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Psilocybin for Treating Psychiatric Disorders: Is it a Psychonaut Legend or a Promising Therapeutic Perspective?

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Abstract

Psychedelics extracted by plants have been used in religious, spiritual and mystic practices for millennia. In 1957, Dr. Hofmann have identified and synthesized the prodrug psilocybin, a substance present in more than 200 species of psychedelic mushrooms. Although the limitations related to the scientific design of many studies, clinical observations performed during the 1950s and the 1960s have shown a potential therapeutic effect of psilocybin in patients affected by depressive symptoms, anxiety, and conversion disorder. Psilocybin was classed as a schedule I substance in 1970, but the fascination for psychedelics remained almost unchanged over time promoting a new scientific interest starting from the 1990s. Recent studies provided further evidences supporting the suggestive hypothesis of a therapeutic use of psilocybin for treating various psychiatric disorders including: pathological anxiety, mood depressive disorder and addiction.

Keywords: psilocybin**;** psilocin; psychedelics; magic mushrooms;

1. Introduction

Psychedelics extracted by plants have been used in religious, spiritual and mystic practices for millennia [1]. Human use of buttons of peyote cactus and red beans containing mescaline is documented since 5700 years in the north eastern region of Mexico [2]. Analysis of archaeological

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artifacts confirms that the use of psilocybin containing mushrooms is ubiquitous since prehistory [3]. The first report of psychedelic mushrooms usage in western medicine was made by Prentiss and Morgan in 1895. Authors described the ceremonial use of buttons of the peyote cactus by indigenous people in Central America [4]. Mescaline, an active alkaloid contained in the peyote, was isolated by Arthur Heffter in 1897 and synthesised by Ernest Spaff in 1919. Subsequently, it was made available as research chemical by Merck [5]. In 1938, at the Sandoz laboratories in Switzerland, Albert Hofmann synthesized the lysergic acid diethylamide, best known as LSD. This substance was synthesized during a systematic study investigation of ergot alkaloids in which the LSD was the 25th compound produced. In 1947, LSD was marketed under the trade name of "Delysid" and it was made freely available to researchers interested in investigating its pharmacological properties [6]. In 1957, Dr. Hofmann have also identified and synthesized the prodrug psilocybin, a substance present in more than 200 species of psychedelic mushrooms. In 1958, psilocybin was made available by Sandoz under the brand name of “Indocybin”. During the 1950s and 1960s psilocybin, LSD and mescaline were largely used for treating non-psychotic disorders. In more than one thousand scientific reports, authors described results obtained from the treatment of about forty thousand patients [7]. Although the limitations related to the scientific design of many studies, clinical observations performed during the pre-prohibition era have shown a potential therapeutic effect of psilocybin in patients affected by depressive symptoms, anxiety, and conversion disorder [8-12]. Contrariwise, there is very limited information about the therapeutic effects of psilocybin in psychotic patients [13,14]. On the whole, patients treated with psycholytic or psychedelic doses of psilocybin reported no significant side effects [15]. In 1960s, psychedelics became recreational drugs largely spread among the population as well as a symbol of a counterculture. Despite the majority of human studies reported a low toxicity, some severe psychiatric reactions and occasional tragic events signaled within the scientific literature produced a socio-politic alerting in many countries [16,17]. Consequently, medical research reduced its interest in studying the potential therapeutic activity of psychedelics considering these substances as

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unethical for the medical use [17]. Psilocybin was classed as a schedule I substance in 1970, but the fascination for psychedelics remained almost unchanged over time promoting a new scientific interest starting from the 1990s [17,18]. Recent studies provided further evidences supporting the suggestive hypothesis of a therapeutic use of psilocybin for treating various psychiatric disorders including: pathological anxiety, mood depressive disorder and addiction [17,18]. In our review, we summarized the clinical, pharmacological and toxicological information currently available about the psilocybin focusing our attntion in evaluationg the therapeutic effects in humans.

2. Chemistry

Psilocybin (Figure 1) and psilocin (Figure 2) are tryptophan indole-based compounds present in mushrooms of the genus *Psilocybe, Panaeolina, Pluteus, Panaeolus, Stropharia, Conocybe and Gymnopilus.* These mushrooms are known and largely distributed worldwide [19-21]. Their indole ring structure derives from a fusion between a pyrrole ring with a benzene ring joined to an amino group by a two carbon side chain [22]. Psilocybin, IUPAC name [3-[2-(dimethylamino)ethyl]-1H-indol-4-yl] dihydrogen phosphate, is a tertiary amino compound belonging to the tryptamine alkaloid group. This substance, molecular weight 284.25 g/mol, has a phosphoryloxy substituent attached at the position 4 of the N,N-dimethyltryptamine structure. Psilocin, IUPAC name 3-[2-(dimethylamino)ethyl]-1H-indol-4-ol, is the dephosphorylated psilocybin derivative representing the active compound of psiclocybin. Psilocin, molecular weight 204.27 g/mol, is a tryptamine alkaloid in which an additional hydroxy group is attached to the N,N-dimethyltryptamine skeleton. Psilocybin, molecular weight 284.25 g/mol, has a water solubility of 2.7 g/L and a melting point of 224 °C. Psilocin, molecular weight 204.27 g/mol, has a water solubility of 4.08 g/L and a melting point of 174.5 °C [23]. Psilocybin is a zwitterion alkaloid with a highly polar phosphate group, consequently, it is more soluble in water than psilocin [24]. Contrariwise, psilocin is more lipid soluble than psilocybin. Both substances are soluble in methanol, ethanol but almost insoluble in ether, chloroform and petroleum. In pure form, psilocybin and psilocin are white crystalline

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powders unstable in light and many stable under inert atmosphere, in the dark and at low temperature [23, 24].

3. Pharmacokinetics

Psilocybin and psilocin are generally administered orally or smoked. Mushrooms contain psilocybin and psilocin at the concentration of up to 2% and 0.5%, respectively [25]. These concentrations may significantly vary in relation to the species, origin, size, age, growing and drying conditions [26]. Studies performed in animal model have shown that after oral administration, 50% of the 14C-labelled psilocin was absorbed and almost evenly distributed throughout the body, including the brain [27]. In pregnant rats , after intravenous administration, 14C-psilocin crossed the placental barrier reaching fetal tissues concentrations lower than maternal tissues, but with slower elimination half life [28]. Following oral administration, psilocybin is dephosphorylated in psilocin within the stomach by acid environment or within the intestine, kidney and blood by alkaline phosphatase and nonspecific esterases [29, 30]. If compared to psilocybin, psilocin is more easily absorbed from the rat jejunum and colon [31]. Furthermore, many other rodent tissues have showed to be able to convert psilocybin in psilocin before the transit into the systemic circulation [31]. Psilocin crosses the blood-brain barrier entering in the central nervous system where it exerts its psychotropic effects [32]. Considering its serotonin like structure, psilocin follows the same metabolic pattways [33]. If administered within an empty stomach, psilocybin is rapidly converted into psilocin and the latter is detectable in the plasma within 20-40 minutes. Maximum psilocin plasma concentration is reached within 80-100 minutes [29]. About 4% of psilicin is metabolized by demethylation and oxidative deamination catalyzed by liver monoamine oxidase or aldehyde dehydrogenase to 4-hydroxytryptophole, 4-hydroxyindole-3-yl-acetaldehyde, and 4-hydroxyindole-3-yl-acetic-acid [34, 35]. After oral administration, plasma elimination half-life extimeted for psilocybin and psilocin is 160 and 50 minutes, respectively [29, 36]. In vivo studies performed in rat have shown that, after oral administration, psilocin is excreted in urine for 65% and in bile and feces for approximately 15-20% within 8 hours [34]. Studies performed in rat have also demonstrated that about 25% of the

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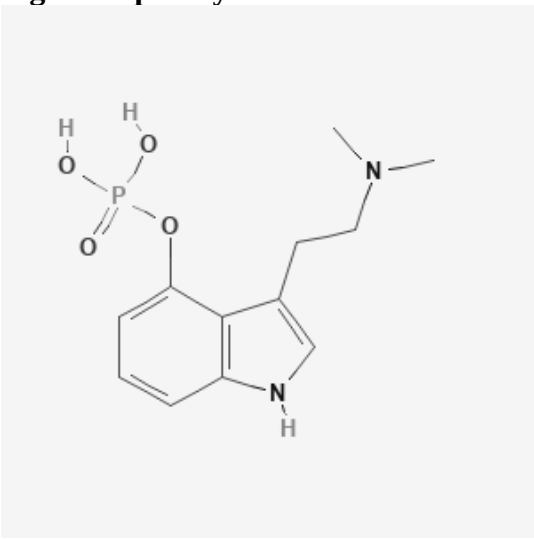
whole psilocybin dose was excreated unaltered while about 10-20% remained in the body with its metabolites detected in urine for 6-7 days [34]. In a study performed in male volunteers, authors have demonstrated that around 3.5% of the oral psilocybin dose was excreted in urine as free psilocybin within 24 hours [29, 39]. As emerged in both pharmacokinetic and forensic studies, approximately 80% of psilocin is eliminated as psilocin-O-glucuronide confirming that the glucuronidation represents an important detoxification step [37, 38]. In the small intestine, glucuronidation is mediated by glucuronosyltransferase UGT1A10 [39]. Instead, when psilocin is administered intravenously, glucuronidation is mediated by glucuronosyltransferase UGT1A9 [39]. Conversely, N-glucuronidation is not observed in cell studies [39]. Finally, the third metabolic pathway might be the oxidation of psilocin by hydroxyindol oxidases to produce compounds with an o-quinone or iminochinone structure [40].

Figure 1: psilocybin



PubChem: https://pubchem.ncbi.nlm.nih.gov/compound/10624#section=2D-Structure

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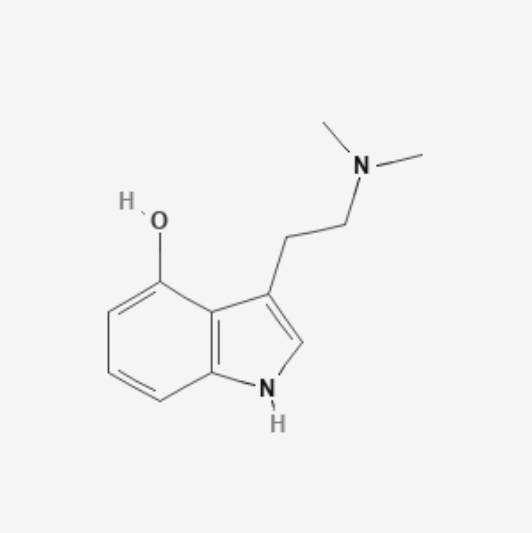
Figure 2: psilocin



PubChem: https://pubchem.ncbi.nlm.nih.gov/compound/4980#section=2D-Structure

4. Pharmacodynamic

Psilocybin and psilocin exert a predominant agonist activity at serotonin receptors, particularly 5HT2A receptor. Agonist activity at 5HT2A receptor is generally considered a key pharmacological mechanism for inducing hallucinogenic effects. The role of other receptors is documented, but less investigated [41]. In all studies, psilocin displayed high affinity for the 5HT2A receptor (ki=6 nM), however, it showed to bind many other serotonin and non serotonin receptors including: 5HT2B, 5HT1D, D1, 5HT1E, 5HT1A, 5HT5A, 5HT7, 5HT6, D3, 5HT2C, 5HT1B. Psilocin have also shown a weak affinity for the imidazoline 1, alpha 2A, alpha 2B, alpha 2C receptors and 5HT transporter [42]. Unlike LSD, there is no information showing a pharmacodynamic activity of psilocin at D2 receptor [43]. In human studies, psychotomimetic effects of psilocybin were completely blocked in a dose-dependent manner using a pretreatment with the 5HT2A receptor antagonist ketanserin [44]. Furthermore, psychotomimetic effects were also blocked using a pretreatment with the atypical antipsychotic risperidone [44]. Counterwise, psychotomimetic effects were increased by the dopamine antagonist and typical antipsychotic haloperidol. This result suggests that psilocybin exserts its psychotropic effect with a mechanism

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of action independent/partially independent from the dopamine stimulation [44]. However, in a Positron emission tomography (PET) study performed in male volunteers using the D2 dopamine receptor antagonist [11C]-raclopride was demonstrated that psilocybin significantly decreased [11C]-raclopride receptor binding bilaterally in the caudate nucleus (19%) and putamen (20%). These results suggest an increase in endogenous dopamine after administration. Changes in [11C]-raclopride receptor binding in the ventral striatum were correlated with both depersonalization and euphoria. Results emerged from the study have permited to hypothesize that the stimulation of both 5-HT1A and 5-HT2A receptors could be important for the modulation of striatal dopamine release. Striatal dopamine release, in combination with the serotonin transmission, could be involved in determining some of the psychotropic effects induced by psilocybin [45]. Clinical studies have demonstrated that an equimolar amounts of psilocybin and psilocin can produce the same psychotropic effects [46]. however, inhibition of dephosphorylation using the alkaline phosphatase competitive antagonist beta-glycerophosphate showed to prevent all symptoms induced by psilocybin. This clinical evidence have strongly confirmed that psilocin is the main active metabolite and the responsible of the psychedelic effects [47].

5. Functional studies

Electroencephalographic alterations induced by psilocybin in humans or in animal model have been studied since 1960s [48-52]. First electroencephalographic studies performed in both primates and humans under psilocybin intoxication showed numerous changes including a decreased in alpha and theta activity, an increased in fast activity, and desynchronization [48-52]. Changes in visually evoked potentials were also described in humans [51, 52]. In a visual-evoked potentials study performed in 26 healthy male volunteers, psilocybin significantly decreased prestimulus parieto-occipital α -power values precluding a subsequent stimulus-induced α -power decrease. Moreover, psilocybin also decreased N170 potentials that were associated with the appearance of visual perceptual alterations, including visual hallucinations. All effects were blocked by pretreatment with the 5-HT2A antagonist ketanserin [53]. In a magnetoencephalography study performed in a

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group of fifteen healthy male volunteers, after intravenous infusion of psilocybin was found a reduction of the spontaneous cortical oscillatory power from 1 to 50 Hz in posterior association cortex, and from 8 to 100 Hz in frontal association cortex. Conversely, no effect was found on low-level visually induced and motor-induced gamma-band oscillations. Dynamic causal modeling showed a correlation between posterior cingulate cortex desynchronization and increased excitability of deep-layer pyramidal neurons. This correlation appear to be triggered by 5-HT2A receptor-mediated excitation of deep pyramidal cells [54]. In a PET and [F-18]-fluorodeoxyglucose (FDG) study performed in 10 healthy volunteers prior to and following a 15 or 20 mg dose of psilocybin, authors found a global increase in cerebral metabolic rate of glucose with a predominant localization in the frontomedial and frontolateral cortex , anterior cingulate, and temporomedial cortex. Instead, a smaller increase of metabolic rate of glucose was found in the basal ganglia, in the sensorimotor area, and in the occipital cortex [55]. In a double-blind, placebo-controlled study performed in healthy volunteers using the [F-18]-fluorodeoxyglucose FDG PET, authors found that psilocybin increased the metabolic rate of glucose in the right anterior cingulate, in the right frontal operculum, and in the right inferior temporal region. Conversely, a significant decrease in the metabolic rate of glucose was found in the right thalamus, in the left precentral region, and in the left thalamus. Authors have further observed a trend decrease in the metabolic rate of gluciose in the composite right hemisphere and in the bilateral subcortical regions as well as a trend increase of the cortical/subcortical ratio of the right hemisphere [56]. Carhart-Harris and colleagues designed a functional MRI study to capture the transition from normal waking consciousness to the state induced by an intravenous infusion of 2 mg of psilocybin. Arterial spin labeling perfusion and blood-oxygen level-dependent functional MRI were used to map cerebral bloodflow and changes in venous oxygenation before and after placebo and psilocybin infusion. Results showed a significant cerebral bloodflow (CBF) decrease in subcortical (bilateral thalamus, putamen, and hypothalamus) and in cortical regions [the posterior cingulate cortex (PCC), retrosplenial cortex, precuneus, bilateral angular gyrus, supramarginal gyrus, rostral and dorsal

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anterior cingulate cortex (ACC), paracingulate gyrus, medial prefrontal cortex (mPFC), frontoinsular cortex, lateral orbitofrontal cortex, frontal opercu-lum, precentral gyrus, and superior, middle and inferior frontalgyrus]. Subjective effects were strongly related to the decreased activity and connectivity in the brain's key connector hubs including thalamus, mPFC, and ACC [57]. In a psilocybin vs placebo cross over study using a functional MRI paradigm Carhart-Harris and colleagues found that psilocybin enhanced autobiographical recollection facilitating the underlying neural processes. Significant activation was found in both limbic and striatal region in the early phase; otherwise a significant activation in the late phase was found in the medial prefrontal cortex . Additional visual and sensory cortical activation in the late phase was found under psilocybin only. Rating of memory vividness and visual imagery was significantly higher after psilocybin than placebo. Futhermore, authors found a significant positive correlation between vividness and subjective well-being at follow-up [58]. In a PET study performed in eight healthy volunteers using the 5-HT2A receptor agonist radioligand [11C]-Cimbi-36, oral intake of 3–30 mg of psilocybin produced a dose-related 5-HT2A receptor occupancy. Moreover, the study highlighted a correlation between subjective effects induced by psilocybin and both 5-HT2A receptor occupancy and plasma psilocin levels [59]. Two PET studies performed in healthy volunteers using the 5-HT2A receptor agonist radioligand [11C]-Cimbi-36 have also shown that, after psilocybin administration, individual brain 5-HT2A receptor binding predicted subjective temporal and mystical effects [60], mindfulness and openness [61].

6. Toxicity

Psilocybin is generally considered a well tolerated and low toxic substance. Some cases of fatal intoxication have been anyway reported, however, the majority of them were not directly linked to the toxic effects induced by psilocybin. They were generally related to a mixed drug intoxication, suicide, and jumping out of the window [26, 62]. In 1996, it was described a case in which a massive dose of psilocybe semilanceata was considered as cause of death. Toxicological examination evidenced a psilocin plasma level of 4 µg/ml [63]. Human lethal dose is not known,

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however, LD50 for rat, mouse and rabbit after intravenous administration of psilocybin was identified in 280 mg/kg, 275 mg/kg, and 13 mg/kg, respectively [64]. Instead, LD50 for rat, mouse and rabbit after intravenous administration of psilocin was identified in 75 mg/kg, 74 mg/kg, and 7 mg/kg, respectively [65]. Human Toxic Dose Low (TDLo) for oral psilocybin administration was identified in 0.04-0.06 mg/kg while the TDLo for intravenous psilocybin administration was determined in 1-2 mg corresponding to a psilocin plasma level of around 4-6 ng/ml. At this dose, patients reported: visual field changes, muscle weakness, nausea and vomiting. In dose-effect studies, psilocybin resulted 66 times more potent than mescaline and 45 times less potent than LSD (65). In two cross-over studies performed in the end of 50s authors found a cross tolerance between psilocybin and LSD [66]. Psilocybin is principally used for its psychedelic effects including altered self perception, impaired perception of time and space, alteration in thought contents, derealization, depersonalization, alteration in body immage, alteration in mood and emotions [67-69]. Symptoms induced by psilocybin can be reverted using the 5HT2A/C antagonist ketanserin or the 5HT2A/C and D2 antagonist risperidone. Haloperidol, a D2 antagonist, was useful to normalize euphoria, derealization and depersonalization [44]. On the other hand, MAO inhibitors have shown to intensify psychedelic effects induced by psilocybin [70]. Alcohol can enhance the psychodelic effects induced by psilocybin since its metabolite acetaldehyde reacts with the endogenous biogenic amines producing the MAO inhibitors tetrahydroisoquinoline and β-carbolines [71]. Psilocybin effects can be prolonged by tobacco because it may reduce the central nervous system and peripheral tissues MAO B levels [72]. In addition to the central nervous system, psilocybin can affect other organs and systems including renal [73], cardiovascular, respiratory, gastrointestinal, visual, and musculoskeletal systems [74] as reported in Table 1. Overall, psychotropic and neuropsychological effects appear to be influenced by both personal expectations and setting [41]. Prolonged hallucinations or psychotic experiences are rarely reported in healthy persons if compared with people affected by psychotic or personality disorders (75). However, long lasting unpleased experiences, best knows as "bad trips" or hallucinogen persisting perception disorder

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(HPPD), are anyhow reported [76]. Psilocybin does not directly affect the mesolimbic dopaminergic pathway involved in the reward system, consequently, it does not induce craving, addiction or withdrawal [41, 75]. Finally, there is no enough information to confirm or exclude both genotoxicity or teratogeni city [77].

Table 1: Psilocybin effects.

Central Nervous System	dream-like state, illusions, hallucinations, synesthesiae, paraesthesia altered state of consciousness, altered self-perception, derealization, depersonalization, altered perception of time and space, altered mood, altered concentration, delusions or unusual ideas, altered emoziona state, euphoria, panic attacks, convulsions, headache, verigo, flushing
Visual system	mydriasis
Cardiovascular system	achicardia, hypertension, hypotension
Respiratory system	hypoxemia
Gastrointestinal system	Nauseas, vomiting, abdominal pain
Renal system	urinary incontinence, renal failure
Musculoskeletal system	muscle weakness

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7. Psilocybin and mood disorders

In a double-blind, placebo-controlled study performed in a sample of 12 patients, 11 women and 1 man, affected by advanced-stage cancer, 0.2 mg/kg of psilocybin administered in a single dose produced a significant reduction in anxiety at 1 and 3 months and depressive symptoms at 6 months if compared with placebo (niacine 250 mg). Symptoms of anxiety and depression were assessed using the State-Trait Anxiety Inventory and the Beck Depression Inventory, respectively [78]. In a two-session, double-blind cross-over study, authors compared the effect of a low (1 or 3 mg/70 kg) versus high (22 or 30 mg/70 kg) psilocybin dose on depressive symptoms, anxiety, and quality of life in 51 patients with life-threatening cancer. High-dose psilocybin produced a significant decrease in depressive symptoms, anxiety and death anxiety along with a significant increase in quality of life and optimism. At 6-month follow-up, improvement in mood, anxiety and quality of life was confirmed in about 80% of patients [79]. In a similar double-blind, placebo-controlled, crossover trial performed in 29 patients affected by life-threatening cancer, a single-dose psilocybin of 0.3 mg/kg improved depressive symptoms, anxiety and quality of life in the weeks after administration. At the 6.5-month follow-up, around 80% of patients had kept clinical benefits [80]. In an open-label study performed in a sample of 12 patients, 6 men and 6 women, affected by moderate-to-severe unipolar, treatment-resistant major depression, two oral doses of psilocybin (10 mg and 25 mg, 7 days apart) in association with psychological support before, during, and after each session produced a marked reduction in depressive symptoms as assessed by the 16-item Quick Inventory of Depressive Symptoms (QIDS) to 1 week and 3 months if compared to the baseline. Patients reported only mild adverse effects such as transient headache, anxiety, confusion and nausea [81]. In another open-label study performed in 20 patients, 12 males and 6 females, affected by severe unipolar, treatment-resistant major depression, two oral doses of psilocybin (10 mg and 25 mg, 7 days apart) in association with psychological support produced a marked reduction in depressive symptoms as assessed by the 16-item Quick Inventory of Depressive Symptoms (QIDS) to 1 week, 5 weeks, 3 months and 6 months if compared to the baseline.

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Depressive symptoms reduction at 5 weeks was predicted by the quality of the acute psychedelic experience [82].

8. Psilocybin and obsessive compulsive disorder

Clinical information regarding the potential therapeutic effects of psilocybin in patients affected by obsessive compulsive disorder is very limited. In a double-blind study performed in a small sample of 9 patients, 7 males and 2 females, affected by resistant obsessive compulsive disorder, psilocybin showed to be safe and effective in reducing obsessive compulsive symptoms for a duration extended beyond the psychedelic effect [83]. Psilocybin was administered in up to 4 different doses in a modified dose escalation from very low dose (25 μg/kg) to high dose (300 μg/kg) [83]. In 2014, Wilcox reported a case report in which a patient self administered psilocybin for years in order to reduce obsessive compulsive symptoms [84]. This case report followed the case report of Leonard and Rapoport in which authors described the history of a 17 years-old patient who used LSD and psilocybin to reduce obsessive compulsive symptoms [85].

9. Psilocybin and addiction

In a proof-of-concept study performed in 10 volunteers, 6 men and 4 women, oral administration of psilocybin in one or two sessions in combination to the Motivational Enhancement Therapy induced a reduction in drinking days during the subseguent 5-12 weeks. Drinking days reduction was correlated to the mystical quality of the psychedelic experience. Patients did not report significant side effects [86]. In the first pilot study performed in 15 people, 10 males and 5 females, involved in a smoking cessation program, psilocybin, in combination with the Cognitive Behavioral Therapy, induced in 12 of 15 partecipants a seven-day point prevalence abstinence at 6-month follow-up [87]. In a similar open-label pilot-study performed in 12 people involved in a smoking cessation treatment, psilocybin in combination with the Cognitive Behavioral Therapy produced 6 months abstinence in 80% of volunteers without significant side effects. In the sample, abstinence was related to the mystical quality of the psychedelic experience [88]. It is currently in progress an open label study in which the primary endpoint is the assessment of the safety of concurrent

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buprenorphine and naltrexone administration. Estimated study completion date is on November 2021 [89].

10. Discussion

In recent years, there has been a resurgence of scientific interest about the potential use of psilocybin and other psychedelics for treating psychiatric disorders, in particular mood disorders, anxiety and addiction [17, 18]. Recent clinical studies have tried to fill the methodological errors presented by the past studies with the aim of obtaining more reliable results. As emerged by 1950s and 1960s studies, psilocybin have shown to be safe and well tolerated, particularly when administered to therapeutic doses. Most commonly reported side effects were: anxiety, headache, nausea, confusion, vomiting and slight sympathomimetic symptoms [67-69, 72, 73, 81]. All symptoms were described as transient and no patient involved in the studies required a pharmacological treatment to address these adverse events. In patients affected by mood depressive disorder and anxiety, psilocybin displayed to be effective in reducing depressive symptom in short, medium and long term analysis [78-82]. Antidepressant activity lasted longer than psychotropic effects, however, the quality of the acute psychedelic experience significantly influenced the therapeutic result [82, 88]. The most important pharmacological property showed by psilocybin in all trials was the rapid onset of antidepressant effect. This effect would allow an improvement if compared to the therapy with traditional antidepressants which have a long latency of action [90]. However, no study compared psilocybin with other rapid acting antidepressants such as ketamine. On the other hand, our analysis of informaion extracted by clinical studies performed in patients affected by depression have shown two principal limitations: first, the small size of samples enrolled; second, the comorbidity between depressive symptoms and severe diseases (cancer) in many patients enrolled for trials. Studies have overall enrolled a few dozen patients and for this reason results cannot be generalized for a more heterogeneous population in terms of age, social status and disease duration. Moreover, depressive symptoms associated to other diseases could have different expression/evolution if compared with a primary mood depressive disorder.

Consequently, the pharmacological response to a therapeutic dose of psilocybin could be different in primary and secondary depression. Besides, no study included expectancy measures as a covariate in statistical analysis of clinical response. Unblinding design of studies and in particular the expectancy of both partecipants and evaluators could be in part responsible of the good results found in all clinical studies. On the whole, despite the methodological limitations showed by clinical studies currently available, the promising antidepressant and anxiolytic effects induced by psilocybin support the need for further and more robust trials in order to better understand the potential therapeutic properties of this psychedelic. Regarding the use of psilocybin for treating other illnesses such as obsessive compulsive disorder and addiction, information currently available are really too limited to be evaluated. Positive results reported by authors can be considered as working hypotheses for future and more robust clinical studies. In conclusion, psilocybin have confirmed to be safe and well tolerated when administered at therapeutic doses. Clinical studies, in particular those performed in patients affected by mood depressive disorder, have shown encouraging therapeutic results supporting the need of further and better designed trials.

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