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IUPHAR-Review: The Integration of Classic Psychedelics into Current Substance Use Disorder Treatment Models

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IUPHAR-review: The integration of classic psychedelics into current substance use disorder treatment models

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ABSTRACT

Substance use disorders (SUDs) have an enormous impact on public health. With classic psychedelic-assisted therapies showing initial promise in treating multiple SUDs, it is possible that these treatments will become legally available options for patients with SUDs in the future. This article highlights how classic psychedelic-assisted therapies might be integrated into current clinical practice. We first describe contemporary evidence-based treatments for SUDs and highlight how classic psychedelic-assisted therapies might fit within each treatment. We suggest that classic psychedelic-assisted therapies can be integrated into most mainstream evidence-based SUD treatments that are currently used in clinical settings, indicating broad compatibility of classic psychedelics with contemporary SUD treatment paradigms.

1. Introduction

Substance use disorders (SUDs) are among the leading causes of preventable morbidity and mortality worldwide [94,95]. According to the National Survey on Drug Use and Health (NSDUH), 20.4 million adults in the US experienced a SUD in 2019 [111]. These statistics underscore persistent difficulties in treating SUDs, with two major problems being relapse (with an estimated rate of 40%−60%) and access to treatment (of those individuals who needed care, only 19% received treatment in 2017; [112]. Innovative approaches and new treatment options are needed to combat the ongoing SUD mental health crisis.

While preliminary, several studies have shown promising results for the use of psychedelics in treating various SUDs (for a comprehensive review, see [48]; [25]. Here we focus on *classic* psychedelics, or those that work predominantly through their agonism at serotonin 2 A receptors (5-HT_{2A}Rs) and include lysergic acid diethylamide (LSD), psilocybin, N,N-dimethyltryptamine (DMT; a primary active component of the Amazonian admixture ayahuasca), and mescaline. Classic psychedelics have garnered considerable research interest for addiction treatment historically [62,75,99] as well as in recent years [47]. Some evidence also suggests that non-classic psychedelics (involving primary mechanisms of action other than 5-HT_{2A}R agonism; including ibogaine, ketamine, and MDMA) may be possible options for treating SUDs [100, 101,22,23,29,63,64,76].

Contemporary pilot studies assessing classic psychedelics in the treatment of SUDs have been conducted for both alcohol use disorder (AUD; [7] and tobacco use disorder (TUD; [50]. While lacking active controls and with relatively small sample sizes, these studies nonetheless reported large within-subject effects, with reductions or cessation of substance use lasting more than 6 months [7,50]. A long-term follow up of the psilocybin-assisted smoking cessation trial, which involved cognitive behavioral therapy (CBT) as well as two to three high-dose psilocybin administrations [50], found 53% of participants to be biochemically confirmed continuously abstinent 12 months after the end of treatment [51]. This is substantially higher than the mean rate of 22.5% continuous abstinence at 12-month follow-up for varenicline, considered the current gold standard smoking cessation medication [44]. Importantly, the first randomized controlled trial using psilocybin to treat AUD was recently completed [9]. Patients received two dosing sessions with psilocybin or active placebo (diphenhydramine), alongside 12 weeks of psychotherapy. The investigators found a significant reduction in self-reported percentage of heavy drinking days, drinking days, and drinks per day in the psilocybin group during the 32-week follow up period [9], suggesting that psilocybin has therapeutic

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potential in this condition.

A number of survey, observational, and correlational studies have also supported the therapeutic potential of psilocybin in not only alcohol use disorder and tobacco use disorder, but more broadly in the treatment of various SUDs including cannabis, opioid, and stimulant use disorders [115,30,34,35,52,54,93] with a number of projects on-going (see Table 1). A pilot study is underway evaluating psilocybin in the treatment of cocaine use disorder with promising preliminary findings (Hendricks et al., ClinicalTrials.gov Identifier: NCT02037126), and larger, randomized controlled trials are following the pilot studies of psilocybin in alcohol use disorder and tobacco use disorder [9]; Johnson et al., ClinicalTrials.gov Identifier: NCT01943994). While rigorous RCTs are needed before the efficacy of classic psychedelics in treating SUDs can be adequately assessed, the encouraging evidence to date informs the present consideration of how classic psychedelic therapies may be effectively incorporated into modern clinical practice.

Further scholarship should explore how classic psychedelics might work alongside current treatment models, and how integration of classic psychedelics might reshape clinical protocols. In this paper, we review current SUD treatment methods, preliminary classic psychedelic therapy intervention designs, and points of possible complementarity. We review each current treatment modality in turn—beginning with pharmacotherapy (i.e. medication assisted treatment [MAT]) followed by psychosocial approaches—and suggest how classic psychedelic therapy could be integrated into these domains. Note that we cover issues related to potential integrations with 12-step and recovery-based treatment models elsewhere (see [122]. Although each SUD and treatment is unique and individualized changes will need to be implemented and scaled to the demands of real-world practice, overall, we propose that classic psychedelics can be integrated into existing treatment models (see Fig. 1)—and that doing so may improve patient outcomes.

2. Medication assisted treatment for SUD

The SUD treatment field has shifted towards medication-assisted treatment (MAT) largely due to its demonstrated success in reducing both substance use and harmful behaviors associated with various SUDs [57]. MAT varies in terms of its frequency of use and target outcomes. For instance, in the treatment of opioid use disorder (OUD) naltrexone and buprenorphine are typically used daily or with sustained delivery in long-acting injectables. MAT can also be utilized as needed such as with some forms of nicotine replacement therapy (NRT) for tobacco cessation or naltrexone for alcohol use disorder. MAT can impact the frequency or intensity of substance use or promote sustained abstinence [61]. MAT may be initiated prior to discontinuation, such as with varenicline in the treatment of tobacco use disorder, during early abstinence, such as with buprenorphine for opioid use disorder, or during ongoing use, such as with naltrexone for alcohol use disorder [114,32,98]. There are currently no FDA approved medications for stimulant use disorders (including cocaine and amphetamine use disorders) nor for cannabis use disorder, but there are FDA approved MATs for alcohol, tobacco, and opioid use disorder. Below we review primary SUDs (those that have FDA-approved MATs) and suggest how classic psychedelic therapies may be incorporated with MAT at different stages of recovery. Note that throughout this paper, "MAT" will refer only to currently FDA-approved pharmacotherapies for SUDs, although we recognize that classic psychedelics as treatments for SUDs could be considered a form of medication assisted treatment in the future.

2.1. Alcohol

There are three FDA-approved medications for alcohol use disorder: disulfiram, acamprosate, and naltrexone. None of these are agonist medications (i.e., they do not bind to the same receptor as alcohol), distinguishing them from the most frequently utilized MATs for both tobacco use disorder and opioid use disorder. Disulfiram—the first drug approved for alcohol use disorder—works by deterring alcohol ingestion via the inhibition of aldehyde dehydrogenase (ALDH), an enzyme that converts acetaldehyde to acetate in the metabolism of alcohol. By blocking this process, acetaldehyde accumulates in the body when alcohol is ingested, causing rapid unpleasant effects including headache, nausea, and hyperventilation. These immediate hangover-like symptoms may deter individuals from drinking alcohol [113]—however, there are significant issues with adherence to disulfiram because individuals who wish to continue drinking without experiencing these negative effects can simply stop taking the medication. Therefore, disulfiram is rarely used today in clinical practice [31]. Naltrexone, an opioid receptor antagonist, has been used in opioid use disorder for some time (discussed below), and seems to have reward-blunting effects in people with alcohol use disorder that can lead to reduced alcohol consumption [37,119]. Similar issues with adherence to this medication arise, which can be partly mitigated through a long acting injectable form of naltrexone [33], although access is often a limitation. Acamprosate, on the other hand, is an NMDA receptor modulator, and may be helpful in sustaining abstinence and reducing withdrawal-associated distress [120]. Unfortunately, acamprosate and other forms of MAT for alcohol use disorder are underutilized—not only because of issues surrounding adherence but also because of stigmatization and unpleasant side-effects [77,117]. Furthermore, most MAT for alcohol use disorder (acamprosate and disulfiram in particular) are oriented toward achieving total abstinence, which may not be the ideal treatment goal for all patients [19]. Unlike naltrexone, acamprosate may not have the same therapeutic benefit in patients prior to abstinence or with continued use of alcohol [58].

2.1.1. Classic psychedelics in AUD treatment

Incorporating classic psychedelic therapies into current MAT for alcohol use disorder may prove helpful, and may be especially valuable at different critical timepoints. While there are no data to inform the ideal timing of classic psychedelic administration, [7,9] report positive outcomes when conducting the first classic psychedelic session around the beginning of a quit attempt, after several sessions of preparatory talk therapy. This might not only bring a degree of salience to the recovery process and facilitate a prolonged commitment, but could also increase adherence to and impact of future MAT treatments. Classic psychedelics have been known to create an 'afterglow' effect wherein individuals experience an elevated mood, an increased willingness to engage in interpersonal connections, and decreased guilt and anxiety [70,90]. This period could potentially be leveraged to enhance adjunct medical and psychological interventions, especially when medically supervised withdrawal is necessary.

Alcohol withdrawal includes negative affect and aversive physical symptoms such as nausea/vomiting, headache, and disorientation. Alcohol withdrawal in those who are physically dependent should be conducted under medical supervision and it is not recommended to engage in psychedelic intervention during this medically critical period. Classic psychedelic treatment prior to initiating abstinence, however, may promote psychological resilience during the eventual withdrawal period (as mentioned) or if conducted following medically supervised withdrawal could further sustain motivation in early abstinence [101]. At this juncture, the patient has overcome the dangers of discontinuation but is at risk of relapse shortly afterwards [102]. A guided classic psychedelic session may focus the individual on the ongoing challenges of recovery and enhance commitment to abstinence or reduced use [8]. Finally, classic psychedelics may reduce concerns of non-adherence typically seen with conventional medications, which can be difficult in the setting of active drinking in alcohol use disorder, since there need only be one to a few supervised classic psychedelic sessions total with beneficial effects that appear enduring for many [38].

Table 1
Interventional studies of classic psychedelic treatments for SUDs since 2000.

Substance Use Disorder Targeted	Full Study Name	Participants (N)	Design	Classic Psychedelic Used, # Sessions, Dose	Adjunctive Intervention Included	Findings	Citation Information
Alcohol use disorder	Psilocybin-assisted treatment for alcohol dependence: A proof-of-concept study	N = 10	Open label	One or two dosing sessions of psilocybin: (1) 0.3 mg/kg at week 4, and (2) 0.4 mg/kg at week 8, (unless participant met exclusionary criteria or was unwilling to increase dose)	MET	Following first psilocybin session, both number of drinking days (mean difference (SD)=27.2 (23.7), t(8)=3.449, p=0.009) and heavy drinking days (mean difference (SD)=26.0 (22.4), t(8)=3.477, p=0.008) decreased relative to baseline.	Bogenschutz, M. P., Forcehimes, A. A., Pommy, J. A., Wilcox, C. E., Barbosa, P. C., & Strassman, R. J. (2015). Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. Journal of Psychopharmacology, 29 (3), 289–299.
	Percentage of Heavy Drinking Days Following Psilocybin-Assisted Psychotherapy vs. Placebo in the Treatment of Adult Patients With Alcohol Use Disorder	N = 93	Randomized, double-blind, placebo controlled	Two dosing sessions of psilocybin (1) 25 mg/70 kg at week 4, and (2) 25-40 mg/70 kg (dosage dependent on Mystical Experience Questionnaire scores at first session) at week 8 Control participants received Diphenhydramine 50 mg at week 4 and 50-100 mg at week 8.	MET, CBT	"Percentage of heavy drinking days during the 32-week double-blined period was 9.7% for the psilocybin group and 23.6% for the diphenhydramine group, a mean difference of 13.9%" (p=0.01). Mean daily alcohol consumption was also lower and rates of abstinence were higher in the psilocybin group, and these effects persisted through final follow-up (weeks 33 to 36).	Bogenschutz, M. P., Ross, S., Bhatt, S., Baron, T., Forcehimes, A. A., Laska, E., Mennenga, S. E., O'Donnell, K., Owens, L. T., Podrebarac, S., Rotrosen, J., Tonigan, J. S., & Worth, L. (2022). Percentage of heavy drinking days following psilocybin-assisted psychotherapy vs placebo in the treatment of adult patients with alcohol use disorder. JAMA Psychiatry, 79(10), 953-962.
	Clinical and Mechanistic Effects of Psilocybin in Alcohol Addicted Patients	N =37	Randomized, double-blind, placebo controlled, parallel group	A single dosing session of 25 mg psilocybin versus placebo (Mannitol)	Medically supervised withdrawal within six weeks of start, unspecified psychological intervention during visits	Data collection complete, publication of results pending	University of Zurich, Zurich, Switzerland, Psychiatric University Clinic, Katrin Preller, PhD; 10/2019; NCT04141501
	Pilot Trial of Visual Healing® in Psilocybin-assisted Therapy for Alcohol Use Disorder	N = 20	Parallel assignment, randomized, open-label	Two dosing sessions of 25 mg psilocybin, 4-weeks apart	Viewing of nature videos pre-treatment and during initial phase of classic psychedelic session versus traditional "set and setting" condition	Alcohol use decreased significantly in the overall sample after the first psilocybin session (mean drinking days: F (6,107)=7.16, p<0.0001, mean heavy drinking days per week: (F(6,107)= 15.76, p<0.0001) and remained low through second session and follow-ups. No significant differences in alcohol use for paticipants reandomized to the Visual Healing versus traditional "set and setting" conditions.	Heinzerling, K.G., Sergi, K., Linton, M., Rich, R., Youssef, B., Bentancourt, I., Bramen, J., Siddarth, P., Schwartzberg, L., & Kelly, D.F. (2023). Nature-themed video intervention may improve cardiovascular safety of psilocybin-assisted therapy for alcohol use disorder. Frontiers in Psychiatry, 14, 1215972.
	Psilocybin for Treatment of Alcohol Use Disorder: A Feasibility Study	N = 10	Open label, single group assignment	Single dosing session of 25 mg psilocybin	Unspecified psychological intervention before, during, and after dosing session	Active, no longer recruiting	The Neurobiology Research Unit at Copenhagen University Hospital Rigshospitalet, Anders Fink-Jensen, MD, DMSci, Psychiatric Centre Rigshospitalet; 1/2021; NCT04718792

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Table 1 (*continued*)

Substance Use Disorder Targeted	Full Study Name	Participants (N)	Design	Classic Psychedelic Used, # Sessions, Dose	Adjunctive Intervention Included	Findings	Citation Information
	The QUANTUM Trip Trial - Psilocybin-assisted Therapy for Reducing Alcohol Intake in Patients With Alcohol Use Disorder **Note: Continuation of pilot study above*	N = 90 expected	Randomized, double-blind, placebo-controlled, parallel-assignement	Single dosing session of 25 mg psilocybin or placebo (Maltodextrin)	Unspecified psychological intervention before, during, and after dosing session)	In progress	The Neurobiology Research Unit at Copenhagen University Hospital Rigshospitalet, Anders Fink-Jensen, MD, DMSci, Psychiatric Centre Rigshospitalet; 6/2022; NCT05416229
	Psilocybin-assisted vs. Ketamine-assisted Psychotherapy for Alcohol Use Disorder	N = 20 expected	Randomized, double-blind, active comparator, parallel assignment	Single dosing session of (1) 25 mg psilocybin, or (2) 200 mg oral ketamine followed by open-label extension to receive psilocybin	Individual psychotherapy during preparation and integration sessions	Not yet recruiting	University of Iowa, Peggy C Nopoulos, MD; 6/2022; NCT05421065
Alcohol use disorder, MDD	Psilocybin Treatment of Major Depressive Disorder with Co-occurring Alcohol Use Disorder	N = 90 expected	Randomized, double-blind, placebo-controlled, parallel assignment	Single dosing session of 25 mg psilocybin or placebo; after completion, all participants eligible to receive unblinded second session with 25 mg psilocybin	MI	In progress	Johns Hopkins University, Baltimore, MD, Frederick S Barrett, PhD; 11/2020; NCT04620759
Cocaine use disorder	Psilocybin-facilitated Treatment for Cocaine Use: A Pilot Study	N = 40	Randomized, double-blind, parallel assignment	Single dosing session of 0.36 mg/kg psilocybin or 100 mg Diphenhydramine	CBT	Active, no longer recruiting	University of Alabama at Birmingham, Peter Hendricks, PhD; 1/2014; NCT02037126
Methamph-etamine use disorder	Psilocybin-Enhanced Psychotherapy for Methamphetamine Use Disorder	N = 30 expected	Randomized, parallel assignment	Two dosing sessions of 25–30 mg psilocybin; two weeks apart	Psychotherapy (unspecified modality) in inpatient residential setting	In progress	Portland VA Research Foundation, Inc., Oregon Health and Science University, Chris Stauffer, MD; 7/2021; NCT04982796
	Study of the Safety and Feasibility of Psilocybin in Adults with Methamphetamine Use Disorder	N = 12 expected	Single group, open label	Two dosing sessions of psilocybin; 25 mg followed by 25 mg or 50 mg; 4 weeks apart	Unspecified supportive intervention	In progress	University of Wisconsin Madison, Wisconsin, United States, Christopher Nicholas, PhD; 4/2022; NCT05322954
Opioid use disorder	Adjunctive Effects of Psilocybin and a Formulation of Buprenorphine	N = 10 expected	Open label pilot study	Two dosing sessions of psilocybin 4 weeks apart, unspecified dose	Suboxone maintenance therapy	In progress	University of Wisconsin, Madison, Randall Brown, MD, PhD; 11/2019; NCT04161066
	Inpatient Buprenorphine Induction with Psilocybin for Opioid Use Disorder	N = 90 expected	Randomized, double-blind, parallel assignment	One high-dose (30 mg) versus one very low dose (1 mg) psilocybin session following standard-of-care buprenorphine induction	Inpatient phase (6-8 day) for standard buprenorphine induction, followed by experimental psilocybin session, followed by 8-week outpatient phase involving standard buprenorphine maintenance and experimental follow-up meetings	In progress	Johns Hopkins University, Sandeep Nayak, MD; 8/2023; NCT06005662
Tobacco use disorder	Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction	N = 15	Open label pilot study	Single dosing session of 30 mg/70 kg psilocybin	CBT	"12 out of 15 participants (80%) showed seven-day point prevalence abstinence at 6-month follow up" Significant reductions in self-reported daily smoking from intake to 6-month follow-up (TLFB; t14 = 11.1, P < .001), breath CO levels (t14 = 3.8, P < .01), and urine cotinine (t14 = 2.3, P	Johnson, M. W., Garcia-Romeu, A., Cosimano, M. P., & Griffiths, R. R. (2014). Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. Journal of psychopharmacology, 28 (11), 983–992.

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Table 1 (*continued*)

Substance Use Disorder Targeted	Full Study Name	Participants (N)	Design	Classic Psychedelic Used, # Sessions, Dose	Adjunctive Intervention Included	Findings	Citation Information
						= .04) for entire study sample	
	Psilocybin-facilitated Smoking Cessation Treatment: A Pilot Study **Note: Continuation of pilot study above*	N = 95 expected	Open label, active comparator, parallel assigment	Single dosing session of 30 mg/70 kg psilocybin. Control participants receive 8-10 weeks of NRT in addition to CBT.	CBT	Data collection complete, publication of results pending	Johns Hopkins University, Baltimore, MD, Matthew W. Johnson, PhD; 9/2013; NCT01943994
	5-HT2A Agonist Psilocybin in the Treatment of Tobacco Use Disorder	N = 66 expected	Multi-site, double-blind, randomized	Two dosing sessions, 1-week apart of either: (1) Psilocybin PO, 30 mg in session 1 and either 30 mg or 40 mg in session 2; (2) Niacin PO, 150 mg in session 1 and either 150 mg or 200 mg in session 2	CBT	In progress	Johns Hopkins University, University of Alabama at Birmingham (UAB), New York University (NYU), Matthew W. Johnson, PhD; 7/2022; NCT05452772

Key terms: MET= Motivational Enhancement Therapy; MI= Motivational Interviewing; MMT= Methadone Maintenance Therapy; CBT= Cognitive-Behavioral Therapy; NRT= Nicotine-replacement therapy

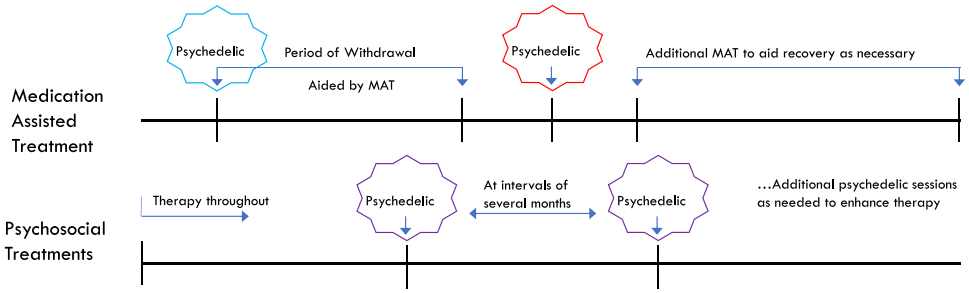

Fig. 1. Potential Points to Integrate Classic Psychedelics into SUD Treatments. We provide some potential points at which a classic psychedelic therapy session could complement existing SUD treatments, though there are likely other ways treatment could occur. Note that we are agnostic regarding whether or not MAT should be ceased in any given case immediately prior and/or during classic psychedelic treatments for SUDs. Furthermore, data is lacking to determine the ideal interval between classic psychedelic administrations, therefore we suggest an interval of several months as nothing more than a placeholder until a more concrete timeline is elucidated.

2.2. Tobacco

Among the most popular treatments for tobacco use disorder are nicotine replacement therapies (NRTs), including the nicotine patch, gum, lozenge, inhaler, and nasal spray [118]. These medications release a controlled amount of nicotine to the user, easing withdrawal symptoms and helping to transition from smoking to abstinence or reduced use. Nicotine replacement therapies provide nicotine in a form without the carcinogens found in tobacco or the carbon monoxide from combusted tobacco largely responsible for cardiovascular disease. Two other medications also used to treat tobacco use disorder are bupropion and varenicline. Bupropion is an atypical antidepressant medication that acts by inhibiting norepinephrine and dopamine reuptake [42]. Bupropion also acts as a nicotinic receptor antagonist, blocking neuronal nicotinic acetylcholine receptors (nAChRs; [106]. The smoking cessation medication varenicline is a partial agonist at $\alpha4\beta2$ nAChRs, moderately stimulating this receptor while also antagonizing the effects of nicotine [46]. The dependence-producing effects of nicotine are mediated by nAChRs, and the $\alpha4\beta2$ subtype is specifically involved in dopaminergic activation [20]. Varenicline acts at these receptors to reduce craving and ameliorate nicotine withdrawal symptoms. Both bupropion and varenicline have several aversive side-effects and suboptimal efficacy rates (see [13]; [14]; [15]; [44].

2.2.1. Classic psychedelics in TUD treatment

Turning to the incorporation of classic psychedelic treatments, these interventions could be used at similar junctions as in alcohol use disorder: prior to abstinence, in early abstinence, or during sustained abstinence. For instance, a classic psychedelic session could coincide with a target quit date as was demonstrated in Johnson et al. [50]. Classic psychedelic sessions in this case could promote sudden discontinuation (dangerous in the alcohol context depending on severity but not with tobacco) as monotherapy but could also be used to support utilization of other evidence-based therapies for smoking cessations such as NRT or bupropion/varenicline subsequently. The benefits of classic psychedelic therapies could be levied not only at the beginning of treatment but also (as previously described) during pharmacologic withdrawal from nicotine, or even afterwards in order to maintain long-term abstinence. While additional research will need to investigate and proceed cautiously given the lack of knowledge of possible drug interactions between bupropion/varenicline and classic psychedelics, medication holidays could be utilized during or prior to classic psychedelic sessions in patients with ongoing use of these medications.

2.3. Opioids

Opioid agonist and partial agonist therapies, which include methadone and buprenorphine, respectively, are commonly used medications for opioid use disorder (OUD; [74,82]. These are opioids and bind to the

same μ-opioid receptors as the drugs of abuse themselves. In doing so, they reduce withdrawal and craving.

However, unlike opioids with quick onset of action and short half-lives (e.g. heroin or fentanyl), the pharmacological effects of these agonist and partial agonist medications are prolonged and produced via less rapid routes of administration (e.g., oral, sublingual) [43,45,66,68], thereby reducing both the reward and risks of problematic substance use [109]. Other medications approved for opioid use disorder are naltrexone (also used in alcohol use disorder) and formulations that combine buprenorphine and naloxone, e.g. Suboxone®. Naltrexone and naloxone are opioid receptor antagonists, meaning that they block opioid receptor binding, quickly inhibiting or reversing the euphoric and sedative effects of opioids. This has utility not only in treating opioid intoxication and overdose but also blocking subsequent receptor binding in the setting of ongoing opioid use. Naltrexone for opioid use disorder has shown some efficacy, especially as an extended release injectable medication given once an individual has demonstrated several days of sustained abstinence. Suboxone®, the daily formulation of naloxone/buprenorphine, was developed to deter injection of buprenorphine, as the naloxone is only active if injected. Methadone maintenance therapy, the most longstanding treatment for opioid use disorder, is still among the most common treatments for opioid use disorder, but in the United States can only be administered for OUD treatment through highly regulated methadone clinics, limiting access [16,60]. Even though methadone [78,79], buprenorphine [56,79], Suboxone® [110], and, to some extent, extended-release naltrexone [65] have demonstrated better outcomes than placebo in both treatment retention and opioid use (for review, see [110], these medications are still underutilized, difficult to access, and present challenges to treatment adherence [1,5,88].

2.3.1. Classic psychedelics in OUD treatment

Our suggestions for classic psychedelic integration in standard opioid use disorder treatment are similar to those of tobacco use disorder, where agonist or partial agonist medications are the standard of care. In this case, a classic psychedelic session could improve MAT adherence, reduce cravings, enhance commitment to abstinence, and overall ease the process of recovery [2,93]. Early LSD research showed findings that suggest classic psychedelics could be effective in the treatment of opioid use disorder [99]. Given the high risk of relapse and overdose in the first days of abstinence following discontinuation of opioids [83], classic psychedelics may play an important role in sustained recovery if utilized during this critical period. In particular, extended release naltrexone performs similarly to Suboxone® therapy after several months but only when participants successfully initiate treatment [65].

Classic psychedelic sessions could support initiation of and adherence to MAT, but possible drug interactions will need to be elucidated first. For example, methadone has been shown to inhibit CYP2D6 [36], which could theoretically prolong the effects of LSD [116]. If such interactions prove negligible and/or safely manageable, another interesting possibility is to harness classic psychedelics to wean patients off of MAT at the conclusion of their treatment. Tapering off of these agents can prove difficult for some patients, in which case it may be helpful to implement a psychedelic session to catalyze the transition to abstinence (as we have argued for in the initiation of treatment for SUDs more generally). Classic psychedelic-assisted treatment could also obviate the need for MAT in some cases should its effects on abstinence and craving prove particularly robust and enduring (though overdose would become an increased concern in such cases), but this remains an open empirical question as there are considerable challenges in ceasing the use of opioids without MAT.

2.4. Psychosocial treatments for SUD

There are a number of non-pharmacologic, psychosocial treatments for SUD. These apply psychological theories related to behavior and cognition into interventions designed to reduce or discontinue problematic substance use. In some cases, these treatments are combined with MAT, as some (contentious) evidence suggests that psychosocial treatments in conjunction with medications improves outcomes (for an opioid focused review, see [26]. Here we cover just a few of the most prominent and empirically supported psychosocial approaches in SUD treatment, and how classic psychedelics may fit within each framework.

2.5. Contingency management

Contingency Management (CM) is an approach based on the idea that drug-use behavior constitutes an instance of pharmacologic reinforcement [107]. It posits that reinforcing drug abstinence with a non-drug reward will decrease drug use. Drug abstinence is objectively determined though biological verification such as negative urine samples monitored during therapy, and abstinence is reinforced by providing rewards such as vouchers for goods or money upon determination of abstinence [41]. The schedule of reinforcement is typically one where a reward is provided upon every drug-free biological sample, or in a partial reinforcement schedule where drug-free samples are reinforced with chances to win prizes [92]. Contingency management has consistently demonstrated increased treatment retention, reduced drug use, and improved medication adherence for several types of SUDs, including opioid use disorder, alcohol use disorder, and tobacco use disorder [18, 41,92]. However, this form of therapy is rarely implemented outside a research setting, likely due to perceived ethical concerns (e.g. “paying people to stay sober”; see [59] and legal limitations—federal antikickback laws severely limit the monetary value incentives can hold if payable by federal health care programs. Recently however, the US Department of Health and Human Services has approved a company’s request for a more generous payment plan, potentially opening the doors for more widespread adoption of contingency management protocols.

2.5.1. Classic psychedelics and CM

While contingency management is effective at maintaining relatively high rates of abstinence while the contingency program is in place, research has repeatedly shown that rates of use frequently return to baseline after contingencies are lifted [108]. Thus, the maintenance of abstinence post-contingency has long been a hope for innovative contingency management methods, which combine contingency management with other approaches, although such attempts have shown mixed results or little success (e.g., [28]; [49]. Given the salience of classic psychedelic sessions and the potential for long-term behavior change with large effects, there is a possibility that classic psychedelics could be leveraged with contingency management in order to achieve post-contingency long-term abstinence.

While classic psychedelics have exceedingly low addictive potential [53], support provided during classic psychedelic sessions as well as the sessions themselves could inadvertently reinforce drug use if only accessible during periods of relapse or increased substance use frequency. However, a random as opposed to contingent schedule of classic psychedelic sessions could be utilized throughout treatment to avoid this possible outcome. Additionally, classic psychedelics could be used at the initiation or conclusion of contingency management to increase long-term motivation and sustained benefits.

2.6. Motivational interventions

Motivational interventions, including Motivational Enhancement Therapy (MET), are grounded in the principles of Motivational Interviewing (MI) (for a review, see [24]. This approach was developed to help individuals overcome ambivalence and dedicate themselves to change [81]. Studies using motivational interviewing have shown promise in treating opioid use disorder (e.g., [11]; [12]; [67], alcohol use disorder (e.g., [97], and tobacco use disorder (e.g., [89]; [39]. In practice, the motivational intervention therapist attempts to evoke

"change talk" from the patient, responding reflectively to reinforce the individual's desires and need for change (for a review, see [40].

2.6.1. Classic psychedelics and motivational interventions

Motivation is a key component to reducing problematic substance use or maintaining abstinence in substance use disorder treatment. Not only could classic psychedelic sessions be helpful in bolstering motivation for individuals undergoing motivational enhancement therapy, but motivational interventions could be utilized before, during, or following classic psychedelic sessions to further enhance their impact. Motivational interviewing strategies may be especially useful in facilitating participant engagement during sessions and integration. Bogenschutz et al. [7] incorporated motivational enhancement therapy sessions before and after psilocybin sessions in their proof-of-concept trial targeting alcohol use disorder, which demonstrated beneficial outcomes. A subsequent double-blind randomized clinical trial (RCT) from the same group using a psychotherapeutic strategy called Motivational Enhancement and Taking Action (Bogenshutz & Forcehimes, 2016), a combination of MI and CBT, found a significantly lower percentage of heavy drinking days post-intervention in the psilocybin group compared to the control (diphenhydramine) group (Bogenshutz et al., 2022). These findings provide evidence that implementation of psilocybin administration during motivational intervention strategies improves efficacy of treatment, and warrants further investigation in other SUDs.

2.7. Cognitive behavioral therapy

Cognitive Behavioral Therapy (CBT) encompasses a range of approaches that aim to identify and change excessively negative or otherwise maladaptive thought patterns and to modify behaviors [4]. The theoretical rationale for the cognitive side of the treatment, as described by Wright and colleagues (1993), is that affect and behavior are impacted by how one construes ongoing experiences. Therefore, in psychological disorders like SUD, it is the "dysfunctional" thinking and beliefs that give way to the unwanted behavior [121]. Cognitive behavioral therapy also integrates insights from behavioral science. By examining maladaptive behaviors such as substance use, these can begin to be challenged, modified (i.e., through reinforcement), and ultimately replaced with healthier ways of behaving [121]. For example, one study of brief cognitive behavioral therapy for cannabis use disorder randomly assigned participants (N = 229) to either a six-session cognitive behavioral therapy intervention, a single session of cognitive behavioral therapy, or a delayed treatment control condition [21]. The cognitive behavioral therapy intervention included exercises on identifying triggers to use, developing strategies for coping with urges, and cognitive restructuring around cannabis use, which consisted of challenging and coming up with alternatives for typical thought patterns related to use. Individuals in the six-session cognitive behavioral therapy showed the most reduction in self-reported cannabis use and cannabis-related problems from baseline, indicating good feasibility of cognitive behavioral therapy approaches for cannabis use disorder [21]. Cognitive behavioral therapy has shown substantial success in SUD more generally, with several large studies and meta-analyses supporting this approach [27,71]; for a review see [80].

2.7.1. Classic psychedelics and CBT

As we have mentioned for other psychosocial interventions, classic psychedelic assisted therapy could function with cognitive behavioral therapy to help initiate, sustain, or extend the benefits of both therapies. For instance, cognitive behavioral therapy may be beneficial before and after classic psychedelic sessions with the aim of treating tobacco use disorder as was demonstrated in Johnson et al. [50]. Foundational aspects of cognitive behavioral therapy including psychoeducation and establishing treatment goals may guide the success of classic psychedelic experiences as well. Classic psychedelic sessions, in turn, could also support the aims of cognitive restructuring, overcoming avoidance, and behavioral change prompted in cognitive behavioral therapy [123].

Both classic psychedelic sessions and cognitive behavioral therapy can be conceptualized as methods of raising awareness about the conditions that maintain substance use. For example, self-monitoring is common in cognitive behavioral therapy for smoking cessation, as in the Johnson et al. [50] psilocybin treatment for tobacco use disorder (e.g., participants kept smoking diaries before their target quit date and used these to identify the antecedents and consequences of smoking; [91]. This approach might highlight for a person that they often smoke in response to particular situations or affective states and cigarette use has short-term positive consequences like bonding with others during smoke breaks or escape/avoidance of negative affect. With more awareness of these patterns, individuals undergoing cognitive behavioral therapy can plan for alternative behaviors in the situations that traditionally prompted smoking and can identify more adaptive methods for achieving positive consequences traditionally afforded by smoking, such as opportunities for social engagement throughout the day without smoking or non-smoking strategies for regulating negative affect. These might be considered the "nuts and bolts" aspects of increased awareness of smoking.

In a putative complement to this approach, classic psychedelic sessions are often credited with more gestalt increases in awareness of one's thoughts and beliefs, such as self-identity as it relates to smoking and how smoking is often inconsistent with one's values and priorities in life [87]. In fact, the work by Johnson and colleagues has explicitly stated to participants that the CBT and psilocybin sessions are intended to mutually increase awareness of personal behaviors and beliefs.

CBT could be used in a number of different ways in future research to complement classic psychedelic therapy. For example, CBT may be useful in integrating challenging classic psychedelic experiences by allowing participants to challenge negative automatic thoughts that might arise during or following these sessions. These same techniques may be useful in addressing psychological content that emerges during and after classic psychedelic drug administration sessions regarding problematic substance use.

2.8. Residential treatment

Residential treatment is an additional SUD context that could potentially incorporate psychedelic treatments. Residential treatment, a treatment program that involve overnight stays for weeks to months, for SUDs is very common, though with variable demonstrable efficacy [72,73,96]. These programs offer several favorable aspects that could facilitate the inclusion of psychedelic therapy. First, patients are likely to be abstinent from the drug of disordered use. Second, appropriate treatment (medically supervised withdrawal, initiation of opioid agonist therapy, etc.) can be initiated in a monitored environment. Third, there is typically a great degree of ongoing counseling. These are perhaps ideal conditions for implementing psychedelic therapy concomitant with treatment as usual. A study of psychedelic use in this context would be relatively easy to implement in an appropriately trained program, and would offer a valuable real-world design that is lacking in many psychedelic clinical trials. Such a design offers several advantages. First, it aids recruitment as there would be a ready source of potential participants. Second, it would target treatment-seeking individuals by virtue of recruiting participants who are in treatment. In contrast, it is possible that studies administered in a purely research context may inadvertently recruit a sample that is in part different from a typical treatment-seeking one. This allows for greater generalizability. Finally, performing such a study may offer cost benefits, by taking advantage of resources, such as facilities and trained staff, that are already employed in clinical care.

2.9. Future directions

A number of near-term possibilities present themselves from the findings and possible clinical applications reviewed above. We

hypothesize that classic psychedelics will increase engagement with both pharmacologic and psychosocial interventions for SUDs and may function to support abstinence or reduction in problematic substance use as an independent treatment. Regarding contingency management, a classic psychedelic experience could help to maximize internal motivation to quit in the setting of other externally reinforced incentives. For motivational interviewing, clinicians might observe more explicit change talk immediately after a classic psychedelic experience that could more vividly highlight the discrepancy between current behavior and core values. In cognitive behavioral therapy, individuals may experience increased flexibility in their ability to interpret situations and consider more functional thoughts and behavioral patterns. Intertwined with each of these possibilities are open empirical questions regarding the causal role(s) of the subjective effects of classic psychedelics [124,125,86].

Importantly, the week or two after the classic psychedelic experience represents a unique window of opportunity classically described as an "afterglow" [10,70,90]. This afterglow period may possibly reflect enhanced brain plasticity observed in nonhuman research with classic psychedelics [103,55,69]. More specifically, this window may constitute the reopening of a critical period, as suggested by recent work [84,85]. It may be that interventions focused in this window of opportunity produce the best outcomes and that changes made during this time in particular are most enduring and predictive of long-term success. Individuals in early recovery from substance use disorders may benefit from additional classic psychedelic sessions during this critical period. For example, as suggested by Johnson et al. [50], multiple sessions may be provided in order to extend this afterglow period during the time of greatest SUD relapse risk [50]. This could extend the time during which cognitive behavioral therapy may have a potentially increased impact. While larger well-controlled trials are required before firm conclusions can be drawn about classic psychedelics as SUD treatments, the available evidence suggests that classic psychedelics represent a treatment that can complement current SUD treatment models. Testing the various pairings reviewed above provides an extensive program of research requiring a number of additional clinical trials over the course of decades.

The possibility of the combination of classic psychedelics with pharmacotherapy and psychosocial treatments for SUDs prompts the importance of a wide variety of comparative research studies. For example, does classic psychedelic therapy for substance use disorders lead to superior outcomes when combined with cognitive behavioral therapy or motivational interviewing? Both interventions may be useful when coupled with classic psychedelic treatments, but which is better? The question may become even more complicated as it is likely that different approaches may work better for different individuals. For example, motivational interviewing may be especially suited for individuals struggling with ambivalence, whereas cognitive behavioral therapies may support those already motivated to change but confronted with cognitive or behavioral barriers [123]. It may be that populations undergoing classic psychedelic treatments that are already seeking abstinence (e.g., the participants in [50] would benefit more from cognitive behavioral therapy while others dealing with more ambivalence (e.g., the participants in [7] may benefit more from motivational interviewing). Additionally, although classic psychedelics are generally considered to have good safety and minimal addictive potential, future research may identify particular individuals or subgroups who could develop emergent issues after psychedelic-assisted treatment and may benefit more from alternative forms of treatment.

Tests of combined non-psychedelic interventions paired with classic psychedelic treatment are also potentially important to investigate in the future. For example, in a non-psychedelic study of substance use disorders, Epstein et al. [28] tested the combination of cognitive behavioral therapy and contingency management and found compounded benefits long-term. Similarly, and as mentioned previously, a combination of MET and CBT specifically designed for psychedelic-assisted psychotherapy by Bogenschutz & Forcehimes [6] had a significant positive impact on AUD (Bogenshutz et al., 2022). These findings suggest that the combination of multiple psychosocial approaches and classic psychedelic therapy may be a fruitful avenue for exploration. The combinations of MAT with psychosocial approaches also deserve exploration with classic psychedelics: for instance, psilocybin with nicotine replacement and cognitive behavioral therapy for smoking cessation. Given the possibility of dozens of classic psychedelic compounds that could be developed as therapeutics (e.g., [104,105], the various psychosocial treatments reviewed here (and others, for example 12-step; [122], and the various forms of MAT, the potential number of treatment combinations ripe for exploration is staggering.

Considering also the opinions of those that deliver SUD treatments will be critical to the implementation and integration of classic psychedelic therapies. For example, a survey of psychiatrists found that common concerns around the integration of psychedelics into medicine were the lack of trained psychedelic-assisted therapy providers and the logistics of delivering these therapies [3]. The authors also found that lower worry around the addictive potential of psychedelics was associated with increased belief in their therapeutic capacity [3]. These sorts of data can help the field of psychedelic medicine address possible barriers and will be imperative to implementing psychedelics into SUD treatments. Thus, it is important that further studies like those presented here be conducted and that communication with SUD professionals be established and maintained.

Finally, we advocate caution around each of these possibilities, as further research is needed regarding the safety, efficacy, and effective clinical application of classic psychedelics in general as well as for SUD in particular [38,53,126,127]. While we have enumerated possible points of synergy between existing therapeutic modalities and classic psychedelic interventions, we hope that all of these will be subjected to scientifically rigorous examination. In addition to reiterating that caution is needed in general when considering classic psychedelic treatments, we also note that withdrawal from certain substances such as benzodiazepines or alcohol can be life-threatening and classic psychedelic therapies must be administered outside of medically critical periods to avoid possible complications (e.g. cardiovascular).

3. Conclusion

Classic psychedelic therapy may become an approved treatment for SUDs in the coming years. If this is the case, clinical protocols will have to be redesigned to incorporate this new treatment option within current practice. Here we suggest that classic psychedelic treatments appear compatible with mainstream SUD treatment models. We have suggested that there are key periods of time wherein classic psychedelic treatments could potentially bolster existing forms of MAT. Additionally, we have argued that classic psychedelic treatments and psychosocial treatments such as CBT, CM, and MET/MI, could be complementary. Of course, research has not evaluated the ideal adjunctive clinical platform for classic psychedelic treatments, and this may be a priority for future studies. While we have argued for the compatibility of classic psychedelic treatments with mainstream SUD treatment models, this does not mean that the implentation of classic psychedelic treatments in real-world practice will come without challenges. Indeed, there has long been a gap between research and practice, and the uptake of classic psychedelic therapy in clinical settings will depend on a number of factors not discussed here, including the generalizability of randomized controlled trial findings to real-world patient populations and settings, training requirements, cost-effectiveness, and the acceptability of this novel approach to clinicians, patients, and payers [17]. Nevertheless, the integration of classic psychedelic treatments into existing interventions may ultimately lead to improved SUD outcomes, addressing a leading cause of death and disability worldwide.

Credit Author Statement

DY and AB conceived of the manuscript and wrote the first draft; PH, MY, ML, JR, SN, MJ, and AGR provided contributions to various sections and crucial edits.

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