Original Paper

Mystical-type experiences occasioned by ketamine mediate its impact on at-risk drinking: Results from a randomized, controlled trial

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Abstract

Background: Sub-anesthetic ketamine administration may be helpful for substance use disorders. Converging evidence suggests that the efficacy of ketamine for certain conditions may implicate a subset of its psychoactive effects.

Aims: The aim of this analysis is to evaluate whether the mystical-type effects of ketamine are critical for clinical efficacy in alcohol-dependent individuals. In this secondary analysis, we determine if a subset of the psychoactive effects of ketamine, the so-called mystical-type experience, mediates the effect of ketamine, when combined with motivational enhancement therapy, on at-risk drinking behavior in alcohol-dependent individuals interested in treatment.

Methods: Forty alcohol dependent adults were randomized to either a 52-minute infusion of ketamine or midazolam, which they received on a designated quit-day during the second week of a five-week motivational enhancement therapy regimen. Psychoactive effects were assessed following the infusion, and alcohol use was monitored for the subsequent 3 weeks at each twice-weekly visit.

Results: We found that ketamine leads to significantly greater mystical-type effects (by Hood Mysticism Scale) and dissociation (by Clinician Administered Dissociative States Scale) compared to the active control. Ketamine also led to significant reduction in at-risk drinking. The Hood Mysticism Scale, but not Clinician Administered Dissociative States Scale score, was found to mediate the effect of ketamine on drinking behavior.

Conclusions: This trial adds evidence to the literature on the importance of mystical-type experiences in addiction treatment. Future research should continue to investigate the relationship between the psychoactive effects of psychedelic therapeutics and clinical outcomes for other substance use and mental health disorders.

Keywords

Ketamine, addiction treatment, alcohol use disorder, at-risk drinking, psychedelic, spirituality, mystical experience, motivational enhancement therapy, hallucinogen

Introduction

Alcohol misuse is a significant problem in the USA, with severe medical, psychological, and economic consequences to both individuals and society at large (Centers for Disease Control and Prevention, 2013; National Highway Traffic Safety Administration, 2017; Sacks et al., 2015; Substance Abuse and Mental Health Services Administration, 2018). The current standard of care for alcohol use disorder (AUD) treatment includes both behavioral health interventions and medication treatment (De Sousa, 2010; Jonas et al., 2014; Kranzler and Kirk, 2001; McHugh et al., 2010), but effects are modest (De Sousa, 2010; Moos and Moos, 2006). Research is needed to identify how to better support alcohol-dependent individuals as they initiate and maintain recovery from problematic drinking.

Treatments that integrate a regimen of behavioral modification with medications aimed at facilitating the process of recovery represent a promising direction for AUD treatment. In a recent randomized, controlled study, we found that a single sub-anesthetic infusion of the N-methyl-D-aspartate antagonist, ketamine, promoted sustained abstinence in individuals engaged in a five-week course of motivational enhancement therapy (MET), a behavioral treatment of modest efficacy that aims to support individuals as they work towards recovery (Dakwar et al., 2020). While it remains unclear how ketamine exerts long-lasting beneficial effects on psychiatric and addicted populations (Dakwar et al., 2014a; Iadarola et al., 2015; Sanacora and Schatzberg, 2015), possible neural mechanisms include the promotion of neurogenesis, dampened functional connectivity, sustained default-mode network attenuation, and glutamate modulation (Duman et al., 2012; Li et al., 2010; Maeng et al., 2008; Scheidegger et al., 2012; Zanos et al., 2016). These may manifest clinically as

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improvements in mood and anxiety, improved craving and motivation to quit, increased resilience, and dampened reactivity (Dakwar et al., 2014a).

Other mechanisms might pertain to the psychoactive effects that emerge at sub-anesthetic doses, which include dissociative, psychotomimetic, and mystical-type effects. This latter category of effects is comparable to phenomena associated with spontaneous "spiritual" experiences: ineffability, metaphysical insight, positive affect, spatiotemporal transcendence, and heightened connectedness with the world and others (Dakwar et al., 2014b, 2018). Narrative accounts of conversion have suggested an important role for such experiences in the transition to a life guided more strongly by ethical or religious values (James, 1907). They may also be helpful, more broadly, in allowing individuals to re-assess their lives in the service of personal transformation, with spontaneous revelatory experience, for example, signaling a transition from problem drinking to sobriety in alcoholics (Kaskutas, Bond, and Weisner, 2003).

Accordingly, infusion-dependent mystical-type effects have been found to mediate the effects of ketamine on motivation to quit drug use, and on drug use and craving, in two human laboratory studies with cocaine-dependent volunteers (Dakwar et al., 2014b, 2018). Other psychoactive effects, such as dissociative phenomena, were not found to serve as mediators, raising the possibility that mystical-type effects implicate unique psychological mechanisms that promote enduring changes in decision-making (Dakwar et al., 2014b, 2018). This is consistent with the central hypothesis guiding early work by Krupitsky and colleagues investigating ketamine psychedelic therapy for alcohol and heroin use disorder (Krupitsky and Grinenko, 1997; Krupitsky, et al., 2002). The mystical-type effects of serotonergic hallucinogens, such as psilocybin, have also been shown to predict a positive response in diverse psychiatric and healthy populations (Garcia-Romeu et al., 2014; Griffiths et al., 2006, 2008; MacLean et al., 2011).

It is therefore possible that infusion-related mystical-type effects are also important to the beneficial impact of ketamine in AUD. This analysis evaluates whether mystical-type phenomena, as opposed to dissociative effects, worked to mediate the impact of ketamine on problem drinking in the trial mentioned above. Forty alcohol dependent individuals were randomized to a 52-minute infusion of ketamine (0.71 mg/kg) or midazolam (0.025 mg/kg), which they received on a designated quit-day during the second week of a five-week regimen of MET. Psychoactive effects were assessed following the infusion, and alcohol use was monitored for the subsequent 3 weeks at each twice-weekly visit. We predict that mystical-type phenomena, and not other psychoactive effects, will mediate the efficacy of ketamine in AUD treatment.

Methods

This is a secondary analysis of results from a five-week, randomized, double-blind, placebo-controlled trial evaluating the impact of a sub-anesthetic ketamine infusion on drinking behavior in healthy adults seeking treatment for alcohol dependence (Dakwar et al., 2020). Study procedures took place at the New York State Psychiatric Institute (NYSPI) from September 2014–September 2017. The study was registered with the National Institute of Health (NIH) Clinical Trials (NCT02539511; https://clinicaltrials.gov/ct2/show/NCT02539511) after approval by the New York State Psychiatric Institute – Columbia University Department of Psychiatry Institutional Review Board (protocol #7014). All participants provided written informed consent, with full awareness of their ability to withdraw from the study at any time and without affecting their relationship with the healthcare team.

Participants

The sample consisted of 40 healthy adults seeking treatment for alcohol dependence (DSM-IV) with a minimum use criteria of at least 4 days of heavy drinking (>4 drinks/day for males; >3 drinks/day for females) over the past 7 days, or minimum weekly use of 35 drinks for males and 28 for females. Participants were excluded if they were physiologically dependent on another substance, or if they met Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for active depressive disorder, or past or current bipolar or psychotic disorders. All participants tolerated study procedures without adverse events, including unexpected psychiatric disturbances and initiation of ketamine or benzodiazepine misuse. A full description of study participants is available in a previous report (Dakwar et al., 2020).

Study design and procedures

All procedures and outpatient visits took place at the New York State Psychiatric Institute on the Columbia University Medical Center campus, between September 2014–September 2017. Forty individuals seeking treatment for alcohol dependence, meeting eligibility criteria, and providing written informed consent were enrolled in this five-week trial where they were randomized to receive an intravenous (IV) infusion of either ketamine or of the active control midazolam, and came in twice weekly for 5 weeks for monitoring and measures, physician visits, and MET. Participants came in twice weekly to the clinic except for week 2 (the IV infusion week), when they met with staff three times. Deficits common to alcohol dependence, such as craving, confidence to maintain abstinence, and withdrawal, were assessed at each visit, as well as urine toxicology (six-panel dipstick) and self-reported drug use using the timeline follow-back (TLFB) method. At the end of the trial, participants were provided with referrals for further treatment. Participants were followed-up with by phone at 1 and 3 months following the completion of the study.

Infusion procedures

On day 2, week 2 of the trial, patients were randomized (1:1) to receive an IV infusion of either ketamine or midazolam. Blinded staff was involved with infusion administration. Infusions occurred on a "quit day" set in advance during week 1 by the participant and his/her MET therapist. The quit day marked when participants would begin implementing the changes discussed until that point during MET. Participants abstained from alcohol for at least 24 h prior to the infusion. Additionally, they refrained from eating from midnight before so as to reduce the risk of nausea and aspiration. Participants were not told that they might only receive ketamine or midazolam, but were informed that they may be infused with any of several medications, or a combination of them: amantadine, buspirone, d-cycloserine, ketamine, lorazepam, midazolam,

memantine, or saline. This blinding procedure was intended to obscure what drug was given as to minimize expectancy effects and address the possibility of participants identifying which drug has been administered.

Relaxation and mindfulness-based exercises were done prior to the start of the infusion to prepare participants for the upcoming experience. They were also guided through these practices if any discomfort or anxiety emerged during infusions. A Clinician Administered Dissociative States Scale (CADSS) and Hood Mysticism Scale (HMS) were administered at the conclusion of the infusion by a trained research assistant. Participants were also asked questions about any other subjective psychoactive effects they may have experienced or were still experiencing.

Drinking outcome measures

Measures of daily drinking behavior were gathered via urine toxicology (six-panel dipstick) and self-reported drug use using the TLFB method. Urine ethyl glucuronide was tested to confirm abstinence. "At-risk" drinking post-infusion was used as the primary outcome measure, defined by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) as more than four drinks on any day or 14 per week for men, and more than three drinks on any day or seven per week for women (NIAAA, 2019). This dependent variable pertained to the entire three-week follow-up period; it is more sensitive to problematic drinking than simply registering heavy drinking days because it also encompasses total alcohol use. The outcome measure was coded as a binary outcome.

Time to relapse, defined as the number of days post-infusion until the participant engaged in a heavy drinking day or dropped out of the study, was used as a secondary dependent variable. If the participant neither engaged in a heavy drinking day nor dropped out of the study, they were given a score of 21 on this outcome measure, referring to the 21-day follow-up period in which they remained abstinent. This dependent variable is a time right-censored variable ranging from 1–21 days (Hosmer et al., 2008). Given the nature of this dependent variable, we also coded for event status, where 1 indicated a subject relapsed and while 0 indicated a censored observation where the subject had not relapsed.

Assessment of psychoactive effects

Mystical experiences. Mystical experience was assessed via the HMS, which is a 32-item questionnaire concerning eight dimensions of mystical experience initially conceptualized by Stace (1960), including unity, ineffability, positive affect, sense of sacredness, and loss of ego (Hood, 1975). The questionnaire was slightly modified for the purpose of the study, with verb tense changed to focus on infusion-related, as opposed to lifetime, experience. The HMS was administered to participants on week 2 day 2, immediately following the infusion.

Dissociative experiences. Dissociative experiences were assessed via the CADSS, which is a 27-item inventory assessing for depersonalization, derealization, psychic fragmentation, and other dissociative states (Bremner et al., 1998). subject-rates scores. The CADSS was administered to participants in the study on week 2 day 2, immediately following the infusion.

Subscales of mystical experience. The eight dimensions of mystical experience are represented by eight subscales on the HMS: ego quality (E), unifying quality (U), inner subjective quality (Is), temporal/spatial quality (T), noetic quality (N), ineffability (I), positive affect (P), and religious quality (R) (Hood, 1975). Each of these scales was analyzed separately in relation to post-infusion treatment outcomes to better understand if any specific qualities of a mystical experience are especially correlated with improvement.

Statistical analyses and calculation

SPSS version 24 was used to carry out the analyses, which uses listwise deletion to treat missing data. The assumptions of normality for the mediating variables (e.g. CADSS and HMS) were checked visually via histograms because our small sample size (n=40) would preclude an adequately powered statistical test for normality like the Kolmogorov-Smirnov. While HMS was approximately normally distributed, the CADSS variable has a positive skew of (statistic=1.183, standard error (SE)=0.383) and a histogram of CADSS clearly showed its positive skew. The error distribution in the model with CADSS as an outcome was not normal, so we used robust regression in all our analyses to cope with the non-normal distribution (Maxwell et al., 2017).

The first step was to look at whether ketamine, as compared to the control substance midazolam, leads to significantly higher levels of mystical (HMS) and dissociative (CADSS) experiences using a univariate analysis of variance (ANOVA) with robust regression. In addition, we investigated whether ketamine decreased the odds of at-risk drinking post-infusion using a binary logistic robust regression. Two-tailed tests at the 0.05 level were used. We then performed a mediation analysis, by including into a multivariate logistic robust regression HMS, CADSS, and medication assignment as independent predictor variables, and with at-risk drinking as an outcome variable. There was evidence for mediation if, in the full model, the mediator being tested remained significant ($p<0.05$) and if the treatment group variable lost or reduced in its significance ($p>0.05$) after controlling for the hypothesized mediators.

The same steps were taken to test if mystical (HMS) and/or dissociative (CADSS) experiences mediated the relationship between treatment group and time to relapse. To investigate whether ketamine delayed time to relapse, a Kaplan-Meier survival model was used. To examine whether increases in HMS and/or CADSS scores predicted longer time to relapse and to examine the full mediation model with treatment group, HMS, and CADSS, Cox proportional hazard models were used (Hosmer et al., 2008). This assumption of a time-independent and constant hazard ratio was checked by adding the relevant time-covariate interactions and using a likelihood ratio test to compare the two models. Additionally, none of the time-varying coefficients were significant. This indicates that the proportional hazard assumption is tenable, and therefore it is unnecessary to treat any of the covariates as time-dependent covariates.

Table 1. Demographic characteristics at baseline.

Characteristic	Treatment group					
	Total sample (*n*=40)		Midazolam (*n*=23)		Ketamine (*n*=17)	
	n	Mean (SD) or %	*n*	Mean (SD) or %	*n*	Mean (SD) or %
Age	40	53.0 (9.8)	23	55.0 (8.3)	17	50.4 (11.3)
Gender						
Female	21	52.5%	14	60.9%	7	41.2%
Male	19	47.5%	9	39.1%	10	58.8%
Race						
Asian	2	5.4%	2	9.1%	0	0.0%
Black or African American	5	13.5%	1	4.5%	4	26.7%
White	26	70.3%	15	68.2%	11	73.3%
Multiracial	4	10.8%	4	18.2%	0	0.0%
Ethnicity						
Not Hispanic/Latino	33	82.5%	20	87.0%	13	76.5%
Hispanic/Latino	7	17.5%	3	13.0%	4	23.5%
Average drinks per day	40	6.6 (4.1)	23	6.5 (4.3)	17	6.8 (3.9)

SD: standard deviation.

In order to examine the HMS subscales, a non-parametric Spearman correlation matrix comparing scores on the eight unique HMS items with drinking outcome measures was used to determine if specific aspects of mystical experience were positively correlated with treatment outcomes.

Results

Participants

Data were available for drinking patterns for all participants post-infusion, *n*=3 participants had missing data in the HMS and *n*=2 participants in the CADSS. Thirty-five individuals were therefore included in the analysis. The average baseline use was 6.6 drinks/day for the total sample (Table 1). No adverse events were reported as a result of either the ketamine or midazolam infusions.

Infusion effects

The administration of ketamine as compared to midazolam led to significantly greater levels of both mystical-type and dissociative effects (using one-way ANOVA) (Figures 1 and 2). Individuals receiving ketamine, on average, scored 38 points higher on the HMS (β=38.1490) ($p<0.05$). Similarly, the ketamine group scored on average 13 points higher on the CADSS (β=12.955) ($p<0.05$). Ketamine decreased the odds of engaging in at-risk drinking by approximately five times ($p<0.05$). Furthermore, as in the primary article by Dakwar et al. (2020), on the basis of the log-rank test, participants in the ketamine group had significantly longer time to relapse (defined as time to first heavy drinking day or dropout) (χ^2=4.133, p=0.042) compared with participants in the midazolam group.

HMS and CADSS scores were highly correlated (R=0.489, $p<0.01$). However, the correlation between HMS score and number of heavy drinking days post-infusion was statistically significant (R=−0.466, $p<0.05$), while the correlation between CADSS score and number of heavy drinking days post-infusion was not (R=−0.315, p=0.054).

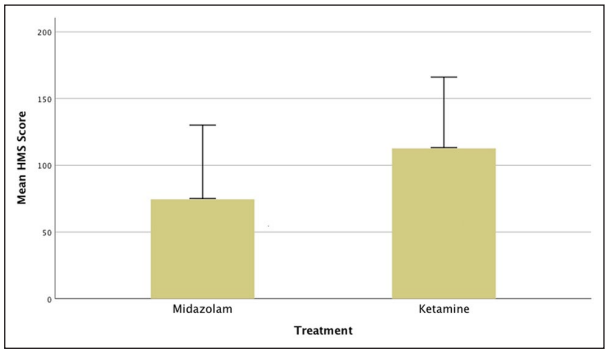

Figure 1. Mean Hood Mysticism Scale (HMS) score by treatment group. Error bars: +2 standard deviations (SDs).

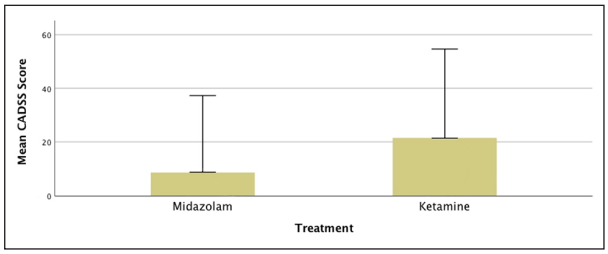

Figure 2. Mean Clinician Administered Dissociative States Scale (CADSS) score by treatment group. Error bars: +2 standard deviations (SDs).

Post-infusion drinking

Post-infusion drinking behavior was recorded for all 40 participants. Data is displayed in Figure 3, Tables 2 and 3.

Mediation

At-risk drinking. HMS (Exp(B)=1.045, $p<0.05$), but not CADSS ($p=0.742$) was found to be a significant mediator for the negative relationship between treatment group and at-risk drinking. Consistent with mediation, the treatment variable (ketamine) lost significance once HMS was included in the multivariate model ($p=0.719$).

Time to relapse. Treatment group (β=0.119, $p=0.902$) and CADSS score (β=−0.008, $p=0.811$) were not significantly related to time to relapse in the full mediation model. However, HMS score remained significant in the model (β=−0.029, $p=0.034$).

HMS subscale analysis

The following correlations were significant in those randomized to the ketamine arm ($n=17$): Scores on the HMS subscale relating to ineffability were significantly correlated with percentage of heavy drinking days ($r_s=0.624$, $p=0.01$) post-infusion. Scores on HMS subscale relating to positive affect were significantly correlated with percentage of days abstinent ($r_s=0.613$, $p<0.05$), and average number of daily drinks post-infusion ($r_s=0.554$, $p<0.05$).

Discussion

As hypothesized, improvements in drinking behavior following the ketamine infusion were mediated by mystical-type psychoactive effects, but not dissociative phenomena. These data suggest that a unique sub-set of psychoactive effects may play a critical role in the efficacy of ketamine-assisted behavioral treatment for alcohol use disorder. These are the first findings in a clinical sample to indicate that such medication-occasioned experiences might facilitate long-term changes in behavior. They build on previous research investigating the impact of ketamine-occasioned mystical-type experience in cocaine-dependent research volunteers engaged in human laboratory studies, as well as on studies investigating psilocybin for end-of-life anxiety and tobacco dependence (Dakwar et al., 2014b, 2018; Garcia-Romeu et al., 2014; Griffiths et al., 2016). They provide further support for a psychological mechanism of action for the therapeutic effects of ketamine on substance use disorder (SUD).

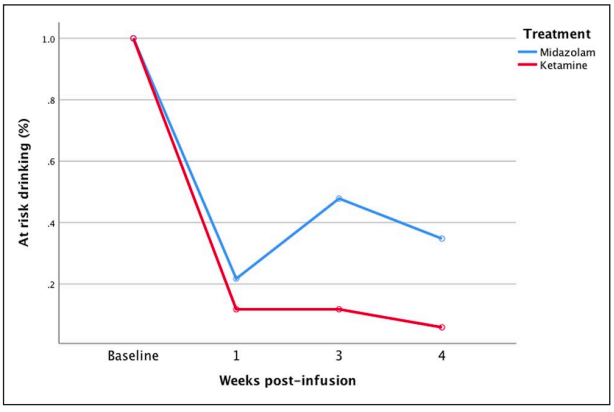

Figure 3. Trajectories of at-risk drinking at baseline and post-infusion by treatment group.

The impact of these phenomena on motivation to quit in a previous study informed our decision to pair a ketamine infusion with MET in the above trial. We assumed that a psychotherapy platform aimed at enhancing motivation and promoting change might provide a framework for focusing these psychoactive effects into more fruitful engagement with a regimen of behavioral modification oriented around existential principles. MET aims at eliciting "change talk" from participants, and at helping them reflect on the goals they wish to achieve, as well as the steps they need to take (Hettema et al., 2005; Smedslund et al., 2011). Mystical-type phenomena, sometimes called "transpersonal" and "peak" experiences, may facilitate this process through effects on mood, outlook, and behavior. These existential mechanisms include a refreshed sense of self, others, and the world; a reappraisal of values and commitments; and a new orientation towards life's purpose and meaning (James, 1907; Miller, 2004; Miller and C'de Baca, 2001).

Other therapeutic mechanisms of mystical-type phenomena are predicated on "psychospiritual" explanations that invoke the "revelation" of a non-ordinary mode of being. These revelatory experiences might include: developing a relationship to an immaterial and sacred dimension, exalted mode of being (such as "cosmic consciousness" or Samadhi), or transcendent entity (e.g. God, spirit, or higher power); finding redemption from sin, or freedom from suffering; and deepening a personal identification with the interconnectedness of the world (Delaney, 2005; James, 1907). Prior to the advent of current evidence-based treatments for AUDs, psychospiritual treatments were the mainstay, including self-help groups such as Alcoholics Anonymous (AA), which promotes "spirituality" as a core tenet of the fellowship. Distinct from religiosity or involvement in religious belief or practice, spirituality is a multidimensional capacity associated with a "search for meaning and purpose, extending to the inclusion of relationships and recognition of holism, and finally to a connection to the environment and cosmos" (Delaney, 2005: 151).

Table 2. Any heavy drinking post-infusion.

Group	Post-infusion statistics	*n*	% Group	% Total
Midazolam	Total participants	23	100	57.5
	Participants engaged in "at-risk" drinking post-infusion	11	47.8	27.5
Ketamine	Total participants	17	100	42.5
	Participants engaged in "at-risk" drinking post-infusion	4	23.5	10
Total	Total participants	40	100	100
	Participants engaged in "at- risk" drinking post-infusion	15	37.5	37.5

Table 3. Post-infusion drinking behavior.

Group	Post-infusion statistics	Mean	*n*	SD	Median
Midazolam	% Days abstinent	72.39	23	30.31	76
	Heavy drinking days	4.52	23	6.26	0
	% Heavy drinking days	4.44	23	20.83	0
	Time to first drink	12.22	23	7.66	10
	Time to relapse	14.22	23	7.66	21
Ketamine	% Days abstinent	87.94	17	17.47	100
	Heavy drinking days	0.53	17	1.33	0
	% Heavy drinking days	0.02	17	0.05	0
	Time to first drink	14.06	17	8.68	21
	Time to relapse	18.12	17	6.42	21
Total	% Days abstinent	79.00	40	26.53	95
	Heavy drinking days	2.82	40	5.18	0
	% Heavy drinking days	2.56	40	15.80	0
	Time to first drink	13.00	40	8.05	12.50
	Time to relapse	15.88	40	7.34	21

SD: standard deviation.

Studies have found an association between spirituality and fewer relapses and longer-term recovery, as well as detected a negative correlation with frequent binge-drinking (Carter, 1998; Kaskutas et al., 2003; Kelly et al., 2011; Leigh et al., 2005; Miller and Saunders, 2011; Robinson et al., 2007; Zemore, 2007). Along these lines, the mystical-type dimension of ineffability was significantly correlated with percentage of heavy drinking days in our sub-analysis; this raises the possibility that the experience of ineffability, which might capture most fully the non-ordinary and transcendent character of a mystical state, is particularly important for therapeutic mechanism.

While spirituality might be deepened through religious community or practice, meaningful relationships, and experiences in nature, it may also be promoted by substances such as the serotonergic hallucinogens, ibogaine, ketamine, and other so-called psychedelics (from *psyche delos*: mind manifesting). Psychedelics are broadly defined as substances that produce shifts in consciousness comparable to trance, meditation, mystical experience, and other non-ordinary experiences (Borgonovi, 2014; Carhart-Harris and Goodwin, 2017; Escohotado, 1999). While "classic hallucinogens" refer to the tryptamine substances that primarily work by activating serotonin (5HT)-2A receptors, such as psilocybin, d-lysergic acid diethylamide (LSD), N,N-dimethyltryptamine (DMT), and mescaline, other natural and synthetic substances that similarly induce neural and perceptual shifts in consciousness via different biological mechanisms, such as ketamine, ibogaine, or *Salvia divinorum*, are also often included in the category of psychedelics (Bogenschutz and Pommy, 2012; Johnson et al., 2008). Psychedelic-occasioned mystical-type experiences might be described as a subset of spiritual experience (Bogenschutz and Pommy, 2012), and encompass many of the same phenomena, including a sense of peace and joy, unity, sacredness, ineffability, a sense of transcending space and time, and an experience of tapping into some more universal aspect of reality (MacLean et al., 2012). In long-term studies, mystical-type phenomena occasioned by psychedelics have been shown to be psychologically beneficial, and experienced as "life-changing" and "spiritually meaningful", in healthy subjects, as well as conducive to a more engaged spiritual practice (Griffiths et al., 2006, 2008; MacLean et al., 2011; Pahnke, 1966).

In the last two decades, there has been a major resurgence of research examining the possible impact of psychedelics on mental health issues, and on addiction and SUDs in particular (Dakwar et al., 2014a, 2017, 2018, 2020; Delaney, 2005; Ezquerra-Romano et al., 2018; Jones et al., 2018; Krupitsky and Grinenko, 1997; Krupitsky et al., 2002, 2007; Savage and McCabe, 1973). LSD, psilocybin, ayahuasca, and ketamine may decrease alcohol misuse and cravings in those with AUDs, according to a meta-analysis of older trials, for LSD (Krebs and Johansen, 2012); small pilot studies or observational studies for psilocybin, ketamine, and ayahuasca (Bogenschutz et al, 2015; Grob et al., 1996; Krupitsky and Grinenko, 1997; Thomas et al., 2013); and a proof-of-concept randomized controlled trial of ketamine for alcohol use disorders (Dakwar et al., 2020). Unlike the other psychedelics, ketamine has been primarily investigated in terms of its neurobiological mechanisms of action, with psychoactive properties often dismissed as distracting or problematic side-effects of the medication (Sanacora and Schatzberg, 2015). Krupitsky was one of the first researchers to recognize that its psychoactive effects might be impactful (Krupitsky and Grinenko, 1997; Krupitsky et al., 2002). He therefore evaluated ketamine in the context of "psychedelic therapy" for alcohol and opioid use disorders, with its mystical type-effects constituting an important component of the therapeutic process. The findings here suggest that these effects are not epiphenomenal, as Krupitsky hypothesized, and that the psychedelic model may be well suited to the use of ketamine in addiction treatment. Future research is needed to evaluate the existential and psychospiritual mechanisms of these effects.

Limitations

There are several limitations. First, it is not possible to conclusively determine whether the mystical type experience was responsible for the therapeutic outcomes observed. It might be the case that neurobiological mechanisms associated with ketamine are responsible for both its observed therapeutic effects and mystical type experiences, with the mystical experiences not having a causal role in efficacy. For example, alterations in default-mode network (DMN) connectivity induced by psilocybin administration were found to be correlated with mystical experiences (Lebedev et al., 2015), might be sustained after a single dose of ketamine (Scheidegger et al., 2012) and may have therapeutic relevance.

Nonetheless, there is good reason to suppose that mystical-type effects are not merely an epiphenomenon of neurobiological action, or a marker of potency. As in the prior work of Dakwar et al. (2014b, 2018), both mystical-type and dissociative experiences were tested in this analysis, but only mystical experiences were found to mediate the effects. This argues against mystical-type effects being interpreted as non-specific markers of psychoactive potency or neural activity. Furthermore, as mentioned previously, the broader literature has suggested that, following mystical experiences (whether occasioned by psychedelics or not), individuals have experienced long-lasting, meaningful impacts on their lives, and shifts in attitudes, decision-making, and behaviors, which they attribute to the experience itself (Griffiths et al., 2006, 2008; MacLean et al., 2011; Miller and

C'de Baca, 2001). Numerous accounts suggest that these experiences have enduring helpful effects on the lives of religious figures and visionaries, as well as in those of ordinary individuals (James, 1907; Miller and C'de Baca, 2001).

Another important factor to consider is the possibility that the well-documented mood-enhancing effects of ketamine are responsible for both its therapeutic action and the associated mystical experiences. Our research revealed a significant correlation between positive affect associated with ketamine-induced mystical experience and drinking outcomes, one of only two HMS subscales directly correlated with drinking outcomes in our study. Our study aimed to focus on the anti-addiction benefits of ketamine by screening out those with depressive symptoms indicative of a DSM-IV disorder (Dakwar et al., 2020). Although our sample is a unique subset of the AUD population without comorbid depression, thus arguing against the ketamine response here implicating anti-depressant mechanisms, it is possible that the mood-boosting effects of ketamine interact with other aspects of mysticism in a meaningful way that impacts on treatment outcomes. Interestingly, these mood-enhancing effects may be more pronounced in individuals with a family history of AUD (Luckenbaugh et al., 2012; Maltbie et al., 2019); a majority of our participants had a first-degree family history of alcoholism (Dakwar et al., 2020), perhaps rendering them more susceptible to this response.

Other limitations to the present study include a relatively small sample size; it would be important in replicating these findings to conduct future studies with a larger number of participants. Additionally, as mentioned above, in order to limit the number of variables that could confound the results, the study was conducted using a non-depressed alcohol-dependent population. Many individuals with AUDs have comorbid mood, anxiety, and other psychological disorders that cause or maintain alcohol use and impact treatment outcomes (Boschloo et al., 2011; Burns and Teesson, 2002; Grant et al., 2004). It is unknown whether these results would generalize to a broader population of alcohol-dependent individuals with psychiatric comorbidity. Finally, as this trial involved MET, it is possible that the therapeutic intervention may have interacted with the psychoactive effects of ketamine to influence the results.

Conclusion

This analysis adds significant evidence to the literature supporting the importance of mystical-type phenomena, as a subset of spiritual experience more broadly, in behavior change in those seeking treatment for addiction. Future studies might endeavor to further examine the psychoactive effects of ketamine and comparable substances, while exploring existential and psychospiritual mechanisms. More detailed analyses of the various facets of mystical experience and their relationship to treatment outcomes will also help us to better understand the aspects of non-ordinary experiences that play a role in recovery. Forthcoming research should continue to investigate the relationship between the subjective psychoactive effects of psychedelic therapeutics, psychotherapy, and clinical outcomes for other substance use and mental health disorders.

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