TREATING POST-TRAUMATIC STRESS DISORDER AND ALCOHOL USE DISORDER COMORBIDITY: CURRENT PHARMACOLOGICAL THERAPIES AND THE FUTURE OF MDMA-INTEGRATED PSYCHOTHERAPY

Brian Gully[1,2], **Erica Eaton**[3,4], **Christy Capone**[1,3,4], **Carolina Haass-Koffler**[1,2,3,5,*]

[1]Center for Alcohol and Addiction Studies, Brown University, Providence, RI, USA

[2]Department of Behavioral and Social Sciences, School of Public Health, Brown University, Providence, RI, USA

[3]Department of Psychiatry and Human Behavior, Warren Alpert Medical School, Brown University, Providence, RI, USA

[4]Providence Veterans Affairs Medical Center, Providence, RI, USA

[5]Carney Institute for Brain Science, Providence RI, Brown University

Abstract

Post-traumatic Stress Disorder (PTSD) and Alcohol Use Disorder (AUD) frequently co-occur in patients who have experienced trauma. This comorbidity leads to a vicious cycle where PTSD symptoms beget heavy drinking and vice versa. There are no FDA-approved medications to treat PTSD-AUD; therefore, individuals suffering from this comorbidity are treated with medication approved to treat the disorders separately or off-label pharmacological interventions. However, these medications are limited in their efficacy for treating PTSD-AUD comorbidity. Emerging research on the non-classical psychedelic drug MDMA suggests that it may be an effective drug used in conjunction with psychotherapy. The following reviews the current research for clinical pharmacotherapies, as well as MDMA-integrative psychotherapy as they pertain to PTSD and AUD in isolation and in co-occurrence. Future directions for the role of psychedelic-integrative therapy for the treatment of this comorbidity are discussed.

*Corresponding Author: Carolina L. Haass-Koffler, PharmD, PhD, 121 South Main Street, Providence, RI 02903, Fax: 401-863-6697, carolina_haass-koffler@brown.edu.

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1. Introduction

Alcohol Use Disorder (AUD) is a condition with longstanding prominence in the United States (US) [1]. *The Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) [2] characterizes AUD by the meeting of two out eleven criteria in which levels of alcohol consumption negatively affect one's physical, mental, and/or social health [3,4]. Furthermore, in severe cases physical dependence on alcohol may keep one from stopping drinking without experiencing physical withdrawal and craving [5]. The epidemiological prevalence of AUD is 13.9% 12-month and 29.1% lifetime occurrence in a representative US sample [6]. Health risk assessment of AUD denotes that much of the burden and mortality associated with alcohol may come indirectly via liver disease, as well as in the form of economic and social loss [7].

Post-traumatic Stress Disorder (PTSD) was defined in early psychological sciences by detriments to physical and mental well-being following experiences of extreme shock [8]. Veteran mental health advocacy groups caring for individuals who fought in the Vietnam War brought PTSD into medical and psychiatric parlance in the US [9]. Later, PTSD became understood to include far more traumatic events than those related to combat, including domestic violence, sexual violence, and childhood abuse [8]. Current epidemiological data cites sexual assault as the most prevalent type of trauma exposure in the United States [10]. The clinical definition of PTSD evolved to include the experiencing of a significant traumatic event that has caused impairment to occupational and social functioning for longer than one month [11]. The DSM-5 denotes four distinguishing features: traumatic exposure, reexperiencing, avoidance, and heightened arousal . Symptoms that may be displayed include intrusion of traumatic memories, negative alterations in cognitions and mood, sleep disturbances, hypervigilance, heightened arousal states, irritability, and exaggerated startle-responses [2].

While PTSD and AUD are important to examine in isolation, the occurrence of AUD following a traumatic life event is highly prevalent even irrespective of a formal PTSD diagnosis [12]. Epidemiological review of PTSD-AUD comorbidity shows that alcohol is the most commonly used substance in patients with PTSD, culminating in a three-fold risk of developing AUD and two-fold risk of lifetime prevalence compared to patients without a PTSD diagnosis [13]. The impact of this comorbidity is particularly troubling as AUD increases the severity of PTSD symptoms [14], diminishes neuropsychological functioning [15], and increases attrition rates in treatment and clinical research [16]. Suicidal ideation and suicide attempts were more significantly associated with PTSD-AUD than with either PTSD or major depression alone [17]. This cycle appears to permeate on a lifelong and generational level, as exposure to a family history of AUD is associated with adult PTSD, particularly in females with corresponding early sexual trauma [18]. The burden of this comorbidity may be elucidated by its effect on quality of life. Men in treatment for AUD who meet criteria for lifelong PTSD exhibit detriments in physical and mental quality of life, particularly in patients who experienced dissociative symptoms [19].

Treatments for PTSD and AUD include psychotherapy and psychopharmacological interventions [20–23]. The following is a narrative review of pharmacological and

psychodynamic treatments for PTSD and AUD as primary and comorbid disorders. Current limited research on this approach will also be reviewed and compared to currently available pharmacotherapies. The primary aim of the current paper is to briefly summarize current treatment practices for PTSD, AUD, and their comorbidity in order to contextualize upcoming research on the novel approach of using the psychedelic compound 3,4-methylenedioxymethamphetamine (MDMA), in conjunction with psychotherapy, as a treatment for PTSD-AUD.

2. Pharmacological interventions for AUD and PTSD

i. AUD Primary

In the US there are four FDA-approved pharmacological interventions for AUD. Disulfiram, the first FDA-approved pharmacotherapy for AUD, creates an aversive physical response when combined with alcohol, causing nausea and vomiting, thereby promoting abstinence through an induced aversion to drinking [24]. A systematic review of eleven randomized control trials (RCT) indicated that this medication is effective in promoting abstinence compared to placebo over short periods of time [25]. However, careful review of its long-term usage shows limitations as an effective agent, as disulfiram relies on strict adherence to promote abstinence [26]. In reviewing over 60 years of research since disulfiram's introduction an emergent theme is that the medication works well when administered under supervision, but lack of supervision leads to lack of compliance, and thereby lack of efficacy [27].

The opiate antagonist naltrexone is used to decrease alcohol craving in heavy drinkers, thereby preventing or limiting drinking recurrence during periods of abstinence. A 6-month RCT showed significant decreases in heavy drinking and craving when patients (n=118) were treated with naltrexone [28]. Like disulfiram, limitations in naltrexone's efficacy are related to medication adherence. A long-lasting intramuscular (IM) injection form of naltrexone is also approved for the treatment of AUD. Intramuscular naltrexone circumvents shortcomings by reducing medication regimens to monthly administration. One RCT (n=624) showed a significant decrease in heavy drinking compared to placebo over six months when naltrexone IM was administered in conjunction with 12 sessions of low intensity supportive therapy [29]. This study did not exclude patients who were actively drinking. The most dramatic decreases in heavy drinking days were in those who were drinking the heaviest upon enrollment.

Lastly, acamprosate reduces overall heavy drinking and manages protracted alcohol withdrawal symptoms [30]. Protracted withdrawal is distinct from acute symptoms like delirium tremens, which typically last between 5-7 days. Protracted withdrawal is characterized by sleep disturbance and anxious cravings that may lead to drinking. A meta-analysis of seventeen RCTs found robust support for acamprosate's ability to promote abstinence rates of at least six months [31]. Limitation again lies in adherence as acamprosate must be taken three times a day.

While the above medications are the only options approved for AUD, other drugs are prescribed off-label based on emerging clinical evidence [32]. Research examining outpatient AUD treatment in the US between 2014 and 2016 suggest that off-label medications are

more commonly prescribed than those with FDA approval [33]. These findings suggest that many potential pharmacological treatments for AUD are yet to be fully explored. For more in depth review of pharmacotherapies for AUD, see: Bahji, Bach, Danilewitz, Crockford, Devoe, El-Guebaly and Saitz [34].

ii. PTSD Primary

There are only two FDA-approved pharmacological interventions for PTSD as a primary disorder – the selective serotonin reuptake inhibitors sertraline and paroxetine. Other medications, like the selective serotonin and norepinephrine reuptake inhibitor venlafaxine, are used off-label [35]. The antihypertensive prazosin (α1-antagonist) prazosin [36] and the antiepileptic topiramate [37] are also currently being investigated for PTSD treatment, particularly in regards to symptoms that disrupt sleep.

Sertraline use in patients with PTSD has been shown to reduce a broad range of symptoms compared to placebo, especially symptoms that relate to psychological or emotional regulation [38]. Results from RCTs indicate significant decreases in reported symptom intensity and investigator rated clinical impressions after twelve weeks of use [39]. Sertraline was studied alongside prolonged exposure (PE) therapy, which teaches patients to gradually approach trauma-related triggers, a doubly randomized preference trial where 200 participants were randomized to either their choice of treatment or no choice [40]. Some comparable beneficial effects were found between sertraline and PE, but advantages for PE emerged over time (which was also the preferred treatment by participants).

Research on the efficacy of paroxetine has yielded similar results. A pilot study contrasted three months of treatment with paroxetine with cognitive behavioral therapy (CBT) [41]. Initial results indicated comparable effects between the two treatments, with slight differences at 6-month follow up where CBT's effects appeared marginally more enduring. In parallel with sertraline research, paroxetine was also studied alongside PE for individuals with PTSD from motor vehicle accidents [42]. Again, PE yielded greater remission results than the pharmacotherapy. Further, paroxetine's efficacy has been examined in mitigating the onset of PTSD for civilian patients [43]. Patients receiving paroxetine showed marginal improvement in quality of life and social functioning from baseline, but no difference from placebo in other PTSD outcomes.

Venlafaxine is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) commonly prescribed for depression and examined as a potential agent for PTSD. One short term trial comparing the medication to both placebo and sertraline found that it was superior to placebo, and broadly similar in efficacy to sertraline in reexperiencing, avoidance/numbing, and hyperarousal subscales [44]. These symptom reductions, as well as secondary effects of remission on the Clinician Administered PTSD scale (CAPS), were observed after 24-weeks of treatment compared to placebo.

Prazosin has mixed evidence in RCTs for reducing PTSD sleep-disturbances. A low dose of prazosin for patients with PTSD was associated with night-terror reduction and, in some cases, a mean-increase in total sleeping time by 94-min [45]. These findings were extended to combat veteran populations within multiple studies, wherein prazosin was administered

trice a day and titrated up to dosages between 9 and 16mg [46,47]. In a secondary analysis, treatment effects of prazosin were shown to be particularly evident in participants with higher baseline blood pressure [48]. Taken together, these promising results offer a pathway for how prazosin may be most effectively used to treat PTSD. Limitations to consider are hypotensive effects that may arise, especially at higher doses.

Topiramate has been shown to be well tolerated in RCTs among civilians with PTSD. Along with reducing CAPS Total Severity scores, one study reported efficacy in reducing specific clusters of symptoms compared to placebo: traumatic event re-experiencing and psychological numbing [37]. Limitations include the modest statistical power of some results supporting topiramate, along with other research suggesting that combat-related PTSD symptoms may not be as responsive to topiramate as other types of trauma in civilian populations [49].

In summary, while sertraline and paroxetine are effective to an extent, they are not guaranteed to forge a path to remission [50]. Prazosin and topiramate are promising new medications with differing action mechanisms for varying symptom clusters, but their specificity offers only modest strength in treatment potential.

iii. PTSD-AUD Comorbidity

Pharmacological trials discussed thus far have focused on PTSD in isolation, often requiring participants to not have co-occurring substance use disorders as criterion for participation. While this type of inclusion criteria may make for a more uniform sample in the laboratory, it does not reflect the reality of differentiating trauma cases in the real world [51]. There are varying hypotheses which attempt to explain the reason behind the PTSD and AUD comorbidity. Chronic stress inducing dysregulation of the hypothalamic–pituitary–adrenal (HPA)-axis, has shown to lead to increase alcohol use [52], with PTSD symptom severity serving as a moderating factor to this process [53]. A self-medication hypothesis is posited to play a role in the development of PTSD and AUD comorbidity, with repeated trauma exposure and further alcohol use perpetuating cyclically. Also, early trauma exposure by way of childhood maltreatment may be at the root of this cycle [54]. Others hypothesize that a general predisposition to anxiety may make an individual equally vulnerable to developing PTSD and AUD, compounded by potential trauma exposure when self-medicating with alcohol [20].

Because AUD is such a prevalent comorbidity with PTSD, the role existing medications play in the treatment of this dual diagnosis is key in the review and discussion of what treatment is available thus far. Currently approved AUD medications have been tested in some studies with a PTSD-AUD population [55]. While only a sub-group of this study's sample was diagnosed with PTSD-AUD, the group's abstinence from alcohol was aided by either or both study medications and was reported to have led to improvements in their PTSD symptoms.

Sertraline was tested in a PTSD-AUD sample (n=94) with mixed-results that varied based on severity and onset of diagnoses [56]. In this study AUD with later onset and lower severity, coupled with early-onset PTSD, showed the most significant decreases in drinking behavior.

These findings may support the use of sertraline in early intervention among patients with PTSD at risk of developing severe AUD.

Paroxetine has been examined among multiple AUD comorbidities including PTSD, social anxiety, and major depression with mixed drinking and trauma outcomes [57,58]. In PTSD-AUD, paroxetine showed no difference in decreasing trauma symptoms when compared to the drug for depression desipramine. In this sub-sample, paroxetine was shown to be less effective than desipramine. Analyses of differing comorbidities and medication combinations in this study demonstrated the varying outcomes that emerge with differing diagnoses [59].

Prazosin has been evaluated as a treatment option for PTSD-AUD comorbidity, but results remain mixed. A six-week pilot study (n=30) found prazosin was effective in reducing the number of drinking days in PTSD-AUD patients, though trauma symptomatology did not show improvement [60]. A thirteen-week RCT with a veteran sample (n=96) titrated prazosin to 16mg, the standard maximum recommended dose [36]. Results did not support prazosin treatment, as neither drinking behavior nor PTSD symptoms showed significant reduction that could be linked to the medication. Despite the results in single disorder samples, the limited number of AUD-PTSD comorbidity studies, and their mixed results, the efficacy for α1-adrenergic receptor antagonists is still under investigation for PTSD-AUD. Interestingly, secondary analyses of two independent trials that used one of two α1-receptor antagonists reported that high blood pressure was a predictor of prazosin's response on PTSD symptoms in US veterans with PTSD [48] and of doxazosin's response on alcohol consumption in individuals with AUD [61,62].

Topiramate has also been examined for its efficacy in treating PTSD-AUD. One study (n=30) examined drinking behavior as a primary outcome of topiramate treatment but found no support for decrease in drinking frequency [63]. Secondary PTSD outcomes of topiramate were supported, particularly in decreases of re-experiencing symptoms. The cluster of PTSD symptoms related to hyperarousal were decreased in this trial due to topiramate but were not examined in previous trials. The authors suggest that the efficacy of topiramate may vary depending on comorbidities.

3. Integrated Psychotherapy and Pharmacotherapy

Meta-analysis of 36 studies on comorbid PTSD and AUD highlights the importance of augmenting pharmacological treatment with psychotherapeutic approaches, particularly trauma-focused behavioral health therapies [64]. A number of therapies previously used to treat either PTSD or AUD have been implemented in comorbid populations. These styles include cognitive behavioral therapy (CBT), cognitive processing therapy (CPT), Relapse Prevention Training (RPT) and Seeking Safety (SS) [65,66]. Cognitive processing therapy is similar in practice to CBT, but with a trauma-informed therapist. Seeking Safety can be best defined by its focus on safety for the patient as an overarching goal. Current literature endorses the safety and efficacy of exposure-based therapies to not exacerbate PTSD or AUD or other substance symptoms [67,68]. By combining these treatments with

pharmacotherapy, a patient may remove symptomatic obstacles and become better equipped with the necessary tools to make therapeutic progress.

An integrated therapy for PTSD-AUD, as well as other substance use disorders (SUD), is Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure (COPE) [69]. Although this model does not incorporate pharmacotherapy, it does attempt to treat PTSD-AUD via combined approaches of relapse prevention, and exposure to triggers [70]. A trial comparing COPE to relapse prevention alone in a military population found beneficial results in all conditions, but greater efficacy for COPE in reducing participants' number of drinks per drinking day and their severity of PTSD symptoms [69]. Another study tested the integration of PE and Motivational Enhancement Therapy (MET) in either an integrated or in staggered approach, finding modest differences, but overall general benefits for comorbid PTSD-SUD from any version of therapeutic intervention [71].

In the first RCT to combine psychotherapy with pharmacotherapy in PTSD-AUD veterans, PE with either naltrexone or placebo was compared to supportive counseling with matched naltrexone/placebo conditions[72]. In both conditions, naltrexone decreased daily alcohol consumption compared to placebo. Participants in both conditions also showed a decrease in PTSD symptom severity. However, no significant difference between PE and supportive counseling was found. This null finding is contrary to the sizable literature supporting PE's efficacy in reducing PTSD symptoms. Reasoning for this contradiction varies from adherence to traits of supportive counseling. Importantly, no alcohol or PTSD symptom increases were found in this study regardless of condition.

Another integrated treatment trial of PTSD-AUD combined sertraline treatment with weekly Seeking Safety (SS) therapy [73]. All participants (n=69) were enrolled in 12 sessions of SS and randomized to receive sertraline titrated from 50mg to 200mg or a matched placebo. Results revealed clinically significant improvements in PTSD and AUD for all participants regardless of medication; however, PTSD symptomology was significantly decreased when sertraline was added compared to placebo. Bolstering psychotherapeutic treatment with pharmaco-intervention may allow patients to move beyond barriers that would normally stand in the way of the therapeutic process.

While the above study is promising, it is one of very few integrated treatment trials for PTSD-AUD. Such a scarcity in this literature is crucial to address considering the prevalence of this comorbidity. Alternative treatments include mindfulness meditation practice, yoga, and acupuncture [35]. At this time, these may be considered alternative or complementary, but a growing interest in these approaches from both the scientific community and patient populations may reveal their utility. Similarly, one such example of a renaissance can be seen in the field of psychedelics.

4. MDMA Integrative Therapy for PTSD, AUD, and Beyond

3,4,-methylenedioxmethamphetamine (MDMA) was synthesized in the early 20th century, but rose to prominence over 60 years later when it was utilized as a tool by psychotherapists to promote openness and therapeutic alliance with their patients [74]. The drug garnered

attention and subsequent illicit Schedule1 status due to its recreational prevalence and structural similarity to methylenedioxyamphetamine (MDA), which holds neurotoxic properties [75]. During the new psychedelic renaissance in recent years, MDMA has been broadly labeled as a "non-classic" psychedelic due to its chemical structure and emotional effects distinct from psilocybin or lysergic acid diethylamide (LSD). It has been described as an "entactogen" a word derived to represent the process of reaching within oneself to grasp things that have otherwise been repressed [76]. In human subjects MDMA is known to induce an altered state of consciousness accompanied by feelings of euphoria, closeness to others, mental stimulation, and empathy. It has been described as a "heart" trip for its prevalence of positive affect, as opposed to the "head" trip of classic psychedelics.

On a neurochemical level MDMA is primarily effective as an agonist to the serotonergic system, releasing and inhibiting reuptake of pre-synaptic serotonin as well as dopamine, norepinephrine, and oxytocin [77]. Potential neurotoxicity for repeated use of MDMA have been examined in some animal populations; however, the generalizability of these findings to humans has been called into question [78]. In light of the reevaluation of MDMA's risks and benefits, there is a renewed interest in its clinical usage. Most significant in this reevaluation is MDMA's potential to adjunctively bolster the efficacy of psychotherapy. Some benefits have been examined in novel areas of study, like social anxiety disorder and socialization on the autism-spectrum [79]. The most well documented clinical usage of MDMA assisted therapy (MDMA-AT) to date is in the area of PTSD.

i. MDMA and PTSD

Phase 2 clinical trials established a standard design of MDMA assisted therapy (MDMA-AT) in research settings. This design involves three preparatory non-drug psychotherapy sessions, leading to 2-to-3 eight-hour experimental MDMA therapy sessions. Each experimental session is followed by three non-drug therapy sessions to integrate insights gained from drug sessions into daily life. The efficacy of these interventions is typically measured with the CAPS [80]. Interventions in early trials were shown to be significantly more effective compared to placebo [81,82]. It should be noted that placebo-controlled conditions in psychedelic trials are difficult to mask if the placebo is inactive [83]. Active placebo options or therapeutically insignificant levels of MDMA have been used in attempts to address this issue [84].

Promising phase 2 results have led to the expansion of MDMA research into multi-site phase 3 trials, which have found significant reduction in CAPS scores and secondary measures of impairment via the Sheehan Disability Scale (SDS) [85]. Approximately 65% of participants had a history of sertraline/paroxetine use, speaking to the growing body of evidence in favor of psychedelic intervention for treatment-resistant PTSD. To add further robustness to this evidence, future research will need to directly compare MDMA-AT with sertraline and paroxetine in a head-to-head design.

The mechanisms of action leading to changes in PTSD symptoms are not well-understood. Pre-clinical trials examining the effects of MDMA in animal-models offer key insights on the drug's impact in traumatic memory processing. One study examining conditioned fear responses in 200 male rats found that MDMA administration did not necessarily extinguish

fear responses during exposure, but rather altered the reconsolidation of those fear memories after recall so that they became more manageable over time [86]. A study using male and female rodents of varying ages found that a single dose of MDMA reopened critical learning periods and promoted reintegration into optimal conditions [87]. Taken together, plasticity appears crucial in disrupting the maladaptive maintenance of PTSD.

ii.   MDMA and AUD

Research examining MDMA specifically as a potential AUD treatment is limited. The first study to examine its safety, tolerability, and efficacy in treatment included patients diagnosed with AUD who recently underwent a medical detox [88]. This study was conducted in an open-label feasibility paradigm. Outcomes examined were the drug's tolerability during an 8-week course of intervention, and subsequent drinking behaviors at follow-up interviews. Results indicated no serious adverse reactions to MDMA or intent to use MDMA illicitly/recreationally following therapeutic intervention. At nine-months post-intervention the number of alcoholic drinks consumed by participants averaged at 18.7 per week, compared to the average 130.6 pre-intervention. While this study did employ a small sample size ($n = 14$), results are promising with regard to MDMA as a feasible treatment with potentially significant results.

There is some history of other psychedelic intervention being utilized to address substance use disorder, particularly AUD. An observational research study queried individuals about their substance use before and after a self-administered naturalistic use of classic psychedelics, like LSD and psilocybin [89]. This study found a 69% decrease in participants who met self-reported criteria for SUD following their psychedelic experience.

When deciding whether to employ classic psychedelics or enactogens, the extent to which a participant is willing to undergo classic psychedelic experiences ought to be considered. While the potential of a mystical-like experience with ego-dissolution may be enticing to some, it may be daunting for others. MDMA's ability to increase mindful awareness of the "here and now" without affecting the ego makes it as a valuable tool for psychotherapeutic insight.

iii.   MDMA in PTSD-AUD comorbidity

Examined in isolation there is strong evidence for the use of MDMA-AT in the treatment of PTSD, and some emerging evidence for its safety and potential value in AUD treatment. Previous MDMA-AT trials also suggest that benefits derived from this intervention for PTSD still occur in the presence of various comorbidities including AUD, major depression, and others. A key next step in future research will be to examine whether PTSD with comorbid AUD can be treated concurrently using MDMA-AT. One such study is in development and set to begin shortly at Brown University (NCT05943665). This study will examine the efficacy of MDMA-AT in a veteran population with comorbid PTSD-AUD. No other MDMA research has been conducted on this comorbidity. Findings from this study will provide important information regarding MDMA's potential benefits in treating PTSD-AUD.

5. Conclusions

The narrative of a "miracle drug" as a *de facto* cure to a disease is not useful in regard to PTSD and AUD. It is unlikely that one treatment approach will be appropriate or effective with all affected patients. The purpose of reviewing existing pharmacotherapies for these disorders is to identify their uses as well as their shortcomings when addressing such complex and debilitating disorders as AUD and PTSD. The current evidence indicates that existing pharmacotherapies have been relied on to manage symptoms of these disorders, thereby reducing harm. This alleviation of symptoms may lead to remission and eventual flourishing. However, the issue for existing pharmacotherapies appears to lie in their strength, duration, and failure to integrate with other forms of treatment.

MDMA's value in the treatment of PTSD and AUD is not a mere result of its pharmacological action or influence on symptoms, but in its removal of barriers so that a patient may turn towards distressing memories and emotions and subsequently address areas that would otherwise be unavailable to them. The ability to integrate MDMA into a highly supportive therapeutic environment makes it a valuable tool, but by no means is the only viable option. Various treatment options for PTSD-AUD, from psychotherapeutic, pharmacological, and other alternatives, are all aimed in the same direction. The integration of psychedelics into treatment may be compared to a bullet-train in said direction, the speed of which may be tolerated or not depending on the individual. Current revitalization of psychedelic research has yielded promising results. By comparing and contrasting these results directly with other treatment options, diverse avenues of care are elucidated.

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