac," "liver") and "adverse event" uncovered only a single case of liver problems. An additional search using the word "psilocybin" alone conducted on August, 2006 also failed to turn up any new cases of adverse events after psilocybin. More commonly, damage or disease to organs (as renal failure) is associated with mistakenly consuming poisonous mushrooms under the belief that they are psilocybin-containing varieties (see for example (Franz et al. 1996)). Research using radiolabeled psilocybin found it evenly distributed throughout the body (Passie et al. 2002). People in Mexico have likely used psilocybin-containing mushrooms for at last hundreds and possibly thousands of years (Hofmann 2005), and research with psilocybin began soon after its isolation and synthesis. A lack of case reports of physical illness or disease arising from exposure to psilocybin despite the long history of use within and outside of research settings is encouraging and indicative of association with few risks outside of the well-known psychiatric and psychological adverse events (described below). The low rate of serious adverse events and lack of fatalities is especially notable.

Approximately 2000 people have received psilocybin during the course of initial psychological and psychiatric investigations of psilocybin (Metzner 2005), and psilocybin has since been administered to over 216 participants during the current wave of neuroscience and psychiatric research. As was true in the case of previous human psilocybin studies described above, no serious adverse events have occurred during recently published research studies (Carter et al. 2005a; Carter et al. 2005b; Gallaher et al. 1993; Gouzoulis-Mayfrank et al. 1998; Gouzoulis-Mayfrank et al. 2002; Griffiths et al. 2006; Hasler et al. 1997; Hasler et al. 2002; Hasler et al. 2004; Lindenblatt et al. 1998; Spitzer et al. 1996; Umbricht et al. 2003; Vollenweider et al. 1997; Vollenweider et al. 1998; Vollenweider et al. 1999; Wittmann et al. 2006). Drug-naïve participants can safely receive intensely e doses of psilocybin if prepared for the effects (Griffiths et al. 2006). Hasler and colleagues halted administration of 3 mg i.v. because participants reported a greater number of side effects and reported finding the subjective effects 3 mg i.v. too intense and frightening (Hasler et al. 1997).

Fatalities

To date, there have been no verified fatalities directly due to ingesting psilocybin or mushrooms containing only psilocybin and related compounds. When reported, it is likely that fatalities attributed to psilocybin-containing mushrooms are due instead to unintended consumption of poisonous mushrooms in the belief that they contain psilocybin. Extremely high doses of psilocybin might induce effects similar to extremely high doses of LSD, such as fever or respiratory failure (Klock 1978). However, to date no cases have described similar responses with respect to psilocybin, and the doses of psilocybin that might provoke these physiological effects would be many times greater than even the highest doses used in early human studies.

Common Adverse Events and Side Effects

Common adverse effects of psilocybin are described above in "Physiological Effects" and "Psychological Effects" above. They include altered perception of time and space,

anxiety, derealization (feeling as if the world is "unreal" or that one is "in a dream), depersonalization (feeling as if the self is unreal or belongs to "someone else"), experiencing both positive and negative moods and mood lability (given to rapid and sometimes intense changes), dilated pupils, dizziness, feeling dazed or fatigued, impaired concentration, unusual body sensations, sporadic, transient increases in blood pressure or heart rate, labile (extremely changeable) mood, nausea, nervousness, unusual body sensations, unusual thoughts, and yawning. Most of these effects are acute and last no longer than the four to six-hour duration of drug effects (Gouzoulis-Mayfrank et al. 1999b; Hasler et al. 2004; Hollister 1961; Passie et al. 2002; Vollenweider et al. 1998; Wittmann et al. 2006).

The adverse effects of psilocybin are all psychological and similar to those reported for the ergoline hallucinogen LSD, and include anxiety or panic response, a prolonged unpleasant experience (or "bad trip"), psychotic reactions, and prolonged perceptual disturbances. Psychological distress is the chief adverse event reported in the literature on the recreational or nonmedical use of psilocybin, which includes extreme anxiety or panic reactions or transient psychosis (Peden and Pringle 1982).

Reckless Behavior

As is true of LSD and other serotonergic hallucinogens, people who have taken psilocybin in uncontrolled settings may engage in reckless behavior, such as driving while intoxicated. Participants in this and all foreseeable studies will remain in a controlled setting throughout the duration of the subjective effects of psilocybin, and in many studies, they will remain at the setting overnight. Thus it will be extremely unlikely that participants will perform high-risk behaviors, including driving motor vehicles, during the period of intoxication.

Anxiety and Panic Response

Reports specific to consumption of psychedelic mushrooms (Hyde et al. 1978; Musha et al. 1986; Peden and Pringle 1982) report the occurrence of usually transient anxiety or psychosis-like symptoms similar to those reported for LSD (Strassman 1984). A survey of 44 individuals admitted to hospital after psilocybin use reported the most common adverse event to be dysphoria that lasting for an average of 3.8 hours, followed by nausea or vomiting in at least half the admissions (Peden and Pringle 1982). As might be expected after compounds known to alter perception (Nichols 2004; see "Previous Human Experience" below), people in this study also reported alterations in perception and parasthesias (unusual body sensations, such as numbness or tingling). These reactions typically resolved spontaneously with supportive care, or, on some occasions, with the use of sedative medications such as benzodiazepines. In most cases, emergency room admissions related to anxiety or psychological distress after psilocybin does not require hospitalization (Strassman et al. 1994). The occurrence and intensity of anxiety or panic responses to psilocybin can be reduced through informing participants about drug effects prior to drug administration, supervision and monitoring participants throughout the duration of drug effects by people trained to deal with panic or anxiety, including

anxiety in response to hallucinogen effects, and exposure to lower doses before receiving higher doses.

Transient and Prolonged Psychotic Reaction

Some individuals enter transient and sometimes prolonged psychotic states after use of psychedelics, including psilocybin (Benjamin 1979; Halpern and Pope 1999; Strassman 1984). Because in nearly all cases, psychosis appears after use without evaluation of psychological state prior to psilocybin use, drawing conclusions about causality is difficult. After examining the literature, Strassman concluded that hallucinogens, including psilocybin, might trigger psychotic episodes, but in a non-specific and non-etiologic manner, and that they did not cause psychosis in people (Strassman 1984). Researchers examining the prevalence of psychiatric reactions through questionnaires sent to researchers conducting controlled studies with the related serotonergic hallucinogen LSD found that 0.08% of 5000 study volunteers experienced psychiatric symptoms that lasted more than two days (Cohen 1960). The rate of occurrence for psychiatric symptoms occurred at the slightly higher rate of 0.18% in psychiatric patients. Another survey of a separate sample of 4300 research volunteers reported a rate of serious, persistent psychiatric reactions in 0.9% of the sample (Malleson 1971). Psilocybin and LSD produce similar subjective effects. Hence these findings suggest that participating in a research study involving the administration of a psychedelic compound similar to LSD is extremely unlikely to trigger transient or persistent psychosis. Past research with LSD and other psychedelics did not apply as stringent criteria for participant selection or screening as are used today, making the low rates of psychosis especially notable (Halpern and Pope 1999), and likely overestimates the likelihood of prolonged psychoses or other psychopathological effects in a study wherein participants are screened for past or present psychotic disorders. The occurrence of transient or persistent psychosis can be prevented or further reduced by excluding people on the basis of the presence of past or current psychotic disorders or such disorders in first-degree relatives, such as biological parent or sibling.

Post-Hallucinogen Perception Disorder (HPPD)

Some people who have used serotonergic hallucinogens, such as LSD or psilocybin, experience persistent, distressing alterations in mostly visual perception that last from weeks to years after use. This condition is now diagnosed as hallucinogen persistent perception disorder (HPPD), and is no longer referred to by the term "flashbacks," which better describe an experience more akin to traumatic recall of an intensely upsetting experience, as a "bad trip." HPPD has occurred after use of psilocybin-containing mushrooms (Benjamin 1979; Espiard et al. 2005). To date, there are no reports describing prevalence of HPPD in the general population, but an examination of previous reports and estimates of psychedelic use in the US suggests that HPPD is very rare (Halpern and Pope 2003; Johnston 2005). Halpern and Pope noted that many to most previous studies were affected by selection bias. These reports also contained information supporting alternative explanations of flashbacks or HPPD, such as use of other drugs or the presence of other mental disorders, and found that people who had not used

hallucinogens sometimes also reported experiencing similar perceptual disturbances. As well, preliminary data collected by Baggott suggests that no more than 1% of hallucinogen users experience HPPD [Baggott 2006; personal communication to L Jerome]. To date, no cases of HPPD have occurred in volunteers given psilocybin in current research studies. The risk of HPPD occurring after psilocybin administration can be reduced by screening participants for potential risk factors such as substance dependence and through excluding people reporting HPPD after prior use of hallucinogens.

Long-Term Personality Changes after Psilocybin

Though the possibility of chronic neuropsychological effects have never been specifically addressed with respect to psilocybin, earlier studies reported detecting changes in personality or neuropsychological function in people reporting frequent or chronic use of LSD, as described in a review by Halpern and Pope (1999). However, later examinations of these studies found that they possessed a number of methodological flaws, including retrospective study design and failure to account for use of other drugs. Halpern and Pope concluded that long-term changes in personality or psychological function after LSD, if they occurred at all, were liable to be subtle and not clinically significant. Psilocybin shares pharmacological mechanisms with LSD, and so these results seem likely to be applicable for this compound as well. Furthermore, a study of the ability of approximately 0.43 mg/kg psilocybin to produce spiritual experiences found that participants reported an increase in positive attitude changes and behavior two months after psilocybin administration, and people who knew these participants concurred (Griffiths et al. 2006). Monitoring personality before and after psilocybin administration will allow researchers to detect personality changes

Abuse Potential

Currently, psilocybin is placed in Schedule 1, defined as having no medical use and possessing high abuse liability. Despite this designation, examining use patterns in humans and studies in nonhuman primates suggest that psilocybin possesses little or no abuse liability. Monkeys in a study of the rewarding properties of four serotonergic compounds found that the animals did not consistently self-administer psilocybin (Fantegrossi et al. 2004). It is also notable that rhesus monkeys found LSD, a drug with similar pharmacological and subjective effects, to be aversive (Hoffmeister 1975). There is no human dependence syndrome for LSD, a drug sharing some similarities with psilocybin, and prevalence of LSD use in adolescents and young adults seems to remain relatively stable over time in the US (Johnston et al. 2005). It seems likely that psilocybin also has the same low abuse liability described for LSD. Surveys of drug use in the US do not even ask specifically about use of psilocybin-containing mushrooms, suggesting that use of these mushrooms is relatively uncommon. While very few studies specifically ask respondents about use of "magic mushrooms," there appears to be little notable change in prevalence of "hallucinogen" use in adults aged 19 to 28 (Johnston and O'Malley 2004), with 19.6% reporting some use in 2002 and 20% in 2003. A survey of national drug use in Canada also indicated that hallucinogens accounted for very few admissions for

substance abuse (Poulin et al. 1999). It is not expected that either psilocybin-naïve or experienced individuals will develop dependence after exposure, even if exposure may lead to pain reduction, as it may in the case of people with cluster headaches.

Reproductive Toxicity

There have been no systematic examinations of the effects of psilocybin in utero. Previous research with LSD had first detected chromosomal abnormalities, but subsequent research failed to detect any abnormalities (Cohen and Shiloh 1977; Cohen 1967; Dishotsky et al. 1971). Psilocybin did not produce any indicators of mutagenicity in the micronucleus model of mutagenicity (Van Went 1978). These findings suggest that psilocybin is unlikely to damage DNA. Furthermore, there do not appear to be any case reports of birth defects arising from psilocybin use. Nevertheless, the reproductive risks of psilocybin, though likely minimal, remain unknown. Reproductive risks can be prevented or eliminated through restricting enrollment to women who are not pregnant or lactating and who are using an effective means of birth control.

6. Trial Data

There are no ongoing sponsor-supported trials of psilocybin at present. In future, data will be collected and reported on psilocybin side effects.

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