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The Therapeutic Potential of Psilocybin in Alcohol Use Disorder Recovery: A Literature Review

Kaden L. Venugopal, BHSc Student [1]*, Nefissa A. Bedri, BHSc Student [2]

[1] Faculty of Health Sciences, University of Ottawa, Ottawa, Ontario, Canada, K1N 6N5

*Corresponding Authors: kvenu065@uottawa.ca

Abstract

Introduction: Psilocybin (the active compound found in "magic mushrooms") has been an area of recent focus in the academic and psychiatric community on account of its potential in treating a spectrum of substance use and concurrent disorders (SUCDs). This paper posits a literature review of the current research pertaining to psilocybin in treating alcohol use disorder (AUD) through a form of therapy known as psilocybin-assisted psychotherapy (PAP).

Methods: To undertake this study, we performed a literature review of peer-reviewed studies examining the efficacy of psilocybin in treating AUD through PAP. Inclusion criteria for papers included papers published from 2010-present, peer-reviewed sources, and clinical studies and controlled experiments observing AUD in PAP settings. Exclusion criteria used in screening papers included those focusing on other psychedelic compounds and experiments examining psilocybin efficacy in non-PAP settings.

Results: Our overview of the extant literature has determined that psilocybin has strong therapeutic potential for use in PAP settings to treat AUD. Furthermore, we have identified three principal pathways through which psilocybin can elicit promising effects: neurobiological alterations (e.g., neuroplastic effects), behavioral and psychological improvements (e.g., increased receptivity towards cognitive therapies), and spiritual development (e.g., spiritual encounters improving abstinence).

Discussion: The use of psilocybin in the clinical context of AUD treatment is well supported in the field of psychedelic research. Behavioural therapies are of high importance when engaging in use of psilocybin for treating AUD patients. There are certain limitations to the applications of PAP, such as predisposition to certain mental illnesses, however, the future of psilocybin therapy is expansive, ranging from subsequent animal testing to microdosing experiments.

Conclusion: While our literature review bears positive findings, we encourage further research and clinical trials to be conducted to establish a larger body of evidence towards supporting or rejecting the validity of PAP. Should future research validate the efficacy of PAP for AUD treatment, therapists and psychiatrists could have another tool in their treatment reserve to assist people with SUCDs.

Keywords: Psilocybin; psychedelics; PAP; AUD; SUCDs; addiction treatment; recovery and rehabilitation therapies; alcoholism; AA; CBT; DBT

Introduction

In recent years, compounds acclaimed for their hallucinogenic and mind-altering effects known as psychedelics have been re-emerging as a source of academic interest and pharmaceutical potential. The impacts of psychedelics therapy could be far-reaching, spanning the fields of medicine, psychiatry, and substance abuse rehabilitation programs. Our study serves as a refreshed overview of the existing literature on the psychedelic psilocybin for alcohol use disorder (AUD) through a technique known as psilocybin-assisted psychotherapy (PAP). AUD is classified as a "substance-related and addictive disorder" in the Diagnostic Statistical Manual for Mental Disorders (DSM) 5, which integrates ethyl alcohol abuse and dependence into a single broader group of substance use disorders. While the DSM-IV included the abuse and dependence categories, DSM-5 newly classified all substance use disorders, including AUD, into three severity groups. The three severity groups are: mild, moderate, and severe; severe AUD is diagnosed when six or more of the eleven DSM 5 AUD symptoms are present [1]. PAP is a novel psychotherapy technique that has been found to have success in the psychiatric treatment of various mental health issues from substance use disorders to internalizing disorders (e.g., depression and anxiety), post-traumatic stress disorder (PTSD), and eating disorders [2]. This form of treatment uses psilocybin in conjunction with psychotherapy sessions to guide the AUD

recovery process. Researchers have been exploring psychedelics such as psilocybin as an addition/alternative to conventional pharmacotherapies for substance use disorders (perhaps given that current pharmacotherapies are not widely successful across demographics) [3-6].

Current therapies for AUD include pharmacotherapies and behavioral therapies. The former includes utilization of medications (e.g., disulfiram and naltrexone) to help deter the sensation of compulsive drinking urges, while the latter focuses on promoting behavioral changes related to alcohol consumption habits. Behavioral therapies can include cognitive-behavioral therapy (CBT), family intervention/support, relationship counseling, community support groups (e.g., Alcoholics Anonymous [AA]), music/visual art therapy, and motivational enhancement therapy. While the former approach leverages pharmacological means to control symptoms and behavioral tendencies associated with AUD, the latter espouses the concept of working with a multidisciplinary team of professionals (e.g., therapists, family doctors, psychiatrists, addiction treatment nurses, and psychologists) to identify and address changes in behaviors/mindsets, and coping skills to induce a cessation in drinking in addition to targeting reduction in risky and heavy drinking.

The United States witnessed an increase in AUD hospitalizations and drinking days per month, which researchers attributed to the COVID-19 global pandemic [7]. Several theories for the recent increased incidence of AUD are explained through the conditions created by the pandemic such as extended periods of physical and social isolation and corollary increased rates of internalizing disorders. In assessing novel treatment methods to mitigate the rising AUD rates, a critical avenue worth exploring is the capacity for PAP as a complementary therapy option to existing therapies (e.g., CBT, AA, pharmacotherapy). It is important to note that while several existing treatments are shown to effectively reduce alcohol intake, their efficacy is modest. Thus, the field seeks to develop new behavioral and pharmacological treatments for AUD with greater efficacy. Our paper aims to provide a comprehensive overview of extant literature on the 1) psilocybin's biological and psychological mechanisms of action, 2) the potential efficacy of psilocybin through PAP for patients with AUD, and 3) the integration of psilocybin into existing AUD therapies.

Methods

Our literature review consisted of screening and aggregating research papers that examined the use of psilocybin in PAP for the treatment of AUD patients. Papers were filtered based on the veracity and rigor of the study (e.g., sample size, the credibility of publishing journal or sponsor, peer-review status), with papers disregarded if not to par. Paper were compiled from databases including PubMed, MEDLINE, SCOPUS, PsycINFO, and Web of Science.

Inclusion criteria and guideline parameters for our review consisted of peer-reviewed studies in the English language that assessed the clinical efficacy of PAP in moderate-severe AUD patient treatment; the efficacy of psilocybin used in concert with pre-existing forms of AUD treatment; efficacy of non-clinical complementary therapeutic treatments (e.g., spirituality/religion, AA); papers published from 2010 onward, and clinical studies and controlled PAP experiments. Exclusion criteria included papers focusing on other psychedelic compounds, experiments with sample sizes of less than 10 patients, and experiments examining psilocybin efficacy in non-PAP settings. Data gathered that relied on self-assessment of alcoholism status (e.g., survey data or diagnosis of "mild/moderate/severe" AUD) was primarily sourced from research published after 2013, as this is when the remodeling of AUD criteria occurred with the release of the DSM 5 [1]. Keywords used in compiling papers included "psilocybin," "psilocin," "psychedelic-assisted psychotherapy," "psilocybin-assisted psychotherapy," "alcohol use disorder," "alcoholism," "alcohol addiction," "alcohol therapy," "behavioral therapy," "risks of psilocybin," and "CBT for AUD."

A supplementary focus was placed on assessing the efficacy of PAP in terms of factors such as abstinence bereavement, perspective reframing, and receptivity to cognitive psychotherapy. To provide a comprehensive analysis, an outline of the existing treatments for AUD have been incorporated, in addition to PAP's potential when used in combination with such other therapies.

Results

Psilocybin has demonstrated potential to trigger anti-craving properties, noted to subsequently reduce symptom count and number of drinking days in AUD patients [8,9]. After consumption, psilocybin is metabolized in the liver where it is converted to its pharmacologically active (psychoactive) compound, known as psilocin. Psilocybin's psychoactive effects include changes in perception, mood, and cognitive processes. There are several pathways through which psilocybin can bear therapeutic potential. This paper distills the available literature regarding PAP for AUD into three respective and congruent therapeutic pathways: 1) neurobiological alterations, 2) behavioral and psychological improvements through PAP, and 3) spiritual development from the psychedelic experience.

Neurobiological Alterations

Underpinning the physiological/neurochemical pathways of psilocybin therapy for SUCDs *in vivo* is difficult as the extant research is limited given its restricted substance classification in Canada and the United States (Canada's Controlled Drugs and Substances Act of 1996; United States' Schedule I classification in 1970) [10,11]. However, researchers from various institutions have identified several neurological changes associated with psilocybin administration, explaining the positive

implications of psilocybin therapy for AUD and its support for PAP.

Psilocybin Promotes Neural Flexibility in the Prefrontal Cortex and Stimulates Neurogenesis

Serotonergic psychedelics (e.g., psilocybin, DMT, LSD) are supported in the literature for stimulating neurogenesis and having neuroplastic effects [12-14]. This class of psychedelics was observed by researchers to increase neuritogenesis (the process of neurite production) and spinogenesis (the development of dendritic spines) *in vitro* and *in vivo*. Further, psilocybin has been found stimulate structural and functional neuronal changes, including increased synapse numbers and function [14,15]. The compound has thereby been categorized by researchers as a "psychoplastogen," indicating that it is a substance capable of inducing neuroplasticity [16].

Severe cases of AUD are often associated with damaging changes in the prefrontal cortex (PFC) such as decrease/elimination of synapses, dendritic spine reductions, and neurite retraction, among other neural circuitry issues in different regions of the brain [16]. The PFC is crucial for executing cognitive control functions, emotional regulation, and impulse inhibition, with literature suggesting it is highly involved in the drug and alcohol addiction regulation system [14]. Research suggests that these deleterious neuroanatomical changes associated with AUD (and other mental illnesses, e.g., PTSD and depression) in the PFC can be counteracted by psychoplastogens, such as psilocybin [14, 17,18].

Psilocybin has been observed to provoke rapid and sustained dendritic spine growth (spinogenesis) and increase neural connectivity via the formation of new synapses (synaptogenesis). These neuroplastic characteristics of psilocybin were observed in an experiment supported by the University of Yale Center for Psychedelic Science. This study found that after a single psilocybin dose, there was 1) increased dendritic spine density (+7±2% on day 1 after dose and +12±3% on day 7 after dose); 2) increased dendritic spine protrusion length; 3) increased spine head width (+11±2% on day 1 after dose and +5±1% on day 7 after dose), and; 4) increased dendritic spine formation rates (+8±2% for females and +4±2% for males). Additionally, these changes were observed to remain after extended periods of time (34 days following the dose, 34±10% of the newly formed spines remained for females, while 37±12% of the newly formed spines persisted for males). The persistent psilocybin-induced spines were comparably stable relative to their control conditions, suggesting that the psilocybin-induced dendritic spines would become functional synapses [15]. These findings display immediate and persistent positive neurostimulating and neuroplastic effects associated with psilocybin. Given that PTSD, depression, and substance use disorders share many overlapping neurobiological pathways [19-21] and have a high incidence of comorbidity, [22] there is further support for psilocybin usage in the clinical treatment of concurrent disorders to AUD in addition to AUD itself.

Psilocybin Restores mGluR2 Deficiencies Responsible for Various AUD Impairments

Glutamate is an excitatory neurotransmitter necessary for functional neural health and interacts with various receptors involved in learning and memory. A receptor targeted by glutamate, mGluR2 (metabotropic glutamate receptor 2), is a C G-protein coupled receptor implicated in neuronal excitability and synaptic transmission modulation [23]. AUD causes suppression of glutamate release and mGluR2 deficits in the infralimbic cortex (the area of the brain involved in executive function, goal-oriented actions, and impulsive behaviors) [24-25]. Ample research supports the critical involvement of mGluR2 in cognitive flexibility and the regulation of synaptic transmission which are both involved in alcohol cravings [24, 26-27].

A recent study from the American Association for the Advancement of Science observed psilocybin's effect on the regulation of the brain's natural glutamate-mGluR2 pathway, providing substantive insight into the biochemical workings of psilocybin. The study found that reduction in mGluR2 expression through a neuron-specific mGluR2 knock-out in the PFC was causally linked with a reduction in cognitive plasticity and increased alcohol-seeking behaviors. They further noted that psilocybin was capable of restoring mGluR2 deficiencies, thereby possibly improving alcohol relapse behaviors, alcohol craving, and cognitive flexibility [28].

Other Neurobiological Benefits of Psilocybin

Psilocybin has been observed to induce changes in blood flow to certain regions of the brain involved in AUD and other substance use disorders. An fMRI study on the functional connectivity of the default mode network (DMN)[1] found a shut-down of DMN activity following psilocybin consumption [29]. A similar study on ayahuasca (a psychedelic structurochemically similar to psilocin) found that this class of psychedelic can induce states of consciousness akin to those in a sleeping state or skilled meditators in active practice [30]. This disengagement of the DMN could be beneficial to psychotherapists engaging in behavioral reconditioning exercises with AUD patients.

AUD is a pro-inflammatory condition [31-32] and a body of literature notes the anti-inflammatory properties of psilocybin in the brain [33-38]. Heavy alcohol use as seen in AUD patients often results in excessive and conserved neuroinflammatory responses which are linked to exacerbation of AUD symptoms [37]. A study by

[1] The DMN is the area of the brain activated when individuals are focused on their internal mental state and its dysfunction is associated with aberrant effects such as craving and relapse in SUCD patients [42].

Nkadimeng et al. found that certain *Psilocybe* fungi are able to significantly reduce/inhibit lipopolysaccharide-induced cyclooxygenase-2 (an enzyme responsible for inducing inflammation) and two important pro-inflammatory cytokines (TNF-α and IL-1β) suggesting a possible mechanism for anti-inflammatory effects observed with psilocybin use [38].

In summary, psilocybin has been observed to generate neuroplasticity, promote neurogenesis, restore mGluR2 deficits in the PFC, and reduce inflammation associated with alcohol abuse.

Behavioral and Psychological Improvements with PAP

Treatment methods for substance use and concurrent disorders include various therapies often categorized into two overarching forms: pharmacotherapy and psychotherapy. This section will address the latter with respect to PAP and provide an overview of the peer-reviewed and human clinical studies where psilocybin was administered with psychological support. The PAP approach incorporates the pharmacological mechanisms of psilocybin into the gold-standard psychotherapeutic processes (e.g., cognitive behavioral therapy) to create an effective therapy chimera against AUD [39-41]. Cognitive behavioral therapy (CBT), dialectical behavior therapy (DBT), and acceptance and commitment therapy (ACT) are at the forefront of used behavioral therapies used in PAP. CBT is the traditional approach of behavioral therapy, while DBT and ACT considered third wave CBTs.

Consistent with the clinical trials conducted thus far, PAP consists of three stages: 1) the pre-treatment stage, where the patients are mentally prepared for the administration of psilocybin; 2) the treatment stage, where psilocybin is administered, and; 3) the post-treatment stage, where the psychotherapist and patient discuss how the patient can translate their PAP treatment outcomes into their daily life [41]. The three stages can have different approaches concerning the respective type of psychotherapy administered (i.e., there may be variance in the PAP process, depending on whether the therapy approach is more based on CBT, DBT, or another neurocognitive behavior remodeling technique). The pre- and post-treatments are often undergone via conventional psychotherapy such as talk therapy to facilitate the treatment process [43]. These three stages serve to prepare the patient for the psilocybin therapy process and administer the substance in an environment safe to the patient [40].

The set and setting are important concepts in the administration process. Ensuring the patient is in the optimal mindset/frame of mind to undertake this form of therapy is referred to as the "set," while the immediate environment and surroundings for the psilocybin experience is referred to as the "setting." The set and setting are designed to create a safe and conducive environment for PAP administration, and to avoid the occurrence of anxiety or paranoia [40,41,43]. Music therapy is among the most common secondary therapies integrated into PAP sessions. Music can have considerable influence on the therapeutic experience and can further promote the occurrence of mystical experiences and insightfulness during psychedelic session(s) [44]. One primary benefit for combining music with PAP is to stimulate and foster a more comforting, self-reflecting, and peaceful environment for the participant. It helps in cognitive reframing and helps the participant learn more adaptive thoughts and behaviors [39,43]. The PAP outcome is heavily influenced by the environment in which psilocybin is administered, the psychotherapy techniques utilized, and strict adherence to the aforementioned three stages of PAP [39]. Among the considered clinical studies, psilocybin was administered in non-directive and supportive settings to promote spiritually meaningful experiences [45]. The non-directive approach provides patients with a platform to lead their own healing process in the treatment with the psychotherapist present to facilitate exploration of the patients' thoughts and emotions [39].

In accordance with the American Psychological Association, several researchers regard traditional CBTs as the leading standard of evidence-based psychotherapy for many SUCDs [43,46]. Third wave CBTs (e.g., DBT and ACT) are more recent subcategories of CBT, incorporating deeper connection with the individual's mindfulness, emotional states and dysregulation, personal values, and metacognition [40,47]. DBT focusses on emotional dysregulation (a facet of AUD symptoms) and provides patients with neurocognitive skills that support recovery. Comparably, ACT focuses on providing the patient with tools to accept their thoughts and emotional states without judgement while accepting and adapting to life events as they arise (an important component of maintaining alcohol abstinence) [43]. Third wave CBTs are propitious in developing mindfulness, decentering, emotional regulation, distress tolerance, identifying targets for psychotherapy, and focusing on establishing a set of patient-specific cognitive behavioral tools for the patient to use in upsetting or disconcerting situations that could lead to relapse [48].

Further, we found that psilocybin aids in substance use bereavement, abstinence perspective reframing, and increased receptivity to the CBTs used in PAP [49]. Increased openness to CBTs can occur since psilocybin elicits psychedelic-induced introspection, a term used in psychedelic research to describe accessing the "unconscious mind" using psychedelic compounds [49]. In controlled settings, psychotherapists can harness psychedelic-induced introspection to engage metacognizant discussions to enhance positive personal growth and self-improvement [43-45,50,51]. A study conducted by Bogenschutz et al. (n=10), found that psilocybin significantly increases alcohol abstinence after its administration to recovering AUD patients (p<0.05), and demonstrated a mutually beneficial relationship between CBT and psilocybin administration [49].

Spiritual Development from the Psychedelic Experience

In addition to the beneficial neurobiological and psychological outcomes from PAP therapy, the potential for spiritual growth and development from high dose PAP is remarkable. According to the dosage administered (among other factors influencing its subjective effects such as hydration level and degree of tolerance), psilocybin can produce spiritual or mystical experiences. Classic (5HT2A agonist) psychedelic compounds (e.g., psilocybin, DMT, mescaline) have been used by various indigenous societies for centuries in sacramental contexts [52]. Correspondingly, this substance has been used for these purposes by a variety of cultures (notably the Aztec and Mayans) to lead to spiritual encounters [45,50]. The effects that psilocybin has in producing such experiences can vary among patients and is subordinate to the individual's personal experience, which can account for its increased personal depth and meaningfulness to the patient in processing their AUD issues [49,51].

Generally, at low doses (e.g., 1-3 mg/70 kg),[53] psilocybin induces mild visual hallucinations (e.g., wavy/ kaleidoscope patterns, perception of colors as being more vibrant, or objects seeming to "flow" into one another), auditory distortions, tingling on the skin, mild anxiety, interpersonal insight, nausea, and a greater understanding of self, euphoria, and increased creativity. At lower doses, the potentially harmful physiological and psychological effects associated with PAP have decreased frequency and intensity. This could be a result of the less extreme psychological, mystical, and perceptual effects experienced at low doses [4,45,53]. At high doses (22 mg/70 kg),[53] psilocybin has the ability to alter the way an individual perceives the meaning their life, their purpose, and death transcendence; trigger stronger hallucinations (e.g., geometric shapes, abstract patterns, imagining people, animals, or objects which are not physically present, ability to visualize one's thoughts); provoke psychological insights, including commitment to change, strengthened patient-therapist relationship, ego-dissolution[2] and a sense of ineffability; transcendence of time and space, and; strong mystical experiences (unifying, noetic, sacred) [54,55].

Various studies articulate the significance of mystical experiences and the intensity of subjective perception changes in patients in improving AUD effects (e.g., decreasing the numbers of drinks). In recent studies conducted regarding the administration of psilocybin for AUD, the combination of mystical experiences and the intensity of subjective effects were associated with improvements in alcohol abstinence [40,49]. The term "Spiritual Awakening" outlines the subjective experience a patient can experience wherein their ego transcends their finite self, and this concept is a key component of the AA program [57]. Given the spiritual experience stimulating effects of psilocybin, PAP can be a highly effective means of achieving a Spiritual Awakening for lasting AUD behavioral change [57]. The term "mysticomimetic" is used by some researchers to denote a substance's ability to induce secular or mystical-mimicking experiences for the user [58]. Mysticomimetic experiences are another hallmark of a high dose psilocybin trip. Current literature supports the efficacy of integrating spirituality practices in AUD recovery programs [59,60]. Since psilocybin is effective in achieving mysticomimetic experiences, from a spiritual perspective, this psychedelic can be viewed as having high utility in treating AUD.

Griffiths et al. observed the occasion of mystical-type experiences in their double-blind study (three cohorts of *n*=25), observing increased feelings of tranquility and mental well-being in participants when psilocybin was administered in high doses and highly supportive environments. Results from the longitudinal study determined PAP with high psilocybin dosages and high support had remarkably longer lasting and positively impactful effects relative to the groups with low dosage and standard support and groups with high dosage and standard support [53].

In a double-blind, placebo-controlled (*n*=698) dose-effect study conducted by Hasler et al., the acute psychological and physiological effects of psilocybin were observed, with findings suggesting alterations in ego function [61]. Ego function is a phenomenological concept that comprises ego-identity, ego-demarcation, ego-vitality etc., initially explained in this context by Scharfetter (1998) and continued by Hasler et al. (2004). Hasler et al. found that patients who received medium (*n*=215) and high doses (*n*=315) of psilocybin during the experiment experienced lost demarcation between their self and environment, resulting in feelings of insightfulness, enlightenment, and being touched by a higher reality (e.g., a Higher Power). In this experiment, they found that some negative effects associated with higher doses included paranoia, panic, and anxiety due to loosened ego-boundaries/lost demarcation [61].

The spiritual approaches towards AUD rehabilitation have been long-standing and empirically supported means of therapy. Among its supporters were Dr. Carl Jung, a Swiss pioneer of the field of psychiatry, and Bill Wilson, co-founder of Alcoholics Anonymous, a spiritual-based worldwide fellowship for alcoholics seeking sobriety [62,63]. A systematic review by Kelly et al. found that AA was the best alcohol abstinence program on behalf of their spiritual and fellowship driven framework, [64] leading to the University of Stanford Medical School to regard AA as the "most effective path to abstinence."[65] The spiritual effects of psilocybin can increase hope and morale for

[2] Ego dissolution is a phenomenon that is characterized by a compromised sense of self which results in a reduction in self-awareness which disrupts the boundaries between the individual and the world. This plays a role in enhancing a sense of belonging to people and one's environment while being completely dissociated from oneself.

patients feeling despondent in their recovery process, while the spiritual practices that can arise from their psychedelic experience (e.g., prayer and transcendental meditation) may help provide a routine and structure for AUD patients staying sober in the long-term [53, 66].

Risks of Psilocybin in AUD Therapy

While psilocybin has been observed to pose minimal psychological or physiological risks to patients, there exist various points of concern for PAP that should be considered.

Psilocybin has the tendency to acutely increase blood pressure which can have harmful effects on patients with cardiac conditions such as hypertension or heart disease [61]. Individuals with existing/ predisposition to psychiatric conditions may have serious side effects from consuming psilocybin as it could trigger the onset of new symptoms from underlying disorders or exacerbate symptoms of existing disorders [64]. Another psychological risk of psilocybin consumption includes the potential occurrence of triggering flashbacks of previous traumatic events given the vivid hallucinations that arise with high doses [67]. At high doses, the hallucinations can cause extreme fear and panic in the individual. Accordingly, this phenomenon is referred to as a "bad trip" in the psychedelic community. During a bad trip, sensations can include paranoia, distorted sense of self, loss of boundaries, panic, and lack of awareness. In this state, the individual will likely have impaired judgment and will be thereby more susceptible to engage in risky behavior [68-69].

A study from the Lancet ranked 20 recreational/street drugs in terms of harms and dangers through 16 risk criteria (9 criteria representing risks to the user and 7 criteria supposing risks to others). They found that while alcohol use was irrefutably of the highest risk to users and others, *Psilocybe* mushrooms ranked the lowest for harm to users and others [70]. Other research shows very incidence of physical or phycological addiction to psilocybin [63].

Limitations of PAP Administration

The central limitations to PAP reside in psilocybin's contraindications for consumption. These contraindications can include cardiac issues in patients of cardiovascular diseases such as hypertension or heart disease; psychiatric conditions such as schizophrenia, and severe anxiety disorders or cases of PTSD, and; medication contraindications for individuals who may be taking prescribed medications that bear drug interactions with psilocybin [41,61]. PAP triggers individualistic responses which despite their largely positive effects can make determining concrete and widely applicable findings more challenging.

Discussion

This paper overviews the benefits and risks associated with using PAP for the treatment of AUD. Our review of the extant literature has found that psilocybin promotes neural flexibility in the prefrontal cortex and stimulates neurogenesis. The PFC is responsible for carrying out cognitive and behavioral responses, obtaining rewards, and inhibiting various behaviors, therefore the issues caused by AUD to this region must be reversed somehow. This is where the neurogenetic and neuroplastic effects of psilocybin can be beneficial. As a psychoplastogen, it has the ability to restore mGluR2 deficiencies for various AUD impairments which had caused glutamate suppression. This helps in subduing alcohol cravings, while improving alcohol relapse behaviors and cognitive flexibility. Psilocybin also has anti-inflammatory properties which as an additional benefit can help combat the neuroinflammatory effects of alcohol abuse. This combination of neurobiological changes is rather unique to psilocybin and psychedelic therapy. Additional support for further study into its AUD treatment potential arises from the changes psilocybin can elicit in the PFC and its persistent neuroplastic effects that can reverse certain neurological damages from AUD.

Further to its neurobiological effects, psilocybin also has shown positive findings in terms of its effect on psychotherapeutic mechanisms. Research in the field of psychotherapy shows a recent trend towards the integration of psychedelic compounds into practice and experimentation, with optimal results observed in patients who underwent the PAP treatment. Various studies leverage different forms of psychotherapies in their PAP process (e.g., music therapy, non-directive supportive approaches to treatment, and mindset-oriented/behavioral psychotherapies such as CBT, DBT, and ACT) [43]. The administration of CBT in PAP includes pre-treatment, treatment and post-treatment stages, and psychotherapists are crucial components to these steps. Their role in PAP is essential and includes: 1) preparing the patient for the psilocybin treatment (during the pre-treatment stage); 2) providing patients with psychological support through the psilocybin administration process (treatment stage); and 3) leading a thoughtful discussion on the psychedelic experience. Their role also includes assisting the patient with the integration of their learnings to the area of desired change (e.g., AUD) as a journey towards psychiatric remission (post-treatment stage) [39-40]. Each stage of the PAP process has built within it specific goals (such as providing patients with the cognitive tools to mentally and emotionally prepare them for psilocybin consumption, and helping the patient learn from their psilocybin experience) to improve recovery. The pre-treatment stage serves to establish a therapist-patient relationship and create a safe and trusting environment, while the treatment stage serves to administer the psilocybin. These stages are facilitated by the set and setting, which are crucial aspects of the administration process, as they reduce the potential for anxiety and panic episodes, and ensure patients are in a comfortable environment to promote healing. Therefore, we

suggest that when designing PAP programs, a pensive consideration of the set and setting take place to avoid negative outcomes and maximize the beneficial results of the PAP. The CBTs discussed must ensure optimal mindset for the patient (set) and the immediate environment (e.g., the psychotherapist's office) for psilocybin experience (setting).

CBT is especially beneficial in the pre- and post-treatment stages of PAP. Current psychotherapeutic/ behavioral treatments for AUD are numerous and can include CBT, DBT, ACT, relapse prevention therapy, motivational enhancement, couples therapy, community reinforcement, mindfulness techniques, and 12-Step Program facilitation through sponsorship with programs such as Alcoholics Anonymous. These methods of treatment can be free-standing or integrated into pharmacotherapy treatment regimens. The study conducted by Bogenschutz et al. indicates that there is a significant relationship between CBT and psilocybin administration [49]. Behavioral therapies, particularly CBTs, focus on the identification and modification of maladaptive cognitions/behaviors that contribute to substance abuse issues, improvement of specific behavioral skills to reduce relapse risk, and foster the motivation for behavior change. While CBT therapies are generally designed for shorter treatment periods, they provide patients with the behavioral and cognitive tools to maintain alcohol abstinence. Since AUD requires longer term solutions, out-patient DBT sessions and programs such as AA can provide longitudinal support [34]. Another therapeutic method also widely used is music therapy. Music therapy is a very common secondary therapy integrated within PAP session on behalf of its substantial influence on the therapeutic experience. Music during PAP can promote the occurrence of mystical experiences and insightfulness, [44] and create a more comforting, self-reflective, and peaceful environment for the patient [39,43]. These are all important factors in optimizing the PAP setting.

Psilocybin is a mysticomimetic substance, efficacious in promoting spiritual experiences in high dose psilocybin studies. The Spiritual Awakening that occurs in such contexts is important for preserving long-term alcohol abstinence for AUD patients. Theological or spiritual experiences for both pious and non-pious participants alike have been found within the literature to strengthen participants' connection to a "Higher Power" (however they interpret it; for some patients this could be through religious interpretation, for others it could be mainly spiritual) [43,45,50]. This connection to a Higher Power is highly beneficial for long-term remission of AUD patients, accredited by programs such as AA as being one of the foremost reasons behind their success [56]. Furthermore, individuals with spiritual/religious connections tend to experience similar tranquility during their recovery timeline as those effectively practicing meditation, mindfulness, and CBT (amidst other traditional behavioral therapy techniques). Psilocybin promotes highly personal and subjective mystical and spiritual experiences; accordingly we note that this variance poses certain issues for replicability and reliability of the studies screened in this review.

While multiple benefits of psilocybin have been discussed, psilocybin does pose certain risk to health and has medical limitations to its usage as well. First, psilocybin increases blood pressure, which can cause vascular issues in patients with underlying cardiovascular conditions, however the literature observing this issue is sparse. Psilocybin has been correlated to inducing, exacerbating, or triggering severe psychiatric disorders (e.g., schizophrenia and hallucinogen persisting perception disorder), which can trigger the manifestation of pre-existing psychiatric conditions [67]. Therefore, we recommend avoiding use of psilocybin therapy with these two classes of patients (patients with cardiovascular issues or underlying psychiatric disorders). The field of PAP treatment for SUCDs does pose certain experimental limitations given that it induces individualistic responses, making obtaining widely applicable findings more challenging. Another limitation that we noted included the extreme variance in emotional state patients can experience at high doses. For instance, one patient could experience euphoria and excitement, while another may experience emotional dysregulation episodes and rapid mood fluctuation. The latter, however, is typically manageable in safe, controlled environments with guidance by the psychotherapist, and can generally be avoided by well-established set and setting. The importance of set and setting was demonstrated by Griffiths et al. in which high dose, high support psilocybin administration increased feelings of tranquility and mental well-being due to the supportive environment and adequate pre-treatment preparation. Equanimity in the psychotherapist's conduct and comportment is paramount to ensuring that any negative emotions (e.g., scary or stressful experiences; "bad trips") during high dose psilocybin sessions do not escalate to a panic attack or cause emotional trauma. Succeeding the psychedelic experience, it is the therapist's role to discuss the trigger of the bad trip, as well as uncover and examine deeper subconscious fears unbeknownst to the patient, uncovered due to the high dose of psilocybin. From this point of humility and learning for the patient, further emotional and spiritual development can take place in the face of AUD treatment. This is to say while they are unpleasant to the patient and should be avoided, bad trips can actually provide the basis for more effective psychotherapy [71].

With respect to its therapeutic potential, psilocybin bears relatively minimal negative effects on patient recovery and minimal risks to health. The Lancet found that alcohol was the most destructive substance, while psilocybin was the least destructive. These findings highlight an addition strength of PAP, in that it leverages the least harmful substance on the list to treat addiction to the most harmful substance on the list. Further, our review yielded minimal evidence of physical or mental addiction to

psilocybin, thereby increasing its potential for implementation into psychiatric treatment methods.

We emphasize that when considering administration of psilocybin for AUD treatment, there should be no dichotomy between the *psychedelic* and *psychotherapy* aspects of PAP. In the PAP context, psilocybin and psychotherapy are not fully effective without the other and should therefore not be treated as mutually exclusive, for they complement each other symbiotically. Therefore, we promote further exploration into the therapeutic capacities for the drug in regulated clinical trials and controlled psychiatric research settings. What we do not promote, however, is consumption of psilocybin in a non-PAP context as a "supernatural cure" to one's AUD issues. The positive results of psilocybin come from the *process* of PAP, including: 1) the patient partaking in routine behavioral therapy sessions prior to and after their psychedelic experience(s); 2) having a psychotherapist guide the patient through their psychedelic experience with specific predetermined goals for their trip; 3) establishing social and personal support networks for long-term success in recovery; 4) engaging in mental-reframing through therapy and developing CBT-based coping mechanisms for quotidian life, and; 5) guiding and establishing specific objectives and intentions of integrating psilocybin into the recovery process. This, therefore, observes psilocybin as a function within a multilateral psychiatric treatment and self-discovery *journey*, rather than merely a hallucinogenic drug for pleasure and enjoyment.

Based on our review of the field, we conclude that prevailing research affirms the therapeutic value of psilocybin in PAP in the context of AUD patient treatment and alcohol abstinence. While certain risks in PAP exist, we find that the benefits of PAP for AUD treatment outweigh these risks. We note, however that this area of research is still in the process of expanding and we are thus still facing a paucity of clinical trials and RCTs to exhaustively support these claims.

Limitations of Extant Pap Research Available for Reference

While a thorough credibility examination was applied to all research referenced and papers were largely sourced from publications recent to the past decade, we would like to note a general shortage of clinical trial data pertaining to PAP for AUD and SUCD treatment. This likely arose from policy factors such as its stringent drug scheduling and regulations in North America. We would like to further note that the studies available for reference were generally conducted in small group sample sizes, which can impact reliability and validity of findings [72].

Future for Psilocybin Therapy

The future applications for PAP are expansive. As described in this review, the available literature presents strong preliminary evidence for the integration of psilocybin with psychotherapy treatment methods given its neurobiological (e.g., neurogenetic and neuroplastic), psychological, and spiritual implications.

Animal Trials on Primates

The neurobiological studies referred to in this literature review were conducted primarily on rat brains, which though provide clinical insight due to anatomical and physiological similarities, lack the degree of specificity to make concrete conclusions for human application. Therefore, we would recommend introducing high-dose psilocybin studies on primate subjects to obtain a more comprehensive understanding of the clinical data and applications of psilocybin in a neurobiological context. The rationale is that primates have the most similar biological makeup to humans and have a higher degree of sentience than other animal subjects used in pharmacological research [73].

Future High-Dose Psilocybin Studies on Human Participants

More extensive research on spiritual and mysticomimetic encounters is required to better understand the effects of psilocybin. The tendency of psilocybin to create connectedness to others and to the environment should also be further investigated. In addition, the hallucinogenic (i.e., visuoauditory) effects should be studied moderately because 1) they are well studied but how their effects are associated with clinically meaningful changes in relation to AUD symptoms still needs additional small human laboratory studies and clinical trials ; 2) while the hallucinogenic effects may vary by individual, there may be certain effects that are more common across individuals that may be helpful to inform participants at the start of; and 3) it is possible that the hallucinogenic effects may serve as a facilitator for some of the psychological and spiritual experiences. We suggest that high-dose studies should focus on the mechanisms by which psilocybin makes the patient more open to psychotherapy and cognitive-based therapies in the pre-treatment stage, the treatment stage, and the post-treatment state. Psilocybin is shown to make patients more open and honest about their sensations and feelings, understand their emotions better and in different ways while under the influence of the compound, and alter their interpersonal interaction dynamic with the psychotherapist after consuming psilocybin. These findings can be attributed to the changes in neural circuitry such as a shutdown of DMN and other neural pathways [29]. With psilocybin being actively studied for its therapeutic efficacies, future clinical studies could include treatment of less studied SUCDs such as cannabis addiction or major depressive disorder.

Future Studies on Microdosing

Though not the focus of this review, microdosing psilocybin (a term used to depict very low dose [1-3 mg/70 kg] administration) [53] has been found to have potential positive impacts on treating concurrent disorders to AUD. A New England Journal of Medicine study found that microdosing psilocybin has comparable results to escitalopram, a selective serotonin reuptake inhibitor

(antidepressant drug), with favored secondary outcomes relative to escitalopram [74]. We thereby encourage future double blind randomized controlled trial (RCT) on psilocybin microdosing versus antidepressant drug prescription in concert with psychotherapy to realize potential improvements and innovations to existing pharmacotherapies.

Conclusion

The available research conducted on treating AUD through PAP largely indicates positive results. The therapeutic potential of psilocybin is attributed to the neurobiological remodeling effects (e.g., neuroplasticity and neurogenesis), increased reception of psychotherapies (e.g., traditional/third-wave CBTs), and spiritual development (e.g., increased mindfulness and appreciation for a Higher Power). Psilocybin was found to pose minimal harm to mental and physical health of patients undergoing PAP. Research on the extent of psilocybin's therapeutic efficacy in AUD and SUCD treatment is ongoing.

Applications of Our Literature Review

This paper brings forth the recent literature available regarding psilocybin in the context of AUD treatment. Our paper can serve as a reference for psychotherapists working in or interested in psilocybin-assisted psychotherapy. It can also be used as reference for individuals working in public affairs and policy influencing sectors. This paper provides an easy-to-comprehend academic reference for psilocybin's integration into the field of psychotherapy for AUD and SUCD treatment. Therefore, our review can serve as a reference for the layman and academic alike, in that our paper was written such that it is clear and accessible for anyone referring to it for academic or professional interests, investing opportunities, or simply personal interest. Finally, our paper provides a timely addition to the PAP research body and cultivates a culture of exploration/innovation of novel therapies to evolve the psychiatric treatment of these long-lived, agonizing mental disorders.

List of Abbreviations Used

AA: alcoholics anonymous
ACT: acceptance and commitment therapy
AUD: alcohol use disorders
CBT: cognitive behavioral therapy
CNS: central nervous system
DBT: dialectical behavior therapy
DMN: default mode network
DMT: dimethyltryptamine
DSM 5: diagnostic and statistical manual of mental disorders
fMRI: functional magnetic resonance imaging
LSD: lysergic acid diethylamide
PAP: psilocybin assisted therapy
PFC: prefrontal cortex
PTSD: post-traumatic stress disorder
SUCDs: substance use and concurrent disorders

Conflicts of Interest

The authors declare no conflicts of interest.

Ethics Approval and/or Participant Consent

As this paper is a literature review, no ethics approval was required.

Authors' Contributions

KV: was the principal author of this manuscript including the design and research of the work, drafting and finalizing the manuscript, collection/analysis of the data, and final approval of the publication.
NB: contributed to the design and research of the paper, including initial scoping of the project and organization of the references and citations, and final approval of the publication.

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