

**Destigmatizing Psychedelic Assisted Therapy as a Treatment Modality
for Individuals with a Diagnosis of Alcohol Use Disorder**

by

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Abstract

Alcohol use disorder (AUD) is a prevalent and debilitating condition with significant public health implications. Traditional treatment approaches achieve limited success which has necessitated the exploration of alternative modalities. Psilocybin-assisted psychotherapy (PAP) has gained recent attention for promising results in several clinical trials, however its efficacy and mechanisms of action remain underexplored. This capstone reviews the existing literature pertaining to PAP as a treatment protocol for AUD while focusing on current research exploring the theories of mechanistic action. Primarily the intention is to explore whether PAP reduces problematic drinking among populations with a diagnosis of AUD.

Keywords: psilocybin assisted psychotherapy, alcohol use disorder, psychedelic, biopsychosocial-spiritual, transtheoretical model of change, recovery, stigma

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Chapter 1: Introduction

Alcohol use disorder (AUD) is understood as a complex set of behaviours, cognitions and experiences which coalesce to cause pronounced suffering. Impacts of AUD across multiple levels in society, from the afflicted individual to the community level, accrue costs to personal and systemic health, economic productivity and civic justice (CSUCHWG, 2023; Government of Canada, 2023; Kendler et al., 2017; Manthey et al., 2021). While more than 50 years of research into the etiology and treatment of AUD and similar substance use disorders exists, the number of individuals suffering from AUD and the costs associated with AUDs is increasing (CSUCHWG, 2023; Glantz et al., 2020). Recently, a resurgence of interest into the therapeutic use psychedelic medicines has led to an expanding body of research investigating potential for the treatment of substance use disorders (Bogenschutz et al., 2015, 2022; Nielson et al., 2018). Early results have been promising, yet substantial stigma attached to the use of psychedelic medicines remains, presenting a barrier to the integration of potentially important treatment options (Andrews & Wright, 2022; Noorani, 2020). The following capstone will evaluate the recent literature on the efficacy of psilocybin-assisted therapy for the treatment of AUD with the intention of providing evidence-based reasoning to counter prevalent social narratives that contribute to the stigmatization of psychedelic medicines.

Overview of AUD and Psilocybin-assisted psychotherapy

Alcohol used disorder is an intractable issue with significant costs affecting millions of Canadians on both an individual and societal level (CSUCHWG, 2023; Kendler et al., 2017; Manthey et al., 2021). While there exist treatment options that meet a segment of the population effectively, there is a growing number of people that are unable to recover from chronic and compulsive alcohol intake (Glantz et al., 2020; Kelson et al., 2023). In a general sense, the

etiology of addiction is a contentious topic characterized by a fractured conceptual landscape which exhibits competing theories. While dispute exists between the proponents of various treatment protocols, agreement is found in the characterization of AUD as a problematic pattern of alcohol intake in spite of consequences which leads to significant clinical impairment across several domains of human wellbeing (APA, 2022; Bartram, 2021; Coriale et al., 2018; Government of Canada, 2023). Diagnosis of AUD occurs by assessment of several dimensions of an individual's experience, covering usage and control patterns, impacts to social networks and wellbeing, intake risk and pharmacological criteria including the phenomena of tolerance and control (APA, 2022; Coriale et al., 2018).

The impacts of AUD are profound and include increased risk of chronic health conditions like organ damage and certain cancers (APA, 2022; Cargiulo, 2007; Carvalho et al., 2019), vulnerability to psychopathologies such as major depressive disorder and anxiety disorders (Canada, 2021; Coriale et al., 2018) and social challenges including unemployment and housing instability (Hammer et al., 2012; Kendler et al., 2017). Progress has been made in therapeutic interventions over the last decades, including applications of certain psychotherapeutic techniques such as cognitive behavioural therapy and motivational interviewing which have been shown to be efficacious treatments for some individuals with a diagnosis of AUD (Bartram, 2021; Rombouts et al., 2020; Walter et al., 2015). Additionally, pharmacological treatments have also progressed and have been incorporated into therapeutic protocols alongside psychotherapy, such as is the case of the opioid antagonist Naltrexone (Kiran, 2019; Rombouts et al., 2020). While these treatments have shown to be efficacious for a segment of the population a large unmet need still exists (CSUCHWG, 2023; Kelson et al., 2023; Kiran, 2019; Rombouts et al., 2020). Given the reality of the current shortfall of treatment protocols to meet the large and

growing population of individuals living with substance use disorders, it is both logically and ethically imperative that alternative and expanded treatments that show promise of therapeutic benefits be investigated with both open minds and rigorous standards.

Prevalence and Cost of AUD in Canada

Despite decades of research and intervention, the number of individuals in Canada suffering from AUD has remained constant, with recent data in Canada estimating a 12-month prevalence of approximately 2.5% (Government of Canada, 2023). Given the advances in treatment protocols, the maintenance of a consistent rate of AUD across the general population indicates a lack of overall success in treatment and highlights the presence of an unmet need among this sub-population. Current data show the annual cost of substance use in Canada equal to \$49 billion dollars annually and costs associated with alcohol use make up over 40% of this total (CSUCHWG, 2023; Sorge et al., 2020; Stockwell et al., 2021). The direct annual healthcare costs associated with alcohol are estimated to be \$165 per person, nearly six-times the total of opioids, methamphetamine and cannabis combined (CSUCHWG, 2023). In terms of indirect costs, AUD is responsible for a further \$167 per person in lost productivity, more than 50% greater than the combined impact of opioids, cocaine, cannabis, barbiturates and methamphetamine (Sorge et al., 2020). From an international perspective, a recent meta-analysis synthesizing economic and social costs of AUD estimated the economic cost of alcohol consumption to be greater than 1300 Int\$ per person. Additionally, this study found costs associated with alcohol consumption in high income countries, such as Canada, as equal to greater than 2.5% of GDP (Manthey et al., 2021). Even without accounting for the significant social costs implicated with alcohol consumption the economic impact of AUD on Canadian society is vast.

Recent data gathered by the government of Canada indicates nearly 1 million people currently live with AUD, or approximately 2.5% of the population (Government of Canada, 2023). Individuals with a diagnosis of AUD are at increased risk of numerous health problems including damage to the organs, including the liver, brain, heart, and stomach. Additionally, increased risk of liver, breast, throat and stomach cancers is associated with AUD (APA, 2022; Canada, 2021; Carvalho et al., 2019). Psychiatric conditions associated with chronic overconsumption of alcohol include major depressive disorder, anxiety disorders and suicide (Cargiulo, 2007; Carvalho et al., 2019). Furthermore, the experience of AUD is associated with psychosocial challenges for individuals, ranging from housing insecurity, homelessness, low employment or unemployment and social isolation, to the subjective experience of prolonged and unresolved grief, depression and suicidality (Carvalho et al., 2019; Hammer et al., 2012; Kendler et al., 2017). The ramifications of refusing to adapt and better manage AUD significantly impact not only the individuals with a diagnosis but also the collective domains of economics, healthcare, social wellbeing and community health (Hammer et al., 2012; Kendler et al., 2017; Manthey et al., 2021; Sorge et al., 2020; Stockwell et al., 2021) .

Psilocybin-assisted psychotherapy

Psilocybin-assisted psychotherapy (PAP) is a medically supported form of psychotherapy which emphasizes evidence-based change interventions in conjunction with the administration of the psychedelic compound psilocybin. Currently a controlled substance, psilocybin is a naturally occurring compound found in certain mushroom species that have been used as traditional plant medicines for thousands of years (Doblin et al., 2019; Ziff et al., 2022). Following a brief academic exploratory period in the mid-twentieth century, psilocybin containing compounds along with a host of other psychedelic substances were classified as harmful and devoid of

medicinal properties and made illegal in North America (Doblin et al., 2019; Luoma et al., 2020; Nichols & Walter, 2021). Recently, however, a psychedelic renaissance has emerged in the academic landscape with renewed interest in the medicinal potential of a range of substances previously excluded from academic inquiry (Sessa, 2012). Psilocybin has seen a dramatic increase in interest as a result, with studies exploring the use of medically supported therapies for depression, PTSD, addiction to cigarettes and alcohol, obsessive compulsive disorder and end of life anxiety associated with terminal illnesses (Daniel & Haberman, 2017; de Veen et al., 2017; Luoma et al., 2020; van der Meer et al., 2023; Ziff et al., 2022).

In the context of AUD, psilocybin has been shown in early clinical trials to produce promising results. Several studies have investigated the use of psilocybin in conjunction with motivational interviewing as a medically supported form of psychotherapy in the treatment of individuals with a diagnosis of AUD (Bogenschutz et al., 2015, 2022; Nielson et al., 2018). Quantitative measures of drinking days and heavy drinking days among the target population were shown to be significantly reduced in individuals that underwent PAP (Bogenschutz et al., 2015, 2022). Qualitative follow up studies identified key change processes experienced by individuals and shed light on potential therapeutic mechanisms (Nielson et al., 2018). Themes included dissolution of ego, heightened motivation, altered and improved beliefs of self, altered perceptions of individual's relationship to alcohol and the expression and resolution of dysphoric experiences (Nielson et al., 2018). Additionally, many participants reported undergoing mystical or mysticomimetic experiences, described as phenomenologically indistinguishable from transcendental religious experiences but differentiated by the use of psychedelic compounds (R. Griffiths et al., 2011; Kangaslampi, 2023; Nielson et al., 2018). These spiritual-like experiences

can be profoundly meaningful and are shown to mediate positive change in populations of psychedelic study participants (R. Griffiths et al., 2016; Nielson et al., 2018).

There is substantial stigma associated with psychedelic medicines in western culture. Social narratives surrounding psychedelic compounds have been influenced by their classification as dangerous and illicit compounds by the governments of Canada and the United States (Hall, 2022). Instances of use by cults as mind control agents have permeated the narrative surrounding psychedelic medicines and created a sizeable degree of skepticism around their potential health benefits (Davis et al., 2022; Hall, 2022). Add to this the already present stigma attached to substance use disorders and you have a compound stigmatization of psychedelic assisted therapies (Andrews & Wright, 2022; Hall, 2022; Nielson et al., 2018). While it is understandable that there is a degree of uncertainty regarding the implications of using a psychedelic compound for the treatment of a substance use disorder, the established treatments for these conditions already utilize a range of medications including methadone, benzodiazepines and a number of antidepressants and anti-anxiety medications (Sessa, 2012). While social perceptions of psychedelic medicines remain cautious, recent research has emerged which supports the use of these substances in conjunction with psychotherapy as being safe and presenting a potentially large benefit in the treatment of AUD (Agin-Liebes et al., 2021, 2023; Bogenschutz et al., 2015, 2022; Griffiths et al., 2011; Ziff et al., 2022). Given the scope and severity of the current landscape of addiction, it is necessary that any treatment protocols which present a substantial benefit with low associated risk be taken into thoughtful consideration.

Purpose Statement

The intent behind the following research project is to explore the relevant research landscape from a perspective of evaluating the therapeutic potential of psilocybin-assisted

therapy to treat AUD. Exploring the efficacy of psilocybin in treating problematic drinking presents an opportunity to articulate the benefits associated with this novel treatment protocol. Additionally, through the communication of evidence-based data supported by clinical trials a destigmatizing narrative may be enacted which may promote adoption of psilocybin-assisted therapy among skeptics and lower barriers to treatment in populations of suffering individuals (Davis et al., 2022; Noorani, 2020). The potential for psilocybin to support individuals in adopting dramatically different perspectives of self, context, and narrative fuel the psychotherapeutic process and provide potential mechanisms of change which may be stagnated in active addiction (Agin-Liebes et al., 2023; R. Griffiths et al., 2011, 2016; Nielson et al., 2018). Furthermore, developments in neuroimaging are steadily increasing the understanding of neurological correlates associated with changes in motivation and behaviour and may provide further insight into the etiology of addiction (Johnson et al., 2019; Kirschner et al., 2020). Relevant questions of safety and effectiveness are important considerations in this field, and currently researchers operate within a framework of rigorous safety standards (Aday et al., 2022, 2023). Ethical standards for the delivery of psychotherapy demand evidence-based practices, particularly with treatments like psychedelic medicines which carry with them historical stigma. Given this, though, and in light of the clear shortfalls of current treatment protocols, it is my belief that exploring this frontier- this collective growth edge- presents significant potential to enact positive change across a broad scale. To evaluate this position, the following research will ask to what degree, if any, does psilocybin-assisted therapy facilitate a reduction in alcohol use in individuals with the diagnosis of AUD. As such, the purpose of this capstone is to address stigma related to PAP through an exploration of the literature with the intention of establishing an

argument for the ethical use of efficacious therapeutic protocols towards the treatment of the intractable problem of AUD.

Conceptual Framework

The landscape of addiction studies is populated with multiple competing theories of etiology and treatment protocols. Given the complex nature of addiction, the multidimensionality of both causes and impacts, the conceptual framework through which the condition is perceived exerts influence over the perception of what recovery looks like. From a biological-dominant perspective, AUD is a conditioned response to substance involving neural-plasticity, alterations in molecular and cellular processes and a complex of processes related to dopamine signalling which include proclivity towards pleasure seeking coupled with hyperbolic discounting- an inclination towards selecting immediate rewards over delayed gratification (Kirschner et al., 2020; Nestler, 2001; Philibin & Crabbe, 2015; Poikolainen, 2023). Early conceptualizations of recovery established under this paradigm were abstinence based, founded on the fundamental belief that the interaction between substance and brain chemistry and neurological functioning represented the primary locus of the disorder (Frawley, 1987). Further developments in the fields of neurobiology and advances in neuroimaging techniques have led to an expanded definition of recovery which includes mindfulness practices, cognitive-behavioural interventions and even harm reduction strategies (Blum et al., 2013; Simpkins & Simpkins, 2013). However, the gold standard of this paradigm is still an abstinence-based approach which is not always feasible or attainable for individuals suffering from AUD.

A more recent development in the field of addictions studies emphasizes the role of social, cultural, environmental, and spiritual forces to shape and perpetuate the experience of addiction (Echevarría-Marrero et al., 2019; Hatala, 2013). While building on and incorporating

the most recent developments in neuroscience, the biopsychosocial-spiritual model also incorporates psychological, sociocultural and spiritual influences in both the etiology and treatment of AUD (Echevarría-Marrero et al., 2019; Hatala, 2013; İşbilen & Mehmedoğlu, 2022; Saad et al., 2017). The theory rests on a multidimensional conceptualization of human experience in which addiction is an emergent condition that arises from the interaction of numerous factors, and which cannot be reduced to simple biological functioning. Successful treatment of AUD, therefore, incorporates a holistic approach that brings forth the best of neuroscience in conjunction with a respect for the social and emotional experience of an individual's intersectional identities while also placing value in the spiritual processes of meaning making and interconnected being (İşbilen & Mehmedoğlu, 2022; Saad et al., 2017). For this research, a biopsychosocial-spiritual perspective will be applied and inform the integration of recent research on the efficacy of PAP for the treatment of AUD.

Contribution to the Field

Presently in Canada the use of psychedelic medicines is severely limited. All psychedelics, including psilocybin, are currently illegal to produce or possess in Canada (Canada, 2023). Exemptions are made on a case-by-case basis and typically access to PAP is contingent on individuals facing end-of-life distress. While recent investment by the federal government has initiated several clinical trials investigating psilocybin-assisted therapy, acceptance and adoption are not yet a reality.

Recent qualitative research has shown significant reductions in drinking days in adults diagnosed with AUD, as well as a reduction in the number of heavy drinking days in this population (Bogenschutz et al., 2015, 2022; Nielson et al., 2018). Follow up qualitative trials shed light on potential therapeutic mechanisms and highlighted the multidimensional nature of

change-related phenomena, including the influence of mysticomimetic experiences, changes in individuals relationship to alcohol and increased commitment to change (Nielson et al., 2018). These findings were supported by concurrent research which investigated the importance of psychedelic-occasioned mystical experiences (Kangaslampi, 2023). In this meta-analysis, participants were shown to have significant reductions in anxiety as a result of the emergent state they experienced due to a mystical-type experience which brought forth novel psychological insights (Agin-Liebes et al., 2021; Kangaslampi, 2023). Additional research has provided evidence that participants in studies utilizing psilocybin-assisted therapy in the treatment of AUD were able to process painful emotions related to past traumatic events (Agin-Liebes et al., 2023). The psilocybin experience was described as providing a basis from which self-compassion could emerge in relation to past behaviours, an important therapeutic concept in the treatment of AUD due to the destructive impact the condition has on social connections and the experience of shame associated with problematic substance use experienced by individuals with a diagnosis of AUD (Agin-Liebes et al., 2023; Healy et al., 2021; McGaffin et al., 2013).

This multifaceted change process is reflective of a multifactorial conceptualization of addiction, similar to a biopsychosocial-spiritual perspective of etiology (Saad et al., 2017). However, Nielson et al., (2018) also found respondents to be dually stigmatized, first for their diagnosis of AUD and secondly for engaging in a therapeutic process which is stigmatized due to its historical conceptualization and current legal status. This present set of circumstances presents significant barriers to treatment. Highlighting the emerging research indicating the clinical value of these therapeutic interventions may serve to conceptually validate psilocybin-assisted therapy while also reducing associated stigma.

This capstone will influence the perception of PAP and psychedelic medicines as a whole and positively influence the social perception of stigma. The therapeutic potential of this new wave of treatments is great, as is the magnitude of suffering experienced by individuals, families and communities afflicted with the economic, social and health consequences of untreated substance use disorders. The possibility of providing insight into the delivery of PAP, the neurological mechanisms of action and the psychosocial-spiritual processes of change that individuals experience as a result of this treatment is one of great opportunity. Given that substance use disorder influences, to some degree, all members of modern western society, the potential audience for this information is vast.

Reflectivity and Positionality Statement

The direction of this research is influenced largely by my own experience with substance use disorder and with forms of psychedelic assisted therapy. I find it natural to pull from this narrative of my life as it has largely shaped the path which I have followed in becoming a counsellor, and the opportunity to explore this academic growth-edge which is receiving so much attention at the current moment is both exciting and intimidating. I would describe myself as a research pragmatist, I see the value in both quantitative and qualitative measurements of a subject. My tendency is to resonate more with a narrative description of experience but given the subject matter and the desired goal of reducing stigma and providing educational material to individuals or groups that are resistant to the idea of psychedelic medicines, it is logical to draw on hard science that brings the measurable and identifiable aspects of neurology into a conversation as ephemeral as this one. I have used psychedelics and continue to as part of a spiritual practice that is a key component of identity for me. As such, I am aware of my bias to believe in the subject matter of this paper and to be liable to overvalue positive results and be

tempted to discredit critiques. Considering this, an investigation of the dissenting literature surrounding PAP will be included as part of this research. Recent data show more than 14% of surveyed psychologists believe there to very likely be disadvantages to using psychedelic assisted therapy (Davis et al., 2022). As such, there exists a reasonable level of skepticism surrounding the use of these treatment protocols, and effective scholarship requires a recognition of the critical perspective. I do believe, however, that the research being undertaken at this time in relation to psychedelic medicines presents a wealth of possibilities to the healing professionals and to individuals of all levels of society. My hope in completing this work is to develop a greater literacy in the scope of factors involved in psychedelic assisted therapies and to broaden my understanding of the neural correlates of psychedelic experiences.

Definition of Terms

Alcohol Use Disorder (AUD): a problematic pattern of alcohol use leading to clinically significant impairment or distress (APA, 2022)

Evidence Based Practice: the integration of the best available scientific research from laboratory and field settings with clinical expertise so as to provide effective psychological services that are responsive to a patient's culture, preferences, and characteristics (APA, 2022)

Mysticomimetic Experience: a psychedelic-induced altered state of consciousness which mimics spontaneous mystical or transcendental experiences (Nielson et al., 2018)

Psilocybin: a serotonergic compound derived from psilocybin-containing mushrooms. In the body it is converted to psilocin, which is a 5-HT_{2A} agonist that causes mind- and consciousness- altering effects (Bogenschutz et al., 2015)

Psychedelic: powerful psychoactive substances that alter perception and mood and affect numerous cognitive processes (Nichols, 2016)

Psilocybin-Assisted Psychotherapy: a therapeutic approach which uses psilocybin, a psychedelic compound found in certain mushrooms, as an adjunct to psychotherapy (Bogenschutz et al., 2015)

Recovery: in the context of AUD, the process through which an individual with a diagnosis of AUD improves in terms of overall well-being and reduces the negative consequences and distress associated with alcohol consumption

Stigma: the social phenomenon or process whereby individuals that are taken to be different in some way are rejected by the greater society in which they lived based on that difference; labels that associate people with unfavourable or disapproved behaviour characteristics (Bell, 2013)

Outline of Capstone Project

This chapter provides a brief overview of the foundational aspects of the following capstone project. The second chapter will contain a literature review of the relevant research, in which I will be seeking connections between recent clinical studies in the form of qualitative and quantitative data, to conceptualizations of recovery through a biopsychosocial-spiritual perspective. The final section will present a pathway towards integrating PAP into an ethical and evidence-based practice with particular emphasis placed on work with individuals with a diagnosis of AUD.

Chapter 2: Literature Review

The philosophical line of questioning which underpins the following inquiry is inherently about movement and the evolution of thought. The question ultimately seeking to be answered is whether there is ample evidence to support and stimulate a paradigmatical shift regarding the conceptualization of one of contemporary society's most intractable and costly issues. Alcohol use disorder (AUD) cuts a path of destruction through the lives of millions of individuals and impacts the social fabric in multitudinous ways. For decades, the etiological framework of AUD has been rooted in the biomedical model which posits a physiological source of problematic substance use and a defined course of treatment focused on the biological mechanisms of disease (Harrison, 2020; Miller, 2013). Tremendous progress has been made in this regard. However, efforts fall far short of and the population with a diagnosis of AUD, as well as the proportion of relapses among individuals that have received treatment, has remained steady over the last two decades (Cornelius et al., 2003; CSUCHWG, 2023; Stillman & Sutcliff, 2022). The primary motivation for exploring Psilocybin-assisted psychotherapy (PAP) as a treatment for AUD is to bring forth a discussion which recognizes the value of current biomedical research while also making space for an expanded conceptualization of etiology and treatment paradigms which include the application of previously disregarded compounds which show promise of being efficacious therapeutics in the treatment of AUD. This intention is grounded in the assumption that the conceptualization of an illness determines axiomatically the focus of treatment interventions. Given this, while the epistemological driver of this work is an exploration of shifting etiological paradigms the focus of inquiry will concern the degree to which, if any, PAP serves to reduce problematic drinking among individuals with a diagnosis of AUD. This chapter

will explore the literature investigating the applicability of PAP as a therapeutic intervention in the treatment of populations with a diagnosis of AUD.

Competing Etiological Frameworks

To support a discussion regarding AUD a grounding in the dominant frameworks which serve to conceptualize this multidimensional issue is necessary. It is a foundational assumption of this paper that the conceptual framework through which AUD is perceived exerts significant force on the type of therapeutic interventions which are appropriate and valid, as well as beliefs about the source and trajectory of AUD related behaviours. Further, resource allocation and social stigma are both influenced significantly by the manner in which AUD is conceptualized which ultimately impacts treatment outcomes within this population (Finn et al., 2023; Manthey et al., 2021; Milan & Varescon, 2022). Additionally, there is not yet an agreed upon set of causative factors involved in the presentation of AUD, and while research has produced therapies which meet the needs of a segment of this population, there is no cure and no treatment protocol which could reasonably be referred to as highly efficacious. This brings forth the question of whether the current dominant paradigm, that of the biomedical model, is appropriately effective to continue supporting. Current evolutions in thought regarding AUD call for a more holistic and integrative approach to understanding this multifaceted condition (Lacks & Lamson, 2018; Miller, 2013). The biomedical model has many strengths. However, the current unmet need, of which in Canada alone measures at least 2 million individuals with a diagnosis of AUD, suggests an alternative conceptualization of AUD treatment may be necessary (CSUCHWG, 2023; Kendler et al., 2017).

Both the etiology and the treatment of AUD involve a complex interplay of biological, psychological, social and spiritual domains which are grounded within a nested system of

environmental conditions that all mutually influence each other in nuanced ways (Lacks & Lamson, 2018; Miller, 2013). For instance, genetic predispositions towards the development of AUD, including variations in genes related to alcohol metabolism or neurotransmitter concentrations, can increase the likelihood of developing AUD (Kirschner et al., 2020; Skewes & Gonzalez, 2013). These biological factors interact with psychological factors, such as stress, and social and environmental factors, including family dynamics and attitudes towards alcohol consumption, to mediate the likelihood of an individual turning towards alcohol as a coping mechanism (Miller, 2013; Stillman & Sutcliff, 2022).

From a therapeutic standpoint, treatment of AUD might be best conceptualized as a multidimensional process requiring attention to multiple intersecting aspects of human experience (Echevarría-Marrero et al., 2019; Lacks & Lamson, 2018). Given this, an appreciation of the intricate and relational nature of AUD development informs the conceptualization of treatment options. The biopsychosocial-spiritual systems metatheory (BPSSS) outlined in Lacks & Lamson (2018) recognizes the interconnection between experiential domains and builds upon the pioneering work of Georg Engel's biopsychosocial model (Engel, 1977). Additionally, the inclusion of a spiritual component in the treatment of AUD has been prevalent in the delivery of biomedical dominant treatment protocols, as seen by the popularity of the abstinence-based, spiritually permeated Minnesota Model of residential treatment (Gallagher et al., 2018; McElrath, 1997). Contextualizing this multidimensional conceptualization of AUD and treatment is Bertalanffy's systems theory (1968) which emphasizes the interconnectedness and interdependence of component parts of a system, and which focuses on the relationships between these parts as contributing to a whole greater than the sum. The BPSSS serves as a guide for this exploration of how recent developments in PAP

intersect with existing treatment paradigms. By considering a range of potential therapeutic mechanisms involved in PAP against a multidimensional conceptual framework of AUD, an evaluation of the potential efficacy of this novel treatment paradigm will be made.

Prevalence and Etiology of AUD

Brown (2012) describes dependency upon substance at its most base as chronic and compulsive numbing; the National Institute on Drug Abuse utilizes a definition which identifies AUD as a chronic brain disease that can result in harmful consequences and destructive behaviours (National Institute on Drug Abuse, 2020). Etymologically, the term addiction originates from the Latin word *addīcō*, meaning enslaved by, or bound to (Smith, 2015). The most recent version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5-TR) defines AUD as a pattern of problematic alcohol use which leads to clinically significant distress or impairment which falls along a continuum of severity (APA, 2022). Diagnostic criteria include issues of consumption control, continued use in spite of adverse consequences, increased or increasing tolerance and symptoms of withdrawal (APA, 2022). Currently, between 2.5% and 3.5% of Canadians live with a diagnosis of AUD, and alcohol is the most common substance for which individuals meet the criteria of abuse (Canada, 2021; Government of Canada, 2023). This prevalence rate has remained relatively unchanged over several decades of data collection (Cornelius et al., 2003; CSUCHWG, 2023; Government of Canada, 2023). Additionally, recent data estimates the direct healthcare costs associated with AUD exceeding \$165 per person annually, more than six-times the combined costs associated with opioids, cannabis and methamphetamine (CSUCHWG, 2023). From this perspective, improving treatment for individuals with a diagnosis of AUD benefits both the individual and the collective community simultaneously.

Impact of AUD

The impacts of AUD are significant and encompass a range of physical, social, and psychological health problems. The multidimensional nature of AUD manifests in a range of consequences which co-occur and may contribute to increased mortality among individuals with a diagnosis. For instance, upwards of twenty-five chronic diseases and conditions are entirely attributable to alcohol consumption according to the International Classification of Disease, and alcohol plays a contributing role in the development of diabetes, cirrhosis of the liver and heart disease (Shield et al., 2014). A causal link between alcohol consumption and cancers of the oral cavity, stomach, esophagus, colon, liver and breast has been established (Connor, 2017). Additionally, increased mortality rates are seen among individuals with a diagnosis of AUD such that life expectancy among inpatient populations ranges from 24-28 years less than the general population (Westman et al., 2015). Consequently, the health impacts and mortality risks associated with AUD are clear and significant.

From a psychological perspective, AUD impacts health and places individuals at increased risk of developing psychopathologies including major depressive disorder and anxiety disorders (Canada, 2021; Coriale et al., 2018). Personality disorders, including Borderline Personality Disorder (BLPD) and Antisocial Personality Disorder (ASPD), are also associated with lifetime AUD prevalence, with pooled estimates of comorbidity equal to 52% and 77%, respectively (Castillo-Carniglia et al., 2019). Additionally, individuals with diagnoses of Attention Deficit Hyperactive Disorder (ADHD) or Post Traumatic Stress Disorder (PTSD) are likewise seen to have a elevated rates of comorbid diagnosis of AUD, with lifetime AUD prevalence rates equal to 25.9% and 54.5%, respectively (Castillo-Carniglia et al., 2019). The overlapping experience of mental health disorders and AUD prevalence lends credence to the

notion that AUD therapies should engage the psychological domain as part of efficacious protocols.

Treatment Modalities for AUD

Current treatment paradigms include a range of evidence backed psychotherapies, often utilized in conjunction with one or more supporting treatment modalities which may include pharmacotherapy. As gold-standard psychotherapeutic interventions, Cognitive Behavioural Therapy (CBT) and Motivational Interviewing (MI) have been applied to treatment protocols for AUD with mixed success. A recent randomized control trial, for instance, looking at the efficacy of CBT in reducing drinking among individuals with a diagnosis of AUD found no significant reductions in drinking days or consumption (Coates, Gullo, Feeney, Young, & Connor, 2018). MI, on the other hand, has been shown to be somewhat more successful when utilized as a treatment option for individuals with AUD that had otherwise not been receiving treatment. A recent study indicated a significant reduction in weekly drinks when compared to control groups (Walker et al., 2017). A further study utilizing group delivery methods found MI to significantly reduce drinking days and anxiety among individuals with a diagnosis of AUD (Csillik et al., 2021). Based in part on positive results such as these, researchers exploring PAP for AUD treatment have sought to incorporate MI into their treatment protocols (Bogenschutz et al., 2015, 2022; Nielson et al., 2018).

Additional treatment methods commonly used with individuals that have a diagnosis of AUD include pharmacotherapy and 12-Step Facilitation Therapy, delivered through such groups as Alcoholics Anonymous (AA). Predominant pharmacotherapies include medications such as naltrexone, an opioid receptor agonist which can help reduce cravings, acamprosate, a neurotransmitter modulator, and disulfiram, an aversive medication used to discourage alcohol

consumption (Bahji et al., 2022). These three drugs are commonly used in conjunction with psychotherapeutic interventions as part of Medication-Assisted Treatment (MAT). Additionally, 12-Step Facilitation Therapy plays a significant role in the treatment plans for many individuals seeking recovery. These groups emphasize the values of community engagement, social connection, acceptance and sobriety and are available widely to individuals, free of charge (Kelly et al., 2020). The low-barrier access model of AA and other 12-Step groups is difficult to replicate in clinical settings, and these services often represent the only form of treatment many individuals with AUD ever receive (Kelly et al., 2020). While measures of success are found in each of these existing treatment modalities, it is the residual unmet need that is of significant interest to the remainder of this paper.

Psilocybin for Alcohol Use Disorder

Ultimately, treatment for AUD is about behaviour change. There are varying definitions of recovery that exist but each share a commonality of seeking to promote changes in problematic drinking behaviours (Miller, 2013; Skewes & Gonzalez, 2013). To ground the often nebulous process of behavior change in a quantifiable framework, the Transtheoretical Model (TTM) will be employed to contextualize the influence of PAP in the treatment of AUD (Del Rio Szupszynski & De Ávila, 2021). A tenant of this stepwise model states that if no change is perceived to be necessary or beneficial, then behaviour change will not progress. In the context of recovery from AUD, change manifests along a continuum which traditionally has been dichotomized into polarities of abstinence and active addiction (Harrison, 2020; Miller, 2013; Yang & Kim, 2021). Data regarding relapse rates among populations that have received treatment for AUD suggest this definition ill-suited to achieving goals of sustained recovery, as many individuals struggle to maintain complete abstinence (Cornelius et al., 2003; Stillman &

Sutcliff, 2022). A more adaptive notion of recovery, grounded in the BPSSS, supposes progress towards behaviour changes in any one of the multiple domains which contribute to AUD development and maintenance could be considered movement towards a state of recovery. Therefore, for the purposes of this exploration of PAP, the inclusion of multiple aspects of recovery will be considered.

There have been several recent clinical trials which have investigated the possible therapeutic role of PAP in the treatment of chronic AUD. Initial evidence has been promising, and PAP has been linked to significant reductions in percentage of heavy drinking days (PHDD) as well as secondary outcomes of percentage drinking days (PDD) and mean drinks per day (DPD) (Bogenschutz et al., 2015, 2018, 2022; Nielson et al., 2018). There are limitations to these studies. Study populations were relatively small and had limited power to evaluate effects between subgroups. Controls for psychedelics are typically inadequate for screening and are subject to effect expectancies (Luoma et al., 2020). Additionally, completed trials utilized a two-group design which limited the evaluation of the psychotherapeutic interventions or the interaction between the psilocybin medication and the psychotherapeutic interventions (Bogenschutz et al., 2018, 2022). However, despite these limitations there is ample evidence to support further investigation, and clinical trials into the therapeutic efficacy of PAP in the treatment of AUD has increased substantially in recent years (Bogenschutz et al., 2022; Doss et al., 2021; Jensen et al., 2022; Shao et al., 2021).

Currently, the primary evidence for the efficacy of PAP in the treatment of AUD comes from several trials conducted through New York University's Langone Center for Psychedelic Medicine, located at the Grossman School of Medicine. The most recent trial completed through this organization utilized a double blind randomized control trial (RCT) testing the influence of

PAP in the reduction of PHDD as the primary outcome (Bogenschutz et al., 2022). Participants were randomly assigned into one of two groups, and each received 12 weeks of supportive, evidence-based psychotherapy. Results showed significant reductions in PHDD ($p=0.01$, $hedges\ g=0.52$) compared to the control group and these differences persisted through the final follow up at 36 weeks. Additionally, abstinence rates and reductions in World Health Organization (WHO) alcohol consumption risk of 1- or 2- levels were seen and persisted through final follow up at 36 weeks (Bogenschutz et al., 2022). Furthermore, the PAP group also saw moderate to large reductions in alcohol related problems according to the Short Index of Problems (SIP-2R) assessment measure, including significant reductions in physical and intrapersonal problems and a significant reduction in total problems overall (Bogenschutz et al., 2022). In connection to earlier studies examining PAP for AUD, the number needed to treat (NNT), a metric for comparing the relative efficacy of medications in treating conditions where a lower number denotes a more effective treatment, was 6-7 for drinking outcomes at first post treatment follow up. These differences persisted throughout the final follow up at week 36, at which point the NNT for these outcomes ranged from 4.0-8.2 (Bogenschutz et al., 2022). For context, Naltrexone, an established medication used to manage cravings associated with alcohol use and opioid use, has a NNT of 9-10 (Bogenschutz et al., 2015; Nielson et al., 2018).

The current research landscape is promising regarding the efficacy of PAP as a potential therapeutic modality in the treatment of AUD. However, the mechanisms of action are still under investigation and much is still unknown regarding the principles which underlie and support change behaviours (Wheeler & Dyer, 2020). Given the relative infancy of clinical trials investigating PAP for AUD, and the limited number that have been completed, it is not yet possible to make conclusions about whether or not PAP is able to definitively reduce drinking

among individuals with a diagnosis of AUD. However, there is strong reason to believe that PAP plays a role in the reduction of problematic drinking among populations with diagnoses of AUD (Bogenschutz et al., 2015, 2022; Nielson et al., 2018). Additionally, there is growing evidence that PAP could develop into an effective treatment protocol for individuals with AUD, and further clinical research is currently underway investigating the mechanisms of action involved. While there is not conclusive evidence linking the utilization of PAP to a reduction in problematic drinking, clinical investigations into this potential are proliferating.

Presently, studies exploring the biological and neurological correlates of change are increasing (Higbed & Sessa, 2023; Jensen et al., 2022; Meinhardt et al., 2021; Shao et al., 2021; Stillman & Sutcliff, 2022). Additionally, a large body of research is exploring the psychological factors involved in behaviour changes amongst populations with a diagnosis of AUD who undergo PAP (Agin-Liebes et al., 2021, 2023; Echevarría-Marrero et al., 2019; Roseman et al., 2019; Wolff et al., 2020). Furthermore, given the prevalent reporting of mystical or spiritual experiences by individuals undergoing PAP, and compounded by the significant relationship observed between reductions in PHDD and high scores on the Mystical Experiences Questionnaire (MEQ), a number of investigations into the spiritual aspects are also being generated (Agin-Liebes et al., 2021; Doblin et al., 2019; Griffiths et al., 2011, 2016). Connecting each of these domains are social themes of connectivity, isolation, and interpersonal and intrapersonal relational repair. These aspects are particularly relevant when considering the fractured and fragmented social landscape typical of individuals suffering with a diagnosis of AUD (Agin-Liebes et al., 2023; Healy et al., 2021; Wangensteen & Hystad, 2022). Taken in concert, the multidimensional nature of AUD is being mirrored by a multidisciplinary investigation of the interrelated mechanisms of action that are thought to be significant in PAP.

Biological Domain

Conditioning

Classical and operant conditioning are two fundamental learning processes which are implicated in the development and maintenance of AUD (Doñamayor et al., 2021; Miller, 2013). Classical conditioning involves the evocation of a response, such as the consumption of alcohol, after the pairing of a previously neutral stimulus with environmental cues. For instance, specific locations or people associated with alcohol consumption become conditioned stimuli which, over time, become cues for craving and influences on alcohol seeking behaviour (Miller, 2013; Skewes & Gonzalez, 2013; Suzuki et al., 2020). Operant conditioning, on the other hand, is a learning process which influences the likelihood of a behaviour being expressed based on positive and negative reinforcement. In the context of AUD, positive reinforcement relates to the pleasurable effects of alcohol consumption and increases the likelihood that this behaviour will be repeated. Negative reinforcement implies the removal of a negative consequence, such as when alcohol consumption reduces stress and relieves tension (Skewes & Gonzalez, 2013; Suzuki et al., 2020). In both cases, environmental stimuli become associated with alcohol consumption and influence the likelihood that an individual will engage in alcohol seeking behaviours.

These two systems operate in synergistic ways and are influenced by biological, psychological, and social factors which influence the likelihood of engaging in alcohol seeking behaviours. In the context of AUD, this has implications for treatment success and relapse prevention. One study explored the phenomena of psychological craving and the relationship between cues and associated learned behaviors (Miller, 2013; Suzuki et al., 2020). In their findings, both classical and operant conditioning were involved in the development of a

behaviour chain whereby a series of antecedents, or cues, prompted a behaviour response which was in turn reinforced by a subsequent cue. These cues prompt the phenomenon of craving which modulates alcohol seeking behaviours. Following the consumption of alcohol, behaviour is reinforced positively by the elicitation of pleasure or negatively by the removal of stress or tension, often associated with the experience of craving (Miller, 2013; Suzuki et al., 2020).

Ultimately these pathways place individuals with AUD at an increased risk for relapse, particularly for individuals with limited capacity to seek new environmental and social contexts. As the embedded nature of the cues associated with alcohol consumption become prevalent over time and relate to outcome appraisal and response inhibition, understanding their impact is an important component of an holistic approach to AUD treatment (Stillman & Sutcliff, 2022).

Neurological Correlates of AUD

A recent study proposed a re-conceptualization of AUD, away from pharmacological models and towards one of behavioural dyscontrol along a spectrum ranging from apathy on one end to compulsion on the other (Kirschner et al., 2020). Physiological differences in tonic and phasic bursts of dopamine in the striatum are related to variations in reward seeking behaviour and influence the development and progression of problematic drinking (Kirschner et al., 2020). Additionally, there is an existing body of research which has focused on dopamine pathways in relation to substance misuse, in part driven by the fact all substances of abuse share the commonality of increasing dopamine release into the striatum and thereby mediating the sensation of reward (de Veen et al., 2017). Further to this point, the dopamine reward systems is foundational to basic learning and decision making through positive reinforcement which has implications for the development of AUD and successful treatment pathways. Additionally, a recent study showed AUD to affect neurotransmission and interactions within the brain's reward

system and observed a deficit of reward circuits in the brains of individuals that had prolonged experiences of AUD (de Veen et al., 2017; Masiak, 2014).

Both genetic factors of heritability and the process of neuroadaptation intersect to influence the development and maintenance of AUD. Research by de Veen (2017) showed there to be a large initial release of dopamine associated with the use of substances of abuse but observed there to be a decrease in sensitivity in response to long term use. This process has implications for the concept of tolerance, which sees individuals with AUD needing increasing amounts of alcohol to attain a desired effect and contributes to the chronic nature of the condition (APA, 2022). Additionally, research into the heritability of substance use disorders showed there to be differential responses to alcohol and variability in metabolism. Ultimately, these variations lead to different reactions to the consumption of alcohol and associated perceptions regarding the value attached to the subjective effects alcohol has on individuals (Masiak, 2014). This is intersected by research which showed children of alcohol dependent parents to have a decreased sensitivity to the negative effects of alcohol which contributed to increased risk of problematic drinking in adolescence and was a predictor of future alcohol related problems (Skewes & Gonzalez, 2013). Taken in concert, these findings highlight the intricate interplay of genetic factors, neuroadaptation and dopaminergic functioning and underscore the multifaceted nature of AUD. This supports the notion that biophysiological factors play a significant role in the development of AUD and remain an important focus of therapeutic interventions.

Neurotransmission

Evidence for the role of primary reinforcement, classical and operant conditioning and psychomotor activation has been supported by observations of neurotransmission patterns in the amygdala and ventral striatum among individuals with AUD (de Veen et al., 2017). Of particular

interest are 5HT_{2A} receptors, a subtype of serotonin receptor which are associated with both AUD and psilocybin mechanisms of action (Bogenschutz et al., 2022; de Veen et al., 2017). One investigation found 5HT_{2A} receptors in the periventricular nucleus (PVN) is involved in regulating the Hypothalamus-Pituitary-Axis (HPA), a crucial neuroendocrine system that plays a central role in the body's response to stress (de Veen et al., 2017; Dunne & Ivers, 2023). The HPA is activated through the release of corticotropin releasing factor (CRF) into the PVN in response to stress, which stimulates the release of cortisol into the bloodstream. Clinical research on non-human subjects suggests this pathway has important implications in the development of AUD, as cortisol is thought to signal arousal and trigger reward in response to the initial acquisition of substance use behaviours (de Veen et al., 2017; Stillman & Sutcliff, 2022). Put more simply, this multifaceted neurological process may relate to AUD through the association of experiential memories paired with alcohol use triggered behavioural responses to environmental stimuli (de Veen et al., 2017; Dunne & Ivers, 2023; Masiak, 2014).

Glutamate is a neurotransmitter, crucial in the functional health of neurons and is involved in learning and memory processes. mGluR2, a glutamate receptor, holds potential as a site of PAP's therapeutic effects for AUD. Chronic alcohol consumption has been linked to dysregulation of glutamate signaling, which has been implicated in addictive behaviour patterns (Meinhardt et al., 2020, 2021; Tyler et al., 2022). Recent research has highlighted the role of mGluR2 in cognitive flexibility and synaptic transmission, both of which are involved in the sensation of craving (Meinhardt et al., 2020, 2021). Chronic alcohol consumption has been linked to the suppression of glutamate release in the infralimbic cortex, a brain region important in executive functioning, goal setting and impulse control. Additionally, increased alcohol seeking behaviour has been linked to mGluR2 deficits in the medial prefrontal cortex (mPFC)

(Meinhardt et al., 2020, 2021; Tyler et al., 2022). Furthermore, alterations in the level of glutamate in the prefrontal cortex (PFC) have also been linked to increased craving intensity among individuals with AUD (Stillman & Sutcliff, 2022). Conversely, restoring mGluR2 levels rescued these behaviours, reducing craving intensity and alcohol seeking behaviours, pointing to the significance of mGluR2 in therapeutic interventions for AUD (Meinhardt et al., 2020).

In a recent animal study investigating the therapeutic relevance of targeting mGluR2 deficits in alcohol dependent rats, evidence was provided for the use of psilocybin to treat relapse-like drinking (Meinhardt et al., 2021). In their work, Meinhardt et al., (2021) showed mGluR2 deficits to be necessary and sufficient for diminished cognitive flexibility and increased alcohol craving in rats. Psilocybin was posited as an effective therapeutic intervention based on its potential to restore mGluR2 deficits. While the link between mGluR2 deficits and alcohol craving have been investigated for some time, no direct mGluR2 treatment has yet been approved by the FDA (Domanegg et al., 2023; Meinhardt et al., 2021). Drawbacks have included a large discrepancy between preclinical and clinical efficacy, as well as relatively poor central nervous system (CNS) penetration by mGluR2 agonists and an increase in tolerance following repeated administration (Domanegg et al., 2023).

More recent studies have shown lower doses in rats to be effective in reducing alcohol intake in dependent rats (Vengeliene & Spanagel, 2022). Further research into the use of positive allosteric modulators (PAM), which enhance the effects of endogenous ligands and increase signaling, is under way but proof of concept studies are still needed (Domanegg et al., 2023). In spite of a lack of direct mGluR2 interventions, studies indicate the efficacy of psilocybin to indirectly restore mGluR2 expression and reduce the likelihood of relapse drinking (Domanegg et al., 2023; Meinhardt et al., 2021). Meinhardt et al., (2021) showed that a single dose of

psilocybin was able to reduce the incidence of relapse significantly. The results of studies into mGluR2 restoration provide additional support to the theory that PAP may be an effective therapeutic intervention for the treatment of AUD.

Cognitive Control and Flexibility

Cognitive control refers to a set of processes which support and allow an individual to manage thoughts, emotions and behaviours in the pursuit of specific goals (de Veen et al., 2017; Wilcox et al., 2014). Impairments to cognitive control, as can be seen in individuals that have used alcohol chronically, can include response inhibition, impairments to working memory tasks and distractor interference control (Wilcox et al., 2014). Deficits in cognitive control negatively impact one's ability to filter out distracting information, a key component of an individual's capacity to focus on tasks. Distractor interference requires an individual to utilize intact response inhibition processes while also engaging selective attention networks. When these are compromised through chronic alcohol consumption an individual's capacity to suppress one response in favor of another, referred to as competing responses, is diminished (Wilcox et al., 2014). This increases an individual's susceptibility to environmental cues and potentially, therefore, increases the likelihood of relapse (Senn et al., 2020; Stillman & Sutcliff, 2022; Wilcox et al., 2014).

In the context of AUD, reduced distractor interference control is especially relevant for those in recovery as environmental cues and subsequent responses to them play a significant role in the likelihood of re-engaging with alcohol seeking behaviours (Senn et al., 2020; Skewes & Gonzalez, 2013; Stillman & Sutcliff, 2022). Operant conditioning and cognitive control intersect through the concept of distractor interference as individuals in early recovery are doubly vulnerable to relapse through the interconnected relationship of these two processes. Given the

extensive network of environmental cues that can become associated with alcohol consumption, particularly in individuals that have suffered with AUD for a prolonged period, a reduction in their capacity to resist these cues inherently increases the risk of returning to alcohol seeking behaviours. The process of behaviour change away from active engagement in AUD involves continuous attention given to competing responses as new patterns and associations take form. Research into the role of motivation in AUD recovery provides evidence for altered hierarchies of self-care behaviours whereby healthy coping mechanisms are supplanted by addictive behaviours (Masiak, 2014). Realigning this takes time and leaves individuals with reduced distractor interference control at risk of reengaging in alcohol seeking behaviours.

Prolonged exposure to alcohol consumption can lead to structural and functional changes in the PFC, a key region responsible for cognitive control (de Veen et al., 2017; Wilcox et al., 2014). Through neurotoxic effects, chronic alcohol consumption can cause neuronal loss and disruptions in neurotransmitter systems, particularly in the PFC. Damage to the functioning of this region of the brain compromises decision making and can reduce one's capacity to set goals and resist habitual behaviour patterns (Wilcox et al., 2014). In the context of AUD treatment, an individual's resilience towards alcohol seeking behaviour patterns is a key component of recovery. In light of the existing data which suggests relapse rates within the first year post-residential treatment among populations with a diagnosis of AUD could be as high as 60%, the additional risk associated with reduced cognitive control is important to consider therapeutically (Senn et al., 2020; Stillman & Sutcliff, 2022).

From a PAP perspective, psilocybin has shown early evidence of being efficacious in restoring diminished cognitive control functionality. One study showed 5HT receptors to strongly modulate behavioural flexibility, providing evidence that 5HT agonism has beneficial

effects and reduces perseveration (de Veen et al., 2017). Clinical trials have observed psilocybin to bond with high affinity to 5HT receptors, and their modulation is one of the leading theories of therapeutic action regarding PAP (Bogenschutz et al., 2015, 2022; de Veen et al., 2017). While the exact mechanisms of action regarding psilocybin's interaction with 5HT receptors are still not fully understood, prevailing theories suggest there to be multiple processes which play roles in altering perceptions, cognitions and subjective experiences in addition to neurological alterations associated with neurogenesis and neuroplasticity (de Veen et al., 2017; Doss et al., 2021).

Neuroplasticity

Following a proof of concept study which initially explored the potential of PAP as a treatment for AUD, one of the first posited mechanisms of action that contributed to clinical change was neuroplasticity (Bogenschutz et al., 2015). A recent study labeled psilocybin as a psychoplastogene, or a compound capable of promoting induced plasticity (Ly et al., 2018). In multiple studies, serotonergic psychedelics, a classification which denotes the serotonin 5HT receptor system in the brain as the locus of interaction, have been shown to stimulate neurogenesis (Ly et al., 2018; Meinhardt et al., 2021; Shao et al., 2021). Results from one animal study investigating psilocybin showed increased neural connectivity through the growth of synapses in addition to rapid and sustained growth of dendritic spines in the PFC (Shao et al., 2021). This work was supported by another study which identified several signaling pathways, including 5HT_{2A}, which mediated psychedelic induced neural plasticity (Ly et al., 2018). Additionally, the structural and functional neuroplastic changes were in part mediated by the TrkB receptor which, when activated by brain-derived neurotrophic factor (BDNF), promotes the growth, proliferation and function of neurons (Ly et al., 2018). The body of literature supporting the neurological benefits of serotonergic psychedelics, including psilocybin, is growing in scope

and legitimacy and continues to provide evidence for the utility of PAP in the treatment of AUD.

In the context of AUD, the capacity to promote and induce neuroplasticity, particularly in the PFC, represents significant therapeutic potential. Research has shown that individuals with substance use disorders, particularly severe AUD, experience neural circuitry changes in different regions of their brain (de Veen et al., 2017; Ly et al., 2018; Venugopal & Bedri, 2023). Several studies have investigated the impacts of alcohol consumption on PFC functioning. In one, alcohol intake was shown to accelerate decreases in PFC volume in adolescent individuals. Longitudinal follow ups with these individuals found a correlated increases in depressive episodes among populations with decreased PFC volumes (Kirsch et al., 2022). Another study identified decreases in both synaptic density and dendritic spines as well as neurite retraction in the PFC in populations of individuals with AUD (Ly et al., 2018).

The relevance of this research to the application of PAP for AUD is twofold. Firstly, the PFC is vital for cognitive control, emotional regulation and impulse inhibition, all important facets when considering both the development of AUD over time and as components of successful behaviour change in recovery. Research supports this notion and indicates the PFC as being highly involved in regulating AUD, with neuroanatomical deficits playing a role in compromised executive functioning and decision making in addition to impulse control and emotional regulatory processes (Ly et al., 2018; Stillman & Sutcliff, 2022; Venugopal & Bedri, 2023). Secondly, the potential of psilocybin to promote rapid and sustained dendritic spine growth and contribute to neurogenesis in the PFC presents the possibility of restorative neurological interventions which support therapeutic approaches that address behaviour change at multiple levels.

Spiritual Domain

Spirituality and Mystical Experiences

Spirituality as a concept is difficult to define in clinically relevant terms due in part to its subjective and multifaceted nature. In general terms, contemporary research into PAP utilizes a definition which speaks to the experience of connection to a transcendent aspect of life and which may include themes of interconnectedness and a personal sense of purpose, and a belief in a higher power (Doblin et al., 2019; Echevarría-Marrero et al., 2019; Swift et al., 2017).

Additional texture for a working definition of spirituality come from the author and activist bell hooks (2000) who emphasizes the importance of connection to an animating source within oneself and to a wider existential reality. In their work they describe spiritual connection and addiction as antithetical poles of experience, overlapping work by Bruce K. Alexander (2014) which showed the importance of social connection and engagement in preventing alcohol seeking behaviour in animal studies. Together, these perspectives emphasize the importance of connection as a therapeutic intervention in the treatment of AUD (Alexander, 2014; hooks, 2000). Drawing on these sources, then, informs an understanding of spirituality as an intersectional nexus of belief and experience regarding one's relationship to self and to a greater reality that serves to connect individuals to a sense of purpose and meaning. This construct may serve as a protective factor against problematic alcohol consumption, particularly amongst a population with the diagnosis of AUD (Alexander, 2014; Echevarría-Marrero et al., 2019; Snodgrass et al., 2023).

Griffiths et al., (2011) showed the capacity of psilocybin to produce dose-dependent mystical-type experiences that can have pervasive and lasting effects on mood, attitudes, and behaviour. This study extended a research base which emphasized the role of mystical or

spiritual experiences occasioned through PAP which were shown to have personal significance for study participants and support improvements in social relationships, psychological and physical self-care and a greater engagement in spiritual practices (R. Griffiths et al., 2008, 2011; R. R. Griffiths et al., 2006). In recent studies of PAP for AUD, high MEQ scores, indicative of mystical-like experiences, were shown to be significantly associated with reductions in PHDD (Bogenschutz et al., 2015, 2022). Meta analysis of the impacts of psilocybin occasioned mystical-like experiences provide evidence for associated reductions in depression (Agin-Liebes et al., 2021; Davis et al., 2019, 2020). Additionally, associations between mystical-type experiences and improvements in problematic alcohol use have been shown in several recent studies (Agin-Liebes et al., 2021; Garcia-Romeu et al., 2019). Furthermore, mystical experiences were seen to be strong mediators of change and be a driver of long-term change in AUD treatment through the promotion of psychological insight, changes in perceptions around personal meaning and purpose and increased experiences of hope (Rieser et al., 2021; Venugopal & Bedri, 2023). Given the range of implications associated with the spiritual and mystical experiences that can be occasioned by PAP, consideration of this domain in the treatment of AUD holds promising potential.

Psychological Domain

Outcome Expectancies

Outcome expectancies (OE) are conditioned cognitions which, in the context of PAP for AUD, relate to an individual's beliefs about the effects that using a particular substance will produce. Research by Skewes & Gonzalez (2013) indicates that OE play a role in the development of AUD by influencing beliefs around the likelihood that alcohol consumption will lead to relaxation, reduction in tension, social and physical pleasure, and interpersonal power,

among others. These factors are incorporated into subjective experiences of alcohol consumption and are mediated through social context, such as the permissiveness of family norms around alcohol consumption and peer attitudes towards substance use (Coates, Gullo, Feeney, Young, Dingle, et al., 2018a; Skewes & Gonzalez, 2013). Recent research has shown that alcohol expectancies are influenced by treatment programs for AUD such that positive expectations around the effects of alcohol are reduced following stays in residential treatment ($p < 0.001$). Additionally, the negative OE associated with alcohol consumption following treatment were higher following treatment for AUD ($p < 0.001$) (Coates, Gullo, Feeney, Young, Dingle, et al., 2018a).

This process, while not measured directly in recent PAP trials, was communicated through patient experiences in a follow up qualitative analysis where expectancies were linked to motivational changes. Changes in perceptions about the positive impacts of alcohol consumption coupled with new beliefs about the potential benefits of sobriety led to alterations in patient motivation to change and beliefs in self efficacy (Bogenschutz et al., 2018; Nielson et al., 2018). One theory from recent trials implicates changes in baseline consciousness as reshaping conditioned cognitions around alcohol use and supporting the taking of new perspectives which support behaviour change (Bogenschutz et al., 2018; de Veen et al., 2017; Nielson et al., 2018).

Commitment to Change

A consistent challenge faced by treatment providers supporting individuals with a diagnosis of AUD is the concept of relapse. Data on relapse rates following stays in residential treatment facilities sit between 40-60% and this has remained steady in the literature at least as far back as 2003 (Cornelius et al., 2003; Stillman & Sutcliff, 2022). While many factors contribute to the presentation of a relapse, commitment to change has been shown to be a strong

modulator of treatment outcomes. Research has shown that individuals with higher motivation to change and greater commitment to change are more likely to successfully implement resilient self-change behaviours (Senn et al., 2020; Skewes & Gonzalez, 2013). Given the complex nature of behaviour change, particularly in the context of AUD, taxation of motivation is inherently demanding. In simple terms, recovery from AUD is challenging and fraught with difficulties that require motivation and a strong commitment to change that is manifest through an internal realignment between thoughts, intentions, and behaviours. One of the strengths of PAP for AUD is the observed capacity to induce changes in motivation and increase individual's commitment to changing behaviour (Agin-Liebess et al., 2023; Bogenschutz et al., 2018; Nielson et al., 2018).

From a theoretical perspective, commitment to change and motivation intersect within the TTM. This framework conceptualizes behaviour change as a step-wise process in which motivation, commitment and expectancy intersect to influence an individual's capacity to bring about behavioural change (Del Rio Szupszynski & De Ávila, 2021). The model breaks behaviour change into five stages, ranging from precontemplation through contemplation, preparation, action, and maintenance. In the context of PAP for AUD, many individuals fall between preparation, characterized by a willingness to change and initial steps towards change, and action, an often challenging phase characterized by an active participation in specific modifications to behaviour (Del Rio Szupszynski & De Ávila, 2021). Due to the often cyclical pattern of recovery from AUD where multiple attempts at recovery are made before sustained sobriety is achieved, motivation, commitment and OE are impacted by perceptions of failure and concomitant beliefs about the likelihood of success (Agin-Liebess et al., 2021; Bogenschutz et al., 2018; de Veen et al., 2017; Skewes & Gonzalez, 2013). In several studies, qualitative accounts of participant attitudes towards committing to change were notably more positive and hopeful.

patients who complete the process of PAP report back a significant difference in their ability to commit to and execute previously unattainable behavioural changes regarding their drinking behavior and these attitudes largely persisted through the end of the follow up period for each study (Bogenschutz et al., 2018, 2022; Nielson et al., 2018)

Self-Efficacy

Self-efficacy has emerged as a crucial cognitive factor involved in the process of recovery from AUD. At its core, self-efficacy relates an individual's belief in their own capacity to perform specific tasks and attain desired outcomes. Self-efficacy as it relates to AUD is a multidimensional construct that influences individual's coping strategies, experiences of withdrawal and dependency and decision making (Agin-Liebes et al., 2023; Johnson et al., 2019; Skewes & Gonzalez, 2013). Across a range of qualitative studies, high measures of self-efficacy were inversely correlated with relapse drinking among individuals who had undergone treatment (Nielson et al., 2018, 2018; Stillman & Sutcliff, 2022; Yang & Kim, 2021). In conjunction with a low reliance on avoidant coping mechanisms, self-efficacy was shown to be a powerful predictor of 3-year remission following treatment (Stillman & Sutcliff, 2022). Additionally, research has shown individuals are more likely to consume alcohol when they feel incapable of coping with demands or negative affective states (Skewes & Gonzalez, 2013). A pattern develops where alcohol use becomes more prevalent through negative reinforcement and subsequently atrophies healthier coping mechanisms. Over time, this pattern erodes an individual's sense of self efficacy and becomes a barrier to treatment for individuals with AUD (Skewes & Gonzalez, 2013; Venugopal & Bedri, 2023).

In relation to recovery, self-efficacy is particularly important for treatment outcomes as belief in self is recognized as an important component in the TTM and is additionally supported

by contemporary AUD research as being a protective factor against relapse (Del Rio Szupczynski & De Ávila, 2021; Nielson et al., 2018; Skewes & Gonzalez, 2013). Accounts of participants in recent clinical trials utilizing PAP for the treatment of AUD highlighted the power changes in self efficacy had to influence behaviour change motivation and subsequent changes to participant expectancy outcomes (Bogenschutz et al., 2018; Skewes & Gonzalez, 2013). Reductions in shame, disappointment and regret were observed in participant accounts following psilocybin dosing sessions, and these changes were linked to increases in self efficacy. Participants highlighted feeling more hopeful about the future and having increased motivation to change following their psilocybin experiences (Bogenschutz et al., 2018; Nielson et al., 2018). Still, behaviour change is a multidimensional process of which self-efficacy is a single factor. However, the facilitative role improvements in self efficacy represents is an intriguing target for therapeutic interventions. Recent research into the capacity of psilocybin to alter individuals' perceptions of self-efficacy provides additional evidence for the potential therapeutic efficacy of PAP for AUD.

Connection

A recent qualitative thematic exploration of the process of change experienced by individuals involved in PAP for AUD revealed several interconnected and reinforcing domains. There was a prevalent theme of chronic and long-term engagement in destructive coping mechanisms among participants, and a recognition that alcohol had come to represent a form of temporary self-soothing which provided some short-term benefit but which ultimately led to negative consequences (Agin-Liebes et al., 2023). This pattern had additional impacts on individuals emotional processing capacity, self-understanding and self-awareness as well as serving to limit or prohibit the processing of painful emotions (Agin-Liebes et al., 2023). This

research intersects with another study which compared PAP with a gold-standard SSRI intervention (escitalopram) in the treatment of experiential avoidance, a transdiagnostically relevant therapeutic mechanism used therapeutically for a range of mental health conditions (Sloan et al., 2017; Zeifman et al., 2023). Results from this study showed reductions in experiential avoidance following PAP which led to improvements in mental health and supported increased openness to emotional processing among participants. These findings highlighted the therapeutic value in shifting towards experiential acceptance as efficacious in the treatment of AUD (Agin-Liebes et al., 2021; Zeifman et al., 2023). Analysis of these results indicated decreases in experiential avoidance as occurring through increases in connectedness amongst participants (Zeifman et al., 2023).

Additionally thematic data was collected on participant experiences with internalized shame and self-criticism, of which almost all reported enduring. Rumination, self-blame, guilt and resentment were also associated with the experience of self-criticism, and this pattern was identified as a significant contributor to destructive self-soothing behaviours associated with alcohol consumption (Agin-Liebes et al., 2023). Supporting research has shown shame to be a deeply-rooted and pervasive emotional experience in individuals with a diagnosis of AUD, and its presence is associated with increased self-stigma, anxiety, depression and rates of alcohol consumption (Milan & Varescon, 2022). Shame is a primary barrier to seeking and receiving help, and is a predictive factor in rates of alcohol consumption (Milan & Varescon, 2022; Randles & Tracy, 2013; Salway et al., 2019; Stuewig et al., 2015). Additionally, alcohol consumption is subject to increased likelihood when shame and social disconnection intersect, implicating an increased risk for individuals with AUD that also lack supportive social networks (Luoma et al., 2018, 2019; Milan & Varescon, 2022). In a recent study, PAP was shown to

significantly reduced measures of internalized shame and complex trauma symptoms (Healy et al., 2021). Additionally, qualitative data support the therapeutic potential of PAP to facilitate the processing of shame and self-criticism amongst populations undergoing PAP through increased measures of self-compassion (Agin-Liebes et al., 2023). Participants reported experiencing profound perspective shifts through insight and mental spaciousness which led to expansive feelings of gratitude and concomitant reductions in cravings for alcohol (Agin-Liebes et al., 2023).

A further theme explored qualitatively was the influence of PAP on the concept of social connectedness. Grounded in the seminal work of Alexander (2014), the concepts of disconnection and dislocation play a prominent role in the development and maintenance of AUD and serve as significant barriers to recovery. Recent research on the therapeutic efficacy of group PAP for AUD supported the notion that connection and social inclusion were therapeutically corrective for individuals with a diagnosis (Agin-Liebes et al., 2021, 2023). Participant reports of increased capacity for connection and kinship were modulated by reductions in self-focus and facilitated increases in self-forgiveness and self-compassion (Agin-Liebes et al., 2021). This process is referred to in the literature as ego-dissolution and is supported by neurological insights into the interaction between psilocybin and the brain's default mode network (DMN) (Nielson et al., 2018). Psilocybin has been observed to decrease metabolic activity in this network of neural structures which is implicated in self-referential thinking and memory, which has led to theorizing about the role the DMN plays in maintaining the 'I-based' ego state (Nielson et al., 2018). Further research connected the dissolution of self and boundaries of identity with an increased sense of connection to, and compassion for, other people and the world at large (Agin-Liebes et al., 2021). Experiences of connection were inversely correlated

with problematic drinking and measures of relapse drinking were subsequently reduced among participants that felt greater connection to social and spiritual sources (Agin-Liebess et al., 2023; Nielson et al., 2018; Snodgrass et al., 2023).

Stigma

Stigma interacts with AUD in a number of ways that have detrimental impacts on the therapeutic trajectories of individuals afflicted with this disorder and it is recognized to be a barrier to recovery (Crozier et al., 2023; Kilian et al., 2021). Social perceptions of, and attitudes towards, individuals with AUD play a significant role in discrimination and social isolation. Judgements contribute to assigning blame and perpetuate stereotypes of flawed moral characters and inadequate willpower among populations with AUD, and this social stigma leads to a range of consequences that inhibit the process of recovery (Finn et al., 2023; Morris & Schomerus, 2023). These attitudes, rooted in part in historical classification of alcohol consumption as sinful, oversimplify the complex interrelated network of factors that contribute to the presentation of AUD and stigmatize individuals as deficient and flawed (Miller, 2013). Among individuals with a diagnosis of AUD, internalized shame associated with social stigma plays a facilitative role in the perpetuation of drinking behaviours and contributes to the concepts of low self-worth and low self-efficacy, as well as intersecting with outcome expectancies and individual perceptions of hope (Crozier et al., 2023; Luoma et al., 2019). Additionally, social networks are strained by stigma associated with AUD which can contribute to isolation and disconnection, both essential factors in mental health and wellbeing (Snodgrass et al., 2023; Watts et al., 2017). Furthermore, these concepts are essential to the process of behaviour change which defines the process of recovery, and factors which reduce an individuals capacity to grow or develop within these

domains represent barriers to their treatment progress (Del Rio Szupczynski & De Ávila, 2021; Morris & Schomerus, 2023).

There is ample evidence that the fear of stigmatization prevents individuals from acknowledging the reality of their condition and from seeking help for AUD (Finn et al., 2023; Kilian et al., 2021; Morris & Schomerus, 2023). The perception of consequences linked to judgement and social ostracism discourage many individuals from recognizing their problematic relationship with alcohol consumption, delaying an individual's process of change by limiting their capacity to move beyond the stage of precontemplation (Del Rio Szupczynski & De Ávila, 2021; Morris & Schomerus, 2023). As explained through the TTM, acceptance of a need for change is a necessary precursor to the process of behaviour change (Del Rio Szupczynski & De Ávila, 2021). This pattern prevents individuals from pursuing treatment and contributes to a prolonging of problematic consumption patterns (Finn et al., 2023; Kilian et al., 2021). Additionally, impacts to social support systems which are influenced by stigmatized attitudes towards individuals with a diagnosis of AUD contribute to isolation and withdrawal during both active consumption and during the process of recovery. Research has shown that this reduction in social connectivity and engagement impedes individuals in accessing community resources and contributes to patterns of relapse (Milan & Varescon, 2022; Morris & Schomerus, 2023). Furthermore, fear of stigma may lead individuals to non-disclose relevant information during the treatment process which may negatively impact the development of treatment plans. This has been shown to also affect an individual's commitment to change and negatively impact the resolution of dysphoric experiences associated with trauma (Milan & Varescon, 2022; Morris & Schomerus, 2023; Nielson et al., 2018). Consequently, treatment trajectories are negatively impacted by stigma by reducing help seeking behaviours among individuals with a diagnosis of

AUD and further impact the efficacy of treatment interventions due to the perceived consequences associated with disclosure.

From a systems perspective, stigma towards AUD has been institutionalized and affects the delivery of treatment within healthcare systems. Limited funding for mental health services and a lack of addictions treatment programs contribute to a shortfall in treatment capacity which contributes to the unmet need observable in this population (Finn et al., 2023). Additionally, stigma intersects with social narratives around race and socioeconomic class to produce systems of inequality and disparity that lead to an increased barrier to treatment experienced by individuals from marginalized populations (Sedarous & Flemming, 2023). Consequences of this pattern include delayed diagnosis, limited access to treatment options and poor health outcomes associated with AUD (Kilian et al., 2021; Sedarous & Flemming, 2023). Additionally, social stigma influences and is influenced by the criminalization of substances and the categorization of individuals with AUD as morally deficient. This leads to policies which pathologize individuals and promotes punitive responses to situations which require therapeutic interventions (Corrigan & Schomerus, 2022).

In Western society, substantial stigma has been associated with the use of psychedelic substances in any form (Hall, 2022). A Schedule-1 designation places these compounds in the most restrictive class of substances despite a lack of evidence of significant harm or addictive potential (Davis et al., 2022; Hall, 2022). This attitude permeates the perception around PAP to such a degree that participants in clinical trials were unlikely to share their involvement in studies for fear of judgement by family members or friends (Bogenschutz et al., 2018; Nielson et al., 2018). The perception that is under renovation at the moment through a wide range of academic explorations is that these compounds are devious and dangerous and present little, if

any, therapeutic benefit. While the timeline associated with changing social attitudes is slow and arduous, the academic vanguard of this process is currently producing convincing evidence that the utilization of psychedelic compounds, like psilocybin, presents a far greater reward than any associated quantifiable risk (Bogenschutz et al., 2015, 2018, 2022; Doss et al., 2021; R. R. Griffiths et al., 2006).

Methodological Considerations

The field of psychedelic studies is still relatively new and interventions using these compounds face a significant degree of scrutiny from both the academic establishment and the wider population. As such, studies investigating PAP for AUD must adhere to rigorous methodological standards to ensure data validity and to work towards a greater acceptance of the therapeutic potential these compounds present. Currently, clinical trials utilizing psilocybin and other psychedelics are undertaken within strict oversight protocols in accordance with their classification as illicit substances (Aday et al., 2022; Davis et al., 2022). A recent meta-analysis examining placebo controlled trials using psilocybin found a number of positive characteristics which contribute to the validity of collected data (Luoma et al., 2020). These included low attrition rates among participants, documented lack of adverse effects and a uniform adherence to preregistered primary outcomes. Additionally, critiques associated with PAP carry much validity, and tend to emphasize the often limited sample sizes in populations, challenges of blinding in clinical trials and determining treatment-specific benefits, and the process of determining therapeutic mechanisms which, as yet, remains indeterminate (Aday et al., 2023). A brief critical analysis of the contemporary methodological paradigms will include both these perspectives.

Strengths

Multiple systemic analyses of current research methodologies have returned evidence which speak to an adherence to rigorous standards that support the validity of findings (Aday et al., 2022; Wheeler & Dyer, 2020). For instance, study populations were regularly subjected to thorough screening through psychotherapy sessions prior to study engagement, and many studies selected for individuals with no prior psychedelic experience to limit expectancy effects (Wheeler & Dyer, 2020). Additionally, recent RCTs uniformly had low attrition rates which supports data integrity through target population retention and minimizing attrition bias (Luoma et al., 2020). Likewise, acceptability and feasibility of PAP as a possible intervention for a broader population was supported by a documented lack of adverse effects. This implied the target interventions were well tolerated, particularly important when considering the safety and ethics of utilizing a controlled substance in clinical settings. These effects strengthen the internal validity of the studies and enhances the generalizability of their findings (Luoma et al., 2020; Wheeler & Dyer, 2020). Furthermore, all trials examined did not deviate from preregistered primary outcomes indicating they were conducted in accordance with a predefined plan. This reduces the risk of bias and contributes to transparency and accountability by publicly documenting outcomes which limits the possibility of post hoc data manipulation and preventing hypothesizing after results are known (HARKing) (Luoma et al., 2020; Wheeler & Dyer, 2020). Finally, data validity was enhanced further by the minimization of potential for engagement in p-hacking, a process whereby researchers engage in multiple analyses until a statistically significant result is found (Luoma et al., 2020). Study reproducibility and result reliability are supported by the intersection of these effects which support the development of the overall evidence base. Taken in concert, recent research into PAP has shown there to be a high degree of methodological rigor applied to contemporary research practices.

Critique

Currently, there are a number of challenges associated with the study of psilocybin for the treatment of AUD. Significant among these is the difficulty encountered with double blinding during RCTs. Expectancy effects exert influence on the efficacy of compounds under study, and recent trials studying psilocybin have reported inadequate blinding due to the intense and easily identifiable effects associated with even low-doses of psilocybin (Aday et al., 2022, 2023; Bogenschutz et al., 2022; Luoma et al., 2020). Failed blinding in RCTs is linked to both placebo and nocebo effects as well as a decrease in internal validity and potentially introduce bias among observations. Additionally, sample sizes involved in clinical trials of PAP for AUD have typically been small and often overrepresented by white, highly educated males (Aday et al., 2022; Bogenschutz et al., 2022; Luoma et al., 2020). Limited sample sizes in studies reduce statistical power and limits generalizability of findings. These effects intersect with diversity concerns surrounding current PAP studies which limit the capacity for subgroup analysis (Bogenschutz et al., 2022). Finally, current studies lack the power to evaluate the effects of psychotherapy on the PAP process or measure the effect of psychotherapy independent of the medication (Bogenschutz et al., 2022; Luoma et al., 2020). There is a recognition within the psychedelic research community that increased study size and greater diversity among treatment populations are necessary, and this process is underway currently. The National Library of Medicine shows over 160 active or recruiting studies involving psilocybin, 10 of which are focused on alcohol intake (*Psilocybin Clinical Trials*, 2024). Consequently, while there exist a number of limitations associated with the current PAP landscape, interest in the potential of the therapeutic potential of this compound is high.

Chapter 3: Summary & Recommendations

The final chapter of this capstone will begin first with a summary of the research findings regarding the efficacy of PAP in the treatment of populations with a diagnosis of AUD.

Following that, recommendations for practicing therapists will be explored based on the evidence provided by the literature review. These will consider the current legislative landscape regarding psychedelic substances and PAP in Canada. A final section will present recommendations for future research for PAP in the field of Canadian mental health practice, after which a closing summary will be provided.

Discussion

A research question is the nexus through which vague, intuitive musings coalesce into intentional and actionable extensions of inquiry.

This capstone proposes a change in thought and perception regarding the current therapeutic landscape of AUD. It is predicated on the argument that the existing dominant paradigm fails to adequately meet the needs of this population, despite notable progress, and an alternative approach to this intractable problem is necessary. Given the recent expansion of research into the potential applications of psychedelic medicines for a range of medical conditions, the prospective therapeutic efficacy of these compounds in the treatment of AUD was of great interest. To test this notion, this research sought to answer whether PAP serves to reduce problematic drinking among individuals with a diagnosis of AUD.

Impacts of AUD

A discussion of the merits of adopting a new treatment paradigm for AUD is predicated on the assumption that impacts associated with this diagnosis are significant and severe enough

to adopt controversial and as yet unproven interventions. The preceding literature review established this to be the case. Prevalence rates have remained largely unchanged over the course of several decades in spite of ongoing research and investment, and treatment outcomes remain underwhelming for a significant proportion of individuals (Cornelius et al., 2003; CSUCHWG, 2023). The consequences of untreated AUD are profound, contributing to an increased risk of developing diabetes, heart disease, and liver disease, as well as several forms of cancer (Connor, 2017; Shield et al., 2014). Increased mortality among AUD populations and decreased life expectancies provide further evidence for the severity of impact (Westman et al., 2015). Beyond the impacts to the individual, AUD represents a significant cost of burden to society. Direct healthcare costs associated with AUD outpace the combined costs of opioids, cannabis and methamphetamine by a factor greater than six (CSUCHWG, 2023). Given the evidence provided in this review it is fair to argue the scope and severity of the issue is significant enough to warrant the discussion of alternative therapeutic modalities.

Psilocybin for Alcohol Use Disorder

Given the fractured etiological landscape associated with AUD treatment, effectively carrying forth this review required the selection of metrics which could accurately describe the multidimensional process of change referred to as recovery. Given this need, therapeutic efficacy was measured against the process of behaviour change in multiple domains. It was argued that the existing dominant etiological paradigm contributes to the preservation of unmet need among the AUD diagnosed population. Therefore, a meta framework incorporating the Transtheoretical Model (TTM) and Biopsychosocial-spiritual model (BPSS) of addiction was selected to frame the discussion and conceptualize the efficacy of PAP as a treatment protocol for problematic drinking (Del Rio Szupszynski & De Ávila, 2021; Lacks & Lamson, 2018).

At present, the most relevant primary data regarding PAP's efficacy in the treatment of AUD has been collected in several small clinical trials over the last five years. Given the multi-decade moratorium on psychedelic research, which has only recently come to an end, the field is still in its relative infancy. However, early results were shown to be highly promising. Significant reductions in percentage of heavy drinking days (PHDD), percentage drinking days (PDD), and mean drinks per day (DPD) have been shown in multiple studies (Bogenschutz et al., 2015, 2018, 2022; Nielson et al., 2018). Likewise, measurable reductions in alcohol related problems have also been seen, as have reductions in risks associated with alcohol consumption as measured against World Health Organization (WHO) standards (Bogenschutz et al., 2022). These results were seen to be resilient, with participants reporting reductions persisting through the final 36-week follow up (Bogenschutz et al., 2015, 2018, 2022; Nielson et al., 2018).

While the early data are encouraging, it is yet too early to make conclusions about the therapeutic utility of PAP in the treatment of problematic drinking. Study designs involving psychedelic substances were shown to be afflicted by ineffective blinding for study participants, and expectancy effects were postulated to influence results (Aday et al., 2022, 2023). This critique represents an ongoing challenge for psychedelic research as the subjective effects associated with these substances are conspicuous, hindering attempts to minimize bias in both participants and researchers.

Additionally, sample sizes in these early trials remain small with low degrees of population diversity. This limits statistical power and currently reduces the generalizability of findings (Bogenschutz et al., 2022). Furthermore, the precise mechanisms of change are still not fully understood, presenting barriers to the predictive capacity of results and to the standardization of therapeutic interventions (Wheeler & Dyer, 2020). Consequently, while early

evidence remains promising, it is not yet possible to answer with confidence whether PAP reduces problematic drinking among individuals with a diagnosis of AUD. Given the ongoing exploration of PAP's mechanistic locus of therapeutic effect, the remaining discussion will summarize the prominent research findings regarding each of the relevant domains of inquiry.

Biological

Biological factors in the development of AUD were linked with current research investigating the neurological correlates proposed to be mechanistically significant variables in PAP. Highlighted were the linkages between serotonin 5HT_{2A} receptor stimulation mediated stress responses and the concepts of cognitive control and cognitive flexibility (de Veen et al., 2017; Meinhardt et al., 2021). This relationship has implications for AUD development risk, alcohol seeking behaviour, relapse, and motivation (de Veen et al., 2017; Meinhardt et al., 2021; Skewes & Gonzalez, 2013). Additionally, evidence for the role of glutamate receptor density was shown through several studies which linked reductions in mGluR2 with increased craving intensity (Meinhardt et al., 2020, 2021). These findings were paired with research which showed psilocybin's capacity to restore mGluR2 in the medial prefrontal cortex (mPFC) which has implications for reducing relapse like drinking among individuals in recovery (Meinhardt et al., 2021; Stillman & Sutcliff, 2022).

Further connections were made showing the impacts chronic alcohol consumption has on regions of the brain, including the prefrontal cortex (PFC), and the diminished capacity for cognitive control which consequentially arises (de Veen et al., 2017). Impairments to cognitive control were shown to impair emotional regulation, goal setting and task completion as well as reduce individual's control of distractor interference (de Veen et al., 2017; Wilcox et al., 2014). These neurological changes were shown to place individuals at greater risk of engaging in

destructive self-soothing habits and relapse drinking (de Veen et al., 2017). This evidence, when coupled with research showing the capacity of psilocybin to strongly modulate behavioural flexibility through 5HT_{2A} agonism imparts further credibility to the application of PAP in the treatment of AUD (de Veen et al., 2017; Doss et al., 2021).

Finally, psilocybin's capacity as a psychoplastogene, a compound capable of promoting induced plasticity in the brain, was explored. Several studies provided evidence for the neurogenetic potential of psilocybin by exhibiting rapid and sustained dendritic growth in the PFC (Ly et al., 2018; Shao et al., 2021). These findings are encouraging given the documented impacts of chronic alcohol consumption on PFC functioning (Senn et al., 2020; Stillman & Sutcliff, 2022). Reduced cognitive control and diminished executive functioning are potential consequences of synaptic density reductions in the PFC and are associated with impaired decision making and challenges with emotional regulation (Kirsch et al., 2022; Ly et al., 2018). Evidence of psilocybin's potential to promote neurogenesis was shown to further support PAP as a viable treatment for individuals with a diagnosis of AUD.

Spiritual

Definitions of spirituality vary, and the concept is difficult to quantify, which has led to a historical rejection of this aspect in the current therapeutic paradigm. However, recovery trajectories of individuals with AUD have been shown to be subject to significant influence by spiritual factors (Echevarría-Marrero et al., 2019; Snodgrass et al., 2023). Additionally, spiritual aspects have been present in both early and contemporary research into psychedelic compounds (Hall, 2022). Despite the inherent challenges in quantifying ethereal phenomena, spirituality was deemed too important to omit from this review. Therefore, in this study spirituality was conceptualized as a continuum extending from one end, characterized by the chronic

disconnection and dislocation of AUD, to another characterized by connection to self and to something greater.

Spirituality was seen to be a protective factor against problematic drinking in several studies (Echevarría-Marrero et al., 2019; Snodgrass et al., 2023). Additionally, the body of PAP research has, since its reemergence under Griffiths et al., (2011), emphasized the role of mystical and spiritual experiences as functionally influencing healing. Significant reductions in PHDD were associated with the presence of mystical experiences, as were changes in self-efficacy, self compassion and motivation for change (Bogenschutz et al., 2022; Rieser et al., 2021; Venugopal & Bedri, 2023). Despite the challenges associated with defining and quantifying mystical or spiritual phenomena, the research strongly supports the notion that PAP's capacity to produce these experiences represents vital potential in the treatment of this population.

Psychological

From a psychological perspective, a range of benefits were shown to be associated with PAP. Significant themes which emerged from research communicated the influential roles of outcome expectancies (OE), modulation of individual's commitment to change, self efficacy and the mediating role of connection on recovery trajectories (Coates, Gullo, Feeney, Young, Dingle, et al., 2018b; Nielson et al., 2018; Senn et al., 2020; Skewes & Gonzalez, 2013). Alterations in OE were communicated by participants as changes in beliefs about the positive impacts of alcohol consumption, as well as regarding the potential consequences associated with engaging in recovery behaviours (Bogenschutz et al., 2018; Nielson et al., 2018). These changes were shown to be related to increases in both self efficacy and motivation, with implications for commitment to change and engagement with difficult behaviour changes (Nielson et al., 2018;

Senn et al., 2020). These psychological changes were seen to be resilient and maintained through the final follow up at 36-weeks.

The pivotal role of self-efficacy was explored through several studies which emphasized the potential of PAP to influence individual's self-concept in profound ways. Contextualized through the lens of the TTM, both self-efficacy and motivation play key roles in supporting movement towards sustainable behaviour change (Del Rio Szupczynski & De Ávila, 2021). Evidence was given for the inverse relationship observed between measures of self-efficacy and relapse drinking (Stillman & Sutcliff, 2022; Yang & Kim, 2021). Additionally, self-efficacy was shown to be a powerful predictor of 3-year abstinence among participants. Improved self efficacy was associated with reductions in internalized shame and regret while also supporting more positive perceptions of self and greater motivation for change (Nielson et al., 2018; Skewes & Gonzalez, 2013; Stillman & Sutcliff, 2022).

Further support was provided supporting PAP as efficacious in the treatment of AUD through the observed reductions in self-criticism, rumination, resentment and self-blame among participants of a recent study (Agin-Liebes et al., 2023). Changes in these behaviours were associated with reductions in experiential avoidance, and important component of behaviour change and significant in the context of AUD treatment (Zeifman et al., 2023). Additionally, participants reported lower rates of depression and alcohol consumption and were more likely to engage in help seeking behaviours (Milan & Varescon, 2022). PAP was seen to play a facilitative role in the processing of shame and self-criticism and was associated with reduced measures of complex trauma symptoms (Healy et al., 2021). Consequently, research into the psychological mechanisms of action in PAP produced promising evidence for the efficacious use of psilocybin in a therapeutic context for the treatment of AUD.

Stigma

The purpose behind this research was two-fold. First, engage in an exploration of the burgeoning field of psychedelic studies as it pertains to an intractable problem. Secondly, address the nature of stigma as it relates to this issue with the intent of raising awareness around the deleterious impact social attitudes have on individuals with a diagnosis of AUD. Furthermore, the hope was to legitimize discussions of psychedelic medicines amongst practicing therapists to garner support for the integration of PAP with mainstream therapeutic perspectives such that barriers to access might be lowered. It is from this philosophical standpoint that the issue of stigma was assessed.

There is ample evidence which emphasize the detrimental impact stigma has on recovery trajectories of individuals with a diagnosis of AUD (Crozier et al., 2023; Kilian et al., 2021; Morris & Schomerus, 2023). Stigma perpetuates social isolation and disconnection and informs a collective bias towards individuals with AUD, and there is evidence this leads to a range of consequences that inhibit recovery behaviour changes (Finn et al., 2023; Morris & Schomerus, 2023). This attitude was shown to be based at least partially on historical biases which oversimplify the experience of AUD and pathologize individuals unnecessarily (Miller, 2013). Consequences of stigma are varied, but significant relationships were shown to exist between stigma and internalized shame, low self-worth and low self-efficacy (Crozier et al., 2023; Luoma et al., 2019). Additionally, experiences of stigma were seen to contribute to isolation and disconnection among individuals with AUD diagnoses. This has been shown to exacerbate depression, increase substance use, decrease motivation for recovery and lead to feelings of loneliness and despair (Milan & Varescon, 2022; Morris & Schomerus, 2023). Furthermore, evidence was provided which showed individuals that fear social stigmatization of their

condition delay seeking help and accrue additional physiological, psychological, and social damage (Finn et al., 2023; Morris & Schomerus, 2023).

Within the context of PAP, stigma presents a further barrier to accessing treatment and to the normalization of psychedelic medicines. Historical biases towards these substances remain from earlier decades when psychedelic compounds were negatively associated with counterculture movements and cult activities (Davis et al., 2022; Hall, 2022). Evidence from recent studies suggests participants were reticent or disinclined to share with close friends and family their involvement in PAP trials due to the fear of stigmatization (Nielson et al., 2018). This further barrier to access is additionally significant as PAP has been shown to alleviate many of the consequences of AUD stigmatization. The concepts of self-efficacy (Stillman & Sutcliff, 2022), motivation to change (Senn et al., 2020), outcome expectancies (Coates, Gullo, Feeney, Young, Dingle, et al., 2018b) and shame (Healy et al., 2021; Milan & Varescon, 2022) have all been shown to be mediated through PAP. That each of these aspects of experience are likewise negatively impacted by stigma, and stigma serves to prevent individuals from accessing treatment and in particular PAP, suggests the need for a more normalized discussion surrounding psychedelic medicines is necessary.

Recommendations for Practice

Become Informed Regarding the Legal Status of PAP

Currently, access to psychedelic therapies in Canada is significantly limited and highly regulated. Psilocybin remains a scheduled substance and there are few approved applications, none of which can be accessed directly by counsellors or psychologists at the present time (Health Canada, 2023). While exceptions can be made on a case by case basis through Canada's

Special Access Program (SAP), this avenue is currently only open to medical doctors and psychiatrists. (Health Canada, 2023). Requests are evaluated based upon need, and conventional treatments are required to have been deemed unsuccessful, unsuitable, or unavailable prior to receiving approval. Only then are the sale of psychedelics through authorized manufacturers exempt from Food and Drug Regulations (FDR) (Health Canada, 2023). However, there are currently several government sponsored clinical trials underway, including one investigating the mechanisms supporting PAP, but these are not scheduled for completion until 2027 (*Psilocybin Clinical Trials*, 2024). Additionally, a legal challenge seeking to obtain legal exemptions for 96 health care professionals to take psychedelics as part of a training program was dismissed, although an appeal is currently underway (Farrah, 2023). Consequently, the landscape of PAP legalization and legislation is currently in flux, and it will take time before regulations emerge from this process. Interested practitioners should therefore stay abreast of ongoing research and legal developments as this process continues to advance.

Explore Alternative Etiologies of AUD

A central premise of this work is that the dominant etiological paradigm addressing AUD falls short of meeting the needs of this population. While acknowledging the progress made under the biomedical model of addiction, unchanged prevalence rates and the retention of high relapse rates among individuals that have completed residential treatment speak to the current shortfall (Cornelius et al., 2003; CSUCHWG, 2023). Alternative etiologies exist, and evidence has been provided which speaks to the potential value in adopting a more holistic understanding of AUD etiology and treatment Pathways. While the BPSS-TTM meta theory has been explored, there are other models which currently have traction. Developing a familiarity AUD and the factors which contribute to it's presentation can prepare practitioners to more effectively meet the

needs of their clients and limit stigmatization of this vulnerable population (Echevarría-Marrero et al., 2019; Lacks & Lamson, 2018).

Understand the Current Landscape of Regulation and Licensing in Canada

In clinical trials, PAP is typically administered under the supervision of trained professionals and done according to predetermined protocols which assure the standardization of therapeutic delivery (Farrah, 2023). Outside of clinical trials, however, there currently is no consensus regarding the type or level of training, licensing or ethical requirements required for the delivery of PAP (Farrah, 2023; Rochester et al., 2022). Recent recommendations made by a collection of Canadian scholars propose the creation of a national advisory council and a credentialing board, as well as a code of ethics for facilitators and integration counsellors. However, these bodies have not yet been established (Farrah, 2023; Rochester et al., 2022).

While nationwide standards do not exist at this time, the Alberta government recently published regulations outlining a framework for the oversight and licensure of PAP providers. These established standards for prescribing, administering and dispensing psychedelic substances and have dictated care practices and requirements for monitoring patients undergoing PAP (Alberta Health, 2024). Given the current state of regulation and licensing in Canada, interested practitioners should maintain awareness of the developing regulatory and licensing standards in their jurisdiction of practice.

Seek Specialized Training in Psychedelic Assisted Therapy Programs

While the foundational skills associated with PAP are common across mental health practitioners, effectively and ethically engaging with psychedelic medicines requires special training. Despite the current legal landscape surrounding psychedelic substances, there are

training programs offered at established post-secondary institutions as well as through private organizations. A recent publication by a multidisciplinary team of Canadian academics outlined recommendations for the training of PAP providers in Canada (Rochester et al., 2022). These emphasized the importance of personal supervised experience with non-ordinary states of consciousness (NOSC), education regarding the psychological, pharmacological and psychiatric aspects of psychedelic substances, and first-hand experience with psychedelic-induced NOSC (Rochester et al., 2022). These suggestions were targeted at reducing the risk of adverse events, promoting patient safety and codifying standard treatment protocols through which PAP could be safely administered (Rochester et al., 2022).

Understand the Risks Associated with PAP

There are several risks associated with psychedelics that are relevant to understand for practitioners seeking to engage with PAP. For instance, recent research exploring the risks of negative responses following the use of psychedelics found an elevated risk factor for individuals who previously had received a personality disorder diagnosis (Marrocu et al., 2024). While the authors did not suggest individuals with this type of diagnosis be precluded entirely from psychedelic therapies, they do emphasize the increased importance of developing a good therapeutic relationship with individuals from this population (Marrocu et al., 2024).

Additionally, exclusion criteria for clinical trials involving psilocybin screen out individuals with a current or previously diagnosed psychotic disorder or an immediate family member with a diagnosed psychotic disorder. This also extends to individuals with histories of serious suicide attempts or mania and individuals who are pregnant, might become pregnant or are currently breastfeeding (Carhart-Harris et al., 2016). Given psilocybin's capacity to activate unresolved

psychological material and prompt strong emotional changes, ethical practice involving PAP should follow standards set by current clinical trials.

Recommendations for Future Research

Long-term Follow-up Studies

It has been noted that the current field of psychedelic research remains in its infancy, and while early results have been promising there are not yet long term studies to support the sustained efficacy of PAP in the treatment of AUD. Additionally, the long term safety has yet to be evaluated as recent research into psychedelics is largely limited to the past decade (Hall, 2022). The lack of long term follow up studies also limits understanding of potential delayed or rare side effects. Relevant possible benefits associated with these studies include evidence of treatment durability and identification of treatment response moderators. Results may then inform relapse prevention and support the maintenance of treatment gains (Cuzick, 2023)

Comparative Effectiveness Research

Current studies investigating PAP utilize small population sizes and have not integrated comparative effectiveness research (CER) criteria into study designs. A key aspect in establishing healthcare interventions as evidence-based, CER can help determine the relative efficacy of PAP against current gold-standard AUD treatments, such as cognitive behavioural therapy. As part of a destigmatizing process, studies which evaluate the relative utility of PAP against established therapeutic protocols would facilitate a normalization of these interventions within a mainstream discourse. Additionally, CER is useful in evaluating the performance of interventions in real-world settings and is an important step in the development of standardized delivery models. In

doing so, CER helps to disseminate clinical findings to relevant stakeholders and contributes to the progression of PAP development. (Chandra et al., 2011)

Health Economics and Policy Analysis

Providing PAP to a wider population requires an analysis of the economics of service delivery. As regulated PAP is not yet approved in Canada outside a narrow scope of medical practice, accurate estimates of service costs have not been established. Developing costing estimates requires empirical research, particularly in the context of the Canadian healthcare system where these services could conceivably be provided through public funding. These studies should provide information on the cost of delivering PAP, compared against existing costing data associated with AUD which could inform discussions around the net impact of providing PAP through public programs. Additionally, these studies should adjust cost against projected future savings associated with mitigating consequences of continued AUD (Marseille et al., 2022).

Furthermore, detailed cost-effectiveness analyses are necessary to calculate the potential value associated with treating AUD with PAP as compared to current treatment standards. Quantification of cost and health benefits associated with PAP will provide credibility to these interventions and serve to destigmatize their use in the treatment of AUD. Further research into the benefit associated with more effective treatment of AUD could explore the change in costs associated with reductions in alcohol related problems within the broader social context. These could include, but are not limited to, reductions in domestic violence, lowered incidence of alcohol related motor vehicle accidents, and reductions in alcohol related criminal justice costs (Marseille et al., 2022).

Conclusion

This work started with ambitions of communicating the value present in furthering the social discourse surrounding PAP as a treatment modality for populations with a diagnosis of AUD. The motivating hope which underlay the effort was to reach a point where deliverance of conclusive evidence supporting the efficacy of this novel treatment protocol was possible. However, despite the mix of personal bias and positive early evidence which support this notion, it's not possible to make broad claims speaking to these points. True, there is a growing interest in the field of PAP, and recent research has produced strong evidence for the advancement of clinical trials. Both quantitative and qualitative studies show profound changes in drinking behaviours through biological, psychological, social, and spiritual pathways. Additionally, federal investment in psychedelic research speaks to a changing social narrative surrounding these medicines and signals an awareness of the potential utility these therapeutics might hold. Against a historical backdrop of prohibition and criminalization, not to mention a ban on clinical research of psychedelic substances which lasted more than three decades, this feels like progress. While there remains a substantial distance to span between the promise of the current moment and the regulated and ethical delivery of PAP to populations of individuals with a diagnosis of AUD, a nascent evolution of consciousness may currently be underway.

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