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Master's Thesis

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Ketamine and Psilocybin: Novel Drug-Assisted Approaches to Addiction Treatment

A Literature Review of Psychedelic Treatment Frameworks

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Abstract

Psilocybin and ketamine, two hallucinogenic drugs already designated breakthrough therapy status for treatment-resistant depression, have both shown positive indications for substance use disorders (SUDs). However, opinions are split on whether antiaddictive outcomes can be attributed to pharmacological actions, psychological change, transformative experience, or all at once. This review aggregated findings from 17 clinical studies that used ketamine or psilocybin to treat SUDs (including alcohol dependence) and found all to fall within three broad therapeutic meta-frameworks: (a) low-to-moderate dose ketamine pharmacotherapy, (b) moderate-dose psychotherapeutic enhancement, and (c) high-dose psychedelic integration therapy. Both psilocybin and ketamine had been utilized to treat SUDs within the psychedelic integration framework, but only ketamine had been administered as a stand-alone pharmacotherapeutic infusion and as a combined treatment with motivational- or mindfulness-based psychotherapeutic enhancement. The clinical outcomes from each trial suggest that psychedelic integration therapy and psychotherapeutic enhancement models may potentiate the effects of psilocybin and ketamine to facilitate stronger and more sustained therapeutic response, with psychedelic integration therapy yielding impressive results in all five studies (three using ketamine, two psilocybin). “Mystical-type experiences” were found to likely mediate sustained abstinence in most studies by promoting a renewed sense of meaning, interconnectedness with the world, and abstinence self-efficacy, but reliable and direct quantitative evidence of mediation was generally lacking. Overall, current empirical data was found to be limited, especially for psilocybin. Nevertheless, the impressive preliminary finding warrants optimism and further research to investigate how ketamine- and psilocybin interact with personal dispositions, therapeutic settings, and psychotherapy.

Keywords: ketamine, psilocybin, addiction, substance use disorder, dependence

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Alcohol dependence and illicit substance use disorders (SUDs) are not only associated with immense mental suffering for those afflicted (Morley et al., 2015; Shmulewitz et al., 2015), but also significant strain on health services (Peacock et al., 2018) and negative impacts on the psychological well-being of loved ones (Orford et al., 2013). While alcohol abuse alone is estimated to be responsible for over 5% of the global disease burden (WHO, 2018) and 3.8% of global deaths (Rehm et al., 2009; Parry et al., 2011), mortality risk factors related to smoked tobacco is more than three times that of alcohol (Peacock et al., 2018).

Despite the need for effective interventions, few conventional addiction treatments have proven effective for most individuals (Grant et al., 2015). Pharmacological interventions can be used to make the drug of choice less enjoyable or help manage craving and withdrawal symptoms; however, none of these alternatives lead to reliable long-term abstinence (Blanco-Gancia & Rodriguez-Arias, 2018; Grant et al., 2015). Addiction-oriented psychotherapeutic- and behavioural treatments, such as motivation-enhancement therapy (MET) or mindfulness-relapse based prevention (MRBP), are popular options for alcohol dependence and other SUDs, but only a minority of participants in these treatment programs see long-term recovery (Grant et al., 2015).

In the 1950s and -60s, lysergic acid diethylamide (LSD) – a serotonergic psychedelic drug – was used extensively in psychiatric settings to treat alcoholism and other mental ailments (Nichols & Walter, 2021; Weston et al., 2020). For alcohol dependence, the "psychedelic-peak" treatment model became the predominant approach; administering high doses of LSD to facilitate "spiritual awakening", encounters with "death", self-insight, and transformational change (Fuentes et al., 2020; Pahnke, 1969). A meta-analysis of the few randomized controlled trials (RCT) published in this period indicates that high doses of LSD (200-800 µg) could significantly reduce alcohol misuse (Krebs & Johansen, 2012).

Unfortunately, despite being researched on a mass-scale at the time (Fuentes et al., 2020), the UN Convention of Drugs placed international restrictions on "classical psychedelics" (including LSD, psilocybin, and mescaline) in 1967, effectively halting the entire psychedelic research field for decades (Rucker et al., 2018). A regrettable consequence of this is that a great wealth of LSD-trials was conducted and published in an era before RCTs became the gold standard for clinical research (Nichols, 2016). Few control groups and other confounding variables makes it difficult to objectively compare anti-addictive indications from this era with the efficacy of modern addiction treatment protocols, hence the initial promise of psychedelic-assisted therapies fell into obscurity for many decades (Dyck, 2005).

In the same year psychedelics were classified as Schedule 1 drugs in the U.S. Controlled Substances Act (CSA) of 1970 – officially labelling them as highly addictive and dangerous substances with no recognized medical applications – ketamine, a dissociative-anaesthetic hallucinogen, was approved by the US Food and Drug Administration (FDA) as an anaesthetic drug, evading scheduling altogether (Mion, 2017). It was known that sub-anaesthetic doses of ketamine could produce psychedelic-like effects at sub-anaesthetic doses (Wolff & Winstock, 2006), but the contemporary stigma and restrictions on psychedelic drugs motivated a "dissociative-anaesthetic" term to describe psychoactive effects (Jelen & Stone, 2021). Although ketamine eventually became scheduled in the CSA in 1999, it was classified in the less restrictive Schedule III due to its preestablished anaesthetic utility (Liao et al., 2017).

Though initially approved only as an anaesthetic, ketamine was used off-label in sub-anaesthetic doses to treat psychiatric disorders throughout the 1970s ((Jelen & Stone, 2021; Khorramzadeh & Lotfy, 1973). During the 1990s, controlled trials in Russia demonstrated that ketamine-assisted psychotherapy (KAP) – administering a single high (sub-anaesthetic) dose of ketamine to promote a transcendental experience guided by concurrent motivational-

based therapy – could be used to effectively treat alcohol dependence (Krupitsky et al., 1992; Krupitsky & Grinenko, 1997). However, it was not until the turn of the century, when ketamine infusions for major depressive disorder (MDD) indicated it as an effective stand-alone antidepressant (Berman et al., 2000; Zarate et al., 2006), that ketamine was taken seriously as a pharmacotherapeutic alternative beyond anaesthesia. In 2019, following almost two decades of comprehensive clinical research (Bahji et al., 2021b; McIntyre et al., 2021), Spravato – an intranasal ketamine spray for treatment-resistant depression (TRD) – became the first FDA approved hallucinogenic treatment (S. Kim et al., 2020).

In parallel with the past few decades of ketamine research, psychedelic research has made a resurgence (Abbott et al., 2020; J.R. Kelly et al., 2019). Psilocybin – a psychedelic drug with LSD-like psychoactive effects – is spearheading the modern clinical research with psychedelics (Andersen et al., 2020; Luoma et al., 2020). Like ketamine, most clinical psilocybin-research has been directed towards depression, leading to psilocybin-assisted therapy (PAT) being designated as a "breakthrough therapy" for TRD in 2018 by the FDA, removing some of the hurdles that previously restricted research (Castro Santos & Gama Marques, 2021).

Preliminary evidence implicates both psilocybin and ketamine as prospective treatments for treatment-resistant OCD (Martinotti et al., 2021; Moreno et al., 2006) and anxiety conditions (Whittaker et al. 2021; Yu et al., 2021), yet it seems more likely that the next major target of ketamine- and psilocybin-based therapies will be addiction and SUDs, as evident by the current literature and planned trials listed on clinicaltrials.gov (Siegel et al., 2021; Walsh et al., 2022; Ziff et al., 2022).

Problem Statement

Addiction treatment programs are often unsuccessful at sustaining long-term recovery. Enthusiasts have touted psychedelic therapy as a revolutionary treatment for addiction

disorders but have until recently lacked reliable empirical data to back up such claims. In the past decade, more experimentally rigorous clinical trials for SUDs using psilocybin or ketamine have been published, showing positive trends for antiaddictive indications (Johnson & Griffiths, 2017; Walsh et al. 2022). However, results and therapeutic approaches vary greatly, and there appears to currently be no consensus regarding the most pragmatic or efficacious implementations.

To the best of the author's knowledge, no published research has yet compared the therapeutic methodologies and associated outcomes from the various forms of psilocybin- or ketamine-based clinical trials targeting addiction disorders. This thesis will therefore examine the eligible psilocybin- and ketamine studies to present an overview of the broad therapeutic frameworks guiding research and the unique therapeutic implementation utilized in each trial. Concomitant follow-up studies analysing therapeutic mediators in the clinical trials will be included in its own section to support a more evidence-based discussion regarding the validity of the various approaches. In summary, this thesis will address three key questions:

(1) How has psilocybin and ketamine been used as a therapeutic for addiction disorders?

(2) Does subjective experience mediate therapeutic response and long-term recovery?

(3) Does the available evidence favour some drug-assisted approaches over others for addiction treatment?

Thesis Demarcations

Despite efforts to include all ketamine- and psilocybin clinical trials relevant to addiction, this thesis is not written as a strict systematic review or meta-analysis. It is better conceptualized as a clinical literature review investigating how these drugs have been used therapeutically to treat addiction disorders. A synopsis of pharmacological drug characteristics will be included in the background section but the results and following discussion is written primarily from a psychotherapeutic/clinical perspective.

Ketamine and psilocybin were used as the basis for an analysis (as opposed to other psychedelics) as they are arguably the two most extensively researched hallucinogenic drugs in recent years, both showing therapeutic indications for addiction. Moreover, from a clinical standpoint, it is striking that two drugs targeting two distinct neurotransmitter systems and receptor complexes appear to overlap in their transdiagnostic applicability – particularly for conditions that have shown resistance to other treatments.

Personal Motivation

Drug addicts still experience daily discrimination and negative attitudes from the general population, even in "progressive" Scandinavian countries. While substance use disorders has become increasingly recognized as legitimate conditions worthy of professional help, illicit drug users still face judicial punishment and serious stigmatization for failing to control their addiction (Tønne & Lie, 2019). With drug-related overdoses in Norway at its highest in two decades (FHI, 2021) and proving a continual problem worldwide (WHO, 2018), it seems timely to seriously consider alternative solutions to addiction rehabilitation. Psychedelic therapy represents a substantial shift away from conventional options and shows a preliminary promise that warrants further examination.

Thesis Outline

Background. The many perspectives on addiction are compressed into two pertinent explanatory frameworks: (a) addiction as a set of neurobiological deviations and (b) addiction as a manifestation of disconnection from the world and a lack of meaning. These conceptualizations mirror the presented theoretical divide in ketamine- and psilocybin research. The background concludes with a summary of some general clinical considerations that inform all (or most) therapeutic applications.

Method. As a non-systematic review of clinical trials targeting addiction, the method section only briefly outlines the search strategy, concomitant search strings, data extraction process, and the rationale informing the presentation of the findings.

Results. Seventeen clinical trials for substance dependence were included in the review: seven strictly pharmacotherapeutic ones and 10 that include psychotherapeutic measures, presented in two separate tables. All 17 trials were classified into one of three therapeutic meta-frameworks, making up the three first main sections: Ketamine Pharmacotherapy, Psychotherapeutic Enhancement, and Psychedelic Integration Therapy. Therapeutic implementations and primary outcomes of each trial was presented individually in appropriate subsections. Finally, a fourth main section was included to summarize the mediating effect of subjective experience, particularly mystical-type experiences.

Discussion and Conclusion. This thesis set out to address three research problems as summarized in the problem statement. The first was covered in the results, but the second and third is addressed by the results, clinical interpretations, and future directions section. The overall impression is that psychotherapeutic implementations can significantly improve long-term addiction outcomes, but current evidence limits conclusions regarding the relative contribution of subjective effects and challenges the premise that high-dose psychedelic integration is superior to all versions of moderate-dose psychotherapeutic enhancement. Psilocybin-based evidence was particularly scarce, as only two trials have targeted SUDs.

Background

Ketamine and Psilocybin

Ketamine and psilocybin are traditionally designated into two separate classes of hallucinogenic drugs – dissociatives and psychedelics. Dissociative hallucinogens are described as such due to their ability to dissociate (or detach) the individual from the external reality or their internal sense of self (Nichols, 2004). The term psychedelic roughly translates to "mind-manifesting" (derived from Greek), alluding to their ability manifest unexplored thoughts, emotions, and alternative concepts of the self into immediate consciousness, sometimes transforming into a sense of personal transcendence (Nichols, 2016).

Despite being classified as two distinct types of hallucinogens, psilocybin and ketamine can occasion similar states of consciousness. For example, a high dose of psilocybin can produce distinctly dissociative effects, such as "the mind leaving the body" (Nichols, 2016). Likewise, ketamine trips can elicit a similar state of mind to psilocybin- or LSD trips (Bowdle et al., 1998; Schartner et al., 2017). Accordingly, ketamine's profound effects are often referred to as "psychedelic" by researchers (e.g., Morgan et al., 2017; Krupitsky & Grinenko, 1997) and will occasionally be referred to as such here as well.

Mechanism of Action

Ketamine – consisting of equal S- and R-ketamine enantiomer proportions (a racemic mixture) - operates primarily as an uncompetitive N-Methyld-D-Aspartate glutamate-receptor (NMDA-R) antagonist by attaching to the PCP binding sites of the NMDA receptor complex (Matveychuk et al., 2020). Antagonism of NMDA receptors by itself has an inhibitory effect on neurons (Gunduz-Bruce, 2009), but since the blockade temporarily elevates the amount of extracellular glutamate, a separate subset of glutamate receptors – the AMPA-receptors – will be activated by the available glutamate (Zunszain et al., 2013).

A higher ratio of AMPA-to-NMDA glutamate receptor expression, combined with ketamine-induced expression of the mTORC1 pathway (Workman et al., 2017) and elevated release of BDNF (brain-derived neurotrophic factor) activating the TrkB receptor pathway (Lin et al., 2021), results in acutely elevated neuroplasticity – a neurobiological milieu where the structural integrity and functional connectivity of the nervous system is more receptive to change and adaptation (Cramer et al., 2011). Beyond glutamate and neuroplasticity-related pathways, fluctuations in cortical monoamine activity have also been observed, including significant changes to the dopaminergic mesolimbocortical system (Kokkinou et al., 2017) and norepinephrine-mediated attention networks (Liebe et al., 2018).

In contrast to ketamine's antagonistic effects at the glutamate NMDA-R complex, psilocybin's active metabolite psilocin operates as an agonist on serotonin 2A receptors (5-HT_{2A}-R) as its primary mechanism of action (Passie et al., 2002). On the single cell/neuron level, 5-HT_{2A}-R stimulation depolarizes the cell, i.e., excites it and increases the firing rate (Araneda & Andrade, 1991). However, psilocybin activates functionally connected 5-HT_{2A}-$mGlu_{2/3}$ (metabotropic glutamate receptor 2/3) receptor complexes in a way that initiates a signalling cascade that is fundamentally different from other non-hallucinogenic 5-HT_{2A}-R agonists (Delille et al., 2012; Gonzalez-Maeso et al., 2007; K. Kim et al., 2020). Psilocybin-induced tachyphylaxis (acute drop in drug-response) has been suggested to occasion 5-HT_{2A}-R downregulation and concomitant compensatory upregulation of $mGlu_{2/3}$-receptors, increasing prefrontal glutamate release associated with improved cognition, reduced craving, and attenuated addiction pathology (Ziff et al., 2022).

Nutt & Carhart-Harris (2017) propose that the psychedelic activation of 5-HT_{2A} receptors – densely distributed in cortical glutamatergic pyramidal neurons of the neocortex (de Almeida & Mengod, 2007; Beliveau et al., 2016) – prompts an adaptive neurobiological stress response where the brain is primed to overcome adversity by neuroplasticity-mediated

processes. Indeed, psilocybin and other serotonergic psychedelics have been shown to rapidly upregulate prefrontal dendritogenesis (Shao et al., 2021), synaptogenesis (Raval et al., 2020), and hippocampal neurogenesis (Catlow et al., 2013). Functional and structural cortical changes induced by psychedelics appear to be mediated by Gq-coupled 5-HT_{2A}-R activation and TrkB-signalling facilitated by elevated BDNF and mTORC activity (de Vos et al., 2021; Ly et al., 2018). In summary, psilocybin- and ketamine induced neuroplasticity appear to be facilitated by a similar downstream signalling cascade, despite their distinct binding profiles at 5-HT2A- and NMDA-receptor targets respectively (Aleksandrova & Phillips, 2021; de Gregorio et al., 2020; Kadriu et al., 2020).

Effects on Brain Networks

The highly influential REBUS ("RElaxed Beliefs Under pSychedelics") and anarchic brain model (Carhart-Harris & Friston, 2019) posits that the overarching "meta-function" of psychedelic 5-HT_{2A} agonists (e.g., psilocybin) is to: (a) attenuate the controlling influence of the hierarchical top-down prediction networks substantiating pre-determined perceptions of the world and oneself (*priors* – roughly analogous to schematic knowledge); (b) increase cortical anarchy or neural "entropy". By compromising the influence of well-established perceptual filters, psychedelics enable a less restricted flow of bottom-up information to be projected via alternative cortical pathways. Carhart-Harris & Friston (2019) compares psychedelic action in the brain to metallurgic annealing, where psychedelic-induced system "heating" (increased neural entropy) transiently makes the brain more malleable to change before a subsequent "cooling" process stabilizes any incurred changes to the neuropsychological system. From a psychological standpoint, this implies that psychedelic-induced revision of high-level schematic-knowledge and acute recontextualization of one's self-schema could (theoretically) lead to enduring changes in self-perceptions, sense of meaning, and beliefs about the world.

The core hypothesis of the REBUS model, namely that the control and integrity of functionally connected "high-level brain networks" is weakened in response to psychedelics, is supported by numerous fMRI-studies (Barnett et al., 2020; Petri et al., 2014; Lord et al., 2019). This disinhibition may facilitate connectivity between functionally separated networks and allow for spontaneous novel activity to unfold. Indeed, blood plasma psilocin levels (a measure of psilocybin uptake) has been shown to be associated with higher *between*-network resting-state functional connectivity (RSFC), and lower *within*-network RSFC, in multiple high-level networks associated with directed attention, executive control, and self-related cognition (Madsen et al., 2021). Stated clearly: psilocybin diminished the influence of high-level perceptual filters and increased communication between separated brain networks.

Although the REBUS model primarily applies to serotonergic psychedelics, fMRI studies indicate comparable influence by ketamine on high-level brain networks, showing the same pattern of decreased connectivity (or "integrity") within the network and increased connectivity with other brain networks (Abdallah et al., 2020; W. Li et al., 2018). With ketamine-induced network flexibility and comparable neuroplasticity-mediated effects (Aleksandrova & Phillips, 2021), it seems reasonable to assume that the REBUS model can serve as an approximated model for the psychopharmacological states occasioned by both psilocybin and ketamine – at least as a pragmatic point of reference to contextualize psychological effects and altered consciousness.

Effects on Consciousness

Psychedelics' ability to increase neural entropy has been posited to also expand the dynamic range of possible consciousness states (Carhart-Harris, 2018; Carhart-Harris et al., 2014). Subanaesthetic doses of ketamine is also associated with a richer repertoire of brain states, contrasted by anaesthetic doses occasioning limited brain states and reduced consciousness (D. Li et al., 2022). In clinical ketamine research, many patients have described

interactions with a dimension or reality that was “more real” than everyday life (Krupitsky & Grinenko, 1997), representing a sort of “hyper-consciousness”. The same concept is a recurrent theme in psilocybin trips as well, with many reporting “seeing reality for what it really is” (Cole-Turner, 2021, Richards, 2008).

Perceptual alterations tend to be experienced as secondary when accompanied by ineffable “mystical-type” experiences, such as separation from the body, feelings of dying (ego dissolution or ego transcendence), meeting God or “a higher power”, and/or experiencing an overwhelming sense of unity with everything (Griffiths et al., 2019; James et al., 2020; Roseman et al., 2018; Vlisides et al., 2018). These types of experiences have historically been linked to the classical psychedelic drugs (e.g., LSD and psilocybin), but clinical trials show that ketamine can elicit the same type of transcendent phenomena in sub-anaesthetic therapeutic doses (Dakwar et al., 2014; Ezquerra-Romano et al., 2018; Rothberg et al., 2020).

Subjective effects will be uniquely manifested into the consciousness of the individual, corresponding to their specific personality, values, mindset, and life experiences (Krupitsky & Grinenko, 1997; Lutkajtis, 2021). For example, a recurring theme in psilocybin-induced mystical-type experience is the concept of “connectedness” (Breeksema et al., 2020). Feelings of connectedness can spur from psychedelic content related to specific personal experience, such as the warm “presence” of a lost father (Bogenschutz et al., 2018) or a therapeutic dialogue with the hallucinatory image of a deceased mother (Podrebarac et al., 2021). Others can feel an increased sense of connection by experiencing an unspecified but omnipresent connection to all beings or the world at large (Roseman et al., 2018). Stanislav Grof, one of the great psychedelic therapy pioneers, conceptualized psychedelics as “non-specific amplifiers of the unconscious” (Grof, 1976), capturing the essence of the individualized experiences they occasion.

Addiction

Moralistic conceptions of addiction as a failure of character have gradually been replaced by increased recognition of a psychological condition worthy of care and professional treatment. In accordance with increased legitimacy, multiple addiction treatment programs have been designed to tackle the issue, but very few can document effective long-term abstinence for most addicts (J.F. Kelly & Mee-Lee, 2019), leaving a vulnerable population in dire need of other alternatives.

Addiction manifests as a symptomatology consisting of strong cravings, risky use, drug/behaviour cue-sensitization, withdrawal symptoms (usually psychological), impaired response inhibition and control, and interpersonal impairment (Jones et al., 2018). Addiction is, however, not the normative response for any reinforcing behaviour – drug related or not. Why is it that only some individuals develop addiction, while others never become dependent on the same rewarding/reinforcing activity?

Liking, Wanting, Needing

When a person develops a SUD, the trajectory from liking to dependence tends to follow a predictable path (Berridge & Robinson., 2016): (1) intense "liking" of the drug causes more frequent and risky use; (2) the dopaminergic reward circuitry is primed to more readily fire when exposed to drug-cues, increasing subjective "wanting" and "craving"; (3) abstinence causes withdrawal, prompting immense discomfort that can only be alleviated by the drug; (4) withdrawal discomfort and drug-associated attentional narrowing promotes a cycle of strong craving and relapses that can feel hopeless to the person trying to recover from their addiction; (5) continued drug use reinforces an automatic cue-use response, making it more and more difficult to consciously break the cycle.

The gradual shift from positive reinforcement and dysregulated impulse control towards more compulsive tendencies motivated by negative reinforcement (i.e., experiencing

relief from discomfort, anxiety, and stress when taking the drug) can be explained relatively well by the proposed trajectory (Berridge & Robinson, 2016), but the necessary context facilitating this transition is still missing. The following section addresses different perspectives on addiction.

Theoretical Perspectives

In accordance with the diathesis-stress model, addiction can be conceptualized as a stress- or trauma induced psychological condition evolving from a set of innate predispositions making certain individuals vulnerable to an addiction problem (Vink, 2016). Genetic studies indicate that individuals with family members diagnosed with alcohol dependence or other SUDs often are more vulnerable to developing an addiction themselves (Hicks et al., 2012). Chronic stress or traumatic experiences can also significantly increase the risk of developing addiction disorders, but primarily for those who have an inherited biological vulnerability (Sinha, 2008; Vink, 2016).

For the scope and purpose of this thesis, an extensive analysis of the theoretical perspectives on addiction was deemed excessive. However, as the purported therapeutic- and antiaddictive mechanisms of psychedelics (including ketamine) often are emphasized as either neurobiological (Aleksandrova & Phillips, 2021) or existential (Moreton et al., 2019), or somewhere in-between (Carhart-Harris et al., 2018; Kolp et al., 2014), their corresponding perspectives for addiction will be expanded on in the following subsections.

The Neurobiological Perspective. Koob and Volkow (2009) propose that the actions of three specific neural circuits can be linked to the "addiction cycle", corresponding to binging, withdrawal, and craving (attentional narrowing). They propose that dysregulated activation of the dopaminergic mesolimbic circuitry (including the nucleus accumbens) facilitates binging behaviour. The so-called "dopamine theory of addiction" prescribes paramount importance to this reward network as an enabler of addictive behaviour (Nutt et

al., 2015). Koob & Volkow (2009) extends the presupposition of the mesolimbic dopamine theory, suggesting that abnormal activity in an arousal-stress network – centred around the extended amygdala – causes the negative emotional states associated with withdrawal, and that a glutamatergic craving/preoccupation network – consisting of functionally connected hubs in the medial PFC and ventral striatum – occasions the anticipatory state of constant craving.

The dopamine theory implies that individuals who are predisposed to dependence release more striatal (nucleus accumbens) dopamine than typical when exposed to their favourite drug (Nutt et al., 2015). While there is legitimate reason to believe that craving intensity is related to mesolimbic dopamine pathways, the association between striatal dopamine and addiction is first and foremost linked to stimulants (Nutt et al., 2015). For a depressant like alcohol, even though striatal dopamine has been implicated (Boileau et al., 2003), reactivity and function of GABA- and glutamate receptors are more reliable indicators of dependence vulnerability (Joffe et al., 2018; Prisciandaro et al., 2018). Antagonism of mu-opioid receptors (e.g., naltrexone) reduce alcohol liking (Carmen et al., 2004), suggesting that the opioidergic system is also involved in alcohol's reinforcing capabilities. In other words, the dopaminergic mesolimbic circuitry alone is insufficient to explain all indulgent addiction behaviour. Other disorder-specific neurobiological markers are comprehensively discussed in state-of-the-art reviews but will not be presented here (see Bahji et al., 2021a for more).

The Humanistic-Existential Perspective. Addiction can be motivated by escapism from a painful and meaningless reality, characterized by loneliness and lack of connectedness to other people (Wiklund, 2008). Viktor Frankl (1979) viewed addiction as a manifestation of lack of purpose and direction in life – a condition where the search for meaning becomes obscured by the attentional narrowing towards immediate gratification. He described addiction as an "existential neurosis", where genuine recovery necessitates a fundamental

shift in perspective and an acquired or rediscovered sense of meaning (Frankl, 1979). This view presents a significant shift away from many clinical perspectives, framing addiction as a human response to inhumane conditions rather than as a collection of psychopathological symptoms.

The search for a greater meaning and spirituality has been implemented in several addiction rehabilitation programs. Bill Wilson – the founder of Alcoholics Anonymous (AA) – was convinced that the connection to God and spiritual insight he experienced on two separate occasions, from belladonna- (a deliriant hallucinogen) and LSD therapy respectively, was crucial to his own recovery from alcoholism and consequently informed the philosophy of the 12-step program (Morgan et al., 2017; Yaden et al., 2021). Unlike Wilson himself, AA currently advises against psychoactive drug interventions as part of the recovery (Frank, 2011), but their rehabilitation programs still emphasize the importance of a spiritual awakening. A review of empirical of findings from the 12-step program found therapeutic response to be linked to increased spirituality and religiosity, specifically for those who experienced a greater sense of meaning either through serving as an AA sponsor and/or by feeling connected to God or another higher power – a "universal spirit" (Dermatis & Galanter, 2015).

Treatment Prognosis

Though somewhat contingent on the specific addiction disorder, most conventional treatments consist of medical management of withdrawal/craving/relapse or behavioural therapies that help patients to change their attitudes/behaviour/unhealthy habits (NIDA, 2020). Drug rehabilitation programs may advertise treatment effectiveness for most of their patients, but as therapeutic efficacy can be operationalized as multiple outcomes beyond attenuated use – such as improved personal/social function and reduced negative impact on

public health and safety (McLellan et al., 1996) – these claims will tend to be overstated and ambiguous.

It is difficult to accurately assess how many patients see long-term recovery from conventional treatments, but sustained abstinence after a typical treatment trajectory is not the norm. For example, many alcohol-dependent patients do not show therapeutic response to conventional pharmacological- or behavioural interventions at all (Grant et al., 2015) and in the landmark COMBINE-study, more than two thirds of patients receiving both types of interventions ended up relapsing within the first year (Anton et al., 2006).

Clinical Considerations

The Therapeutic Context

"Set" and "setting" has been recognized as important determinants of the valence, content, and trajectory of psychedelic experiences since the first era of LSD-research (Pahnke, 1969). Set (or "mindset") refers to the psychological dispositions the user possesses at the time of administration. Setting describes all external- and contextual factors that may influence the set (Carhart-Harris et al., 2018). For example, taking magic mushrooms (containing psilocybin) in nature with friends will tend to instil a different mindset – and hence psychedelic experience – than a similar dose consumed in solitude in a dark room. Likewise, a setting where the user feels safe enough to be vulnerable and explore psychological turmoil can facilitate the right set to resolve inner conflicts (Gorman et al., 2021).

PAT has largely emphasized psychotherapeutic support and contextual considerations as foundations of effective therapy (Ziff et al., 2022); not just as additive elements, but as synergistic parts of a holistic treatment model (Carhart-Harris et al., 2018). Modern clinical PAT trials (i.e., since 2006) have consistently opted for a classic "psychedelic-peak therapy"

approach, administering few high-dose, non-directive, psychedelic sessions with psychological support (van Amsterdam & van den Brink, 2022). Non-directive implies minimal patient-therapist interaction during the psychedelic experience, providing only psychological support when necessary (Gorman et al., 2021). The intention is to facilitate the transcendental- or mystical-type experiences that can nurture a meaningful change in perspective and valuable insights (Griffiths et al., 2006, 2008, 2011) or increased self-acceptance and sense of purpose (Watts et al., 2017; Watts & Luoma, 2020).

A primary objective of the "psychedelic therapist" is to provide a competent, secure, and empathetic presence that can help nurture trust and a therapeutic alliance before, during, and after a dosing session (Phelps, 2017; Tai et al., 2021). During preparation, the therapist initiates alliance building by listening to patients' life stories and providing continuous psychological support, thus priming a therapeutic set for positive change (Greenway et al., 2020). For the psychedelic sessions themselves, the quiet (non-directive) presence of allied therapists while placed in a comfortable chair/bed in an aesthetically pleasing room – often accompanied by contemplative music playing through speakers or headphones – encourages patients to safely navigate through difficult thoughts and emotions without distracting themselves with external engagement (Gorman et al., 2021). The experience can be profoundly meaningful, but sometimes also intensely distressing and confusing (Gashi et al., 2021; Johnstad, 2021; Mason et al., 2020). Helping patients understand the experience and further integrate newfound insight into their self-narrative and self-concept is therefore considered an essential part of the PAT process (Greenway et al., 2020).

Unlike PAT, ketamine therapy has often been administered as a pseudo-pharmacotherapeutic treatment, considering the drug itself as the primary – or only – instigator of recovery (Walsh et al., 2022). While this method can provide rapid, transient, relief from depression at moderate doses, there is little evidence that it sustains reliable long-

term improvement (W. Li et al., 2022). Adjunct psychotherapy, e.g., CBT (Wilkinson et al., 2017), can extend and possibly potentiate the mood-elevating effect of ketamine; however, whether it does so significantly better than psychotherapy combined with conventional antidepressants is not well-established. Some argue that ketamine treatment may yield better long-term outcomes if administered as a facilitative tool for peak-experiences and transformative change (Dore et al., 2019; Kolp et al., 2006, 2014).

Ketamine treatment based on psychedelic-peak therapy models – KAP – follow many of the same therapeutic principles as PAT but have simultaneously opted for a more directive communicative approach during dosing sessions in SUD trials to explicitly guide participants' transcendental experience towards previously declared motivations to live a better life in abstinence (Krupitsky et al., 2002; Krupitsky & Grinenko, 1997). Some have argued that directive therapy during high-dose sessions could disrupt intrapsychological exploration, but the comparative evidence is lacking to suggest that any *specific* psychedelic-therapeutic technique is superior to other implementations (Neuhaus & Slavich, 2022).

Dosing

Routes of Administration. While psilocybin has been administered orally (P.O.: per os) in all modern clinical trials (Garcia-Romeu et al., 2021), ketamine has been administered intramuscularly (IM; Krupitsky et al., 2007), intravenously (IV; Dakwar et al., 2020), intranasally (Lapidus et al., 2014), subcutaneously (Cavenaghi et al., 2021), and sublingually (Dore et al., 2019), and P.O. (Rosenblat et al., 2019).

The IV route is ideal to maximize drug bioavailability but may also induce some discomfort in patients and require more practical resources than other options (Walsh et al., 2022). The IM route is often used as a longer-lasting alternative, but lower bioavailability necessitates ~50% higher doses for comparable effect (Grabski et al., 2022).

Systematic reviews indicate that all (or most) administration routes can produce rapid and transient antidepressant effects (Chilikuri et al., 2014; Cavenaghi et al., 2021; Rosenblat et al., 2019); but similar comparisons are missing for addiction studies. In SUD trials, the IV route has been used for moderate ketamine dosing (0.50-0.71 mg/kg) and the IM route has been used for "transformative doses" (2.0-3.0 mg/kg) to extend the psychedelic experience (Dakwar et al., 2019, 2020; Krupitsky et al., 1992, 2007).

Effective Dose. The effective dose depends on what the drug is supposed to achieve. For example, some believe that ketamine's therapeutic potential lies in its ability to increase neuroplasticity (Aleksandrova & Phillips, 2021) and/or facilitate trust and therapeutic alliance with a psychotherapist (Kolp et al., 2014). In this case, the latter would be heavily moderated by lucid communication with the therapist, thus a low 25-50 mg IM injection could achieve the desired effect (Kolp et al., 2014). In contrast, for those convinced of the mediating effect of mystical-type experiences, a significantly higher dose (150-200 mg IM) may be required to achieve the therapeutic effect (Ezquerra-Romano et al., 2018). High, fully psychedelic doses (> 0.20 mg/kg) have consistently been used in psilocybin trials as the therapeutic dose (Garcia-Romeu et al., 2021). Dose-response reviews imply that psilocybin-induced challenging experiences are not much more prevalent with higher doses – though current data is limited (Hirschfeld & Schmidt, 2021)

For ketamine, IV doses below 0.3 mg/kg, and IM doses below 0.5 mg/kg, tend to not induce altered states of consciousness beyond the effects of an active placebo (Fava et al., 2018; Lofwall et al., 2006). Some findings indicate 0.5 mg/kg IV injections as efficacious antidepressant doses, and possibly even superior to 1.0 mg/kg (Fava et al., 2018). However, acquired cross-tolerance from excessive drug use can necessitate higher than normal doses to achieve therapeutic response. For example, 0.8 mg/kg IV or 1.2 mg/kg IM ketamine may be the lowest effective dose for most alcohol dependent patients (Grabski et al., 2022). Likewise,

based on varied (psychedelic) response to relatively high doses of psilocybin (0.30 – 0.40 mg/kg, P.O.) in an alcohol dependence pilot study (Bogenschutz et al., 2015), the researchers have increased the dose range to 0.36-0.57 mg/kg for the ongoing follow-up phase II clinical trial (clinicaltrials.gov identifier: NCT02061293). While cross-tolerance may also be an issue with other substances, alcohol's broad effect on the GABA- and glutamate systems may dull the effects of ketamine (a glutamatergic NMDA-R antagonist) in particular (Vengeliene et al., 2008).

Adverse Effects

As an anaesthetic, ketamine requires special considerations. Green et al. (2021) strongly argues against the nonmedical use of ketamine, due to complicated dosing procedures, broad pharmacodynamic effects, as well as being potentially fatal when not used correctly. About half of all observed ketamine patients demonstrate transient elevations in blood pressure, but rarely serious enough to warrant infusion termination (Riva-Posse et al., 2018). Risk of physical harm with psilocybin is virtually non-existent (Johnson et al., 2018), though regular use could hypothetically lead to cardiovascular complications due to increased activation of 5-HT_{2B} receptors regulating the structure and function of the heart valves (Elangbam et al., 2008; Kuypers et al., 2019). More common side effects of psilocybin include nausea and small changes in heart frequency and arterial blood pressure (Passie et al., 2002).

Hallucinogen persisting perception disorder (HPPD) – including flashbacks or perceptual distortions that persist after the psychoactive effects of the drug have worn of – is occasionally reported as a side effect of hallucinogen use, but primarily from serotonergic psychedelics (Litjens et al., 2014). The HPPD phenomenon tend to manifest itself as optical illusions, such as visual tracers or colour abnormalities, but sometimes also as more lucid flashbacks (Vis et al., 2021). A recent review of controlled psilocybin- and LSD trials

enrolling healthy subjects, showed that almost 10% of all participants (13/142) experienced some form of mild perceptual distortions consistent with HPPD; however, none of the cases met DSM-V criteria for a HPPD-diagnosis, partially because the transient phenomena were short-lived and perceived as either neutral or interesting/pleasant – not distressing (Müller et al., 2022).

In the ketamine literature, some consider the mind-altering manifestations themselves as unwanted side-effects or "adverse events" that may compromise or complicate therapeutic outcomes (Katalinic et al., 2013). However, a comprehensive systematic review assessing 83 clinical ketamine trials, reported that only two patients in total – a single participant from two separate studies - dropped out of their respective studies due to ketamine's mind-altering effects (Walsh et al., 2022). Likewise, controlled psilocybin administration has been shown to be highly tolerability and no serious adverse events have, thus far, been attributed to psilocybin in clinical trials (Bender & Hellerstein, 2022; Roscoe & Lozy, 2022; van Amsterdam & van Den Brink, 2022). However, both ketamine- and psilocybin trials exclude participants at risk for mania (e.g., bipolar disorder) or psychosis (e.g., familial schizophrenia risk), and are otherwise very specific with who they include for their studies (Gard et al., 2021; Grabski et al., 2022). The relative safety and tolerability of these drugs can therefore not yet be generalized beyond the specific clinical setting that they have been administered in. Moreover, as a general safety precaution, patients with serious cardiovascular conditions are typically excluded from trials with psilocybin and ketamine, even though serious cardiovascular events are exceedingly rare (Riva-Posse et al., 2018).

Challenging psychedelic experiences are relatively common with higher psilocybin doses (Griffiths et al., 2011). However, they are generally not labelled adverse reactions in the PAT paradigm, and sometimes reattributed as manifestations of direct confrontation with the inner conflict at the core of their suffering (Barrett et al., 2016). These experiences can then

instead accommodate key turning points in the healing process (Belser et al., 2017; Gashi et al., 2021). In some KAP research, challenging psychedelic experiences have even been explicitly provoked: Krupitsky et al. (1992) injected alcohol dependent patients with an anxiogenic substance prior to a high-dose ketamine infusion, intended to intensify a negative emotional state that can be associated with alcohol via aversive conditioning. Nevertheless, in cases where the patient is not able to stop resisting the challenging experience, distress and fear may spiral out of control, possibly limiting the therapeutic benefits.

Abuse Potential

Following the controversial placement of classical psychedelics in 'Schedule I' (Belouin & Henningfield, 2018), psilocybin was officially labelled as: (a) highly addictive; (b) not accepted as medicine; (c) not safe to consume in any situation (Johnson et al., 2018). Ketamine on the other hand – due to its approval as an anaesthetic – did not become scheduled before 1999, and was then only classified as a Schedule III drug, indicating that ketamine: (a) is less likely to be abused than drugs in Schedule I and II; (b) currently has accepted medical applications; (c) may lead to only low or moderate physical dependency, or high psychological dependence, when abused (Mathai & Mathew, 2017).

These classifications suggest that ketamine has a lower potential for abuse and physical dependence than psilocybin. While neither rank among the most addictive illicit substances (Nutt et al., 2010), low abuse potential is most clearly indicated for psilocybin (Liu et al., 2016; Johnson et al., 2018). A smoker compared the addictive nature of cigarettes and psilocybin as follows: "*... There is no comparison. One is addiction – the other is, um, psilocybin ... an inner journey"* (Noorani et al., 2018). Clinically significant hallucinogen dependence is rare, but typically linked to dissociatives (e.g., ketamine) or MDMA when diagnosed (Liu et al., 2016; Wu et al., 2008).

When treating a patient group with addictive tendencies as the primary indicator, special safety measures might be necessary before administering a drug that could be abused. Clinical administration of ketamine has not yet been linked to acquired ketamine dependency, but long-term data is still lacking (Walsh et al., 2022). Ketamine's abuse potential is, as with other rewarding/reinforcing drugs, determined by the pattern of use (Rhodes et al., 2003). Regular administration would be particularly concerning, as increased frequency of drug self-administration elevates the risk of developing dependency and addiction (Allain et al., 2015). In contrast, the occasional administration used in clinical settings is very unlikely to cause addiction – even in predisposed individuals (Allain et al., 2015; Rhodes et al., 2003).

In summary, despite the risk of challenging experiences and an acute negative emotional state, the safety characteristics and tolerability profile of both ketamine and psilocybin – when administered in a controlled setting – demonstrates two hallucinogenic drugs that are highly unlikely to impose long-term negative consequences in addicted individuals or other patient groups. However, when taken in less controlled settings, ketamine may have some abuse potential and increased risk of serious physiological harm, and the risk of psychological distress increases for both psilocybin and ketamine.

Method

Search Strategy

To get an initial overview of the psilocybin- and ketamine-related addiction literature, a scoping search was conducted via the Web of Science, Scopus, and APA PsycInfo databases, screening abstracts of all recent addiction reviews (systematic or not) containing either ketamine or psilocybin in the title. The following search string was used: ("psilocybin" OR "ketamine") AND ("addiction" OR "substance use disorder" OR "dependence" OR "abuse"). The most recent systematic reviews (published since 2020) were copiously analysed, with the purpose of identifying relevant follow-up studies from clinical SUD trials

assisted by ketamine or psilocybin. Relevant primary sources, specifically clinical trials and follow-ups, were identified via a snowballing/citation tracking process, prioritising sources pertaining to addiction and therapeutic use.

To identify additional clinical trials, studies analysing the mediating effects of subjective experience, and other papers of interest not already extracted from the systematic reviews, a basic “ketamine” OR “psilocybin” search string was utilized in a tripartite search strategy: (1) as the input in PubMed’s medical subject heading (MeSH) database, applying the “therapeutic use” subheading and a subsequent filter for clinical trials (no filter for publication year); (2) as the input in Scopus, APA PsycInfo, and Web of Science databases, screening all articles and reviews published since the 2017 with “psilocybin” or “ketamine” as the topic or present in the title/abstract; (3) as unfiltered input in Google Scholar to identify all new clinical trials/papers published since 2021 yet to be included in even the most recent reviews. This search strategy amalgamated in thousands of hits, but a significant portion of titles were quickly identified as irrelevant, thus negating the need to screen all abstracts. Though somewhat tedious, this method conserves the advantage of identifying relevant papers that would have been filtered out in a narrower search, especially studies that follow-up on the clinical trials. As a final step, the “related article” functionality in Google Scholar was used for each identified clinical trial to find research associated with the same sample and study team.

Data Extraction

Essential data extracted from the clinical reviews included: (1) empirical data indicating anti-addictive properties; (2) references to clinical trials conducted with ketamine or psilocybin for substance use disorders; (3) experiential mediators of transdiagnostic therapeutic response, (4) the therapeutic principles guiding PAT and the many forms of KT.

The most important information extracted from the clinical trials pertained to the therapeutic approaches, addiction-related clinical outcomes, and therapeutic mediators (only some trials include a mediation analysis in the primary study). The psychotherapeutic methodology of each trial was extensively analysed and extracted as seen fit.

Presentation

First, the therapeutic methodologies used in each trial and their associated outcomes is presented. Ketamine- and psilocybin trials for SUDs are still in a highly experimental phase with many different therapeutic approaches; hence, all the unique implementations were classified into three broad meta-frameworks: (a) ketamine psychotherapy; (b) psychotherapeutic enhancement; (c) psychedelic-integration therapy. The clinical outcomes from each trial is presented in subsections of each meta-framework, where the specific methodologies are also described. The final pre-discussion section presents quantitative and qualitative evidence of experiential mediators influencing therapeutic response. The discussion itself synthesizes all findings and interprets how the various therapeutic implementations may relate to the experiential mediators and subsequent clinical outcomes.

Results

Seventeen eligible SUD trials were identified and included in the review. Seven of the studies are pharmacotherapeutically oriented, all using ketamine infusions as the active treatment (Table 1). Five studies use a therapeutic approach consistent with psychedelic-peak therapy (“Psychedelic Integration Therapy”): two PAT trials and three KAP trials (Table 2). The five remaining trials describe ketamine-adjunct psychotherapy that fall somewhere in-between pharmacotherapeutic infusions and psychedelic integration therapy, summarized in the first half of Table 2 and the “Psychotherapeutic Enhancement” section. Eight trials treat alcohol-related problems, four opiate-dependence, three cocaine-dependence, and two solitary studies target nicotine- and cannabis dependence (Table 1, 2).

Table 1

Pharmacotherapeutic Trials

Studies: Design	Participants	Active Dosing[a]	Therapeutic Method	Outcome Summary[b]
Dakwar et al. (2014): Crossover	8 cocaine-dependent, non-treatment seeking, participants	IV ketamine x2 (0.41-0.71 mg/kg/52 min)	Infusions only	Ketamine increased spontaneous motivation to quit and reduced cue-induced craving and use.
Dakwar et al. (2016): Crossover	20 cocaine-dependent, non-treatment seeking, participants	IV ketamine (0.71 mg/kg/52 min)	Infusions only	Ketamine reduced cocaine craving and use for up to three days post-infusion but not after six days.
Das et al. (2019): RCT	90 undiagnosed problematic drinkers	IV ketamine (dose N.A.)[c]	Infusion paired with retrieval of MRM	Ketamine disrupted reconsolidation of MRM, decreasing craving and drinking behaviour.
Jovaisa et al. (2006): RCT	58 opiate-dependent patients with severe withdrawal syndrome	IV ketamine (0.5 mg/kg/60 min)	Infusion prior to acute opiate antagonist detoxification under general anaesthesia	Ketamine reduced acute physiological withdrawal symptoms during opiate detoxification.
Wong et al. (2014): RR	23 alcohol-dependent patients with severe withdrawal syndrome	IV ketamine (0.20 mg/kg/60 min)	Supplement to withdrawal management with BZDs	Ketamine led to insignificant reductions in BZD requirements.
Pizon et al. (2018): RR	63 alcohol-dependent patients with severe withdrawal syndrome	IV ketamine (0.15-0.30 mg/kg/60 min)	Supplement to withdrawal management with BZDs	Ketamine led to fewer days spent in withdrawal care and lower likelihood of intubation than BZD-treatment alone.
Shah et al. (2018): RR	30 alcohol-dependent patients with severe withdrawal syndrome	IV ketamine (0.75-1.60 mg/kg/60 min)	Alternative treatment for patients showing BZD-resistance	Ketamine led to significant symptom relief and lower BZD requirements.

Note. RCT: Randomized Controlled/Clinical Trial; RR: Retrospective Review; IV: Intravenous route of administration; N.A.: Not Available; MRM: Maladaptive Reward Memory; BZD: Benzodiazepine (anxiolytic drug used for alcohol withdrawal).

[a] The (inactive or active) placebo conditions in all included trials (Table 1 and 2) are described in their associated text section.

[b] Exact outcomes and concomitant statistical data is thoroughly presented in the main text sections.

[c] The only provided information states that ketamine and placebo concentrations were maintained at 350 ng/ml for 30 min.

Table 2

Extrapharmacological and Psychotherapeutic Trials

Studies: Design	Participants	Active Dosing	Therapeutic Method	Outcome Summary
Dakwar et al. (2020): RCT	40 detoxified alcohol-dependent participants	IV ketamine (0.71 mg/kg/52 min)	Infusion and adjunct MET	Ketamine group showed lower relapse rates but not sustained changes in craving/withdrawal.
Grabski et al. (2022): RCT	96 detoxified alcohol-dependent participants	IV ketamine (0.80 mg/kg/40 min)	Infusion and adjunct MBRP or alcohol education	Ketamine led to more abstinence days
Dakwar et al. (2019): RCT	55 detoxified cocaine-dependent participants	IV ketamine (0.50 mg/kg/40 min)	Infusion and adjunct MBRP	Lower craving and relapse rates in ketamine group.
Azhari et al. (2020): OL	8 cannabis-dependent participants	IV ketamine x1-2 (0.71-1.41 mg/kg/50-90 min)	Infusion(s) with adjunct MBRP and MET	Increased abstinence confidence and reduced cannabis use, but not significantly lower craving.
Pradhan & Rossi (2020): OL	3 opiate-dependent participants	IV ketamine (0.75 mg/kg/45 min)	Infusion and adjunct rTMS and TIMBER	Reduced craving
Bogenschutz et al. (2015): OL	10 detoxified alcohol-dependent participants	PO psilocybin x1-2 (0.30-0.40 mg/kg)	PAT and adjunct MET	Fewer drinking days after psilocybin dosing
Johnson et al. (2014): OL	15 nicotine-dependent smokers	PO psilocybin x2-3 (0.29-0.43 mg/kg)	PAT and adjunct CBT	Reduced craving and withdrawal; higher abstinence confidence. The majority showed long-term cessation.
Krupitsky & Grinenko (1997): CT	211 detoxified alcohol-dependent patients	IV bemegride + IM aethimizol + IM ketamine (2.5 mg/kg/N.A.)[a]	KAP	Majority stayed abstinent after one year, one-third abstinent after three years.
Krupitsky et al. (2002): CT	70 detoxified heroin-dependent patients	IM ketamine (2.0 mg/kg/N.A.[b])	KAP	High abstinence rates after two months (> 70%) dropped to under 20% after two years.
Krupitsky et al. (2007): CT	59 detoxified heroin-dependent patients	IM ketamine x1-3 (2.0 mg/kg/N.A.)	KAP	Repeated ketamine sessions sustained abstinence more than twice as often as single sessions; one-year follow-up

Note. OL: Open-Label; CT: Controlled Trial (containing control group but not truly randomized to allocations); PO: Per Os (oral administration); IM: intramuscular (route of administration); MET: Motivational Enhancement Therapy; MBRP: Mindfulness-Based Relapse Prevention, rTMS: repeated Transcranial Magnetic Stimulation; TIMBER: Trauma Interventions using Mindfulness Based Extinction and Reconsolidation of memories, PAT: Psilocybin-Assisted Therapy; CBT: Cognitive-Behavioural Therapy; KAP: Ketamine-Assisted Psychotherapy.

[a] The researcher incorporated elements from aversive therapy the clinical trial, thus an anxiogenic agent (bemegride) and a cognitive enhancer (aethimizol) were combined with ketamine to strengthen aversive associations between alcohol and negative experiences.

[b] Infusion duration was not reported but the ketamine sessions were said to last from 90 to 120 minutes. The psychoactive effects from IM infusion can linger up to an hour, hence it is likely infusions were injected over a period of 30-60 minutes.

Ketamine Pharmacotherapy

In this context, pharmacotherapy (or psychopharmacotherapy) describes the administration of pharmaceutical drugs as the stand-alone treatment, i.e., not supplemented with psychotherapy or other interventions. Considering this is a clinical psychology review, the trials described here can be considered a comparative point of reference for the impact of psychotherapeutic implementations. Therefore, only a brief synopsis of the seven pharmacotherapeutic trials (Table 1) will be presented here, encompassing drug-induced changes in drinking memories, attenuated alcohol- and opiate withdrawal symptoms, and changes in cue-induced craving and spontaneous motivation to quit in non-treatment seeking cocaine-dependent individuals.

Craving and Motivation to Quit in Non-Treatment Seeking Individuals

In a proof-of-concept study, cue-induced craving and motivation to quit following ketamine infusions in eight cocaine-dependent, non-treatment seeking, participants, were investigated (Dakwar et al., 2014b). Participants were administered three 52-minute IV infusions in counterbalanced order: two infusions contained ketamine (one 0.41 mg/kg, the other 0.71 mg/kg dose) and the third an active placebo (2 mg of lorazepam). The

administration order of ketamine and placebo was randomized, but as a precautionary measure the lower 0.41 mg/kg IV ketamine infusion always preceded the 0.71 mg/kg dose. Each infusion was separated by 48 hours to "wash out" residual effects from prior dosing.

Relative to the lorazepam infusion, the median motivation to quit – assessed by 32 questionnaire items in the University of Rhode Island Change Assessment (URICA) – was significantly higher 24 hours after the first ketamine infusion (0.15 versus 3.60, $p = .012$), but not more so following the second infusion – possibly/probably due to ceiling effects from first infusion (Dakwar et al., 2014b). Likewise, cue-induced craving, as measured by a 100-mm Visual Analogue Scale (VAS) in response to cocaine-cue presentation, decreased more after the first ketamine infusion (-126 median, estimated to 60% change from baseline) than with placebo infusion (65 median, $p = .012$). The second ketamine infusion also led to significant drops in VAS craving scores when compared to the lorazepam condition (median of -18 vs. 53, $p = .046$). The 4-week follow-up period showed that this translated to far less frequent (from 22/28 cocaine days to 5/28, $p = .012$) and less excessive cocaine use compared to baseline median (from $149.30 to $10.50 spent per day on cocaine, $p < .001$).

In a related follow-up trial, Dakwar et al. (2016) investigated whether ketamine could disincentivize 20 non-depressed, non-treatment seeking, cocaine-dependent participants from choosing 25mg of smoked free-base cocaine over $11 (a laboratory model the researcher had previously used to gauge pharmacologically initiated abstinence). Participants were hospitalized for six consecutive days on three separate occasions, each separated by two weeks. The purpose of the first hospital stay was to: (I) use the two first days to wash out residual cocaine in the system; (II) a following "cocaine sample day" intended to intensify craving in participants and measure the value they assign to the "laboratory cocaine"; (III) administer a 52-minute long IV infusion of saline (inactive placebo) on Day 4; (IV) give participants Day 5 to choose between free-base cocaine (25 mg) and $11 to confirm a strong

favourability for cocaine pre-treatment and exclude those who prefer cash at baseline; (V) discharge on Day 6. During the remaining hospitalizations, the same procedure was conducted, but with infusions of ketamine (0.71 mg/kg) or the active placebo midazolam (0.025 mg/kg) instead, administered in a double-blinded 1:1 counterbalanced order (Dakwar et al., 2016).

Compared to average cocaine preference (CF) baseline values (up to five choices) measured during the "cocaine sampling" day of the first hospitalization stay (CF = 4.78/5.00), ketamine infusions significantly reduced cocaine preference (CF = 1.61, $t_{17} = 5.48$, $p < .0001$) 28 hours post-infusion; the active placebo midazolam did not (CF = 4.33; Dakwar et al., 2016). Moreover, only ketamine was shown to increase "non-reactivity" (ability to not enact problematic addiction behaviour in response to distress) for at least 48 hours post-infusion ($t_{17} = -2.39$, $p < .05$). Cocaine craving (VAS) and use in natural ecology (outside the lab, measured by money spent) was reduced significantly more by ketamine than midazolam in the first follow-up measure after three days (craving reduction: 59.6% vs. 15.3%, $p < .01$; money spent: $3.20 vs. $22.45, $p < .05$). At the second follow-up (six days after hospitalization), there was no significant difference in use or craving between ketamine and (active) placebo condition. No adverse reactions or sustained dissociative effects post-treatment were observed (Dakwar et al., 2016).

Maladaptive Reward Memories

In the context of SUDs, maladaptive reward memories (MRMs) describe biased recall of how rewarding drug intake is going to be, thought to be a significant perpetrator of continued drug overuse (Gale et al., 2020). In alcohol dependent individuals (as with other SUDs), MRMs are presumed chronic and unusually stable; however, the alcohol-related MRMs have been hypothesized to be modifiable when retrieved and re-encoded under some

conditions, such as creating alcohol-consumption cues (activating the MRM) that is followed by no alcohol (withholding) or by aversive disgust-based conditioning (Das et al., 2019).

In a pharmacological clinical study, researchers hypothesized that ketamine administered during a reconsolidation window of alcohol-related MRM retrieval would attenuate the valence and salience of the MRM by effectively disrupting reconsolidation of the maladaptive memory (Das et al., 2019). To investigate, 90 problematic drinkers (with no formal diagnosis) were asked to retrieve either (A) an alcohol-related MRM or (B) a non-alcohol related "control memory" (orange juice), while concomitantly receiving a 30-minute IV ketamine infusion (350 ng/dl, weight-adjusted dose not described). A third group (C) were asked to also retrieve alcohol-related MRM while receiving a placebo infusion of saline instead of ketamine (Das et al., 2019).

Participants' cue reactivity and urge to drink were assessed by being presented with 150ml of beer (as all 90 were beer-preferring drinkers) and presented with a series of drink-related images, including orange juice, beer, wine, and sodas (Das et al., 2019). To assess discrepancy from actual enjoyment (reward), the participants were asked to evaluate their urge to drink while being presented with the respective pictures and how enjoyable the beer actually was post-consumption (-5 to 5 scale). To destabilize the MRM during the infusion, researchers commenced with a similar procedure, but unexpectedly withheld the beer at the point where participants expected to drink it, creating a neurological prediction error that has been shown to be a crucial element of effective memory destabilization (Das et al., 2019; Sevenster et al., 2013).

Unlike the two control groups (B and C) who showed no significant attenuation of alcohol reactivity on any measures, retrieval of alcohol-related MRM with ketamine (Group A) led to less anticipated enjoyment of beer before drinking ($F_{1.87} = 19.70$, $p < .001$), significant decreases in drinking urges when presented the glass of beer ($F_{1.87} = 20.27$, $p <$

.001), and decreased urge to continue drinking after commencement ($F_{1.87} = 24.46$, $p < .001$; Das et al., 2019). Over the following week, only the ketamine groups drank significantly less ($p < .01$), with Group A showing the greatest drop in consumption. At 9-months follow-up, all groups showed reductions in weekly drinks, though Group A showed an additional "blockade" effect from the MRM + ketamine treatment, resulting in weekly U.K. units being reduced by more than 50%, from roughly 84 to 41 units (Das et al., 2019). Measures of bioavailable ketamine during memory reactivation showed a positive correlation to beneficial outcomes only for the MRM + ketamine group, not for the ketamine group who were primed for orange juice drinking memories (Das et al., 2019).

Attenuated Withdrawal Symptoms

The four following studies describe ketamine procedures that were designed to manage opiate- or alcohol withdrawal, and not directly intended as a therapy for dependence. These trials are therefore only tangentially related to addiction outcomes and the research problem; hence, their outlines will be significantly briefer than the other trials presented before and after this subsection.

The first study describes the outcomes from a double-blinded RCT where 58 opiate-dependent patients received infusions of IV ketamine (0.5 mg/kg/h) or saline (placebo) prior to acute opiate antagonist detoxification (naloxone and naltrexone) administered under general anaesthesia (Jovaisa et al., 2006). During the first- and second hour of anaesthesia, the ketamine group (N = 22) showed significantly lower scores on the Objective Opiate Withdrawal Scale (OOWS-A), including perspiration, tremor, restlessness, and other sympathetic activation ($p < .05$; Jovaisa et al., 2006). OOWSA-A group difference was non-significant at the 3-hour measure. Opiate antagonist-induced cardiovascular response was significantly attenuated at all anaesthesia assessment points (peak and 1st, 2nd and 3rd hour into

anaesthesia; $p < .05$; Jovaisa et al., 2006). A single ketamine infusion was concluded to be to be an effective way to manage acute opiate withdrawal, but not long-term opioid dependence.

The second withdrawal study describes a retrospective review of 23 alcohol dependent patients who received low-dose IV ketamine infusions (median: 0.20 mg/kg/hour) as an adjunct to withdrawal management with benzodiazepines (BZDs; Wong et al., 2014). Twelve hours after the ketamine infusion, patients required 40.0mg less BZD than baseline; after 24 hours they required 13.3mg less. None of these reductions were statistically significant (Wong et al., 2014). The authors conclude that low doses of ketamine can be a safe alternative to reduce BZD use during the acute alcohol withdrawal phase, but that the doses used may be insufficient.

The third included withdrawal study is also a retrospective study for alcohol withdrawal, comparing the results of 29 patients who were administered a BZD-based treatment with 34 other patients who received the same treatment supplemented with IV ketamine infusions (0.15-0.30 mg/kg/hour) to resolve delirium tremens – the most severe manifestation of alcohol withdrawal, excluding death (Pizon et al., 2018). Patients treated under the new protocol, i.e., with adjunct ketamine infusions, were significantly less likely to require intubation (OR = 0.14, $p < .01$) and spent an average of 2.83 fewer days ($p = .043$) at the intensive care unit, compared to BZD-only patients (Pizon et al., 2018).

To conclude this section, the results from a final retrospective study looking at the effect of administering IV ketamine infusions (0.75-1.60 mg/kg/hour) to thirty BZD-resistant patients with acute alcohol withdrawal (Shah et al., 2018), is presented. After showing insufficient response to lorazepam (BZD) infusions for more than 40 hours after commencement, all 30 patients administered IV ketamine showed adequate symptom relief within the first hour when adjusted to initial response of the 0.75 mg/kg/hour infusion. Moreover, BZD-requirements (lorazepam infusion rates) were significantly decreased 24

hours after the ketamine infusion (p = .01; Shah et al., 2018). At these doses, ketamine provided significant symptom relief for this patient group, and further consolidated the prior findings suggesting that ketamine may limit the need of BZD to manage alcohol withdrawal symptoms (Shah et al., 2018).

Psychotherapeutic Enhancement

Unlike most clinical ketamine research for mood disorders, the new wave of ketamine trials for SUDs integrates some sort of psychotherapy and/or behavioural intervention in their treatment protocols; however, the dosing sessions themselves are still mostly pharmacotherapeutic in nature. Motivational- and mindfulness-based interventions – popular options for SUD rehabilitation in general (Roos et al., 2020; Santa Ana et al., 2021) – have been the two major types of psychotherapeutic supplementation in recent clinical trials.

Motivational Enhancement Therapy

Motivational Enhancement Therapy (MET) represents a therapeutic model that builds on the basic principles of Motivational Interviewing (MI) and extends them to better align with the therapeutic needs of addicted individuals (Miller, 1994). Its original iteration is a brief four-session intervention designed for problematic drinkers in the U.S. (MATCH), helping them reflect on why they would want to quit drinking, partially by providing incisive feedback and probing non-directive exploration of underlying motivational factors (Miller, 1994). However, some redesigns of the original intervention have been implemented to better align with other addiction disorders, for example cannabis dependence (Blevins et al., 2018) or addiction to social media (Manwong et al., 2018).

As with MI, MET consists of five core ideas that guide therapy (Miller, 1994): (a) expressing empathy; (b) developing discrepancy; (c) avoiding arguments; (d) rolling with resistance, (e) supporting self-efficacy. In other words, an important job of the MET-therapist is to quickly establish a therapeutic alliance based on mutual respect and trust, facilitated by

non-engagement in confrontational statements and not directly challenging patients' resistance to change. With a strong therapeutic alliance, it is easier to openly discuss the discrepancies between the patient's current situation and where they want to be, and how that discrepancy is fortified by their addiction; therapist encouragement and expressed belief in the patient's capability to change may also be more positively attributed (Elvins & Green, 2008).

One benefit of combining MET sessions with ketamine or psilocybin is that their ability to increase neuroplasticity (Aleksandrova & Phillips, 2021) and openness (Dore et al., 2019; Erritzøe et al., 2018) may enhance learning, discrepancy salience, and self-efficacy from MET, thus increasing long-term motivation to stay abstinent. In this model, MET would be the primary treatment, assisted by psychoplastogenic drugs. Conversely, MET could alternatively be used to enhance the antiaddictive effects of a transformative psychedelic experience, helping integrate acquired insight into meaningful change in everyday life.

Alcohol Dependence. In a recent double-blinded RCT, 40 alcohol dependent participants with minimal psychiatric comorbidities were administered a single 52-minute infusion of ketamine (0.71 mg/kg) or midazolam (0.025 mg/kg), combined with six MET sessions over a 5-week study period (Dakwar et al., 2020). To maintain blinding integrity and control some expectancy effects, participants were (deceitfully) informed that they could receive a wide variety of psychoactive drugs (including ketamine and midazolam); midazolam was used as the active placebo/active control due to its sedative and relaxing properties mirroring some of ketamine's effects. To be eligible for ketamine infusions, at least 24 hours of abstinence was required before the session; individuals with severe withdrawal symptoms were excluded (Dakwar et al., 2020).

Personnel trained in accordance with the MATCH-manual administered the first MET session in Week 1, encouraging participants to explore and express goals for the treatment and motivations to quit, and counselling them on how to gradually reduce their alcohol intake

prior to the mandatory target quit date at least 24 hours before the infusion in Week 2 (Dakwar et al., 2020). To capitalize on ketamine's hypothesized ability to transiently increase motivational drive, participants were offered two MET sessions during Week 2, thus leaving only three weekly sessions left for the final three weeks of the study (Week 3 to 5). Leading up to the infusion, participants also met with a psychiatrist to prepare for the infusion, accumulating in three consecutive visit days around the time of infusion. On the day of the ketamine (and placebo) infusion, the research team assisted participants in mindfulness practice and relaxation exercises before and during the session (Dakwar et al., 2020).

In the three-week period following infusion, eight of 17 participants (47.1%) allocated to the ketamine group had consumed alcohol, while three (17.6%) reported a heavy drinking day (Dakwar et al., 2020). For those administered midazolam, 13 of 23 (59.1%) had alcohol in the same period and nine (40.9%) had a heavy drinking day. At the end of the study period, abstinence (adjusted for baseline intake) and time to relapse was significantly higher in the ketamine group ($F_{1.797} = 25.1$, $p < .001$; $X^2 = 4.2$, $p = .04$). Moreover, heavy drinking days were significantly less likely to occur in participants administered ketamine ($F_{1.798} = 12.34$, $p < .001$); heavy drinking days did not become more likely over time (in the 21-day study period) for this group (Dakwar et al., 2020). After the five weeks of treatment, no statistically significant group difference could be established for the secondary measures of addiction symptomatology (craving, withdrawal etc.).

While none of the participants from the ketamine group dropped out of the study, five in the midazolam group dropped out after the first week and another one never returned post-infusion. Of the 19 (of 40) participants who could be reached by phone after 6 months, 75% (6/8) of ketamine respondents claimed to be abstinent, while only 27% (3/11) of midazolam participants reported the same (Dakwar et al., 2020).

Mindfulness-Based Relapse Prevention

Mindfulness practice has been integrated into many facets of psychotherapy in recent years (source). For addiction and SUDs, Mindfulness-Based Relapse Prevention (MBRP) has become an increasingly popular therapeutic tool, helping the person become more aware of the automatic processes that initiates craving and precedes relapse (Bowen et al., 2010, Witkiewitz et al., 2013). As a mindfulness-based treatment program, MBRP emphasizes meditative practice and acceptance of thoughts and emotions as they arise, including cravings or urges (Bowen et al., 2010). In conjunction with mindfulness-based stress reduction and relapse prevention, the MBRP curriculum also includes elements of CBT, constituting a tripartite therapeutic framework for addiction rehabilitation. Specific relapse-prevention techniques used in MBRP programs may vary, though meditation, explicitly outlining high-risk situations (for relapse), activity scheduling, and urge surfing – i.e., improving the ability/skill to acknowledge the presence of urges without enacting upon them – represent common MBRP implementations (Bowen et al., 2010).

Repeated Ketamine Infusions and MRBP for Alcohol Dependence. In a recently published phase II RCT for alcohol use disorder, Grabski et al. (2022) recruited 96 alcohol dependent participants for a four-arm double-blind placebo-controlled ketamine treatment program, investigating whether three weekly ketamine infusions combined with MRBP would be more effective at attenuating drinking behaviour than the same ketamine treatment combined of alcohol education (AE). MRBP sessions were conducted as psychotherapeutic sessions focusing on mindfulness-based techniques such as urge surfing and meditative practice; AE centred around informative communication regarding alcohols negative impact the body, how to live a healthier life, and the causes of addiction. Each session for both intervention-types were administered over 90 minutes to control for confounding variables beyond the psychotherapeutic approach (Grabski et al., 2022).

To compare the therapeutic efficacy of each combination, participants were randomized to one of four treatment groups: (1) IV ketamine and MBRP (N = 24); (2) IV ketamine and AE; (N = 24) IV saline (placebo) and MBRP (N = 23); (4) IV saline and AE (N = 25). Regardless of group allocation, participants were scheduled for eight study visits before the subsequent follow-ups at 3- and 6-months after group randomization (Visit 2). Participant (re)screening was conducted at Visit 1 for baseline data. IV ketamine (0.8 mg/kg over 40 minutes) or placebo (0.9% saline) was infused at Visit 2, 4, and 6 over a period averaging 17.1 days (with a minimum of one week pause between each session). MBRP or AE treatment was administered the day after each infusion (Visit 3, 5, and 7), as well as in a concluding session (Visit 8) where participants were given an alcohol diary to record alcohol use in the following period preceding the final outcome measures recorded at Visit 9 (3-months after Visit 2) and Visit 10 (6-months after Visit 2).

Before each infusion (regardless of group allocation as therapists were blind to experimental condition), participants were prepared for the type of experience the infusion might induce and concomitantly taught relaxation exercises to deal with psychological resistance (Grabski et al., 2022). During the infusions, participants were placed in a hospital room with a single bed and were equipped with headphones playing instrumental music to minimize external distractions. The therapist instructed patients to make their motivations to live a life in sobriety salient/explicit prior to the infusion and provided the necessary psychological support throughout the experience.

To assess therapeutic response, the primary outcomes was defined as self-reported relapse (> 1 day of heavy drinking – i.e., more than 8.1 or 6.5 standard U.K. units for men and women respectively) and percentage of days abstinent. The same outcomes at 3-month follow up, as well as changes in depression, alcohol craving, and general health, were categorized as secondary outcomes (Grabski et al., 2022).

The mean percentage difference (MD) in abstinence days between the ketamine groups and saline groups was significant both three months (MD = 9.0, 95% CI = 1.3, 16.7) and six months (MD = 10.1, 95% CI = 1.1, 19.0) after the first infusion (Visit 2); however, relapse rates did not differ significantly at any time (Grabski et al., 2022). The largest abstinence difference was observed when comparing only the IV ketamine + MBRP group with IV saline + AE (MD = 15.9, CI = 3.9, 28.1), but relapse rate differences did not reach statistical significance in this comparison either. Though with some small indications favouring MBRP over AE, no significant difference was seen between these ketamine groups for neither abstinence nor relapse (Grabski et al., 2022).

In this study, there was no difference in post-study illicit ketamine use between the groups (three in each drug condition tried ketamine on a single occasion). However, severe (but not "serious") adverse events were reported for three participants administered ketamine (high blood pressure and heartrate, depressed mood, and hypomania/euphoria) and not for any placed in the placebo groups (Grabski et al., 2022).

A Single Ketamine Infusion and MBRP for Cocaine Dependence. In another recent double-blinded RCT (Dakwar et al., 2019), 55 cocaine-dependent, treatment-seeking, participants were administered a single 40-minute IV ketamine (0.50 mg/kg) or midazolam (0.025 mg/kg) infusion during a 5-day hospitalization, followed by weekly MBRP sessions during the remainder of the 5-week study (daily MBRP sessions were provided from Day 2 to Day 5 of hospitalization). The MBRP sessions were individualized according to each participant's needs but always focused on assisting mindfulness practices (e.g., breathing exercises) and integrating a mindful state of mind (e.g., non-reactivity) into everyday life. After the five-week study period, participants were referred to continued treatment elsewhere before follow-up by six months post-infusion (Dakwar et al., 2019).

During the final two weeks of the trial (Week 4 and 5), urine tests for 13 out of 27 (48.2%) participants in the ketamine group indicated cocaine abstinence; only three out of 28 (10.7%) did the same in the active placebo group (Dakwar et al., 2019). At the end of the study, those who received ketamine were almost six times as likely to remain abstinent compared to those who received midazolam (OR = 5.7, 95% CI = 1.3, 25.1; $X^2 = 5.34$, $p = .02$). In the final main-effects model, the ketamine group scored 58.1% lower on the craving scale than the placebo group ($t_{100} = -2.57$, 95% CI = 18.6, 78.6, $p = .01$) and had 53% lower likelihood of relapsing (hazard ratio = 0.47, 95% CI = 0.24, 0.92; $X^2 = 4.78$, $p = .03$). At the study's primary endpoint, 26 out of 28 (92.9%) participants in the midazolam group had relapsed; "only" 15 out of 27 (57.7%) in the ketamine group did the same (Dakwar et al., 2019). At the 6-months telephone follow-up, 12 ketamine participants (44%) reported abstinence while none of the participants who received midazolam managed to stay abstinent ($X^2 = 15.92$, $p < .001$).

Combined Techniques

This section summarizes findings from two small-scale ketamine studies that does not fit the other categories: one combined MET and MBRP with ketamine infusions to treat eight cannabis dependent individuals (Azhari et al., 2020); the other used repetitive transcranial magnetic stimulation (rTMS) and a mindfulness-based program (Trauma Interventions using Mindfulness Based Extinction and Reconsolidation of memories: TIMBER) to potentiate a ketamine-based treatment for three opioid dependent patients (Pradhan & Rossi, 2020).

A Single Ketamine Infusion With MET & MBRP for Cannabis Dependence. During a 6-week treatment period, the eight participants would initially only be administered a single 0.71 mg/kg ketamine infusion on Day 2 of Week 2, but for non-responders, i.e., those who were struggling to maintain abstinence after first infusion, a second 1.41 mg/kg IV dose was administered Week 4 for those willing (Azhari et al., 2020). For both doses, an initial 2-

minute 0.11 mg/kg bolus was administered; however, while the remaining 0.60 mg/kg in the first session was administered over 50 minutes, the second infusion administered the remaining 1.30 mg/kg over 90 minutes, attenuating a massive jump in subjective intensity that could be elicited by a doubled dose (Azhari et al., 2020).

Three MET sessions were incorporated into the treatment: the first commenced at Day 1 of Week 1, the second a week later (the day before infusion), and the final session shortly after the ketamine experience (Week 2, Day 2). A fourth and fifth MET session was added for non-responders the day before, and shortly after, the second infusion (Week 4). MBRP treatment was conducted semi-weekly from Week 3 to 6 (i.e., eight MBRP sessions in total). The drug administration sessions were pharmacotherapeutically oriented with few measures made to promote a therapeutic setting.

The average baseline cannabis use frequency (B = 5.12/7.00 days of the week, SD = 1.89) was significantly reduced a week after the first IV ketamine session (B = 0.75, SD = 1.17, $p < .05$) and second non-responder infusion (B = 0.13, SD = 0.35, $p < .05$); reductions were sustained towards the end of the 6-week study period (B = 0.50, SD = 0.93, $p < .05$). In other words, the baseline frequency of weekly cannabis use was reduced by more than 90% at the end of the study. Cannabis craving at the end of study had not changed significantly, but significant increases in Drug-Taking Confidence Questionnaire scores from baseline (44.7, SD = 21.8) to the end of the study (87.5, SD = 20.9, $p < .05$) suggests that participants became more confident in their ability to resist relapse from stress-induced craving (Azhari et al., 2020). Three of the eight participants were administered a second infusion due to insufficient response, but no significant difference in primary- (use frequency) and secondary (abstinence-confidence and craving) outcomes could be established between single- and double infusion (Azhari et al., 2020).

A Single Ketamine Infusion with rTMS and TIMBER for Opioid dependence.

Based on prior positive indications for ketamine, rTMS, and mindfulness-based interventions in addiction treatment (Pradhan et al., 2015), Pradhan & Rossi (2020) infused three opiate dependent participants with a single session of IV ketamine (0.75 mg/kg) that was subsequently combined with 1-2 weeks of targeted rTMS, supplemented with concomitant TIMBER sessions in the same period. Participants were instructed to conduct mindfulness-based practices at home at least two times daily; cravings should initiate additional practice.

In this "micro-scale" open-label study, participants had an average craving score of 23.6 (SD = 4.2) on the Opiate Craving Scale (OCS – max score is 30) and a 28.45 (SD = 9.61) "mindfulness-score" on the Assessment Scale for Mindfulness Interventions (ASMI) at baseline. Following infusion and five rTMS + mindfulness sessions, OCS scores decreased to 8.2 (SD = 2.7, t = 6.5, 95% CI = 8.8, 21.85, p = .002) and ASMI scores increased to 49.67 (SD = 7.72, t = 4.2, 95% CI = 33.48, 7.18, p = .01), representing a 65.7% drop in craving scores and 41.21% increase in mindfulness scores, respectively (Pradhan & Rossi, 2020). Actual measures for abstinence/relapse or continued use were not included in this study.

Psychedelic Integration Therapy

In this section, modern psychedelic SUD research utilizing the principles of psychedelic-peak therapy (Pahnke, 1969) is presented. These modern analogues are sometimes called "psychedelic integration therapy" (PIT), alluding to the emphasis put on post-psychedelic psychological integration ("psychedelic debriefing"). This process, as well as other common PIT elements, will be briefly summarized in the next section before the specific implementations and therapeutic outcomes of each individual SUD trial follows.

Preparation, Administration, Integration

PIT presents a therapeutic framework diverging considerably from traditional pharmacotherapeutic-, psychotherapeutic, and combined treatment options. The purpose of

PIT is to create the right conditions for a psychedelic drug to induce a transformative "peak-experience" where patients gain deep insight into the causes and consequences of their condition, often complemented with spontaneous and compelling alternatives for a better life (Gorman et al., 2021; Krupitsky & Grinenko, 1997; Wolfson, 2014). The "right conditions" facilitating these experiences will be moderated by individual idiosyncrasies and situational variables (Carhart-Harris et al., 2018), but all forms of PIT follow a general three-stage treatment model: (1) preparation, (2) therapeutic dosing sessions, (3) integration.

During the preparation stage, therapists work with the patient to increase motivation for treatment and to prime their mindset (set) for transformative change (Gorman et al., 2021). In PIT studies for SUDs, some explicitly instil expectations regarding what will transpire during the psychedelic experience and how it will resolve patients' addictive behaviour (e.g., Krupitsky et al., 2002). Others opt for more general guidance, focusing on how to surrender to experience and how to manage challenging experiences (e.g., Johnson et al., 2014).

For the psychedelic sessions themselves – while not exclusive to this mode of psychedelic treatment – all PIT studies describe the same basic setting for ketamine- or psilocybin administration, hereby referred to as the "PIT standard setting" (Bogenschutz et al., 2015; Johnson et al., 2014; Krupitsky & Grinenko, 1997; Krupitsky et al., 2002, 2007). The PIT standard setting consists of four common factors: (a) an inviting/homely environment centred around a comfortable bed or chair; (b) psychotherapist(s) offering directive or non-directive psychological support throughout; (c) a curated musical playlist designed to elicit a wide range of emotions and climactic peaks guiding and anchoring the psychedelic journey; (d) equipment limiting disruptive sensory input (e.g., eyeshades and headphones). Other specific measures may be included to further emphasize a therapeutic environment, but the common factors are never omitted.

The final step in the PIT-model – integration – describes the process of manifesting psychedelic insight into meaningful action and lasting change (Gorman et al., 2021). Psychedelic content can often be highly ambiguous and symbolic in nature (Grof, 1976), hence constructive (re)interpretations of the experience can help the person contextualize the experience into their present- and prospective life narrative. This revelatory process will typically be guided by session therapists but can also be conducted in a group therapy format with patients who have undergone the same treatment sharing experiences and interpretations (Krupitsky et al., 1992). The extent of formal integration work may vary.

Psilocybin-Assisted Therapy

To date, there are only two published clinical trials using PAT for addiction, specifically alcohol- (Bogenschutz et al., 2015) and nicotine dependence (Johnson et al., 2014). Their treatment protocols include psychotherapeutic treatment and behavioural interventions, but the therapeutic framework is still primarily oriented towards peak-experience PIT, and thus not categorized as a combined treatment in this thesis. Both trials are small-scale proof-of-concept studies that have been used to generate empirical data for larger phase II clinical trials that are currently underway (clinicaltrials.gov identifiers: "NCT02061293" and "NCT01943994"). Some case reports from these upcoming trials have been reported (Bogenschutz et al., 2018; Podrebarac et al., 2021), but formal clinical outcomes have not yet been published.

Psilocybin and Psychosocial Intervention for Alcohol dependence. In the only published proof-of-concept study for alcohol dependence, Bogenschutz et al. (2015) recruited 10 treatment-resistant participants (on average 15.1 years dependent and 11.5 prior attempts to quit) for an open-label 12-week PAT trial. The researchers included three preparation sessions to prepare participants for two high dose psilocybin sessions (0.30-0.40 mg/kg, P.O.) administered in a PIT standard setting. Each psilocybin session was supplemented with a

debriefing/integration session and the whole 12-week study period was anchored in a structured MET-based psychosocial interventions program. In total, each participant was by default scheduled to 14 therapeutic meetings: three sessions to prepare for the psychedelic experience, seven MET sessions, two psilocybin sessions (in Week 4 and 8), and two concomitant sessions for integration. Participants met with the therapists four times before each dosing session and received the four remaining therapy sessions after the final psilocybin session in Week 8 (Bogenschutz et al., 2015).

For the psychedelic sessions, participants could decide whether they wanted to increase the initial 0.30 mg/kg psilocybin dose (Week 4) to 0.40 mg/kg in the second session (Week 8). However, if participants either experienced a "complete" mystical-type experience or significantly adverse effects from 0.30 mg/kg, the research team would not administer a higher dose in the second session (Bogenschutz et al., 2015). Of the 10 participants included in the study, one withdrew before the first session, one decided to partake in the second session without increasing dose, and another one was recommended to do the same due to having a complete mystical experience at the initial moderate dose. The remaining seven participants were administered a 0.40 mg/kg oral dose in the second session (Bogenschutz et al., 2015).

Self-reported "drinking days" (any amount of alcohol) and "heavy drinking days" (more than four or five daily "standard drinks" for women and men respectively) was used as the measure of therapeutic response (Bogenschutz et al., 2015). At the study's primary endpoint (Week 12) eight weeks after the first psilocybin session (Week 4), participants reported 26% (SD = 22.4) fewer heavy drinking days (95% CI = 8.7, 43.2, $t_8 = 3.477$, p = .008) and 27.2% (SD = 23.7) fewer drinking days (95% CI = 9.0, 45.4, $t_8 = 3.449$, p = .009) in the period between Week 5 and 12, compared to baseline. Relative to the last measure after four weeks of only MET-based treatment (before first dosing), participants reported 18.2 %

(SD = 20.0) reduction in "heavy drinking days" (95% CI = 2.8, 33.5, $t_8 = 2.723$, $p = .026$) and 21.9% (SD = 21.8) fewer drinking days (95% CI = 5.1, 38.6, $t_8 = 3.010$, $p = .017$). The four weeks of MET-based psychosocial intervention prior to psilocybin administration did not lead to significant change in drinking behaviour (Bogenschutz et al., 2015); changes in drinking measures after psilocybin indicated moderate to large effect sizes (Cohen's $d = 0.75\text{-}1.38$, $p < .05$).

A Psilocybin-Assisted Smoking Cessation Program. As the first modern clinical PAT trial targeting addiction, Johnson et al.'s (2014) smoking cessation study combined (up to) three high-dose psilocybin sessions (0.29 - 0.43 mg/kg) with structured smoking-oriented CBT therapy over a 15-week treatment period for 15 nicotine dependent participants. In the open-label trial, participants were thoroughly prepared for a psychedelic experience that could be psychologically- and emotionally challenging, but also potentially highly meaningful and spiritually significant if they are able to trust the therapists (or "trip-sitters") and surrender to the experience.

The researchers included the second and third higher-dose psilocybin sessions primarily for those who did not manage to quit after the first 0.29 mg/kg dosing in Week 5, but also as an option for those who remained abstinent after the first session to consolidate their resolve (Johnson et al., 2014). In the end, excluding only one individual who preferred to redose with 0.29 mg/kg in the second session, all remaining participants (14/15) commenced with a higher-dose second session (0.43 mg/kg); none opted for just the single dose, and 12 participants wanted the third and final psilocybin session (Johnson et al., 2014). Over the 15-week study period, participants had a total of 19 personal meetings with the research team and were called daily (brief check-ups lasting less than five minutes) in the two-week period following the first psilocybin session (Johnson et al., 2014).

In four weekly preparatory 90-minute therapy sessions preceding the first dosing session in Week 5 (the second and third dosing were scheduled for Week 7 and 13, respectively), therapists spent about half the time preparing participants for the psychedelic psilocybin-sessions and the other half providing therapy centred around smoking-oriented CBT modules (Johnson et al., 2014). In the time allocated to psychedelic preparation, participants were introduced to the general idea of PAT and what to expect in the session(s). This time was also used help participants reflect on their life, particularly regarding their values, current relationships, and hobbies/activities that made their life meaningful. For the CBT modules, utilized tools included: assigning a target quit date (TQD) corresponding to first psilocybin session and signing a contract to abstain; working with a smoking diary to get an objective overview of the smoking habits; reading program cards each time an urge arises ("*what triggered this urge?")* or a cigarette is smoked ("*this cigarette gives me no satisfaction"*); lessons on how to deal with withdrawal and urges; emphasizing and reframing smoking's financial costs; and developing brief motivational statements (e.g., "*I want to be free, clean, and clear"*; Johnson et al., 2014).

The dosing sessions were conducted in the PIT standard setting, with concomitant preparation and integration sessions the day after each psilocybin experience. Six months after the first psilocybin session, 12/15 (80%) participants demonstrated complete smoking cessation on biomarker measures over a seven-day period; 11 reported no relapse since the TQD (Johnson et al., 2014). Compared to baseline, significantly lower scores on the Wisconsin Smoking Withdrawal Scale ($F_{4.46} = 4.0$, $p < .001$) and Questionnaire on Smoking Urges ($F_{3.39} = 12.7$, $p = .009$), as well higher scores on the Smoking Abstinence Self-Efficacy confidence scale ($F_{2.34} = 24.9$, $p < .001$), was observed (Johnson et al., 2014). Some participants reported psychologically challenging moments during at least one dosing session, but no clinically significant adverse effects were observed. In a long-term follow-up of the 15

study participants, 10 (67%) were confirmed to still be abstinent 12-months after the first psilocybin session (Johnson et al., 2016).

Ketamine-Assisted Psychotherapy

KAP is often utilized in a similar fashion to psilocybin-assisted therapy or other PIT modalities, facilitating a therapeutic context conducive to an acute transformative mystical-type experiences that can guide a new and better life (Wolfson, 2014). Preparation sessions are spent building a therapeutic alliance between the patient and session therapist(s), reflecting on core values, discrepancy from their ideal-self, problems that needs to be resolved, and so on (Dore et al., 2019; Wolfson, 2014). The ketamine sessions are often conducted in a PIT standard setting, typically with IM injections instead of IV infusions as post-infusion psychedelic effects are extended from 15-20 minutes to 45-60 minutes (Dore et al., 2019; Krupitsky et al., 1997). However, the psychoactive effects of sub-anaesthetic ketamine – even with IM injections – will typically dissipate significantly quicker than psilocybin P.O. (Brown et al., 2017; Kamp et al., 2020). As a PIT model based on the principles of psychedelic peak-therapy, post-session integration is always included in KAP to some degree (Krupitsky et al., 1992; Wolfson, 2014).

In the recent surge of published ketamine trials for SUD, none conduct KAP-based treatment. The only relevant SUD research (for this section) is therefore the work conducted by Krupitksy and colleagues over two decades (from 1985) at the Leningrad Regional Center of Addiction in Russia (St. Petersburg) – targeting alcohol- and heroin dependent individuals (Krupitsky et al., 1992, 2002, 2007; Krupitsky & Grinenko, 1997). The four studies are based on the same general KAP methodology, though certain modifications are implemented in each trial. Here, the basic approach and methodological variations will be presented first, subsequently followed by clinical outcomes from each trial.

Throughout the ten first years of research on alcohol dependent patients, the researchers experimented with various infusion combinations to prime certain emotional states in the patients. Their initial therapeutic model – "the affective contra-attribution method" – was based on aversion-therapy and PIT principles for alcoholism, with the intention of creating a strong negative association between the smell of alcohol and a "torturous" psychedelic experience while simultaneously changing patients' lifestyle attitudes (Krupitsky et al., 1992).

The Krupitsky Method. The modified infusion procedure in the heroin dependence trials reflects a psychotherapeutic shift away from the affective contra-attribution method to a more standard form of PIT. Even with its aversive-therapy elements, the original alcohol-dependence trial implements the same basic psychotherapeutic methodology that has been used in all the following KAP (or "ketamine psychedelic therapy") trials, based on the classic three-stage format (Krupitsky & Grinenko, 1997).

In the first stage of Krupitsky's KAP method – preparation – patients are invited for introductory psychotherapeutic sessions. As there was no psychedelic revolution in Russia (USSR) akin to the 1960s "counter-culture" movement in the West, the preparation sessions started with very basic concepts of what a psychedelic drug is and how it changes your consciousness (Krupitsky & Grinenko, 1997). Treatment specialists induced a sense of expectancy by explaining to patients that this altered state of consciousness would give them relief from their addiction by causing profound and meaningful experiences that provides insight into the benefits of a life in abstinence (Krupitsky et al., 2002; Krupitsky & Grinenko, 1997).

Following a general introduction to ketamine, unconscious attitudes and processes linked addiction is explained to the participants, framed as something that can be removed from the psyche when the psychedelic experience makes such content consciously available

(Krupitsky et al., 1992). The therapist(s) expands on this "psychotherapeutic myth" to include the unique condition and life situation of each patient, emphasizing the vague nature of unconscious constructs manifested into consciousness and how these symbolic images metaphorically represent the unconscious origins of their addiction. However, they emphasize that these concepts must be introduced gradually in dialogue with the patient, building a strong therapeutic alliance before the psychedelic session (Krupitsky et al., 1997). Patients' painful realization of the consequences of their addiction, combined with the sudden clairvoyancy of its unconscious aetiology, is hypothesized to lead the person to reject their addiction and live a purposeful life in sobriety (Krupitsky & Grinenko, 1997).

During the second stage – dosing – Krupitsky and colleagues administer IM ketamine in the PIT standard setting but include directive psychotherapy during the session, directing the content towards the therapeutic narrative of each individual (Krupitsky et al., 2002). By communicating directly (verbally), therapists are trained to guide the experience in line with the atmospheric music playing in the background, encourage patients to face the symbolic (and hallucinogenic) manifestations of their unconscious conflicts, and tell them to surrender to the experience, even if it feels like they are dying or is otherwise terrifying (Krupitsky et al., 2002, 2007). In alcohol dependent patients, the researchers also introduced the smell of alcohol at the most negatively charged moments of the psychedelic experience – attempting to create the strongest possible negative association/aversion to alcohol (Krupitsky et al., 1992; Krupitsky & Grinenko, 1997).

Finally, for the integration stage, the researchers initially preferred a single 2–4-hour group therapy session the day after the ketamine infusion for groups of four or five people, as it was assumed that it would be beneficial for other people who had similar experiences to help each other interpret the personal significance of their unique trip, integrating the experience into meaningful change in everyday life (Krupitsky et al., 1992; Krupitsky &

Grinenko, 1997). Group psychotherapy was, however, eventually dropped in the heroin dependence trials in favour of individual integration sessions, conducting multiple sessions in the days following ketamine injection(s) with the same basic aim of content interpretation and integration (Krupitsky et al., 2002, 2007). The following sections will summarize the outcomes from the Krupitsky-trials and some specific therapeutic implementations and techniques described in each study.

A Single High-Dose Ketamine Infusion for Alcohol Dependence. The two Krupitsky-papers published for alcohol dependence describe the initial results (Krupitsky et al., 1992) and extended outcomes (Krupitsky & Grinenko, 1997) for an overlapping sample (using the same control group at the very least). The findings reported in the extended study will therefore be presented here to see the overall therapeutic response for the whole sample over a 10-year period.

Starting in 1985, 211 alcohol dependent patients (all male) were sequentially recruited over the next 10 years to participate in a standard 3-month treatment program at an addiction center/hospital in St. Petersburg (Krupitsky et al., 1997). First, patients underwent alcohol detoxification and concurrent treatment of comorbid psychiatric disorders (mostly depression) or somatic ailments (Krupitsky & Grinenko, 1997). This was followed by individual CBT and group therapy designed to emphasize the negative effects alcohol had on patients' life and subsequently instil a motivational set (mindset) for a life in abstinence. Interpersonal relationships, patients' life narrative, world views, and other adjacent factors were also discussed (Krupitsky & Grinenko, 1997).

Of the 211 patients, 111 consenting participants were later sequentially recruited over a four-year period to ketamine treatment using Krupitsky's method supplemented with elements from aversive alcohol therapy (Krupitsky & Grinenko, 1997). The remaining 100 were used as the control group – receiving only the standard treatment described in the last

paragraph with conventional psychotherapy instead of KAP. Pre-treatment alcohol dependence severity was not significantly different between the groups before treatment (Krupitsky & Grinenko, 1997).

As part of the treatment model was inspired by aversion-therapy, patients first received aethimizol (1.5%, 3ml; a "cognitive enhancer") with IM injection and IV infusion of the anxiogenic compound bemegride (0.5%, 10ml), before finally being administered the high-dose IM ketamine infusion (2.5 - 3.0 mg/kg; Krupitsky et al., 1992; Krupitsky & Grinenko, 1997). To reliable create negatively reinforced aversive psychedelic experiences, the idea was that IV bemegride would acutely intensify emotionally charged ketamine-induced hallucinations while aethimizol would help establish a long-term memory of an aversive connection to alcohol (Krupitsky et al., 1992). This infusion-cocktail was used throughout study period, but the 3.0 mg/kg IM ketamine dose was at some point reduced to 2.5 mg/kg (Krupitsky & Grinenko, 1997).

At the one-year follow-up, the group who received KAP treatment were almost three times more likely than the control group to remain abstinent from alcohol (65.8% vs. 24.0%; Krupitsky & Grinenko, 1997). In the initial study, 69.8% (42/60) of the KAP group were reported abstinent after one year (Krupitsky et al., 1992). During the four-year period where participants were recruited for KAP, additional two- and three-year follow-ups were only conducted once, thus 81/111 were eligible for two-year follow up and only 42/111 for three-year follow-up (Krupitsky & Grinenko, 1997). For the KAP group, 40.7% (33/81) and 33.3% (14/42) remained abstinent two and three years after treatment, respectively. Two- and three-year follow-up could not be collected for the control group due to financial limitations (Krupitsky & Grinenko, 1997). The authors report no serious adverse effects/complications in this study sample, nor with any of the other alcoholic patients (> 1000) they have treated with ketamine since 1985 (Krupitsky & Grinenko, 1997).

Single Versus Multiple High-Dose Ketamine Infusions for Heroin Dependence. In the first KAP trial for heroin dependence (Krupitsky et al., 2002), 70 detoxified addicts (15 females) were randomly allocated (1:1, double-blind) into one of two infusion groups, receiving a single infusion of either (a) 2.0 mg/kg IM ketamine or (b) 0.2 mg/kg IM ketamine (active placebo). The research team moved away from aversive therapy techniques (see Krupitsky et al., 1992) for the heroin dependence trials, hence neither aethimizol nor bemegride was used before the ketamine infusion (Krupitsky et al., 2002, 2007). The 0.2 mg/kg IM ketamine condition was considered an active placebo because it induces some pharmacological change without occasioning comparable psychedelic effects (Krupitsky et al., 2002).

The ketamine session, lasting from 90 to 120 minutes, was conducted in a PIT standard setting, prepared with 10 hours of psychotherapy and five hours of post-infusion integration – conducted by a psychiatrist trained in the Krupitsky KAP method (Krupitsky et al., 2002). Psychotherapy during the session was individualized to each specific case and was transpersonal and existential in nature – priming patients to think about their ideals and how their addiction limits opportunities for a more meaningful life. The preparation and integration sessions were conducted in the same spirit as described earlier (Krupitsky & Grinenko, 1997), with the notable exception of extended individualized integration rather than a single group therapy session (Krupitsky et al., 2002).

Throughout a two-year follow-up period, the high-dose group (N = 35) showed significantly greater rates of abstinence ($p < .05$) than the low-dose group (N = 35) throughout all 16 assessment points, excluding a statistically non-significant difference (favouring high-dose) for a brief period in Month 7 and 8 (Krupitsky et al., 2002). After two months, the abstinence percentage in the high-dose group (> 70%) was twice that of the low-dose group ($p < .01$); after two years, abstinence rates dropped under 20% for the high-dose group, but this

was still significantly higher than the low-dose group who had no confirmed abstinence ($p < .05$; Krupitsky et al., 2002). Heroin craving, as assessed by a VAS, was attenuated significantly more in in the high-dose group than the low-dose group at every follow-up before Month 6 ($p < .05$). After 6 months, significant attrition, particularly in the low-dose group, underpowered the group comparisons, and only one person from the low-dose group was present at the final two-year assessment (Krupitsky et al., 2002).

Following the initial findings, Krupitsky et al. (2002) hypothesized that repeated KAP sessions might be necessary to maintain majority abstinence beyond the first few months. Subsequently, in a second trial, researchers repeated the same basic study design and therapeutic procedure for 59 heroin-dependent patients (10 females); however, half the sample was randomized to undergo two additional KAP sessions – each spaced a month apart (Krupitsky et al., 2007). All sessions, regardless of group allocation, were conducted in double-blinded fashion, according to the principles of the Krupitsky method. Prior to the initial dosing session, each participant received five hours of individualized addiction therapy with concurrent preparation to the ketamine experience. After the session, five hours of integration psychotherapy was provided (Krupitsky et al., 2007). Only a single session (60 minutes) of addiction counselling and integration was given before and after each additional dosing session. To limit the confounding effects of additional psychotherapy for the group receiving three infusions, monthly addiction counselling was provided for the single-infusion group as well (Krupitsky et al., 2007).

As a result of six participants relapsing and dropping out of the study shortly after the first KAP session, only 53 were randomized to the two group conditions: 26 were designated to repeated dosing group; 27 were allocated to the single-dosing group (Krupitsky et al., 2007). In the repeated dosing group, 15.4% relapsed between the second and third dosing sessions; 25.9% did the same in the single dosing group, representing a non-significant

retention difference between the groups during this intermediate period. However, a year later, following a third KAP session, the abstinence rate was significantly higher ($p < .05$) in the repeated dosing group (50%: 13/26) than it was in the single dose group (22.2%: 6/27), the latter showing comparable abstinence rates to the one-year follow-up assessment in the original study (Krupitsky et al., 2002, 2007). None of the secondary measures for depression, anxiety, or heroin craving, indicated statistically significant differences between the groups, though this may be confounded by data missing from those who relapsed and dropped out of the study (Krupitsky et al., 2007).

Experiential Mediators of Therapeutic Response

Mystical-type experiences, describing transformative experiences containing compelling phenomenological content that take on deep personal meaning and spiritual significance (Griffiths et al., 2006), have been linked to better therapeutic outcomes in psilocybin trials yet remained largely unexplored in ketamine-based therapies amidst the slew of depression trials that have been conducted in the past two decades (Grabski et al., 2022; Mathai et al., 2020). However, there are anecdotal and qualitative reports suggesting that those who respond to treatment often attribute their recovery to experiences aligning with prototypical mystical-type experiences (Ezquerra-Romano et al., 2018). Some of the included trials have not assessed the mediating role of mystical-type experiences, either due to irrelevance (e.g., the low-dose pharmacotherapeutic withdrawal studies), awaiting secondary analysis (e.g., Azhari et al., 2020; Grabski et al., 2022), or other unspecified reasons. The following sections presents findings from the trials that did – either in the primary paper itself or in a concomitant follow-up study.

Quantitative Measures

Ketamine trials. In their first cocaine-dependence study, Dakwar et al. (2014b) used two measurement scales to assess ketamine's psychoactive effects: The Clinician

Administered Dissociative Symptoms Scale (CADSS) and a modified Hood's Mysticism Scale (HMS). The CADSS is a 27-item scale measuring multiple facets of dissociation, such as derealization (e.g., grayscale vision), depersonalization (e.g., out-of-body experiences), or fragmentation of the self/identity structure (Bremner et al., 1998). The HMS is a 32-item questionnaire with four statements intended to assess each of the eight mysticism dimensions (Hood et al., 2001): (1) unity – "*something greater than myself seemed to absorb me*"; (2) timelessness/spacelessness – "*I have had an experience that was both timeless and spaceless*"; (3) ineffability – "*I have had an experience that is impossible to communicate*"; (4) unity in diversity – "*… I realized the oneness of myself with all things*"; (5) inner subjectivity – "*all things seemed to be conscious*"; (6) noetic quality – "*a new view of reality was revealed to* me"; (7) religious holiness – "*an experience which I knew to be sacred*"; (8) positive affect – "*I felt that all was perfection*". In the ketamine trial, the authors made the HMS briefer (covering each dimension with just one statement) and phrased items to apply to the drug-induced experience more directly, rather than asking for mystical experience throughout a lifetime (Dakwar et al., 2014a).

Compared to the active placebo lorazepam (a BZD), both IV ketamine infusions (0.41 and 0.71 mg/kg/52 min) lead to significant higher HMS scores 24 hours post-infusion (p = .012), but the high dose ketamine condition (0.71 mg/kg) increased scores even further (p = .027; Dakwar et al., 2014a). Even with a small sample size (N = 8), HMS scores were shown to significantly mediate motivation to quit cocaine (adjusted $R^2 = 0.775$, $p < .005$), though not for craving. When controlling for HMS scores, infusion condition no longer mediated motivation to quit or craving, suggesting that mystical-type experiences – rather than dose alone – were important for spontaneous motivation to quit in the non-treatment seeking cocaine-dependent participants (Dakwar et al., 2014a). There was a low-to-moderate, but insignificant (p = .012), correlation between dissociative- (CADSS) and mystical experience;

however, the dissociation scores were not found to significantly mediate primary outcomes (Dakwar et al., 2014a).

In a follow-up study for the second cocaine dependence study (Dakwar et al., 2016), the mediating impact of psychoactive effects, gauged by scores on the HMS (full 32-item version), CADSS, and the 16-item Near-Death Experiences Scale (NDES), were analysed (Dakwar et al., 2018). The primary outcome was operationalized as "global improvement", constituting decreased cocaine use in natural ecology, decreased cocaine self-administration (in lab), and decreased cocaine craving – all shown to be reduced after the 0.71 mg/kg IV ketamine infusion (Dakwar et al., 2016). As with the first cocaine study, mystical-type experiences – operationalized by high HMS scores – was the only type of psychoactive effects shown to significantly mediate global improvement in cocaine use ($\beta = 0.431$, $p = .0175$), estimated to account for 35.7% of the treatment response (Dakwar et al., 2018). Near-death experiences, as measured by the NDES, has been recognized as a form of mystical-type experiences (Pennachio, 1986), but was not itself a significant mediator of treatment outcomes.

In Dakwar et al.'s (2020) double-blinded RCT for 40 alcohol dependent participants, the mediating effect of mystical-type experiences was investigated further. The modified (for drug-induced mysticism) full 32-item HMS was once again used, as was the CADSS for dissociative symptoms. However, unlike the insignificant correlation between HMS scores and CADSS scores observed in the first cocaine-dependence study using the short-form version of the HMS (Dakwar et al., 2014a), a high correlation ($R = 0.489$, $p < .01$) was observed between dissociative- and mystical-type experiences in this study (Rothberg et al., 2020).

The group receiving the ketamine infusion (0.71 mg/kg/52 min; N = 17) reported significantly higher dissociation and mystical-type effects ($p < .05$) than those who received

the active placebo (Rothberg et al., 2020). Once again, HMS scores – and not CADSS scores – were shown to significantly mediate the relationship between ketamine infusions and positive treatment outcomes, specifically at-risk drinking ($p < .05$) and "time to relapse" ($p = .034$). When controlling for mystical-type effects (HMS-scores), ketamine infusions ceased to be significantly better than midazolam infusions for at-risk drinking (Rothberg et al., 2020). In a subscale analysis of the mediating effect of all eight mysticism dimensions of the HMS, "ineffability" was shown to significantly correlate with fewer heavy drinking days ($r_s = 0.624$, $p = .01$) while "positive affect" was correlated with more abstinence days ($r_s = 0.613$, $p < .05$) and a lower number of daily drinks ($r_s = 0.554$, $p < .05$; Rothberg et al., 2020).

As Krupitsky et al. started their research with a combined psychedelic-aversive technique for their alcohol dependent patients, they also wanted to assess whether "negative experiences" – or challenging experiences as they are now often – could predict how long the person would stay abstinent (Krupitsky & Grinenko, 1997). Negative experiences marked by intense horror, fear, or anxiety, were purposefully linked to alcohol by the researchers (aversive therapy element) but would also be spontaneously associated with alcohol by the patients themselves, as their mind was already primed for its negative effects in the preparation sessions (Krupitsky & Grinenko, 1997). Krupitsky and his team found a significant correlation between the intensity of negative experiences (self-reported quantitatively from 0 to 3) and a longer abstinence period ($p < .01$).

Psilocybin trials. In Bogenschutz et al.'s (2015) alcohol dependence pilot study, the acute hallucinogenic effects of psilocybin were thoroughly assessed by more than 200-questionnaire items from three assessment instruments: the 99-item Hallucinogen Rating Scale (HRS), the 94-item 5-Dimensional Altered States of Consciousness Scale (5D-ASC), and the 100-item States of Consciousness Questionnaire (SOCQ). However, only the "Intensity" subscale was used from the HRS – containing statements intended to capture

subjective drug intensity (Strassman et al., 1994). Two of the five dimensions of the 5D-ASC can be said to pertain to mystical-type experiences, namely “Oceanic Boundlessness” (OBN) and “Dread of Ego Dissolution” (DED). OBN is a construct that includes many of the facets measured by the HMS (e.g., unity, blissful state/positive affect, spiritual experience/holiness) while DED operationalize intense fear, resistance, and anxiety associated with the subjective feeling of dying that can occur during psychedelic influence (ego death/dissolution); both have previously been shown to significantly mediate antidepressant outcomes in PAT for treatment-resistant depression (Roseman et al., 2018). The SOCQ is a scale intended primarily to measure mystical-type effects, containing the 43-items of the Mystical Experience Questionnaire (MEQ) – supplemented with 57 “distracter” statements to complete the 100-item scale (Griffiths et al., 2006).

In the small-scale trial, the subjective intensity of the drug experience varied significantly (possibly due to alcohol-induced cross-tolerance), making it difficult to establish mediating effects of the experiential content (Bogenschutz et al., 2015). However, significant and substantial correlations were observed between MEQ-total scores and all four measures treatment response, including drinking days ($r = -.885$, $p = .002$), heavy drinking days ($r = -.852$, $p = .004$), alcohol craving ($r = -.810$, $p = .008$), and abstinence self-efficacy confidence ($r = .762$, $p = .017$). Comparable correlation sizes were observed for HRS-intensity scores; 5D-ASC summary score only significantly correlated with changed drinking behaviour, not craving or abstinence self-efficacy confidence (Bogenschutz et al., 2015). No clinical conclusions can be drawn from these correlations.

In Johnson et al.’s (2014) proof-of-concept PAT trial for nicotine dependence (smoking cessation), the authors assessed the psychoactive effects of psilocybin by using three assessment instruments: the full (modified) HMS, the HRS-Intensity subscale, and the SOCQ. To define “complete” mystical-type experiences, researchers defined such experiences

for participants who scored 60% or higher on an average score of the six subscales of the SOCQ/MEQ: (a) a sense of unity, (b) noetic quality, (c) profound positive mood, (d) a sense of awe/sacredness, (e) transcendence of time/space, and (f) ineffability/paradoxicality (Garcia-Romeu et al., 2015), corresponding roughly to the eight dimensions of the HMS (Hood et al., 2001; Pahnke & Richards, 1966). Nine participants (of 15 in total) scored above the complete mystical experience cut off after at least one of the psilocybin sessions. Out of 42 psilocybin dosing sessions in total, 13 of these (31%) led to complete mystical-type experiences; 10 complete mystical-type experiences (77%) occurred after 0.43 mg/kg dosing while only three (23%) occurred after 0.29 mg/kg dosing (Garcia-Romeu et al., 2015).

T-test comparisons between the 12 participants who managed to quit smoking for six months after the first psilocybin sessions and the three participants that did not manage to stay abstinent, showed that both groups had similarly intense drug experiences (2.51 vs 2.50 on HRS), however, quitters scored significantly higher on the SOCQ (65.2%, SD = 2.8) than those who relapsed (52.1%, SD = 7.9; $t_{40} = 2.02$, $p < .05$); HMS scores were also higher, but not significantly so (Garcia-Romeu et al., 2015). SOCQ scores, gauging mystical-type experiences, showed significant negative correlations with craving scores ($r = -0.65$, $p = .009$). Interestingly, three of the 13 complete mystical-type experiences (23%) were assigned to two of the participants who continued smoking (Garcia-Romeu et al., 2015).

A 12-month follow-up showed that 13 of 15 participants (86.7%) considered the psychedelic psilocybin experiences among the five most personally meaningful/spiritually significant happenings of their life (Johnson et al., 2016). At 6-months, the 12 participants who managed to quit reported the psilocybin experience(s) to be more personally meaningful ($t_{12} = 2.22$, $p < .05$), spiritually significant ($t_{55} = 2.11$, $p < .05$), and had a higher impact on wellbeing ($t_{55} = 2.07$, $p < .05$), than what relapsing participants reported (Garcia-Romeu et al., 2015). Personal meaning attributed to the psilocybin experiences were shown to positively

correlate with confidence to stay abstinent (r =-0.68, p = .005) and negatively correlate with temptation to smoke (r = -0.70, p = .004; Garcia-Romeu et al., 2015).

Key Change Phenomena

Challenging experiences. Among the alcohol dependent patients receiving KAP in Russia, many of them reported similar thematic content, even though it was highly individualized to their personal disposition (Krupitsky & Grinenko, 1997). While some of the themes describe classic dissociative phenomena, e.g., speeding through long corridors or tunnels (derealization) and out of body experiences (depersonalization), other recurring themes were more personally related to the pain associated with the alcoholism, such as estrangement from family members, a collapsing self-image, and profound loneliness (Krupitsky & Grinenko, 1997). The researchers found the intense psychologically challenging experiences to often be attributed as an intensive cleanse of the misery that had amassed over years, sometimes directly preceding feelings of spiritual rebirth, a sense of unity with the universe, feeling connected to a higher power, and other facets mystical-type experiences as taxonomized by the HMS and SOCQ/MEQ (Krupitsky et al., 1992; Krupitsky & Grinenko, 1997).

In a qualitative content analysis of 17 psilocybin sessions in Bogenschutz et al. (2015), "dysphoric experiences" were often identified by the alcohol dependent participants as meaningful manifestations of their challenges, which could invigorate their resolve to live a better life (Nielson et al., 2018). In a qualitative analysis of Grabski et al.'s (2022) ketamine trial for alcohol dependence, participants reported some transient negative experiences of paralysis, nausea, and vomiting, but did not appear to explicitly attribute these experiences as particularly meaningful (Mollaahmetoglu et al., 2021).

Ego-Dissolution and Insights into Life and Self-identity. One of the participants in the KAP alcohol dependence study stated: "*I ceased to exist, I disappeared, yet still just my*

consciousness existed" (Krupitsky & Grinenko, 1997). For many people, the subjective feeling of dying or ceasing to exist instils an intense sense of dread, but the parallel realization that unfiltered consciousness continues after their self-identity "dies" can be a monumental moment that leads to lasting changes in perspectives on life and meaning. For example, the only alcohol participant who experienced intense mystical-type experiences in both psilocybin sessions in Bogenschutz et al. (2015) – "Adam" – emphasized that the sense of separation between the old and new Adam, the one who drinks and the one who does not, was strengthened by the experience of "losing himself" as an individual, especially in the second session where his self-knowledge periodically faded completely (Nielson et al., 2018). A similar experience was described by a participant in Johnson et al.'s (2015) PAT smoking cessation trial, who felt as if she had died as a smoker and gone through a rebirth as a person who does not smoke (Noorani et al., 2018).

For an unnamed participant in Grabski et al.'s (2022) ketamine trial for alcohol dependence, their experience of ego dissolution led to a profound feeling of life's preciousness and brevity, making it easier to let go of self-deprecating thoughts and doubt (Mollaahmetoglu et al., 2021). For a different participant, ego-dissolution sparked a sense of pragmatic acceptance regarding the transition from life to death, and for another one it helped him/her contextualize trauma as something intrinsically "attached" to them – something that can and should be integrated into their being rather than fought or avoided with alcohol (Mollaahmetoglu et al., 2021).

Discussion

The reviewed material illustrates significant methodological heterogeneity between the clinical trials in terms of approaches to preparation, dosing sessions, treatment setting, adjunct therapies, debriefing/integration, and other factors. In other words, the necessary evidence to directly compare therapeutic outcomes between the therapeutic frameworks is

lacking. However, all trials (excluding Wong et al., 2014) showed at least partial therapeutic response, and some results and follow-up analyses indicate that certain implementations may serve as valuable additions to ketamine- or psilocybin-based addiction treatments. The following section will elucidate key findings and contextualize their implications.

Clinical Interpretations

Excluding the four withdrawal studies (Jovaisa et al., 2006; Pizon et al., 2018; Shah et al., 2018; Wong et al., 2014), all the trials reviewed reported less drug misuse in response to treatment. However, while some of the treatments reported long-term abstinence for the majority, e.g., Krupitsky et al. (2007) and Johnson et al. (2014), others saw only transient improvements that quickly ceased to be statistically superior to placebo within the first week (e.g., Dakwar et al., 2016). The following sections looks at treatment effects that may play a role for immediate and sustained recovery from addiction.

Withdrawal

First, a note on the alcohol- and opiate withdrawal studies is warranted. Two retrospective reviews used 60-minute IV ketamine infusions ranging from 0.15 mg/kg to 0.30 mg/kg to supplement BZD-based withdrawal management (Pizon et al., 2018; Wong et al., 2014). These ketamine-doses have previously been shown to elicit no more psychoactive effects than BZD themselves (Fava et al., 2018) but still led to significantly better therapeutic response than BZD in one of the studies (Pizon et al., 2018). Shah et al. (2018) reviewed ICU-patients that received significantly higher ketamine doses (0.75-1.60 mg/kg/h) for BZD-resistant alcohol withdrawal and found reliable withdrawal attenuation absent of any adverse events. The alcohol-withdrawal reviews indicate that ketamine may have utility in withdrawal management resistant to BZD, but there is currently little convincing evidence to suggests that it is a better supplemental alternative than other eligible alcohol withdrawal medications, such

as acamprosate or gabapentin (Ghosh et al., 2020). No other addiction related outcomes were assessed in these studies.

In contrast to the alcohol-withdrawal reviews, the opiate-withdrawal RCT followed patients up for four months following a general anaesthesia procedure that included a 0.5 mg/kg/h IV ketamine infusion and acute opiate detoxification (Jovaisa et al., 2006). This presents one of the few opportunities to observe the effects of sub-anaesthetic ketamine in therapeutic doses administered without any associated psychoactive effects, isolating the pharmacological effect of ketamine alone. Interestingly, despite clear response to ketamine and reduced physiological withdrawal symptoms during anaesthesia, ketamine did not predict higher abstinence rates four months later compared to the control group (Jovaisa et al., 2006).

Johnson et al.'s (2014) psilocybin-based smoking cessation program saw 80% of the long-term chronic smokers stay abstinent for six months after the first dosing session. As is expected with acute smoking cessation in general, withdrawal symptoms were reported as relatively high the week after the target quit date (on the day of the first psilocybin session). Moreover, withdrawal symptoms steadily declined for the next three weeks (Johnson et al., 2014), following the typical pattern of homeostatic normalization after a period of accommodating pharmacological processes compensating for the effects of an external agent (nicotine). In other words, it does not seem like psilocybin acutely attenuated immediate withdrawal, though no formal mediation analysis was conducted to back up this interpretation. It seems likely that the psilocybin-sessions and accompanying treatment program helped participants deal with cessation-related withdrawal and urges rather than directly attenuate them.

Craving

While none of the withdrawal-studies assessed short- or long-term changes in craving/urges, all other studies except Krupitsky & Grinenko (1997) reported craving-related

outcomes. Craving is not simply another symptom of addiction – it is arguably *the* defining psychological aspect driving risky use and the addiction-relapse cycle. This section discusses craving-related changes reported throughout the study periods. The outcomes are discussed in in the following order corresponding to drug-specific cravings: (1) cocaine-craving, (2), alcohol-craving, (3) opiate-craving, (4) tobacco- and cannabis-craving.

In their two initial cocaine-dependence trials, Dakwar et al. (2014b, 2016) recruited unmotivated non-treatment seeking participants, yet – in the first trial – participants reported significantly higher motivation to quit 24 hours after the ketamine infusions, even after the "low" 0.41 mg/kg IV infusion. Craving was significantly reduced in both studies (about 60%) but the accompanying analysis from the first trial suggests that the psychoactive effects, specifically mystical-type effects, only mediated motivation to quit, not craving (Dakwar et al., 2014a). Mediation analysis in the second trial concluded that mystical-type experiences could explain 35.7% of the variance in global improvement, but as craving was only of three constituent of the composite "global" measure, its relationship with craving remains unclear.

In their third trial, and first study with treatment-seeking cocaine-dependent participants, the treatment group who received the IV ketamine infusion with concomitant weekly MBRP sessions showed sustained reductions in craving at the end of the 5-week study period (-58.1%), with 12 of 27 participants (44%) remaining abstinent at the final 6-month follow-up; none in the active placebo group reported the same (0/28; Dakwar et al., 2019). Statistical analysis has not yet confirmed a relationship between reduced craving and abstinence, but one possible interpretation is to posit that MBRP – a relapse prevention program – may have made craving related biases (priors) and triggers particularly salient during a ketamine-induced neuroplastic brain environment, opening them up to modification and reconsolidation (consistent with the REBUS model and MRM findings reported by Das et

al. 2019). Unfortunately, this review could not identify any related follow-up studies that analyse therapeutic mediators.

Four studies assessed changes in alcohol-craving after ketamine- or psilocybin sessions. In Dakwar et al.'s (2020) RCT combining IV ketamine (0.71 mg/kg/52 min) with a MET program, sustained changes in craving were not statistically better than active placebo. The same conclusion was reached in the most recent RCT combining IV ketamine (0.80 mg/kg/40 min) with MBRP or alcohol education, finding no statistically significant craving difference between ketamine- and placebo (saline) groups at the 3-month primary outcome measure (Grabski et al., 2022). Das et al.'s (2019) "problematic drinkers" scored significantly lower on all three craving-related measures (anticipated enjoyment, cue-induced craving from presentation, and urge to binge/drink more) in the post-acute ketamine infusion phase (the day after), but only in the group that simultaneously retrieved a maladaptive reward memory (MRM) associated with alcohol. This may indicate that even the short-lived craving-attenuation observed in other studies may depend on contextual factors.

In the only published psilocybin-trial for alcohol dependence, Bogenschutz et al.'s (2015) participants did not demonstrate significantly lower craving in the immediate period after the first 0.30 mg/kg psilocybin dose (Week 5), but the craving scores had dropped significantly from baseline four weeks later (Week 8; $p < .05$) and were further reduced the week after (Week 9) – following the second 0.40 mg/kg dosing session (Bogenschutz et al., 2015). At the last follow-up in Week 36 (eight months after first dosing in Week 4), alcohol craving had dropped even lower. What is interesting about these findings is that craving seemed to gradually decrease throughout the study period without psilocybin sessions seeming to acutely attenuate craving immediately. While it is possible to speculate that psilocybin may induce some delayed pharmacological effects, akin to the typical two-week waiting period associated with antidepressant effects from conventional psychotropic drugs

(Commons & Linnros, 2019), it seems more likely that other non-craving related changes initiated by the psilocybin session can better account for drinking-related outcomes.

For opiate craving, the "micro-scale" pilot study (N = 3) combining a single 0.75 mg/kg IV ketamine infusion with multiple rTMS and mindfulness-based interventions (five sessions over 1-2 weeks) found that the craving scores had dropped by 65.7% after their combined treatment protocol (Pradhan & Rossi, 2020). Although three participants clearly limit the validity and value of clinical interpretations, it is worth noting that the opiate-craving reductions observed here are comparable to the cocaine-craving reductions Dakwar et al. (2019) reported after a 0.71 mg/kg IV ketamine infusion combined with MBRP – another mindfulness-based protocol. Indeed, the synergy between mindfulness training and ketamine may prove especially effective at controlling craving and promoting non-reactivity to stressful situations and drug-cues. However, drug use outcomes were not reported by Pradhan and Rossi (2020), hence no meaningful abstinence-contribution can be attributed to the craving scores.

In the KAP-studies for heroin-dependent participants, the high IM ketamine infusion (2.0 mg/kg) condition led to significantly less heroin craving the first six months following the psychedelic experience (compared to a 0.2 mg/kg "microdose"), but repeated sessions did not attenuate craving further (Krupitsky et al., 2002, 2007). Despite insignificant differences in craving outcomes between the group who received one dose and the group that were infused three times, the latter showed more than twice the abstinence rate a year later (50% vs. 22.2%). If attenuated craving was an important independent mediator of long-term outcomes, the two treatment conditions should have been far more comparable than the results suggest. Alternatively, prolonged craving attenuation may have been substantial enough in the single-dose group for additional reductions to result in non-significant

differences given the statistical power of the sample. Nevertheless, these findings point towards treatment effects beyond craving alone.

Finally, for cannabis- and nicotine-craving, the respective ketamine- and psilocybin trials reported disparate results. Azhari et al. (2020) administered a single 0.71 mg/kg IV infusion supplemented with a combined MBRP and MET treatment program (tailored for cannabis-dependence). However, despite significantly less cannabis use reported throughout the study period, no significant changes in craving were observed (though a negative trend indicated craving reductions in the post-acute phase). In contrast, Johnson et al.'s (2014) participants reported significantly lower craving at all assessment points throughout the 6-month study period. Considering the high abstinence rate (80%) it is not surprising that cigarette-craving remained significantly lower than baseline. Conversely, the relatively high withdrawal scores after one week after was not accompanied by comparably high craving scores, suggesting that the automatic link between drug withdrawal and craving was at least partially broken after psilocybin-dosing.

Modification and Reconsolidation of Biased Reward Memories

In the study examining ketamine as a disrupter of drinking-related MRM reconsolidation (Das et al., 2019), ketamine combined with MRM retrieval led to lower anticipated enjoyment of alcohol and lower cue-induced craving when presented with a glass of beer. Interestingly, the group who received ketamine while not simultaneously retrieving drinking-related MRMs, did not show significant reductions in alcohol cue-reactivity and craving after the dosing (Das et al., 2019).

These findings are consistent with the general premise of the REBUS-model (Carhart-Harris & Friston, 2019) if the MRM is framed as a biased prior (belief) about the value of alcohol. During a malleable reconsolidation window, the activation and concurrent salience of the MRM (prior) allows it to be revaluated or "reweighted" by the associative network –

particularly the mesolimbic/ventrostriatal reward and salience projections – during psychedelic/hallucinogenic influence, possibly leading to lasting changes in alcohol's appeal when the drug wears off and neural entropy stabilizes. In other words, despite the trial itself being classified as a pharmacotherapeutic study in the review, such an interpretation would implicate a clear drug-interaction with psychological phenomena (memories) and not strictly pharmacological events.

Das et al. (2019) alludes to some overlap between their memory reconsolidation method and the directive session-work Krupitsky & Grinenko (1997) conducted with their alcohol dependent patients, though emphasizing that the latter did not *explicitly* utilize reconsolidation-based mechanisms. It is, however, worth noting that the Krupitsky method is one of the only cases of directive psychotherapeutic exploration during the psychedelic sessions, which may – in hindsight – be justified if their more directive approach facilitates reconsolidation of MRMs. In their original report, Krupitsky et al. (1992) did in fact describe an aversive-therapeutic psychedelic model as their framework, with the explicit purpose of creating strong aversive associations to alcohol and alcohol-related memories. While the therapeutic rationale for doing so differs significantly from Das et al. (2019), it seems reasonable to assume that both settings can activate MRMs for modification and reconsolidation in the acutely entropic neural environment instigated by ketamine.

Abstinence Self-Efficacy

One way to understand the relatively low explanatory power attributable to withdrawal- and craving outcomes, is to instead look at how ketamine- and psilocybin sessions impacted participants' belief that they could control their dependence, or so-called "abstinence self-efficacy". For example, while alcohol-dependent participants in Bogenschutz et al. (2015) did not experience significantly less temptation or craving after the first psilocybin session, abstinence confidence was significantly higher in Week 5 than it was

right before session 1 in Week 4 ($p < .01$). This was reflected by higher motivation and commitment to change, or as one participated put it: "… *If those urges come up, I plan on fighting them*" (Nielson et al., 2018). In the other PAT trial, the smokers showed a similar resolve to stay abstinent (Johnson et al., 2014). Quantitative measures of smoking abstinence self-efficacy were arguably the most prominent and sustained change after the first psilocybin session: the abstinence confidence doubled after the psilocybin session and remained at the same high level throughout the 6-month study period, virtually unchanged by time or additional sessions (as confidence was already approaching max scores; Johnson et al., 2014).

Increased abstinence confidence was reported in several ketamine trials. One pertinent example is Azhari et al. (2020), whose cannabis-dependent participants had doubled their confidence scores on cannabis-craving non-reactivity (not enacting on impulses), which translated into far less cannabis use in the weeks following the ketamine infusion, regardless of inconsistent craving reductions. Dakwar et al. (2014b, 2016) also observed significant spontaneous motivation to quit in non-treatment seeking cocaine-dependent, manifesting as significantly less cocaine use the following week(s), even with craving scores not being significantly lower at the 6-day assessment in the second trial (Dakwar et al., 2016). Other studies included secondary measures of abstinence confidence/self-efficacy but did not report the necessary statistics to make meaningful interpretations (despite clear trends showing acute increases in motivation to quit and reduced stress/craving-reactivity). In summary, higher commitment to change and better control of craving impulses appear to be more crucial for reduced drug use than attenuated craving itself.

Mystical-Type Experiences

Spiritual experiences are notoriously difficult to formulate and quantify, making their therapeutic appeal limited in many scientific circles. However, between all the talk of transdiagnostic pharmacology, rapid upregulation in neuroplasticity, and regulated brain

networks, mystical experiences represent the undeniable elephant in the room for psychedelic researchers. These experiences are not mere phenomenological curiosities that accompany a psychotropic drug; they represent momentous, transformative, events that can go on to change the person's life forever.

Johnson et al. (2016) found that most participants (86.7%) considered their psilocybin experiences among the five most personally meaningful happening of their life – even after a year had passed. At face value, such findings seem unprecedented, yet comparable outcomes have been observed in both healthy subjects (Griffiths et al., 2008) and individuals approaching the end of their life, suffering from existential distress (anxiety and depression) due to terminal illness (Agin-Liebes et al., 2020). From a clinical standpoint, such findings are difficult to adequately contextualize.

If we look at addiction from Frankl's (1979) existential, psychospiritual perspective, mystical-type experiences occasioned by psychedelics may release the person from the solitude of their "existential neurosis" by reinvigorating a sense of purpose and meaning in life. The review found some quantitative evidence associating mystical-type experiences with addiction-related outcomes, but only Dakwar et al. (2018) seemed to have the necessary data to calculate their relative mediating contribution, estimating HMS scores (mysticism scale) to account for 35.7% of attenuated cocaine use in the non-treatment seeking sample.

Though not directly measuring mediation, significant and substantial correlations were found between HMS scores and motivation to quit cocaine (Dakwar et al., 2014a), reduced cocaine use (Dakwar et al., 2018), and at-risk drinking (Rothberg et al., 2020); dissociative effects alone, as measured by the CADSS, was not significantly correlated with the same outcomes. In the PAT trials, SOCQ/MEQ scores (a different mysticism scale) were associated with attenuated smoking urges, smoking cessation, less alcohol craving, less at-risk drinking, and increased confidence to stay abstinent (Bogenschutz et al., 2015; Garcia-Romeu et al.,

2015). Drug intensity alone was not associated with smoking cessation but did show significant correlations with drinking related outcomes.

Overall, in all included studies that quantitatively analysed experiential mediators, measures for mystical-type experiences were the only type of subjective effect that was consistently associated with therapeutic outcomes. Based on follow-up interviews, participants themselves often attributed the utmost importance to their unique experience; even the challenging moments were seen as important turning points in their therapeutic journey (Krupitsky & Grinenko, 1997; Bogenschutz et al., 2015).

Participants who experienced full ego dissolution also typically interpreted it as a spiritual rebirth or "shedding of their old, addicted skin", reporting reconnection with the world in the process. Moreover, the interviews clearly illustrated the "ineffability" of the subjective experience, though descriptions included recurring themes of transcendence of time and space, intensely felt positive mood, shift from external to internal locus of control, commitment to change, a sense of unity or interconnectedness, deep understanding/insight into their addictive behaviour, and a changed relationship to themselves and the drug of choice (Krupitsky et al., 2002; Mollaahmetoglu et al., 2021; Nielson et al., 2018; Noorani et al., 2018). Notably, the qualitative descriptors from the interviews often corresponded with the assessment items included in the quantitative mysticism scales (HMS and SOCQ/MEQ). This may be explained by narrative editorial choices by the authors, items accurately representing the prototypical mystical-type experiences, or the participants being influenced/primed by the initial administration of questionnaires prior to interviewing – replacing their ineffability with statements offered by the questionnaires.

In summary, even though there is limited data to conclusively establish mystical-type experiences as fundamental to antiaddictive outcomes in ketamine- and psilocybin treatment, the preliminary indicative correlations and paramount significance attributed to their influence

by the experiencer, suggests that the accompanying insights into alternative world views, profound sense of awe, and restructucturalization of the self-concept, may help the person transform a “meaningless” life in addiction into a meaningful life marked by autonomy and purpose.

Interactions Between Pharmacology, Psychotherapy, and Phenomenology

Beyond the mystical-type experiences, participants found the strong therapeutic alliance with the researchers, which was initiated during preparation and strengthened after the session, to be important for the quality and long-term outcomes of the psychedelic experience (Mollaahmetoglu et al., 2021; Noorani et al., 2018). For example, two participants in the smoking cessation trial (Johnson et al., 2014) expressed that preparation sessions with the psychotherapist helped them think of their self-concept beyond “smoker”, reframing it as a behaviour rather than a personal disposition; this preparation “set” was subjectively experienced as reinforced during the psilocybin sessions – “cementing” their resolve to quit (Noorani et al., 2018). The preparation themes were found to become salient during sessions in the Krupitsky KAP trials too, but the Russian researchers were directly prompting participants to think about the therapeutic themes during the ketamine sessions themselves. As both directive- and non-directive approaches appear to bring forth therapeutic material during psychedelic sessions, the therapeutic context may become salient by virtue of enrolment in a treatment program or full hospitalization.

Few studies compared the relative contribution of one therapeutic setting with another, excluding a follow-up investigating the effects of overtone-based music (e.g., Indian classical music) and Western classical music for the smokers in Johnson et al’s (2014) sample. They found that the sessions playing overtone-based music was associated with higher mystical-type experience scores, but effects on smoking abstinence could not be established (Strickland

et al., 2020). However, the impact of many other therapeutic variables remain completely unexplored.

Regardless of the psychotherapeutic program used as the adjunct therapy – be it smoking cessation CBT, drinking cessation MET, or cocaine cessation MBRP – all appeared to synergize with psilocybin and ketamine. Even the basic alcohol education program used as a control to MBRP in Grabski et al. (2022) took on a new meaning after the ketamine infusion: "*… I probably wouldn't have listened to deeply … ketamine made me more willing to engage with it.*" (Mollaahmetoglu et al., 2021). Another participant in the same study felt that all parts of the program worked together: "*… I feel that it is really important that when you are split open, you know, in such an intense and life changing way that you are given new thoughts and, you know, that someone gives you something to refill that, so you change stuff.*" (Mollaahmetoglu et al., 2021).

The dualistic divide between those who attribute therapeutic response to neurobiological processes versus those favouring meaning-oriented explanations, represents perspectives that possibly – or probably – observe the same phenomenon from each side of a contrived demarcation line. Scientific monism does not necessitate a dogmatic materialistic conviction disregarding the influence of consciousness on physical brain states. Compared to contemporary ketamine literature, modern psilocybin research has to a much greater extent held phenomenological manifestations to the same level of scientific scrutiny as pharmacological events (Carhart-Harris et al., 2018; Walsh et al., 2022).

Dakwar and colleagues represents one of the few currently active ketamine research teams that investigates the clinical implications mystical-type experience; however, their methodology and dosing protocols diverges significantly from the psychedelic integration principles guiding PAT and KAP treatment. In their two most recent trials (Dakwar et al., 2019, 2020), the cocaine-dependent and alcohol-dependent participants showed impressive

and sustained abstinence half a year after ketamine: 44% (none in active placebo group) and 75% (27% in active placebo group), respectively. Other than a slightly higher dose in the alcohol-dependence study (0.71 mg/kg/52min versus 0.50 mg/kg/40 min), the studies only decidedly differed with regards to the adjunct treatment programs: MBRP for cocaine dependence and MET for alcohol dependence – both treatment protocols lasted for five weeks.

Even though higher absolute abstinence rates were reported in the alcohol-dependence study, only 8 of 17 participants could be reached by phone (Dakwar et al., 2020); conversely, the full ketamine-group was reached in the cocaine-dependence study (27/27; Dakwar et al., 2019). Furthermore, the difference between treatment and placebo response were comparable in both studies, hence the outcomes from the MBRP-cocaine-dependence trial were arguably more impressive and conclusive than the MET-alcohol-dependence trial. Yet, the overall impression is that ketamine showed significant synergy with both treatment programs. While none of these studies directly examined the synergy between the psychotherapeutic techniques and ketamine infusions, there is prior evidence indicating that ketamine can spontaneously increase motivation (Dakwar et al., 2014; Nogo et al., 2022) and mindfulness (Pradhan et al., 2015; Pradhan & Rossi, 2020), which may enhance engagement with these treatment modes. However, Grabski et al. (2022) could did not observe a significant advantage for ketamine combined with MBRP over ketamine combined with basic alcohol education – not because ketamine and MBRP was not effective, but rather because ketamine also seemed to significantly potentiate engagement with the alcohol education.

To summarize, both psilocybin and ketamine appear to synergize significantly with psychotherapy on a general level, but unexplored interactions with specific therapeutic frameworks may yet prove to potentiate therapeutic outcomes even more. It seems like there

is a clear bidirectional relationship between psychotherapeutic measures, pharmacological drug effects, and experiential content, but exactly how they link together remains unclear.

Future Directions: The Path Towards an Evidence-Based Framework

One of the key issues at heart of this thesis was to examine whether the current evidence favours some ketamine- or psilocybin-based addiction treatments over others. The dearth of directly comparative data makes it difficult to conclude that one broad framework is better than another. However, there are indications that point towards some specific implementations.

First, a look at dosing. If we exclude the withdrawal-management studies, ketamine doses ranged from 0.5 mg/kg to 3.0 mg/kg while psilocybin doses were administered within a more limited range from 0.30 mg/kg to 0.43 mg/kg. It would be easy to simply conclude that higher doses trended towards better long-term outcomes than doses, thus higher equals better. However, high sustained abstinence rates observed in the Dakwar et al.'s (2019, 2020) trials, using 0.50 mg/kg IV and 0.71 mg/kg IV for cocaine- and alcohol-dependence respectively, suggests that moderate doses can be effective when paired with a well-designed psychotherapeutic treatment protocol.

Krupitsky initially favoured 3.0 mg/kg IM injections for alcohol dependent patients but reduced this to 2.0 mg/kg IM for the heroin-dependence trials. If we use the relative bioavailability/potency difference between IV and IM injections, estimated at around 50% by Grabski et al. (2022), a corresponding IV infusion would be slightly above 1.3 mg/kg. Interestingly, single ketamine infusions led to slightly higher abstinence rates among the cocaine-dependent participants receiving 0.5 mg/kg IV (Dakwar et al., 2019) than the heroin-dependent patients receiving 1.3 mg/kg "IV" (2.0 IM; Krupitsky et al., 2002) at the 6-month follow-up (44% vs. ~ 35%). Likewise, comparable outcomes were observed between their alcohol dependence studies, administering 0.71 mg/kg IV and ~ 1.67 mg/kg IV (2.5 mg/kg

IM) respectively: after six months, 75% of reachable ketamine participants (6/8) reported abstinence in Dakwar et al. (2019); after one year, 65.8% (73/111) remained abstinence in Kruptisky et al.'s (1997) KAP study.

Based on these results, future research could benefit from experimenting with 0.5-1.7 mg/kg IV ketamine infusions within the same treatment protocol, as various doses within this range have been shown to be effective when combined with different treatment programs. What seems clear, is that repeated dosing – especially in a psychedelic integration paradigm – may significantly prolong and strengthen the therapeutic response, given the high one-year abstinence rates observed in Krupitsky et al. (2007) and Johnson et al. (2014) whom both administered psilocybin/ketamine on three occasions with monthly intervals between each dosing. Notably, a single KAP session was significantly more efficient at promoting sustained abstinence in the alcohol-dependence trial than it was in the heroin-dependence trials (65.8% vs. ~ 22.2-25.7%); however, with repeated (three) sessions heroin dependent patients were approaching similar one-year abstinence rates (50%; Krupitsky et al., 2007). This may indicate a drug-specific interaction, or it could reflect different contextual factors perpetuating a legal addiction (alcohol) versus an illegal one (heroin).

One way future trials could control the effect of drug-specific "pharmacological confounds", is to enrol participants with recognized behavioural addictions, such as gambling- or gaming disorder. The addiction profile of these individuals tends to mirror the psychopathology of individuals addicted to substances (Brand et al., 2020). A behavioural addiction trial could control for possible alcohol-induced NMDA-altercations, mu-opioid receptor downregulation through heroin abuse, and countless other possible polydrug interactions, arguably providing more "distilled" antiaddictive indications that apply to all addictions.

The evidence reviewed in this thesis is insufficient to conclude that one specific treatment framework is superior to all others, but it seems reasonable to state that psychotherapeutic implementations significantly improve sustained abstinence relative to basic pharmacotherapeutic therapy. Qualitative interviews indicated that the therapeutic set and setting was important in both ketamine- and psilocybin-based treatments, but quantitative evidence is still sorely lacking. Combining MRM retrieval with ketamine (or possibly psilocybin) seems to be a promising and simple addition to attenuate craving and compulsive use, hence future research should add similar measures in their treatment protocols. It can be argued that the preparation sessions essentially accomplish the same by priming the individual to think about their drug of choice during the psychedelic sessions, thus the extent of preparation work should also be experimentally manipulated and examined in future trials.

Overall, the "givenness" of set and setting as therapeutic mediators needs to be supported by more empirical evidence. However, the most pressing issue limiting contextual analysis is the overall lack of SUD/addiction trials, especially for psilocybin. Eleven SUD psilocybin studies, many of which are phase II clinical trials (a/b), are currently ongoing or in a formal planning/recruitment-phase (clinicaltrials.gov), representing a drastic increase in available data in the coming years. A comparable number of upcoming ketamine SUD trials are also registered, representing increased focus on addiction disorders in clinical ketamine research.

In summary, in addition to consolidating the initial indications from the pilot studies, future research should devote additional resources to manipulating set and setting variables that may be important mediators of addiction recovery, with the purpose of generating data for evidence-based therapeutic frameworks for both psilocybin- and ketamine treatment.

Thesis Limitations

In efforts to include all therapeutic designs and outcomes from relevant clinical trials, some concessions were necessary to fit the scope of the thesis. For example, the implicated therapeutic role of music was only tangentially mentioned (see reviews by Kaelen et al., 2018 or O'Callaghan et al., 2020), and comorbidity resolution of depression and anxiety as a possible mediator of addiction recovery was not explored at all. Furthermore, recent papers analysing the mediating role of the therapeutic alliance (Murphy et al., 2022) could have added an interesting perspective to the analysis but did unfortunately not fit within the thesis parameters. Analysis of the potentially significant impact of experimental unblinding and expectancy effects (see Muthukumaraswamy et al., 2021) was excluded for the same reason.

Finally, a major complication affecting the whole thesis was the lack of psilocybin SUD trials relative to ketamine SUD trials, which counterintuitively corresponded with less interpretative information regarding ketamine's antiaddictive properties. In other words, the two PAT trials alone had more related follow-ups and theoretical articles analysing the outcomes than all the ketamine trials combined (most of which consisted only of the primary study/paper). While it is fair to draw some parallels between ketamine and psilocybin's therapeutic mechanisms, this dissertation may arguably have overextended their similarities as a result of few studies meaningfully analysing the psychoactive effects of ketamine in clinical interventions conjoined with limited clinical data from psilocybin-based treatments. Relatedly, unique pharmacological interactions between various drugs of dependence (e.g., cocaine vs. alcohol) and psilocybin or ketamine may play a more significant role for therapeutic outcomes than what has been implicated here.

Conclusion

This review addressed the three research questions formulated in the problem statement but could only provide a conclusive answer for the first one. Analysis of 17 clinical studies revealed that both psilocybin and ketamine has been used for high-dose psychedelic

integration therapy (or psychedelic-peak therapy), but only ketamine has been used in other ways as well, including pharmacotherapeutic interventions and combined treatments supplementing moderate-dose ketamine infusion(s) with adjunct psychotherapy based on motivational- or mindfulness interventions. Subjective effects, particularly mystical-type experiences characterized by great personal meaning, was consistently attributed as crucial to recovery by participants and further consolidated by significant correlations with increased abstinence-confidence and reduced drug use; however, only one trial calculated a direct mediation coefficient, limiting clinical conclusions for the study sample.

Lastly, evidence suggests that repeated high-dose psychedelic integration therapy, using either psilocybin or ketamine, can sustain abstinence for at least a year in 50% of participants or more. Notably, comparable 6-month abstinence rates were observed in some combined ketamine treatment trials, suggesting that moderate ketamine doses also can facilitate addiction recovery when combined with appropriate psychotherapy. Overall, evidence pointed towards a significant synergy between ketamine/psilocybin-related effects and concomitant psychotherapy, though few indications favoured one specific psychotherapeutic framework over another. In conclusion, eligible evidence currently supports psilocybin only as a psychedelic integration therapy for SUDs (due to no comparative data) while ketamine shows significant antiaddictive promise in both integrative peak-therapy settings and other adjunctive therapies combining IV infusion(s) with psychotherapy. In any case, mystical-type experiences appear to be associated with attenuated drug use and positive outcomes overall, even though their relative contribution remains uncertain. Future research should focus on manipulating the therapeutic set and setting to estimate how contextual factors interact with pharmacological effects, mystical-type effects, and therapeutic outcomes.

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