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Review Article

Surfing the Psychological Consequences of the Coronavirus Pandemic Waves. Is Psilocybin an Alternative for the Treatment of Post Pandemic Depression?

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Abstract

On March 20, 2020, the President of the Argentine Republic declares on the national network, preventive and compulsory social isolation throughout the country. Faced with a global situation that spreads to a second and third wave of infections, it is essential to consider the most obvious symptomatic behaviors, which constitute the first line of defense in what appears to be a new normal. Studies carried out around the world show the deep traces in the individual and collective mind that deepen as more and more waves arrive. Depression is a mood disorder that involves feelings of sadness, loss, anger, or frustration. It can manifest itself in periods of a few weeks or more and interfere with the patient's daily life. Depression is the number one cause of disability and the relative risk of mortality for people with depression is 1.7 times greater than the risk for the general public. This work collects data reported around the world on the alarming increase in depressive and anxious symptoms in the world population during compulsory isolation. We also present the data collected so far regarding clinical studies on a potential solution to recurrent symptoms. The use of psilocybin microdoses, to treat emotional conditions, and cases of major depression disorders. This work presents the results and advantages and disadvantages, described by the scientists involved. The covid-pandemic put us all in confinement, not only physical but social and introspective and forever changed our way of seeing the world.

Keywords: Post-pandemic depression, Psilocin microdoses treatment, Clinical trials

INTRODUCTION

On December 31, 2019, the Wuhan Municipal Health Commission (Hubei province, China) reports a cluster of pneumonia cases in the city. It is later determined that they are caused by a new coronavirus. On January 5, 2020, the WHO publishes its first part on epidemic outbreaks related to the new virus. The part contains a risk assessment and a series of recommendations, as well as information provided by China to the WHO on the situation of patients and the public health response to the cluster of cases of pneumonia in Wuhan [1]. On March 20, 2020, the President of the Argentine Republic declares on the national chain, preventive and mandatory social isolation throughout the country. I think so begin the chronicles of this pandemic observed from my perspective.

Faced with a world situation that seems to extend into a second and third wave of infections and without foreseeing a near horizon, it is essential to consider the silent claims that show our most evident symptomatic behaviors. Listening to and heeding the body's messages and reactions is the first line of defense in what appears to be a new normal situation. Studies carried out around the world, show the deep traces both in the individual and collective mind that are becoming more pervasive, as more and more waves arrive. As we crash the second and, in some cases, the third wave of COVID-19, it is time to take steps to maintain, if not mental health, then at least mental hygiene in times of uncertainty.

According to the international medical consultation page, Midline plus, clinical depression is a mood disorder that involves feelings of sadness, loss, anger, or frustration. It can manifest itself in periods of a few weeks or more, and interfere with the daily life of the patient. The most common symptoms of depression include: irritability, apathy, difficulty falling asleep or drowsiness, significant change in eating habits, negative feelings of self-perception, inactivity and withdrawal from usual activities, hopelessness or abandonment, repetitive thoughts of death or suicide, loss of pleasure, including sexual drive [2]. Depression is the number one cause of disability [3], and the relative risk of all-cause mortality for those with depression is 1.7 times greater than the risk for the general public [4].

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A series of clinical studies were recently approved that introduce this indole alkaloid from the group of tryptamines, as a potential agent in the treatment of so-called emotional illnesses. Biologically psilocin is a metabolite present in varying concentrations in about 200 species of basidiomycete fungi. This work aims to explore psilocin as an alternative that is widely present in nature and historically consumed as entheogenic.

MATERIALS AND METHODS

All the works published in google scholar with the keywords: depression, anxiety, COVID lockdown, psilocybin, psilocybin microdosing, treatment of depression between 2018 and 2021 were reviewed. Those that had systematized the data collection method were selected.

RESULTS AND DISCUSSION

According to the report published in 2020 by the Social Research Center (CIS) of the UADE University - Argentina, the pandemic of SARs COVID-19 and the compulsory social isolation, generated sleep and appetite disorders, increased consumption of narcotic drugs and recreational drugs such as tobacco and alcohol, with respect to its habitual consumption in the Argentine Republic [5]. Preventive isolation was maintained from March to November 2020, although there are provinces of our country that lengthened the time of confinement and intensified the measures to maintain it. These data presented correspond to the month of May 2020. The analysis was approached by comparing the data with a study carried out previously in 2015, based on the responses of 1.315 respondents. The groups were sampled in all social strata and in an age range of 16 years or more. Researchers found that 100% of those surveyed: 67% manifested anxiety symptoms, 60% did not want to be informed about the disease, 58% had difficulty sleeping, 56% reported eating disorders (under and supra-alimentation), 37% reported feeling depressed, 31% feeling lonely. 12% of those surveyed stated that they had consumed narcotic drugs or other types of tranquilizers. Consumption was higher among the female population over 50 years of age [6].

A study carried out by the applied social psychology observatory of the University of Buenos Aires [7], yielded data on the psychological impact at 7-11, 50-55 and 115-124 days of lockdown in the population of the Argentine Republic. The percentage of people at risk of psychological disorder doubled, registering 4.86% of the total respondents during the 7–11-day period compared to 8.10% during the 115–145-day period in data collected throughout the country. In the Metropolitan Area of Buenos Aires (AMBA), this increase went from 4.9% to 9.5% ($z = 4$; $p = .01$). In the period of 115-145 days, 75.83% of the participants reported experiencing psychological distress, 54.2% of participants reported consume alcohol and 43.75% considered 7necessary psychological treatment [7].

Langsi [8], evaluate mental health and emotional responses to the effects of COVID-19 lockdown in sub-Saharan Africa (SSA). Data collected was analyzed by using a web-based cross-sectional study on mental health and emotional features from 2005 respondents in seven SSA countries. Their study was conducted between April and May 2020 period corresponding to the lockdown in SSA countries. Respondents aged 18 years and above and the self-reported symptoms were feeling anxious, being worried, angry and frustrated. Univariate and multivariate logistic regression analyses were used to identify the factors associated with these symptoms. They found that 52.2% of the participants reported any of the mental health symptoms and the prevalence of 59.1% feel anxiety, 57.5% being worried, 51.5% feel frustrated, and 22.3% feel angry during the COVID-19 pandemic [8].

In one study made in India [9] reported 30.5% of depression prevalence. The survey was conducted during second and third week of lockdown. Depression symptoms reaches the highest among the variables of psychological health. Anxiety was reported by 22.4%, followed by stress which was seen in 10.8% of respondents. Stress was of only mild to moderate degree on the mental health category. However, 1.7% from de respondents reported severe degree of depression and anxiety and 0.7% reported extremely level of anxiety. On week-wise analysis of impact of lockdown reported an increasing negative impact. In the third week the incidence of depression (37.8% versus 23.4%; $p<0.001$), anxiety (26.6% versus 18.2%; $p<0.001$) and stress (12.2% versus 9.3%; $p<0.045$) was reported to be significantly higher as compared to second week. In the scale of severity also all the studied components of mental health showed a deteriorating trend. These results suggest a progressively detrimental impact of lockdown on various aspects of psychological health. This work found an eight-to-ten-fold increase in the prevalence of depression (30.5%) and anxiety (22.4%) during lockdown, as compared to baseline statistics in Indian population (3.1 - 3.6% for depressive disorders and 3.0- 3.5% for anxiety disorders) [10].

Bueno-Novitol 11] conducted a study of the prevalence of depression during confinement. A total of 12 studies were included in the meta-analysis, with prevalence rates of depression ranging from 7.45% to 48.30%. The results suggest that depression rates in the general population could be 7 times higher during the COVID-19 outbreak compared to data collected in 2017 [12], the latest global estimated prevalence of depression is showing a proportion of 3.44% (ranging between 2 and 6%).

In another meta-analysis published in December 2020 [13], a systematic review was carried out to determine the prevalence of anxiety in the general population during the COVID-19 pandemic. Two researchers independently searched for cross-sectional community-based studies published between December 1, 2019 and August 23, 2020 with a percentage of

anxiety in the population in non-lockdown conditions of 7.5% [14]. Their results suggest that rates of anxiety in the general population could be more than 3 times higher during lockdown [13]. Also results shows that anxiety tends to reach its highest point at the peak of the epidemic, then waning in concert with its decline as it was previously observed in H1N1 outbreak [15].

Major depressive disorder (MDD) affecting more than 300 million individuals worldwide [16]. In the United States, approximately 10% of the adult population has been diagnosed with MDD in the past 12 months [17], 3 and the yearly economic burden of MDD is estimated to be $210 billion [18].

Patients with depression are treated with conventional pharmacological therapy. Previous studies showed a reduction or remission of symptoms of approximately 30% after treatment with drugs [19]. Also 50% of patients do not respond completely to the action of antidepressants, having to modify the doses permanently. Between 10% and 30% of patients were considered resistant to treatment, resulting in average effects that were only modestly larger than placebo effects [20,21].

Psilocybin belongs to the group of tryptamine derivatives or indole alkaloids. Biologically psilocin is a metabolite present in varying concentrations in about 200 species of basidiomycete fungi. Among them, 116 species of the genus *Psilocybe* stand out followed in order of abundance in nature by 14 species of *Gymnospilus*. The cap mushroom contains a higher concentration of psilocybin in the cap than in the thallus, and its mature mycelium may contain low concentrations of the metabolite, while the spores do not [22]. As with natural compounds in general, the doses and potencies vary from one specimen to another and as individual from the same batch of culture. Generally, a maximum dose of approximately 1.5% of the dry weight of the fungus is calculated (this can vary according to gender and species). The concentration also depends on environmental factors, such as growth conditions (temperature in the fruiting period between 25-28ºC), the drying conditions and the susceptibility to oxidation of the molecule, are factors that affect the concentration of the alkaloid.

Chemically, psilocybin or 4-PO-DMT or 4-phosphoryloxy-N, N-dimethyltryptamine, is a tryptamine that has a chemical structure derived from tryptophan with an indole-like configuration attached to an ethylamine substituent. Psilocybin belongs to the group of indole alkaloids also known as tryptamine psychedelics. The tryptamine psychedelics are structurally related to the endogenous neurotransmitter serotonin (5-HT; 5-hydroxytryptamine) and induce their psychological and physiological effects mainly through agonism of the 5-HT2A receptor [23,24].

Pharmacologically, it is a pro-drug whose active compound psilocin is synthesized by dephosphorylation through a dephosphorylation reaction once consumed [25]. The oxidation of psilocin by the enzyme hydrox-indole oxidase gives the dark blue compound ortho-quinone [26,27]. This electronic transfer that generates its color could be involved in the physiological activity of the alkaloid [28]· Its activity is mainly due to the structural similarity with the neurotransmitter serotonin.

Pharmacotechnologically, it must be considered that it is a zwitterionic alkaloid, soluble in polar solvents, fundamentally in water; it is easily oxidizable, which affects its stability during handling [29].

This tryptamine alkaloid is currently being studied in clinical trials for the treatment of depression and anxiety. There are two ways for its therapeutic administration that are the most studied. Single dose, given only once and the entire psychic journey process is carried out under the supervision of the therapist. And the way we will address in this review, which is microdosing.

The psychedelic ‘microdosing’ has gained a significant interest and prevalence in psychological treatments [30-32]. This method describes the frequent (e.g., near daily) intake of sub-threshold or threshold perceptible amounts of psychedelic substances. One of the most commonly described microdosing regimens involves dosing with a psychedelic every third or fourth day (e.g., 2 times per week) over a period of a few weeks [32].

Recommended and commonly used dose ranges lie between 5 and 20 µg of lysergic acid diethylamide (LSD), or 0.1- 0.5 g of dried psilocybin containing mushrooms (e.g., psilocybe cubensis) [32]. However, there is no scientifically established definition on what microdosing entails or what constitutes a typical, or indeed effective, microdose [33,34].

Kaertner [35] carried out a clinical study to evaluate the effect of microdoses of psilocybin in London. According to pandemic protocols, the work was carried out through an online observational study. They used a prospective and naturalistic design introducing as a reference the expectations of voluntary participants in the face of the imminent experience. Parameters such as anxiety and depression, measured on a numerical scale, were recorded weekly during the 5 weeks of the experiment.

Parameters such as neurosis vs emotional stability were evaluated before the first dose and at the end of the fourth week. Exploratory analyzes were designed to assess other changes in secondary psychological outcomes of interest, such as general well-being, and relaxation in everyday stressful situations. The study was approved by the Imperial College Research Ethics Committee (ICREC reference 18IC4361) and all procedure was explicit explained on informed consents. In this prospective study, volunteers were asked to answer an online survey in 5 periods: the week before the start of the clinical study, and once a week during the four weeks of the individual microdosing protocol. Some

volunteers carried out the microdosing regimen for 6 weeks, as part of the clinical study data were collected from the 5 and 6 weeks.

The 14-item Warwick-Edinburgh Mental Well-Being Scale (WEMWBS) [36] was used as the primary indicator of mental health and well-being. A questionnaire was used to identify variations in the subject's perception of well-being during the study.

WEMWBS also monitors hedonic and eudaimonic aspects of positive mental health, such as affect, psychological functioning, and the development of positive interpersonal relationships.

Variables such as depressive symptomatology, severity of symptoms and change in symptoms were recorded using the QIDS-SR16 model [37]. Anxiety state was assessed using the abbreviated form of the Spielberger Trait-State Anxiety Inventory (STAI-6) [38].

Kaertner [35] reported that the participants perceiving positive changes, such as a feeling of well-being and a decrease in depressive symptoms, a decrease in anxiety episodes, and greater emotional stability after 4 weeks of treatment.

Improvements were reported in some social skills that also contribute to the perception of well-being such as friendliness, social connection, and greater discursive flexibility. Also, a state of attention prone to the relationship with nature, resilience and creativity were reported.

These findings are consistent with other previously published data [39-42] and could be interpreted as further support for the positive statements about microdosing; set and setting are two factors to take into account to monitor the results of the treatment. There was no evidence that early side-effects such as an increase in anxiety predicted drop-out at 4 weeks. Almost ~ 50% of the present sample reported to have been diagnosed with one or more psychiatric disorders, suggesting its clinical relevance. The severity of self-reported depression and anxiety symptom scores approximated the normal/ healthy range within the first week of microdosing.

Along with the positive effects mentioned, there are also the acute negative effects. Feeling of anxiety and in some cases physiological discomfort, nausea and muscle cramps were reported [43,44]. Although it might seem negative, the anxiety experienced by the patients was later related to latent emotional content that surfaced from microdosing. Could this reaction help speed up the process of managing these discomfort-generating emotions? [45]. Albert Hofmann declared decades ago that "very small doses, perhaps 25 micrograms," could be useful as an antidepressant [46].

Moreno [47] reported the results obtained in a prospective clinical study (n = 9). The study consisted of the administration of variable microdoses in voluntary patients. The group had obsessive compulsive disorders. In addition to a low dose of psilocybin (25 mcg / kg body weight = 1.75 mg / 70 kg), three higher doses (100, 200, 300 mcg / 70 kg) were included. The reduction of symptoms was experienced after treatment with the lowest dose [48]. A very low dose of psilocybin was shown to bring about a state of balance between habitual behavior and cognitive control. This is relevant evidence for patients suffering from depression where emotional balance plays a fundamental role in controlling the condition [49]. However, future studies in (large) patient samples have to confirm this.

Administration of psilocybin to treat anxiety and depression in patients with terminal cancer [50]: Cancer diagnosis has a huge impact on most patients. Feelings of depression, anxiety, and fear are very common and are normal responses to this experience. With the aim of trying to reduce the anxiety and depressive symptoms associated with this pathology, several studies have been carried out with promising results [51]. With a group of 12 patients, a prospective study was carried out in which a control group with placebo (niacin) also participated. Selected patients had at least one DSM-IV anxiety-related disorder. The dose of psilocybin administered to the 12 end-stage cancer patients was 0.2 mg / kg orally, in sessions separated by several weeks apart. Depression scales such as Beck's Depression Inventory (BDI) and anxiety scales such as State Trait Anxiety Inventory (STAI) were used to measure the projection of the experiments and the effectiveness of the administered dose. The results showed that the patients who were treated with the microdose of psilocybin, showed a decrease in the scales and that the results were maintained over time, without the appearance of symptoms until 6 months after the treatment. No clinically significant adverse effects were recorded.

Another study [52] looked at 29 cancer patients diagnosed with one of several DSM-IV anxieties-related disorders. Patients were treated with a moderate oral dose of 0.3mg kg of psilocybin and the active placebo control group (niacin) in separate sessions every 7 weeks. Like the study described above, this study found significant clinical improvements in numerous domains when comparing the group that had received psilocybin with the control group. Benefits from therapy including reduced anxiety and depression, and increased quality of life. At a follow-up of approximately 6 months, the study showed lasting anxiolytic and antidepressant effects compared to baseline measures. The results show that the clinical response with antidepressant and anxiolytic response rates of 60% to 80% at 6 months of follow-up, and the reductions in anxiety and depression were greater for those patients who had subjective mystical experiences during the psilocybin sessions. No serious adverse events were attributed to psilocybin administration [52].

MDD-Resistant Depression [53,54]

MDD patients resistant to conventional treatments were tested with a first oral dose of 10 mg of psilocybin after a first

session and 25 mg in a second session seven days later. The evolution of symptoms was measured using the rapid inventory of depressive symptoms (BDI). Measurements decreased dramatically up to 3 months after the end of treatment compared to the initial scores.

The same pattern was found for anxiety symptoms measured by the STAI. Each individual participant showed a reduction in the severity of depression from the first week that was maintained in the majority for 3 months. Based on the standard criteria for determining remission with the BDI, 8 out of 12 reached the threshold for complete remission. Psilocybin did not cause any unexpected or serious adverse events.

The modification in the laws that approve the use in clinical trials of psychedelics in the last two years, opens a plethora of possibilities to have more systematic data and fundamentally with a greater statistical number of volunteers with emotional disorders. This has recently led to approval by the FDA of ketamine as a first in a new class of antidepressants [55]. Other compounds are being tested in multicenter phase III and II clinical trials, such as 3, 4-methylenedioxymethamphetamine (MDMA)-augmented psychotherapy for treatment-resistant post-traumatic stress disorder (PTSD) and psilocybin for treatment-resistant major depressive disorder (MDD) (ClinicalTrials.gov) [56]. Intriguingly, the potential use of psilocybin in alcohol use disorder and obsessive-compulsive disorder seems also promising, and several clinical trials are ongoing (Clinical and Mechanistic Effects of Psilocybin in Alcohol Addicted Patients, 2020; Efficacy of Psilocybin in OCD: A Double-Blind, Placebo-Controlled Study, 2020 [57].

CONCLUSION

With the current data and awaiting the results of the ongoing clinical trials, we can say that although encouraging about psychedelic microdosing and its therapeutic value for depression, the data is still inconclusive. This is due not to its demonstrated therapeutic potential, but to the number of volunteer subjects in the studies published so far. However, as discussed throughout this paper it is interesting to mention: that the effects on selective cognitive processes were demonstrated, resembling in a milder way the psychedelic effects of a higher single dose. This is a positive trait since psychosis and dissociative mental states are eliminated or significantly reduced as a risk of treatment. The so-called psychedelics do not produce cognitive impairment, accustoming, addiction and have a very wide therapeutic window. Some underlying cognitive mechanisms of action reported are the increase in synaptic connections during the administration session, the slowdown in the perception of time and the increase in cognitive flexibility and production of a heightened experience of "being in the present" or awake. All these sensations of mental well-being, favor the decrease of anchor thinking, the feeling of self-pity and symptoms such as listlessness and apathy, typical depressive symptoms. Classic psychedelic management can bring about a plastic state with respect to brain activity, and the psychotherapeutic context surrounding classic psychedelic management (including session preparation, session monitoring, and interpersonal support that encourages internal focus and post-session discussion, session experiences, session to harness those experiences to encourage lasting changes in behavior and attitude change) can serve to establish longer-term changes in brain activity.

The ability of these substances to "defragment" behavior patterns when they have reached an excessive level of petrification and obsessiveness is today the best hope of massive cure for all the millions of people suffering from depression, addictions and antisocial personality disorders. These authors are waiting for new data from the angoing clinical trials, for its final say. However, these advantages suggest that low doses of psychedelics could play a role in treating depression, when more and more waves past thrue the collectives and individuals' minds around the world. As I write these last few lines, the president of Argentina, is speaking on national television and presenting the new decree of necessity and urgency for our country to face the second wave of infections.

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