Spring 5-18-2021

Making the Case for Psychedelics: Comparing Alternative Treatment Options for Depression

Nicole Amavisca
University of San Diego

Honors Thesis Approval Page

Student Name: Nicole Amavisca

Title of Thesis: Making the Case for Psychedelics: Comparing Alternative Treatment Options for Depression

Accepted by the Honors Program and faculty of the Department of Psychological Sciences, University of San Diego, in partial fulfillment of the requirements for the Degree of Bachelor of Arts.

FACULTY APPROVAL

Jena Hales		
Faculty Project Advisor (Print)	Signature	Date
Dr. Susannah Stern		
Honors Program Director	Signature	Date

Making the Case for Psychedelics:
Comparing Alternative Treatment Options for Depression

A Thesis

Presented to

The Faculty and the Honors Program

Of the University of San Diego

By

Nicole Amavisca

Behavioral Neuroscience

2021

Abstract

Given the number of people who are treated for depression each year and the knowledge that treatments work differently for everyone, there is a pressing need to provide a variety of treatment options. Although psychedelic research had been halted for a few decades due to recreational abuse, there has been revived interest due to its therapeutic potential in the treatment of mood disorders and addiction. As an example, the hallucinogen ketamine has recently been approved as a treatment for depression, which has opened the door for broadening the discussion on psychedelic research. Although the research is limited, psilocybin mimics ketamine in that it shows promising results as a fast-acting antidepressant—especially when paired with psychotherapy. The rapid onset of relief is a novel characteristic for depression treatment, as traditional antidepressants take 4-6 weeks before taking full effect. Additionally, current antidepressants must be ingested daily, whereas research suggests that just a single treatment of ketamine or psilocybin can provide rapid antidepressant effects. This review will compare the antidepressant potential of the hallucinogens ketamine and psilocybin against the traditional antidepressants, bupropion and selective serotonin reuptake inhibitors (SSRIs). Efficacy and tolerability will be discussed, along with safety and abuse potential. Although more data are needed, current research suggests that ketamine and psilocybin are safe, effective, tolerable, and fast-acting treatments for depression.

Introduction

The COVID-19 pandemic has been the greatest medical concern worldwide since the beginning of 2020; however, one of the dangerous and unseen effects of the stay at home orders and disruption to daily activities has been a drastic increase in the prevalence and severity of depression (Ettman et al., 2020). The prevalence of US adults experiencing depression symptoms more than doubled in April and March of 2020. While less than 25% of the population was experiencing depressive symptoms of mild or greater severity in 2017 and 2018, this number increased to 52.5% during the spring of 2020. Major Depressive Disorder (MDD), or clinical depression, is diagnosed if someone experiences persistent depression symptoms for extended periods of time. The lifetime prevalence of MDD is around 20%; however, as the number of people experiencing depressive symptoms has increased due to COVID-19, it is anticipated that the prevalence of MDD will also increase (Hasin et al., 2018).

If rates of clinical depression increase, then the societal and economic burdens that are associated with depression will increase, as well. The increased risk of mortality for people with depression puts stress on families, work places, and communities (McLaughlin, 2011). The increased mortality risk is due to higher rates of suicide, as well as the psychological stress of depression that leaves patients more vulnerable to other health problems (Bica et al., 2017). People with depression are not only more likely to contract COVID-19, but they also experience higher death and hospitalization rates as a result (Wang et al., 2021). The increased use of health resources that people with depression utilized was approximately $83 billion in 2012 (McLaughlin, 2011). However, with depression being a risk factor for COVID-19 hospitalization, it is probable that this will create an even greater stress on the economy by way of increased use of health resources. Additionally, people with depression lose an extra four

hours of productivity compared to those without depression (McLaughlin, 2011). The loss of productivity amounts to approximately 225 million lost work days per year, creating a significant burden for employers. In order to mediate these social and economic burdens, some of the treatment options that are offered include psychotherapy, drug-based options, and brain stimulation therapies such as electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS). Of the currently available options, antidepressants are one of the most common treatments suggested by doctors.

Antidepressant use has gone up 64% between 1999 and 2014, where 13% of the population was given a prescription in 2014 (Winerman, 2017). Although antidepressants cause a decrease in depressive symptoms in most patients, there is no treatment that provides relief for everyone. Currently, as many as 30-50% of people with depression are left without symptom relief from antidepressants (Mrazek et al., 2014). Around 12-20% of patients do not see a response to two or more antidepressants and are designated as having treatment resistant depression (TRD). Patients with TRD pose even higher societal and economic burdens, using an additional $29-$48 billion in health resources annually when compared to people with treatment responsive depression.

These increased burdens resulting from TRD and treatment non-responders in general should encourage the exploration of depression treatments that may provide a necessary clinical solution to TRD. Recently, the hallucinogens ketamine and psilocybin have been of interest due to their therapeutic potential in treating depression. As an example, a synthesized component of ketamine, esketamine, was recently approved by the FDA as a treatment for TRD, and the first clinical trial comparing psilocybin to an antidepressant was published in 2021. These recent advances indicate a renewed interest in the therapeutic potential of hallucinogens, which

encourages discussing antidepressants and hallucinogens side by side. The current review will compare SSRIs, bupropion, ketamine, and psilocybin to better understand the therapeutic potential of each in treating depression.

Comparisons will be made based on three main traits: effectiveness, safety, and tolerability. This review will be looking at effectiveness in achieving response and remission separately. A response is considered a reduction in score from baseline of at least >50% in either the Quick Inventory of Depressive Symptomatology-Self Rated (QIDS-SR) or the Hamilton Depression Rating Scale (HAM-D). A HAM-D score of less than eight or a QIDS-SR of less than 5 is the accepted standard for having obtained remission. For the purposes of this review, the drug must produce a response in at least 50% of patients to consider it effective in achieving response. Analogously, the drug must produce remission in at least 50% of patients to consider it effective in achieving remission. In addition to looking at the therapeutic effects of the drug, the effectiveness will also review how quickly the drug causes effects, and the effects are sustained. Tolerability will discuss side effects experienced by the patient. Safety will include information regarding toxicity and long term effects of each drug.

Neuroscience Background

Some of the basic characteristics of depression are low levels of brain-derived neurotrophic factor (BDNF), increased atrophy of neurons in the prefrontal cortex, and insufficient neurogenesis. Raising levels of BDNF may enhance neuroplasticity and play a role in increased neurogenesis (Baumeister et al., 2014). SSRIs, bupropion, ketamine, and psilocybin all target low levels of BDNF in different ways, with the overall result of encouraging neurogenesis and improvement in symptomatology of depression (Krystal et al., 2013; Martinowich & Lu, 2008; Tafseer et al., 2021; Tyls et al., 2016).

Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressant. Although there are different types of SSRIs (eg Citalopram/Celexa, Escitalopram/Lexapro, Sertraline/Zoloft), there is a general lack of evidence that supports one over the other, which is why they can be talked about as a class rather than as individuals. SSRIs act with a relatively straightforward mechanism. They work by targeting and blocking serotonin transporters to inhibit the uptake of serotonin, thereby increasing the amount of serotonin in the synapse. An increase in extracellular serotonin has been linked to increased levels of BDNF due to enhanced BDNF gene expression caused by serotonin (Martinowich & Lu, 2008).

Bupropion is the only type of norepinephrine reuptake inhibitor (NDRI) that is currently FDA approved. It has a similar mechanism to SSRIs in that it blocks the reuptake of neurotransmitters to increase the levels in the synapse, however it instead focuses on norepinephrine and dopamine. Bupropion blocks the reuptake of norepinephrine and dopamine by blocking the norepinephrine transporter (NET) and the dopamine transporter (DAT), and is associated with an increase in BDNF levels (Tafseer et al., 2021).

Ketamine is rather unique as it is the only drug of this review that achieves antidepressant effects through the glutamatergic system. Glutamate neurons are targets for the monoamine systems, meaning the glutamatergic system is indirectly implicated in the neurobiology depression (Krystal et al., 2013). Specifically, ketamine is an NMDA receptor antagonist. It is thought to exert antidepressant effects by blocking extrasynaptic NMDA receptors, which leads to an increase in brain-derived neurotrophic factor (BDNF) levels. It also stimulates glutamate release in the synapse and enhances synaptic AMPA receptor signaling. Antagonization of NMDA receptors reduces activation of GABA neurons in hippocampus and PFC, raises extracellular glutamate levels in the PFC and increases neuronal firing, and may play a role in

increasing neuroplasticity. The targeting of the glutamatergic system may provide relief for those who are not responding to other antidepressants.

Psilocybin also exerts an effect on the serotonergic system, however in a way that is distinct from SSRIs. Instead of blocking serotonin transporters, it works by mimicking the action of serotonin (Tyls et al., 2016). SSRIs exert activity on the 5-HT transporter SERT, whereas psilocybin is related to the activity on the 5-HT receptor. Part of the antidepressant effects may come from the fact that patients with depression have lower postsynaptic binding potential at 5-HT receptors, and psilocybin increases postsynaptic binding potential at 5-HT receptors. Additionally, psilocybin induces rapid 5-HT_{2A} downregulation. Studies on depressed patients post-mortem have seen increased levels of these receptors, and activation of 5-HT_{2A} receptors increases neurogenesis through increased expression of BDNF.

Antidepressants

Effectiveness

A meta-analysis of seven clinical trials comparing bupropion and SSRIs found both drugs to have statistically identical rates of remission and response (Thase et al., 2005). Both drugs take around 4-6 weeks to take effect, however research suggests that bupropion begins to reduce negative biases in emotional processing before clinical ratings of depression are affected significantly (Walsh et al., 2017). Response and remission rates of both antidepressants were 62-63% and 47% after 8 weeks, respectively. If reached, remission is typically maintained through the course of treatment. SSRIs and bupropion are ideally prescribed for six months to a year, however many patients have a prescription for an undetermined amount of time because relapse is more likely after discontinuation (Berwian et al., 2017). SSRIs and bupropion cause

statistically identical response and remission rates, where both drugs are considered effective in causing a response, but not in achieving remission (Nieuwstraten & Dolovish, 2001; Thase et al., 2005).

Safety

SSRIs and bupropion are commonly prescribed because they effectively reduce depressive symptoms with a low risk of serious adverse events. However, no drug is completely without risk. Some serious concerns for these treatment options are the emergence of suicidality, serotonin syndrome (for SSRIs), increased risk of bleeding and stroke, and discontinuation syndrome (Carvalho et al., 2016; Shin et al., 2014). The emergence of suicidality is an increase or appearance of suicidal thoughts or tendencies that typically emerge within the beginning of treatment. The emergence of suicidality is more common in young adults and adolescents starting antidepressant treatment, but should be monitored for everyone starting SSRIs or bupropion. Serotonin syndrome typically is caused by drug-drug interactions that overload serotonin in the synapse, and also may be caused by SSRI overdose. Serotonin syndrome is a concern for SSRIs, but not bupropion, as SSRIs increase the amount of serotonin in the synapse and bupropion does not. If left untreated, serotonin syndrome could be fatal and providers should exercise extreme caution when prescribing other drugs for SSRI users to ensure there are no interactions. The increased risk of bleeding is due to the reduced capacity for blood to clot when on SSRIs or bupropion. Use of other drugs which are also known to increase risk of bleeding, such as NSAIDs, may intensify this risk. Additionally, risk of stroke is as much as 40% greater for people on SSRIs or bupropion than the general public (Shin et al., 2014). Discontinuation syndrome may occur when a dose is missed or the drug is discontinued. The symptoms of discontinuation syndrome mimic withdrawal symptoms, and may include flu-like symptoms,

tremors, tinnitus, vertigo, and other withdrawal symptoms. A complete discussion of all of the serious adverse events that may occur when taking SSRIs or bupropion are beyond the scope of this paper, however the most common ones have been highlighted. Although not without risks, incidence of serious adverse effects are rare for SSRIs and bupropion.

Tolerability

A disadvantage of SSRIs and bupropion are the high numbers of patients who experience side effects. In the same meta-analysis mentioned previously, the researchers found that 7% of patients chose to discontinue treatment due to intolerable side effects (Thase et al., 2005). Although relatively few patients experienced side effects so disrupting that they chose to discontinue treatment, 81% of bupropion users and 83% of SSRI users claimed to have experienced side effects of any sort. The most common ones reported by patients are headache, dry mouth, increased sweating (approximately 10% of SSRI users experience this), insomnia, agitation, diarrhea, weight changes and somnolence. Patients reported nausea and sexual side effects to be the most intolerable. While sexual side effects are commonly reported by SSRI users, bupropion does not carry this difficulty. Sexual desire disorder was reported by 27% of SSRI users at week 8, which was significantly higher than the bupropion group at 18%. Additionally, 37% of SSRI users experienced orgasmic dysfunction, but only 12% of bupropion users did. Thus, bupropion may be preferred by users who are concerned about sexual side effects. Although the list of side effects is extensive, the side effects are expected to improve after a few weeks. Nonetheless, side effects may lead to nonadherence if daily life is disrupted too much and could cause a patient to discontinue before seeing the full therapeutic effects.

Hallucinogens

Effectiveness

Ketamine and psilocybin are unique in that they produce a rapid reduction of depressive symptoms in as soon as 24 hours. Although ketamine and psilocybin produce similar results, ketamine's relief of depression symptoms are short-term. For single ketamine infusions, most participants relapsed within a week (Murrough & Iosifescu et al., 2013; Zarate et al., 2006). Multiple ketamine infusions (done thrice weekly for two weeks) produced a more sustained response, with over half of the participants not relapsing until 18 days after the last infusion, or 30 days from the first (aan het Rot et al., 2010; Berman et al., 2000; Murrough & Perez et al., 2013). While multiple infusions had a positive influence on the amount of time before relapse, it did not affect the response or remission rates, meaning that if a patient did not respond after the first infusion, they were unlikely to respond to subsequent infusions (Murrough & Perez et al., 2013). At 24 hours, ketamine had a response rate ranging from 60%-90% (aan het Rot et al., 2010; Berman et al., 2000; Murrough & Iosifescu et al., 2013; Murrough & Perez et al., 2013; Zarate et al., 2006). Single infusion studies saw a decrease in response rate for each day following infusion day, where the response rates were no longer significant after the seventh day (Murrough & Iosifescu et al., 2013; Zarate et al., 2006). Remission rates were variable at 24 hours, ranging from 30%-80% (aan het Rot et al., 2010; Berman et al., 2000; Murrough & Iosifescu et al., 2013; Murrough & Perez et al., 2013; Zarate et al., 2006). Ketamine is effective in producing a response, however there is not enough research to conclude if ketamine is effective at causing remission.

For psilocybin, response rates at 24 hours were always greater than 50% (Carhart-Harris 2016), but more commonly ranged from than 70%-80% (Carhart-Harris 2021; Davis et al., 2020; Griffiths et al., 2016: Ross et al., 2016). At 24 hours, psilocybin produced remission in upwards

of 70% of patients (Carhart-Harris 2021; Carhart-Harris 2016; Davis et al., 2020; Griffiths et al., 2016; Ross et al., 2016), and these results were sustained at six months for at least 60% of participants (Carhart-Harris 2016; Davis et al., 2020; Griffiths et al., 2016; Ross et al., 2016). Although the limited number of studies makes it difficult to draw conclusions, psychotherapy sessions after a treatment of psilocybin seems to produce increases in response and remission rates (Davis et al., 2020; Ross et al., 2016). These data suggest, however, that psilocybin is effective in achieving response and remission with or without psychotherapy.

Safety

Although ketamine has been safely used as an anaesthetic for decades, there are risks associated with use. Some of the commonly reported concerns for ketamine use are addiction and negative long-term effects after repeated infusions. In a review of over 6000 patients receiving repeated ketamine infusions, no patients were identified as having acquired an addiction to ketamine (Feifel et al., 2020). Additionally, patients do not seek out ketamine for illicit use after having completed a research study (Perry et al., 2007). Long-term ketamine use has been associated with bladder dysfunction and cognitive deficits in a handful of cases (Feifel et al., 2020). Although there are risks associated with ketamine use, research supports the safety of single or repeated ketamine infusions under medical supervision, as the risk of addiction and serious adverse side effects are low.

Although the stigma associated with psilocybin has halted research for decades, the evidence continues to demonstrate that psilocybin can be used safely in clinical settings. One of the most notable things about psilocybin is the overall lack of toxicity and long-term adverse effects (Carhart-Harris et al., 2016; Dijkstra et al., 2016; Tylš et al., 2016; Tylš et al., 2013). There have been no recorded psilocybin overdoses as the ratio of a lethal dose of psilocybin to a

psychoactive dose is approximately 1000:1; this ratio would be the equivalent to eating one's own body weight in psilocybin-containing mushrooms (Tylš et al., 2016; Tylš et al., 2013). While psilocybin has low toxicity and may promote neurogenesis (Ly et al., 2018; Tylš et al., 2013), the abuse potential and long-term adverse effects of psilocybin remain a topic of concern.

A pooled analysis of the experimental studies done using psilocybin found low rates of negative long-term effects (Studers et al., 2011). Flashbacks to the visual effects caused by psilocybin, known as hallucinogen persisting perception disorder (HPPD), is a commonly cited concern for the use of hallucinogens. Some patients reported vague flashbacks to the drug experience, however none met the criteria for HPPD. Although there were no reported cases of psychosis, some patients reported instances of cognitive impairment and mood changes during the first few weeks after psilocybin administration. All cases resolved after a few weeks, but the risk of negative changes in cognition or mood nonetheless underline the importance of follow up after drug treatments.

Tolerability

Studies have found both ketamine and psilocybin to be generally well tolerated with minimal adverse events during treatment (aan het Rot et al., 2010; Carhart-Harris 2021; Carhart-Harris 2016; Davis et al., 2020; Griffiths et al., 2016; Murrough & Iosifescu et al., 2013; Murrough & Perez et al., 2013; Ross et al., 2016; Zarate et al., 2006). Some patients receiving psilocybin or ketamine complained of anxiety, nausea (which was more common in psilocybin sessions), and dissociation and blurred vision (which were more common in ketamine sessions) (aan het Rot et al., 2010; Carhart-Harris et al., 20201; Carhart-Harris et al., 2018; Davis et al., 2020; Griffiths et al., 2016; Murrough & Iosifescu et al., 2013; Murrough & Perez et al., 2013; Ross et al., 2016; Zarate et al., 2006). A mild to moderate headache appearing 12-24 hours after

a psilocybin session and resolving within 48 hours was the only adverse effect that lasted past the treatment day, and was more common with higher dosages (Carhart-Harris et al., 20201; Carhart-Harris et al., 2018; Davis et al., 2020; Griffiths et al., 2016; Ross et al., 2016). As for potentially dangerous side effects, a number of patients experienced unusual changes in blood pressure and heart rate, which usually resolved during the course of the administration sessions (aan het Rot et al., 2010; Murrough & Iosifescu et al., 2013; Murrough & Perez et al., 2013; Zarate et al., 2006). Notably, almost all of the adverse effects experienced by patients resolved themselves before the end of the treatment, and no patients reported side effects lasting longer than 48 hours. Although only one case required medical intervention, these side effects suggest that patients should be under constant medical supervision during treatment days (Murrough & Iosifescu et al., 2013).

Discussion

Because of the lack of FDA approval, the research done with ketamine or psilocybin for treating depression is fairly limited. Although ketamine has been FDA approved as an anaesthetic since 1970 and research shows similar effectiveness and safety as esketamine, ketamine is not currently approved for treating depression. Although esketamine approval is a step towards continued research of the therapeutic potential of hallucinogens, it is too expensive for widespread use (Ross et al., 2020). The accessible and affordable nature of ketamine makes it a more viable treatment option, and although not FDA approved for such purposes, it is not uncommon for doctors to prescribe it as an "off label" treatment.

The widespread abuse of psychedelics in the 1970s has left psilocybin with an FDA classification that hindered research for decades. Psilocybin is a Schedule 1 drug: labeled with

high abuse potential, no accepted safety under medical supervision, and no therapeutic promise. After an extensive review of the abuse potential of psilocybin, Johnson et al., (2018) suggest that Schedule IV classification would be more appropriate for psilocybin, arguing that psilocybin has a moderate abuse potential, can be used safely in clinical settings with FDA approval, and a real therapeutic promise.

SSRIs and bupropion are effective in achieving a clinical response in over 50% of participants, but not effective in reaching remission. Ketamine and psilocybin are effective in achieving a clinical response as well as reaching remission, however they lack the long-term research that SSRIs and bupropion have undergone. The fast-acting nature of ketamine and psilocybin gives providers an immediate insight as to whether or not the treatment is producing a response. The well-tolerated nature of ketamine infusions may encourage concurrent usage alongside SSRIs or bupropion. Ketamine could provide an immediate liberation from depressive symptoms while patients are waiting for the effects of SSRIs or bupropion to take over. As SSRIs and bupropion have a serious risk of increasing suicidality in the first few weeks of treatment, concurrent ketamine infusions could minimize this risk as ketamine reduces suicidality even among non-responders (Murrough & Perez et al., 2013).

Psilocybin research is extremely limited due to the current FDA classification; however, these studies demonstrate its potential as a rapid and sustained antidepressant with minimal side effects. Due to a lack of long-term research with psilocybin in clinical settings, future research should aim to further explore side effects and long-term effects of therapeutic psilocybin use.

Treatment Resistant Depression

Ketamine and psilocybin not only effectively treat MDD, but they are also uniquely successful in treating patients with treatment resistant depression (TRD) (aan het Rot et al., 2009;

Carhart-Harris et al., 2016; Davis et al., 2020; Murrough & Iosifescu et al., 2013; Murrough & Perez et al., 2013; Zarate et al., 2006). In contrast to SSRIs and bupropion, ketamine and psilocybin produce an immediate reduction of symptoms and do not need to be taken everyday. Some of the risk factors that are associated with TRD that could be minimized through the unique characteristic of ketamine or psilocybin are: non-adherence to the treatment plan, unpleasant side effects, and drug interactions (Al-Harbi 2012). Given that SSRIs and bupropion must be taken up to three times per day, patients may have difficulty following these treatment guidelines as patients with depression are 2-3 times more likely to be noncompliant with treatment recommendations compared to non-depressed patients (Grenard et al., 2011; DiMatteo et al., 2000). Thus, having to take medication potentially multiple times per day may not be feasible for a person with depression. Not only can it become a burden to have to take medication every day, but the lack of immediate relief, combined with the possibility of experiencing side effects, make it reasonable that a patient may want to discontinue the medication before waiting weeks for it to take full effect. Not only do patients experience a rapid reduction in symptoms with ketamine and psilocybin, but these results are seen after a single session. Although repeated doses of ketamine are suggested for a longer-lasting remission period, these repeated doses are typically done over the course of two weeks, with patients seeing symptom reduction after the first session. However, if a patient experiences immediate relief after the first dose, it is more likely that they will be motivated to be able to follow through with the rest of the ketamine infusions. Additionally, a single dose of psilocybin has maintained remission for six months. With this information in mind, hallucinogens may provide a benefit to patients who struggle to adhere to the treatment plan, either due to failure to take the medicine everyday or quitting before it has reached the full drug effect.

In addition to helping with treatment non-adherence, ketamine and psilocybin both have minimal side effects compared to typical antidepressants. Although side effects that come with psilocybin and ketamine may be reported as uncomfortable to some patients, an advantage of these drugs is the transient nature of the side effects. Other than a mild-moderately severe headache that may appear the day after treatment, neither psilocybin nor ketamine results in side effects lasting longer than the supervised drug effects. Thus, while SSRI and bupropion users may be experiencing side effects that range from mildly annoying to overall intolerable and potentially last over the course of their treatment, the unpleasant side effects that patients may experience from ketamine and psilocybin are short-lived. A limitation of this research on psilocybin and ketamine is the lack of long-term studies that have been conducted and the small sample sizes compared to the research on SSRIs and bupropion.

Another advantage of the hallucinogens requiring fewer treatment sessions is that there are less chances for drug interactions to occur. The interaction of psilocybin and SSRIs may increase the risk of serotonin syndrome as both drugs are serotonin-focused, but otherwise, there are few known drug interactions for psilocybin or ketamine (Andrade, 2017; Strassman, 1992). Rather than having to consider the interactions of each new drug that a patient may use if on SSRIs or bupropion, providers only have to be concerned with drug interactions during the treatment session for hallucinogens. As previously mentioned, a patient on SSRIs or bupropion must exercise caution when taking ibuprofen due to the increased risk of bleeding caused by this drug interaction. If such an interaction were seen with ketamine or psilocybin, subjects would only need to be concerned about the drug interaction risk on the day of treatment.

Conclusion

With the current resurgence of interest in hallucinogens as treatment options for depression, the first clinical trial comparing SSRIs and psilocybin was published a month before the completion of the present paper. Carhart-Harris et al., (2021) conducted a study on a small sample size in order to compare the effects of Citalopram (a type of SSRI) and psilocybin. Psilocybin and citalopram had statistically similar results in terms of response and remission rates. Psilocybin caused response in 70% of participants and remission in 57% of participants at six weeks, whereas Citalopram caused response in 48% and remission in 28% in the same amount of time. The extremely limited sample size meant that no conclusion could be drawn about any statistical differences between psilocybin and Citalopram (Carhart-Harris, et al., 2021). According to the criteria used to discuss effectiveness in the current review, this study supports the previous findings in that SSRIs effectively produce a response but not remission, and psilocybin effectively produces both. The effectiveness, safety, and tolerability of psilocybin when compared to the most widely prescribed class of antidepressants shows the therapeutic potential of the drug in treating depression.

Research suggests that ketamine and psilocybin are effective, safe, and tolerable treatments for depression. Further research is warranted to continue to learn more about potential long-term risks. Although SSRIs and bupropion are not effective at causing remission, they are effective in producing a response and are providing a relatively accessible, safe and tolerable treatment for depression. The rising levels of depression continue to push researchers to find treatments that will provide relief for people who do not experience relief from what is currently available. Ketamine and psilocybin may be able to fulfill that role, and further research is warranted in order to definitively establish their potential role as novel antidepressants.

References

aan het Rot, M., Collins, K. A., Murrough, J. W., Perez, A. M., Reich, D. L., Charney, D. S., & Mathew, S. J. (2010). Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. *Biological psychiatry*, *67*(2), 139–145. https://doi.org/10.1016/j.biopsych.2009.08.038

Al-Harbi K. S. (2012). Treatment-resistant depression: therapeutic trends, challenges, and future directions. Patient preference and adherence, 6, 369–388. https://doi.org/10.2147/PPA.S29716

Andrade C. (2017). Ketamine for Depression, 5: Potential Pharmacokinetic and Pharmacodynamic Drug Interactions. *The Journal of clinical psychiatry*, *78*(7), e858–e861. https://doi.org/10.4088/JCP.17f11802

Baumeister, D., Barnes, G., Giaroli, G., & Tracy, D. (2014). Classical hallucinogens as antidepressants? A review of pharmacodynamics and putative clinical roles. *Therapeutic advances in psychopharmacology, 4*(4), 156–169. https://doi.org/10.1177/2045125314527985

Berman, R. M., Cappiello, A., Anand, A., Oren, D. A., Heninger, G. R., Charney, D. S., & Krystal, J. H. (2000). Antidepressant effects of ketamine in depressed patients. *Biological psychiatry*, *47*(4), 351–354. https://doi.org/10.1016/s0006-3223(99)00230-9

Berwian, I. M., Walter, H., Seifritz, E., & Huys, Q. J. (2017). Predicting relapse after antidepressant withdrawal - a systematic review. *Psychological medicine*, *47*(3), 426–437. https://doi.org/10.1017/S0033291716002580

Bica, T., Castelló, R., Toussaint, L. L., & Montesó-Curto, P. (2017). Depression as a Risk

Factor of Organic Diseases:An International Integrative Review. *Journal of nursing scholarship : an official publication of Sigma Theta Tau International Honor Society of Nursing*, *49*(4), 389–399. https://doi.org/10.1111/jnu.12303

Carhart-Harris, R., Giribaldi, B., Watts, R., Baker-Jones, M., Murphy-Beiner, A., Murphy, R., Martell, J., Blemings, A., Erritzoe, D., & Nutt, D. J. (2021). Trial of Psilocybin versus Escitalopram for Depression. *The New England journal of medicine*, *384*(15), 1402–1411. https://doi.org/10.1056/NEJMoa2032994

Carhart-Harris, R. L., Bolstridge, M., Day, C., Rucker, J., Watts, R., Erritzoe, D. E., Kaelen, M., Giribaldi, B., Bloomfield, M., Pilling, S., Rickard, J. A., Forbes, B., Feilding, A., Taylor, D., Curran, H. V., & Nutt, D. J. (2018). Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. *Psychopharmacology, 235*(2), 399–408. https://doi.org/10.1007/s00213-017-4771-x

Carvalho, A. F., Sharma, M. S., Brunoni, A. R., Vieta, E., & Fava, G. A. (2016). The Safety, Tolerability and Risks Associated with the Use of Newer Generation Antidepressant Drugs: A Critical Review of the Literature. *Psychotherapy and psychosomatics*, *85*(5), 270–288. https://doi.org/10.1159/000447034

Davis, A. K., Barrett, F. S., May, D. G., Cosimano, M. P., Sepeda, N. D., Johnson, M. W., Finan, P. H., & Griffiths, R. R. (2020). Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. *JAMA psychiatry*, e203285. Advance online publication. https://doi.org/10.1001/jamapsychiatry.2020.3285

Dijkstra, F. M., Jacobs, G. E., & Cohen, A. F. (2016). Question-based Drug Development for psilocybin. *The lancet. Psychiatry, 3*(9), 806–807. https://doi.org/10.1016/S2215-0366(16)30214-0

DiMatteo MR, Lepper HS, Croghan TW. Depression Is a Risk Factor for Noncompliance With Medical Treatment: Meta-analysis of the Effects of Anxiety and Depression on Patient Adherence. *Arch Intern Med.* 2000;160(14):2101–2107. doi:10.1001/archinte.160.14.2101

Ettman CK, Abdalla SM, Cohen GH, Sampson L, Vivier PM, Galea S. Prevalence of Depression Symptoms in US Adults Before and During the COVID-19 Pandemic. *JAMA Netw Open. 2020;3*(9):e2019686. doi:10.1001/jamanetworkopen.2020.19686

Feifel, D., Dadiomov, D., & C Lee, K. (2020). Safety of Repeated Administration of Parenteral Ketamine for Depression. *Pharmaceuticals* (Basel, Switzerland), 13(7), 151. https://doi.org/10.3390/ph13070151

Grenard, J. L., Munjas, B. A., Adams, J. L., Suttorp, M., Maglione, M., McGlynn, E. A., & Gellad, W. F. (2011). Depression and medication adherence in the treatment of chronic diseases in the United States: a meta-analysis. Journal of general internal medicine, 26(10), 1175–1182. https://doi.org/10.1007/s11606-011-1704-y

Griffiths, R. R., Johnson, M. W., Carducci, M. A., Umbricht, A., Richards, W. A., Richards, B. D., Cosimano, M. P., & Klinedinst, M. A. (2016). Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *Journal of psychopharmacology (Oxford, England), 30*(12), 1181–1197.

Hasin, D. S., Sarvet, A. L., Meyers, J. L., Saha, T. D., Ruan, W. J., Stohl, M., & Grant, B. F. (2018). Epidemiology of Adult DSM-5 Major Depressive Disorder and Its Specifiers in the United States. *JAMA psychiatry*, *75*(4), 336–346. https://doi.org/10.1001/jamapsychiatry.2017.4602

Johnson, M. W., Griffiths, R. R., Hendricks, P. S., & Henningfield, J. E. (2018). The abuse potential of medical psilocybin according to the 8 factors of the Controlled Substances Act. *Neuropharmacology, 142,* 143–166. https://doi.org/10.1016/j.neuropharm.2018.05.012

Krystal, J. H., Sanacora, G., & Duman, R. S. (2013). Rapid-acting glutamatergic antidepressants: the path to ketamine and beyond. *Biological psychiatry*, *73*(12), 1133–1141. https://doi.org/10.1016/j.biopsych.2013.03.026

Ly, C., Greb, A. C., Cameron, L. P., Wong, J. M., Barragan, E. V., Wilson, P. C., Burbach, K. F., Soltanzadeh Zarandi, S., Sood, A., Paddy, M. R., Duim, W. C., Dennis, M. Y., McAllister, A. K., Ori-McKenney, K. M., Gray, J. A., & Olson, D. E. (2018). Psychedelics Promote Structural and Functional Neural Plasticity. *Cell reports, 23*(11), 3170–3182. https://doi.org/10.1016/j.celrep.2018.05.022

Martinowich, K., & Lu, B. (2008). Interaction between BDNF and serotonin: role in mood disorders. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*, *33*(1), 73–83. https://doi.org/10.1038/sj.npp.1301571

McLaughlin K. A. (2011). The public health impact of major depression: a call for interdisciplinary prevention efforts. *Prevention science : the official journal of the Society for Prevention Research, 12*(4), 361–371. https://doi.org/10.1007/s11121-011-0231-8

Mrazek, D. A., Hornberger, J. C., Altar, C. A., & Degtiar, I. (2014). A review of the clinical, economic, and societal burden of treatment-resistant depression: 1996-2013. *Psychiatric services (Washington, D.C.), 65*(8), 977–987. https://doi.org/10.1176/appi.ps.201300059

Murrough, J. W., Iosifescu, D. V., Chang, L. C., Al Jurdi, R. K., Green, C. E., Perez, A. M.,

Iqbal, S., Pillemer, S., Foulkes, A., Shah, A., Charney, D. S., & Mathew, S. J. (2013). Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. *The American journal of psychiatry*, *170*(10), 1134–1142. https://doi.org/10.1176/appi.ajp.2013.13030392

Murrough, J. W., Perez, A. M., Pillemer, S., Stern, J., Parides, M. K., aan het Rot, M., Collins, K. A., Mathew, S. J., Charney, D. S., & Iosifescu, D. V. (2013). Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. *Biological psychiatry*, *74*(4), 250–256. https://doi.org/10.1016/j.biopsych.2012.06.022

Nieuwstraten, C. E., & Dolovich, L. R. (2001). Bupropion versus selective serotonin-reuptake inhibitors for treatment of depression. *The Annals of pharmacotherapy*, *35*(12), 1608–1613. https://doi.org/10.1345/aph.1A099

Perry, E. B., Jr, Cramer, J. A., Cho, H. S., Petrakis, I. L., Karper, L. P., Genovese, A., O'Donnell, E., Krystal, J. H., D'Souza, D. C., & Yale Ketamine Study Group (2007). Psychiatric safety of ketamine in psychopharmacology research. *Psychopharmacology*, *192*(2), 253–260. https://doi.org/10.1007/s00213-007-0706-2

Ross, E. L., & Soeteman, D. I. (2020). Cost-Effectiveness of Esketamine Nasal Spray for Patients With Treatment-Resistant Depression in the United States. *Psychiatric services (Washington, D.C.)*, *71*(10), 988–997. https://doi.org/10.1176/appi.ps.201900625

Ross, S., Bossis, A., Guss, J., Agin-Liebes, G., Malone, T., Cohen, B., Mennenga, S. E., Belser, A., Kalliontzi, K., Babb, J., Su, Z., Corby, P., & Schmidt, B. L. (2016). Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. *Journal of*

psychopharmacology (Oxford, England), 30(12), 1165–1180. https://doi.org/10.1177/0269881116675512

Shin, D., Oh, Y. H., Eom, C. S., & Park, S. M. (2014). Use of selective serotonin reuptake inhibitors and risk of stroke: a systematic review and meta-analysis. *Journal of neurology*, *261*(4), 686–695. https://doi.org/10.1007/s00415-014-7251-9

Strassman R. J. (1992). Human hallucinogen interactions with drugs affecting serotonergic neurotransmission. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*, *7*(3), 241–243.

Studerus, E., Kometer, M., Hasler, F., & Vollenweider, F. X. (2011). Acute, subacute and long-term subjective effects of psilocybin in healthy humans: a pooled analysis of experimental studies. Journal of psychopharmacology (Oxford, England), 25(11), 1434–1452. https://doi.org/10.1177/0269881110382466

Tafseer, S., Gupta, R., Ahmad, R., Jain, S., Bhatia, M. S., & Gupta, L. K. (2021). Bupropion monotherapy alters neurotrophic and inflammatory markers in patients of major depressive disorder. *Pharmacology, biochemistry, and behavior*, *200*, 173073. https://doi.org/10.1016/j.pbb.2020.173073

Thase, M. E., Haight, B. R., Richard, N., Rockett, C. B., Mitton, M., Modell, J. G., VanMeter, S., Harriett, A. E., & Wang, Y. (2005). Remission rates following antidepressant therapy with bupropion or selective serotonin reuptake inhibitors: a meta-analysis of original data from 7 randomized controlled trials. *The Journal of clinical psychiatry, 66*(8), 974–981. https://doi.org/10.4088/jcp.v66n0803

Tylš, F., Páleníček, T., & Horáček, J. (2014). Psilocybin--summary of knowledge and new perspectives. *European neuropsychopharmacology : the journal of the European College*

of Neuropsychopharmacology, 24(3), 342–356. https://doi.org/10.1016/j.euroneuro.2013.12.006

Tylš, F., Páleníček, T., & Horáček, J. (2016). Neurobiology of the Effects of Psilocybin in Relation to Its Potential Therapeutic Targets. V. R. Preedy (Ed.), *Neuropathology of Drug Addictions and Substance Misuse* (pp. 782-793). Elsevier Academic Press. https://doi.org/10.1016/B978-0-12-800212-4.00073-X

Walsh, A., Browning, M., Drevets, W. C., Furey, M., & Harmer, C. J. (2018). Dissociable temporal effects of bupropion on behavioural measures of emotional and reward processing in depression. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, *373*(1742), 20170030. https://doi.org/10.1098/rstb.2017.0030

Wang, Q., Xu, R., & Volkow, N. D. (2021). Increased risk of COVID-19 infection and mortality in people with mental disorders: analysis from electronic health records in the United States. World psychiatry : official journal of the World Psychiatric Association (WPA), 20(1), 124–130. https://doi.org/10.1002/wps.20806

Winerman, L. (2017, November). By the numbers: Antidepressant use on the rise. *Monitor on Psychology, 48*(10). http://www.apa.org/monitor/2017/11/numbers

Zarate, C. A., Jr, Singh, J. B., Carlson, P. J., Brutsche, N. E., Ameli, R., Luckenbaugh, D. A., Charney, D. S., & Manji, H. K. (2006). A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Archives of general psychiatry*, *63*(8), 856–864. https://doi.org/10.1001/archpsyc.63.8.856