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Review

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Ketamine for the Treatment of Psychiatric Disorders: A Systematic Review and Meta-Analysis*

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Abstract

Background. Inadequate response to first- and second-line pharmacological treatments for psychiatric disorders is commonly observed. Ketamine has demonstrated efficacy in treating adults with treatment-resistant depression (TRD), with additional off-label benefits reported for various psychiatric disorders. Herein, we performed a systematic review and meta-analysis to examine the therapeutic applications of ketamine across multiple mental disorders, excluding mood disorders.

Methods. We conducted a multidatabase literature search of randomized controlled trials and open-label trials investigating the therapeutic use of ketamine in treating mental disorders. Studies utilizing the same psychological assessments for a given disorder were pooled using the generic inverse variance method to generate a pooled estimated mean difference.

Results. The search in OVID (MedLine, Embase, AMED, PsychINFO, JBI EBP Database), EBSCO CINAHL Plus, Scopus, and Web of Science yielded 44 studies. Ketamine had a statistically significant effect on PTSD Checklist for DSM-5 (PCL-5) scores (pooled estimate = –28.07, 95% CI = [–40.05, –16.11], $p < 0.001$), Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) scores (pooled estimate = –14.07, 95% CI = [–26.24, –1.90], $p = 0.023$), and Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores (pooled estimate = –8.08, 95% CI = [–13.64, –2.52], $p = 0.004$) in individuals with PTSD, treatment-resistant PTSD (TR-PTSD), and obsessive compulsive disorder (OCD), respectively. For alcohol use disorders and at-risk drinking, there was disproportionate reporting of decreased urge to drink, increased rate of abstinence, and longer time to relapse following ketamine treatment.

Conclusions. Extant literature supports the potential use of ketamine for the treatment of PTSD, OCD, and alcohol use disorders with significant improvement of patient symptoms. However, the limited number of randomized controlled trials underscores the need to further investigate the short- and long-term benefits and risks of ketamine for the treatment of psychiatric disorders.

Highlights

- Preliminary acute ketamine treatment holds promise for psychiatric disorders.
- There is a need for more randomized controlled trials investigating ketamine treatment in psychiatric disorders other than depressive disorders.
- Long-term safety and efficacy data is required.

Introduction

There are more than 200 types of mental disorders defined and operationalized in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR), and World Health Organization (WHO) Eleventh Revision of the International Classification of Diseases (ICD-11).[1] The current conceptualization of mental disorders indicates a lack of specificity in the psychopathology of individual mental disorders, supporting a transdiagnostic perspective on various psychopathological manifestations. Notably, pharmacological treatments in psychiatry are not exclusive in practical application to a particular psychiatric disorder.

Therefore, the application of most pharmacological treatments in psychiatry is recognized for their utility across many psychiatric disorders (ie, transdiagnostic usage).

The pharmacological treatment of psychiatric disorders is complicated by factors such as adverse event profiles, interindividual variability in treatment response, and the development of resistance to conventional treatments. Inadequate response to conventional treatments for a psychiatric disorder is a significant, commonly encountered unmet need. A pertinent example of treatment-resistant psychiatric disorders is treatment-resistant depression, which exemplifies the suboptimal efficacy of both approved and off-label pharmacotherapies in approximately 30% of affected persons.[2] Notwithstanding the prevalence of treatment-resistant psychiatric illnesses, there are a limited number of approved medications for such conditions.[3]

Several research groups have evaluated innovative treatments for treatment-resistant depressive disorders. Ketamine has demonstrated efficacy in the management of adults with treatment-resistant depression.[4] In addition, ketamine has been shown to benefit a variety of mental disorders that are often difficult to treat, including, but not limited to, post-traumatic stress disorder (PTSD).[5–14] The aim of this review is to summarize available literature reporting on the efficacy and safety of ketamine in a transdiagnostic context. While multiple reviews have previously summarized the efficacy of ketamine in mood disorders, herein we evaluate conditions other than mood disorders.

Methods

Search strategy

This study followed the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines.[15] In accordance with the 2020 Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines, OVID (MedLine, Embase, AMED, PsychINFO, JBI EBP Database), EBSCO CINAHL Plus, Scopus, and Web of Science were systematically searched from database inception to March 2024.[16] The search string implemented for the systematic search is in Supplementary Materials Table S1. In addition to searching the aforementioned databases, we also manually searched the references of all relevant articles and Google Scholar/Google for additional studies. In all databases except OVID, no language or publication status/type restrictions were imposed. On OVID, searches were restricted to randomized controlled trials (RCTs), articles published in English, studies with adult (age: $18 \leq x \leq 64$ years) participants/patients, human studies, and journal articles to reduce the number of search results to a maximum of 15,000 articles.

Study selection and eligibility criteria

Only RCTs and open-label studies were included in this systematic review and meta-analysis. We sought articles reporting on the study variables defined in Table 1 in patients with confirmed diagnoses according to the DSM-5. Articles that did not report outcome measures of the variables of interest but instead reported on other variables were still included in the systematic review.

Using the Covidence platform, titles and abstracts were independently screened by two reviewers, and duplicates were removed (A.T.H.K and G.H.L.).[17] Articles deemed potentially relevant by at least one reviewer were retrieved for further examination. Subsequently, two independent reviewers (A.T.H.K and G.H.L.) screened full-text articles. Discrepancies in judgments were resolved through discussion. When necessary, authors of the potentially eligible studies were contacted to acquire additional clarification and/or supplementary data for analysis.

The inclusion and exclusion criteria were established prior to article screening and review to identify literature focused on investigating the use of ketamine for the treatment of alcohol use disorder (AUD), anxiety disorders, obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), substance use disorders (eg, opiate use disorder/opiate withdrawal, nicotine dependency, and cocaine dependency), eating disorders, borderline personality disorder (BPD), and/or schizophrenia spectrum disorder (Table 2).

Data extraction

For the studies included in this systematic review and meta-analysis, two independent reviewers (G.H.L and D.D.) extracted data from the RCTs and open-label studies using a piloted data extraction template. Extracted data was corroborated and discrepancies in data extraction were resolved through discussion. Information to be extracted was established a priori and included (1) the primary author and year of publication, (2) the country in which the study was conducted in, (3) study design, (4) total sample/population, (5) mean age and range of participants, (6) sample size of participants treated with ketamine, (7) treatment regimen, (8) duration of intervention, (9) the placebo/control, and (10) primary and secondary outcome measures.

Quality assessment

In accordance with the Cochrane Collaboration tool, adapted from Higgins and Altman, three reviewers (A.T.H.K., G.H.L., and D.D.) conducted the risk of bias/quality assessment for the included studies.[18,19] Due to the nature of open-label studies, three bias domains were removed when assessing the risk of bias in these studies, including selection (ie, random sequence generation and allocation concealment), performance (ie, blinding of participants and personnel), and detection (ie, blinding of outcome assessment) bias. Results between the three reviewers were corroborated and discrepancies were resolved through discussions and votes. See supplementary material for further information on the bias domains and sources of bias considered when assessing the methodological quality/risk of bias for each study type (Table S2) and the methodological quality ratings for each study (Table S3).

Data synthesis and analysis

A meta-analysis of estimated mean differences was conducted using MedCalc® Statistical Software version 22.013 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2023). Both the statistical analysis and the forest plots were created on MedCalc. An α level of 0.05 was chosen to indicate statistical significance. In anticipation of marked heterogeneity, a generic inverse-variance method was used to create a random-effects model to pool the studies. Mean difference estimates were measured by changes in psychological assessment scores from baseline to the original study's primary endpoint in the participant group that received

[1]NIAAA 2019 definition of at-risk drinking (which was the outcome used in both trials who studied patients with alcohol dependence (DSM-IV)

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Table 1. Definition of Study Variables for Each Disorder for Meta-Analysis

Disorder	Outcome Measures
PTSD	PTSD symptom severity, including re-experiencing, avoidance, negative alterations in cognition/mood, and hyperarousal. Expected outcome measures included the PCL–5 and CAPS–5 scales; however, other validated self-report and/or clinician-rated tools (eg, IES-R, MADRS, CGI-I/S) were eligible for inclusion.
TR-PTSD	PTSD symptom severity, including re-experiencing, avoidance, negative alterations in cognition/mood, and hyperarousal. Expected outcome measures included the PCL–5 and CAPS–5 scales; however other validated self-report and/or clinician-rated tools (eg, IES-R, MADRS, CGI-I/S) were eligible for inclusion. TR-PTSD differs from PTSD on the basis of a prespecified number of prior failed treatments.
AUD	Alcohol-abstinence duration; expected outcome measure included the alcohol Timeline Followback (TLFB); however, all validated self-report and/or clinician-rated tools were eligible for inclusion.
At-risk Drinking	More than 4 drinks in the same day or more than 14 drinks in the same week (males) or more than 3 drinks in the same day or more than 7 drinks in the same week (females)[1]
Suicidal Ideation	Suicidal ideation includes severity, frequency, and duration. Expected outcome measures included SSI. However, validated self-report and/or clinician-rated tools were eligible for inclusion.
Cocaine Dependence	Cocaine dependence includes the duration of abstinence or frequency and/or duration of cocaine use. Expected outcome measures included self-report of cocaine abstinence and/or use [eg, Addiction Severity Index (ASI)].
OUD	Opiate use disorder includes the duration of abstinence or frequency and/or duration of opiate use. Expected outcome measures included self-report of opiate abstinence and/or use [eg, Addiction Severity Index (ASI)].
Nicotine Dependence	Nicotine dependence includes the duration of abstinence or frequency and/or duration of nicotine use. Expected outcome measures included self-report of nicotine abstinence and/or use (eg, FTCD).
AD	Anxiety symptom severity, including negative alterations to mood and behavior, was ascertained via any validated clinician-rated tools (ie, HAM-A).
BPD	BPD symptom severity. Expected outcome measures included BSL–23; however, any validated self-report and/or clinician-rated tool was eligible for inclusion.
Schizophrenia	Schizophrenia symptom severity. Expected outcome measures included the PANSS; however, any validated self-report and/or clinician-rated tool was eligible for inclusion.
OCD	OCD symptom severity including the time occupied, negative alterations in cognition/mood, and interference of activities, ascertained via any clinician-rated tool (ie, Y-BOCS) or self-report tools (ie, OCD-VAS).

PTSD = Post-traumatic stress disorder; TR-PTSD = Treatment-resistant post-traumatic stress disorder; AUD = Alcohol use disorder; OUD = Opiate use disorder; AD = Anxiety disorders; BPD = Borderline personality disorder; OCD = Obsessive compulsive disorder; PCL-5 = Posttraumatic stress disorder checklist for DSM-5; CAPS-5 = Clinician-administered PTSD scale for DSM-5; MADRS = Montgomery–Åsberg Depression Rating Scale; CGI-I/S = Clinical global impression-improvement/severity scale; IES-R = Impact of event scale-revised; TLFB = timeline followback;HAM-A = Hamilton Anxiety Rating Scale; Y-BOCS = Yale-Brown Obsessive Compulsive Scale; OCD-VAS = Obsessive Compulsive Disorder–Visual Analog Scale.

Table 2. Inclusion and Exclusion Criteria

Inclusion Criteria	1. Randomized controlled trials (RCTs) (from inception to June 10, 2023). 2. Open-label studies 3. Participants aged 18 years and above diagnosed with alcohol use disorder, anxiety disorder, borderline personality disorder, obsessive compulsive disorder, post-traumatic stress disorder, substance use disorder, eating disorder, and schizophrenia according to the DSM (preferably the 5th edition). No limitations imposed on sex, ethnicity, or nationality 4. Pharmacological treatment involving ketamine therapy only (oral, subcutaneous, intramuscular, or intravenous) with a control/placebo group (psychoactive or inactive) or without a comparator. 5. Include participants that have 2 or more of the above disorders or other comorbidities. 6. Outcome measures of symptom improvement or elimination. 7. Available full-text article. 8. English language.
Exclusion Criteria	1. Non-RCTs (eg, case reports, case-control studies, cohort studies, observational studies, pilot studies, preprints, or other study designs). 2. Animal/preclinical studies 3. Non-primary research (eg, review papers). Abstracts, dissertations, editorials, guidelines, conference papers, perspective papers, protocol, or unpublished studies. 4. No ketamine intervention. 5. No main outcomes of interest.

ketamine. Studies were pooled based on the psychiatric disorder of interest, the psychological assessment used, and the availability of estimate and standard error data.

Heterogeneity was quantified using the I^2 statistic, where the cut-offs 30.0%, 50.0%, and 75.0% denote moderate, substantial, and considerable heterogeneity, respectively, as recommended by the Grading of Recommendations, Assessment, Development and Evaluations) criteria and the Cochrane Handbook (GRADE) interpretation of heterogeneity scores.[20,21] The Egger regression intercept test and the Begg and Mazumdar rank correlation test, as well as visual inspection of funnel plots for asymmetry, were used to assess publication bias via MedCalc. Qualitative analysis via narrative synthesis was performed for secondary outcomes, which were not sufficiently homogenous to meta-analyze.

Results

Search results

The literature search yielded a total of 17,220 studies. Moreover, 13 additional studies were obtained from citation searching. After identifying duplicates and abstract screening, 17,175 studies were removed. An additional 20 studies were removed after full-text screening. A total of 37 studies were included in this systematic review (N = 37).[5,7,22–52] Further details on the study selection process are described in the PRISMA flow diagram (Figure 1).

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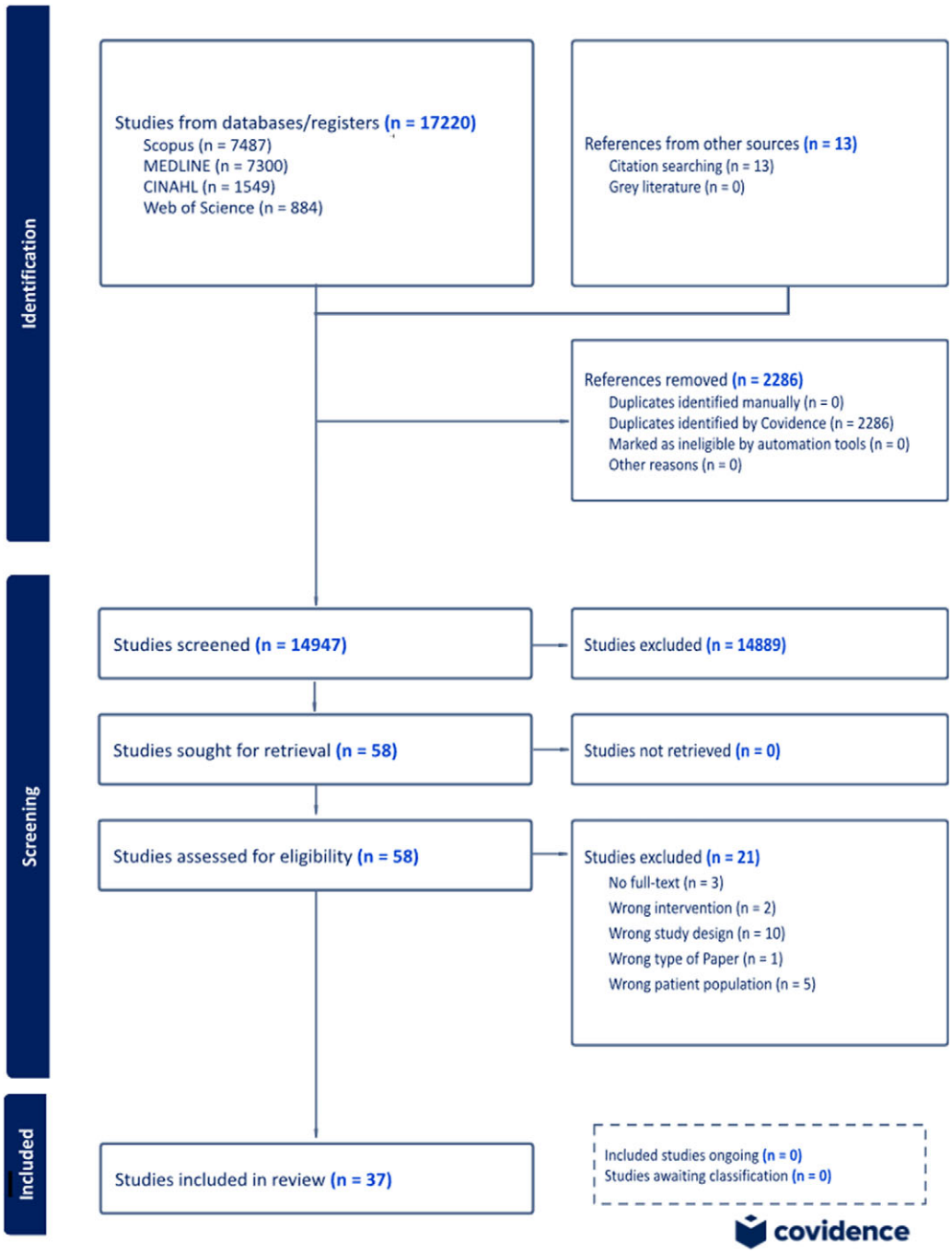

Figure 1. PRISMA flowchart of the selection of randomized controlled trials.

Study characteristics

From the search results of studies investigating the effects of ketamine in psychiatric disorders, six of them investigated PTSD, nine studies for TR-PTSD, four studies for AUD, two studies for at-risk drinking, two for SI, three for cocaine dependence/use disorder, two for opiate use disorder, three for anxiety disorders, one for BPD, two for schizophrenia, and four for OCD. Sample sizes ranged from 8 to 223 participants. Due to differences in both the psychological assessments and statistical methods used to report primary and secondary outcomes, only 12 of the studies could be used in the meta-analysis to pool estimates (ie, the identified PTSD studies, three TR-PTSD studies, and two OCD studies). Further details for each study are reported in Table 1.

Changes in psychiatric symptom severity following ketamine

Of the six studies that investigated the efficacy of ketamine for the treatment of PTSD, the PCL-5 and CAPS-5 scales were commonly used to measure changes in PTSD symptom severity. Among the included studies, there was a disproportionate reporting of significantly decreased PCL-5, CAPS-5, and MADRS scores over time following both single and repeated dosing of ketamine

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treatment.[5,6,27,53,54] This notion is further represented through the meta-analysis generic inverse-variance calculation, where ketamine had a statistically significant effect on PCL-5 scores (pooled estimate = –28.07, 95% CI = [–40.05, –16.11], p < 0.001) in persons with PTSD (Figure 2). Notably, the study conducted by Duek et al.[2023] was the only PTSD study that included a control group. While this study consistently reported a significant within-group change in PCL-5 scores over time, there was no statistically significant between-group difference in the rate of PCL-5 score change after treatment and during the follow-up period.

When considering TR-PTSD, two studies measured symptom severity using PCL-5, which yielded mixed results, where Abdallah et al. 2022 did not find any significant difference.[55] Contrarily, with respect to CAPS-5 and MADRS scores, studies that utilized repeat-dose ketamine reported a significant improvement in scores over time. When the mean CAPS-5 scores were pooled using the generic inverse variance method, ketamine had a statistically significant effect on CAPS-5 scores (pooled estimate = –14.07, 95% CI = [–26.24, –1.90], p = 0.023) in individuals with TR-PTSD (Figure 3). Both Dadabayev et al.2020 and Feder et al.2014 who investigated a single infusion of ketamine over 40 minutes also observed a statistically significant decrease in IES-R scores in persons with TR-PTSD.

For AUD and at-risk drinking, there was disproportionate reporting of decreased urge to drink, increased rate of abstinence, and a longer time for relapse following ketamine treatment.[56,57] Separately, data have also been reported on the use of ketamine in the treatment of generalized anxiety disorder and social anxiety disorder.[29]

The four studies that investigated single-dose ketamine in OCD reported a statistically significant improvement in OCD symptom severity measured by decreases in OCD-VAS and Y-BOCS scores. However, Bloch et al. 2012 reported that while OCD symptom severity significantly decreased from baseline to 3 days post-treatment, none of the participants experienced a clinically meaningful response, ascertained by a >35% decrease in Y-BOCS score. When the Y-BOCS scores were pooled across the four studies, ketamine displayed a statistically significant effect (pooled estimate = –8.08, 95% CI = [–13.64, –2.52], p = 0.004) (Figure 4). Notably, these studies only measured the acute effects of ketamine treatment, so further study should be performed to establish efficacy and safety for long-term usage, as well as in repeat ketamine infusions.

Finally, while this systematic review also included the use of ketamine for suicidal ideation, opiate use disorder, nicotine dependence, BPD, schizophrenia, and eating disorders, there were an

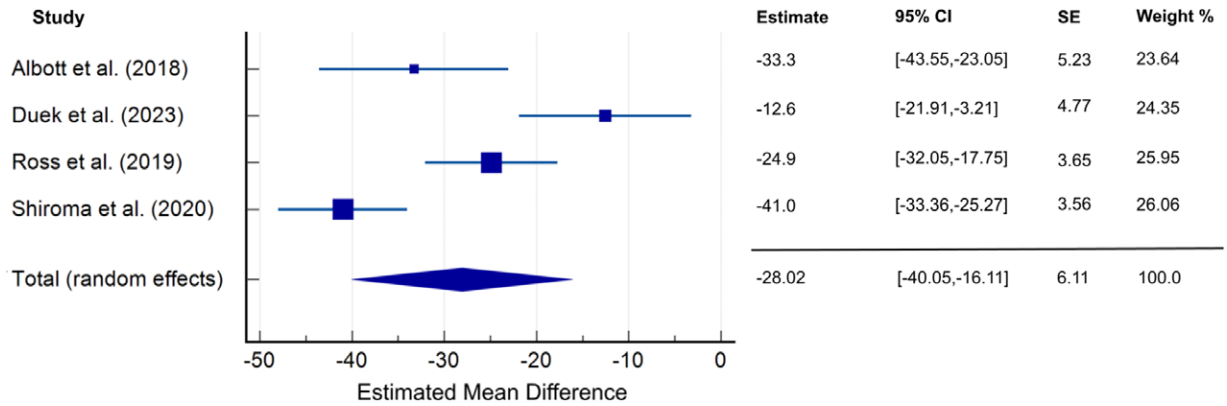

Figure 2. Weighted forest plot of studies investigating ketamine in post-traumatic stress disorder (PTSD). Estimated mean differences were measured by changes in post-traumatic stress disorder checklist (PCL-5) scores from baseline to the primary endpoint in PTSD patients that received ketamine. Estimates and standard error were manually extracted from each study. 95% Wald confidence intervals were calculated using a generic inverse variance method. The weight of each study was determined using a random effects model.

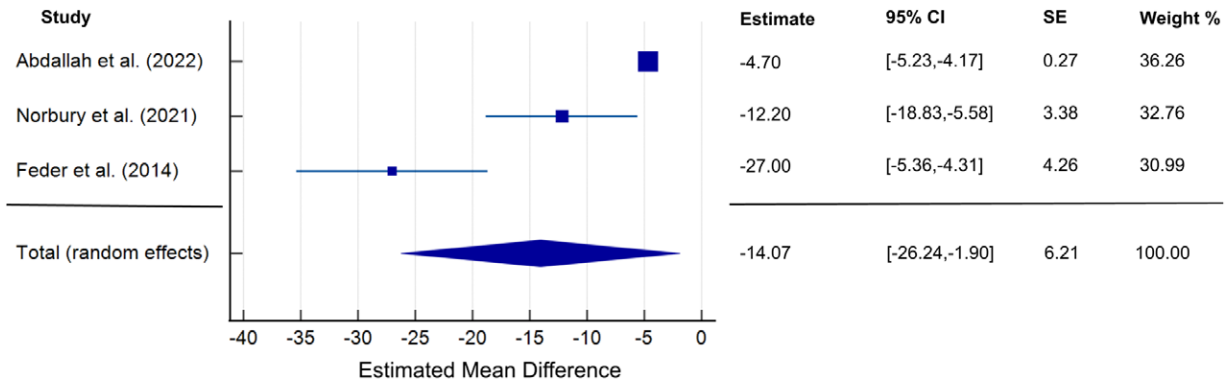

Figure 3. Weighted forest plot of studies investigating ketamine in treatment-resistant post-traumatic stress disorder (TR-PTSD). Estimated mean differences were measured by changes in clinician-administered PTSD Scale for DSM-5 (CAPS-5) scores from baseline to the primary endpoint in treatment-resistant post-traumatic stress disorder (TR-PTSD) patients who received ketamine. Estimates and standard error were manually extracted from each study. 95% Wald confidence intervals were calculated using a generic inverse variance method. The weight of each study was determined using a random effects model.

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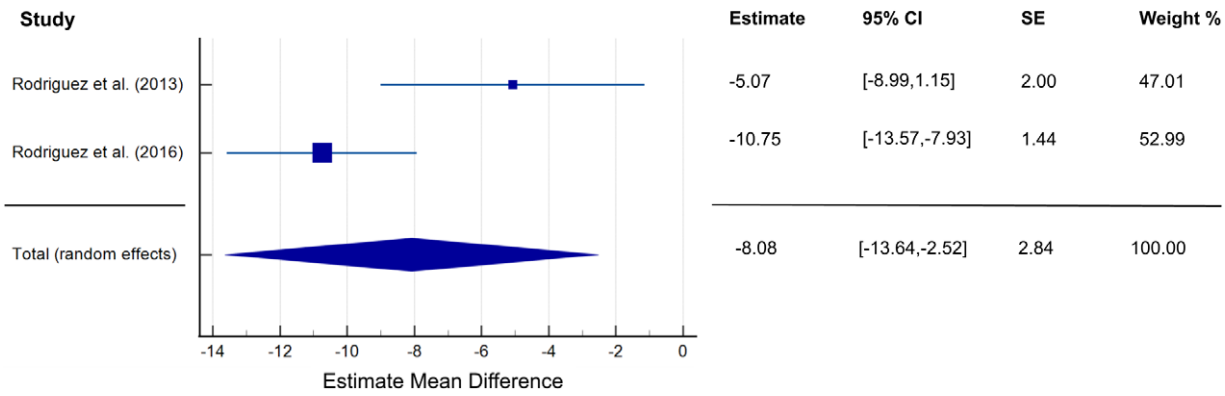

Figure 4. Weighted forest plot for studies investigating ketamine in obsessive compulsive disorder (OCD). Estimated mean differences were measured by changes in Yale-Brown Obsessive Compulsive Scale (YBOCS) scores from baseline to the primary endpoint in OCD patients who received ketamine. Estimates and standard error were manually extracted from each study. 95% Wald confidence intervals were calculated using a generic inverse variance method. The weight of each study was determined using a random effects model.

insufficient number of studies to evaluate the safety and efficacy of ketamine for each of the listed psychiatric disorders. In the cases of these psychiatric disorders, the search only yielded two or fewer studies. Furthermore, in many of the disorders where two studies were included, they utilized different mood assessments. In cases where different mood assessments were used, the results were not pooled to limit heterogeneity and ensure accurate estimations of ketamine's efficacy on specific symptom domains were generated.

Methodological quality and risk of bias

In the tests for heterogeneity, PTSD had an I^2 value of 88.07% (Q = 25.16, 95% CI = 71.87 to 94.94, p < 0.0001), TR-PTSD had an I^2 value of 93.76% (Q = 32.07, 95% CI = 85.17 to 97.38, p < 0.0001), and OCD had an I^2 value of 81.17% (Q = 5.31, 95% CI = 19.85 to 95.58, p = 0.02). Therefore, this is indicative of a high level of heterogeneity across the studies.

When considering the funnel plot for the PTSD studies (Figures S1-3), while the distribution of studies is symmetrical on either side of the y-axis, two of the studies lie beyond the 95% CI and the studies are on the lower half of the plot, which would indicate a lack of precision. For the TR-PTSD funnel plot, there is asymmetry; the plots lay on the left side of the y-axis. While there is one study at the top of the funnel, indicating high precision, the other two studies are outside the 95% CI and on the lower half of the funnel. Finally for the OCD studies, there was an even distribution of studies on both sides of the y-axis, but are on the lower half of the funnel plot indicating a lack of precision.

When assessed for publication bias using Egger's test and Begg's test, the PTSD studies reported positive for possible publication bias in the Egger's test (intercept = 10.14, p < 0.0001), but not in Begg's test (τ = 1.00, p = 0.32). The TR-PTSD studies did not report any publication bias for either Egger's test (intercept = –4.03, p = 0.24) or Begg's test (τ = –1.00, p = 0.12). Similarly to the PTSD studies, the OCD studies reported positive for possible publication bias in Egger's test (intercept = 10.14, p < 0.0001), but not in Begg's test (τ = 1.00, p = 0.32). Additional data for bias assessment is available in the Supplementary Materials (Figure S2, S3).

Discussion

In this systematic review and meta-analysis, we present preliminary findings that support the efficacy of ketamine treatment in the improvement of symptom severity across a wide range of mental disorders including PTSD, TR-PTSD, AUD, at-risk drinking, cocaine dependence/cocaine use disorder, anxiety disorders, and OCD. Ketamine was significantly associated with the improvement of PTSD symptoms in both persons with PTSD and TR-PTSD as well as symptomatic improvement in persons with OCD.[58] Despite the variations in the number of ketamine infusions in each study, treatment with ketamine consistently demonstrated a significant reduction in within-group symptom severity, as measured by multiple validated external mood assessments over time.

Many recent studies have continued to indicate the transdiagnostic treatment potential of ketamine for a variety of different psychiatric conditions, which aligns with the findings presented in this review. Additionally, recent meta-analyses suggest ketamine has a broad ability to treat treatment-resistant anxiety spectrum disorders and reported that ketamine reduced anxiety scores.[59,60] The aforementioned meta-analyses suggest ketamine has therapeutic potential across various psychiatric disorders, a finding that is concordant with the results of this review. Other recent studies have reported inconclusive findings with respect to the efficacy of ketamine in disorders such as PTSD, suggesting a lack of sufficient research in these areas.[61]

There are several methodological limitations to consider when interpreting the findings of this paper. Despite the many ongoing studies on clinicaltrials.gov, existing controlled trial evidence on the effects of ketamine on psychiatric disorders other than major depressive disorder remains insufficient.[62,63] There is also insufficient evaluation of the safety and efficacy of ketamine in real-world settings.[64] Moreover, while a diverse set of study populations was included in this analysis, the samples were often disparate, indicating sample heterogeneity and consequently raising questions about the generalizability of the findings.

Despite the aforementioned limitations, this systematic review and meta-analysis provides a comprehensive synthesis of the existing literature evaluating ketamine across various psychiatric disorders. Future research directions with ketamine include the need for adequately controlled long-term studies with repeat dosing in adults with treatment-resistant major depressive and bipolar disorders. Other near-term research vistas include evaluating non-pharmacological approaches (eg, manualized psychotherapy) and alternative pharmacological strategies (eg, dextroamphetamine-bupropion) as maintenance treatments in individuals with treatment-resistant depression (TRD) who are acute responders to IV ketamine. Additionally, assessing ketamine in the treatment of

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individuals with substance and alcohol use disorders, post-traumatic stress disorder (PTSD), and borderline personality disorder, where trans-domain pathology outcomes (eg, positive valence and general cognitive effects) can be considered, would be valuable. Moreover, there is a need for head-to-head comparisons of IV racemic ketamine with intranasal esketamine in the treatment of adults with TRD and for identifying moderators of treatment outcomes. Overall, the current evidence suggests that ketamine has transdiagnostic efficacy and safety across many mental disorders.

Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1017/S1092852924000580.

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