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Are psychedelics effective in treating anxiety associated with a lifethreatening disease?

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Are psychedelics effective in treating anxiety associated with a life-threatening disease?

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ABSTRACT

OBJECTIVE: The objective of this selective Evidence Based Medicine (EBM) review is to determine whether or not "Are psychedelics effective in treating anxiety associated with a life-threatening disease?"

STUDY DESIGN: Review of two double-blind, randomized, placebo-controlled pilot studies and one randomized controlled trial (RCT).

DATA SOURCES: All studies were published in peer-reviewed journals found via the use of PubMed Database.

OUTCOMES MEASURED: The outcome measured in this EBM was the effect of psilocybin or LSD on the reduction in anxiety. Reduction in anxiety was measured using either the Hamilton Anxiety Rating Scale (HAM-A) or the State-Trait Anxiety Inventory (STAI). Participants subjectively rated their anxiety pre- and post-drug administration.

RESULTS: The results of each study reached statistical significance, indicating psilocybin or LSD to be an effective form of treatment for anxiety in patients with a life-threatening disease. The study by Gasser et al. showed a significant reduction in state anxiety from baseline to 2 months post-LSD administration ($p = 0.021$). Grob et al. showed a significant decrease in trait anxiety at the 1-month ($p = 0.001$) and 3-month ($p = 0.03$) follow-ups after psilocybin administration. Lastly, Griffiths et al. found that 76% of patients administered high-dose psilocybin had a $\geq$50% reduction in their anxiety 5 weeks after treatment as compared to 24% of those participants in the control group, with a number needed to treat (NNT) of 2.

CONCLUSION: Both pilot studies and the RCT included in this review indicate that LSD or psilocybin are an effective treatment for anxiety associated with a life-threatening disease.

KEY WORDS: Psilocybin, Lysergic Acid Diethylamide, Anxiety

INTRODUCTION

Anxiety is among the most prevalent mental health disorders in the United States. It is an expected, normal, and transient response to stress; however, anxiety is pathologic when it has no identifiable internal or external trigger, exceeds a patient's capacity to bear discomfort, the symptoms are persistent, and it results in avoidance and/or withdrawal behaviors. Anxiety is characterized by persistent feelings of apprehension and excessive worry, and can be accompanied by somatic symptoms (e.g. palpitations, chest tightness, lightheadedness, restlessness). It also has the ability to alter one's cognitive and affective functioning.

Anxiety disorders are the most common mental illness in the United States. Approximately 40 million people older than the age of 18 are affected.[1] Individuals with a life-threatening disease, such as pancreatic cancer or Parkinson's disease, are especially vulnerable to developing anxiety. It is estimated that 2-14% of terminally ill patients suffer from anxiety disorders, with generalized anxiety disorder (GAD) and panic disorder being the most common manifestations.[2] Roughly 25-48% of patients exclusively with cancer experience both psychological and physical anxiety-related symptoms.[2] Not only is the prevalence of anxiety high, but so too is the cost. In the U.S., anxiety disorders have been estimated to cost between $42.3 and $46.6 billion annually.[3] The mean total medical cost for a patient diagnosed with an anxiety disorder is $6,475.[3] An estimated total of $18.4 billion has been spent on prescription medications for those individuals diagnosed with anxiety or a mood disorder.[4] It is also one of the most common reasons for psychiatric consultation among those patients suffering from fatal illness.[2] No recent estimates have been made on the number of annual visits made for anxiety; however, a study published in 2002 noted an increase from 9.5 million visits in 1985 to 12.3

million visits in 1997-1998, indicating a rising trend in the number of healthcare visits scheduled for anxiety-related conditions.[5]

Anxiety is thought to arise from an unknown internal stimulus or is an inappropriate or excessive response when compared to an external stimulus. The cause of anxiety is multi-factorial, involving environmental, social, and biological factors. Several environmental and social factors can predispose one to anxiety. For instance, more recent stressful life events, especially those characterized by illness and death, increase the risk of anxiety and depression.[6] In patients with a known medical illness, the condition, its complications, and the treatment of the illness are all suspected to be causes of anxiety. Biologically, both the hippocampus and activation of the amygdala are also noted to have a role in the development of anxiety. Connections between the amygdala and pre-frontal cortex are responsible for the conscious experience and regulation of emotion.[6] Brain imaging studies have demonstrated that individuals with anxiety show amplified responses in these areas of the brain when confronted with an emotionally intimidating stimulus. This indicates that individuals with anxiety may have a pre-existing abnormality in the neural connection between the pre-frontal cortex and amygdala that predisposes them to anxiety disorders.[6] Many neurotransmitters also generate and modulate anxiety symptoms, including norepinephrine, serotonin, dopamine, and GABA.

Many treatments are available to control episodes of anxiety as well as exacerbations of anxiety. Most commonly used at the selective serotonin reuptake inhibitors (SSRIs), such as paroxetine (Paxil), fluoxetine (Prozac), sertraline (Zoloft), citalopram (Celexa), and escitalopram (Lexapro). These medications block the reuptake of serotonin at pre-synaptic receptors. Second line medications that have been used are serotonin-norepinephrine (NE) reuptake inhibitors (SNRIs). These medications include duloxetine (Cymbalta) and venlafaxine (Effexor), and are

similar to SSRIs, but also block the reuptake of NE and dopamine. Benzodiazepines are indicated for short-term use in the management of anxiety. These medications include, lorazepam (Ativan), alprazolam (Xanax), and diazepam (Valium). The treatment options described above are effective in treating anxiety. However, each class of medication has demonstrated various gastrointestinal and cardiac side effects (e.g. hypertension) in different types of people. Cancer patients, specifically, fail to achieve satisfactory relief from the available medications previously listed. Without appropriate treatment, anxiety persists as a serious problem for these people. This population thus warrants the need for more effective interventions. Psilocybin and LSD are potential alternatives that may be effective in the treatment of anxiety associated with cancer. This paper evaluates two double-blind, randomized, placebo-controlled pilot studies and 1 randomized control trial (RCT) surveying the effects of psychedelics, specifically psilocybin or lysergic acid diethylamide (LSD), in the treatment of anxiety related to a life-threatening disease.

OBJECTIVE

The objective of this selective Evidence Based Medicine (EBM) review is to determine whether or not "Are psychedelics effective in treating anxiety associated with a life-threatening disease?"

METHODS

This investigation looks at two double-blind, randomized, placebo-controlled pilot studies and one randomized controlled trial (RCT). The population of the studies used for this review includes both men and women diagnosed with a life-threatening disease as well as a *DSM-IV* anxiety disorder diagnosis. Participants across all studies were older than 35 years of age. All studies used a psychedelic, either LSD or psilocybin, as the intervention and an active

placebo. Active placebos were chosen in order to produce mild and detectable effects of the drugs, but were not substantial enough to produce any therapeutic effects. The purpose of the active placebo is to aid in the blinding of the study. In Gasser et al., the intervention addressed was LSD. LSD was administered orally as capsules consisting of 200 μg. The subjects acted as their own control. The comparison group consisted of an active placebo of 20 μg of LSD. In Grob et al., the intervention addressed was psilocybin. Subjects were administered active psilocybin (0.2 mg/kg). The placebo was niacin (250 mg).[8] Griffiths et al. utilized psilocybin as the therapeutic intervention. High dose psilocybin (22 or 30 mg/70 kg) was administered orally in opaque, size 0 gelatin capsules with lactose as the capsule filler. A placebo-like low dose of psilocybin (1 or 3 mg/70 kg) was utilized as the comparison group.[9] The main outcome measured was a reduction in anxiety as demonstrated by either the State-Trait Anxiety Inventory (STAI) or the Hamilton Anxiety Rating Scale (HAM-A).

The author, using the key words "lysergic diethylamide acid," "psilocybin," and "anxiety," carried out a detailed search using the Cochrane Systematic Review and PubMed. All studies were published in English in peer-reviewed journals. All studies were published after the year of 2010 and were selected based on their relevance to the topic and whether or not they included patient oriented evidence that matters (POEMs). Inclusion criteria for this systematic review randomized controlled trials. Exclusion criteria included previous Cochrane reviews as well as systematic reviews submitted by previous students. Inclusion and exclusion for the individual studies are included in Table 1. The statistics of this study used to evaluate patient outcomes included *t*-value, *p*-value, *F*-score, RBI, ABI, NNT. All studies used similar statistics to evaluate the outcomes where *p*-value is considered statistically significant if it is ≤ 0.05 or ≤ 0.025 (two-tailed). The demographics of the studies are included and outlined in Table 1.

Table 1: Demographics & Characteristics of Included Studies

Study	Type	Number of Patients	Age (years)	Inclusion Criteria	Exclusion criteria	W/D	Interventions
Gasser, et al. (2014)[7]	double-blind, randomized, placebo-controlled pilot study	12	39-64 y/o	patients w/ a life-threatening disease with a score greater than 40 on either the state or trait scale on the Spielberger State-Trait Anxiety Inventory	current alcohol or drug dependence; bipolar I, dissociative disorders; neurocognitive impairment; women pregnant or nursing	2	lysergic diethylamide acid (200 μg) in capsules
Grob, et al. (2011)[8]	double-blind, randomized, placebo-controlled pilot study	12	36-58 y/o	advanced-stage cancer and a *DSM-IV* diagnosis of acute stress disorder, generalized anxiety disorder, anxiety disorder due to cancer, or adjustment disorder with anxiety	CNS involvement of the cancer, severe cardiovascular illness, untreated HTN, abnormal hepatic or renal function, DM, life-time history of schizophrenia, bipolar disease, anxiety or affective disorders within 1 year prior to the onset of the cancer, active cancer chemotherapy, antiseizure medications, insulin/hypoglycemic medications, or psychotropic medications 2 weeks prior to treatment	4	psilocybin (0.2 mg/kg) with 100 mL of H_2O in clear 00 capsules with corn starch
Griffiths, et al. (2016)[9]	randomized controlled trial	56	mean age of 56 y/o	life-threatening cancer diagnosis and a *DSM-IV* diagnosis that included chronic adjustment disorder with anxiety, chronic adjustment disorder with mixed anxiety and depressed mood, dysthymic disorder, generalized anxiety disorder, or major depressive disorder	CNS involvement of cancer, hepatic dysfunction, paraneoplastic syndrome, uncontrolled HTN, angina, EKG abnormality, stroke, epilepsy, renal insufficiency, DM1, pregnant females	10	psilocybin (22 or 30 mg/70 kg) administered in opaque, size 0 gelatin capsules with lactose as the capsule filler

OUTCOMES MEASURED

The main outcome measured in the selected studies is the effectiveness of psychedelics, specifically LSD and psilocybin, in the reduction of anxiety associated with a life-threatening disease. Gasser et al. and Grob et al. utilized the State-Trait Anxiety Inventory (STAI).[7,8] Participants subjectively rated their anxiety pre- and post-drug administration. The STAI measures anxiety by assessing feelings of apprehension, tension, nervousness, and worry.[8] The

STAI measures state and trait anxiety separately. State anxiety refers to a temporary state of anxiety. The state anxiety subscale of the STAI gears its questions towards the patient's present feelings of anxiety. Trait anxiety refers to long-standing and enduring feelings of anxiety. The trait anxiety subscale assesses the patient's overall view of him or herself as a person. The STAI has 20 items for assessing trait anxiety and 20 items for state anxiety. All items are rated on a 4-point scale (e.g., from "Almost Never" to "Almost Always"). Higher scores indicate greater anxiety.

Griffiths et al. utilized the Hamilton Anxiety Rating Scale (HAM-A). HAM-A is a clinician-rated scale that consists of 14 items (anxious mood, tension, fears, insomnia, intellectual depressed mood, somatic (muscular) symptoms, somatic (sensory) symptoms, cardiovascular symptoms, respiratory symptoms, gastrointestinal symptoms, genitourinary symptoms, autonomic symptoms, and behavior during the interview). Each item is graded on a scale from 0 to 4. The HAM-A score can range from 0 to 56. A score < 17 is indicative of mild anxiety, 18-24 indicates mild to moderate anxiety, and 25-30 indicates moderate to severe anxiety.

RESULTS

Gasser et al. conducted a pilot study that was 12 months in duration. Subjects were randomly assigned to an experimental or comparison group. Those in the experimental group (n = 8) received 200 μg of LSD. Those in the comparison group were administered 20 μg (n = 4) of LSD. This dose of LSD was chosen to produce mild and detectable effects of LSD, but were not substantial enough to produce any therapeutic effects. The purpose of using LSD as an active placebo was to produce noticeable effects to convince the subject that he/she was receiving the legitimate treatment. All subjects were blinded to the condition assignment. LSD was

administered to the subjects at two separate times, 2-3 weeks apart, in the setting of a quiet and safe private practice office. The STAI was administered to the subjects prior to treatment, after each experimental session, and then again at a 2-month follow-up. After the 2-month follow-up, the conditions were revealed to the subjects. Those subjects that received the placebo were offered the opportunity to crossover to receive the active intervention; however, this was not blinded. All subjects, including those that participated in the open-label crossover, were required to complete a 12-month follow-up of the STAI. At the conclusion of the 2-month follow-up, all subjects that entered the trial were accounted for; however, at the 12-month follow-up after the open-label crossover, only 6 of the 8 subjects in the original experimental group completed the 12-month follow-up evaluation (1 subject died due to cancer, 1 subject did not complete the evaluation). One subject from the active placebo group was not analyzed due to the development of exclusion criteria. Therefore, only 3 subjects from the active placebo completed the open-label crossover. Those 3 subjects participated in the 12-month follow-up evaluation. Thus, only 9 total subjects completed the 12-month follow-up.

The effect of LSD on anxiety was measured utilizing the STAI. Analysis of variance (ANOVA) was used to assess for significant changes in anxiety from baseline to post-LSD administration. State and trait anxiety were analyzed separately. Significance was demonstrated by $p < 0.025$ (two-tailed). Prior to treatment, no significant difference was found in the mean STAI-Trait scores ($p = 0.261$) or STAI-State scores ($p = 0.563$) between the groups at baseline. There was no significant difference in trait anxiety from baseline to 2 months post-LSD administration in the experimental group ($F(2,18) = 4.151$, $p = 0.033$). Those subjects receiving the active placebo experienced increased trait anxiety, but this was not found to be statistically significant. There was a significant difference in state anxiety from baseline to 2 months post-

LSD administration in the experimental group ($F(2,18) = 4.846$, $p = 0.021$), see Table 2. The F-score is higher than its respective F-critical value, indicating that LSD was effective in reducing state anxiety 2 months after drug administration. The p-value indicates that this effect is significant ($p < 0.025$). Those individuals receiving the active placebo experienced an elevation in state anxiety, but again, this was not found to be statistically significant. At the 12-month follow-up after the open-label crossover, the mean difference between state anxiety at 2 months and state anxiety at 12 months was 1.0 ($p = 0.531$). This indicates there was no significant change in state anxiety from 2 months to 12 months, indicating that the effect of LSD in reducing state anxiety was maintained over time.

Table 2. Mean Change in STAI-State or STAI-Trait Anxiety as Measured by Gasser et al. 2014

	Baseline		2-Month Follow-Up		12-Month Follow-Up
	Experimental	**Placebo**	**Experimental**	**Placebo**	**All**
STAI-Trait	53.2	43.3	45.2	49.0	41.1
STAI-State	53.1	47.7	41.5*	51.7	36.1

*$p = 0.021$

Grob et al. conducted a pilot study that was 6 months in duration. Subjects participated in two experimental sessions that took place several weeks apart. Subjects acted as his/her own control, and were informed that they would receive 0.2 mg/kg of psilocybin during one session and 200 mg of niacin during the other session; however, the order in which the subjects received those treatments was randomized. The STAI was administered to and completed by participants 1 day prior to treatment, 6 hours after treatment, 1 day after treatment, and 2 weeks after treatment. The STAI was then also administered at monthly intervals for 6 months following the study. A t-test was used to compare the STAI at baseline to the STAI values 1, 2, 3, 4, 5, and 6 months following psilocybin treatment. The t-test determines if the 2 groups being compared (pre-psilocybin administration and post-psilocybin administration) differ significantly. The t-value is compared to a critical value. If the intervention in question has an effect, the t-value will

be greater than the critical value. The significance of this effect is then determined by a *p*-value. In this study, $p < 0.05$ was considered clinically significant. At the conclusion of the 3-month follow-up, all subjects that entered the trial were accounted for; however, only 8 of the 12 subjects completed the 6-month follow-up STAI (2 participants died and 2 were too sick to continue participating).

The numerical values of the STAI mean scores, as well as the mean change from baseline, were not presented within the article. Data were presented graphically. The STAI did not show any significant changes in state or trait anxiety from baseline to 2 weeks after psilocybin administration. There was a decrease in state anxiety 6 h following psilocybin administration, but it was not found to be clinically significant. There were no significant findings of the effect of psilocybin on state anxiety for follow-up. However, there was a decrease in trait anxiety at the 1-month follow-up ($t_{11} = 4.36$, $p = 0.001$) and 3-month follow-up ($t_{10} = 2.55$, $p = 0.03$). The *t*-scores indicate that the psilocybin had an effect on STAI trait anxiety 1 and 3 months following treatment. The *t*-scores from the 1- and 3-month follow-ups are higher than their respective critical *t*-values. Therefore, the large *t*-scores demonstrate that psilocybin had a large effect in reducing trait anxiety 1 and 3 months following psilocybin administration. Psilocybin's effect was large, and the *p*-values indicate that its effect in reducing trait anxiety is significant ($p < 0.05$).

Griffiths et al. conducted a RCT that was 6 months in duration.[9] The subjects acted as their own controls. Subjects were told they would be receiving psilocybin, but the order of administration of the treatments was randomized. In this study, a low dose and high dose of psilocybin was used. Subjects in the comparison group were administered a placebo-like low dose of psilocybin (1 or 3 mg/70 kg). The low dose was decreased from 3 to 1 mg/70 kg after

concern that the 3 mg/70 kg dose may show significant therapeutic effects, and thus would not be an inactive placebo. Subjects in the experimental group were administered 22 or 30 mg/70 kg. The high dose was decreased from 30 to 22 mg/70 kg after 2 of the first 3 participants that received the 30 mg/70 kg dose of psilocybin were removed from the study (1 subject vomited shortly after capsule administration and 1 left due to personal reasons). The study also indicated that psychologically challenging experiences were more likely to occur with a 30 mg/70 kg dose of psilocybin.

A clinical response to the psilocybin was defined as a ≥50% decrease in the HAM-A score relative to baseline. Five weeks after the first session and prior to crossover, there was a significant difference between subjects in the High-Dose-1st group compared to subjects in the Low-Dose-1st group. Significance was indicated by $p < 0.001$. Approximately 76% of patients administered the high-dose psilocybin (22 or 30 mg/70 kg) had a ≥50% reduction in their anxiety 5 weeks after treatment as compared to 24% of those participants receiving the low-dose psilocybin. The NNT was calculated to be 2 (see Table 3). This positive number indicates that two patients are needed to treat in order for one patient to have a ≥50% decrease in their anxiety (as measured with the HAM-A score) compared to the placebo.

Table 3: Efficacy of Psilocybin in the Treatment of Anxiety Associated with a Life-Threatening Disease as Measured by Griffiths et al. 2016

Study	Control Event Rate (CER)	Experiment Event Rate (EER)	Relative Benefit Increase (RBI)	Absolute Benefit Increase (ABI)	Number Needed to Treat (NNT)	*p*-value
Griffiths et al. (2016)	0.24	0.76	2.2	0.52	2	< 0.001

DISCUSSION

The three RCTs analyzed in this systematic review demonstrated a significant reduction in state or trait anxiety through the administration of either LSD or psilocybin.[7,8,9] Lysergic acid diethylamide is a semisynthetic compound that produces many psychosensory changes, such as

increased sensory perception and hallucinations, when administered in large doses. It exhibits its psychedelic effects through the activation of 5-HT_{2A} receptors.[7] Psilocybin is a natural hallucinogen found in various types of mushrooms. It is a 5-HT_{2A} receptor agonist that, when administered in larger doses, produces fluctuations in thoughts, perceptions, and emotions.[8,9] There are no current uses for psilocybin and LSD in medicine today. They are considered "street drugs" used primarily for the purpose of experiencing euphoria. Both drugs are frequently associated with triggering panic attacks or feelings of extreme anxiety when used in excess. However, in a controlled environment, when LSD and psilocybin are administered at higher doses, it is thought that they induce moments of catharsis.[7] These drugs are capable of provoking powerful spiritual experiences, during which users feel they have come in contact with a greater existence and sense of liberation.[7,8,9] It is these psychosensory effects of LSD and psilocybin that enable those with anxiety to persevere through the mental and emotional burden that they carry. Therefore, by establishing an appropriate treatment protocol and therapeutic window of both LSD and psilocybin, these drugs can serve as effective anxiolytics, especially in those patients with a terminal disease.

Both LSD and psilocybin are not currently approved for use in medicine by the FDA. Furthermore, they are on the illicit market and are illegal in the U.S. due to their high potential for abuse and side effect profile. However, psychedelic properties of these drugs in a controlled setting may play a role in the reduction of anxiety. Serotonin deficiency is a proposed causal theory of anxiety.[6] LSD and psilocybin exhibit their psychedelic effects through the activation of 5-HT_{2A} receptors.[7,8,9] In activating 5-HT_{2A} receptors, these drugs may also stimulate the release of more serotonin, thus replenishing the serotonin that is lacking in those individuals with anxiety.

It is important to acknowledge the limitations that exist across each of the studies. Although the participants were kept blind, when administering a hallucinogenic drug like psilocybin or LSD, the blinding of each of the studies was challenged. Psilocybin and LSD, when compared to the alternative placebo, produced discriminable effects; therefore, the order in which the drugs were administered was made apparent to some of the subjects. Across all studies, a strict exclusion criteria were also used, resulting in a small sample size. A small sample size reduces the precision of statistics and does not adequately reflect an entire population. The population addressed is also a challenging population due to their advanced-stage cancer diagnoses. When advanced, cancer has the potential to alter the patients' physical and mental states, thus potentially altering the patients' overall interpretations of the therapy.

CONCLUSION

Psilocybin and LSD are effective alternatives for the treatment of anxiety associated with a life-threatening disease. The randomized controlled trials analyzed in this systematic review showed significant reduction in anxiety after the administration of psilocybin or LSD. Although not specifically addressed in this systematic review, psychotherapy in addition to the use of psychedelics yields the most effective treatment for anxiety.[7,8,9]

Despite the promising results presented within each of these articles, further research is warranted to draw conclusions regarding the best treatment protocol. Given the hallucinogenic properties of these drugs, it is important to establish a therapeutic window that proves most beneficial without eliciting undesired psychical and psychological side effects, such as tremors, hyperglycemia, hyperreflexia, visual hallucinations, suicidal ideations, etc. The populations enrolled in each of the studies were substantially limited due to a strict inclusion/exclusion criteria. Future studies should aim to broaden the inclusion/exclusion criteria to include a wider

and more generalized population of individuals affected by anxiety. By enrolling a wider range of subjects, psychedelics will not only be used for anxiety associated with a terminal disease, but are also likely to be utilized for the treatment of anxiety in the generalized population.

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