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SHORT REVIEW

Psilocybin - A Drug to be Considered for the Treatment of Anxiety and Depression in Cancer Patients

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Abstract

Cancer patients are more vulnerable to developing psychiatric disorders like anxiety and depression. These conditions give an additional burden leading to poor quality of life. The available antidepressant and antianxiety drugs are not very useful in improving quality of life by reducing anxiety and depressive episodes. Therefore, there is a need for good drugs to alleviate the psychiatric problems among cancer patients. The recent reviews deal with the pharmacodynamics, pharmacokinetics and efficacy of psilocybin in the treatment of patients suffering from anxiety and depression.

Keywords: Anti-anxiety, Anti-depressant, Cancer, Psilocybin

1. Introduction

Psychiatric disorders are a major public health concern affecting 350 million people and produce social and economic burdens worldwide[1]. Despite various efforts to understand the pathophysiological factors of mental illness, the treatment for depression and anxiety is not well addressed[2]. Patients with life-threatening diseases like cancer more often develop depression, anxiety, worthlessness, hopelessness and helplessness[3]. Anxiety and depression are common symptoms in cancer patients. The important causes are unbearable pain, treatment modalities such as chemotherapy and uncertainty about death have created a strong negative impact on patients[4]. Depression and anxiety are the main reasons for poor recovery and decreased survival time of cancer patients[5]. Most of the cancer survival patients exhibit psychological distress, reduced drug and treatment adherence, extended hospitalisation and decreased quality of life[6]. Patients with depression and anxiety among cancer are treated with antidepressants and benzodiazepines[7]. However, clinical improvement with these drugs has a high relapse rate and significant adverse effects[8].

2. Prevalence of Depression and Anxiety in Cancer Patients

Depression is one of the major problems in cancer patients. There is limited information regarding the prevalence of cancer in Asian countries. There are many therapeutic modalities available to treat cancer. However, the psychological problems experienced by cancer patients have not been well addressed. Many oncologists fail to detect psychiatric symptoms in cancer patients and fail to refer them to psychologists and psychiatrists. It has been found that there is a

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problem in diagnosing anxiety and depression in cancer patients due to the different factors contributing to the illness.

Based on the type of cancer, the patient receives different modalities of treatment like surgery, radiotherapy, and chemotherapy. Chemotherapy which is mainly composed of chemical agents either causes apoptosis of the cells or stops them from dividing. The side effects of chemotherapy are highly unbearable like pain, hair loss, diarrhoea, loss of appetite, bleeding, fatigue and increased risk of infection. These side effects are associated with loss of energy and motivational level which ultimately can lead to insomnia, anxiety and becoming emotionally labile. It has been found that some inflammatory cytokines are released due to the cancer treatment which is responsible for the mood disorder and fatigue. Poor adherence to drugs and suicidal ideations are a common problem associated with depression among cancer patients. As shown in Table 1, it has been observed that depression among cancer patients is mainly seen in the early stage of diagnosis and anxiety is usually observed when the chemotherapy session increases.

3. Role of Conventional Anti-depressants in Cancer Patients with Depression and Anxiety

Mianserin, fluoxetine and paroxetine were studied for their anti-depressant effects in cancer patients suffering from depression. It has been observed that Mianserin showed a positive effect whereas fluoxetine and paroxetine did not show much efficacy in treating depression and anxiety among cancer patients[10]. In a random control trial in the Netherlands, it was shown that 102 patients were administered venlafaxine for 12 weeks among depressive patients having breast cancer. In addition to the anti-depressant drug, they received chemotherapy and radiotherapy. The outcome of the study has shown a significant reduction in depression which was measured by the hospital anxiety and depression scale[11]. In another random control trial conducted in the USA, it was found that 163 patients having depression with metastatic cancer were administered fluoxetine for 12 weeks along with chemotherapy and radiotherapy. The results showed a significant reduction in depression and there was an improvement in the quality of life[12]. Further random control trial studies were conducted with citalopram for 16 weeks in 28 patients for the prevention of depression in head and neck cancer patients along with the regular treatment of chemotherapy, radiation therapy and surgical intervention. The study concluded that citalopram effectively prevented depression[13]. Escitalopram was administered for 16 weeks in 148 patients who were suffering from head and neck cancer to prevent depression. The result showed a significant effect in preventing depression and promoting quality of life[14]. Several random control trials were conducted on paroxetine in different types of cancer and it prevented depression in these patients. Cochrane database of systematic review has shown that there is no significant different in the efficacy of various antidepressant drugs compared with placebo, with only the exception of Mianserin[15].

Table 1. Prevalence of depression and anxiety among different types of cancer[9]

Sr. No.	Type of Cancer	Level of Depression (%)	Type of Cancer	Level of Anxiety (%)
1	Sarcoma	60	Blood	43
2	Lung	59	Gynecological	29
3	Blood	57	Breast	38
4	Gastro intestinal	50	Nasoph aryngeal	42
5	Neuroendocrine	50	Sarcomatous	30

4. Psilocybin in Cancer Patient with Depression and Anxiety

4.1 Molecular Structure of Psilocybin

As shown in Figure 1, Psilocybin is an alkaloid obtained from various genera of fungi like psilocybe. *In vivo*, psilocybin which actively gets converted into psilocin interacts with the 5-HT2A receptor in the central nervous system, thus mimicking the effect of serotonin. By looking into the molecular structure of serotonin and psilocybin there is a strong similarity between them suggesting a possible role in the treatment of depression and anxiety[16,17].

4.2 Pharmacokinetic and Pharmacodynamics Effects of Psilocybin

When psilocybin is ingested, it is broken down by the liver in a process called dephosphorylation.

Figure 1. Molecular structure of psilocybin and its related substance.

The resulting compound is called psilocin, which is responsible for the psychedelic effects[18]. Psilocybin and psilocin create a short-term increase in users' tolerance, thus making it difficult to misuse them because the more often they are taken within a short period, the weaker the resultant effects are[19]. Psilocybin mushrooms have not been known to cause physical or psychological dependence (addiction)[20].

The psychedelic effects tend to appear around 20 minutes after ingestion and can last up to 6 hours. Physical effects including nausea, vomiting, euphoria, muscle weakness or relaxation, drowsiness, and lack of coordination may occur. As with many psychedelic substances, the effects of psychedelic mushrooms are subjective and can vary considerably among individual users. The mind-altering effects of psilocybin-containing mushrooms typically last from three to eight hours depending on dosage, preparation method, and personal metabolism. The first 3–4 hours after ingestion are typically referred to as the 'peak'—in which the user experiences more vivid visuals and distortions in reality. The effects can seem to last much longer for the user because of psilocybin's ability to alter time perception[21].

Sensory effects include visual and auditory hallucinations followed by emotional changes and altered perception of time and space[22]. The exact mechanism of psilocybin is still mysterious. Few research postulated that hyperactivity of the medial Prefrontal Cortex (mPFC) could cause depression and the therapeutic effect of psilocybin might deactivate the medial prefrontal cortex[23]. Functional magnetic resonance imaging has detected that psilocybin effectively deactivating the medial prefrontal cortex. Other studies also have suggested that psilocybin reduces the amygdala activation[24]. The primary essential role of the amygdala is to recognise and experience emotion. Hyperactivity of the amygdala is a major cause of negative thought which is associated with an undesirable state of mood in depressive patients[25]. In depression, the default mode network activity is completely taken over by the parts of the brain which results in negative thought rumination. Therefore psilocin causes a change in the ability of the visceral cortex which can lead to modulation of perception and reduce the default mode network. Psilocybin also has an effect on brain's prefrontal cortex which regulates the thought analysis and play an important role in mood and perception[26,27]. It is a well-known fact that imbalance of serotonin is responsible for causing depression and other affective disorders. The drugs like SSRI, TCA and MOI are capable of increasing the concentration of serotonin at the receptor site. Therefore, these drugs are mainly used in the treatment of depression. Psilocin and psilocybin have been designated as a 5HT agonist by their high affinity with 5-HT_{1A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_6 and 5-HT_7 receptors. Therefore, there is a strong involvement of psilocin in the treatment of psychiatric disorders including anxiety, cognitive deficit and depression[28].

5. Clinical Studies on the Effect of Psilocybin in Cancer Patients with Depression and Anxiety

Conventional anti-depressant therapy is shown to produce limited efficacy in addressing depression and anxiety in cancer patients. The Clinical study of psilocybin in treating cancer patients with depression is still in the infantile stage. However, a few studies are been conducted in several countries. A double-blind, placebo-controlled trial was conducted among patients with end-stage cancer and the presence of anxiety disorder. The study employed 12 participants having an age range between 36 to 58 years. The participants were recruited based on the eligibility criteria like confirmed end-stage cancer with anxiety disorder, and the duration of cancer ranged from 2 months to 18 years. Cancer involvement in the central nervous system, uncontrolled hypertension, and hepatic and renal dysfunction patients were excluded from the study. Out of 12 participants, 4 patients had cancer of the breast, 3 ovarian, 1 peritoneum 1, salivary

gland and 1 suffered with multiple myeloma. All the participants were divided into 3 groups. The first group subjects were administered 0.2mg/kg of psilocybin in the first session and niacin 250mg in the second session. Psilocybin and a placebo were administered in the second group and a niacin placebo was given in the third group. The safety and subjective experience of the psilocybin was monitored with the use of the Beck depression inventory and anxiety inventory scale for 6 months after treatment. The study also showed a significant reduction in anxiety after the first and third months of treatment. Further, it was observed that there was a significant reduction in depressive symptoms and improvement in the mood state after 6 months of psilocybin treatment.

In another study, a random controlled crossover research was conducted to find out the effectiveness of a single dose of psilocybin 0.3mg/Kg versus one dose of active control Niacin 250mg given along with psychotherapy to treat anxiety and depression in patients with cancer. The trial had two sessions, Twenty-nine subjects were randomly allocated into two treatment groups. In the first group, psilocybin was administered initially with 0.3mg/kg and niacin 250mg/Kg after 7 weeks of interval. The second group was initially treated with niacin 250mg and psilocybin with 0.3mg/kg after 7 weeks. The efficacy of the drug was examined one day prior to the psilocybin administration and 2, 6, and 7 weeks after the first dose respectively. The second dose efficacy was also examined as it was done in the first dose. The antianxiety and antidepressant effects were examined even after 9 months of two-session treatment. The study revealed immediate and sustained improvement in depression and anxiety among patients suffering from cancer. Further psilocybin has shown significant improvement in the quality of life. The mystical effect of psilocybin showed that cancer patients were able to overcome the anxiety and depressant even after the 6-month follow-up[29].

In the third random crossover trial, 15 patients having cancer-related psychiatric distress like depression and anxiety were involved in the study. Selected patents were randomly divided into two groups. Group one was administered psilocybin 0.3mg/kg in the first session followed by the second session of niacin 250mg after 7 weeks. In the second group, niacin 250mg was administered in the first session followed by 0.3mg/kg psilocybin in the second session. Along with that nine sessions of psychotherapy were delivered. The parameters were investigated at 6.5 months after the second session of administration and the results showed a significant reduction in depression. The second follow-up was conducted after 4.5 years and it was shown that 60-80 % of patients exhibited antidepressant and anti-anxiety responses. Further, it is concluded that psilocybin in conjunction with psychotherapy facilitates the promotion of psychological, emotional and spiritual well-being of the patient with cancer[30].

A further random crossover trial was conducted to examine the effect of a very low dose of psilocybin 3mg/70kg versus a high dose of psilocybin 22 or 30mg/70kg was administered. The follow-up was examined at six months. Subjects, staff and community observer scales were used to assess the mood, attitude and behaviour of the participants. The results revealed that participants who received high doses of psilocybin have shown a substantial decrease in depression, anxiety, death anxiety and improvement in the quality of life. About 80% of the participants continued to show a marked reduction in depression and anxiety among cancer patients[31,32].

6. Conclusion

Since conventional anti-depressant drugs have limited efficacy with side effects, it is necessary to search for a new drug with a lower frequency of administration. In this context, psilocybin can be considered an ideal agent for treating anxiety and depression in cancer patients. Treatment with psilocybin to primary depressive patients may tend to develop addiction. However, administering to advanced cancer patients with depression and anxiety would be a great benefit to their better quality of life. In this regard, no clinical study has been done in India for the benefit of cancer patients suffering from anxiety and depression. Therefore it is necessary to conduct a clinical study with psilocybin in an Indian scenario. If psilocybin-containing medicines get approved, they should be included in the Schedule IV of Controlled Substances. Terminally ill cancer patients who are suffering from depression may have a dignified life with the help of psilocybin. The development of addiction after psilocybin in this case is not a concern.

Further, this drug should be monitored for any kind of misuse. Finally, the drug should be categorised under orphan drug if approved.

7. References

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