Psilocybin

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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. Psilocybin was marketed by Sandoz as Indocybin for basic psychopharmacological and therapeutic clinical research, rising in popularity during the 1960s and classified as a Schedule I drug in 1970.
Psilocybin is a naturally occurring tryptamine known for its psychedelic properties. Recent research indicates that psilocybin may constitute a valid approach to treat depression and anxiety associated to life-threatening diseases.
 Kekulé, skeletal formula of canonical psilocybin

psilocybin depression anxiety clinical trials sistematic review meta-analysis

1. Introduction

Depression and anxiety are independent risk factors of early death in patients with life-threatening diseases, like cancer [1] and most of these individuals develop a chronic syndrome of psychological distress, usually associated with decreased treatment adherence, prolonged hospitalization, decreased quality of life and increased suicidality [2]. Antidepressants and benzodiazepines are used to treat depressed mood and anxiety in patients with life-threatening diseases [3], although there are no Food and Drug Administration (FDA) approved pharmacotherapies for the psychological distress related to those diseases. In addition, the onset of clinical improvement with antidepressants is delayed, relapse rates are high and significant side effects compromise adherence to therapy [4].

Regarding the treatment of severe depression and anxiety, special attention should be paid to the approval of intranasal Spravato® by the FDA in March 2019. Its active compound is esketamine, a ketamine enantiomer, which is a non-competitive *N*-methyl-d-aspartate (NMDA) glutamate receptor antagonist. The effects of ketamine have made it a popular recreational drug, due to its euphoric and dissociative properties [5]. Nonetheless, esketamine appears to provide significant short-term symptom improvement in severe depression and anxiety and it is considered an innovative and promising therapeutic approach. Moreover, molecules such as 3,4-methylenedioxy-methamphetamine (MDMA) and lysergic acid diethylamide (LSD) are also being studied for the treatment of anxiety conditions, namely, post-traumatic stress disorder (PTSD) and generalized anxiety disorder (GAD). Nevertheless, none of these drugs has been approved by the FDA.

In spite of all studies and therapeutic innovations in this area, further research is needed, notably on classic hallucinogens like psilocybin, to provide patients with depression and anxiety associated with life-threatening diseases better chances of recovery and consequently better quality of life.

Recently, Goldberg et al., 2020 [6] published a meta-analysis concerning the use of psilocybin and symptoms of anxiety and depression. The approach used in their meta-analysis is different from the one we present in several aspects, for instance—it does not include data on previous pathologies of the patients receiving psilocybin and did not analyze physiological effects induced by the drug. Also, the authors did not examine psilocybin dose and administration duration as moderators of treatment effects [6].

In this context, this paper aims to perform a systematic review, complying with the Preferred Reported Items for Systematic Reviews and Meta-Analysis (PRISMA) statement, followed by a meta-analysis of clinical trials on the therapeutic potential of psilocybin in anxiety and depression associated with life-threatening diseases.

2. Primary Outcomes: Effects of Psilocybin on Depression and Anxiety

BDI and STAI were considered the psychometric scales for this work since they are the most widely used in clinical settings to quantify symptoms of either depression or anxiety.

The meta-analysis results for the effects of psilocybin in depression through BDI are graphically reported in Figure 1A and Table 1. For BDI, 11 effect sizes were considered, including 92 patients, with a diagnosis of depression and anxiety associated with a life-threatening disease. It was concluded that the intervention group was significantly favored when compared to the control group (WMD = −4.589; 95% CI = −4.207 to −0.971; *p*-value = 0.002). For these results, a fixed effects model was used, given the homogeneity of the studies (I^2 = 0%).

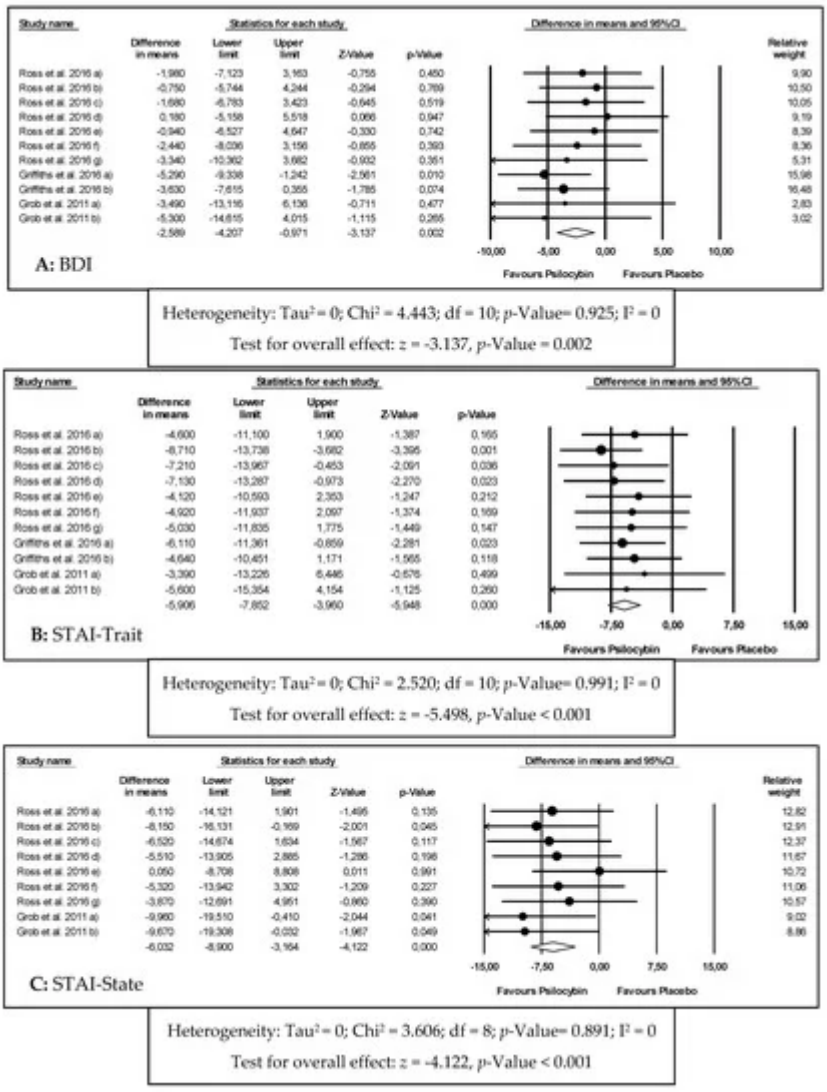

Figure 1. Forest plots of comparisons of the effects of psilocybin on the primary outcomes of this meta-analysis ((**A**) Beck Depression Inventory (BDI); (**B**) State-Trait Anxiety Inventory (STAI)-Trait; (**C**) STAI-State).

Table 1. Effects of psilocybin on depression and anxiety.

Outcome Analyzed	Number of Effect Sizes	WMD Observed (95% CI)	*p*-Value	I^2 (%)	Model USED	WMD Adjusted (95% CI)
BDI	11	−4.589 (−4.207 to −0.971)	0.002 *	0	Fixed	−4.589 (−4.207 to −0.971)
STAI-Trait	11	−5.906 (−7.852 to −3.960)	<0.001 *	0	Fixed	−6.389 (−8.151 to −4.626)
STAI-State	9	−6.032	<0.001 *	0	Fixed	−6.032

Outcome Analyzed	Number of Effect Sizes	WMD Observed (95% CI)	*p*-Value	I^2 (%)	Model USED	WMD Adjusted (95% CI)
		(−8.900 to −3.164)				(−8.900 to −3.164)

WMD—weighted mean differences; CI—confidence interval; * Indicates a significant result.

The meta-analysis results for the effects of psilocybin in anxiety through STAI-Trait and STAI-State are graphically reported in Figure 1B,C, respectively and Table 1.

For STAI-Trait, 11 effect sizes were considered, including 92 patients, with a diagnosis of depression and anxiety associated with a life-threatening disease. Among these, 28 patients had genitourinary cancer, 26 had breast cancer, 16 had digestive cancer, 12 had hematologic malignancies, and 10 had other oncologic pathologies. All patients were in advanced stages of their illnesses and some had recurrent metastatic diseases. Apart from that, all patients had also been diagnosed using the DSM V meeting criteria for either chronic adjustment disorder with anxiety, chronic adjustment disorder with mixed anxiety and depressed mood, dysthymic disorder, GAD, MDD or dual diagnosis between GAD and MDD or GAD and dysthymic disorder.

It was concluded that the intervention group was significantly favored when compared to the control group (WMD = −5.906; 95% CI = −7.852 to −3.960; *p*-value < 0.001). For these results, a fixed effects model was used, given the homogeneity between studies (I^2 = 0%).

For STAI-State, 9 effect sizes were considered, including 41 patients, with a diagnosis of depression and anxiety associated with a life-threatening disease (oncologic conditions). For this outcome, it was concluded that the intervention group was significantly favored when compared to the control group (WMD = −6.032; 95% CI = −8.900 to −3.164; *p*-value < 0.001). For these results, a fixed effects model was used, given the homogeneity between studies (I^2 = 0%).

3. Discussion

Psilocybin is a molecule with structural similarities to serotonin, an endogenous neurotransmitter. It can be found in some mushrooms and has been widely used to induce hallucinations and altered states of consciousness. Its laboratory synthesis was performed by Albert Hofmann while working at Sandoz Laboratories and it was marketed later under the commercial name Indocybin® for basic psychopharmacology and clinical research [7].

Nonetheless, it was withdrawn in the early 1970s and was classified as a Schedule I drug due to its use outside of medical research and in association with emerging countercultures. Despite withdrawal and criminalization, its potential therapeutic value led many scientists to study the effects and mechanisms of action of the drug. There is preliminary evidence that psilocybin may be useful in the treatment of anxiety and depression in life-threatening diseases, depression, obsessive-compulsive disorder, alcoholism and nicotine addiction, cluster headaches and autism [7]. Although further research is needed to assess the efficacy and safety in the treatment of these

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The increases of both SBP and DBP and heart rate are consistent with the sympathetic effects of psilocybin reported in the literature [18]. The sympathetic effects may also be noticeable through the induction of pupil dilatation [19]. Psilocybin, however, is not likely to cause changes on electrocardiograph or body temperature nor to affect the ionic balance, blood glucose or cholesterol [13].

There were not reported serious adverse effects following psilocybin administration. Besides transient moderate increases in SBD, DBP and heart rate, there are some references to nausea, both physical and psychological discomfort, transient episodes of psychological distress and anxiety. There are, however, no cases of hallucinogen persisting perception disorder (HPPD) neither prolonged psychosis, although literature points these effects to be quite dangerous and life-impairing following hallucinogen consumption [20]. This may occur because in all studies included in the present meta-analysis, patients were carefully monitored in a calm and relaxed environment and had been previously informed about the effects that the drug might have in their bodies and mind. This is known as “set and setting” and it is designed to facilitate a mystical experience and to increase the probability of a positive outcome after the administration of any hallucinogen [7]. In fact, many drug-related and not drug-related variables may influence the adverse effects experienced by patients, namely, age, gender, education, experimental setting, and drug dose [21].

According to the literature, besides the mentioned adverse effects, psilocybin may also cause somatic symptoms such as dizziness, weakness, tremor, drowsiness, yawning, paresthesia, blurred vision, and increased tendon reflexes [22]. Although not applicable to the studies included in this meta-analysis, psilocybin is very likely to induce nausea when consumed through psilocybin-containing mushrooms [23].

Classical hallucinogens are not likely to cause addiction, as it is mainly linked to the dopaminergic system, while classical hallucinogens act mostly on the serotoninergic system. Furthermore, these drugs lead to tachyphylaxis, the rapid decrease in the effect of a drug in consecutive doses, related to their mechanism of action. Thus, the development of addiction by patients after treatment with psilocybin is not of concern. However, authors suggest that if a psilocybin-containing medicines is approved, it should be included in the Schedule IV of Controlled Substance Schedules [24].