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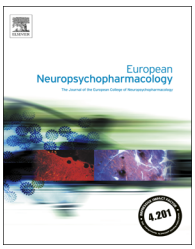

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REVIEW

Psilocybin – Summary of knowledge and new perspectives

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Abstract
Psilocybin, a psychoactive alkaloid contained in hallucinogenic mushrooms, is nowadays given a lot of attention in the scientific community as a research tool for modeling psychosis as well as due to its potential therapeutic effects. However, it is also a very popular and frequently abused natural hallucinogen. This review summarizes all the past and recent knowledge on psilocybin. It briefly deals with its history, discusses the pharmacokinetics and pharmacodynamics, and compares its action in humans and animals. It attempts to describe the mechanism of psychedelic effects and objectify its action using modern imaging and psychometric methods. Finally, it describes its therapeutic and abuse potential.

Contents

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1. Introduction

Psilocybin and psilocin, the main psychedelic ingredients of hallucinogenic mushrooms (Guzman et al., 1998; Laussmann and Meier-Giebing, 2010) (Table 1), have recently been given a lot of attention as a research tools (Geyer and Vollenweider, 2008) as well as a potential therapeutic agents (Grob et al., 2011; Moreno et al., 2006; Sewell et al., 2006). History of the ritual use of hallucinogenic mushrooms dates back 3000 years in Mexico and regionally its use is still conventional practice today (Carod-Artal, 2011; Hofmann, 2005). Western science was introduced to these mushrooms in 1957 by Robert G. Wasson and they were later systematically ranked by Roger Heim (Aboul-Enein, 1974). Psilocybin was first isolated and identified in 1958 and synthesized in 1959 by Albert Hofmann (Hofmann et al., 1958). The content of psilocybin and psilocin in hallucinogenic mushrooms varies in the range from 0.2% to 1% of dry weight (Table 2.).

In the 1960s psilocybin was widely used in the experimental research of mental disorders and even in psychotherapy (Metzner, 2005). Soon, however, psilocybin containing mushrooms spread amongst the general public and became a popular recreational drug. Consequently, psilocybin (and psilocin) was classed as a schedule I drug in 1970 (Nichols, 2004) and all human experiments were gradually discontinued. Since the late 1990s, interest in human experimental research into psilocybin and other psychedelics has become revived (Figure 1). Nowadays, psilocybin is one of the most used psychedelics in human studies due to its relative safety, moderately long duration of action and good absorption after oral administration (Hasler et al., 2004; Johnson et al., 2008).

The aim of this paper is to bring together the most detailed and up to date list of known properties and effects

Table 1 Systematic classification and the selected representatives of mushrooms containing psilocybin. Representatives of species currently freely distributed in the SmartShop network in the Netherlands are depicted in bold.

Mushrooms containing psilocybin					
Division	**Class**	**Order**	**Family**	**Genus**	**Best know representative**
Basidiomycotina	Hymenomycetes	Agaricales	Bolbitiaceae	Conocybe	*Conocbe cyanopus*
			Coprinaceae	Copelandia	***Copelandia cyanescens***
				Panaeolina	
				Panaeolus	*Panaeolus africanus*
					Panaeolus subbalteus
			Cortinariaceae	Gymnopilus	*Gymnopilus Purpuratus*
				Galerina	
				Inocybe	*Inocybe aeruginascens*
			Plutaceae	Pluteus	*Pluteus salicinus*
			Strophariaceae	Psilocybe	*Psilocybe azurescens*
				(115 representatives)	*Psilocybe bohemica*
					Psilocybe cubensis
					Psilocybe cyanescens
					Psilocybe mexicana
					Psilocybe semilanceata
					Psilocybe tampanensis
				Hypholoma	
			Tricholomataceae	Gerronema	
				Mycena	

Table 2 Content of psilocybin and psilocin in the dry state of selected representatives of psychoactive mushrooms, x=content is not known.

Species	Psilocybin (%)	Psilocin (%)	Study
Psilocybe azurenscens	1.78	0.38	Stamets and Gartz (1995)
Psilocybe bohemica	1.34/0.78/0.85	0.11/0.01/0.02	Gartz and Moller (1989) and Gartz (1993, 1994)
Psilocybe semilanceata	0.98/0.96	x/x	Gartz (1994, 1993)
Psilocybe baeocystis	0.85	0.59	Repke et al. (1977) and Beug and Bigwood (1982)
Psilocybe cyanescens	0.85/0.45/0.32	0.36/0.06/0.51	Repke et al. (1977), Stijve and Kuyper (1985), and Gartz (1993, 1994)
Psilocybe tampanensis	0.68	0.32	Gartz (1993)
Psilocybe cubensis	0.63	0.6	Gartz (1994) and Stijve and De Meijer (1993)
Psilocybe mexicana	0.3	0.05	Hofmann et al. (1959)
Psilocybe hoogshagenii	0.6	0.1	Heim and Hofamnn (1958)
Psilocybe stuntzii	0.36	0.12	Repke et al. (1977) and Beug and Bigwood (1982)
Psilocybe cyanofibrillosa	0.21	0.04	Stamets et al. (1980)
Psilocybe liniformans	0.16	x	Stijve and Kuyper (1985)
Gymnopilus Purpuratus	0.34	0.29	Gartz (1994)
Inocybe aeruginascens	0.40	x	Gartz (1994)
Copelandia cyanescens	0.32	0.51	Barceloux (2012)
Panaeolus subbalteus	0.39	x	Gartz (1993)
Conocbe cyanopus	0.88	0.15	Gartz (1993)
Pluteus salicinus	1.09	x	Gartz (1993)

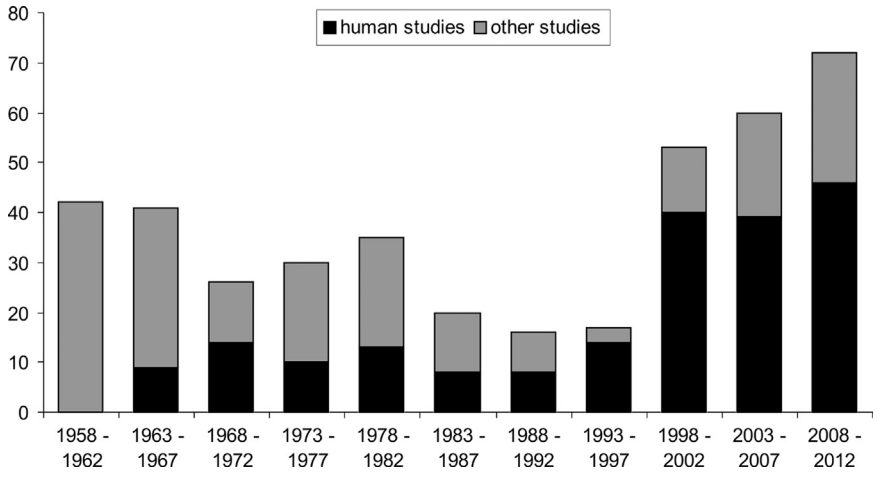

Figure 1 Number of publications dealing with psilocybin/psilocin (*y* axis) in five-year intervals from its synthesis to the present day (source PubMed dated 06/02/2013. Advanced searched terms were "psilocybin"[Title/Abstract] OR "psilocin"[Title/Abstract] AND Date "YYYY-YYYY"[Date – Publication]; for human studies available selection box was checked).

of psilocybin, starting with its chemical characteristics, metabolism, pharmacokinetics and ending with the use of psilocybin in human research and therapy.

2. Structural and chemical characteristics of psilocybin

Psilocybin (O-phosphoryl-4-hydroxy-N,N-dimethyltryptamine) and its active dephosphorylated metabolite psilocin (N,N-dimetyltryptamine) structurally belong to the group of tryptamine/indolamine hallucinogens and are structurally related to serotonin (Hasler et al., 1997; Horita and Weber, 1961a) (Figure 1). An equimolar dose to 1 mol of psilocin is 1.4 mol of psilocybin (Wolbach et al., 1962). Substitution of the indole nucleus in position 4 probably plays a substantial role in its hallucinogenic effects (Nichols, 2004; Troxler et al., 1959).

Psilocybin and psilocin in their pure forms are white crystalline powders. While psilocybin is soluble in water, psilocin on the other hand is more lipid-soluble (Ballesteros et al., 2006). However, psilocin can be also diluted in an acidified aqueous solution and in dimethylsulfoxide (DMSO; up to 100 mM). Furthermore, both substances are soluble in

methanol and ethanol, but almost insoluble in petroleum ether and chloroform (Barceloux, 2012; Berle, 1974). Both drugs are unstable in light (in particular in the form of solutions), their stability at low temperatures in the dark under an inert atmosphere is very good (Anastos et al., 2006).

3. Metabolism and pharmacokinetics of psilocybin

Psilocybin is rapidly dephosphorylated to psilocin in the intestinal mucosa by alkaline phosphatase and nonspecific esterase. After ingestion, about 50% of the total volume of psilocin is absorbed from the digestive tract of the rat (Kalberer et al., 1962). After systemic parenteral administration of psilocybin tissue phosphatases play the same role with the kidneys being among the most active (Horita and Weber, 1961b, 1962). Given that the competitive blockade of dephosphorylation (beta-glycerolphosphate) blocks the psychotropic effects of psilocybin, it is clear that psilocin is the main active metabolite of psilocybin (Horita, 1963). Psilocin is further glucuronidated by endoplasmic enzymes UDP-glucuronosyltransferase (UGTs) to psilocin-O-glucuronide (Manevski et al., 2010) and in this form 80% of it is excreted from the body (Grieshaber et al., 2001; Sticht and Kaferstein, 2000). Of the 19 tested recombinant UGTs (from the families 1A, 2A and 2B) UGT1A10 in the small intestine and UGT1A9 in the liver have the greatest activity (Manevski et al., 2010).

In addition to the above-described metabolic pathway, psilocin itself is subject to oxidative metabolism. Psilocin undergoes a demethylation and deamination to 4-hydroxyindol-3-yl-acetaldehyde (4-HIA) and subsequent oxidation (presumably by hepatic aldehyde dehydrogenase and monoamine oxidase) to 4-hydroxyindol-3-acetic acid (4-HIAA) and 4-hydroxytryptofol (4-HT) (Hasler et al., 1997; Passie et al., 2002). These minor metabolites (about 4% psilocin being degraded in this way) can also be detected in vivo in human plasma (Hofmann, 1968; Lindenblatt et al., 1998). The third possible pathway is the oxidation of psilocin by hydroxyindol oxidases to a product with an o-quinone or iminochinon structure (Kovacic, 2009).

In rats and mice after oral administration of extracts from mushrooms (Chen et al., 2011) maximum plasma levels are achieved after approximately 90 min. Psilocin is distributed to all tissues, including the brain, and is excreted within 24 h – the majority in the first 8 h (65% in the urine and 15–20% in the bile and feces); small amounts can be detected in the urine even after a week (Hofmann, 1968). The highest levels of psilocin in various animals were detected in the neocortex, hippocampus, extrapyramidal motor system and reticular formation (Hopf and Eckert, 1974). In mice, preceding the brain, psilocin accumulates in the kidneys, and the liver (Horita and Weber, 1962).

In humans, psilocybin and psilocin can be found in blood plasma 20–40 min after oral administration of psilocybin, maximum levels of psilocin are achieved between 80 and 105 min and can be detected for up to 6 h (Hasler et al., 1997; Passie et al., 2002). The half-life of psilocin in plasma is 2.5 h after oral ingestion of psilocybin, following intravenous administration the half-life is 1.23 h. Eighty percent of psilocin in plasma was found to be in a conjugated form. Both psilocin (at 90–97%) and psilocybin (3–10%), are detectable in human urine, unmodified (only 3–10%) and particularly conjugated with glucoronic acid (Hasler et al., 2002; Kamata et al., 2006; Passie et al., 2002). The elimination half-life of psilocybin is 50 min and the elimination constant is 0.307/h (Lindenblatt et al., 1998). The majority is excreted within 3 h after oral administration and is completely eliminated from the body within 24 h (Hasler et al., 2002; Holzmann, 1995).

4. Pharmacodynamics

Psilocybin and psilocin are the substances with predominant agonist activity on serotonin $5HT_{2A/C}$ and $5HT_{1A}$ receptors (for specific affinities see Table 3). Interestingly, psilocybin's affinity to human $5HT_{2A}$ receptors is 15-fold higher than in rats (Gallaher et al., 1993). While the $5HT_{2A}$ receptor agonism is considered necessary for hallucinogenic effects (Nichols, 2004), the role of other receptor subtypes is much less understood. Contrary to the previous report (Creese et al., 1975), a recent study found that psilocin binds to many different receptors including dopamine in the following order:

Table 3 Affinity of psilocin to serotonin receptors. x=missing data.

Constant	Subtypes of serotonin receptors														Study
	$5HT_{1A}$	$5HT_{1B}$	$5HT_{1D}$	$5HT_{1E}$	$5HT_{1F}$	$5HT_{2A}$	$5HT_{2B}$	$5HT_{2C}$	$5HT_3$	$5HT_4$	$5HT_{5A}$	$5HT_{5B}$	$5HT_6$	$5HT_7$	
Ki (nM)	49, [3H] 8-OH-DPAT	x	x	x	x	25, [125I] DOI	x	10, [125I] DOI	x	x	x	x	x	x	Blair et al. (2000)
Ki (nM)	190, [3H] 8-OH-DPAT	x	x	x	x	6, [125I] DOI	410, [3H] ketanserin	x	x	x	x	x	x	x	McKenna et al. (1990)
npKi[a]	2.88	2.19	3.4	3.03	x	2.14	4	2.52	x	x	2.83	x	2.82	2.82	Ray (2010)
Ki (nM)	567.4	219.6	36.4	x	x	107.2	4.6	97.3	>10000	x	83.7		57	3.5	Halberstadt and Geyer (2011)

[a]npKi is logarithmated and normalized value of Ki. It is calculated as follows: npKi=4+pKi−pKiMax, where pKi=−log 10(Ki).

$5HT_{2B} > 5HT_{1D} > D_1 > 5HT_{1E} > 5HT_{1A} > 5HT_{5A} > 5HT_7 > 5HT_6 > D_3 > 5HT_{2C} > 5HT_{1B} > 5HT_{2A}$. According to this data it also weakly binds to the receptors for $Imidazoline_1$, $Alpha_{2A/B/C}$ and 5HT transporters (Ray, 2010).

Using selective agonists and antagonists $5HT_{1A}$ and $5HT_{2A}$ activity has also been confirmed in rodents in discrimination studies with hallucinogens (Appel and Callahan, 1989; Fantegrossi et al., 2008; Winter et al., 2007) and in studies on head twitch behavior and wet dog shakes (typical signs of the stimulation of the 5-HT_{2A} receptor) (Fantegrossi et al., 2008; Halberstadt et al., 2011). On the other hand, psilocybin/psilocin-induced locomotor inhibition was restored by antagonists 5-HT_{1A} and 5-$HT_{2B/C}$ receptors (Halberstadt et al., 2011; Palenicek et al., 2006; unpublished data). Finally, inhibition of dorsal raphe nucleus activity by psilocybin was shown to be mediated via agonism at 5-HT_{1A} autoreceptors (Aghajanian and Hailgler, 1975) and electroencephalographic changes induced by psilocin were partly normalized by antagonists of 5-HT_{1A}, $5HT_{2A/C}$ as well as dopamine D_2 receptors (Tyls et al., 2012a).

The effects of psilocybin in humans are also blocked by the 5-$HT_{2A/C}$ antagonists (Vollenweider et al., 1998). The role of 5-HT_{1A} receptors in human psilocybin studies is yet to be investigated, certain clues can be derived from a study of a related hallucinogen N,N-dimethyltryptamine (DMT). Here the 5-HT_{1A} partial antagonist pindolol magnified the hallucinogenic effects by two to three times (Strassman, 1996). Psilocybin also indirectly increased (via 5HT receptors) the release of dopamine in the ventral striatum in humans, an effect that correlated with symptoms of depersonalization and euphoria (Vollenweider et al., 1999).

In neurons expressing the $5HT_{2A}$ receptor, but not in $5HT_{2A}$ knockouts, psilocybin increases the expression of early genes (*erg-1*, *erg-2*, *c-fos*, *jun-B*, *period-1*, *gpcr-26*, *fra-1*, *N-10*, *I-κBα*) and reduces the expression of *sty-kinase* (Gonzalez-Maeso et al., 2007; Gonzalez-Maeso and Sealfon, 2009). Needless to say, the precise signaling pathway leading from the receptor to the activation of early genes is not yet known. Given that a non-hallucinogenic lisuride also activates the *c-fos*, it is likely that the expression of *c-fos* only reflects increased neuronal activity (Day et al., 2008), while the expression of *egr-1*/*egr-2* is specific for the hallucinogenic effect (Gonzalez-Maeso et al., 2007). Gonzales-Meaeso explained this selectivity with the "agonist trafficking of receptor signaling theory", where hallucinogens activate the $5HT_{2A}/mGlu_2$ receptor heterocomplex and different G proteins compared to non-halucinogenic 5-HT2A agonists (Gonzalez-Maeso et al., 2003). This hypothesis is supported in a study where the mice with the knockout gene for the $mGlu_2$ receptor do not display any head twitch behavior (Moreno et al., 2011).

5. Behavioral effects of psilocybin/psilocin in animals

Psilocybin and psilocin are used in animal behavioral experiments in the range of 0.25–10 mg/kg; however doses up to 80 mg/kg have also been used. Psilocybin dose of 10 mg/kg has mild sympathomimetic effects (piloerection and hyperventilation) in rodents and small carnivores (Passie et al., 2002). Characteristic effect of psilocybin is enhancement of monosynaptic spinal reflexes in cats (Hofmann, 1968).

Peak of behavioral changes are typically observed within 30–90 min after drug administration. Locomotor behavior of rodents is dose-dependently inhibited by the drug with signs of ataxia (Halberstadt et al., 2011; Palenicek et al., 2005). Psilocin also suppresses exploration and habituation elements and induces manifestations of behavioral serotonin syndrome (e.g. head twitch behavior) and in a very high doses (80 mg/kg) also induces atypical behavioral of backward walking (Geyer et al., 1979; Halberstadt et al., 2011). Behavioral excitation was observed anecdotally (Chauchard, 1967; Sugrue, 1969). Furthermore, psilocybin decreases aggressive behavior in rodents (Kostowski et al., 1972; Uyeno, 1978) and inhibits normal dominance behavior (Uyeno, 1967, 1972).

Psilocybin has increased prepulse inhibition of acoustic startle response (PPI)[1] up to doses of 4.5 mg/kg in mice (Halberstadt and Geyer, 2011). Using a lower dose of psilocin (1 mg/kg), it attenuated PPI (via 5-HT_{2A} agonism predominantly) and with 4 mg/kg had no effect in Wistar rats (Palenicek et al., 2011, unpublished data). Psilocin also seems to have biphasic effects on startle reaction per se, with lower doses slightly increasing and higher doses (4–8 mg/kg) decreasing startle (Davis and Walters, 1977; Palenicek et al., 2011). Psilocybin also increased the starting latency in a special conditioned task (swimming through an underwater tube) (Uyeno, 1971) and attenuated responses in a passive avoidance task (Collins et al., 1966; Sugrue, 1969). It is probable that attenuation of startle response as well as altered performance in cognitive tasks could be related to the motor inhibition and ataxia produced by the drug as well as to an altered perception of the environment.

In psilocybin self-administration experiments with macaques at sufficiently high doses the drug provoked stereotypical visual scanning, head shaking, bizarre postures, hyperactivity and focusing on an empty spot in a room with catching non-existent flies (Fantegrossi et al., 2004b). It is therefore very likely that this is a direct manifestation of an altered perception, especially visual hallucinations.

6. Human studies with psilocybin

6.1. Dosage and time course of effects

In terms of efficacy, psilocybin is 45 times less potent than LSD and 66 times more potent than mescaline (Isbell, 1959; Wolbach et al., 1962). Clinical studies indicate that the effective dose of oral (p.o.) psilocybin is 0.045–0.429 mg/kg

[1] PPI is a commonly evaluated parameter, which reflects sensorimotor processing. It is the evaluation of the startle response to a sudden unexpected stimulus (usually tactile or audio) and the prepulse inhibition of startle response. The principle of prepulse inhibition relies on the ability of slightly supraliminal stimulus (prepulse; cannot be consciously processed) preceding in an order of milliseconds the startle stimulus (pulse) to reduce the extent of the startle response. These measurements can be used to evaluate a number of parameters, such as latency response and amplitude. A frequently evaluated parameter is the habituation to a startle response and PPI.

and 1–2 mg per adult intravenously (i.v.) (Table 4). Psychedelic effects occur at doses above 15 mg of oral psilocybin (Hasler et al., 2004) or plasma psilocin levels of 4–6 ng/ml (Hasler et al., 1997). Safety guidelines for the experimental use of hallucinogens state high but not dangerous oral doses of psilocybin as being anything higher than 25 mg (Johnson et al., 2008).

The psilocybin onset of action is between 20 and 40 min, maximum is 60–90 min and the duration is 4–6 h after oral administration. The main effects disappear entirely within 6–8 h, completely in 24 h (Hasler et al., 2004; Vollenweider et al., 1998). For i.v. application, the effect starts after 1–2 min, peaks at 4–5 min and lasts for about 20 min (Carhart-Harris et al., 2011; Hasler et al., 1997). Evaluation of the effects of psilocybin after one week of administration did not confirm any breach of perception or cognition (Gouzoulis-Mayfrank et al., 1999b).

6.2. Effects on somatic, physiological and endocrine functions

Analogously as in animals, in humans psilocybin slightly stimulates sympathetic activity (mydriasis, mild increase in blood pressure and increased heart rate) at doses higher than 3–5 mg p.o. with the full effect at 8–25 mg p.o. (Griffiths et al., 2006; Hasler et al., 2004; Isbell, 1959). The increase of systolic and diastolic pressure is approximately 10–30 mmHg each. The average heart rate was in the range of 82–87, maximal values reached 140 beats per minute. Furthermore, psilocybin had no effect on electrocardiograph (ECG) or body temperature (Hasler et al., 2004). Other common somatic symptoms are as follow: dizziness, weakness, tremor, nausea and vomiting (mainly after ingestion of psilocybin-containing mushrooms (Peden and Pringle, 1982), drowsiness, yawning, paresthesia, blurred vision, and increased tendon reflexes (Hollister, 1961; Johnson et al., 2008).

Psilocybin does not acutely affect the ionic balance, blood glucose or cholesterol, and even in high doses has only a negligible effect on plasma concentration or the activity of various enzymes (lactate dehydrogenase, alanine transaminase, alkaline phosphatase and cholinesterase, mild elevation of aspartate aminotransferase and γ-glutamyl transferase) (Hasler et al., 2004; Hollister, 1961). However, psilocybin increases levels of prolactin, and in high doses also corticotropin, cortisol and thyreotropin. Hormone levels have returned to normal within 5 h (Gouzoulis-Mayfrank et al., 1999b; Hasler et al., 2004).

Table 4 Subjective effects after administration of psilocybin versus placebo in the Dittrich scale of ASCs shown as a measure of significance. Number of arrows indicates significance (p values – 0.05, 0.01, 0.001) according to corresponding studies, ↑ – increase, ↓ – decrease. *Abbreviations*: OSE=Oceanic Boundlessness, AED=Anxious Ego Dissolution, VUS=Visionary Restructuralization, AA=Auditory Alterations, RV=Reduction of Vigilance, Psi=psilocybin, Pla=placebo, Ket=ketanserine, Risp=risperidone, Hal=haloperidol, n/a=not analyzed, n.s.=not significant, x=versus.

ASC subscales	OSE	AED	VUS	AA	RV	**Study**
Example of symptoms	Euphoria +derealization/ depersonalization	Anxiety, loss of self-control	Visual hallucinations	Auditory hallucinations	Reduced awareness	
Drugs and dosage						
Psi 0.045 mg/kg p.o. **xPla**	n.s.	n.s.	n.s.	n.s.	n.s.	
Psi 0.115 mg/kg p.o. **xPla**	↑	↑n.s.	↑n.s.	↑n.s.	↑↑↑	**Hasler et al.** (2004)
Psi 0.215 mg/kg p.o. **xPla**	↑↑↑	↑n.s.	↑↑↑	↑n.s.	↑↑↑	
Psi 0.315 mg/kg p.o. **xPla**	↑↑↑	↑↑	↑↑↑	↑↑	↑↑↑	
Psi 5 mg/70 kg p.o. **xPla**	↑	↑	↑	n/a	n/a	**Griffiths et al.** (2011)
Psi 10 mg/70 kg p.o. **xPla**	↑↑	↑↑	↑↑	n/a	n/a	
Psi 20 mg/70 kg p.o. **xPla**	↑↑↑	↑↑↑	↑↑↑	n/a	n/a	
Psi 30 mg/70 kg p.o. **xPla**	↑↑↑	↑↑↑	↑↑↑	n/a	n/a	
Psi 1.5 mg i.v. **xPla**	n.s.↑	n.s.↑	n.s.↑	n.s.↑	n.s.↑	**Carhart-Harris et al.** (2011)
Psi 2 mg i.v. **xPla**	n.s.↑	n.s.↑	n.s.↑	n.s.↑	n.s.↑	
Psi 0.25 mg/kg p.o. **xPla**	↑↑-↑↑↑	↑-↑↑	↑↑-↑↑↑	n/a	n/a	**Vollenweider et al.** (1998)
Psi 0.25 mg/kg p.o.+**Ket** 40 mg p.o. **xPsi** 0.25 mg/kg p.o.	↓↓	↓↓	↓↓↓	n/a	n/a	
Psi 0.25 mg/kg p.o.+**Risp** 1 mg p.o. **xPsi** 0.25 mg/kg p.o.	↓↓	↓↓	↓↓	n/a	n/a	
Psi 0.25 mg/kg p.o.+**Hal** 0.021 mg/kg i.v.**xPsi** 0.25 mg/kg p.o.	↓↓	↑	n.s.↓	n/a	n/a	

6.3. Psychotropic and neuropsychological effects of psilocybin

Very low doses cause drowsiness and emphasize the pre-existing mood (Hasler et al., 2004). Medium doses induce a well controllable altered state of consciousness (Passie et al., 2002) and higher doses evoke a strong psychedelic experience. The phenomenology of psilocybin intoxication includes changes in perception (dream-like states, illusions, hallucinations, synesthesiae) including changes in body image (e.g. paraesthesia in the form of a tingling, dreaminess or somatic hallucinations), altered self-perception, derealization and depersonalization, impaired perception of time and space, impaired attention, thought content disorder (magical thinking, unusual ideas or delusions), change of intuition and sometimes also mood swings, symptoms of anxiety or elation, impaired concentration, and nervousness (Geyer and Vollenweider, 2008; Hasler et al., 2004; Hollister, 1961). Emotions during intoxication can vary greatly from ecstatic and pleasant feelings to anxiety (Vollenweider et al., 1997). The effects of psilocybin as with other hallucinogens are quantified with five subscales of the Altered States of Consciousness scale (ASCs) (Dittrich, 1998) (Table 4). Comparing psilocybin with the dissociative anesthetic ketamine it was found that psilocybin has greater visual hallucinatory effects (VUS scale) but feelings of loss of physical integrity (AED scale) are more pronounced in ketamine (Studerus et al., 2012; Vollenweider and Geyer, 2001; Vollenweider and Kometer, 2010). Psilocybin-induced changes were uniformly normalized by ketanserin (5-$HT_{2A/C}$ antagonist) and risperidone (mixed 5-$HT_{2A/C}$ and D_2 antagonist). On the other hand, an antagonist of the D_2 receptor, haloperidol, normalized only euphoric symptoms, derealization and depersonalization (OSE scale) and had no effect on the visual hallucinations (VUS scale) and even slightly potentiated the feeling of a loss of self-control (AIA scale) (Vollenweider et al., 1998). A positive correlation between psilocybin-induced reduction of visually evoked potentials and score on the VUS scale was also described (Kometer et al., 2013).

According to the Adjective Mood Rating Scale (AMRS)[2] (Janke and Debus, 1978) psilocybin induced an overall inactivation and tiredness, dazed state, introversion, increased emotional excitability, increased sensitivity and persisting dreaminess for up to 24 h (Hasler et al., 2004; Studerus et al., 2011). Psilocybin altered several domains of cognitive function and information processing. It selectively reduced the ability to visually distinguish between faces with negative and neutral expressions but not positive-neutral faces (Schmidt et al., 2012), disrupted sustained attention (Umbricht et al., 2003; Vollenweider et al., 2007) and altered visual information processing (Carter et al., 2004; Gouzoulis-Mayfrank et al., 2002; Wittmann et al., 2007). Interestingly, some of the alterations in a binocular rivalry test (visual processing) were also observed during deep meditative states realized by experienced meditation practitioners (Vollenweider, 2013). Effect of psilocybin on sensorimotor gating (PPI) was found to be dependent on the parameter "prepulse-pulse interval", with PPI disruption for short intervals (30 ms) and PPI increase in longer intervals (120–2000 ms) (Gouzoulis-Mayfrank et al., 1998; Vollenweider et al., 2007).

Psilocybin intoxication also brings about numerous spiritual and mystical experiences, as first documented in the famed Good Friday Experiment[3] (Pahnke, 1963). Positive long-term changes in life attitudes of participants were reported 25 years later (Doblin, 1991). These pioneering experiments have recently been confirmed by double-blind placebo and active comparator controlled studies. Volunteers without any previous experience with psychedelics, two months after taking psilocybin rated the experience as having substantial personal meaning and spiritual significance with sustained positive changes in attitudes and behavior (Griffiths et al., 2006). A 14 months follow-up revealed it as being one of the most significant spiritual experiences (Griffiths et al., 2008). In another follow-up survey with subjects from studies carried out in Switzerland between 1999 and 2008, most described the experience as pleasurable, enriching and non-threatening (Studerus et al., 2011). A third of subjects positively evaluated their experience 8–16 months after the session (positive change in world view, values, awareness of personal problems, relationships to one's body as well as to other people, relationships to nature, aesthetic experiences and their attitude to altered states of consciousness). Only 8% of the subjects reported moderate negative changes in their psychological well-being, however no subsequent long-term impairment of functioning was detected. Another recent study, assessing domains of personality in order to objectify long term subjective changes, found a significant increase in "openness" after psilocybin in participants who had mystical experiences during the session which remained for more than one year (MacLean et al., 2011).

7. Acute somatic toxicity of psilocybin

According to a number of toxicological and clinical studies psilocybin has a very low toxicity (Nichols, 2004; Passie et al., 2002). Psilocybin showed no specific signs of toxicity in the isolated organs (intestine, heart) of rats and pigs (Cerletti, 1958), it is also not neurotoxic (Johnson et al., 2008). Psilocybin LD_{50} for rats and mice is 280–285 mg/kg, and for rabbits it is 12.5 mg/kg. Psilocin LD_{50} is significantly lower for mice and rats 75 mg/kg and for rabbits 7 mg/kg (Usdin and Efron, 1972). The LD_{50}/ED_{50} ratio is 641 according to the National Institute for Occupational Safety and Health Registry of Toxic Effects (compare this with 9637 for vitamin A, 4816 for LSD, 199 for aspirin and 21 for nicotine). Fatalities associated with ingestion of psilocybin containing mushrooms have been described, however these were not linked to direct toxicity of psilocybin but most victims died after jumping out of the window or committing suicide (van Amsterdam et al., 2011). The only reported fatality was described after ingestion

[2] AMRS: this subjective scale, allowing repeated assessment of the current state of mind, is based on the principle of assigning the degree of conformity to various adjectives that are typical for a certain mental disposition (Janke and Debus, 1978).

[3] Experiment performed by Walter N. Pahnke, a graduate student in theology at Harvard Divinity School, under the supervision of Timothy Leary in 1962, in which theology students were administered psilocybin or a placebo during divine service. Those intoxicated with the drug had a much greater spiritual and mystical experience than those with the placebo (Pahnke, 1963).

of an extreme dose (psilocin plasma level was 4 μg/ml) of *Psilocybe semilanceata* (Gerault and Picart, 1996).

A human lethal dose of psilocybin is difficult to estimate, it is clear that it is much higher than the psychoactive dose. One would have to eat approximately 19 g of the pure drug or consume their body weight in fresh psilocybin containing mushrooms to bring on death (www.erowid.org). Doses have not exceeded 0.429 mg/kg in clinical trials (Griffiths et al., 2006), which is approximately 30 × less than the LD_{50} for rabbits.

Theoretically, hypertension and tachycardia may affect predisposed individuals and extremely high doses of psilocybin (several times higher than in clinical trials) can cause coma, hyperthermia, and respiratory failure (symptoms of serotonin syndrome), similar to high doses of LSD (Klock et al., 1975). However, no such case has been reported to-date. During the long history of psilocybin use in the form of hallucinogenic mushrooms there have been no documented cases of somatic toxicity (Hofmann, 2005). Organ damage (e.g. renal failure) only occurs due to confusion between psilocybin mushrooms and other morphologically similar mushrooms (Franz et al., 1996).

8. Risks and side effects of psilocybin, long-term toxicity

The safety of psilocybin use is given mainly by personal expectations (set) and the nature of the environment (setting), which is the cause of the great variability of the subjective effects (Nichols, 2004). Due to the altered perception, hallucinations and intensified emotions, dangerous behavior may occur during non-medical administration (Johnson et al., 2008). These complications can be significantly reduced by educating an individual, creating a safe environment and building rapport with an experienced intoxication guide (sitter). (Johnson et al., 2008; Leary et al., 1963). Thus well-prepared hallucinogen-naïve participants can safely take higher doses of psilocybin (over 25 mg) (Johnson et al., 2008) and experienced volunteers can be administered with psilocybin even in magnetic resonance (Carhart-Harris et al., 2011).

Approximately 2000 subjects had received psilocybin under controlled experimental conditions during psychological and psychiatric research by 2005 (Metzner, 2005), without causing any serious side effects (Johnson et al., 2008). Anxiety, paranoid experiences, derealization, depersonalization, long lasting unpleasant experiences (bad trips), psychotic reactions and rare hallucinogen persisting perception disorder (HPPD)[4] are the main side effects described (Strassman, 1984) and are more likely than any physical risks (Johnson et al., 2008). Psychological interventions are mostly sufficient, anxiolytics and/or atypical antipsychotics can be used in extreme cases, and commitment is only very rarely required (Johnson et al., 2008; Strassman et al., 1994).

Generally, although the use of hallucinogens can trigger nonspecific psychotic episodes or accentuate psychotic symptoms in patients (Roubicek and Drvota, 1960), these substances are not the etiological agents (Gouzoulis-Mayfrank et al., 1994; Parashos, 1976). The risk of prolonged psychosis (lasting longer than 48 h) in otherwise healthy subjects after a single dose of psilocybin is rare and in most cases it is associated with personality predisposition (Johnson et al., 2008). The prevalence of prolonged psychiatric symptoms after serotonergic hallucinogens in thousands of healthy subjects and psychiatric patients was 0.08–0.09% and 0.18%, respectively. Attempts to commit suicide occurred in psychiatric patients only (in 0.12%) with few (0.04%) succeeding (Cohen, 1960; Malleson, 1971; Perala et al., 2007). Finally, incidence of HPPD is estimated to be in only a few cases per million users (Johnson et al., 2008). Since chronic administration of hallucinogens reduces the number of $5HT_{2A}$ receptors leading to a rapid onset of short-lasting tolerance (Roth et al., 1998) the risk of addiction to hallucinogens, including psilocybin is very low. Furthermore, monkeys did not seek psilocybin as a reward (Fantegrossi et al., 2004a), and in the case of LSD they even reacted aversely (Hoffmeister, 1975). In humans, psilocybin does not cause craving or withdrawal (Johnson et al., 2008) and it does not directly affect the mesolimbic dopaminergic pathway and therefore does not activate the reward system (Nichols, 2004).

Psilocybin is very likely to have no genotoxic effects. One study that directly focused on the mutagenic potential of psilocybin did not prove this type of toxicity (van Went, 1978). However, due to the lack of direct data on the teratogenicity of psilocybin, this substance should not be administered to pregnant women.

Despite the high level of safety and absence of risk of addiction psilocybin is included in the U.S. list of "Schedule I" controlled substances (Jerome, 2007; Nichols, 2004). However, substances on this list must have the following three characteristics: the drug or other substance has no currently accepted medical use in treatment, there is a lack of accepted safety for use of the drug or other substance under medical supervision, the drug or other substance has a high potential for abuse. It is clear from this text that psilocybin does not meet the first two criteria and the third point is disputable.

9. Functional brain imaging studies of psilocybin

9.1. Electroencephalography (EEG), Magnetoencephalography (MEG)

Early electrophysiological studies (limited to a visual assessment) documented increases of fast activity, reduction of amplitude and desynchronization in both primates and humans (Fink, 1969; Horibe, 1974; Meldrum and Naquet, 1971). Changes in visually evoked potentials and a decrease in alpha and theta activity were also described in humans (Da Fonseca et al., 1965; Rynearson et al., 1968).

Recent findings with psilocin and other hallucinogens in rats showed an overall reduction in EEG absolute power and coherence (fronto-temporal mainly); relative power was decreased in the delta and theta bands and increased in the alpha, beta, high beta and gamma bands (Palenicek et al., 2013; Tyls et al., 2012b, 2013, unpublished data). Since the theta band in rats is the main basic activity, this

[4] DSM IV code 292.89, ICD10 code is F16.7. – psychotic reminiscence or flashback. HPPD manifests itself as persistent changes in visual perception after the pharmacological effects of the substance have worn off (Halpern and Pope, 2003).

may be analogous to the aforementioned EEG desynchronization in primates and humans. As similar patterns of coherence were also observed for dissociative anesthetics (Tyls et al., 2012b) we hypothesize that the reduction of coherence might nonspecifically reflect the hallucinogenic effects. Observed fronto-temporal disconnection is also a characteristic finding correlating with the distortion of several cognitive parameters and might also reflect sensorimotor processing deficits that are typically induced by hallucinogens (Friston and Frith, 1995; Palenicek et al., 2013).

Recent quantitative EEG analysis in healthy volunteers revealed that psilocybin (0.215 mg/kg p.o.) decreased basal alpha power precluding a subsequent stimulus-induced α-power decrease and attenuated VEP N170 in the parieto-occipital area (Kometer et al., 2013). Psilocybin (2 mg i.v.) also decreased broadband spontaneous cortical oscillatory power during resting state in MEG, with large decreases being in the areas of the default-mode network (DMN) and other resting state networks. On the other hand, visually and motor-induced gamma activity remained unchanged. Subsequent effective connectivity analysis revealed that posterior cingulate (central hub of DMN) desynchronization can be explained by increased excitability of deep-layer pyramidal neurons (Muthukumaraswamy et al., 2013).

The assumption that all these findings could be generalized to hallucinogens is supported by a human Ayahuasca[5] study with low-resolution brain electromagnetic tomography (LORETA), where a global current density reduction was observed (Riba et al., 2004).

9.2. Positron emission tomography (PET), Functional magnetic resonance imaging (fMRI)

In an ^{18}fluorodeoxyglucose (^{18}FDG) PET study psilocybin 15–25 mg p.o. increased metabolism in both the lateral and medial prefrontal cortex (mPFC) including the anterior cingulum (ACC), temporomedial cortex and basal ganglia. Interestingly, the ^{18}FDG uptake positively correlated with psychotic positive symptoms (especially ego disintegration) and mirrored the metabolic pattern typical for acute psychotic episodes (Vollenweider et al., 1997). Analogously, other PET studies have demonstrated increased metabolism in the frontotemporal cortex and ACC, and a reduction of ^{18}FDG uptake in thalamus. In addition, the same study documented a blunted metabolic increase during cognitive activation in the left frontal cortex (Gouzoulis-Mayfrank et al., 1999a).

On the contrary, a recent fMRI study with psilocybin (2 mg i.v.) documented only a decrease of both BOLD (blood-oxygen-level-dependent) and perfusion (arterial spin labeling) in a variety of subcortical regions, high-level association between fronto-temporo-parietal regions and in the important connectivity hubs of thalamus and midline cortex (anterior and posterior cingulum and precuneus). The intensity of the subjective effects was predicted by decreased activity in the anterior cingulate and mPFC. The subsequent mPFC seed connectivity analysis revealed that psilocybin induced reduction of connectivity between the posterior cingulate and mPFC, indicating that subjective effects of psilocybin could be caused by decreased activity and connectivity in the brain's key hubs of functional connectivity (Carhart-Harris et al., 2012a).

There are several explanations for the substantial discrepancy between PET and fMRI findings in a resting state. Firstly, the individuals in the PET study were at the peak of the effect (90 min after p.o.), whilst the fMRI study may have captured the onset of effect, thus the findings may correlate with anxiety rather than the psychedelic experience (King, 2012). Secondly, psilocybin as a 5-HT$_{1B/D}$ agonist induces the vasoconstriction (like triptans, anti-migraine drugs). This vasoactive reaction could directly influence the fMRI signal but not the resting ^{18}FDG uptake. Finally, the above-mentioned reduced power and desynchronization in MEG may be congruent with the fMRI as well as PET results (Muthukumaraswamy et al., 2013). The MEG study describes an increased excitability of deep-layer pyramidal neurons rich in 5-HT$_{2A}$ receptors. These glutamatergic neurons could induce both desynchronization of ongoing oscillatory rhythms (a decrease in resting connectivity and fMRI signal) and an increase in glutamate turnover which leads to an increase in glial metabolism reflected by an increase in ^{18}FDG uptake (Pfund et al., 2000).

Recent fMRI activation studies verifying the psychotherapeutic effectiveness of psilocybin revealed a robust increase in the BOLD signal in the early phases of autobiographical memory recollection (within 8 s) in the striatum and limbic areas, and in the later phases also in the medial prefrontal cortex and sensory areas of the cortex (Carhart-Harris et al., 2012b). The most recent fMRI studies by the same group documented the increased functional connectivity after 2 mg i.v. of psilocybin between the two specific neuronal networks. The first, DMN, is typically activated during a resting state and introspection, whilst the second, task-positive network, is activated during focused attention. These two networks reciprocally alternate in their activity under physiological circumstances but under meditation, psychosis, propofol sedation or under the influence of psilocybin they closely interact. However, unlike propofol, thalamo-cortical connectivity was preserved after the administration of psilocybin and it would discriminate in a substantial way the psychedelic experience from sedation (Carhart-Harris et al., 2012b).

10. Psilocybin as a model of psychosis

Hallucinogens including psilocybin induce complex changes at various levels of the brain which lead to altered states of consciousness. The neurobiology of the hallucinogenic effect was described elsewhere (Gonzalez-Maeso and Sealfon, 2009; Nichols, 2004; Palenicek and Horacek, 2008; Vollenweider, 2001).

Psilocybin is used as one of the major acute serotonergic models of psychosis/schizophrenia (Geyer and Vollenweider, 2008; Hanks and Gonzalez-Maeso, 2013) due to its phenomenological and construct validity characterized by: induction of positive psychotic symptoms (alterations in

[5]Ayahuasca, a hallucinogenic beverage used by indigenous tribes in Amazonia, contains the hallucinogen N,N-Dimethyltryptamine (DMT; structurally and pharmacologically very close to psilocybin) and harmine and harmaline with monoaminooxidase inhibiting activity.

perception, thinking and emotivity), changes in information processing, changes of brain metabolism and/or activity and induction of a hyperdopaminergic state in the striatum (Gouzoulis-Mayfrank et al., 1998; Vollenweider et al., 1998). Further support follows from the mechanism of action of atypical antipsychotics, of which most of them show antagonist properties at 5-$HT_{2A/C}$ receptors and congruently also restored changes induced by psilocybin (Horacek et al., 2006; Vollenweider et al., 1998). More evidence of the role of these receptors in psychosis is given by the fact that an increased amount of 5-HT_{2A} receptors was described in the cortex of young untreated subjects with schizophrenia postmortem (Gonzalez-Maeso et al., 2008; Muguruza et al., 2013).

The validity of serotonin models of psychosis, however, is hampered by the fact that antagonism at dopamine D_2 receptors but not 5-HT_{2A} antagonism is essential to treat psychotic symptoms in patients, whereas 5-HT_{2A} antagonism might be important for amelioration of negative symptoms (Horacek et al., 2006). Further on, unlike auditory hallucinations typical in schizophrenia, hallucinations after psilocybin intoxication are primarily visual (Gonzalez-Maeso and Sealfon, 2009; Hasler et al., 2004) and there is an absence of negative symptoms and cognitive deficits, otherwise typical for schizophrenia. However, psilocybin intoxication may be phenomenologically more similar to the early stages of the psychotic process in which the serotonin system may be crucial (Geyer and Vollenweider, 2008). The lack of negative symptoms can be attributed to the chronification of the disease related to the adaptation of the brain to information overload (Geyer and Vollenweider, 2008). In relation to this, however, theoretical modeling of psychosis using the chronic administration of psilocybin is not possible due to the rapid development of shortly lasting tolerance to the drug and to ethical issues. On the other hand, a chronic animal model with LSD has already been created (Marona-Lewicka et al., 2011).

11. Therapeutic uses and recent clinical studies

Most clinical studies with psilocybin were performed in the 1960s, often using synthetic Sandoz's Indocybin® (Passie et al., 2002). Hallucinogens were considered as key tools for understanding the etiopathogenesis of some mental illnesses and to have some therapeutic potential. In spite of often being considered as methodologically inaccurate from a current perspective, thousands of scientific papers published by 1965 described positive results in more than 40,000 patients who had taken psychedelics with minimal side effects and a high level of safety (Grinspoon and Bakalar, 1981; Masters and Houston, 1970).

By 2005, approximately 2000 subjects had undergone psycholytic and psychedelic psychotherapy[6] in clinical studies with psilocybin (Metzner, 2005). Use of psychedelic psychotherapy encountered varying degrees of success in neurotic disorders, alcohol dependence and psychotherapeutic adjunct to the dying (Grinspoon and Bakalar, 1981). There are also records of the successful application of psycholytic therapy with repeated administration of psilocybin in treatment resistant autistic and schizophrenic children (Fisher, 1970). For decades, due to law restrictions, the use of psychedelics including psilocybin in the treatment was considered a closed chapter, however the idea has been recently revived (Sessa, 2005; Vollenweider and Kometer, 2010).

In a recent pilot study psilocybin at low doses (0.2 mg/kg) acted as an anxiolytic and antidepressant in terminally ill cancer patients without clinically significant side effects (Grob et al., 2011). This study follows on from another three where effects on psychosocial distress/inner psychological well-being, anxiety and depression, attitudes to the disease and towards death, quality of life and spiritual/mystical states of consciousness, secondarily changes in the perception of pain and plasma markers of stress and immune system function are evaluated (Griffiths, 2007; Kumar, 2009; Ross, 2009).

Case reports and clinical trials have also reported improvement of obsessive-compulsive disorder (OCD) symptoms after psilocybin. In one patient the effect persisted for five months (Leonard and Rapoport, 1987; Moreno et al., 2006). In studies devoted to the treatment of alcohol dependence (Bogenschutz, 2012) and smoking cessation (Johnson and Cosimano, 2012) it is suggested that psilocybin deepens spirituality (Griffiths et al., 2006) and stimulates motivation to overcome the addiction. Further on, a potential future use of psilocybin in the treatment of anxiety depressive disorder is also emerging (Carhart-Harris et al., 2012b; Vollenweider and Kometer, 2010).

The last reported effect of psilocybin is in the treatment of cluster headaches: mushrooms containing psilocybin improved individual attacks but also stopped the cycle of otherwise intractable cluster headache attacks (Sempere et al., 2006; Sewell et al., 2006). A possible explanation is a reduction in blood flow to the hypothalamus induced by the psilocybin (Carhart-Harris et al., 2012a) or the activity of psilocybin at 5-$HT_{1B/D}$ receptors (Ray, 2010), similar to triptans (Cologno et al., 2012). Further research, however, will be necessary in the future in order to clarify the above.

12. Conclusion

In summary, psilocybin has a strong research and therapeutic potential. Due to the good knowledge of its pharmacodynamics and pharmacokinetics, beneficial safety profile and zero potential to cause addiction it is frequently used both in animal and human research. It brings a number of key findings regarding the functioning of the human brain, in particular the role of the serotonergic system in complex functions such as perception and emotions. It also serves as a useful tool for the study of the neurobiology of psychoses. Due to its considerable degree of translational validity of animal and human studies, a psilocybin model of psychosis plays a key role in the development of new treatments for psychotic disorders. Finally, the most recent human studies also suggest its potential therapeutic use in the treatment of several psychiatric and neurological disorders.

[6] In psycholytic therapy a low dose is given and analysis and interpretation are performed during the course of its effects, psychedelic therapy uses high doses of psilocybin and the processing of experiences and their interpretation takes place after the effects have worn off.

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Contributors

Author Filip Tylš designed the layout of the article and collected the relevant literature. He contributed to all parts of the text.

Author Tomáš Páleníček supervised the layout and wrote the abstract. He also greatly contributed to the pharmacokinetic and pharmacodynamic parts of the text.

Author Jiří Horáček supervised the whole article and contribute mainly to the discussion about imaging studies with psilocybin.

Conflict of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. We confirm that we have given due consideration to the protection of intellectual properly associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

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