

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.

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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	<i>Conocybe cyanopus</i>
				Copelandia	<i>Copelandia cyanescens</i>
			Cortinariaceae	Panaeolina	<i>Panaeolus africanus</i>
				Panaeolus	<i>Panaeolus subbalteus</i>
				Gymnopilus	<i>Gymnopilus Purpuratus</i>
				Galerina	
			Plutaceae	Inocybe	<i>Inocybe aeruginascens</i>
				Pluteus	<i>Pluteus salicinus</i>
			Strophariaceae	Psilocybe	<i>Psilocybe azurescens</i>
				(115 representatives)	<i>Psilocybe bohemica</i>
			Tricholomataceae		<i>Psilocybe cubensis</i>
					<i>Psilocybe cyanescens</i>
					<i>Psilocybe mexicana</i>
				Hypholoma	<i>Psilocybe semilanceata</i>
				Gerronema	<i>Psilocybe tampanensis</i>
				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
<i>Psilocybe azurescens</i>	1.78	0.38	Stamets and Gartz (1995)
<i>Psilocybe bohemica</i>	1.34/0.78/ 0.85	0.11/0.01/ 0.02	Gartz and Moller (1989) and Gartz (1993, 1994)
<i>Psilocybe semilanceata</i>	0.98/0.96	x/x	Gartz (1994, 1993)
<i>Psilocybe baeocystis</i>	0.85	0.59	Repke et al. (1977) and Beug and Bigwood (1982)
<i>Psilocybe cyanescens</i>	0.85/0.45/ 0.32	0.36/0.06/ 0.51	Repke et al. (1977), Stijve and Kuyper (1985), and Gartz (1993, 1994)
<i>Psilocybe tampanensis</i>	0.68	0.32	Gartz (1993)
<i>Psilocybe cubensis</i>	0.63	0.6	Gartz (1994) and Stijve and De Meijer (1993)
<i>Psilocybe mexicana</i>	0.3	0.05	Hofmann et al. (1959)
<i>Psilocybe hoogshagenii</i>	0.6	0.1	Heim and Hofmann (1958)
<i>Psilocybe stuntzii</i>	0.36	0.12	Repke et al. (1977) and Beug and Bigwood (1982)
<i>Psilocybe cyanofibrillosa</i>	0.21	0.04	Stamets et al. (1980)
<i>Psilocybe liniformans</i>	0.16	x	Stijve and Kuyper (1985)
<i>Gymnopilus Purpuratus</i>	0.34	0.29	Gartz (1994)
<i>Inocybe aeruginascens</i>	0.40	x	Gartz (1994)
<i>Copelandia cyanescens</i>	0.32	0.51	Barceloux (2012)
<i>Panaeolus subbalteus</i>	0.39	x	Gartz (1993)
<i>Conocbe cyanopus</i>	0.88	0.15	Gartz (1993)
<i>Pluteus salicinus</i>	1.09	x	Gartz (1993)

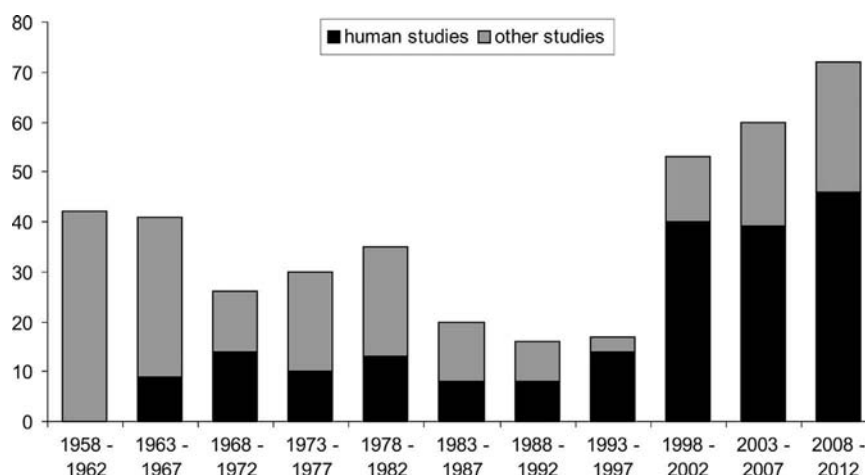


Figure 1 Number of publications dealing with psilocybin/psilocin (y axis) in five-year intervals from its synthesis to the present day (source PubMed dated 06/02/2013. Advanced searched terms were “psilocybin”[Title/Abstract] OR “psilocin”[Title/Abstract] AND Date “YYYY-YYYY”[Date - Publication]; for 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-dimethyltryptamine) 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 iminoquinon 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 glucuronic 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; Holzmans, 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 (Gallagher 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] ketanserin DOI	410, [3H]	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			57	3.5	Halberstadt and Geyer (2011)
											83.7				

^anpKi 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} > D₁ > 5HT_{1E} > 5HT_{1A} > 5HT_{5A} > 5HT₇ > 5HT₆ > D₃ > 5HT_{2C} > 5HT_{1B} > 5HT_{2A}. According to this data it also weakly binds to the receptors for Imidazoline₁, 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 D₂ receptors (Tyliš 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 Sealton, 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). Gonzalez-Maeso explained this selectivity with the “agonist trafficking of receptor signaling theory”, where hallucinogens activate the 5HT_{2A}/mGlu₂ receptor heterocomplex and different G proteins compared to non-hallucinogenic 5-HT_{2A} agonists (Gonzalez-Maeso et al., 2003). This hypothesis is supported in a study where the mice with the knockout gene for the mGlu₂ 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 (Pascie 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

¹PPI 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 thyrotropin. 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, $\uparrow$ - increase, $\downarrow$ - 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.	Hasler et al. (2004)
Psi 0.115 mg/kg p.o. xPla	$\uparrow$	$\uparrow$ n.s.	$\uparrow$ n.s.	$\uparrow$ n.s.	$\uparrow\uparrow\uparrow$	
Psi 0.215 mg/kg p.o. xPla	$\uparrow\uparrow\uparrow$	$\uparrow$ n.s.	$\uparrow\uparrow\uparrow$	$\uparrow$ n.s.	$\uparrow\uparrow\uparrow$	
Psi 0.315 mg/kg p.o. xPla	$\uparrow\uparrow\uparrow$	$\uparrow\uparrow$	$\uparrow\uparrow\uparrow$	$\uparrow\uparrow$	$\uparrow\uparrow\uparrow$	
Psi 5 mg/70 kg p.o. xPla	$\uparrow$	$\uparrow$	$\uparrow$	n/a	n/a	Griffiths et al. (2011)
Psi 10 mg/70 kg p.o. xPla	$\uparrow\uparrow$	$\uparrow\uparrow$	$\uparrow\uparrow$	n/a	n/a	
Psi 20 mg/70 kg p.o. xPla	$\uparrow\uparrow\uparrow$	$\uparrow\uparrow\uparrow$	$\uparrow\uparrow\uparrow$	n/a	n/a	
Psi 30 mg/70 kg p.o. xPla	$\uparrow\uparrow\uparrow$	$\uparrow\uparrow\uparrow$	$\uparrow\uparrow\uparrow$	n/a	n/a	
Psi 1.5 mg i.v. xPla	n.s. $\uparrow$	n.s. $\uparrow$	n.s. $\uparrow$	n.s. $\uparrow$	n.s. $\uparrow$	Carhart- Harris et al. (2011)
Psi 2 mg i.v. xPla	n.s. $\uparrow$	n.s. $\uparrow$	n.s. $\uparrow$	n.s. $\uparrow$	n.s. $\uparrow$	
Psi 0.25 mg/kg p.o. xPla	$\uparrow\uparrow\uparrow\uparrow\uparrow$	$\uparrow\uparrow$	$\uparrow\uparrow\uparrow\uparrow\uparrow$	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.	$\downarrow\downarrow$	$\downarrow\downarrow$	$\downarrow\downarrow\downarrow$	n/a	n/a	
Psi 0.25 mg/kg p.o. +Risp 1 mg p.o. xPsi 0.25 mg/kg p.o.	$\downarrow\downarrow$	$\downarrow\downarrow$	$\downarrow\downarrow$	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.	$\downarrow\downarrow$	$\uparrow$	n.s. $\downarrow$	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 D₂ antagonist). On the other hand, an antagonist of the D₂ 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 Experiment³ (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 LD₅₀ for rats and mice is 280–285 mg/kg, and for rabbits it is 12.5 mg/kg. Psilocin LD₅₀ is significantly lower for mice and rats 75 mg/kg and for rabbits 7 mg/kg (Usdin and Efron, 1972). The LD₅₀/ED₅₀ 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

²AMRS: 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).

³Experiment 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 LD₅₀ 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

⁴DSM 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 (Tyliš 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 Ayahuasca⁵ 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 ¹⁸fluorodeoxyglucose (¹⁸FDG) 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 ¹⁸FDG 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 ¹⁸FDG 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 ¹⁸FDG 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 ¹⁸FDG 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 Sealton, 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

⁵Ayahuasca, 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 monoamine oxidase 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 D₂ 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 Sealton, 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 psychotherapy⁶ 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.

⁶In 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 property 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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References

- Aboul-Enein, H.Y., 1974. Psilocybin: a pharmacological profile. *Am. J. Pharm. Sci. Support. Public Health* 146 (3), 91-95.
- Aghajanian, G.K., Hailgler, H.J., 1975. Hallucinogenic indoleamines: preferential action upon presynaptic serotonin receptors. *Psychopharmacol. Commun.* 1 (6), 619-629.
- Anastos, N., Barnett, N.W., Pfeffer, F.M., et al., 2006. Investigation into the temporal stability of aqueous standard solutions of psilocin and psilocybin using high performance liquid chromatography. *Sci. Justice* 46 (2), 91-96.
- Appel, J.B., Callahan, P.M., 1989. Involvement of 5-HT receptor subtypes in the discriminative stimulus properties of mescaline. *Eur. J. Pharmacol.* 159 (1), 41-46.
- Ballesteros, S., et al., 2006. Natural sources of drugs of abuse: magic mushrooms. In: Cole, S.M. (Ed.), *New Research on Street Drugs*. Nova Science Publishers, Inc., New York, pp. 167-186.
- Barceloux, B.G., 2012. Psilocybin and hallucinogenic mushrooms. In: Barceloux, B.G. (Ed.), *Medical Toxicology of Drugs Abuse: Synthesized Chemicals and Psychoactive Plants*. John Wiley and Sons, New Jersey.
- Berle, J., 1974. Isolation and Identification of Drugs in Pharmaceuticals, Body Fluids and Post-mortem Material. Pharmaceutical Society of Great Britain. Department of Pharmaceutical Sciences, London, UK.
- Beug, M.W., Bigwood, J., 1982. Psilocybin and psilocin levels in twenty species from seven genera of wild mushrooms in the Pacific Northwest, U.S.A. *J. Ethnopharmacol.* 5 (3), 271-285.
- Blair, J.B., Kurrasch-Orbaugh, D., Marona-Lewicka, D., et al., 2000. Effect of ring fluorination on the pharmacology of hallucinogenic tryptamines. *J. Med. Chem.* 43 (24), 4701-4710.
- Bogenschutz, M., 2012. Effects and Therapeutic Potential of Psilocybin in Alcohol Dependence (ClinicalTrials.gov Identifier NCT01534494). University of New Mexico, ClinicalTrials.gov [online] Available From URL: <http://www.clinicaltrials.gov/ct2/show/study/NCT01534494?term=Psilocybin&rank=2> (accessed 17.07.2013).
- Carhart-Harris, R.L., Erritzoe, D., Williams, T., et al., 2012a. Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. *Proc. Natl. Acad. Sci. USA* 109 (6), 2138-2143.
- Carhart-Harris, R.L., Leech, R., Williams, T.M., et al., 2012b. Implications for psychedelic-assisted psychotherapy: functional magnetic resonance imaging study with psilocybin. *Br. J. Psychiatry* 200 (3), 238-244.
- Carhart-Harris, R.L., Williams, T.M., Sessa, B., et al., 2011. The administration of psilocybin to healthy, hallucinogen-experienced volunteers in a mock-functional magnetic resonance imaging environment: a preliminary investigation of tolerability. *J. Psychopharmacol.* 25 (11), 1562-1567.
- Carod-Artal, F.J., 2011. Hallucinogenic drugs in pre-Columbian Mesoamerican cultures. *Neurologia*.
- Carter, O.L., Pettigrew, J.D., Burr, D.C., et al., 2004. Psilocybin impairs high-level but not low-level motion perception. *Neuroreport* 15 (12), 1947-1951.
- Cerletti, A., 1958. Etude pharmacologique de la psilocybine. In: Heim, R., Wasson, R.G. (Eds.), 1st ed. Editions du Museum National d'Histoire Naturelle 1958, 1965-66, Paris, pp. 268-271.
- Chauchard, A., 1967. The Hallucinogens. Academic, New York.
- Chen, J., Li, M., Yan, X., et al., 2011. Determining the pharmacokinetics of psilocin in rat plasma using ultra-performance liquid chromatography coupled with a photodiode array detector after orally administering an extract of *Gymnopilus spectabilis*. *J. Chromatogr. B Anal. Technol. Biomed. Life Sci.* 879 (25), 2669-2672.
- Cohen, S., 1960. Lysergic acid diethylamide: side effects and complications. *J. Nerv. Ment. Dis.* 130, 30-40.
- Collins, R.L., Ordy, J.M., Samorajski, T., 1966. Psilocin: effects on behaviour and brain serotonin in mice. *Nature* 209 (5025), 785-787.
- Cologno, D., Mazzeo, A., Lecce, B., et al., 2012. Triptans: over the migraine. *Neurol. Sci.* 33 (Suppl. 1), S193-S198.
- Creese, I., Burt, D.R., Synder, S.H., 1975. The dopamine receptor: differential binding of d-LSD and related agents to agonist and antagonist states. *Life Sci.* 17 (11), 1715-1719.
- Da Fonseca, J.S., Cardoso, C., Salgueiro, E., et al., 1965. Neurophysiological and psychological study of psilocybin-induced modification of visual information processing in man. *Neuropsychopharmacology* 4, 315-319.
- Davis, M., Walters, J.K., 1977. Psilocybin: biphasic dose-response effects on the acoustic startle reflex in the rat. *Pharmacol. Biochem. Behav.* 6 (4), 427-431.
- Day, H.E., Kryskow, E.M., Nyhuis, T.J., et al., 2008. Conditioned fear inhibits c-fos mRNA expression in the central extended amygdala. *Brain Res.* 1229, 137-146.
- Dittrich, A., 1998. The standardized psychometric assessment of altered states of consciousness (ASCs) in humans. *Pharmacopsychiatry* 31 (Suppl. 2), 80-84.
- Doblin, R., 1991. Pahnke's Good Friday Experiment: A Long-Term Follow-Up and Methodological Critique. New College of Florida, Florida.
- Fantegrossi, W.E., Murnane, K.S., Reissig, C.J., 2008. The behavioral pharmacology of hallucinogens. *Biochem. Pharmacol.* 75 (1), 17-33.
- Fantegrossi, W.E., Woods, J.H., Winger, G., 2004a. Transient reinforcing effects of phenylisopropylamine and indolealkylamine hallucinogens in rhesus monkeys. *Behav. Pharmacol.* 15 (2), 149-157.
- Fantegrossi, W.E., Woods, J.H., Winger, G., 2004b. Transient reinforcing effects of phenylisopropylamine and indolealkylamine hallucinogens in rhesus monkeys. *Behav. Pharmacol.* 15 (2), 149-157.

- Fink, M., 1969. EEG and human psychopharmacology. *Annu. Rev. Pharmacol.* 9, 241-258.
- Fisher, G., 1970. The psycholytic treatment of a childhood schizophrenic girl. *Int. J. Soc. Psychiatry* 16 (2), 112-130.
- Franz, M., Regele, H., Kirchmair, M., et al., 1996. Magic mushrooms: hope for a 'cheap high' resulting in end-stage renal failure. *Nephrol. Dial. Transpl.* 11 (11), 2324-2327.
- Friston, K.J., Frith, C.D., 1995. Schizophrenia: a disconnection syndrome? *Clin. Neurosci.* 3 (2), 89-97.
- Gallagher, T.K., Chen, K., Shih, J.C., 1993. Higher affinity of psilocin for human than rat 5-HT₂ receptor indicates binding site structure. *Medicinal Chem. Res.* 3, 52-66.
- Gartz, J., 1993. *Narrenschwämme*. Heuinkel, Geneva.
- Gartz, J., Moller, G.K., 1989. Analyses and cultivation of fruitbodies and mycelia of *Psilocybe bohemica*. *Biochem. Physiol. Pflanz.* 184, 337-341.
- Gartz, J., 1994. Extraction and analysis of indole derivatives from fungal biomass. *J. Basic Microbiol.* 34 (1), 17-22.
- Gerauld, A., Picart, D., 1996. Intoxication mortelle a la suite de la consommation volontaire et en groupe de champignons hallucinogenes (Fatal poisoning after a group of people voluntarily consumed hallucinogenic mushrooms). *Bull. Soc. Mycol. Fr.* 112 (1), 1-14.
- Geyer, M.A., Light, R.K., Rose, G.J., et al., 1979. A characteristic effect of hallucinogens on investigatory responding in rats. *Psychopharmacology (Berlin)* 65 (1), 35-40.
- Geyer, M.A., Vollenweider, F.X., 2008. Serotonin research: contributions to understanding psychoses. *Trends Pharmacol. Sci.* 29 (9), 445-453.
- Gonzalez-Maeso, J., Ang, R.L., Yuen, T., et al., 2008. Identification of a serotonin/glutamate receptor complex implicated in psychosis. *Nature* 452 (7183), 93-97.
- Gonzalez-Maeso, J., Sealfon, S.C., 2009. Psychedelics and schizophrenia. *Trends Neurosci.* 32 (4), 225-232.
- Gonzalez-Maeso, J., Weisstaub, N.V., Zhou, M., et al., 2007. Hallucinogens recruit specific cortical 5-HT_{2A} receptor-mediated signaling pathways to affect behavior. *Neuron* 53 (3), 439-452.
- Gonzalez-Maeso, J., Yuen, T., Ebersole, B.J., et al., 2003. Transcriptome fingerprints distinguish hallucinogenic and nonhallucinogenic 5-hydroxytryptamine 2A receptor agonist effects in mouse somatosensory cortex. *J. Neurosci.* 23 (26), 8836-8843.
- Gouzoulis-Mayfrank, E., Heekeren, K., Thelen, B., et al., 1998. Effects of the hallucinogen psilocybin on habituation and prepulse inhibition of the startle reflex in humans. *Behav. Pharmacol.* 9 (7), 561-566.
- Gouzoulis-Mayfrank, E., Hermle, L., Sass, H., 1994. Psychedelic experiences at the onset of productive episodes of endogenous psychoses. *Nervenarzt* 65 (3), 198-201.
- Gouzoulis-Mayfrank, E., Schreckenberger, M., Sabri, O., et al., 1999a. Neurometabolic effects of psilocybin, 3,4-methylenedioxethylamphetamine (MDE) and d-methamphetamine in healthy volunteers. A double-blind, placebo-controlled PET study with [¹⁸F]FDG. *Neuropsychopharmacology* 20 (6), 565-581.
- Gouzoulis-Mayfrank, E., Thelen, B., Habermeyer, E., et al., 1999b. Psychopathological, neuroendocrine and autonomic effects of 3,4-methylenedioxethylamphetamine (MDE), psilocybin and d-methamphetamine in healthy volunteers. Results of an experimental double-blind placebo-controlled study. *Psychopharmacology (Berlin)* 142 (1), 41-50.
- Gouzoulis-Mayfrank, E., Thelen, B., Maier, S., et al., 2002. Effects of the hallucinogen psilocybin on covert orienting of visual attention in humans. *Neuropsychobiology* 45 (4), 205-212.
- Grieshaber, A.F., Moore, K.A., Levine, B., 2001. The detection of psilocin in human urine. *J. Forensic Sci.* 46 (3), 627-630.
- Griffiths, R., Richards, W., Johnson, M., et al., 2008. Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. *J. Psychopharmacol.* 22 (6), 621-632.
- Griffiths, R.R., 2007. Psychopharmacology of Psilocybin in Cancer Patients (ClinicalTrials.gov Identifier NCT00465595). Sidney Kimmel Comprehensive Cancer Center, ClinicalTrials.gov (online) Available From URL: <http://www.clinicaltrials.gov/ct2/show/study/NCT00465595?term=Psilocybin&rank=5> (accessed 17.07.2013).
- Griffiths, R.R., Johnson, M.W., Richards, W.A., et al., 2011. Psilocybin occasioned mystical-type experiences: immediate and persisting dose-related effects. *Psychopharmacology (Berlin)* 218 (4), 649-665.
- Griffiths, R.R., Richards, W.A., McCann, U., et al., 2006. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacology (Berlin)* 187 (3), 268-283.
- Grinspoon, L., Bakalar, J.B., 1981. The psychedelic drug therapies. *Curr. Psychiatr. Ther.* 20, 275-283.
- Grob, C.S., Danforth, A.L., Chopra, G.S., et al., 2011. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. *Arch. Gen. Psychiatry* 68 (1), 71-78.
- Guzman, G., Allen, J.W., Gartz, J., 1998. A worldwide geographical distribution of the neurotropic fungi, an analysis and discussion. *Ann. Mus. Civ. Rovereto* 14, 189-280.
- Halberstadt, A.L., Geyer, M.A., 2011. Multiple receptors contribute to the behavioral effects of indoleamine hallucinogens. *Neuropharmacology* 61 (3), 364-381.
- Halberstadt, A.L., Koedood, L., Powell, S.B., et al., 2011. Differential contributions of serotonin receptors to the behavioral effects of indoleamine hallucinogens in mice. *J. Psychopharmacol.* 25 (11), 1548-1561.
- Halpern, J.H., Pope Jr., H.G., 2003. Hallucinogen persisting perception disorder: what do we know after 50 years? *Drug Alcohol Depend.* 69 (2), 109-119.
- Hanks, J.B., Gonzalez-Maeso, J., 2013. Animal models of serotonergic psychedelics. *ACS Chem. Neurosci.* 4 (1), 33-42.
- Hasler, F., Bourquin, D., Brenneisen, R., et al., 1997. Determination of psilocin and 4-hydroxyindole-3-acetic acid in plasma by HPLC-ECD and pharmacokinetic profiles of oral and intravenous psilocybin in man. *Pharm. Acta Helv.* 72 (3), 175-184.
- Hasler, F., Bourquin, D., Brenneisen, R., et al., 2002. Renal excretion profiles of psilocin following oral administration of psilocybin: a controlled study in man. *J. Pharm. Biomed. Anal.* 30 (2), 331-339.
- Hasler, F., Grimberg, U., Benz, M.A., et al., 2004. Acute psychological and physiological effects of psilocybin in healthy humans: a double-blind, placebo-controlled dose-effect study. *Psychopharmacology (Berlin)* 172 (2), 145-156.
- Heim, R., Hofmann, A., 1958. La psilocybine et la psilocine chez les psilocybe et strophaires hallucinogenes. *Les champignons hallucinog. du Mexiq.* 6, 258-267.
- Hoffmeister, F., 1975. Negative reinforcing properties of some psychotropic drugs in drug-naïve rhesus monkeys. *J. Pharmacol. Exp. Ther.* 192 (2), 468-477.
- Hofmann, A., 1968. Psychomimetic agents. In: Burger, A. (Ed.), *Drugs Affecting the Central Nervous System*, Medicinal Research Series 2. Dekker, New York, pp. 169-235.
- Hofmann, A., Heim, R., Brack, A., et al., 1959. Psilocybin und Psilocin, zwei psychotrope Wirkstoffe aus mexikanischen Rauschpilzen. *Helv. Chim. Acta* 42 (5), 1557-1572.
- Hofmann, A., 2005. LSD: My Problem Child. Multidisciplinary Association for Psychedelic Studies (MAPS), Sarasota, FL.
- Hofmann, A., Frey, A., Ott, H., et al., 1958. Elucidation of the structure and the synthesis of psilocybin. *Experientia* 14 (11), 397-399.
- Hollister, L.E., 1961. Clinical, biochemical and psychological effects of psilocybin. *Arch. Int. Pharmacodyn. Ther.* 130, 42-52.

- Holzmann, P.P., 1995. Bestimmung von Psilocybin-metaboliten im Humanplasma und -urin. University of Tübingen, Tübingen, Germany.
- Hopf, A., Eckert, H., 1974. Distribution patterns of 14-C-psilocin in the brains of various animals. *Act. Nerv. Super. (Praha)* 16 (1), 64-66.
- Horacek, J., Bubenikova-Valesova, V., Kopecek, M., et al., 2006. Mechanism of action of atypical antipsychotic drugs and the neurobiology of schizophrenia. *CNS Drugs* 20 (5), 389-409.
- Horibe, M., 1974. The effects of psilocybin on EEG and behaviour in monkeys. *Act. Nerv. Super. (Praha)* 16 (1), 40-42.
- Horita, A., 1963. Some biochemical studies on psilocybin and psilocin. *J. Neuropsychiatr.* 4, 270-273.
- Horita, A., Weber, L.J., 1961a. Dephosphorylation of psilocybin to psilocin by alkaline phosphatase. *Proc. Soc. Exp. Biol. Med.* 106, 32-34.
- Horita, A., Weber, L.J., 1961b. The enzymic dephosphorylation and oxidation of psilocybin and psilocin by mammalian tissue homogenates. *Biochem. Pharmacol.* 7, 47-54.
- Horita, A., Weber, L.J., 1962. Dephosphorylation of psilocybin in the intact mouse. *Toxicol. Appl. Pharmacol.* 4, 730-737.
- Isbell, H., 1959. Comparison of the reactions induced by psilocybin and LSD-25 in man. *Psychopharmacologia* 1, 29-38.
- Janke, W., Debus, G., 1978. Die Eigenschaftswörterliste (EWL-K) - Ein Verfahren zur Erfassung der Befindlichkeit, 1st ed. Hogrefe, Göttingen.
- Jerome, L., 2007. Psilocybin: Investigators Brochure. (<http://www.maps.org>).
- Johnson, M., Richards, W., Griffiths, R., 2008. Human hallucinogen research: guidelines for safety. *J. Psychopharmacol.* 22 (6), 603-620.
- Johnson, M.W., Cosimano, M.P. 2012. Psilocybin in Smoking Cessation: A Pilot Study (ClinicalTrials.gov Identifier NCT01943994). Beckley Foundation. Available From URL: (<http://www.beckleyfoundation.org/2010/11/psilocybin-in-smoking-cessation-a-pilot-study/>) (accessed 17.07.2013).
- Kalberer, F., Kreis, W., Rutschmann, J., 1962. The fate of psilocin in the rat. *Biochem. Pharmacol.* 11, 261-269.
- Kamata, T., Nishikawa, M., Katagi, M., et al., 2006. Direct detection of serum psilocin glucuronide by LC/MS and LC/MS/MS: time-courses of total and free (unconjugated) psilocin concentrations in serum specimens of a "magic mushroom" user. *Forensic Toxicol.* 24, 36-40.
- King, C., 2012. Entheogens, the conscious brain and existential reality. *J. Conscious. Explor. Res.* 3, 579-757.
- Klock, J.C., Boerner, U., Becker, C.E., 1975. Coma, hyperthermia, and bleeding associated with massive LSD overdose, a report of eight cases. *Clin. Toxicol.* 8 (2), 191-203.
- Kometer, M., Schmidt, A., Jancke, L., et al., 2013. Activation of serotonin 2A receptors underlies the psilocybin-induced effects on alpha oscillations, N170 visual-evoked potentials, and visual hallucinations. *J. Neurosci.* 33 (25), 10544-10551.
- Kostowski, W., Rewerski, W., Piechocki, T., 1972. II. The effects of some hallucinogens on aggressiveness of mice and rats. *Pharmacology* 7 (4), 259-263.
- Kovacic, P., 2009. Unifying electron transfer mechanism for psilocybin and psilocin. *Med. Hypotheses* 73 (4), 626.
- Kumar, S. 2009. Psilocybin-assisted Psychotherapy in the Management of Anxiety Associated With Stage IV Melanoma (ClinicalTrials.gov Identifier NCT00979693). Multidisciplinary Association for Psychedelic Studies, ClinicalTrials.gov (online) Available From URL: (<http://www.clinicaltrials.gov/ct2/show/study/NCT00979693?term=Psilocybin&rank=1>) (accessed 17.07.2013).
- Laussmann, T., Meier-Giebing, S., 2010. Forensic analysis of hallucinogenic mushrooms and khat (*Catha edulis* Forsk) using cation-exchange liquid chromatography. *Forensic Sci. Int.* 195 (1-3), 160-164.
- Leary, T., Litwin, G.H., Metzner, R., 1963. Reactions to psilocybin administered in a supportive environment. *J. Nerv. Ment. Dis.* 137, 561-573.
- Leonard, H.L., Rapoport, J.L., 1987. Relief of obsessive-compulsive symptoms by LSD and psilocin. *Am. J. Psychiatry* 144 (9), 1239-1240.
- Lindenblatt, H., Kramer, E., Holzmann-Erens, P., et al., 1998. Quantitation of psilocin in human plasma by high-performance liquid chromatography and electrochemical detection: comparison of liquid-liquid extraction with automated on-line solid-phase extraction. *J. Chromatogr. B Biomed. Sci. Appl.* 709 (2), 255-263.
- MacLean, K.A., Johnson, M.W., Griffiths, R.R., 2011. Mystical experiences occasioned by the hallucinogen psilocybin lead to increases in the personality domain of openness. *J. Psychopharmacol.* 25 (11), 1453-1461.
- Malleson, N., 1971. Acute adverse reactions to LSD in clinical and experimental use in the United Kingdom. *Br. J. Psychiatry* 118 (543), 229-230.
- Manevski, N., Kurkela, M., Hoglund, C., et al., 2010. Glucuronidation of psilocin and 4-hydroxyindole by the human UDP-glucuronosyltransferases. *Drug Metab. Dispos.* 38 (3), 386-395.
- Marona-Lewicka, D., Nichols, C.D., Nichols, D.E., 2011. An animal model of schizophrenia based on chronic LSD administration: old idea, new results. *Neuropharmacology* 61 (3), 503-512.
- Masters, R.E.L., Houston, J., 1970. Therapeutic applications of LSD and related drugs. In: Aaronson, B., Osmond, H. (Eds.), *The Uses and Implications of Hallucinogenic Drugs*. Hogarth Press, London.
- McKenna, D.J., Repke, D.B., Lo, L., et al., 1990. Differential interactions of indolealkylamines with 5-hydroxytryptamine receptor subtypes. *Neuropharmacology* 29 (3), 193-198.
- Meldrum, B.S., Naquet, R., 1971. Effects of psilocybin, dimethyltryptamine, mescaline and various lysergic acid derivatives on the EEG and on photically induced epilepsy in the baboon (*Papio papio*). *Electroencephalogr. Clin. Neurophysiol.* 31 (6), 563-572.
- Metzner, R., 2005. *Sacred Mushroom of Visions: Teonanácatl: A Sourcebook on the Psilocybin Mushroom*. Park. St. Press Rochester, Vermont.
- Moreno, F.A., Wiegand, C.B., Taitano, E.K., et al., 2006. Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. *J. Clin. Psychiatry* 67 (11), 1735-1740.
- Moreno, J.L., Holloway, T., Albizu, L., et al., 2011. Metabotropic glutamate mGlu2 receptor is necessary for the pharmacological and behavioral effects induced by hallucinogenic 5-HT2A receptor agonists. *Neurosci. Lett.* 493 (3), 76-79.
- Muguruza, C., Moreno, J.L., Umali, A., et al., 2013. Dysregulated 5-HT(2)A receptor binding in postmortem frontal cortex of schizophrenic subjects. *Eur. Neuropsychopharmacol.* 23 (8), 852-864.
- Muthukumaraswamy, S.D., Carhart-Harris, R.L., Moran, R.J., et al., 2013. Broadband cortical desynchronization underlies the human psychedelic state. *J. Neurosci.* 33 (38), 15171-15183.
- Nichols, D.E., 2004. Hallucinogens. *Pharmacol. Ther.* 101 (2), 131-181.
- Pahnke, W.M., 1963. *Drugs & Mysticism: An Analysis of the Relationship between Psychedelic Drugs and Mystical Consciousness*. Harvard University, Cambridge Massachusetts.
- Palenicek, T., Fújaková, M., Brunovsky, M., et al., 2013. Behavioral, neurochemical and pharmacological profiles of the psychedelic drug 4-bromo-2,5-dimethoxyphenethylamine (2C-B) in rats. *Psychopharmacology (Berlin)* 225 (1), 75-93.
- Palenicek, T., Valesova-Bubenikova, V., Horacek, J., 2011. Sex differences in the behavioural profile of ecstasy (MDMA), LSD and psilocin in rats. In: Abstract CD-ROM of the 10th World Congress of Biological Psychiatry. 29 May-2 June 2011, Prague, Czech Republic.

- Palenicek, T., Bubenikova, V., Votava, M., et al., 2005. Účinky MDMA, LSD a psilocinu na lokomoci potkana. *Adiktologie* 5, 121-130.
- Palenicek, T., Bubenikova-Valesova, V., Horacek, J., et al., 2006. Účinky selektivního antagonisty serotoninového 5-HT_{2c} receptoru SB242084 na lokomoci potkana v animálních modelech psychóz. *Psychiatrie* 10 (Suppl. 3).
- Palenicek, T., Horacek, J., 2008. Neurobiologie halucinogenů a disociativních anestetik. *Psychiatrie* 12 (Suppl. 3), 33-45.
- Parashos, A.J., 1976. The psilocybin-induced "state of drunkenness" in normal volunteers and schizophrenics. *Behav. Neuropsychiatry* 8 (1-12), 83-86.
- Passie, T., Seifert, J., Schneider, U., et al., 2002. The pharmacology of psilocybin. *Addict. Biol.* 7 (4), 357-364.
- Peden, N.R., Pringle, S.D., 1982. Hallucinogenic fungi. *Lancet* 1 (8268), 396-397.
- Perala, J., Suvisaari, J., Saarni, S.I., et al., 2007. Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Arch. Gen. Psychiatry* 64 (1), 19-28.
- Pfund, Z., Chugani, D.C., Juhasz, C., et al., 2000. Evidence for coupling between glucose metabolism and glutamate cycling using FDG PET and 1H magnetic resonance spectroscopy in patients with epilepsy. *J. Cereb. Blood Flow Metab.* 20 (5), 871-878.
- Ray, T.S., 2010. Psychedelics and the human receptorome. *PLoS One* 5 (2), e9019.
- Repke, D.B., Leslie, D.T., Guzman, G., 1977. Baecystin in psilocybe, conocybe and panaeolus. *Lloydia* 40 (6), 566-578.
- Riba, J., Anderer, P., Jane, F., et al., 2004. Effects of the South American psychoactive beverage ayahuasca on regional brain electrical activity in humans: a functional neuroimaging study using low-resolution electromagnetic tomography. *Neuropsychobiology* 50 (1), 89-101.
- Ross, S., 2009. Psilocybin Cancer Anxiety Study (ClinicalTrials.gov Identifier NCT00957359). New York University, ClinicalTrials.gov (online) Available From URL: <http://www.clinicaltrials.gov/ct2/show/NCT00957359?term=Psilocybin&rank=4> (accessed 17.07.2013).
- Roth, B.L., Berry, S.A., Kroeze, W.K., et al., 1998. Serotonin 5-HT_{2A} receptors: molecular biology and mechanisms of regulation. *Crit. Rev. Neurobiol.* 12 (4), 319-338.
- Roubicek, J., Drvota, S., 1960. Psilocybin, nové fantastikum. *Československá Psychiatrie* 56, 44-55.
- Ryngerson, R.R., Wilson Jr., M.R., Bickford, R.G., 1968. Psilocybin-induced changes in psychologic function, electroencephalogram, and light-evoked potentials in human subjects. *Mayo Clin. Proc.* 43 (3), 191-204.
- Schmidt, A., Kometer, M., Bachmann, R., et al., 2012. The NMDA antagonist ketamine and the 5-HT agonist psilocybin produce dissociable effects on structural encoding of emotional face expressions. *Psychopharmacology (Berlin)* 225 (1), 227-239.
- Sempere, A.P., Berenguer-Ruiz, L., Almazan, F., 2006. Chronic cluster headache: response to psilocybin. *Rev. Neurol.* 43 (9), 571-572.
- Sessa, B., 2005. Can psychedelics have a role in psychiatry once again? *Br. J. Psychiatry* 186, 457-458.
- Sewell, R.A., Halpern, J.H., Pope Jr., H.G., 2006. Response of cluster headache to psilocybin and LSD. *Neurology* 66 (12), 1920-1922.
- Stamets, P., Beug, M., Bigwood, J., et al., 1980. A new species and a new variety of psilocybe from North America. *Mycotaxon* 11, 476-484.
- Stamets, P., Gartz, J., 1995. A new caeruleuscent Psilocybe from the Pacific Coast of Northwestern North America. *Integration* 6, 21-27.
- Sticht, G., Kaferstein, H., 2000. Detection of psilocin in body fluids. *Forensic Sci. Int.* 113 (1-3), 403-407.
- Stijve, T., De Meijer, A.A.R., 1993. Macromycetes from the state of Parana, Brazil. 4. The psychoactive species. *Arq. Biol. Technol.* 36 (2), 313-329.
- Stijve, T., Kuyper, T.W., 1985. Occurrence of psilocybin in various higher fungi from several European countries. *Planta Med.* 51 (5), 385-387.
- Strassman, R.J., 1984. Adverse reactions to psychedelic drugs. A review of the literature. *J. Nerv. Ment. Dis.* 172 (10), 577-595.
- Strassman, R.J., 1996. Human psychopharmacology of N,N-dimethyltryptamine. *Behav. Brain Res.* 73 (1-2), 121-124.
- Strassman, R.J., Qualls, C.R., Uhlenhuth, E.H., et al., 1994. Dose-response study of N,N-dimethyltryptamine in humans. II. Subjective effects and preliminary results of a new rating scale. *Arch. Gen. Psychiatry* 51 (2), 98-108.
- Studerus, E., Gamma, A., Kometer, M., et al., 2012. Prediction of psilocybin response in healthy volunteers. *PLoS One* 7 (2), e30800.
- Studerus, E., Kometer, M., Hasler, F., et al., 2011. Acute, subacute and long-term subjective effects of psilocybin in healthy humans: a pooled analysis of experimental studies. *J. Psychopharmacol.* 25 (11), 1434-1452.
- Sugrue, M.F., 1969. A study of the role of noradrenaline in behavioral changes produced in the rat by psychotomimetic drugs. *Br. J. Pharmacol.* 35 (2), 243-252.
- Troxler, F., Seeman, F., Hofmann, A., 1959. Abwandlungsprodukte von Psilocybin und Psilocin. *Helv. Chim. Acta* 42 (6), 2073-2103.
- Tyts, F., Palenicek, T., Fujakova, M., et al., 2012a. Selective antagonism of 5HT_{2A} receptors treated psilocin-induced disconnection in the rat brain. In: Proceedings of 17th Biennial Conference, Abstract Book. IPEG, New York, p. 83.
- Tyts, F., Palenicek, T., Fujakova, M., et al., 2012b. A comparison of electroencephalographic activity in serotonergic and glutamatergic models of psychosis. Abstract Book from 28th CINP Congress. 3-7 June 2012, Stockholm, Sweden, p. 211.
- Tyts, F., Palenicek, T., Fujakova, M., et al., 2013. The impact of serotonin receptor antagonism on psilocin-induced disconnection in the rat brain. Abstract CD-ROM of the 11th World Congress of Biological Psychiatry. 23-27 June 2013, Kyoto, Japan.
- Umbricht, D., Vollenweider, F.X., Schmid, L., et al., 2003. Effects of the 5-HT_{2A} agonist psilocybin on mismatch negativity generation and AX-continuous performance task: implications for the neuropharmacology of cognitive deficits in schizophrenia. *Neuropsychopharmacology* 28 (1), 170-181.
- Usdin, E., Efron, D., 1972. Psychotropic Drugs and Related Compounds, 2nd ed. National Institute of Mental Health, Washington.
- Uyeno, E.T., 1967. Effects of mescaline and psilocybin on dominance behavior of the rat. *Arch. Int. Pharmacodyn. Ther.* 166 (1), 60-64.
- Uyeno, E.T., 1971. Relative potency of amphetamine derivatives and N,N-dimethyltryptamines. *Psychopharmacologia* 19 (4), 381-387.
- Uyeno, E.T., 1972. In: Miller, L. (Ed.), Effects of Psychotropic Drugs on The Competitive Behavior of The Rat. Israel Events Ltd., Jerusalem, pp. 84.
- Uyeno, E.T., 1978. Effects of psychodysleptics on aggressive behavior of animals. *Mod. Probl. Pharmacopsychiatry* 13, 103-113.
- van Amsterdam, J., Opperhuizen, A., van den, B.W., 2011. Harm potential of magic mushroom use: a review. *Regul. Toxicol. Pharmacol.* 59 (3), 423-429.
- van Went, G.F., 1978. Mutagenicity testing of 3 hallucinogens: LSD, psilocybin and delta 9-THC, using the micronucleus test. *Experientia* 34 (3), 324-325.
- Vollenweider, F.X., 2001. Brain mechanisms of hallucinogens and entactogens. *Dialogues Clin. Neurosci.* 3 (4), 265-279.
- Vollenweider, F.X., 2013. Neuroscience of Psychedelics - Presentation at Psychedelic Science 2013. Oakland, CA, USA.

- Vollenweider, F.X., Csomor, P.A., Knappe, B., et al., 2007. The effects of the preferential 5-HT_{2A} agonist psilocybin on prepulse inhibition of startle in healthy human volunteers depend on interstimulus interval. *Neuropsychopharmacology* 32 (9), 1876-1887.
- Vollenweider, F.X., Geyer, M.A., 2001. A systems model of altered consciousness: integrating natural and drug-induced psychoses. *Brain Res. Bull.* 56 (5), 495-507.
- Vollenweider, F.X., Kometer, M., 2010. The neurobiology of psychedelics: implications for the treatment of mood disorders. *Nat. Rev. Neurosci.* 11 (9), 642-651.
- Vollenweider, F.X., Leenders, K.L., Scharfetter, C., et al., 1997. Positron emission tomography and fluorodeoxyglucose studies of metabolic hyperfrontality and psychopathology in the psilocybin model of psychosis. *Neuropsychopharmacology* 16 (5), 357-372.
- Vollenweider, F.X., Vollenweider-Scherpenhuyzen, M.F., Babler, A., et al., 1998. Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. *Neuroreport* 9 (17), 3897-3902.
- Vollenweider, F.X., Vontobel, P., Hell, D., et al., 1999. 5-HT modulation of dopamine release in basal ganglia in psilocybin-induced psychosis in man - a PET study with [¹¹C]raclopride. *Neuropsychopharmacology* 20 (5), 424-433.
- Winter, J.C., Rice, K.C., Amorosi, D.J., et al., 2007. Psilocybin-induced stimulus control in the rat. *Pharmacol. Biochem. Behav.* 87 (4), 472-480.
- Wittmann, M., Carter, O., Hasler, F., et al., 2007. Effects of psilocybin on time perception and temporal control of behaviour in humans. *J. Psychopharmacol.* 21 (1), 50-64.
- Wolbach Jr., A.B., Miner, E.J., Isbell, H., 1962. Comparison of psilocin with psilocybin, mescaline and LSD-25. *Psychopharmacologia* 3, 219-223.