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Cognitive Behavioral Therapy, Ketamine, and Combination Treatment for Depression: Impressions of Credibility in Participants with Self-Reported Depressive Symptoms

Mitch Earleywine Ph.D.[a,b], Brianna R. Altman M.A.[a], and Joseph De Leo Ph.D. C Psych[b]

[a]Department of Psychology, University at Albany, State University of New York, Albany, NY, USA; [b]Centre for Compassionate Care, Hamilton, Ontario, Canada

ABSTRACT

Ketamine, a novel treatment for depression, has generated considerable interest and research. Few experiments address lay impressions of the credibility of ketamine treatment relative to another popular intervention for depression, CBT. Over 500 participants with depressive symptoms read descriptions of CBT, ketamine, and a treatment that combined the two. Descriptions included pros and cons of each approach. Participants found the combination treatment more credible than ketamine but no better than CBT alone. They rated the credibility of CBT alone significantly higher than ketamine alone. Participants with psychotherapy experience tended to view ketamine as less credible than those who did not report previous psychotherapy. Depression scores did not covary with credibility ratings for any treatment. Despite media coverage and Internet claims, potential clients are cautious about ketamine. These results suggest that providing descriptions of treatments might help reveal important information about their credibility to potential clients. Extended work assessing impressions of many approaches to the treatment of psychopathology and other problems appears justifiable. Given established links between credibility and treatment outcome, additional research on individual differences in perceptions of ketamine and varied treatments for depression seems warranted.

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Introduction

Major Depressive Disorder's symptoms, which are often chronic and recurring, create considerable personal suffering and economic burden. Lifetime prevalence in the United States can be as high as 1 in 5 (Hasin et al. 2018). Worldwide estimates exceed 300,000,000 (WHO 2017), and global incidence has increased nearly 50% in the last three decades (Liu et al. 2020). Although approximately 50% of those who experience one episode recover, nearly 15% report that depression is unremitting (Eaton et al. 2008). Although commodifying health care has generated criticism and potentially lowers trust in treatment providers (Huang et al. 2018), the economics of this disorder are noteworthy. An analysis in the US from over 90,000 patients hospitalized for depression suggests that hospital costs exceeded $9,000 per person (Lin et al. 2019). A classic estimate suggests costs in the US surpassed $210 billion per year (Greenberg et al. 2015), but the data are from 2010. Inflation alone would raise this price by 19% (US Bureau of Labor Statistics 2020) to $250 billion.

Publications on psychological and pharmacological treatments now include at least 500 randomized clinical trials and 70 meta-analyses (Cuijpers 2017). Success rates for both types of treatment leave considerable room for improvement (Earleywine and De Leo 2020). A review of 21 relevant medications reported that the best antidepressant drug was 2.37 times better than placebo (Cipriani et al. 2018). Standard antidepressant medications, including selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors, tricyclic antidepressants and monoamine oxidase inhibitors, frequently take several weeks before onset. These standard antidepressants also create side effects that range from sexual dysfunction (Read and Williams 2018) to increased mortality (Konttinen et al. 2016). Up to 30% of depression cases are "treatment resistant," requiring more than two medications (Rush et al. 2006). These medications also generate months of severe withdrawal in nearly half of patients (Davies and Read 2019).

After decades of use as an anesthetic and recreational drug, ketamine (and related molecules like *esketamine*)

CONTACT Mitch Earleywine Mearleywine@albany.edu Department of Psychology, University at Albany, State University of New York, 1400 Washington Avenue SS 217, Albany, NY 12203.

have generated considerable excitement as a novel pharmacological treatment for depression (Li and Vlisides 2016). Unlike standard antidepressants that alter monoamine function, ketamine primarily targets brain-derived neurotrophic factor and NMDA glutamate receptor antagonism. The majority of clinical research focuses on treatment-resistant depression, which usually means that patients have not responded to at least two different medications. Most trials focus on intravenous administration, but intramuscular, nasal, oral, rectal, subcutaneous, and sublingual forms are available, each with differences in bioavailability and dosage strategies (Peltoniemi et al. 2016). Its rapid onset has remarkable appeal, especially for those who experience acute suicidality. Symptoms can recede within hours instead of weeks, but most trials have no more than seven days of follow-up (McIntyre et al. 2020). Higher doses and repeated administrations likely have more impact but might also increase risk of unwanted side effects (Marcantoni et al. 2020; Zheng et al. 2019).

A recent consensus statement estimated ketamine's treatment efficacy between 38 and 54% at two-week follow-up (Sanacora et al. 2017). An earlier meta-analysis suggested efficacy of 46% at three days but only 31% at seven days (Newport et al. 2015). Side-effects of acute administration include nausea, dissociation, and hypertension, but they resolve spontaneously after several hours. Long-term effects identified in recreational users and pain patients include hepatic problems and a risk for dependence symptoms. These problems appear only rarely in depression trials, but follow-up and reporting might be lax (Short et al. 2018).

Cognitive behavioral treatment (CBT), the most widely researched psychological treatment for depression, helps approximately 1/3 to ½ of patients, much like other manualized, non-pharmacological options, including interpersonal, behavioral activation, and short-term psychodynamic therapy (See Cuijpers 2017). These psychological interventions might create longer-lasting effects, but pharmacotherapy's effect sizes are slightly larger (by .13 to .16) for some symptoms (Boschloo et al. 2019). The combination appears to help, at best, 65% of patients (Corriger and Pickering 2019; Cuijpers 2017), and has the advantageous appeal of the biopsychosocial model. Given these findings, the quest for alternative treatment approaches seems justified. An ideal treatment for depression with rapid onset of long-lasting, dramatic improvement remains elusive (Earleywine and De Leo 2020).

Publications on psychotherapy and ketamine combined as a treatment for depression (and no comorbid disorder) are rare. Many reviewers communicate optimism about the idea and outline strategies for maximizing each approach's impact (e.g. Becker 2015; Hasler 2020). Others detail subjective and physiological effects with recommendations for clinicians to take advantage of the rapid onset of improvements in mood (Ionescu, Rosenbaum, and Alpert 2015; Walter, Li, and Demenescu 2014). Other studies that combine ketamine and psychotherapy show promising effects in open-label trials but lack control groups (Dore et al. 2019; Irwin et al. 2013). Recent work warns that the approach is not a panacea and provide two cautionary case studies (Talbot, Phillips, and Blier 2019). The impact of data like these on lay impressions of credibility remains difficult to assess. A google search of "ketamine" and "depression" leads to over eight million links. Clinic websites report "between 75% and 80%" (https://www.psycom.net/ketamine-depression; https://thriveketamine.com/ketamine-for-depression/) as well as 83% (https://ketamineclinics.com/) success rates, apparently based on open-label administration at individual sites. These claims exceed any that appear in empirical publications. These estimates might lead to exaggerated impressions of credibility, potentially leading consumers to expect more than the treatment might deliver.

A recent meta-analysis suggests that early treatment credibility predicts treatment outcomes (Constantino et al. 2018), but the review focused on empirically validated psychological treatments rather than pharmacological ones. Lay impressions of ketamine, alone or in combination with psychotherapy, seem under-investigated. We examined treatment credibility ratings of each intervention. We also explored links between credibility and previous therapy experience, ketamine use, and depression severity, with the hypothesis that previous psychotherapy would enhance impressions of CBT's credibility. Previous ketamine use might enhance impressions of ketamine treatment if participants benefited enough to ingest it on more than one occasion. Those with worse symptoms frequently view treatment as less credible, suggesting that impressions should decline as depression increased (Cohen, Beard, and Björgvinsson 2015; Constantino et al. 2014)

Methods

Overview of procedures

Potential participants read a description of the study, the consent form, and then completed the first 8 items of the Center for Epidemiologic Studies Depression Scale Revised (CESD-R-10) to measure depression (Andresen et al. 1994). Only those who consented and scored at least a 4 (details below) were allowed to continue. They then answered details about health and

demographics, read therapy descriptions one at a time, and provided ratings of the impressions of each therapy immediately after reading about it, as detailed below.

Participants

Participants (N = 1,004) were recruited from Amazon's MTurk, a crowdsourcing platform commonly used to identify convenience samples for psychological surveys. Previous work successfully recruited depressed participants from this same crowdsourcing platform (Zimmerman and Papa 2020). In fact, the base rate of depression is likely elevated among the workers (Arditte et al. 2016; McCredie and Morey 2019; Walters et al. 2018), perhaps because of social, demographic, health, and lifestyle factors that covary with the decision to work on the site (See Ophir et al. 2020). These samples are likely more educated than average, over-representative of some ethnic groups, and generally unemployed or underemployed (Chandler and Shapiro 2016).

Only those over the age of 18, who reported symptoms of depression (described below) were eligible. Upon meeting inclusion criteria (N = 819) and providing informed consent, participants reported demographic information, depression symptoms, prior treatment history and prior ketamine use. They then read brief descriptions of three depression treatments in a paradigm closely aligned to previous work that spearheaded this approach (Beshai et al. 2019). Participants read descriptions one at a time and answered credibility items after each one. Participants were assigned randomly to read either a description of CBT much like one used previously (Beshai et al. 2019), or a comparable one for a *ketamine condition* (KET). All participants read a combined CBT and ketamine condition (COM) last, as pilot testing suggested that any attempt to present the combined treatment earlier led to confusion. Three clinical psychologists, a psychology trainee, and a board-certified anesthesiologist currently providing ketamine treatment reviewed multiple drafts of the descriptions to confirm an accurate presentation.

Participants who failed attention checks (N = 196) were removed. These checks included questions that specifically asked for a single answer, e.g. "Please choose option '3' here," as well as a final query about self-perceived accuracy of reporting that read: "You will not be penalized in any way for an honest response to this question. Should we include your data in our analyses?" Previous work suggests that these approaches can decrease error variance and improve correlations among indicators of the same construct (Meade and Craig 2012). Those who stopped mid-survey (N = 65) or who did not provide consent to having their data included in analysis (N = 40) were also excluded, leaving 518 participants. The excluded group did not differ from valid participants on any demographic variables. All procedures were approved by the University at Albany, State University of New York Institutional Review Board.

The sample was predominantly male (53.9%) and 32.47 years of age on average (SD = 10.08). Participants were mostly Caucasian (53%), followed by Asian (26.3%,), Hispanic/Latino (10%), African American (4.8%), multi-racial (2.3%), Native American (2.1%), with remaining participants choosing not to answer or missing. Over 65% of the sample reported holding a Bachelor's degree or higher, though education ranged from those with only some high school (2.1%) to 14.5% with an advanced degree. Over 41% reported being married or in a domestic partnership with 37.9% reporting that they were single. For job status 42.7% reported being employed full time with 15.6% (81) employed part time and 10.1% self-employed.

Prior treatment

A total of 34.6% participants reported taking a psychiatric medication at some time in their lives. A total of 38.6% reported participating in psychotherapy at some time. Participants chose among cognitive behavioral (81), dialectical behavior therapy (13), acceptance and commitment therapy (13), psychodynamic or psychoanalytic therapy (5) eclectic (2) not sure (17) or talk therapy (5), and 63 did not report type of psychotherapy received.

Hallucinogen use

Participants reported the number of times they used lysergic acid diethylamide, psilocybin mushrooms, psilocybin, dmt, 5-meo-dmt, salvia, peyote, mescaline, PCP, MDMA, ketamine, Ibogaine, DOT, ayahuasca, and other hallucinogens in their lives. About one–quarter (22.0%) had used hallucinogens at least once whereas 17.4% had used multiple times. Of the 27 participants reporting previous use of ketamine, 18 endorsed using more than once. The distribution for the number of times participants had used hallucinogens had a vast range (0-330) and severe positive skew (4.11) that could not be transformed for parametric statistics. Participants also answered an ordinal question on frequency of use in the last 5 years with categories that included daily, weekly, monthly, a few times per year, yearly, less than once a year, only once, zero times, or prefer not to answer.

Depression severity

We administered The Center for Epidemiologic Studies Depression Scale Revised (CESD-R–10) to measure depression (Andresen et al. 1994). This measure includes 10 items that participants endorse on a scale from 0 "Rarely or none of the time" to 3 "All of the time." Possible scores range from 0-30, with scores of 10 or higher indicating probable depression. Most (82.4%) scored 10 or higher. This current experiment used a cutoff score of 4 to exclude individuals who did not report any symptoms of depression. Previous work used a comparable approach successfully (Ophir et al. 2014). Among our sample, the average CESD-R–10 score was 15.80 (SD = 5.80, Range = 4–30). Internal consistency (Cronbach's alpha) was .795.

Descriptions of treatments

Participants read from 540-600 words on CBT, Ketamine, and Combination treatments, each emphasizing five advantages and five disadvantages of the treatment as well as data-based descriptions of how the treatment would proceed. The full descriptions appear in online Appendix A. The CBT condition drew on meta-analytic reviews (Cuijpers 2017) and emphasized a 55%–65% rate of some improvement, the learning of skills that can generalize to other areas of life, flexibility to meet individual's needs, the capacity for remote delivery via technology, and an absence of physiological side effects. Potential disadvantages included that 35-45% might not receive significant benefit, and that up to 25% can have a return of some symptoms at one-year follow-up. Additional disadvantages included that the treatment requires time and effort and that success rates can depend upon an individual therapist's skills. The last disadvantage emphasized that knowledge of exactly how, why, and for whom the treatment works is limited.

The ketamine condition (KET) also drew on reviews (Cipriani et al. 2018; McGirr et al. 2015; Xu et al. 2016) and emphasized potential advantages including fast relief, prompt alleviation of suicidal ideation, the potential for fewer sessions than many other therapies, a 40% response rate at seven-day follow–up, and 40-60% rate of improvement. Disadvantages mentioned: acute side effects like nausea, dissociation, and high blood pressure, the absence of long-term data on efficacy, potentially high costs, a risk of dependence symptoms, and a potential lack of availability in rural areas.

The Combined condition (COM) relied on published work as well (Dore et al. 2019; Hasler 2020) and emphasized potential advantages that included the chance to connect to multiple supportive providers, the chance for the combination of rapid relief and new skills, the advantage of more motivation for CBT given the rapid relief from symptoms, a potential for a more time-limited approach to treatment, and an opportunity to treat those who might not respond to either approach by itself. Potential disadvantages included that the combined treatment might prove more time intensive and leave the source of improvement less than clear given the number of potential mechanisms. Other disadvantages emphasized that rapid onset of ketamine-induced changes might dampen motivation for psychotherapy, that infusions have physiological side effects, and research on outcome of the combination treatment is limited.

Credibility ratings

We based credibility items on comparable work but added an item to assess participant's expectations about the percentage of people who would no longer qualify for a depression diagnosis at treatment's end (Devilly and Borkovec 2000). Participants rated the credibility of each treatment in multiple domains on sliders that ranged from 0 "Not at all" to 100 "A great deal." Items queried about how logical the therapy was, how successful they believed the treatment would be, and how confident they would be recommending the treatment to someone else. We also assessed participants' beliefs about the effectiveness of the treatment (e.g. "Of all the people who complete this therapy, what percentage do you think are no longer depressed?"). Participants rated this last item on a comparable slider ranging from 0% to 100%. These sliders function much like Likert scales and provide sufficient variance to uncover findings consistent with theory even when Likert scales fail because of restricted ranges (Kemper et al. 2019). Cronbach's alpha of these items across the three treatments (e.g. CBT, ketamine, and combined) was .88.

Results

Sixteen participants (3%) were missing at least one of the 12 items used to compute the credibility scales across the three different treatments. We used all 12 items as well as the demographic variables to examine if data were missing completely at random. Little's MCAR test was not significant ($p.$ = .079), suggesting data might be missing completely at random (MCAR). To preserve power and decrease potential bias, we used the regression imputation approach in SPSS 26 to generate 20 imputation samples to replace missing items. (Graham,

Olchowski, and Gilreath 2007; Van Buuren 2018). Analyses with deletion had the same pattern of statistical significance as those reported. Given the number of analyses performed, we used a modified Bonferroni approach to maintain power but minimize Type I error. Only $p < .001$ was considered significant.

Credibility ratings

A 2 × 3 repeated-measures ANOVA with order as a between–subjects factor (CBT presented first vs. KET presented first) and treatment (CBT vs. KET vs. COM) required tests of assumptions. Skew was negative but not more than −0.5 for any of the dependent measures. Standardization revealed 5 outliers with Z scores less than −3.0. We removed those participants, leaving scores that ranged from 58–400 for CBT, 0–395 for ketamine, and 20-394 for the combination. Normal Q-Q plots looked excellent and none of the Kolmogorov-Smirnov tests reached significance, suggesting that parameter estimates would be normally distributed. (A non-parametric Friedman test produced identical patterns of significance). Mauchly's test of sphericity did reach statistical significance, W = .897, chi-square = 55.196(2), $p < .001$, necessitating Greenhouse-Geiser corrections. The F tests with corrected degrees of freedom (1.814) showed no effect of order (F = 2.534, $p = .085$) but a significant treatment effect (F = 46.24, $p < .001$). Within-subjects planned contrasts revealed that CBT's credibility (M = 242.393, SD = 60.355) exceeded KET's (M = 212.579, SD = 73.872) significantly (paired t(512) =8.386, $p < .001$; Mdiff = 29.814, SDdiff = 80.524), Cohen's d= 0.370). CBT's credibility relative to the COM's credibility (M = 235.329, SD = 75.635) did not satisfy the modified Bonferroni correction for significance, and the size of the trend appeared small (t(512) = 2.103, $p = .036$; Mdiff = 7.064, SD = 76.069, d= 0.093). KET's credibility was significantly lower than the COM's (Mdiff = −22.75, SD = 60.297, d= 0.377). Box and whisker plots with descriptive data appear in Figure 1.

Covariation with demographic variables

Demographic variables did not link to ratings for CBT but occasionally had an impact on ketamine conditions. Age, marital status, employment status, and CESD scores were not associated with ketamine condition.

A trend for women to view ketamine as less credible did appear (Men's mean = 220.07 (SD = 59.48) vs Women's mean 204.00 (SD = 67.35), $d = .25$ $p = .015$ *without correction)*. When ethnic groups were divided

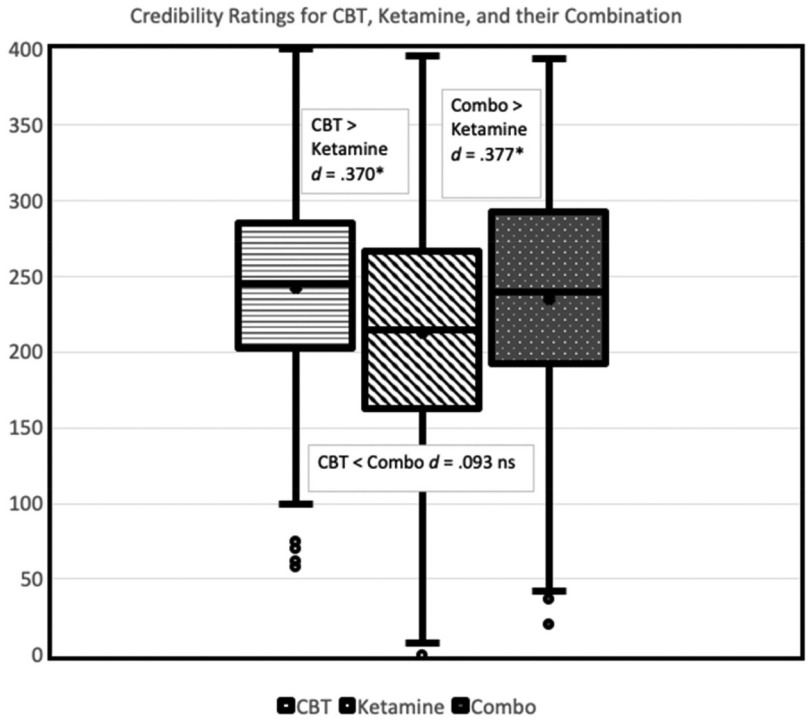

Figure 1. Box and whisker plots for credibility ratings for cognitive-behavioral, ketamine, and their combination as treatment for depression. Filled points at the center of boxes show means and cross bars within boxes show medians. Hinges appear at the 25th and 75th percentile of each distribution. Lower circles reveal outliers that were dropped for analyses. The ends of each whisker show maximum and minimum scores when outliers are removed.

into Caucasian or Other, Caucasians rated ketamine as less credible (N = 274, Mean = 196.53 (SD = 77.57)) than Other participants (N = 243, Mean = 229.99 (SD = 67.34)) d = .46, p = *.001*). Caucasians also showed a trend for rating the combined treatment as less credible than those of other ethnic groups did (Mean = 226.55 (SD = 82.72) vs. 244.12 (SD = 68.62) d= 0.23, p= .009 *without correction*).

Dividing the sample into those with a Bachelor's degree or more vs. others suggested that the more educated group showed trends for finding ketamine more credible than their peers did. (More Education (ME) N = 338; Less Education (LE) N = 179). Ketamine ratings ME = 220.09 (SD = 71.16), LE = 197.48 (SD = 79.25), d= .30, p = .002 *without correction*. Combination treatments ME = 242.90 (SD = 70.19), LE = 219.53 (SD = 86.21), d = .30 p = .002 *without correction*.

Given the small samples for individual types of therapy, we created three groups that included a more cognitive-behavioral approach (CBT, dialectical behavior therapy, acceptance and commitment therapy), an alternative approach, and no psychotherapy. Comparisons among groups did not reach statistical significance.

The 27 participants who reported ever using ketamine did not differ from the rest of the sample in any of their ratings (all p-values > .20). Lifetime hallucinogen use was orthogonal to ratings of treatment credibility, all *p-values* > .20. Frequency of use of hallucinogens in the last 5 years showed a trend for increasing ketamine's credibility (Spearman's Rho = 0.20, p = .027) but had no significant link with CBT or combined treatment ratings.

Discussion

A convenience sample of participants with depressive symptoms rated descriptions of CBT, ketamine, and the combination on a four-item, internally consistent index of credibility (i.e., how logical, and how successful they thought the therapy would be, how confident they would be recommending it, and the percentage of patients who would no longer be depressed at termination). Ratings did not covary significantly with CES-D scores, suggesting that even the most depressed participants viewed these treatments comparably. Few participants claimed previous experience with ketamine, limiting statistical power for any examination of its use on ratings. A trend appeared for those who had previous psychotherapy experience to rate ketamine lower. Those who had used hallucinogens more frequently in the past five years had a small tendency to rate the ketamine treatment as more credible. Demographic variables had no impact on ratings of CBT. Women (rather than men), Caucasians (rather than other ethnic groups), and those who had less than a bachelor's degree (as opposed to those who had at least that much education) tended to view ketamine as less credible. No other links with demographics were significant.

We found that participants rated the combination and CBT alone comparably (COM > CBT d= 0.093 non-significant), but also significantly higher than ketamine (COM > KET, d = 0.377; CBT > KET, d = 0.370, both p–values < .001). Interpreting these effect sizes requires careful thought. Even the trend here between CBT and the combination therapy (d= 0.197) exceeds the superiority antidepressant medications appear to have on select symptoms over CBT (d= 0.13-0.16; Boschloo et al. 2019; Cuijpers 2017), which might offer some perspective. Meta-analytic reviews suggest that a difference just short of a quarter of a standard deviation (d= 0.24) might be a threshold for clinical relevance in depression (Cuijpers 2017). Differences for credibility ratings, given their less-than-perfect link to outcome (Constantino et al. 2018), likely require a higher threshold, but the effect sizes appear potentially meaningful.

Despite some reports of efficacy on the websites of individual ketamine clinics and effusive individual case narratives on the Internet, participants rated the credibility of CBT, ketamine, and their combination in ways that were consistent with the summaries provided (See Appendix A). Our fears that ketamine-related news might exaggerate impressions of credibility appear unfounded. In this study sample, participants appeared to understand brief presentations of empirical work. Thus, recommendations of CBT for depression as a straightforward intervention likely face less resistance than recommendations for ketamine. Nevertheless, the results also imply that recommendations for ketamine treatment might face an uphill battle, even for the most depressed clients.

Credibility ratings did not change as CES-D scores increased, suggesting that those with the worst symptoms did not find ketamine, CBT, or the combination any more compelling than others who were less depressed. In addition, the CBT and combination conditions did not differ from each other. Apparently, participants viewed CBT as effective in the presence or absence of ketamine. Perhaps participants view ketamine as an aid to rapid onset of relief rather than an approach that is categorically more credible that CBT alone. Empirical work does emphasize that ketamine's rapid onset is a distinct advantage, but follow-ups have been relatively brief (e.g., McIntyre et al. 2020). Participants might have reasoned that rapid onset of relief does not equate with improved efficacy overall,

though dropouts and engagement might benefit. Additional work that queries along these lines could address the rationales that underly these similar ratings for CBT with and without ketamine's assistance. Future work on expectations for the onset, as well as the impact, of antidepressant effects appears justified.

Most work with ketamine has focused on treatment-resistant depression (Cipriani et al. 2018; McGirr et al. 2015; Xu et al. 2016), and those who have used at least two medications with little improvement might respond to more detailed descriptions or individualized discussions of ketamine under ideographic conditions. But any concerns that depressed clients might be uniquely at risk of drug-seeking at ketamine treatment clinics to address their depression might be unfounded. The apparent appreciation for CBT as a monotherapy, or in combination with ketamine, suggest that informed patients hold reasonable expectations about the utility of psychotherapy treatments for depression.

The current study has multiple limitations that suggest cautious interpretation and careful generalization. Although this sample was large, the majority of the sample was well–educated and predominantly Caucasian. The current data showed no links between ratings and any demographic variables, but a larger sample with more participants from understudied populations would strengthen generalizability.

The stimuli, 540-600-word summaries of relevant literature, also limit generalizability. Further work comparing these and other treatments for depression, as well as treatments for other disorders, might offer insights into lay impressions of credibility. Adding a condition that provided no information about the treatments but asked about the same ketamine, CBT, and combination therapies might reveal more about public stereotypes for these approaches in the absence of additional information. Extending this work to other psychedelic-assisted therapies, including ayahuasca (Palhano-Fontes et al. 2019), MDMA (Vermetten and Yehuda 2020), and psilocybin (Carhart-Harris et al. 2016) for depression, might illuminate the credibility of these alternative treatments for depression and other refractory mental health conditions as well (Earleywine and De Leo 2020). We can also see how researchers could adapt this paradigm to assess unique aspects of set and setting so participants can reveal key expectancies about psychedelic experiences, psychological treatment, and their combination that might improve treatment outcome.

In addition, given ketamine's potential for ameliorating symptoms of post-traumatic stress disorder (Collins, Rutter, and Feder 2020), anxiety disorders (Glue et al. 2020), and other trauma- and stressor-related conditions, a comparable paradigm addressing these problems might inform researchers about public perceptions of ketamine's potential as monotherapies or in combination as part of integrative treatment approaches. A thorough assessment of individual differences in familiarity with the treatment rationale, strengths, and limitations, could also offer valuable information. Should the current findings replicate, the idea that those with depressive symptoms might be discerning consumers of research who hold a generally positive view of the credibility of CBT and understandable reservations about ketamine as a treatment for depression seems reasonable. The current data suggest that potential clients can educate themselves quickly when informative summaries of empirical work are available. The thought of an open-minded, discerning, educable populace provides optimism for psychotherapies assisted by psychoactive medications.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Mitch Earleywine Ph.D. http://orcid.org/0000-0002-6870-0623
Brianna R. Altman M.A. http://orcid.org/0000-0001-9254-2939

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Appendix A

Descriptions of cognitive-behavioral therapy (CBT), ketamine, and combined treatments. Participants read each of these descriptions and answered to questions about the intervention's credibility.

Cognitive Behavior Therapy

Cognitive behavior therapy (CBT) is a type of therapy that research evidence indicates reduces symptoms of depression. CBT focuses on helping patients understand how certain thoughts and actions affect emotions, like intense sadness or depression. Patients with depression may have thoughts that they are not loved or wanted, or that they are worthless. In terms of behaviors, patients may withdraw from the world around them, or neglect important tasks like their health and hygiene. Patients may also stop doing pleasurable or enjoyable activities.

The goal of CBT is to change thoughts and behaviors in ways that will help reduce depression. CBT often happens in a therapist's office. In order to give you a sense of CBT, we would like to provide you with specific information about how CBT for depression is done. CBT for depression typically consists of 12 to 20 face-to-face sessions, wherein a depressed patient meets on a weekly basis with a qualified cognitive-behavioral therapist. In the first few therapy sessions, patients are provided facts about depression and on common depression related thoughts and behaviors. In later sessions, the therapist helps the patient learn new ways to cope with depression. The therapist helps the patient identify and change negative thoughts that were untrue or unhelpful (e.g., "I am worthless"). The patient and therapist also work together to create a list of activities that should be accomplished during the course of treatment. The activities are either important for day-to–day functioning (e.g., paying the electric bill) or pleasurable for the patient (e.g., going for a walk, cycling). The patient then gradually works on accomplishing these tasks and goals, beginning with something that was small (e.g., bathing, cooking) and moving to more difficult tasks (e.g., being more assertive at work).

Treatment completes with patients developing a plan for how they would cope if symptoms of depression reappeared. Skills are first practiced in therapy sessions with the therapist present. Patients are assigned homework exercises at the end of each session. The homework exercises might include tracking symptoms, thoughts, and behaviors related to depression, as well as completing important and pleasurable tasks outside of the therapist's office. The amount of time needed for homework varies for each patient, but typically requires at least some time each day.

Advantages of CBT:

(1) According to several scientific studies, most patients (55-65%) with depression who undergo CBT see significant reductions in their depression symptoms, in comparison to patients who are not offered any treatment.
(2) The skills gained during a course of CBT for depression (e.g., identifying and challenging negative thoughts) may have positive impact on a lot of different aspects of patients' lives.
(3) The therapist can easily adapt information to the needs of the patient.
(4) CBT for depression has been successfully delivered remotely via technology (i.e., online or over the phone).
(5) CBT for depression has no physiological side–effects.

Disadvantages of CBT:

(1) A large minority (35-45%) of patients who undergo CBT for depression do not experience significant reductions in their symptoms.
(2) Within one year after treatment's end, about a quarter of the patients (25%) who first respond to CBT experience a return of some depression symptoms.
(3) CBT requires time and effort in order to reduce depression.
(4) The success of CBT for depression depends to a large degree on the delivery techniques of the therapist.
(5) To date, there is little scientific consensus as to why, how, or for whom CBT may work.

Ketamine

Ketamine, a substance used in medicine for multiple purposes for decades, also has research support as an antidepressant. Medical professionals have used ketamine as an anesthetic since the 1960s. Unlike other anesthetics, it doesn't dramatically alter heart function or breathing, making it particularly helpful for emergency surgeries in the field. Patients also report that they experience less pain after surgeries if they have ketamine administered. The drug's dissociative and hallucinogenic qualities led many to use it recreationally, and a subset suggested their moods were better even after these effects subsided. Around the year 2000, researchers noted that smaller doses of ketamine did not have anesthetic effects but lifted mood and decreased suicidality without creating extensive hallucinogenic or dissociative effects. Many patients found that their moods improved dramatically, and unlike other antidepressant medications, ketamine could have a positive impact within hours instead of weeks.

This relief from depressive symptoms could also enhance functioning, helping people experience more motivation to go to work, attend to their daily obligations, and interact with family and friends. The medicine appears to create changes in brain chemicals, but researchers haven't pinpointed the exact mechanism. Ketamine seems to alter the way cells communicate with each other in the brain, but it does not target the same cells altered by common antidepressants like Prozac or Zoloft.

Professionals can administer ketamine in many different forms, including intravenously or through a nasal spray. Health professionals monitor vital signs before administering the drug. At this dosage, most patients feel extremely relaxed but they can keep their minds fully engaged. Initially, patients may receive as many as three doses a week until they reach a therapeutic dose. They then taper off to approximately one dose per month. The effects of ketamine can last for spans of days to weeks. Common side effects include nausea, vomiting, high blood pressure of dissociation; these effects typically wear off after the ketamine infusion ends. Most sessions are 60 minutes or fewer. Physicians often request that patients refrain from driving after sessions, and some patients report some fatigue afterward, but others can go about their day and even get some work done.

Advantages of Ketamine:

(1) Ketamine appears to provide faster relief than other treatments for depression, including cognitive behavioral therapy and antidepressant medications.
(2) The faster relief from depressive symptoms may be especially important for patients who are at risk for committing suicide.
(3) Given the longer lasting effects of ketamine, people do not need to be treated as often as they might with other treatments.
(4) Ketamine might work best for depression that persists even after other treatments have failed, such that 40% of individuals treated for treatment-resistant depression still felt its benefits after 7 days.
(5) Research indicates that between 40 to 60% of patients experience decreases in their depression after a ketamine infusion session.

Disadvantages of Ketamine:

(1) Ketamine can cause several unpleasant side effects including nausea, vomiting, high blood pressure, or dissociation.
(2) Very little is known about the long-term effects of ketamine.
(3) Ketamine treatments might be costly and are typically not covered by insurance.
(4) Ketamine may have some addictive properties that warrant consideration.
(5) Finding providers who are willing to provide ketamine infusions may be difficult to come across in rural areas.

Ketamine-assisted Psychotherapy

Ketamine can be used in conjunction with cognitive behavior therapy (CBT) to help treat depression. The combination of these two therapies has the potential to take advantage of the best of both. Ketamine-assisted psychotherapy includes two phases of treatment spanning 12 weeks.

In phase one, patients receive four 40-minute sessions of ketamine infusions at the standardized dosage used in previous research (.5 mg/kg). Health professionals deliver the ketamine intravenously twice a week for two weeks. The goal of these infusions would be to provide patients with more immediate relief from their depressive symptoms. A rapid improvement in mood and a drop in any suicidal thoughts might have the potential to make the CBT work better. Within 24 to 48 hours after their first infusion, patients would also receive their first 50-minute session of cognitive-behavioral therapy provided by a therapist. This treatment would focus on helping patients change their negative, unhelpful thoughts to more adaptive, positive ones. Additionally, a therapist would work with a patient to become reacquainted with positive activities that may have been neglected or avoided during a depressive episode. During the first phase of treatment, ketamine infusions and twice weekly sessions of cognitive-behavioral therapy would occur concurrently. This approach can allow the therapist and client to form a good therapeutic relationship while the ketamine's impact on mood and motivation remains. Ideally, the new skills and outlook developed with the CBT sessions will lead to a better mood and more valued activities before the impact of the ketamine might dissipate.

During the second phase of treatment, cognitive-behavioral therapy would be provided by a therapist on a weekly basis for 8 weeks. In this treatment, patients receive both the immediate effects of ketamine and learn better coping skills to help them recover from their depressive symptoms. This later phase will include the usual homework and discussions designed to teach the clients to maintain their gains, connect to their values, and behave in ways that are consistent with those values. These sessions will also help them learn to identify when their thoughts do not seem to serve them well, reflect reality, or create the kind of moods they want to experience.

Advantages of Ketamine-assisted Psychotherapy:

(1) Patients receive care from multiple providers, connecting the patient with multiple sources of support.
(2) In addition to receiving immediate relief from their symptoms, patients learn skills to cope with depression that they can apply if they experience depression again.
(3) Ketamine infusions might allow severely depressed patients to more actively participate in cognitive-behavioral therapy by immediately enhancing their mood.
(4) This treatment is time-constrained, meaning that it will not continue indefinitely and allowing patients to proceed with their lives after the intervention ends.
(5) Patients who may not have responded to one treatment on its own might benefit from combined treatment.

Disadvantages of Ketamine-assisted Psychotherapy:

(1) Being that this treatment includes both ketamine infusions and therapy sessions, it may be more time intensive than other interventions.
(2) Concurrent treatment might make it difficult to tell which aspect of treatment helped a patient most.
(3) Ketamine infusions might cause physiological side effects, including nausea, vomiting, and high blood pressure.
(4) Patients might not be motivated to engage in the cognitive behavioral intervention, especially if they experience immediate relief from ketamine.

Research related to combining these two treatments has been limited so far, even though each component has empirical support.

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