

Possible use of psilocybin in psychiatric care, including COVID-19 sequelae

Possível uso da Psilocibina no tratamento psiquiátrico, incluindo sequelas da COVID-19

Posible uso de la psilocibina en el tratamiento psiquiátrico, incluyendo las secuelas de COVID-19

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Abstract

This paper discuss psilocybin's effect on the human organism and its therapeutic potential as a main or adjuvant medication for certain psychiatric diseases, more specifically, depression and anxiety, such as found in palliative care patients which are facing the end-of-life process, but also on those patients in which the conventional treatment was not effective. Recent studies also present the possibility of the use of psilocybin in the treatment of long-term psychiatric consequences of COVID. The available literature indicates that psilocybin promotes heightening of quality of life, modifications in the perception of self, perception of wholeness with the environment and spiritual experiences, which have great importance in the aforementioned groups of patients. Besides, it shows little to no side effects. This paper presents a review to reinforce the hypothesis of the therapeutic use of psilocybin in depression and anxiety in populations that can benefit the most of psychedelic therapy.

Keywords: Psilocybin; Psychiatry; Depression; Anxiety; Palliative care; Hallucinogens.

Resumo

Este trabalho discute acerca da ação da psilocibina no organismo humano e seu potencial terapêutico enquanto tratamento principal ou adjuvante para certos distúrbios psiquiátricos, mais especificamente a depressão e a ansiedade, como aquelas encontradas em pacientes que estão em cuidados paliativos e enfrentando o processo de fim de vida, mas também em pacientes nos quais o tratamento convencional não demonstrou eficácia. Estudos recentes também indicam a possibilidade da utilização da psilocibina no tratamento de sequelas psiquiátricas a longo prazo decorrentes da COVID. A literatura disponível indica que a psilocibina promove aumento da qualidade de vida, alterações na percepção do *self*, percepção de integralidade com o meio e experiências espirituais, o que se mostra especialmente importante nos grupos de pacientes supracitados. Além disso, demonstra pouco ou nenhum efeito colateral. Este trabalho realiza uma revisão para ratificar a hipótese do uso terapêutico da psilocibina na depressão e na ansiedade em populações que mais podem se beneficiar da terapia psicodélica.

Palavras-chave: Psilocibina; Psiquiatria; Depressão; Ansiedade; Cuidados paliativos; Alucinógenos.

Resumen

Este artículo analiza la acción de la psilocibina en el organismo humano y su potencial terapéutico como tratamiento principal o coadyuvante de ciertos trastornos psiquiátricos, más concretamente de la depresión y la ansiedad, como los que se dan en pacientes que reciben cuidados paliativos y se enfrentan al proceso de finalización de la vida, pero también en pacientes en los que el tratamiento convencional no ha mostrado eficacia. Estudios recientes también

indican la posibilidad de utilizar la psilocibina en el tratamiento de las secuelas psiquiátricas a largo plazo derivadas del COVID. La literatura disponible indica que la psilocibina favorece el aumento de la calidad de vida, los cambios en la percepción del *self*, la percepción de la integralidad con el entorno y las experiencias espirituales, lo que es especialmente importante en los grupos de pacientes mencionados. Además, presenta pocos o ningún efecto secundario. Este trabajo realiza una revisión para ratificar la hipótesis del uso terapéutico de la psilocibina en la depresión y la ansiedad en las poblaciones que más pueden beneficiarse de la terapia psicodélica.

Palabras clave: Psilocibina; Psiquiatría; Depresión; Ansiedad; Cuidados paliativos; Alucinógenos.

1. Introduction

Since prehistoric times, hallucinogenic agents such as psychedelics have been used by different populations. Forms of consumption include ingestion and inhalation, inter alia, aimed at seeking happiness, excitement, and/or to reveal hidden aspects of the mind (Salih and Kaushik, 2013) or personality (Schmid and Liechti, 2018).

In terms of function, psychedelics, in general, cause a decrease in danger-related amygdala activities (Kraehenmann et al., 2015; Carhart-Harris et al., 2017); additionally, they can decrease depressive and anxious states through actions on 5-hydroxytryptamine receptors (Preller et al., 2017; Dos Santos et al., 2018; Erritzoe et al., 2018). Due to the importance of serotonin in mood and other pleasure-related behavior (Kraehenmann et al., 2015) and/or due to the need for new treatments for some psychiatric disorders (Mithoefer, Grob and Brewerton, 2016), interest in the use of psychedelics in various fields of science has increased (Byock, 2018), putatively in pursuit of understanding their neurological functions (Preller et al., 2017) and therapeutic uses (Erritzoe et al., 2018; Rucker, Iliff and Nutt, 2018). However, more clinical studies should be performed (Erritzoe et al., 2018; Ly et al., 2018).

Some examples of psychedelics, also called serotonergic hallucinogens or entheogens (when applied in ritualistic contexts), are lysergic acid diethylamide (LSD), psilocybin, N,N-dimethyltryptamine, ayahuasca, and mescaline (Byock, 2018; Dos Santos et al., 2018). Among them, psilocybin appears to show interesting therapeutic potential as an adjuvant in some neural disorders, such as anxiety (Gandy, 2017), as well as in cancer (Griffiths, 2016; Nutt, 2016; Gandy, 2017; Dos Santos, 2018; Erritzoe et al., 2018; Ross, 2018) and other conditions associated with palliative care (Byock, 2018), such as depression (Erritzoe et al., 2018; McCorvy, Olsen, and Roth, 2016). Psilocybin has generated identical results to fluoxetine (Cowen, 2016) in the treatment of alcoholism, smoking, obsessive-compulsive disorders, and treatment-resistant depression (Carhart-Harris et al., 2016; McCorvy, Olsen, and Roth, 2016; Carhart-Harris et al., 2017; Watts et al., 2017; Erritzoe et al., 2018).

Regardless of potential problems and biases, it has been noted that the use of psychedelics, especially psilocybin, can be applied to improve quality of life (Byock, 2018), especially in palliative care patients and treatment-resistant depression (Cowen, 2016), problems for which the traditional pharmacological treatment approach has demonstrated poor psychiatric, medical (Ross, 2018), and psychological outcomes. More specifically, psilocybin was first isolated from *Psilocybe mexicana* in 1958 by Hoffmann (Lim, Kangas, and Bergman, 2018) and is found in several species of mushrooms. Its chemical name is O-phosphoryl-1-1-hydroxy-N,N-dimethyltryptamine, which, along with its active metabolite, 4-hydroxy-N,N-dimethyltryptamine, is categorised in the group of hallucinogenic indolamines, which possess psychoactive activity (Dos Santos et al., 2016).

Oral or intravenous administration of psilocybin has about 74 to 120 minutes of half-life, respectively (Tylš et al., 2014) with a peak time in plasma of 20 to 40 minutes after oral administration (Passie et al., 2002). Over the past two decades (Ross, 2018), preliminary studies have indicated that modifications in personality caused by psilocybin are generally not too divergent from typical antidepressant effects (Erritzoe et al., 2018). Like other psychedelic compounds, psilocybin alters cognition and emotion. However, it does not trigger addiction, delirium, or memory loss (Halberstadt, 2015), while also stimulating actions on the sympathetic nervous system and causing a kind of “spiritual experience” (Griffiths et al., 2006).

In this sense, recent studies have demonstrated the benefits of psilocybin use for treatment in patients with terminal

conditions and for conditions other than depression and anxiety, such as the long-term psychiatric consequences of COVID (Kelly et al., 2020). According to this, it is necessary to study, at least hypothetically, the possibilities of psilocybin use in depressed patients and those undergoing palliative care.

In fact, studies have shown that 70% of patients with terminal conditions present anxiety and in 49% of them this symptom is severe, with depression developing concomitantly (Gripp et al., 2007; Bloch, 2007; Sorger et al., 2007; Hebert et al., 2009; Kolva et al., 2011; Phelps et al., 2009) with distress (Chochinov et al., 2008; Chochinov et al., 2009).

The mystical experience promoted by psilocybin promotes a deep sense of love, reverence, and sacredness (Griffiths et al., 2016), which allows for a transformation in the patient's attitude toward death, self, life, and others, through a process of breaking with the ego and connecting with the sacred (Gandy, 2017). There is also the scenario where psilocybin use simulates a death event, which can help reduce end-of-life anxiety and reiterate the patient's still-living priorities (Gandy, 2017). Accordingly, this new drug approach can be studied as an adjuvant to provide support for suffering patients, and psilocybin seems to demonstrate a remarkable effect in this regard.

Therefore, the aim of this review is to verify the possibility of psilocybin use in patients who need special care regarding death and dying, specifically palliative care patients with depression/anxiety, patients with treatment-resistant depression, and possibly patients with sequelae of COVID, not aiming to discuss each of these conditions.

2. Methodology

For the purpose of this systematic review, articles from 2002 onward with the keyword's psilocybin; palliative care; psilocybin and depression; psilocybin and anxiety; psilocybin and terminal patients; psilocybin, anxiety and depression were searched. The search was conducted using PubMed, Scopus, and ScienceDirect.

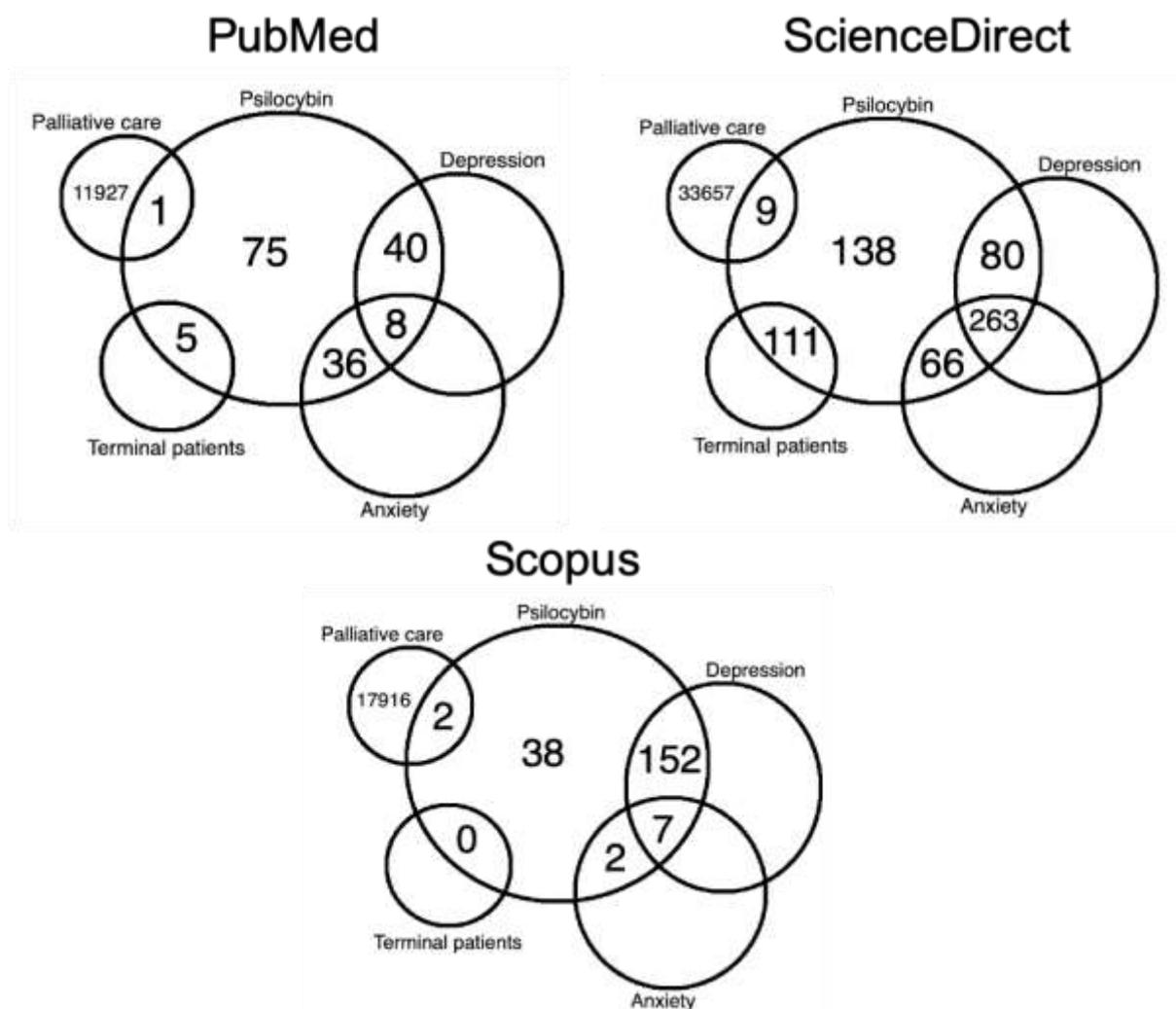
Articles that were deemed most appropriate to the purpose of this review were used; more specifically, dealing with the effect of psilocybin on various patients. Books were not used. For articles that dealt with similar subjects, only the most recent ones were selected. For example, 165 articles on the subject "psilocybin", 11,928 on "palliative care", 48 on "psilocybin and depression", 44 on "psilocybin and anxiety", only 1 on "psilocybin and palliative care", 5 on "psilocybin and patients with terminal conditions", and 8 on "psilocybin, depression, and anxiety" were found in PubMed (Figures 1 and 2).

From Scopus, 197 articles on the subject 'psilocybin' were found, 17,918 on "palliative care", 159 on "psilocybin and depression", 9 on "psilocybin and anxiety", only 2 on "psilocybin and palliative care", 0 on "psilocybin and patients with terminal conditions", and 7 on "psilocybin, depression and anxiety" (Figure 1).

From ScienceDirect, 667 articles were found on the subject "psilocybin", 33,606 on "palliative care", 343 on "psilocybin and depression", 329 on "psilocybin and anxiety", 9 on "psilocybin and palliative care", 111 on "psilocybin and patients with terminal conditions", and 263 on "psilocybin, depression and anxiety" (Figure 1).

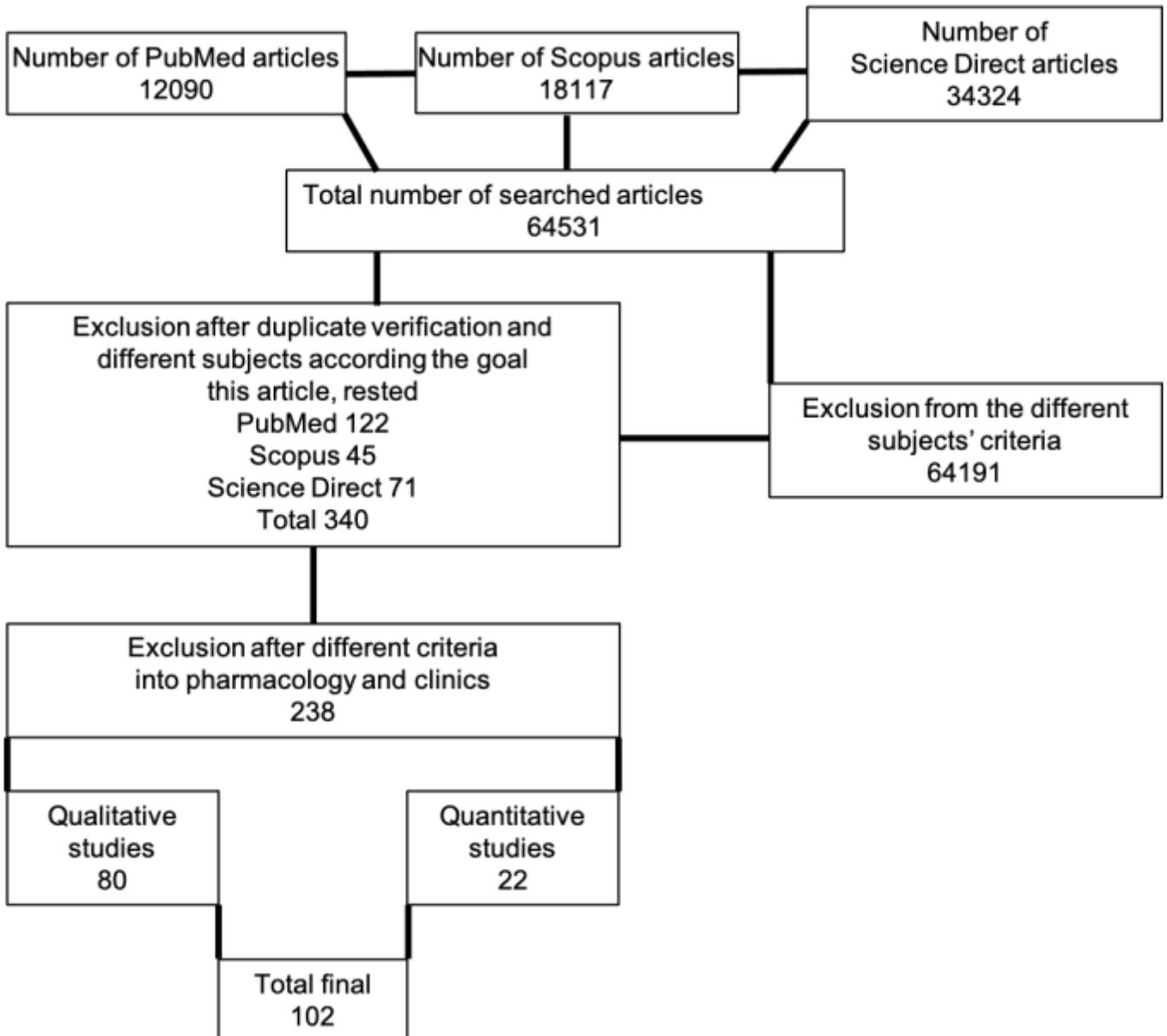
After that, 102 articles did not conform to the exclusion criteria and were used for the purposes of this study (Figure 2).

Figure 1. Venn diagram of found papers in the PubMed, Scopus and Science Direct without to consider the exclusion and inclusion criteria.



Source: Authors.

Figure 2. Diagram of exclusion and inclusion criteria of the papers used in this work.



Source: Authors.

3. Results and Discussion

Some articles discussed the use of psilocybin in the treatment of depression, and due to its ability to control fear through its action on the amygdala, anxiety was observed as a possible condition to be treated by psilocybin. This was the main information about psilocybin for the purpose of this paper.

Regarding keywords, considering the descriptors about psilocybin, 28 articles were used; palliative care and patients with terminal conditions, 7 articles; anxiety and depression, 9 articles; regarding the sets of keywords “psilocybin, anxiety and depression”, 41 articles; “anxiety and depression, palliative care and terminal patients”, 8 articles; and “psilocybin, anxiety and depression, palliative care and terminal patients”, 9 articles (Table 1).

Of the 102 articles studied, 22 were quantitative studies and 80 were qualitative studies.

Table 1. Association between the searched keywords, authors and article titles.

Descriptor: Psilocybin				
Author		Title	Quantitative	Qualitative
1	Byock, I. (2018).	Taking Psychedelics Seriously.		X
2	Erritzoe, D. et al. (2018).	Effects of psilocybin therapy on personality structure.	X	
3	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.	X	
4	Halberstadt, A. L. (2015).	Recent advances in the neuropsychopharmacology of serotonergic hallucinogens.		X
5	Ly, C. et al. (2018).	Psychedelics Promote Structural and Functional Neural Plasticity.	X	
6	Passie, T. et al. (2002).	The pharmacology of psilocybin.	X	
7	Preller, K. H. et al. (2020).	Psilocybin Induces Time-Dependent Changes in Global Functional Connectivity.	X	
8	Preller, K. H. et al. (2017).	The Fabric of Meaning and Subjective Effects in LSD-Induced States Depend on Serotonin 2A Receptor Activation.	X	
9	Tylš, F.; Páleníček, T. & Horáček, J. (2014).	Psilocybin – Summary of knowledge and new perspectives.		X
Descriptors: Palliative care and terminal patients				
Author		Title	Quantitative	Qualitative
1	Chang, V. et al (2007).	Pain and palliative medicine.		X
2	Hebert, R. et al (2009).	Preparing Family Caregivers for Death and Bereavement. Insights from Caregivers of Terminally Ill Patients.	X	
3	Phelps A. C. et al. (2009).	Association between religious coping and use of intensive life-prolonging care near death among patients with advanced care.	X	
4	Aversi-Ferreira, T. A. et al. (2013).	Confrontation between ethnopharmacology and scientific results of the herbal medicaments from Brazil to be applied in primary health care.		X
Descriptors: Anxiety and depression				
Author		Title	Quantitative	Qualitative
1	Rubinstein, E. et al. (2015).	A call to action: the global response to dementia through policy innovation.		X
2	Singewald, N. et al. (2015).	Pharmacology of cognitive enhancers for exposure-based		X

		therapy of fear, anxiety and trauma-related disorders.		
3	Tancer M. & Johanson C. E. (2003).	Reinforcing, subjective, and physiological effects of MDMA in humans: A comparison with d-amphetamine and mCPP.	X	
4	Valentiner D. P., Mounts N. S. & Deacon B. J. (2004).	Panic attacks, depression and anxiety symptoms, and substance use behaviors during late adolescence.	X	
5	Young, K. S. et al. (2017).	Treatment for social anxiety disorder alters functional connectivity in emotion regulation neural circuitry.	X	
6	Costa et. al. (2018)	The Confrontation between Ethnopharmacology and Pharmacological Tests of Medicinal Plants Associated with Mental and Neurological Disorders	X	
7	Erritzoe, D. et al. (2019)	Serotonin release measured in the human brain: a PET study with [¹¹ C]CIMBI-36 and d-amphetamine challenge	X	

Descriptors: psilocybin, anxiety and depression

Author	Title	Quantitative	Qualitative
1 Barnby, J. M. & Mehta, M. A. (2018).	Psilocybin and mental health-don't lose control.		X
2 Bershad, A. K. et al. (2019).	Acute Subjective and Behavioral Effects of Microdoses of Lysergic Acid Diethylamide in Healthy Human Volunteers	X	
3 Bonn-Miller, M.O, et al. (2007).	Associations between psychedelic use, abuse, and dependence and lifetime panic attack history in a representative sample.	X	
4 Carhart-Harris, R. L. et al. (2017).	Psilocybin for treatment-resistant depression: FMRI-measured brain mechanisms.	X	
5 Carhart-Harris, R. L. et al (2016).	Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study.	X	
6 Carhart-Harris, R. L.; Bolstridge, M.; Day & C. M. J. et al (2018).	Psilocybin with psychological support for treatment-resistant depression: six-month follow-up.	X	
7 Cowen, P. (2016).	Altered states: psilocybin for treatment-resistant depression.		X
8 Dos Santos, R. G. et. al. (2016).	Antidepressive, anxiolytic, and antiaddictive effects of ayahuasca, psilocybin and lysergic acid diethylamide (LSD): a systematic review of clinical trials published in the last 25 years.	X	
9 Dos Santos, R. G. et. al. (2018).	Efficacy, tolerability, and safety of serotonergic psychedelics for the management of mood, anxiety, and substance-use disorders: a systematic review of systematic reviews.		X

10	Dos Santos, R. G. & Hallak, J. E. C. (2019).	Therapeutic use of serotonergic hallucinogens: A review of the evidence and of the biological and psychological mechanisms.		X
11	Kraehenmann, R. et al. (2015).	Psilocybin-induced decrease in amygdala reactivity correlates with enhanced positive mood in healthy volunteers	X	
12	Kraehenmann, R. et al. (2016).	The mixed serotonin receptor agonist psilocybin reduces threat-induced modulation of amygdala connectivity.	X	
13	Mithoefer, M. C.; Grob, C. S & Brewerton, T. D. (2016).	Novel psychopharmacological therapies for psychiatric disorders: psilocybin and MDMA.		X
14	Roseman et. al. (2018).	Increased amygdala responses to emotional faces after psilocybin for treatment-resistant depression.	X	
15	Roseman, L.; Nutt, D. J. & Carhart-harris, R. L. (2018).	Quality of acute psychedelic experience predicts therapeutic efficacy of psilocybin for treatment-resistant depression.	X	
16	Schmid, Y. & Liechti M. E. (2018).	Long-lasting subjective effects of LSD in normal subjects.	X	
17	Watts, R. et al. (2017).	Patients' Accounts of Increased "Connectedness" and "Acceptance" After Psilocybin for Treatment-Resistant Depression.	X	

Descriptors: anxiety and depression, palliative care and terminal patients

Author		Title	Quantitative	Qualitative
1	Kolva, E. et al. (2011).	Anxiety in terminally ill cancer patients.	X	
2	Sorger, B. et al. (2007).	Decision-making capacity in elderly, terminally ill patients with cancer.	X	
3	Gripp, S. et al. (2007).	Survival prediction in terminally ill cancer patients by clinical estimates, laboratory tests, and self-rated anxiety and depression.	X	
4	Chochinov, H. M. et al. (2008).	The Patient Dignity Inventory: A Novel Way of Measuring Dignity-Related Distress in Palliative Care.	X	
5	Bloch, S. et al. (2007).	Psychological adjustment of men with prostate cancer: A review of the literature.		X
6	Chochinov, H. M. et al. (2009).	The Landscape of Distress in the Terminally Ill.	X	
7	Kelly, J. R. et al. (2020).	Psychedelic science in post-COVID-19 psychiatry.	X	

Descriptors: psilocybin, anxiety and depression, palliative care and terminal patients

Author		Title	Quantitative	Qualitative
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1	McCorvy, J. D; Olsen, R. H. J. & Roth, B. L. (2016).	Psilocybin for depression and anxiety associated with life-threatening illnesses.		X
2	Ross, S. (2018).	Therapeutic use of classic psychedelics to treat cancer-related psychiatric distress.	X	
3	Nutt, D. (2016).	Psilocybin for anxiety and depression in cancer care? Lessons from the past and prospects for the future.		X
4	Lim, C. H.; Kangas, B. & Bergman, J. (2018)	The Utility of Psilocybin in Managing Anxiety and depression in Cancer Patients.	X	
5	Gandy, S. (2017).	Dying to live: The power of transcendence in the treatment of existential anxiety.		X
6	Rucker, J. J. H.; Iliff, J. & Nutt; D. J. (2018).	Psychiatry & the psychedelic drugs. Past, present & future.		X
7	Salih, L. H; Kaushik, A. (2013).	Mini Review on psychedelic drugs: illumination on the hidden aspects of mind.		X
8	Griffiths, R. R. et al. (2016).	Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial.	X	
9	Ross S. et al. (2016).	Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: A randomized controlled trial.	X	

Source: Authors.

Many studies on medicinal plants have already been conducted as adjuvants to industrial drugs (Aversi-Ferreira et al., 2013), but restrictions and pharmacological testing are of great importance before general population use is approved (Costa et al., 2018). In this regard, psilocybin appears to be suitable for use by the population as a medicinal derivative of medicinal fungi (Lim, Kangas, and Bergman, 2018). However, due to the fact that it is a psychedelic, special care is required (Ly et al., 2018).

Indeed, psychedelic hallucinogens have an important therapeutic role in brain health, due to their action on serotonin receptors, increasing the availability of this neurotransmitter (Erritzoe et al., 2019) and consequently acting on mood and pleasure (Kraehenmann et al., 2015). With the increase in cases of mental level problems in modern society, various types of treatments need to be available for use by the general population, not only for patients refractory to traditional medical treatment, but also for those who suffer from more intense side effects due to certain types of medication.

Interestingly, psilocybin is rarely used as a therapeutic agent, even though it has few or no side effects. When applied, studies have shown beneficial effects for the treatment of anxiety and depression, with especially notable results in palliative care patients, in smoking, alcoholism, and obsessive compulsive disorders, according to recent studies (Byock, 2018; Erritzoe et al., 2018; Gandy, 2017; Watts et al., 2017). Above all, psilocybin demonstrates important action on treatment-resistant depression (Erritzoe et al., 2018; Carhart-Harris et al., 2017). According to this, its main use could be related to increasing quality of life in complex cases, as is the case for patients in palliative care (Cowen, 2016; Byock, 2018).

In this paper, the main objective was to draw attention to the use of psilocybin in the treatment of anxiety (due to its similar effects to fluoxetine), treatment-resistant depression, and for patients in palliative care in order to decrease end-of-life related anxiety and depression. Considering the articles studied, the hypothesis appears to make sense, indicating psilocybin for treatment of the cited conditions. Nevertheless, most of the articles consider the need for further studies.

Recently, psilocybin has been indicated as a medication for psychiatric problems related to the long-term consequences of COVID as a promising form of treatment (Kelly et al., 2020). This information, in addition to the aforementioned treatment indications, show the importance and use of psilocybin as a primary or adjunctive medication for anxiety and depression in palliative care. Palliative care manages a variety of difficult situations for patients, which require special attention to promote increased quality of life considering the fear of the unknown, at least for most of them.

4. Conclusion

According to several studies, psilocybin is indicated for the treatment of depression, anxiety, psychiatric consequences of long-term COVID, and especially in palliative care.

Considering the information present in this review of the studied papers, psilocybin is a suitable medication, either as the main treatment or adjuvant, in therapy for the cited morbidities. However, there is a consensus on the need for more studies on this psychedelic for use on a larger scale.

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