Capstone Project: What is the Efficacy of Psilocybin for Cancer-Related Depression?

Bryan A Johnson

Capstone

Master's of Science in Nursing

AGACNP Program

Hawaii Pacific University

Honolulu, Hawaii

Summer Semester 2018

Disclaimer: The views presented here are those of the author and are not to be construed as official or reflecting the views of Hawaii Pacific University

Advisor: Dr. Beverly Inocencio

Cancer, Depression and Psilocybin

Cancer is one of the world's leading causes of death, and annual cancer cases are projected to almost double within the next two decades from 14 million to 22 million (Stewart & Wild, 2014). Currently, within the United States, cancer affects approximately 40% of the population (American Cancer Society, 2016; National Cancer Institute, 2016). Psychosocial distress is common among patients with cancer; up to 40% meet the criteria for a mood disorder, compared to 7%-10% of the general population (Holland et al., 2013; Mitchell et al., 2011; Ostuzzi et al., 2015; Vergo et al., 2017). Patients with comorbid cancer and depression are at increased risk for poorer outcomes, including increased mortality (Arrieta et al., 2013; Lloyd-Williams et al., 2009; Pinquart & Duberstein, 2010). Unfortunately, there is scarce evidence supporting the efficacy of current interventions for cancer-related depression (Breitbart et al., 2010; Faller et al., 2013; Grassi et al., 2014; Iovieno et al., 2011; Kirsch et al., 2008; Laoutidis, Zacharias & Mathiak, 2013; Ostuzzi et al., 2015). In fact, current data on treatment of cancer depression has shown no statically significant benefit over placebo and thus no clear implications for practice can be drawn (Ostuzzi et al., 2015). However, research has emerged supporting the use of the classical serotonergic psychedelic Psilocybin as a novel pharmacological treatment for those suffering with depression related to life-threatening cancer (Bernasconi et al., 2013; Carhart-Harris et al., 2012a; Carhart-Harris et al., 2012b; Carhart-Harris et al., 2016; Carhart-Harris et al., 2017; Carhart-Harris et al., 2018; Carillo et al., 2018; Griffiths et al., 2006; Griffiths et al., 2008; Griffiths et al., 2016; Grob, Bossis & Griffiths, 2013; Grob et al., 2011; Kometer et al., 2012; Kraehenmann et al., 2015; Roseman, Nutt & Carhart-Harris, 2018; Ross et al., 2016; Rucker et al.,2016; Schmidt et al., 2013; Stroud et al., 2017; Vollenweider & Kometer, 2010). The purpose of this capstone project is to review the current evidence surrounding the use of

Psilocybin as treatment for cancer-related depression and compare to current treatments in therapeutic efficacy, safety and cost effectiveness to make evidence-based practice recommendations regarding its schedule I status.

Theoretical Framework

Cancer-related depression can be debilitating and has been show to compound health problems for those afflicted. Margret Newman developed a theoretical nursing theory to help address treatments for patients that find themselves lost in this particular circumstance. Her nursing theory, 'Health as Expanding Consciousness', asserts that every person in every situation, no matter now disordered and hopeless it may seem, is part of the universal process of expanding consciousness – a process of becoming more of oneself, of finding greater meaning in life, and of reaching new dimensions of connectedness with other people and the world. According to Newman, 'the theory of health as expanding consciousness was stimulated by concern for those for whom health as the absence of disease or disability is not possible,' (Nursing Theories, 2016). For people with life-threatening cancer, health can be accomplished through their own expansion of consciousness. So even if a patient's physical health is compromised by cancer, he or she may still achieve health by growing mentally, emotionally and spiritually through expanding consciousness. Margret Newman wrote of lofty and ethereal ideals, but if we are to take her theory as serious as she wrote it, then we are faced with the responsibility of the mission she entailed, to find greater meaning in life through connection of oneself and the world by expanding consciousness. There is no other therapy as fitting to this description as the serotonergic psychedelic Psilocybin. The cliché of these classical psychedelic as 'consciousness expanding' drugs is not be taken lightly. The mystical experience of a psychedelic 'trip' of expanding consciousness could be the very healthy healing that Newman

describes in her grand nursing theory, which eludes the many suffering life-threatening cancer with cancer-related depression.

Background

Cancer patients face complex, and clinically challenging, mental and emotional hurdles as they consider death along with the deterioration of their health and self-integrity. Existential distress is common for those threatened with a possible life-ending diagnosis and is characterized by feelings of hopelessness and helplessness secondary to a loss of purpose and meaning (Robinson et al., 2016). It is just as important to address the mental health of this population along with their physical health. Patients with cancer and depression have decreased treatment adherence, prolonged hospitalizations, increased adverse medical outcomes, decreased social function, increased disability, increased hopelessness, increased suicidality, increased pain, decreased quality of life, and decreased survival rates (Arrieta et al., 2013; Colleoni et al., 2000; Griffiths et al., 2016; Prieto et al., 2002; Ross et al., 2016; Shim, Eun-Jung & Park, 2012; Skarstein et al., 2000). Furthermore, depression has been shown to be an independent risk factor of early death in patients with cancer, with estimates as high as 39% higher mortality rate among those diagnosed with major depression (Arrieta et al., 2013; Lloyd-Williams et al., 2009; Pinquart et al., 2010; Satin, Linden & Phillips, 2009).

Current Therapy

The primary treatment for cancer-related depression is antidepressants. Most psychiatrists today simply provide medication to their patients and do not do psychotherapy themselves (Carlat, 2010). This category of medications is comprised of several classes, -including: SSRIs, SNRIs, Atypical antidepressants, Serotonin modulators, Tricyclics, and MAOIs. Most take 6-12 weeks to see full effects (Simon & Clechanowski, 2017). Often antidepressants need to be

adjusted, including dose, frequency, combinations of medications or even the type of antidepressant (Ross et al., 2016). This can lead to lengthy trial-and-error provider visits, which are discouraging, frustrating and hard to manage along with cancer and depression. Antidepressants can sometimes cause a wide range of unpleasant side effects as well, including: nausea, weight gain, loss of sexual desire, fatigue and drowsiness, insomnia, dry mouth, blurred vision, dizziness, irritability anxiety and potential birth defects (Simon & Clechanowski, 2017). The use of antidepressants significantly increases the risk of serious adverse events, which includes death, disability, significant loss of function or life-threatening event that requires hospitalization at a rate of 9 persons for every 1000 treated, or approximately 1% (Jakobsen et al., 2017). Treatment with antidepressant medications are effective in 40-60% of people, but 70-80% of this effect may be attributable to 'the placebo effect' (Kirsch, 2010; PubMed Health, 2017). To put this into perspective the Hamilton Depression Rating Scale (HDRS), a standard scale for quantifying depression that is commonly used in clinical studies, measures from 0-52 points ranging from the absence of any depressive-like symptoms to severe acute-depression. An altered sleep pattern with some form of insomnia causes a 6-point reduction on this scale and the average effectiveness of antidepressants above placebo is 1.8-point reduction on this scale (Kirsch, 2010). Most meta-analysis using the HDRS determine 'clinical significance' at 3 points or great reduction and less the 3 points reduction is considered 'no clinical change' (Jakobsen et al., 2017). Several meta-analysis show no clear effect of antidepressant treatment over placebo in those with cancer-related depression (Iovieno et al., 2011; Kirsch, 2010; Laoutidis, Zacharias & Mathiak 2013; Ostuzzi et al., 2015). There are no current FDA approved pharmacotherapies for cancer-related psychological distress (Prieto et al., 2002).

5-HT2A Receptor Agonist Psilocybin

Psilocybin, a 5-HT2A receptor agonist, is the 'magic' in the more commonly referred to psychedelic 'magic mushrooms'. In animals, 5-HT2A receptor agonism has been reported to show enhanced cognitive flexibility, associative learning, antidepressant responses and cortical neural plasticity (Carhart-Harris et al., 2008). In humans, 5-HT2A receptor agonism has been shown to increase and sustain improvements in wellbeing and optimism being highly suggestive of antidepressant potential (Carhart-Harris et al., 2008). 5-HT2A agonists produce a distinctive profile of positive changes in cognition, alterations in emotions, perceptions, thoughts and feelings, allowing users to feel more open and connected emotionally and spiritually (Griffiths et al., 2006; Griffiths et al., 2008; Griffiths et al., 2016). The main therapeutic effects of Psilocybin in the treatment of depression and anxiety result from the down-regulation of 5-HT2A receptors (Vollenweider & Kometer, 2010). In humans, 5-HT2A receptor density in the fronto-limbic system is correlated with both anxiety and an individual's difficulty in managing stress (Vollenweider & Kometer, 2010). Activation of these receptors in the medial prefrontal cortex (mPFC) also has effects of increasing serotonin in the mPFC and dopamine in the mesocortical areas, which correlate with euphoria and depersonalization phenomena (Vollenweider & Kometer, 2010). In line with the notion that antidepressant effects can be achieved through modulation of serotonergic neurotransmission, Psilocybin not only acutely induces mood changes towards positive states, it also reduces neural responses to negative stimuli (Bernasconi et al., 2013; Carhart-Harris et al., 2012b; Kometer et al., 2012; Kraehenmann et al., 2015; Vollenweider & Kometer, 2010).

Methods

I performed an integrative review of the current literature regarding Psilocybin therapy. I searched CINAHL Complete (EBSCO), PubMed @ HPU, and Google Scholar data bases. The medical subject headings and key terms included 'Psilocybin' + 'Treatment' + 'Depression'. Inclusion criteria for this paper comprised of the use or commentary of Psilocybin as treatment therapy specifically regarding its safety and efficacy. Dates of articles included range from 2006 to 2018.

Literature Review- Psilocybin Safety and Efficacy

From 2011 to 2018 there have been five clinical trials, providing direct level II evidence addressing the efficacy of Psilocybin for depression (Griffiths et al., 2016, Ross et al., 2016, Carhart-Harris et al., 2016, Carhart-Harris et al., 2018, Grob et al., 2011). Two of the largest double-blind clinical trials regarding the safety and efficacy of Psilocybin treatment for depression were undertaken in 2016, Griffiths et al., and Ross et al., and both show dramatic, acute, significant, and enduring reductions in depression after one dose of Psilocybin in a supportive clinical setting. Antidepressant rates as high as 92% after the first dose were noted with lasting antidepressant effects with 60-80% of participants for 6.5 months, which were as far as the studies measured (Griffiths et al., 2016; Ross et al., 2016). The Griffiths et al., 2016 study, which included 51 patients, showed a dramatic change from a baseline of 'severe depression' (HAM-D of 22.84) to a 'normal/not depressed' level (HAM-D of 6.64) after a single dose of Psilocybin. The most recent clinical trial on this topic in 2018 had similar results with 20 participants showing mean scores for depression decrease from a baseline of 'severe depression' (HAM-D of 24.1) to the low end of 'mild depression' (HAM-D of 9.3) at week 1, 65% remission at week 5 with continued positive results at 3 and 6 months (Carhart-Harris et al., 2018). These

results were further substantiated by two other clinical trials, Carhart-Harris et al., 2016 and Grob et al., 2011, with similar significant antidepressant results for cancer related depression. For those clinical trials which measured depression with the Hamilton Depression Scale (HAM-D), when adjust for placebo effect, the average point reduction was approximately -10-points, compared to antidepressants of only -1.8-points (Carhart-Harris et al., 2016; Carhart-Harris et al., 2018; Griffiths et al., 2016; Kirsch, 2010). By this measure, Psilocybin is nearly 6 times as efficacious as the current treatment options.

In addition to these clinical trials there has been one large systematic review with level I evidence which showed not only was Psilocybin safe but strongly suggest Psilocybin has clinically beneficial effects for unipolar mood disorders such as depression and major depressive disorder (Rucker et al., 2016). This systematic review found that through 19 studies of 423 individuals, 79.2% showed clinician-judged improvement after treatment with Psilocybin or similar 5-HT2A receptor agonist (Rucker et al., 2016). It has been demonstrated that the therapeutic efficacy for treatment of depression is related to the quality of the Psilocybin experience (Roseman, Nutt & Carhart-Harris, 2018; Griffiths et al., 2008; Griffiths et al., 2006). The more ‘spiritual’, ‘mystical’, or ‘insightful’ the participants experience, as determined by Altered States of Consciousness Rating Scale (11D-ASC) the more they tended to benefit from the reduction in depressive symptoms (Carhart-Harris et al., 2018). It was found in the Griffith et al., 2008 study that 67% rated Psilocybin treatment among the five most spiritually significant experiences of their lives with 17% indicating it was the single most spiritually significant experience and 11% indicating it was the single most meaningful experience of their life. These results were also dose dependent correlated to higher doses. The therapeutic dose has been found to be in the range of 25 mg to 30 mg or 0.3 mg/kg oral route and is more efficacious then lower

doses of 10 mg. Additionally, it was found that even when doubling the therapeutic dose to 0.6 mg/kg or approximately 50 mg oral dose there was no serious physical or psychosocial effects during or within 30 days of administration (Brown et al., 2017).

Some of the most interesting data revealed how the profound effects of Psilocybin directly affect the brain on a neuro-vascular level with fMRI scans, event-related potential measured with EEG, Automated Emotional Analysis and Dynamic Emotional Expression Recognition Task (Carhart-Harris et al., 2012; Carhart-Harris et al., 2017; Carrillo et al., 2018; Kometer et al., 2012; Kraehenmann et al., 2015; Schartner et al., 2017; Schmidt et al., 2013; Stroud et al., 2017). Psilocybin was found to enable a state of unconstrained cognition by decreasing blood flow and activity to major connector hubs of the brain like the thalamus, anterior/posterior cingulate cortex and the medial prefrontal cortex (Carhart-Harris et al., 2012). It was also found that the acute treatment with Psilocybin will decrease amygdala reactivity during negative emotion processing and impair the encoding of fearful facial expressions but does not affect positive emotional processing or the encoding of happy facial expressions (Kometer et al., 2012; Kraehenmann et al., 2015; Schmidt et al., 2013). These finding are relevant to addressing negative mood states and the hyperactivity of the amygdala in patients with major depression without blunting positive emotional processing. For those with treatment-resistant depression, Psilocybin improved the processing of emotional faces and was correlated with reduced anhedonia (Stroud et al., 2018). Psilocybin seems to produce behavioral and electrophysiological changes that are opposite to the defective emotional processing bias, negative mood states and reduced goal directed behavior seen in depressed subjects (Kometer et al., 2012). Additionally, the areas of decreased blood flow and activity during the acute phase of Psilocybin treatment, specifically in the Default Mode Network (DMN), were found to have

increased resting-state functional connectivity post-treatment at 5 weeks. This has led to the proposal of a 'reset' therapeutic mechanism (Carhart-Harris et al., 2017). Another interesting aspect of study looked at natural speech analytics and was able to not only differentiate depressed patients from healthy controls but also identified those patients that would effectively respond to treatment with Psilocybin versus non-responders with a significant level of 85% accuracy (Carillo et al., 2018). This has the implication of a highly cost-effective tool for screening individuals for treatment suitability and sensitivity.

Psilocybin has been used ritualistically for over 3,000 years in Mexico and has been generally regarded as safe and non-addictive (Tyls, Palenicek & Horacek, 2013). In a large retrospective cohort study observing a randomly chosen group of 21,967 individuals it was found that there was no increase in incidence of mental health issues associated with the use of Psilocybin (Krebs et al., 2013). In fact, in the United States classic psychedelic use, such as Psilocybin is associated with reduced psychological distress and suicidality (Hendricks et al., 2015). Over 2000 participants have received Psilocybin in controlled experimental trials for psychological research from 1965 to 2005 without any serious side effects (Metzner, 2005). Since 2005, this literature review of Psilocybin use in the clinical setting for depression determined 565 dose-sessions were documented among 377 participants without any serious adverse effect (Bogenschutz et al., 2015; Brown et al., 2017; Carhart-Harris et al., 2012; Carhart-Harris et al., 2016; Carhart-Harris et al., 2017; Carhart-Harris et al., 2018; Carillo et al., 2018; Griffith et al., 2006; Griffith et al., 2008; Griffith et al., 2016; Grob et al., 2011; Johnson et al., 2014; Kometer et al., 2012; Kraehenmann et al., 2015; Roseman et al., 2018; Ross et al., 2016; Schmidt et al., 2013; Stroud et al., 2017).

Despite the dramatic psychological effects that Psilocybin can produce, its safety profile exceeds many common drugs such as caffeine, nicotine, alcohol and cannabis (Nutt, King & Phillips, 2010). Psilocybin is not neurotoxic or genotoxic and has an LD50 requiring an individual to eat their bodyweight in mushrooms or consume approximately 19 grams of pure isolated Psilocybin (Tyls, Palenicek & Horacek, 2013). Also, Psilocybin is not considered to be a drug of addiction. Psilocybin does not directly affect the mesolimbic dopaminergic pathway, which is the biological reward system of the brain, and thus does not cause the craving or withdrawal that is associated with addiction (Johnson et al., 2008). When given to monkeys, Psilocybin does not cause reward seeking behavior and usually causes active aversion (Fantegrossi et al., 2004). In fact, several other clinical trials have found positive results using Psilocybin as treatment for tobacco or alcohol addiction (Bogenschutz et al., 2015; Bogenschutz & Johnson, 2016; Johnson et al., 2014).

The main safety concern with Psilocybin use is the dramatic alteration of perception, intensified emotions and hallucinations that can be unsafe in a precarious environment (Tyls, Palenicek & Horacek, 2013). One study found that 39% of participants had extreme ratings of fear and 44% of participants had paranoid thinking at some point during the Psilocybin session (Griffiths et al., 2014). Thus, when given clinically, set and setting need to be addressed and controlled. All clinical research trials in this literature review implemented and controlled for this aspect of the experience by providing adequate education for realistic personal expectations and addressing the nature of the environment by creating a homely, calm, dimly lit room with personnel near by to assist as needed. Due to Psilocybin's sympathomimetic effects there is also some reasonable concern for patients with severe cardiovascular disease. Psilocybin has been found to raise the heart rate by an average of approximately 10 bpm, and blood pressure

approximately 20/10 mmHg (Griffiths et al., 2014). Although these changes are transient and dose dependent, any patient undergoing treatment with Psilocybin should be cleared for cardiovascular disease. Professional opinion agrees with Psilocybin in conjunction with psychological support as an early option in the treatment of depression (Carhart-Harris & Goodwin, 2017; Johnson & Griffiths, 2017; McCorvy, Olsen, & Roth 2016; Nutt, 2016). Notably it has been found to have areas of superiority above SSRIs and CBT specifically in its rapid and enduring action, positive side-effect profile, low dose exposure, and specific therapeutic actions which address, rather than suppress, memories and emotions (Carhart-Harris & Goodwin, 2017). When it comes to depression, the pinnacle of treatment or 'cure' is considered remission. Objectively this can be defined on the HDRS as a score less than or equal to 7 or a relative reduction greater than or equal to 50% (Giffiths et al., 2016; Zimmerman, Posternak & Chelminski, 2005). Antidepressants have a track record of remission above control groups at 8.9% (Jakobsen et al., 2017). This is in stark comparison to the remission rates for Psilocybin the clinical trials of 67%, 65%, 65% and 60% (Carhart-Harris et al., 2016; Carhart-Harris et al., 2018; Griffiths et al., 2016; Ross et al., 2016).

Cost comparison

Escitalopram, an SSRI commonly used for depression, has been identified in a large systematic review as the most efficacious with the highest acceptability in the treatment for major depressive disorder (Cipriani et al., 2018). Healthcare bluebook (2018) has a 30-day fair cost supply of Escitalopram priced at $15. A 6 months treatment supply would cost approximately $90. For the 180 days of treatment a patient may visit their provider once for the initial visit with 1 to 5 follow-up visits. According to Healthcare bluebook (2018), a fair price for a 45-minute new patient office visit would cost $175 and each follow up 15-minute established

patient office visit would cost $79. This calculates to $254 to $570 for office visits. Thus, the uninsured cost for 6 months of treatment with Escitalopram can approximately be calculated to cost in the range of $344 to $660 or averaged out to $502 for 6 months. Importantly this cost should be applied to the measured effect on the Hamilton Depression Rating Scale (HDRS) to determine the cost per effect benefit of this treatment. For 6 months of treatment on Escitalopram a patient would pay $502 for the averaged 1.8-point reduction of the HDRS, which means that each point reduction costs the patient approximately $279.

According to Matthew Johnson, a psychiatry and behavioral sciences professor and lead researcher at John Hopkins University, the current cost of Psilocybin is approximately $7,000 per gram (Goldhill, 2018). The typical administered dose across many clinical trials has been 25 mg, which cost approximately $175 per treatment. Since most clinical trials measured out to 6 months and the antidepressant effects are observed after only one dose, cost of treatment will be calculated from a single dose of psilocybin within a 6-month period. Due to the unique treatment features of Psilocybin, set and setting must be accounted for and treatment should be performed in a controlled setting with a trained healthcare staff member observing for approximately 6 hours. The cost for a clinical room of an established patient is $156 for 40 minutes, which for a 6-hour treatment of Psilocybin would cost $1404 (Healthcare bluebook, 2018). A trained medical staff observing being paid a fair price of $15 per hour for 6 hours of observation would cost $90. The total for uninsured Psilocybin treatment can be calculated to cost approximately $1669 for 6 months. Psilocybin provides an average, placebo-adjusted, point reduction on the HDRS of 10. The price per point reduction on the HDRS for Psilocybin is $167.

Limitations with Psilocybin Research

When analyzing the data from the Psilocybin clinical trials it became apparent there were a few limitations that could impact the quality of the data presented in this paper. First, every study involved had a small sample size. Sizes varied from 12 to 51 participants, and this is likely due the legal restriction surrounding Psilocybin's schedule I status preventing or at least making it extremely difficult to perform larger clinical trials. Given this predicament, it should be noted that all studies with a small sample size have a larger probability that chance can affect the outcome of the study. For Psilocybin research, confidence that chance has not grossly affected the results is supported by multiple clinical trials with similar outcomes. But, due to the very nature of small samples sizes in research, this cannot be wholly excluded. Second, for every study involved there appeared to be a selection bias. Whenever participants differ systematically from the general population the results of the study will be applied to, there is a selection bias. For Psilocybin research most participants were volunteers, with a disproportionately high level of education and previous use of hallucinogens. Volunteer bias is intrinsic to the very nature of those that are willing to volunteer. The fact the group of participants had been self-selected excludes from the study any of the portion of the population that would not have volunteered themselves. This inherently sets up a bias that is not fully representative of the population at large. Additionally, the participants selected for the studies were largely more well educated than the general population. Three out of the five clinical trials had between 48-53% of participants with post-graduate level education. Also, to this point, there was an exceptionally high occurrence of previous psychedelic use in participants across several studies. This sets up for the possibility of a confirmation bias. Participants with previous exposure to Psilocybin may have

preconceived notions that it has ‘healing’ or ‘curing’ potential and unknowing confirm the results they expect to have.

Another major limitation with a lack of control with placebo. Three out of the five studies were not placebo-controlled and studied the effects of Psilocybin against itself in high versus low doses. The placebo effect is some form of psychobiological phenomenon attributable to several mechanisms including expectation of perceived realities and pavlovian conditioning and must be accounted for in clinical trials (Benedetti et al., 2005). The placebo effect has been demonstrated to have efficacy as high as 50% but is variable across different studies (Kam-Hansen et al., 2014). This limits the extent to which conclusions can be drawn about Psilocybin’s efficacy above placebo. But to this point comes the difficulty of blinding Psilocybin in a study against a placebo. Psilocybin’s dramatic effects are almost impossible to blind against, especially with an inactive placebo. This can have set up a bias in the study if the participants are unblinded to the substance they are taking. Some studies have used active placebo such as methylphenidate which has similar sympathomimetic effects and helps with the blinding to creates results less burdened by the possibility of bias. Future studies of Psilocybin should have larger samples sizes up to 100 or more participants, if allowed by a reduction of current restrictions, implement a more diverse sample representative of the general population, and utilize an active placebo for blinding.

Schedule I Status

Any substance that Schedule I in the United States, is nearly impossible to research due to stringent legal restrictions essentially making it illegal for medical use without special limited permission (Andreae et al., 2016). In addition to these restrictions there are other barriers that attribute to this difficulty which dissuade most enthusiastic researchers including a general lack of funding, professional stigma, and a high-risk low-rewards landscape. It has been shown that

classification under Schedule I is rarely based on scientific evidence alone (Andreae et al., 2016). Schedule I status requires three conditions: the substance has no currently accepted medical use in treatment, there is lack of accepted safety for use under medical supervision, and the substance has a high potential for abuse (Drug Enforcement Agency, 2018). Each of these three conditions is untrue for Psilocybin. Across many research clinical trials, it has been shown that not only does Psilocybin have a medical use in treatment, it is nearly 6 times as effective in treating depression as the current therapy with antidepressant (Carhart-Harris et al., 2016; Carhart-Harris et al., 2018; Griffiths et al., 2016; Grob et al., 2011; Kirsch, 2010; Ross et al., 2016). To the second condition, Psilocybin safety profile has been shown to be less dangerous than most common drugs such as caffeine, nicotine, alcohol, and cannabis (Nutt, King & Phillips, 2010). And to the last condition, Psilocybin is not considered to be a drug of abuse and has a low potential for addiction. Psilocybin does not directly affect the mesolimbic dopaminergic pathway, which is the biological reward system of the brain, and thus does not cause the craving or withdrawal that is associated with addiction (Johnson et al., 2008). Since none of the schedule I conditions are true for Psilocybin, and there is a large unmet need for cancer-related depression therapy, it would be unjustified to not consider rescheduling Psilocybin out of the Schedule I category so that it can be fully explored as a valid treatment option. One major study looked that the abuse potential of Psilocybin and recommend rescheduling Psilocybin to schedule IV (Johnson, Griffiths, Hendricks and Hennigfield, 2018).

Conclusion

Cancer directly affects 40% of the populations, with around 40% of this population suffering from depression. Currently there is a large unmet need for cancer-related depression treatment in the United States since there is no approved treatment for cancer related depression.

Antidepressants are the most frequent means of treatment but several meta-analyses have shown there is no clinically significant benefit of antidepressants above placebo for cancer-related depression. Psilocybin has been shown to outperform the current treatment options on every front including, efficacy, safety, side effect profile, and cost. Psilocybin is approximately 6 times more effective at reducing depressive symptoms than a leading antidepressant Escitalopram on the HDRS. Across clinical trials Psilocybin averaged 64% remission of depression whereas SSRI's, the most widely prescribed antidepressant, averaged only 8.9% remission. Psilocybin's safety profile far exceeds that of any antidepressant and has not been linked to any serious adverse events, whereas SSRI have serious adverse events at a rate of approximately 1%. When measured objectively, price per point reduction on the HDRS even favored Psilocybin. The leading antidepressant on the market in terms of efficacy, Escitalopram, costs approximately $502 for 6 months of treatment. Escitalopram provides on average 1.8-point reduction on the HDRS, costing $279 per point reduction of depression. Psilocybin on the other hand cost $1669 for 6 months of treatment and provides approximately a 10-point reduction on the HDRS, costing $167 per point reduction of depression. In terms of cost, each point reduced on the HDRS was over $112 more cost effective with Psilocybin. Not only can more antidepressant results be achieved with Psilocybin in terms of remission and direct HDRS point reduction, they can be achieved more safely and more cost effectively than the current therapy. The overall quality of evidence for this proposal is quite strong. Although the largest limitation to this evidence has been studies with small sample sizes, this is more born out of Psilocybin's current schedule I status than a lack of Psilocybin's ability to provided strong evidence. This schedule change recommendation is the exact solution to provide the evidence for its medical benefit on a large scale and removal of the particular dilemma which schedule I substances inherit.

This intervention although significant, and clinically relevant in its rapid, robust and lasting effects for treatment of depression with those facing life-threatening cancer, is currently a schedule I drug and illegal to use or prescribe. An important and unfortunate result of Schedule I status makes research into mechanisms of action and therapeutic uses nearly impossible. Now that Psilocybin has been shown to be medically useful in treatment along with being non-addictive with low abuse potential and has been demonstrated to be safety administered under medical supervision, it is time to change its scheduling status so that future research can begin to implement its anti-depressive properties for those that are suffering. A major study directly analyzed the abuse potential of medical Psilocybin to the 8 factors of the controlled substance act and found that Psilocybin should have no more restrictive scheduling that Schedule IV (Johnson et al., 2018).

Although this project is advocating for a schedule change for research purposes, the direct result of this may be applicable to treatment which could then be prescribed by providers including Nurse Practitioners. This could have a direct impact on Advanced Nursing Practice as Nurse Practitioners are increasing caring for patients in the provider role. If Psilocybin was rescheduled and future research continues to show significant anti-depressive results, the entire paradigm of depression treatment could change. Patients would be unburdened by a daily pill regimen, long trial periods, frequent provider visits and unsettling side effects. Patients could come to an outpatient clinic, every 6 months for counseling and a 6-hour treatment session with Psilocybin guided by a medically trained assistant. They would then be able to spend the next 6 months or longer enjoying the anti-depressive effects until their next therapeutic session. The importance of the evidence for a schedule change and continued research with Psilocybin is as significant as the burden of depression itself. A quote from an unknown author captures this

sentiment perfectly, “The real fear of depression isn’t dying, it’s living with yourself, forever”. It would be imprudent to allow an opportunity as significant as this to be missed at the expense of untreated depressive suffering.

The process by which Psilocybin can be further researched is directly tied to its scheduling status. As a schedule I substance Psilocybin has been severely limited in its scope for current research trials. The largest trial to date with Psilocybin has a modest 51 participants. The results of these studies have been very promising and larger trials are warranted. Thus, the future of this research and Psilocybin’s potential for treatment will proceed through the rescheduling by the DEA and the Department of Health and Human Services. Advocates for this research must meet with the DEA and present this data among other areas of research around Psilocybin. Those who should present this data should be medical professionals including clinical researchers and providers such as Nurse Practitioners. Another option for getting Psilocybin rescheduled is simpler and entails sending the DEA a petition from any interested party including a drug manufacturer, a medical society or association, a state or local government agency, a public interest group such as a major publishing journal or even from an individual citizen. When the petition is received, the DEA then begins their own investigation on the drug and the potentials for the request. It would be sufficiently feasible to have petitions send to the DEA from several nursing associations including the American Nurses Association (ANA). The ANA has been at the forefront for the state level changes and prescribing authority for medical cannabis which could be instrumental for guiding this process. Several other major nursing associations include, the American association of Nurse Practitioners (AANP), the National Organization of Nurse Practitioner Faculties (NONPF), the Society of Nurses in Advanced Practice (SNAP), the American Psychiatric Nurses Association (APNA), the American Holistic Nurses Association

(AHNA), the Hawaii Nurses Association (HNA), the Gerontological Advanced Practice Nurses Association (GAPNA), and the Oncology Nursing Society (ONS). Currently, Psilocybin legalization is on the ballot in California. Thus, state level governmental authorities could also petition the DEA for federal rescheduling. This could also be requested from the Hawaii local government. Additionally, publishing journal that have advocated for treatments with Psilocybin could also send petitions. Some of these journals include the journal of Psychopharmacology, Neuropharmacology, Lancet Psychiatry, JAMA Psychiatry, Proceedings of the National Academy of Sciences, and Biological Psychiatry among many others. The recent publication in the Journal of Neuropharmacology calling for the rescheduling of Psilocybin as a schedule IV medication, legitimizes the very research they promote if they were to send in a petition (Johnson et al., 2018). With growing support across many medical associations, major publishing journals and local governments the DEA would be sufficiently petitioned and obligated to reevaluate Psilocybin's scheduling status, as well as to now have enough data to make an evidence base decision. Put in this position the DEA would have to justify their decision to continue to limit future research in the face of mounting evidence for its potential life-saving benefits.

References

American Cancer Society. (2016). Retrieved from https://www.cancer.org/cancer/cancer-basics/lifetime-probability-of-developing-or-dying-from-cancer.html

Andreae, M. H., Rhodes, E., Bourgoise, T., Carter, G. M., White, R. S., Indyk, D., ... & Rhodes, R. (2016). An ethical exploration of barriers to research on controlled drugs. *The American Journal of Bioethics*, *16*(4), 36-47.

Arrieta, Ó., Angulo, L. P., Núñez-Valencia, C., Dorantes-Gallareta, Y., Macedo, E. O., Martínez-López, D., ... & Oñate-Ocaña, L. F. (2013). Association of depression and anxiety on quality of life, treatment adherence, and prognosis in patients with advanced non-small cell lung cancer. *Annals of surgical oncology*, *20*(6), 1941-1948.

Benedetti, F., Mayberg, H. S., Wager, T. D., Stohler, C. S., & Zubieta, J. K. (2005). Neurobiological mechanisms of the placebo effect. *Journal of Neuroscience*, *25*(45), 10390-10402.

Bernasconi, F., Schmidt, A., Pokorny, T., Kometer, M., Seifritz, E., & Vollenweider, F. X. (2013). Spatiotemporal brain dynamics of emotional face processing modulations induced by the serotonin 1A/2A receptor agonist Psilocybin. *Cerebral Cortex*, *24*(12), 3221-3231.

Bogenschutz, M. P., Forcehimes, A. A., Pommy, J. A., Wilcox, C. E., Barbosa, P. C. R., & Strassman, R. J. (2015). Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. *Journal of psychopharmacology*, *29*(3), 289-299.

Bogenschutz, M. P., & Johnson, M. W. (2016). Classic hallucinogens in the treatment of addictions. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *64*, 250-258.

Breitbart, W., Rosenfeld, B., Gibson, C., Pessin, H., Poppito, S., Nelson, C., ... & Sorger, B. (2010). Meaning-centered group psychotherapy for patients with advanced cancer: a pilot randomized controlled trial. *Psycho-Oncology*, *19*(1), 21-28.

Brown, R. T., Nicholas, C. R., Cozzi, N. V., Gassman, M. C., Cooper, K. M., Muller, D., ... & Hutson, P. R. (2017). Pharmacokinetics of escalating doses of oral Psilocybin in healthy adults. *Clinical pharmacokinetics*, *56*(12), 1543-1554.

Carhart-Harris, R. L., Bolstridge, M., Day, C. M. J., Rucker, J., Watts, R., Erritzoe, D. E., ... & Rickard, J. A. (2018). Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. *Psychopharmacology*, *235*(2), 399-408.

Carhart-Harris, R. L., Bolstridge, M., Rucker, J., Day, C. M., Erritzoe, D., Kaelen, M., ... & Taylor, D. (2016). Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. *The Lancet Psychiatry*, *3*(7), 619-627.

Carhart-Harris, R. L., Erritzoe, D., Williams, T., Stone, J. M., Reed, L. J., Colasanti, A., ... & Hobden, P. (2012a). Neural correlates of the psychedelic state as determined by fMRI studies with Psilocybin. *Proceedings of the National Academy of Sciences*, *109*(6), 2138-2143.

Carhart-Harris, R. L., & Goodwin, G. M. (2017). The therapeutic potential of psychedelic drugs: past, present, and future. *Neuropsychopharmacology*, *42*(11), 2105.

Carhart-Harris, R. L., Leech, R., Williams, T. M., Erritzoe, D., Abbasi, N., Bargiotas, T., ... & Wise, R. G. (2012b). Implications for psychedelic-assisted psychotherapy: functional magnetic resonance imaging study with Psilocybin. *The British Journal of Psychiatry*, *200*(3), 238-244.

Carhart-Harris, R. L., Roseman, L., Bolstridge, M., Demetriou, L., Pannekoek, J. N., Wall, M. B., ... & Leech, R. (2017). Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms. *Scientific reports*, *7*(1), 13187.

Carlat, D. (2010). *Unhinged: The trouble with psychiatry-a doctor's revelations about a profession in crisis*. Simon and Schuster.

Carrillo, F., Sigman, M., Slezak, D. F., Ashton, P., Fitzgerald, L., Stroud, J., ... & Carhart-Harris, R. L. (2018). Natural speech algorithm applied to baseline interview data can predict which patients will respond to Psilocybin for treatment-resistant depression. *Journal of affective disorders*, *230*, 84-86.

Cipriani, A., Furukawa, T., Salanti, G., Gedded, J., Higgins, J., Churchill, R., & … Nakagawa, A., (2018). Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet, 373 North American Edition* (9665), 765-758. Doi: 10.1016/S0140-6736(09)60046-5

Colleoni, M., Mandala, M., Peruzzotti, G., Robertson, C., Bredart, A., & Goldhirsch, A. (2000). Depression and degree of acceptance of adjuvant cytotoxic drugs. *The Lancet*, *356*(9238), 1326-1327.

Drug Enforcement Agency. (2018). Diversion Control Division. Retrieved from https://www.deadiversion.usdoj.gov/schedules/

Faller, H., Schuler, M., Richard, M., Heckl, U., Weis, J., & Küffner, R. (2013). Effects of psycho-oncologic interventions on emotional distress and quality of life in adult patients with cancer: systematic review and meta-analysis. *Journal of Clinical Oncology*, *31*(6), 782-793.

Fantegrossi, W. E., Woods, J. H., & Winger, G. (2004). Transient reinforcing effects of phenylisopropylamine and indolealkylamine hallucinogens in rhesus monkeys. *Behavioural pharmacology*, *15*(2), 149-157.

Goldhill, O. (2018). *Scientists who want to study psychedelic mushrooms have to pay $7,000 per gram.* Retrieved from https://qz.com/1235963/scientists-who-want-to-study-psychedelic-mushrooms-have-to-pay-7000-per-gram/

Grassi, L., Caruso, R., Hammelef, K., Nanni, M. G., & Riba, M. (2014). Efficacy and safety of pharmacotherapy in cancer-related psychiatric disorders across the trajectory of cancer care: a review. *International Review of Psychiatry*, *26*(1), 44-62.

Griffiths, R. R., Richards, W. A., Johnson, M. W., McCann, U. D., & Jesse, R. (2008). Mystical-type experiences occasioned by Psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. *Journal of psychopharmacology*, *22*(6), 621-632.

Griffiths, R. R., Richards, W. A., McCann, U., & Jesse, R. (2006). Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacology*, *187*(3), 268-283.

Griffiths, R. R., Johnson, M. W., Carducci, M. A., Umbricht, A., Richards, W. A., Richards, B. D., ... & 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*, *30*(12), 1181-1197.

Grob, C. S., Bossis, A. P., & Griffiths, R. R. (2013). Use of the classic hallucinogen Psilocybin for treatment of existential distress associated with cancer. In *Psychological aspects of cancer* (pp. 291-308). Springer, Boston, MA.

Grob, C. S., Danforth, A. L., Chopra, G. S., Hagerty, M., McKay, C. R., Halberstadt, A. L., & Greer, G. R. (2011). Pilot study of Psilocybin treatment for anxiety in patients with advanced-stage cancer. *Archives of general psychiatry*, *68*(1), 71-78.

Healthcare Bluebook. (2018). Consumer Front. Retrieved from https://www.healthcarebluebook.com/ui/consumerfront

Hendricks, P. S., Thorne, C. B., Clark, C. B., Coombs, D. W., & Johnson, M. W. (2015). Classic psychedelic use is associated with reduced psychological distress and suicidality in the United States adult population. *Journal of Psychopharmacology*, *29*(3), 280-288.

Holland, J. C., Andersen, B., Breitbart, W. S., Buchmann, L. O., Compas, B., Deshields, T. L., ... & Greiner, C. B. (2013). Distress management. *Journal of the National Comprehensive Cancer Network*, *11*(2), 190-209.

Iovieno, N., Tedeschini, E., Ameral, V. E., Rigatelli, M., & Papakostas, G. I. (2011). Antidepressants for major depressive disorder in patients with a co-morbid axis-III disorder: a meta-analysis of patient characteristics and placebo response rates in randomized controlled trials. *International clinical psychopharmacology*, *26*(2), 69-74.

Jakobsen, J. C., Katakam, K. K., Schou, A., Hellmuth, S. G., Stallknecht, S. E., Leth-Møller, K., ... & Krogh, J. (2017). Selective serotonin reuptake inhibitors versus placebo in patients with major depressive disorder. A systematic review with meta-analysis and Trial Sequential Analysis. *BMC psychiatry*, *17*(1), 58.

Johnson, M. W., Garcia-Romeu, A., Cosimano, M. P., & Griffiths, R. R. (2014). Pilot study of the 5-HT2AR agonist Psilocybin in the treatment of tobacco addiction. *Journal of psychopharmacology*, *28*(11), 983-992.

Johnson, M. W., & Griffiths, R. R. (2017). Potential therapeutic effects of Psilocybin. *Neurotherapeutics*, *14*(3), 734-740.

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*.

Johnson, M. W., Richards, W. A., & Griffiths, R. R. (2008). Human hallucinogen research: guidelines for safety. *Journal of psychopharmacology*, *22*(6), 603-620.

Kam-Hansen, S., Jakubowski, M., Kelley, J. M., Kirsch, I., Hoaglin, D. C., Kaptchuk, T. J., & Burstein, R. (2014). Altered placebo and drug labeling changes the outcome of episodic migraine attacks. *Science translational medicine*, *6*(218), 218ra5-218ra5.

Kirsch, I. (2010). *The emperor's new drugs: Exploding the antidepressant myth*. ReadHowYouWant. com.

Kirsch, I., Deacon, B. J., Huedo-Medina, T. B., Scoboria, A., Moore, T. J., & Johnson, B. T. (2008). Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. *PLoS medicine*, *5*(2), e45.

Kometer, M., Schmidt, A., Bachmann, R., Studerus, E., Seifritz, E., & Vollenweider, F. X. (2012). Psilocybin biases facial recognition, goal-directed behavior, and mood state toward positive relative to negative emotions through different serotonergic subreceptors. *Biological psychiatry*, *72*(11), 898-906.

Kraehenmann, R., Preller, K. H., Scheidegger, M., Pokorny, T., Bosch, O. G., Seifritz, E., & Vollenweider, F. X. (2015). Psilocybin-induced decrease in amygdala reactivity correlates with enhanced positive mood in healthy volunteers. *Biological psychiatry*, *78*(8), 572-581.

Krebs, T. S., & Johansen, P. Ø. (2013). Psychedelics and mental health: a population study. *PloS one*, *8*(8), e63972.

Laoutidis, Z. G., & Mathiak, K. (2013). Antidepressants in the treatment of depression/depressive symptoms in cancer patients: a systematic review and meta-analysis. *BMC psychiatry*, *13*(1), 140.

Lloyd-Williams, M., Shiels, C., Taylor, F., & Dennis, M. (2009). Depression—an independent predictor of early death in patients with advanced cancer. *Journal of affective disorders*, *113*(1-2), 127-132.

McCorvy, J. D., Olsen, R. H., & Roth, B. L. (2016). Psilocybin for depression and anxiety associated with life-threatening illnesses. *Journal of Psychopharmacology*, *30*(12), 1209-1210.

Metzner, R. (Ed.). (2005). *Sacred mushroom of visions: Teonanacatl: A sourcebook on the Psilocybin mushroom*. Simon and Schuster.

Mitchell, A. J., Chan, M., Bhatti, H., Halton, M., Grassi, L., Johansen, C., & Meader, N. (2011). Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. *The lancet oncology*, *12*(2), 160-174.

National Cancer Institute. (2016). Retrieved from https://seer.cancer.gov/statfacts/html/all.html

Nursing Theories. (2016, April 1). Current Nursing. Retrieved from http://currentnursing.com/nursing_theory/Newman_Health_As_Expanding_Consciousness.html

Nutt, D. (2016). Psilocybin for anxiety and depression in cancer care? Lessons from the past and prospects for the future.

Nutt, D. J., King, L. A., & Phillips, L. D. (2010). Drug harms in the UK: a multicriteria decision analysis. *The Lancet*, *376*(9752), 1558-1565.

Ostuzzi, G., Matcham, F., Dauchy, S., Barbui, C., & Hotopf, M. (2015). Antidepressants for the treatment of depression in people with cancer.

Pinquart, M., & Duberstein, P. R. (2010). Depression and cancer mortality: a meta-analysis. *Psychological medicine*, *40*(11), 1797-1810.

Prieto, J. M., Blanch, J., Atala, J., Carreras, E., Rovira, M., Cirera, E., & Gastó, C. (2002). Psychiatric morbidity and impact on hospital length of stay among hematologic cancer patients receiving stem-cell transplantation. *Journal of Clinical Oncology*, *20*(7), 1907-1917.

PubMed Health. (2017). U.S. National Library of Medicine. Retrieved from https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0087089/.

Robinson, S., Kissane, D. W., Brooker, J., & Burney, S. (2016). A review of the construct of demoralization: History, definitions, and future directions for palliative care. *American Journal of Hospice and Palliative Medicine®*, *33*(1), 93-101.

Roseman, L., Nutt, D. J., & Carhart-Harris, R. L. (2018). Quality of acute psychedelic experience predicts therapeutic efficacy of Psilocybin for treatment-resistant depression. *Frontiers in pharmacology*, *8*, 974.

Ross, S., Bossis, A., Guss, J., Agin-Liebes, G., Malone, T., Cohen, B., ... & Su, Z. (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*, *30*(12), 1165-1180.

Rucker, J. J., Jelen, L. A., Flynn, S., Frowde, K. D., & Young, A. H. (2016). Psychedelics in the treatment of unipolar mood disorders: a systematic review. *Journal of Psychopharmacology*, *30*(12), 1220-1229.

Satin, J. R., Linden, W., & Phillips, M. J. (2009). Depression as a predictor of disease progression and mortality in cancer patients: a meta-analysis. *Cancer*, *115*(22), 5349-5361.

Schartner, M. M., Carhart-Harris, R. L., Barrett, A. B., Seth, A. K., & Muthukumaraswamy, S. D. (2017). Increased spontaneous MEG signal diversity for psychoactive doses of ketamine, LSD and Psilocybin. *Scientific reports*, *7*, 46421.

Schmidt, A., Kometer, M., Bachmann, R., Seifritz, E., & Vollenweider, F. (2013). The NMDA antagonist ketamine and the 5-HT agonist Psilocybin produce dissociable effects on structural encoding of emotional face expressions. *Psychopharmacology*, *225*(1), 227-239.

Shim, E. J., & Park, J. H. (2012). Suicidality and its associated factors in cancer patients: Results of a multi-center study in Korea. *The International Journal of Psychiatry in Medicine*, *43*(4), 381-403.

Simon, G. & Clechanowski, P. (2017). Patient Education: Depression Treatment Options for Adults (Beyond the Basics). 2017. UpToDate. Document. 23 March 2017.

Skarstein, J., Aass, N., Fosså, S. D., Skovlund, E., & Dahl, A. A. (2000). Anxiety and depression in cancer patients: relation between the Hospital Anxiety and Depression Scale and the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire. *Journal of psychosomatic research*, *49*(1), 27-34.

Stewart, B. W. K. P., & Wild, C. P. (2014). “World Cancer Report 2014.”. *World Health Organization*.

Stroud, J. B., Freeman, T. P., Leech, R., Hindocha, C., Lawn, W., Nutt, D. J., ... & Carhart-Harris, R. L. (2018). Psilocybin with psychological support improves emotional face recognition in treatment-resistant depression. *Psychopharmacology*, *235*(2), 459-466.

Tylš, F., Páleníček, T., & Horáček, J. (2014). Psilocybin–summary of knowledge and new perspectives. *European Neuropsychopharmacology*, *24*(3), 342-356.

Vergo, M. T., Whyman, J., Li, Z., Kestel, J., James, S. L., Rector, C., & Salsman, J. M. (2017). Assessing preparatory grief in advanced cancer patients as an independent predictor of distress in an American population. *Journal of palliative medicine*, *20*(1), 48-52.

Vollenweider, F. X., & Kometer, M. (2010). The neurobiology of psychedelic drugs: implications for the treatment of mood disorders. *Nature Reviews Neuroscience*, *11*(9), 642.

Zimmerman, M., Posternak, M. A., & Chelminski, I. (2005). Is the cutoff to define remission on the Hamilton Rating Scale for Depression too high? *The Journal of nervous and mental disease*, *193*(3), 170-175.

Appendix A

The Griffiths et al., 2016 study was a randomized double-blind cross-over study with 51 participants. Out of the 17 therapeutically relevant measures, 11 achieved conservative criteria for demonstrating efficacy of the high dose of Psilocybin (Griffiths et al., 2016). Specifically, depression was considerably reduced after a single high dose of Psilocybin, across several measurement tools including: GRID-HAMD from 22.84 to 6.64 with a mean reduction of -6.4 points ($p<0.001$), BDI from 17.77 to 7.00, with a mean reduction of -10.77 points ($p<0.01$), and HADS depression from 9.81 to 3.92 with a mean reduction of -5.89 points ($p<0.05$) (Griffiths et al., 2016). The Ross et al., 2016 study utilized 29 participants and was also randomized, controlled, and blinded. Across the six primary outcome measures, the Psilocybin group demonstrated immediate, substantial and sustained clinical benefits in terms of anxiety and depression symptoms with 83% of participants meeting the criteria for anti-depressant response out to 7 weeks (Ross et al., 2016). Specifically, for measures of depression two tools were used, and both showed significant reduction in depression after the first dose of Psilocybin, HADS depression 5.5 to 2 with a mean reduction of -3.5 points ($p<0.001$) and BDI from 15 to 4 with a mean reduction of -11 points ($p<0.01$) (Ross et al., 2016). The Carhart-Harris et al., 2016 study was a smaller, open label single arm feasibility pilot study with only 12 participants. Even though this was a much smaller pilot study, the results show dramatic changes in depression and substantiate the larger studies. For depression four different measurement tools were used and show significant reductions in depression after the first dose of Psilocybin, QIDS from 19.2 to 7.4 with a mean reduction of -11.8 points ($p<0.002$), BDI from 33.7 to 8.7 with a mean reduction of -25 ($p<0.002$), HAM-D from 21.4 to 7.4, with a mean reduction of -14 points ($p<0.003$) and MADRS from 31.0 to 9.7 with a mean reduction of -21.3 points ($p<0.002$) (Carhart-Harris et al.,

2016). The Carhart-Harris et al., 2018 study was an open label feasibility study with 20 patients suffering from treatment resistant depression. The measures of depression in this study shows dramatic reductions in included QIDS-SR 16 with a mean reduction of -9.2 points ($p<0.001$), BDI with a mean reduction of -22.7 points ($p<0.001$), SHAPS mean reduction of -4.6 ($p<0.001$) and HAM-D mean reductions of -14.8 points ($p<0.001$) (Carhart-Harris et al., 2018). Lastly, the Grob et al., 2011 study, which was also a pilot study, utilized 12 participants in a double-blind, placebo-controlled design. This study implemented 5 measurement tools which all demonstrated marked subjective difference between Psilocybin and placebo (Grob et al., 2011). The psychological measure that reached p value ($p<0.01$) included 'oceanic boundlessness' and 'visionary restructuralization' (Grob et al., 2011). Measures that reached p value ($p<0.05$) included 'positive derealization', 'positive depersonalization', 'positive mood', 'changed meaning of perception', 'facilitated recollection' and 'facilitated imagination' (Grob et al., 2011). Specifically, for depression, only one tool was used BDI, and this reached a clinical significant p value from 15 to 7 with a mean reduction of – 8 points ($p<0.05$) at the 6-month interval (Grob et al., 2011).

Appendix B

Patient Name:_____ Date _____

Hamilton Rating Scale for Depression (17-items)

Instructions: For each item select the "cue" which best characterizes the patient during the past week.

1. **Depressed Mood**
   (sadness, hopeless, helpless, worthless)
   0 Absent
   1 These feeling states indicated only on questioning
   2 These feeling states spontaneously reported verbally
   3 Communicates feeling states nonverbally, i.e., through facial expression, posture, voice and tendency to weep
   4 Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and nonverbal communication

2. **Feelings of Guilt**
   0 Absent
   1 Self-reproach, feels he has let people down
   2 Ideas of guilt or rumination over past errors or sinful deeds
   3 Present illness is a punishment. Delusions of guilt
   4 Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3. **Suicide**
   0 Absent
   1 Feels life is not worth living
   2 Wishes he were dead or any thoughts of possible death to self
   3 Suicide ideas or gesture
   4 Attempts at suicide (any serious attempt rates 4)

4. **Insomnia - Early**
   0 No difficulty falling asleep
   1 Complains of occasional difficulty falling asleep i.e., more than ½ hour
   2 Complains of nightly difficulty falling asleep

5. **Insomnia - Middle**
   0 No difficulty
   1 Patient complains of being restless and disturbed during the night
   2 Waking during the night – any getting out of bed rates 2 (except for purposes of voiding)

6. **Insomnia - Late**
   0 No difficulty
   1 Waking in early hours of the morning but goes back to sleep
   2 Unable to fall asleep again if gets out of bed

7. **Work and Activities**
   0 No difficulty
   1 Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies
   2 Loss of interest in activity; hobbies or work – either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)
   3 Decrease in actual time spent in activities or decrease in productivity. In hospital, rate 3 if patient does not spend at least three hours a day in activities (hospital job or hobbies) exclusive of ward chores.
   4 Stopped working because of present illness. In hospital, rate 4 if patient engages in no activities except ward chores, or if patient fails to perform ward chores unassisted.

8. **Retardation**
   (slowness of thought and speech; impaired ability to concentrate; decreased motor activity)
   0 Normal speech and thought
   1 Slight retardation at interview
   2 Obvious retardation at interview
   3 Interview difficult
   4 Complete stupor

9. **Agitation**
   0 None
   1 "Playing with" hand, hair, etc.
   2 Hand-wringing, nail-biting, biting of lips

10. **Anxiety - Psychic**
    0 No difficulty
    1 Subjective tension and irritability
    2 Worrying about minor matters
    3 Apprehensive attitude apparent in face or speech
    4 Fears expressed without questioning

11. **Anxiety - Somatic**
    0 Absent
    1 Mild
    2 Moderate
    3 Severe
    4 Incapacitating
    Physiological concomitants of anxiety such as:
    Gastrointestinal - dry mouth, wind, indigestion, diarrhea, cramps, belching
    Cardiovascular – palpitations, headaches
    Respiratory - hyperventilation, sighing
    Urinary frequency
    Sweating

12. **Somatic Symptoms - Gastrointestinal**
    0 None
    1 Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen.
    2 Difficulty eating without staff urging. Requests or requires laxatives or medications for bowels or medication for G.I. symptoms.

13. **Somatic Symptoms - General**
    0 None
    1 Heaviness in limbs, back or head, backaches, headache, muscle aches, loss of energy and fatigability
    2 Any clear-cut symptom rates 2

14. **Genital Symptoms**
    0 Absent
    1 Mild
    2 Severe
    0 Not ascertained
    Symptoms such as: loss of libido, menstrual disturbances

15. **Hypochondriasis**
    0 Not present
    1 Self-absorption (bodily)
    2 Preoccupation with health
    3 Frequent complaints, requests for help, etc.
    4 Hypochondriacal delusions

16. **Loss of Weight**
    A. When Rating by History:
    0 No weight loss
    1 Probable weight loss associated with present illness
    2 Definite (according to patient) weight loss

    B. On Weekly Ratings by Ward Psychiatrist, When Actual Changes are Measured:
    0 Less than 1 lb. weight loss in week
    1 Greater than 1 lb. weight loss in week
    2 Greater than 2 lb. weight loss in week

17. **Insight**
    0 Acknowledges being depressed and ill
    1 Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
    2 Denies being ill at all

Total Score:_____