See commentary by Goldberg

The Effects of Ketamine on Cognition in Unipolar and Bipolar Depression: A Systematic Review

Sophie R. Vaccarino, MSc[a,b]; Fathima Adamsahib, BScPA[c]; Roumen V. Milev, MD, PhD[d]; Sagar V. Parikh, MD[e]; Raymond W. Lam, MD[f]; Pierre Blier, MD, PhD[g]; Sidney H. Kennedy, MD[a,b,c,h,i,j]; Karim S. Ladha, MD[h,k]; and Venkat Bhat, MD[a,c,h,i,j,*]

ABSTRACT

Objective: To determine the objective neurocognitive effects of (1) single-dose ketamine, (2) repeated-dose ketamine, (3) ketamine adjunct to electroconvulsive therapy (ECT), and (4) ketamine as the anesthetic for ECT in major depressive disorder (MDD) and depression in bipolar disorder (BD).

Data Sources: Cochrane, MEDLINE, Embase, and PsycINFO databases were searched on March 19, 2020 (updated July 2, 2020), using the terms terms *major depressive disorder bipolar disorder* and *ketamine* and their synonyms. Clinical trial registries (search date May 4, 2020) and reference sections of included articles were also searched. There was no restriction on language or year of publication.

Study Selection: Of 4,035 identified articles, 17 met inclusion criteria. Controlled and open-label studies of adults who received at least 1 ketamine treatment for a current major depressive episode, as part of MDD or BD, were included. Only studies measuring cognition using at least 1 validated, objective neurocognitive assessment were eligible.

Data Extraction: Results are presented using a narrative review format. Data regarding change in cognitive performance from baseline to end-of-treatment and/or differences in cognition between ketamine and control groups were extracted.

Results: There were no negative effects of single- or repeated-dose intravenous ketamine up to 2 weeks post-treatment in MDD. Limited data were available for BD populations, as well as on other routes of ketamine administration.

Conclusions: Data to definitively answer the question of whether ketamine has substantive or persistent cognitive effects are insufficient; thus, larger controlled trials measuring cognition as the primary outcome are needed. Future research should focus on different routes of ketamine administration, ketamine enantiomers, and BD populations.

J Clin Psychiatry 2022;83(1):21r13870

To cite: Vaccarino SR, Adamsahib F, Milev RV, et al. The effects of ketamine on cognition in unipolar and bipolar depression: a systematic review. *J Clin Psychiatry.* 2022;83(1):21r13870.

To share: https://doi.org/10.4088/JCP.21r13870

[a]Centre for Depression and Suicide Studies, St Michael's Hospital, Toronto, Ontario, Canada
[b]Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada
[c]Department of Psychiatry, St Michael's Hospital, Toronto, Ontario, Canada
[d]Department of Psychiatry, Queen's University, Kingston, Ontario, Canada
[e]Department of Psychiatry, University of Michigan, Ann Arbor, Michigan
[f]Department of Psychiatry, University of British Columbia, Vancouver, British Columbia, Canada
[g]Department of Psychiatry, University of Ottawa, Ottawa, Ontario, Canada
[h]Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto, Ontario, Canada
[i]Krembil Research Institute, University Health Network, Toronto, Ontario, Canada
[j]Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada
[k]Department of Anesthesia and Pain Medicine, St Michael's Hospital and the University of Toronto, Toronto, Ontario, Canada
**Corresponding author:* Venkat Bhat, MD, 193 Yonge St 6-012, Toronto, Ontario, Canada, M5B 1M4 (venkat.bhat@utoronto.ca).

Depression in the context of major depressive disorder (MDD, ie, unipolar depression) and bipolar disorder (BD) is the leading cause of disability worldwide, affecting more than 264 million people.[1,2] While numerous antidepressants and other medications have been studied for the treatment of major depressive episodes (MDEs), 40%–50% of patients do not respond to their first prescribed antidepressant treatment,[3–5] and 20%–30% continue to be unresponsive to 2 or more treatment trials.[4,6] One treatment for these cases of "treatment-resistant depression" that has attracted considerable attention over the past several years is ketamine.

Ketamine has been used since the 1970s as a general anesthetic[7] and more recently was found to exert rapid antidepressant and antisuicidal effects in individuals with MDD and BD, likely via its action as an *N*-methyl-D-aspartate receptor (NMDAR) antagonist.[8–15] Ketamine for depression can be administered intravenously (IV), intranasally (IN), subcutaneously, intramuscularly, and orally[16]; the most commonly studied routes of administration are IV, 0.5 mg/kg over 40–45 minutes, and IN, 56 mg or 84 mg delivered twice weekly.[8,9,16–18] IN administration of esketamine, the *S*-enantiomer of ketamine, received regulatory approval for TRD in Europe and the United States in 2019 and in 2020 in Canada. While IV ketamine is currently considered a third-line treatment option for TRD,[17] large-scale clinical trials are underway,[19,20] and initial trials have found response rates of 59%–80% within 24 hours.[9,10,21–26] In fact, a recent (2021) systematic review[27] concluded that IV ketamine is more effective in treating an MDE than IN esketamine in terms of response and remission rates.

While the antidepressant effects of ketamine have been, and continue to be, rigorously studied in clinical research, the cognitive effects of this drug have not been as thoroughly investigated in depressed populations. In healthy volunteer populations, ketamine significantly impaired cognition, namely memory and executive function, during infusion or minutes after bolus injection

Clinical Points

- Ketamine is an increasingly popular treatment for severe depression, but the potential cognitive effects of this drug among patients with depression are unknown.
- While preliminary evidence does not suggest negative cognitive effects when ketamine is given intravenously, there are insufficient data on substantive or persistent cognitive effects of ketamine in patients with depression.
- Evidence in bipolar disorder and for other routes of administration is limited.

(variable dosages; see Supplementary Table 1).[28–31] Further, chronic users of recreational ketamine (ie, "special K") display significant cognitive impairments.[32–35] However, the doses administered by recreational users are likely much higher than therapeutic doses, and results may have been confounded by coconsumption of other drugs of abuse. Considering MDD and BD are associated with significant cognitive impairments,[36,37] it is critical that the cognitive effects of ketamine are better understood as this treatment is accepted for widespread use.

Researchers have also studied IV ketamine given during electroconvulsive therapy (ECT), either as the anesthetic agent or as an adjunct agent given concurrently at a subanesthetic dose with another anesthetic. Although no favorable antidepressant effects are reported,[38] it has been suggested that, via NMDAR antagonism, ketamine may confer neuroprotective effects during ECT,[39] a treatment that is historically associated with cognitive impairment.

A few reviews have briefly looked at the cognitive effects of ketamine in depression,[40,41] but no articles to date have systematically reviewed ketamine with cognition as the primary outcome of interest. In a 2018 systematic review of side effects of ketamine for depression,[40] the authors found ketamine use was associated with short-term memory loss, poor concentration, confusion, and cognitive impairment or diminished mental capacity. More recently, a narrative review[41] concluded that ketamine administration was not associated with cognitive impairments in MDD and that selected cognitive domains including processing speed, verbal learning, cognitive inhibition, and memory improved after treatment.

With the high prevalence of cognitive impairment in MDD and BD,[36,37] and increasing interest in the clinical use of ketamine as an adjunctive treatment of major depressive episodes, it is important for patient recovery and quality of life that the potential cognitive effects of ketamine be better understood. The aim of this systematic review is to determine the objective neurocognitive effects of (1) single -dose ketamine, (2) repeated-dose ketamine, (3) ketamine adjunct to ECT (ie, subanesthetic doses of ketamine given during ECT), and (4) ketamine as the anesthetic for ECT in depressive disorders by critically analyzing and synthesizing available data on this topic.

METHODS

We followed PRISMA reporting guidelines in this systematic review, and the protocol is registered with PROSPERO (number CRD42020159148).

Eligibility Criteria

1. Study population adults aged 18 to 65 years
2. Participants diagnosed with a current MDE as part of MDD or BD, according to the *Diagnostic and Statistical Manual of Mental Disorders* (version IV, IV-TR, or 5) or the *International Classification of Diseases* (10th or 11th edition)
3. Controlled and open-label clinical trials of ketamine or its enantiomers (ie, *R*-ketamine and *S*-ketamine)
4. Trials assessing cognition using at least 1 validated, objective neurocognitive assessment as a primary or secondary outcome
5. Studies of single-dose ketamine, repeated-dose ketamine, ketamine adjunct to ECT, or ketamine anesthesia for ECT
6. Studies that did not restrict other "standard of care" treatments (eg, antidepressants, antimanic agents) were permitted
7. Participants were not diagnosed with comorbid psychiatric disorder(s); specifically, participants with schizophrenia spectrum disorders or current substance use disorder were ineligible
8. Participants who were not diagnosed with a comorbid cognitive disorder (eg, traumatic brain injury, mild cognitive impairment, dementia) were ineligible
9. Participants who were not diagnosed with any serious medical conditions were ineligible
10. Participants were not administered any other investigational agents concurrent to ketamine

Search Strategy and Selection Criteria

Two authors (S.R.V. and F.A.) conducted a comprehensive database search of Cochrane and MEDLINE, PsycINFO, and Embase through Ovid on March 19, 2020 (updated July 2, 2020), using the following search terms and their synonyms: (*major depressive disorder* OR *bipolar disorder* OR *treatment-resistant depressive disorder*) AND (*ketamine* OR *r-ketamine* OR *s-ketamine*). The full search strategy is presented in Supplementary Appendix 1. Results were limited to human studies. There was no restriction on language or year of publication.

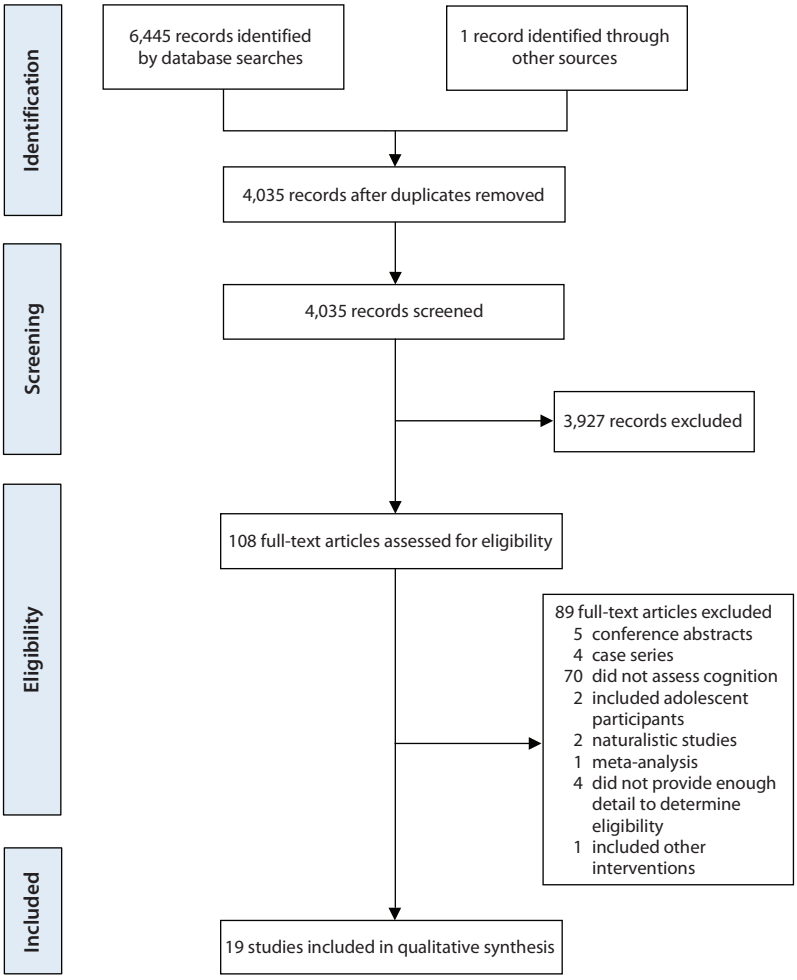
Study Selection and Data Extraction

The reference sections of included articles were also screened, and clinical trial registries were searched on May 4, 2020. One author (S.R.V.) removed duplicates manually using Microsoft Excel, and 2 authors (S.R.V. and F.A.) independently identified articles of potential interest by title and/or abstract and subsequently assessed the full texts of these articles for eligibility. Discrepancies were

discussed with another author (V.B.) to reach a consensus. Authors of articles were contacted in cases of missing data required to assess eligibility.

Data from the included articles were extracted manually and independently by 1 author (S.R.V.). The following data items were extracted from each article: author, year, country of origin, mean age, percent female, age at MDE onset, duration of illness, MDE length, number of antidepressant treatment failures, number of subjects enrolled versus final number of subjects, reasons for withdrawal, number of subjects receiving ketamine versus number of control subjects, percent with MDD versus BD diagnosis, diagnostic criteria used, study design, route of administration, dosage, ketamine administration schedule, mean number of ketamine treatments, control/placebo used (if applicable), length of follow-up, concomitant medications permitted (Y/N), cognitive outcome measures, assessment timepoints, and whether cognitive performance was a primary or secondary outcome measure. Further, for those studies that included adjunct ECT, the following information was also extracted: ECT administration schedule, type of ECT given (eg, bilateral vs unilateral), anesthesia used, and mean number of ECT treatment sessions.

Figure 1. PRISMA Flow Diagram of Studies Identified, Screened, and Assessed for Inclusion



Data Analysis and Risk-of-Bias Assessment

Using a narrative review format, we present findings on the change in cognitive performance from baseline to end of study and/or differences in cognition between ketamine and control groups post-intervention. Results of any validated, objective neurocognitive tests were used as outcome measures. Differences were considered significant at $P < .05$. We did not complete a meta-analysis as part of this review because the heterogeneity among the cognitive assessments used and timepoints at which cognition was measured significantly limited the value of quantitative synthesis. Risk of bias of included studies was assessed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) checklist.[42,43]

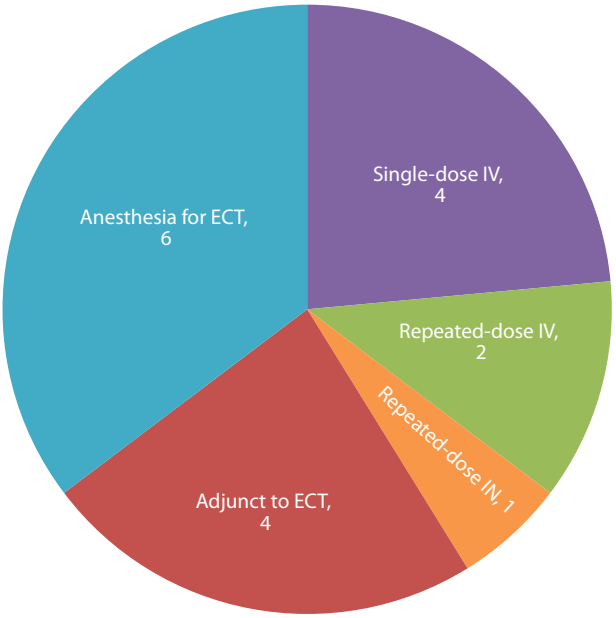
RESULTS

Of the 4,035 articles identified in the database search, 107 full-text articles were assessed for eligibility and 18 met inclusion criteria (Figure 1). One additional article was identified via ClinicalTrials.gov. Among these 19 articles, 2 were subanalyses of a larger study; therefore, 17 unique studies were included. The most frequent reason for exclusion of a publication was failure to measure cognition. Of the included studies, published between 2006 and 2020, 13 were controlled trials and 4 were open-label.

Across the included studies, participants were, on average, middle-aged (mean age range, 31–55 y) and female (all studies > 50% female, with the exception of 2 studies). Participants were moderately to severely depressed (Montgomery-Asberg Depression Rating Scale score > 30 or Hamilton Depression Rating Scale score > 24).

Four included studies administered a single dose of IV ketamine (0.2 or 0.5 mg/kg). In 3 of these studies, the effects of ketamine were compared to control conditions (midazolam or saline placebo); the study by Permoda-Osip and colleagues[47] used an open-label design. Two studies of repeated-dose IV ketamine (6 infusions of 0.5 mg/kg) were identified, both of which used an open-label study design. Two studies administered 6 infusions of IV ketamine (0.5 mg/kg), over 2 weeks. One open-label study of intranasal esketamine, delivered repeatedly over 8 weeks (1–2 times per week at 28–84 mg), was identified (Figure 2).

Figure 2. Total Numbers of Studies by Route of Ketamine Administration



Abbreviations: ECT = electroconvulsive therapy, IN = intranasal, IV = intravenous.

The remaining 10 studies explored the cognitive effects of ketamine adjunct to ECT: 4 studies administered subanesthetic doses of ketamine (0.3 or 0.5 mg/kg), delivered over 6 to 11 ECT treatments. The final 6 studies administered ketamine as anesthesia for ECT (0.8–2 mg/kg) for 6 to 11 ECT treatments. All of these studies compared the effects of ketamine to those under controlled conditions (saline placebo, midazolam, or another standard anesthetic agent).

A wide variety of cognitive domains were measured across studies, using a multitude of different cognitive tests. In the following sections, changes in cognitive domains before and after ketamine treatment(s) are discussed. For details regarding the specific cognitive tests used in each study, please see Tables 1 and 2 as well as Supplementary Table 2.

Risk of Bias

Overall, there was a low risk of bias across included articles. Open-label trials had a high detection bias, as is expected for studies of this design (as outcome assessments are typically unblinded in open-label trials). The study by McDaniel and colleagues[44] presented high selection, performance, and detection biases; while the study used a control population, this population was not randomly assigned nor double-blinded. Finally, the study by Rybakowski and colleagues[45] presented high selection bias, as random sequence generation was not used to assign participants to ketamine and control groups. Importantly, several studies did not provide enough information to determine their risk of bias: Rybakowski and colleagues[45] did not describe how participants were blinded, and Rybakowski et al,[45] Zhong et al,[46] and Permoda-Osip et al[47] did not provide details on dropout rates. The risk of bias of all included articles is detailed in Supplementary Table 3.

Cognitive Effects of Single-Dose Ketamine

Single-dose ketamine trials are summarized in Table 1. We identified 4 studies of single-dose ketamine; in total, 178 participants were enrolled and 155 received ketamine. All of these studies excluded participants with psychotic features. Ketamine did not affect processing speed, executive function, or working memory among participants with MDD and BD, and it was associated with an improvement in these domains among a small group of participants with bipolar depression. There were contradictory findings in the cognitive domain of verbal skills in BD.

Null findings. We identified 2 randomized controlled studies with moderate-to-large sample size that enrolled participants with MDD only. In the first study (n = 73)[48], there was no difference in processing speed, problem solving, or working, visual, and verbal memory between the 2 groups 1 week after a 40-minute IV infusion of ketamine (0.5 mg/kg) or midazolam control (0.045 mg/kg). In the second study (n = 71),[49] there was no difference in performance between individuals who received a single-dose of IV ketamine (0.5 or 0.2 mg/kg over 40 minutes) or saline placebo on measures of working memory or executive function 3 days and 14 days post-infusion.

Negative findings. Among 16 participants who received a 40-minute infusion of ketamine (0.5 mg/kg) or midazolam control (0.02 mg/kg), the ketamine-treated group displayed a deterioration in verbal fluency 1 day post-infusion, but the midazolam group did not.[50] Further, the ketamine group performed inferiorly compared to the midazolam group on measures of simple and complex reaction time: both groups improved, but improvement was greater in the midazolam-control group.[50] There was no effect of ketamine on measures of attention, executive function, processing speed, or global, visual, and working memory.[50]

Positive findings. The final study[47] was an open-label trial of 18 participants diagnosed with bipolar depression. Participants were given a single dose of 0.5 mg/kg IV ketamine, infused over 45 minutes. Working memory and executive function, as well as processing speed, attention, and verbal skills, improved from baseline to 3 days post-infusion, independent of changes in depressive severity.[47]

Cognitive Effects of Repeated-Dose Ketamine

Repeated-dose ketamine trials are summarized in Table 1. Three studies were identified: 917 participants were enrolled in total, and 901 received ketamine. We identified 2 open-label studies[51,52] of repeated IV ketamine infusions: 6 infusions were administered over 2–3 weeks (0.5 mg/kg/40 min.). Further, 1 large-scale open label study of intranasal esketamine for MDD[55] was identified (28–84 mg, twice weekly). Repeated-dose ketamine was associated with improvements in attention, executive function, processing speed, and spatial memory, maintained up to 4 weeks post-treatment. There was no effect on visual and working

Table 1. Summary of Studies Assessing the Cognitive Effects of Intravenous or Intranasal Ketamine Treatment

Study	N	Age, Mean (SD), y	Female, %	With MDD (vs BD), %	Ketamine Dosage, mg/kg	Control Condition	Cognitive Measures	Assessment Periods (After Last Infusion)[a]	Main Findings*
Single-Dose Intravenous Ketamine Infusion									
Permoda-Osip et al (2015)[47]	18	50 (11)	78	0	0.5	NA	TMT, Stroop test	3 days	• Improved processing speed (TMT), attention, working memory, and executive function (Stroop, TMT-B) from BL to 3 days post-infusion ($P < .001$)
Murrough et al (2015)[48]	73	46 (12)	55	100	0.5	Midazolam (0.045 mg/kg)	TMT-A, WMS-SS, BACS-SC, LNS, HVLT, BVMT, CF, NAB mazes	7 days	• Improved processing speed (TMT-A, CF, BACS-SC) and verbal (HVLT) and visual learning (BVLT) in both groups, BL to 1-week FU • No difference between treatment and control groups
Grunebaum et al (2017)[50]	16	39 (10)/ 43 (14)[b]	63	0	0.5	Midazolam (0.02 mg/kg)	Simple and choice RT, WAIS-DC, TMT, CPT-IP, Stroop test, BSRT, BVRT, A not B, N-back, COWAT, Go/No-Go, time production	1 day	• Improved RT, attention, and memory from BL to 1 day post-infusion in both groups; RT improvement was greater in control than ketamine group ($P = .003$) • Decrease in verbal fluency (COWAT) in ketamine group only (time × treatment interaction: $P = .008$)
Chen et al (2018)[49]	71	48 (11)/ 45 (12)/ 49 (8)[b]	75	100	0.2 or 0.5	Saline placebo	Working memory task, Go/No-Go	3 days, 14 days	• No time-by-treatment effect 3- and 14-days post-infusion
Repeated-Dose (6 infusions) Intravenous Ketamine Infusion									
Shiroma et al (2014)[52]	15	52 (15)	0	100	0.5	NA	IDN, N-back, GML, GMR, GMCT, CPAL, OCL, ISL, DET, set-shifting	1 week, 2 weeks, 3 weeks, 4 weeks	• Improved visual (OCL; $P = 0{\cdot}002$) and working memory (N-back; $P = .008$) from BL to 1-week FU, and maintained at 4 weeks FU • No change on other measures
Zhou et al (2018)[51]	100	35 (12)	52	81	0.5	NA	BACS-SC, CF, TMT-A, WMS-SS, LNS, HVLT, BVMT	1 day, 14 days	• Improved processing speed (BACS, CF, TMT-A) 1-day (Cohen $d = 0.58$, $P = .001$) and 14-days (Cohen $d = 0.663$, $P = .001$) FU • Improved verbal memory (HVLT) 1-day FU (Cohen $d = 0.46$, $P = .013$) • No change on any other measures
Liu et al (2019)[54] (subanalysis of Zhou et al [2018][51])	50	34 (11)	56	100	0.5	NA	BACS-SC, CF, TMT-A, WMS-SS, LNS, HVLT, BVMT	1 day, 14 days	• Participants with anxious depression, but not non-anxious, improved processing speed day 1 (Cohen $d = 0.95$, $P < .001$) and 14 (Cohen $d = 0.97$, $P < .001$) FU • Improved verbal memory at day 1 FU in anxious group only (Cohen $d = 0.52$, $P = .028$)
Zheng et al (2019)[53] (subanalysis of Zhou et al [2018][51])	80	33 (11)	61	100	0.5	NA	BACS-SC, CF, TMT-A, WMS-SS, LNS, HVLT, BVMT	1 day, 14 days	• Improved processing speed 1 day (Cohen $d = 0.59$, $P < .001$) and 14 days (Cohen $d = 0.63$, $P < .001$) PT • Improved verbal learning 1-day PT (Cohen $d = 0.43$, $P = .002$) • No change on any other measures
	N	Age, Mean (SD), y	Female, n (%)	With MDD (vs BD), n (%)	Ketamine Dosage, mg	Control Condition	Cognitive Measures	Assessment Periods (After Last Infusion)[a]	Main Findings
Repeated-Dose Intranasal Esketamine Administration									
Wajs et al (2020)[55]	802	52 (14)	502 (63)	802 (100)	28, 56, or 84 mg	NA	SRT-DET, IND, OCL, N-back, GML, HVLT	28 days after start of treatment; week 20, week 32, and week 44 FU	• Performance on all tests either improved or remained stable over 44 weeks (P value not reported)

[a]All studies included baseline assessments.
[b]Treatment and control group reported separately, first number is treatment group.
*All differences are significant ($P < .05$).

Abbreviations: BACS-SC = Brief Assessment of Cognition in Schizophrenia—symbol coding, BD = bipolar disorder, BL = baseline, BSRT = Buschke Selective Reminding Test, BVMT = Brief Visuospatial Memory Test, BVRT = Benton Visual Retention Test, CF = category fluency, COWAT = Controlled Oral Word Association Test, CPAL = Continuous Paired Associative Learning Task, CPT-IP = continuous performance test—identical pairs, DET = detection task, FU = follow-up, GMCT = Groton Maze Chase Test, GML = Groton Maze Learning Test, GMR = Groton Maze Learning Test—delayed recall, HVLT = Hopkins Verbal Learning Test, IDN = Identification Task, ISL = International Shopping List Task, LNS = letter-number sequencing, MDD = major depressive disorder, NA = not applicable (open-label trial), NAB = Neuropsychological Assessment Battery, OCL = one card learning task, PT = post-treatment period, RT = reaction time, SRT = simple reaction time—detection, TMT = Trail Making Test, WAIS-DC = Wechsler Adult Intelligence Scale—Digit Symbol Coding, WMS-SS = Wechsler Memory Scale—spatial span.

Table 2. Summary of Studies Assessing the Cognitive Effects of Ketamine Administered During Electroconvulsive Therapy

Study	N	Age, mean (SD), y	Female, %	With MDD (vs BD), %	Ketamine Dosage, mg/kg	Control Condition	No. of ECT Treatments, mean (SD)	Cognitive Measures	Assessment Periods[a]	Main Findings
Subanesthetic Ketamine Adjunct to Electroconvulsive Therapy										
Loo et al (2012)[57]	51	45 (16)/ 41 (12)[b]	61	80	0.5	Saline placebo	9.5 (4.7)/ 9.7 (3.3)[b]	MCG-CFT, HVLT, COWAT, SDMT, WJ-COT, AMI-SF	After 6th ECT session; 1–3 days after last ECT session; 1 month FU	• No difference between groups 1–3 days after final session and at 1-month FU
Anderson et al (2017)[56]	79	55 (13)	63	84	0.5	Saline placebo	11.4 (4.1)/ 11.3 (4.5)[b]	HVLT, COWAT, AMI-SF, MCG-CFT, WAIS-DS	After 4th (± 1) ECT session, after last ECT session, 1- and 4-month FU	• No difference between treatment groups after final session, and at 1- and 4-month FU
Chen et al (2017)[59]	132	41 (15)/ 37 (14)[b]	65	100	0.3	Saline placebo	8.1 (2.0)/ 9.1 (1.8)[b]	WMS-RC, MMSE	24 hours after last ECT session	• Worsening of memory (WMS-RC) and global cognition (MMSE) in both groups, BL to 1 day post-treatment; impairment was greater in control group vs ketamine ($P < .001$)
Altinay et al (2019)[58]	15	39 (11)/ 38 (15)[b]	83	UNK	0.5	Midazolam (0.045 mg/kg)	6.0 (0.0)	MoCA, COWAT	After 4th ECT session, after last ECT session	• No difference between groups after 6 infusions
Ketamine Anesthesia During Electroconvulsive Therapy										
McDaniel et al (2006)[44]	10	45 (UNK)/ 47 (UNK)[b]	UNK	UNK	1	Etomidate (0.3 mg/kg)	6.0 (0.0)	MMSE-STM	≥ 48 hours after last ECT session	• STM worsened in both groups, BL to ≤ 1-week FU; impairment was greater in control group vs ketamine
Yoosefi et al (2014)[62]	31	44 (UNK)	48	100	1–2	Thiopental (2–3 mg/kg)	6.0 (0.0)	MMSE	48 hours after 1st ECT session, 3–7 days after last ECT session, 1 month FU	• Improved global cognition from BL to 3–7 days after final session ($P = .004$) and 1-month FU in ketamine group only ($P = .023$)
Rybakowski et al (2016)[45]	45	53 (12)	76	44	1–1.5	Thiopental (2–3 mg/kg)	10.8 (1.5)	BVRT, RO-CFT, WAIS-DS, RAVLT, VF, Stroop test	2–4 days after last ECT session	• No difference between treatment groups 2–4 days after final session
Zhong et al (2016)[46]	90	31 (9)	60	62	0.8	Propofol (0.8 mg/kg)	8.0 (0.0)	VF, WAIS-DC, WAIS-DS, WCST, ToH, TMT, VRT	48–72 hours after last ECT session	• Worsening of executive function (WCST, TMT part B), problem solving (ToH), and some measures of processing speed (TMT part A) in control versus ketamine group 2–3 days after final session ($P < .05$) • No difference between groups on other measures
Carspecken et al (2018)[61]	52	50 (12)/ 47 (12)[b]	18	88	1–2	Methohexital (1–2 mg/kg)	5.5 (2.7)/ 5.8 (1.6)[b]	MoCA	72 hours after last ECT session	• No difference between treatment groups 3 days after final session
Jagtiani et al (2019)[60]	60	35 (8)/ 35 (9)[b]	50	100	1	Thiopentone (2.5 mg/kg)	5.6 (0.7)/ 8.3 (1.2)[b]	MMSE	6 hours after each ECT session	• No difference between treatment groups 6 hours after final session

[a]All studies included baseline assessments.
[b]Treatment and control group reported separately, first number is treatment group.
Abbeviations: AMI-SF = Autobiographical Memory Interview—Short form, BD = bipolar disorder, BL = baseline, BVRT = Benton Visual Retention Test, COWAT = Controlled Oral Word Association Test, ECT = electroconvulsive therapy, FU = follow-up, HVLT = Hopkins Verbal Learning Test, MCG-CFT = Medical College of Georgia Complex Figures, MDD = major depressive disorder, MMSE = Mini-Mental State Exam, MMSE-STM = Mini-Mental State Examination Short Term Memory Item, MoCA = Montreal Cognitive Assessment, RAVLT = Rey Auditory Verbal Learning Test, RO-CFT = Rey-Osterrieth complex figure test, SDMT = Symbol Digit Modalities Test, TMT = Trail Making Test, ToH = Tower of Hanoi, UNK = unknown (not reported), VF = verbal fluency test, VRT = visual regeneration test, WAIS-DC = Wechsler Adult Intelligence Scale—Digit symbol coding, WAIS-DS = Wechsler Adult Intelligence Test—Digit span, WCST = Wisconsin Card Sorting Test, WJ-COT = Woodcock Johnson Cross-Out Test, WMS-RC = Wechsler Memory Scale-Chinese Revision.

Table 3. Change in Cognitive Domain Scores at Different Follow-Up Points Across Studies[a]

	Single-Dose Intravenous Ketamine Studies			Repeated-Dose Intravenous Ketamine Studies					Ketamine Adjunct to Electroconvulsive Therapy			Ketamine Anesthesia for Electroconvulsive Therapy		
Domain	1–4 d	1 wk	2 wk	1 d	1 wk	2 wk	3 wk	1 mo	1–3 d	1 mo	4 mo	6 h	2–7 d	1 mo
Global cognition									70[b]			30	37[c]	14
Global memory	7								63					
Working memory	54	43	47	84	15	99[c]	15	15	33	33	33		90	
Short-term memory													5[e]	
Spatial memory					15	15	15	15						
Verbal memory		43		84	15	99	15	15	62	55			45	
Visual memory	7	43		84	15[d]	99[d]	15[d]	15[d]					90	
Autobiographical memory									55	55	33			
Executive function	72[c]		47		15	15	15	15					90[b,e]	
Problem solving		43											60[e]	
Verbal fluency	7								62	55	33		90	
Visuospatial function									55	55	33		30	
Processing speed	25[b]	43		84	15	99[b]	15	15	22	22			90[c]	
Attention	25[b]				15	15	15	15	33	33	33		90	
Reaction time	7													

Legend: No difference from baseline/control; Improvement from baseline/relative to control; Worsening from baseline/relative to control; Not measured

[a]Numbers of participants who received ketamine and were assessed at each time point are listed within the table.
[b]Improvement not observed in all studies, but was observed in studies with larger sample sizes.
[c]Only studies with small sample sizes observed a change in cognitive domain score.
[d]Improvement observed on some tests, but not most.
[e]Both groups worsened, but ketamine group worsened less than control group.

memory. Long-term intranasal esketamine treatment did not negatively affect cognition across a wide range of cognitive domains.

Null findings. Among 100 participants with MDD or BD, there was no change on visual or working memory from baseline to 1 day post-treatment; this was maintained at 14 day follow-up.

Positive findings. In the aforementioned study,[51] processing speed improved significantly from baseline at 1 and 14 days post-treatment, with a moderate effect size. However, these improvements were significantly mediated by changes in depressive symptoms.[51] Verbal learning also improved significantly from baseline to 1 day post-treatment, but this significance was lost at 14-day follow up. In a subanalyses of this population (published separately), findings remained significant when only MDD participants (n = 80) were evaluated, but with a smaller effect size.[53] In this MDD subpopulation, findings remained significant even when controlling for change in depressive severity; however, subsequent analysis revealed that cognitive changes were significantly mediated by change in depression scores.[53] The authors also concluded that there were no differences in findings between participants with MDD versus BD; however, the BD group made up only 19% of the study population.[51] Interestingly, in another subanalysis (published separately),[54] improvements in processing speed were specific to participants with anxious depression only.

The second study of repeated-dose IV had a significantly smaller sample size (n = 15) and included only participants with MDD. The authors found a significant improvement from baseline on tests of working memory and some measures of visual memory 1 week after treatment. These findings were maintained at 2-, 3-, and 4-week follow-up. However, when mood was included as a covariate, the observed cognitive improvements were no longer significant.[52]

We identified 1 open-label, long-term safety trial of IN esketamine,[55] the *S*-enantiomer of ketamine, comprising 802 participants with MDD recruited across 21 countries. Participants were followed for a total of 44 weeks after completing their treatment course, which consisted of 8 weeks of 28, 56, or 84 mg IN esketamine. Esketamine was administered twice weekly for 4 weeks and weekly or every other week for the next 4 weeks, in combination with a daily oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine).[55] Processing speed, choice reaction time, visual learning and recall, working memory, episodic memory, and executive function either improved or remained stable from baseline (statistical results not reported).[55]

Cognitive Effects of Subanesthetic Ketamine Adjunct to Electroconvulsive Therapy

Table 2 summarizes trials of ketamine adjunct to ECT. We identified 4 randomized controlled trials of subanesthetic doses of ketamine administered with ECT; in total, 277 participants were enrolled and 125 received ketamine. All of these studies measured cognition as the primary outcome and excluded participants with psychotic features. Ketamine did not negatively affect global cognition, verbal fluency, visuospatial function, attention, and verbal, working, and autobiographical memory relative to control

conditions and was superior to control on measures of global cognition and memory.

Null findings. In 2 moderate-sized (n = 51, n = 79) trials of participants with MDD or bipolar depression,[56,57] there was no effect of adjuvant ketamine on attention; verbal fluency; verbal, working, or autobiographical memory; or visuospatial function 1–3 days after the completion of ECT compared to placebo. These findings were consistent at 1- and 4-month follow-up.[56,57] Both of these studies gave a relatively large number of ECT treatments, with 10–11 sessions on average.[56,57]

In a smaller study of ketamine compared to midazolam (n = 15),[58] there was no effect of ketamine on global cognition or verbal fluency shortly after 6 ECT treatments (exact time point not provided). Of note, this study differed slightly in design, as ketamine/midazolam was provided on alternate days from ECT, while ketamine was given during ECT in the other studies. No information about differences between MDD and BD groups was reported in any of these studies. All of the aforementioned studies provided ketamine dosed at 0.5 mg/kg.

Positive findings. In the largest (n = 132) placebo-controlled trial, both ketamine (0.3 mg/kg) and placebo groups experienced a worsening of global cognition and memory from baseline to one day post-treatment (approximately 8–9 ECT sessions); however, this impairment was worse in the placebo group.[59] This study included participants with MDD only and had a ketamine dosage of 0.3 mg/kg.

Cognitive Effects of Ketamine

Anesthesia for Electroconvulsive Therapy

Table 2 summarizes trials of ketamine anesthesia for ECT. We identified 6 studies of this type. In total, 288 participants were enrolled, with 162 receiving ketamine anesthesia. Three of these studies included participants with psychotic features, and all studies included a mix of MDD and BD populations. None reported data separately for MDD and BD subgroups. Ketamine did not negatively affect global cognition, processing speed, executive function, verbal memory, or visuospatial function and was superior to control on measures of global cognition, processing speed, executive function, problem solving, and short-term memory.

Null findings. There was no effect of ketamine anesthesia (1–2 mg/kg) on global cognition 6 hours and 3-days post-treatment, compared to thiopemtone (n = 60) and methohexital control (n = 52), respectively [60,61] Further, there was no difference between those receiving ketamine versus thiopental on measures of processing speed, executive function, verbal memory, or visuospatial function 2–4 days after treatment, among 45 participants with MDD or BD.[45]

Positive findings. In a study of 31 participants,[62] global cognition improved significantly from baseline to 3–7 days post-ECT among those receiving ketamine, but not among those receiving thiopental anesthesia; this improvement was maintained at 1-month follow-up.

Among 90 participants anesthetized with ketamine or propofol, it was found that, while both groups worsened 2–3 days post-treatment on measures of executive function, problem solving, and processing speed after treatment, the ketamine-anesthetized group experienced significantly less impairment.[46] The effects of subanesthetic ketamine (0.5 mg/kg), mixed with propofol (0.5 mg/kg), were also explored; there was no difference between the ketamine + propofol and propofol-only groups on all cognitive measures.[46]

Finally, in a small study (n = 10),[44] while both participants receiving ketamine and those receiving etomicate anesthesia experienced a worsening of short-term memory 2–7 days post-treatment, the etodimate-anesthetized group worsened more severely.

DISCUSSION

Based on the results of this systematic review, the data suggest that single- or repeated-dose IV or IN may not have detrimental effects on cognition in MDD populations in the short-term (ie, a few days) and at least 2 weeks post-treatment (Table 3).[48,51,59] Further, IV ketamine given during ECT, either as anesthesia or as adjunct treatment, may be less likely to exhibit negative effects on cognition than placebo or other anesthetics and could potentially confer cognitive benefits. However, small sample sizes and confounding variables may restrict the scope of findings.

Single-Dose Ketamine

Based on the available studies, single-dose IV ketamine infusion did not have any cognitive effects in participants with MDD up to 2 weeks post-treatment.[48,49] The findings for BD were less clear: 2 studies assessed BD populations only, with 1 finding specific measures of cognition either stayed the same or worsened[50] and another finding improved cognition[47] within a few days of a single infusion. However, this latter study was open-label so we cannot eliminate the possibility of practice effects.[47] Further, both of these studies were limited by a small sample size (n = 16, n = 18), and therefore any conclusions made from these data are limited.[47,50]

Repeated-Dose Ketamine

While definitive conclusions cannot be made due to the open-label design of the identified studies, preliminary results suggest there may be limited detrimental effects of repeated-dose IV ketamine on a wide variety of cognitive domains (attention, executive function, working memory, spatial memory, and visual memory) in MDD populations, and there may be positive effects on verbal learning and processing speed, maintained for a minimum of 2 weeks post-treatment.[51,52] While no detrimental effects of ketamine on cognition were found in 1 population of patients with BD,[51] there were not enough data to draw conclusions about the effects in individuals with BD.

We identified only 1 report[55] on ketamine's effects on cognition when delivered by an alternate route and/or using

an enantiomer compound. This study found that cognition either improved or remained stable up to 44 weeks after an 8 week trial of IN esketamine, but cognition was not the primary outcome.[55] With the anticipated increased prescribing of this drug after its recent approval in Canada (2020), the United States (2019), and Europe (2019), there is a need for placebo-controlled trials of IN esketamine that include cognition as a primary outcome.

Ketamine and Electroconvulsive Therapy

When given during ECT, the available studies did not find cognitive impairments related to adjunct ketamine infusion up to 4 months post-treatment nor related to ketamine anesthesia up to 1 month post-treatment. Interestingly, in several controlled trials,[44,46,59] impairments in memory and global cognition were observed several days after ECT with subanesthetic ketamine, but the control groups worsened significantly more than the ketamine groups. Those studies that measured only specific cognitive subdomains,[56–58] however, did not find any difference between ketamine and control groups. This may suggest that adjunct, subanesthetic ketamine has an effect on global memory and cognition, but not on more specific cognitive functions.

Among ketamine anesthesia studies, the opposite seemed to be true: there was an apparent positive effect of ketamine in certain cognitive subdomains (short-term memory, executive function, problem solving, and processing speed), but the effects on global cognition were unclear.

ECT has long been implicated in short-term cognitive decline, specifically memory loss.[63–65] These results may suggest a role for ketamine in moderating cognitive impairments caused by ECT. A 2017 systematic review[38] concluded that ketamine was not associated with any procognitive effects when given during ECT. However, cognition was not the primary outcome of this study. Further, we identified 5 additional studies not included in this review,[44,58–61] 2 of which[44,59] found procognitive effects of ketamine, including the largest randomized controlled trial of this type to date.[59]

In a previous (2018) systematic review by Short and colleagues[40] on the side effects of ketamine for depression, the authors concluded that "cognitive side effects [of ketamine] included poor memory or memory loss, poor concentration, confusion, and cognitive impairment or diminished mental capacity… reported over the short-term only."[40(p7)] However, that review was not focused on cognition, and multiple studies included in our review have been published since the time of that earlier review. Further, that conclusion relied heavily on case studies.[40] More recently (2020), a narrative review of preclinical and clinical studies of ketamine for cognition[41] concluded that there were no significant impairments in cognitive function after ketamine treatment in depression. While ketamine does not appear to have detrimental effects on individuals with MDD, based on the current literature, it is important to recognize that several studies of healthy volunteers[28–31] have found ketamine to significantly impair cognition. While these studies assessed only the immediate effects of ketamine and therefore may not provide insight into the lasting cognitive implications, they were powered to measure cognition as a primary outcome and therefore may have detected more subtle cognitive effects.

Further insights into the cognitive and neurobiological effects of ketamine come from animal studies. Similar to in human studies, high doses of ketamine are found to induce acute cognitive impairments that model cognitive symptoms of schizophrenia. At high doses, ketamine is found to cause Olney's lesions, a cytotoxic lesion similar to those found in schizophrenia.[66,67] In animal models of ketamine-induced schizophrenia symptoms, ketamine was associated with deficits in contextual processing, attentional set-shifting, and novel object recognition.[68–71] Contrarily, other animal studies have found positive effects of ketamine injection. Importantly, those studies finding detrimental effects of ketamine tested cognition immediately after injection,[68–71] while those with positive outcomes assessed the longer-term effects of ketamine. For example, cognitive impairments in set-shifting, object recognition, and reversal learning induced by chronic-stress were reversed 24 hours post-ketamine treatment in rodent models of depression.[72–74] These positive effects on object recognition were also observed after 5 weeks of chronic ketamine infusion.[73] Interestingly, subanesthetic ketamine had positive long-term effects on functional connectivity in rats: 48 hours post-infusion, chronically stressed animals displayed normalization of habenula, thalamus, and hippocampal activity.[75]

It is hypothesized that ketamine affects cognition via its glutamatergic action on neural systems: glutamate indirectly increases synaptogenesis and functional connectivity in cognitive regions of the brain, and improvements in functional connectivity are observed in these brain regions after a single dose of ketamine.[76] However, ketamine appears to affect cognition differently depending on parameters of administration. Chronic ketamine use (eg, recreational use) results in memory impairment, specifically spatial memory.[77] However, there were no apparent negative effects of ketamine when used for depression, likely because ketamine is given in much lower doses and frequencies than would be common among recreational and/or chronic users. Supporting this conclusion are results from patients with chronic pain who were given ketamine for its analgesic effects. No cognitive impairments were found in patients who received only 5 days of ketamine infusion (n = 8; continuous ketamine blood level of 250–300 μg/dL),[78] but there were cognitive deficits among those treated with ketamine over several years (n = 14; mean ± SD treatment duration, 3.8 ± 1.3 years; variable dosages).[79] Of note, 93% of patients in the long-term study were also using opioid analgesics, as were a percentage of patients in the 5-day trial (percentage not provided), which likely affected cognition.[80]

With the recent approval of IN esketamine for treatment-resistant depression, and increased off-label use of IV ketamine in clinical settings, it is increasingly important

that the cognitive effects of ketamine (and esketamine) treatment be fully understood. There are insufficient data to definitively examine the substantive or persistent cognitive effects of ketamine in patients with mood disorders. Only one other treatment for depression, vortioxetine, is approved for its procognitive effects.[81] There is a need for more research on procognitive agents for depression, which is associated with deficits in processing speed, attention, executive function, learning, and memory.[82,83] Further, cognitive deficits may persist despite remission from an MDE.[84] Future research on ketamine should assess cognition as a primary outcome so that the cognitive effects can be better elucidated.

Limitations

There are several limitations that should be considered when interpreting the results of this review. First, many studies used a heterogeneous population of participants with either MDD or BD. This makes it difficult to extrapolate the effects of ketamine on a single, homogenous psychiatric population, particularly in BD, as this group was commonly mixed with MDD participants. Further, our eligibility criteria excluded multiple studies[85–93] that examined the cognitive effects of ketamine infusion. While we chose to enact strict inclusion/exclusion criteria to eliminate as many confounds as possible (such as the effects of other medications, age, or comorbidities), these articles may have provided important insight into the overall cognitive effects of ketamine, particularly in naturalistic populations.

Cognitive improvement may be a general consequence of improvements in mood.[94,95] It remains unclear whether certain medications used in the treatment of MDD associated with cognitive improvement exert a "direct" or "indirect" (ie, mediated by mood) effect on cognition[96]; therefore, we cannot eliminate the possibility that depression is a mediating factor for cognitive improvement and is unrelated to ketamine. Some studies included in this review found an association between improvements in mood and cognition,[51,52] while others did not.[47,48] In open-label studies included in our review, "no change" in cognition post-ketamine may actually represent a negative effect of ketamine on cognition, as cognition may be expected to improve as depressive symptoms improve. Improvements or lack of change in cognitive performance may also be explained by practice effects in open-label studies.

To fully understand the cognitive effects of ketamine in depressed populations, it is important that future studies control for the effects of change in mood in their methodology. Currently, there is not enough evidence to determine whether changes in cognition associated with ketamine are independent of mood improvements or if observed cognitive benefits are a byproduct of reduced depressive severity induced by ketamine treatment.

More than half (ie, 10) of the studies included in this review included cognition as a secondary outcome and mood improvement as the primary outcome. Hence, these studies were powered to detect changes in mood, not cognition per se. Therefore, the studies may not have been adequately powered to detect more subtle changes in cognition, and improvements or impairments in cognition may have gone undetected. Further, there was variability in the cognitive measures used across studies; different tests may be more or less sensitive to cognitive change or measure slightly different aspects of a specific cognitive domain.

Several of the ECT + ketamine studies included participants with psychotic depression.[44,45,60] Psychotic depression is associated with more severe cognitive impairments than nonpsychotic depression,[97,98] which may have affected the cognitive outcomes in these studies. Importantly, these study populations were not exclusively of the psychotic subtype, and the results from these studies were similar to those that excluded patients with psychosis (ie, no negative effect on cognition). Many studies included a heterogeneous population of MDD and BD and did not compare outcomes between these two groups; therefore, we cannot eliminate the possibility that ketamine affects these two disorders differently, given the unique pathology of each.

Importantly, with the exception of one article, every trial assessed IV ketamine. However, other routes of administration (IN, subcutaneous, oral, and intramuscular) and ketamine enantiomers (ie, *S*-ketamine and *R*-ketamine) have been studied for their antidepressant effects. The results of this review, therefore, may not be generalizable to all forms of ketamine treatment. Of note, *S*-ketamine has a greater affinity for the NMDAR than *R*-ketamine or racemic ketamine[99,100] and therefore may have more potent effects on cognition, as was found in a study of 24 healthy volunteers who experienced less cognitive decline after receiving *S*-ketamine (0.25 mg/kg) compared to with *R*-ketamine (1.0 mg/kg) and racemic ketamine (0.5 mg/kg).[101] These results have yet to be replicated in depressed populations.

CONCLUSION

In this systematic review, we did not find any reported negative effects of single- or repeated-dose IV ketamine on cognition in individuals with MDD. However, there were insufficient data to definitively answer the question of whether ketamine has substantive or persistent cognitive effects, as cognition was not a primary outcome in the majority of studies and different outcome assessments were used to measure cognitive domains. Therefore, larger controlled studies in which cognition is the primary outcome and that use similar and consistent cognitive measures are needed before conclusions can be made. The findings for bipolar depression were less conclusive, as the number of identified studies was small; however, we found no long-term negative effects of repeated-dose ketamine in this population.

Interestingly, IV ketamine given during ECT may confer protective effects against ECT-associated short-term cognitive impairment. Considering the breadth of research

of ketamine given with ECT, head-to-head studies of ECT versus ketamine are needed to compare the relative cognitive effects of these two treatment modalities.[19,20]

The results of this review may be beneficial in the study of ketamine-assisted psychotherapy, an emerging treatment strategy for mood disorders[102,103]: if ketamine were, in fact, able to promote cognitive functioning, this would likely enhance psychotherapy outcomes.

Unfortunately, only one clinical trial has examined the cognitive effects of non-IV routes of ketamine administration and enantiomers in depressive disorders. Esketamine has garnered significant interest as a treatment for depression in recent years, and with the recent approval of IN esketamine for TRD there is a need for larger, randomized trials focused on cognition as a primary outcome using validated and objective neurocognitive measures.

Submitted: January 6, 2021; accepted August 3, 2021.

Published online: January 4, 2022.

Author contributions: Ms Vaccarino and Ms Adamsahib completed the literature search, screened results, and extracted the data. Ms Vaccarino and Dr Bhat interpreted the data. Ms Vaccarino and Drs Bhat, Lam, Milev, Parikh, Blier, Kennedy, and Ladha wrote and edited the article. Ms Vaccarino created figures and tables.

Potential conflicts of interest: **Dr Milev** reports grants from Janssen, Canadian Biomarker Integration Network in Depression (CAN-BIND), Canadian Institutes of Health Research (CIHR), Lallemand, Lundbeck, Nubiyota, Ontario Brain Institute, and Ontario Mental Health Foundation (OMHF) and personal fees from AbbVie, Allergan, Janssen, KYE, Lundbeck, Otsuka, and Sunovion, outside the current work. **Dr Parikh** reports grants from Assurex and personal fees from Takeda, Janssen, Mensante, Aifred, and Sage, outside the current work, and holds minor equity in Mensante. **Dr Lam** reports grants from Asia-Pacific Economic Cooperation, VGH-UBCH Foundation, BC Leading Edge Endowment Fund, Janssen, Lundbeck, Pfizer, St Jude Medical, Mitacs, Michael Smith Foundation for Health Research, Healthy Minds Canada, Ontario Brain Institute, and University Health Network Foundation and personal fees from Allergan, Canadian Network for Mood & Anxiety Treatments, Janssen, Lundbeck, Lundbeck Institute, Pfizer, Otsuka, Hanosh, and Myriad Neuroscience, outside the current work. **Dr Blier** reports grants from Allergan, Janssem, Lundbeck, and Otsuka and personal fees from Allergan, Bristol-Myers Squibb, Janssen, Lundbeck, Otsuka, Pierre Fabre Medicaments, Pfizer, and Eisai, outside of the current workd. **Dr Kennedy** reports grants from Allergan, Janssen, Brain Canada CIHR, Lundbeck, Ontario Brain Institute, and Pfizer and personal fees from Abbott, Alkermes, Allergan, Bristol-Myers Squibb, Janssen, Lundbeck, Lundbeck Institute, Otsuka, Pfizer, Servier, Sunovion, and Xian-Jannsen, outside the current work. **Dr Bhat** reports grants from CIHR, Brain & Behaviour Foundation, Roche, MOH Innovation Fund, The Royal College of Physicians and Surgeons of Canada (RCPSC), and Department of Defense Canada, outside the current work. **Dr Ladha** is a co-principal investigator of a study on medical cannabis funded by Shoppers Drug Mart. **Ms Vaccarino** and **Ms Adamsahib** have no declarations of interest.

Funding/support: None.

Acknowledgment: None.

Supplementary material: Available at PSYCHIATRIST.COM

REFERENCES

1. World Health Organisation. Fact Sheet: Depression. WHO website. https://www.who.int/en/news-room/fact-sheets/detail/depression. Published 2018. Accessed May 4, 2020.
2. James SL, Abate D, Abate KH, et al; GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. *Lancet*. 2018;392(10159):1789–1858.
3. Nemeroff CB. *J Clin Psychiatry*. 2007;68(suppl 8):17–25.
4. Rush AJ, Trivedi MH, Wisniewski SR, et al. *Am J Psychiatry*. 2006;163(11):1905–1917.
5. Gartlehner G, Hansen RA, Morgan LC, et al. *Ann Intern Med*. 2011;155(11):772–785.
6. Rizvi SJ, Grima E, Tan M, et al. *Can J Psychiatry*. 2014;59(7):349–357.
7. Kurdi MS, Theerth KA, Deva RS. *Anesth Essays Res*. 2014;8(3):283–290.
8. Berman RM, Cappiello A, Anand A, et al. *Biol Psychiatry*. 2000;47(4):351–354.
9. Zarate CA Jr, Singh JB, Carlson PJ, et al. *Arch Gen Psychiatry*. 2006;63(8):856–864.
10. Murrough JW, Perez AM, Pillemer S, et al. *Biol Psychiatry*. 2013;74(4):250–256.
11. Diazgranados N, Ibrahim L, Brutsche NE, et al. *Arch Gen Psychiatry*. 2010;67(8):793–802.
12. Zarate CA Jr, Brutsche NE, Ibrahim L, et al. *Biol Psychiatry*. 2012;71(11):939–946.
13. Zheng W, Zhou Y-L, Liu W-J, et al. *J Psychiatr Res*. 2018;106:61–68.
14. Wilkinson ST, Ballard ED, Bloch MH, et al. *Am J Psychiatry*. 2018;175(2):150–158.
15. Reinstatler L, Youssef NA. *Drugs R D*. 2015;15(1):37–43.
16. Andrade C. *J Clin Psychiatry*. 2017;78(7):e852–e857.
17. Swainson J, McGirr A, Blier P, et al. *Can J Psychiatry*. 2021;66(2):113–125.
18. Vaccarino SR, Kennedy SH. Treatment Resistant Depression. In: Vasquez GH, Zarate CA, Brietzke E, eds. *Ketamine for Treatment Resistant Depression: Neurobiology and Applications*. Academic Press; 2020:33-84.
19. Phillips JL, Jaworska N, Kamler E, et al; CAN-BIND Investigator Team. *BMC Psychiatry*. 2020;20(1):268.
20. ELEKT-D. Electroconvulsive Therapy (ECT) vs Ketamine in Patients With Treatment Resistant Depression (TRD) (ELEKT-D) - Identifier NCT03113968. ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT03113968?term=ketamine+OR+esketamine+OR+s-ketamine+OR+r-ketamine+OR+arketamine&recrs=ab&cond=Major+Depressive+Disorder&cntry=US&draw=3&rank=15. Published 2017. Accessed September 14, 2020.
21. Vidal S, Gex-Fabry M, Bancila V, et al. *J Clin Psychopharmacol*. 2018;38(6):590–597.
22. Murrough JW, Iosifescu DV, Chang LC, et al. *Am J Psychiatry*. 2013;170(10):1134–1142.
23. Mathew SJ, Murrough JW, aan het Rot M, et al. *Int J Neuropsychopharmacol*. 2010;13(1):71–82.
24. Shiroma PR, Johns B, Kuskowski M, et al. *J Affect Disord*. 2014;155(1):123–129.
25. aan het Rot M, Collins KA, Murrough JW, et al. *Biol Psychiatry*. 2010;67(2):139–145.
26. Phillips JL, Norris S, Talbot J, et al. *Am J Psychiatry*. 2019;176(5):401–409.
27. Bahji A, Vazquez GH, Zarate CA Jr. *J Affect Disord*. 2021;278:542–555.
28. Ghoneim MM, Hinrichs JV, Mewaldt SP, et al. *J Clin Psychopharmacol*. 1985;5(2):70–77.
29. D'Souza DC, Ahn K, Bhakta S, et al. *Biol Psychiatry*. 2012;72(9):785–794.
30. Harborne GC, Watson FL, Healy DT, et al. *J Psychopharmacol*. 1996;10(2):134–140.
31. Malhotra AK, Pinals DA, Weingartner H, et al. *Neuropsychopharmacology*. 1996;14(5):301–307.
32. Zhang C, Xu Y, Zhang B, et al. *Psychiatry Res*. 2020;291:113206.
33. Ke X, Ding Y, Xu K, et al. *Psychiatry Res*. 2018;266:124–131.
34. Chan KWS, Lee TMC, Siu AMH, et al. *Addict Behav*. 2013;38(5):2128–2132.
35. Morgan CJA, Curran HV. *Psychopharmacology (Berl)*. 2006;188(4):408–424.
36. Rock PL, Roiser JP, Riedel WJ, et al. *Psychol Med*. 2014;44(10):2029–2040.
37. Martínez-Arán A, Vieta E, Reinares M, et al. *Am J Psychiatry*. 2004;161(2):262–270.
38. McGirr A, Berlim MT, Bond DJ, et al. *Br J Psychiatry*. 2017;210(6):403–407.
39. MacPherson RD, Loo CK. *J ECT*. 2008;24(1):52–56.
40. Short B, Fong J, Galvez V, et al. *Lancet Psychiatry*. 2018;5(1):65–78.
41. Crisanti C, Enrico P, Fiorentini A, et al. *J Affect Disord*. 2020;276:1109–1118.
42. Guyatt GH, Oxman AD, Schünemann HJ, et al. *J Clin Epidemiol*. 2011;64(4):380–382.
43. Meader N, King K, Llewellyn A, et al. *Syst Rev*. 2014;3(1):82.
44. McDaniel WW, Sahota AK, Vyas BV, et al. *J ECT*. 2006;22(2):103–106.
45. Rybakowski JK, Bodnar A, Krzywotulski M, et al. *J ECT*. 2016;32(3):164–168.
46. Zhong X, He H, Zhang C, et al. *J Affect Disord*. 2016;201:124–130.
47. Permoda-Osip A, Kisielewski J, Bartkowska-Sniatkowska A, et al. *Pharmacopsychiatry*. 2015;48(2):78–79.
48. Murrough JW, Burdick KE, Levitch CF, et al. *Neuropsychopharmacology*. 2015;40(5):1084–1090.
49. Chen M-H, Li C-T, Lin W-C, et al. *J Affect Disord*. 2018;241(201):1–7.
50. Grunebaum MF, Ellis SP, Keilp JG, et al. *Bipolar Disord*. 2017;19(3):176–183.
51. Zhou Y, Zheng W, Liu W, et al. *J Psychopharmacol*. 2018;32(10):1118–1126.
52. Shiroma PR, Albott CS, Johns B, et al. *Int J Neuropsychopharmacol*. 2014;17(11):1805–1813.
53. Zheng W, Zhou Y-L, Liu W-J, et al. *J Affect Disord*. 2019;246:241–247.
54. Liu W, Zhou Y, Zheng W, et al. *J Affect Disord*. 2019;259:1–6.
55. Wajs E, Aluisio L, Holder R, et al. *J Clin Psychiatry*. 2020;81(3):19m12891.
56. Anderson IM, Blamire A, Branton T, et al; Ketamine-ECT Study team. *Lancet Psychiatry*. 2017;4(5):365–377.
57. Loo CK, Katalinic N, Garfield JBB, et al. *J Affect Disord*. 2012;142(1-3):233–240.
58. Altinay M, Karne H, Anand A. *Psychopharmacol Bull*. 2019;49(1):8–16.

59. Chen Q, Min S, Hao X, et al. *J ECT*. 2017;33(2):89–95.
60. Jagtiani A, Khurana H, Malhotra N. *Indian J Psychiatry*. 2019;61(3):258–264.
61. Carspecken CW, Borisovskaya A, Lan S-T, et al. *J Neurosurg Anesthesiol*. 2018;30(4):305–313.
62. Yoosefi A, Sepehri AS, Kargar M, et al. *J ECT*. 2014;30(1):15–21.
63. Sackeim HA, Prudic J, Fuller R, et al. *Neuropsychopharmacology*. 2007;32(1):244–254.
64. Lisanby SH, Maddox JH, Prudic J, et al. *Arch Gen Psychiatry*. 2000;57(6):581–590.
65. Fraser LM, O'Carroll RE, Ebmeier KP. *J ECT*. 2008;24(1):10–17.
66. Olney JW, Farber NB. *Neuropsychopharmacology*. 1995;13(4):335–345.
67. Olney JW, Labruyere J, Price MT. *Science*. 1989;244(4910):1360–1362.
68. Brunamonti E, Mione V, Di Bello F, et al. *J Psychopharmacol*. 2014;28(9):881–887.
69. Blackman RK, Macdonald AW 3rd, Chafee MV. *Neuropsychopharmacology*. 2013;38(11):2090–2100.
70. Kos T, Nikiforuk A, Rafa D, et al. *Psychopharmacology (Berl)*. 2011;214(4):911–921.
71. Nikiforuk A, Hołuj M, Kos T, et al. *Neuropharmacology*. 2016;105:351–360.
72. Patton MS, Lodge DJ, Morilak DA, et al. *Neuropsychopharmacology*. 2017;42(6):1220–1230.
73. Papp M, Gruca P, Lason-Tyburkiewicz M, et al. *Behav Pharmacol*. 2017;28(1):1–8.
74. Jett JD, Boley AM, Girotti M, et al. *Psychopharmacology (Berl)*. 2015;232(17):3123–3133.
75. Gass N, Becker R, Reinwald J, et al. *Transl Psychiatry*. 2019;9(1):172.
76. Lee Y, Syeda K, Maruschak NA, et al. *J Clin Psychopharmacol*. 2016;36(1):50–56.
77. Zhang MWB, Ho RCM. *Front Psychiatry*. 2016;7:47.
78. Koffler SP, Hampstead BM, Irani F, et al. *Arch Clin Neuropsychol*. 2007;22(6):719–729.
79. Kim M, Cho S, Lee J-H. *Pain Med*. 2016;17(8):1447–1451.
80. Ersek M, Cherrier MM, Overman SS, et al. *Pain Manag Nurs*. 2004;5(2):75–93.
81. Al-Sukhni M, Maruschak NA, McIntyre RS. *Expert Opin Drug Saf*. 2015;14(8):1291–1304.
82. Hasselbalch BJ, Knorr U, Hasselbalch SG, et al. *Eur Psychiatry*. 2013;28(6):349–355.
83. Murrough JW, Iacoviello B, Neumeister A, et al. *Neurobiol Learn Mem*. 2011;96(4):553–563.
84. Bhalla RK, Butters MA, Mulsant BH, et al. *Am J Geriatr Psychiatry*. 2006;14(5):419–427.
85. Fernie G, Currie J, Perrin JS, et al. *Br J Psychiatry*. 2017;210(6):422–428.
86. Loo CK, Gálvez V, O'Keefe E, et al. *Acta Psychiatr Scand*. 2016;134(1):48–56.
87. Rasmussen KG, Kung S, Lapid MI, et al. *Psychiatry Res*. 2014;215(2):362–365.
88. Ray-Griffith SL, Eads LA, Han X, et al. *J ECT*. 2017;33(4):268–271.
89. Dong J, Min S, Qiu H, et al. *Psychiatry Res*. 2019;281:112573.
90. Zhang M, Rosenheck R, Lin X, et al. *J Affect Disord*. 2018;227:372–378.
91. Basso L, Bönke L, Aust S, et al. *J Psychiatr Res*. 2020;123:1–8.
92. Wilkinson ST, Katz RB, Toprak M, et al. *J Clin Psychiatry*. 2018;79(4):17m11731.
93. Murrough JW, Wan L-B, Iacoviello B, et al. *Psychopharmacology (Berl)*. 2013;231(3):481–488.
94. Otto MW, Fava M, Penava SJ, et al. *Cognit Ther Res*. 1997;21(4):409–420.
95. Antikainen R, Hänninen T, Honkalampi K, et al. *Eur Arch Psychiatry Clin Neurosci*. 2001;251(1):6–11.
96. Pan Z, Park C, Brietzke E, et al. *CNS Spectr*. 2019;24(1):22–29.
97. Fleming SK, Blasey C, Schatzberg AF. *J Psychiatr Res*. 2004;38(1):27–35.
98. Gomez RG, Fleming SH, Keller J, et al. *Biol Psychiatry*. 2006;60(5):472–478.
99. Ebert B, Mikkelsen S, Thorkildsen C, et al. *Eur J Pharmacol*. 1997;333(1):99–104.
100. Vollenweider FX, Leenders KL, Øye I, et al. *Eur Neuropsychopharmacol*. 1997;7(1):25–38.
101. Pfenninger EG, Durieux ME, Himmelseher S. *Anesthesiology*. 2002;96(2):357–366.
102. Kolp E, Friedman HL, Krupitsky E, et al. *Int J Transpers Stud*. 2014;33(2):84–140.
103. Dore J, Turnipseed B, Dwyer S, et al. *J Psychoactive Drugs*. 2019;51(2):189–198.

See supplementary material for this article at PSYCHIATRIST.COM.

THE JOURNAL OF
CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: The Effects of Ketamine on Cognition in Unipolar and Bipolar Depression: A Systematic Review

Author(s): Sophie R. Vaccarino, BScH; Fathima Adamsahib, BScPA; Roumen V. Milev, MD, PhD; Sagar V. Parikh, MD; Raymond W. Lam, MD; Pierre Blier, MD, PhD; Sidney H. Kennedy, MD; Karim S. Ladha, MD; and Venkat Bhat, MD

DOI Number: https://doi.org/10.4088/JCP.21r13870

List of Supplementary Material for the article

1. **Table 1** Placebo-controlled trials of single-dose ketamine in healthy volunteers
2. **Table 2** Cognitive tests and related cognitive domains measured in included studies
3. **Table 3** Grading of Recommendations, Assessment, Development and Evaluations (GRADE) Criteria
4. **Appendix 1** Search Strategy

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Table 1: Placebo-controlled trials of single-dose ketamine in healthy volunteers

Study	N	Route	Dose	Assessment time points	Results
[1]	34	IM	0·25 or 0·5 mg/kg bolus	10 min.	KET < PBO: immediate and delayed recall
[2]	19	IV	0·5 mg/kg/40 min.	During infusion	KET < PBO: verbal fluency, executive function, sustained attention; KET = PBO: global cognition
[3]	12	IM	10 or 25 mg/kg bolus	45 min.	KET < PBO: verbal learning and memory, parallel visual search, some measures of psychomotor performance; KET = PBO: simple attention, executive function
[4]	15	IV	0·12 mg/kg bolus + 0·65 mg/kg/h	During; 30, 60 min.	KET < PBO: free recall, recognition memory, attention
[5]	10	IV	0·12 mg/kg bolus + 0·65 mg/kg/h	0, 30 min.	KET < PBO: working and semantic memory
[6]	23	IV	0·26 mg/kg bolus + 0·65 mg/kg/h	During infusion	KET < PBO: executive function
[7]	20	IV	0·26 mg/kg bolus + 0·65 mg/kg/h	During infusion	KET < PBO: delayed recall, global cognition; KET = PBO: immediate recall, verbal fluency
[8]	15	IV	Max. 0·27 mg/kg bolus + 0·26 mg/kg/h	During infusion	KET < PBO: declarative memory; KET = PBO: selective and sustained attention, working memory, executive function
[9]	26	IV	0·5 mg/kg/h	During infusion	KET < PBO: episodic memory encoding; KET = PBO: episodic memory retrieval
[10]	18	IV	0·3 mg/kg/40 min + 0·05 mg/kg/10 min + 0·21 mg/kg/85 min	During infusion	KET = PBO: selective attention
[11]	20	IV	0·24 mg/kg bolus + 0·9 mg/kg/h	During infusion; 30 m	KET < PBO: cognitive control during infusion; KET = PBO: cognitive control 30 min. post-infusion
[12]	8	IV	0·5 mg/kg/h	During infusion	KET < PBO: reaction time
[13]	12	IV	Plasma level 50 or 100 ng/ml	During infusion	100 ng/ml KET < PBO: manipulation tasks of verbal working memory; KET = PBO: maintenance tasks of verbal working memory, and spatial working memory and planning
[14]	54	IV	0·4 or 0·8 mg/kg/80 min	During infusion; 3 d.	KET < PBO: episodic memory during infusion; KET = PBO: episodic memory at 3 d., semantic memory at both time points
[15]	54	IV	0·4 or 0·8 mg/kg/80 min	During infusion	KET < PBO: episodic, working, and recognition memory, procedural learning, and semantic processing; KET = PBO: attention, perceptual priming, executive function
[16]	12	IV	Plasma level 50 or 100 ng/ml	During infusion	KET < PBO: episodic memory encoding
[17]	41	IV	0·23 mg/kg bolus + 0·5 mg/kg/h	During infusion	KET < PBO: attention, delayed recall, working memory
[18]	13	IV	0·27 mg/kg/10 min. + 0·12 mg/kg/50 min.	During infusion; 3, 15, 30 min.	KET < PBO: delayed recall and reaction time during infusion; KET = PBO: delayed recall and reaction time at all post-infusion time points
[19]	12	IV	Plasma level 100 ng/ml	During infusion	KET < PBO: episodic recognition memory
[20]	18	IM	0·2 or 0·4 mg/kg bolus	Repeatedly up to 5 hr.	KET < PBO: encoding, working memory, psychomotor speed; KET = PBO: retrieval, attention, psychomotor accuracy, overall episodic memory
[21]	15	IV	8 mg bolus + 0·01 mg/kg/min	During infusion	KET < PBO: lexical and semantic verbal fluency; KET = PBO: phonological verbal fluency
[22]	37	IV	0.23 mg/kg bolus + 0.58 mg/kg/30 min + 0.29 mg/kg/64 min.	Immediately post-infusion	KET < PBO: reaction time, sustained attention, processing speed, working memory, executive function, verbal fluency, immediate and recognition recall; KET = PBO: motor speed, visual memory
[23]	18	IV	0.24 mg/kg bolus + 0.5 mg/kg/h	During infusion	KET = PBO: attention
[24]	20	IM	0.2 or 0.4 mg/kg bolus	5, 10, 125 min.	KET < PBO: working memory
[25]	44	IV	Plasma level 100 ng/ml	During infusion	KET < PBO: visual working memory
[26]	21	IV	Plasma level 100 ng/ml	5 d.	KET < PBO: memory
[27]	24	IN	84 mg	40 min; 2, 4, 6 hr.	KET < PBO: processing speed, attention, and visual, spatial, and working memory at 40 min. post-infusion; KET = PBO: processing speed, attention, and visual, spatial, and working memory at 2-6 hr.

mg/kg: milligram per kilogram; min.: minute; KET: ketamine; PBO: placebo; mg/kg/h: milligrams per kilograms per hour; d.: day; ng/ml: nanograms per millilitre; hr.: hour

Supplementary Table 1 References:

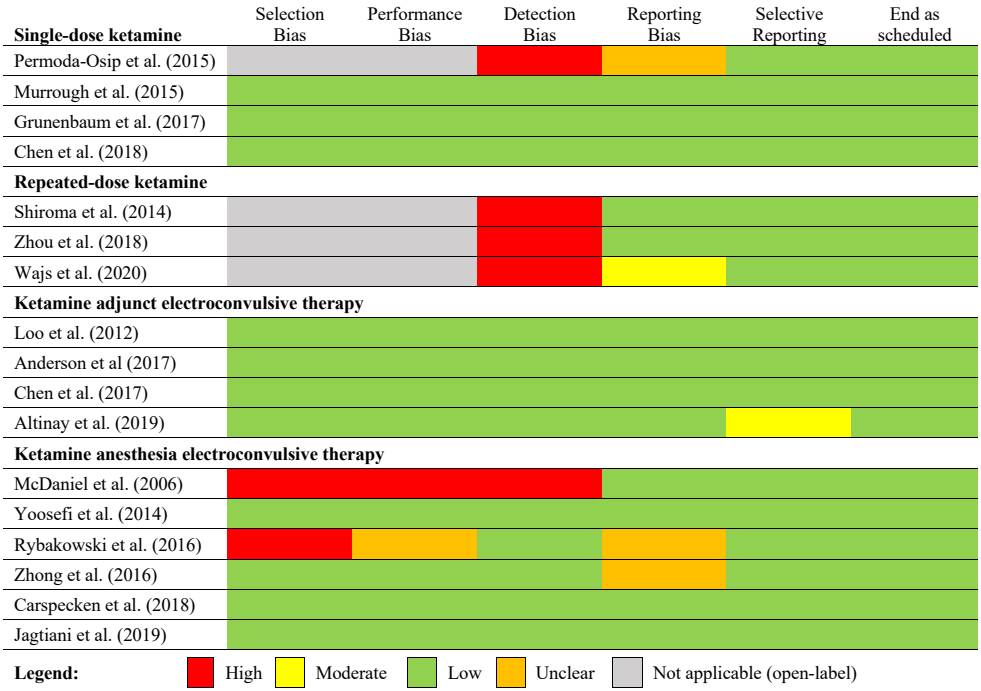
1. Ghoneim MM, Hinrichs J V, Mewaldt SP, Petersen RC. Ketamine: Behaviorual effects of subanesthetic doses. J Clin Psychopharmacol. 1985;5(2):70-77.
2. Krystal JH, Karper LP, Seibyl JP, et al. Subanesthetic Effects of the Noncompetitive NMDA Antagonist, Ketamine, in Humans. Arch Gen Psychiatry. 1994;51(3):199-214. doi:10.1001/archpsyc.1994.03950030035004
3. Harborne GC, Watson FL, Healy DT, Groves L. The effects of sub-anaesthetic doses of ketamine on memory, cognitive performance and subjective experience in healthy volunteers. J Psychopharmacol. 1996;10(2):134-140. doi:10.1177/026988119601000208
4. Malhotra A, Pinals DA, Weingartner H, et al. NMDA Receptor Function and Human Cognition: The Effects of Ketamine in Healthy Volunteers. Neuropsychopharmacology. 1996;14(5):301-307. doi:10.1016/0893-133X(95)00137-3
5. Adler C, Goldberg T, Malhotra A, Pickar D, Breier A. Effects of Ketamine on Thought Disorder, Working Memory, and Semantic Memory in Healthy Volunteers. Biol Psychiatry. 1998;43(11):811-816. doi:10.1016/S0006-3223(97)00556-8
6. Krystal JH, Karper LP, Bennett A, et al. Interactive effects of subanesthetic ketamine and subhypnotic lorazepam in humans. Psychopharmacology (Berl). 1998;135(3):213-229. doi:10.1007/s002130050503
7. Krystal JH, D'Souza DC, Karper LP, et al. Interactive effects of subanesthetic ketamine and haloperidol in healthy humans. Psychopharmacology (Berl). 1999;145(2):193-204. doi:10.1007/s002130051049
8. Newcomer JW, Farber NB, Jevtovic-Todorovic V, et al. Ketamine-Induced NMDA Receptor Hypofunction as a Model of Memory Impairment and Psychosis. Neuropsychopharmacology. 1999;20(2):106-118. doi:10.1016/S0893-133X(98)00067-0
9. Hetem LAB, Danion JM, Diemunsch P, Brandt C. Effect of a subanesthetic dose of ketamine on memory and conscious awareness in healthy volunteers. Psychopharmacology (Berl). 2000;152(3):283-288. doi:10.1007/s002130000511
10. Oranje B, van Berckel BN, Kemner C, van Ree JM, Kahn RS, Verbaten MN. The Effects of a Sub-Anaesthetic Dose of Ketamine on Human Selective Attention. Neuropsychopharmacology. 2000;22(3):293-302. doi:10.1016/S0893-133X(99)00118-9
11. Umbricht D, Schmid L, Koller R, Vollenweider FX, Hell D, Javitt DC. Ketamine-Induced Deficits in Auditory and Visual Context-Dependent Processing in Healthy Volunteers. Arch Gen Psychiatry. 2000;57(12):1139-1147. doi:10.1001/archpsyc.57.12.1139
12. Micallef J, Guillermain Y, Tardieu S, et al. Effects of Subanesthetic Doses of Ketamine on Sensorimotor Information Processing in Healthy Subjects. Clin Neuropharmacol. 2002;25(2):101-106. doi:10.1097/00002826-200203000-00008
13. Honey RAE, Turner DC, Honey GD, et al. Subdissociative Dose Ketamine Produces a Deficit in Manipulation but not Maintenance of the Contents of Working Memory. Neuropsychopharmacology. 2003;28(11):2037-2044. doi:10.1038/sj.npp.1300272
14. Morgan CJA, Mofeez A, Brandner B, Bromley L, Curran HV. Ketamine impairs response inhibition and is positively reinforcing in healthy volunteers: a dose-response study. Psychopharmacol. 2004;172(3):298-308. doi:10.1007/s00213-003-1656-y
15. Morgan CJA, Mofeez A, Brandner B, Bromley L, Curran HV. Acute Effects of Ketamine on Memory Systems and Psychotic Symptoms in Healthy Volunteers. Neuropsychopharmacology. 2004;29(1):208-218. doi:10.1038/sj.npp.1300342
16. Honey GD, Honey RAE, Sharar SR, et al. Impairment of specific episodic memory processes by sub-psychotic doses of ketamine: the effects of levels of processing at encoding and of the subsequent retrieval task. Psychopharmacology (Berl). 2005;181(3):445-457. doi:10.1007/s00213-005-0001-z
17. Krystal JH, Perry EB, Gueorguieva R, et al. Comparative and Interactive Human Psychopharmacologic Effects of Ketamine and Amphetamine. Arch Gen Psychiatry. 2005;62(9):985-994. doi:10.1001/archpsyc.62.9.985
18. Parwani A, Weiler MA, Blaxton TA, et al. The effects of a subanesthetic dose of ketamine on verbal memory in normal volunteers. Psychopharmacology (Berl). 2005;183(3):265-274. doi:10.1007/s00213-005-0177-2
19. Honey GD, O'Loughlin C, Turner DC, Pomarol-Clotet E, Corlett PR, Fletcher PC. The Effects of a Subpsychotic Dose of Ketamine on Recognition and Source Memory for Agency: Implications for Pharmacological Modelling of Core Symptoms of Schizophrenia. Neuropsychopharmacology. 2006;31(2):413-423. doi:10.1038/sj.npp.1300846
20. Lofwall MR, Griffiths RR, Mintzer MZ. Cognitive and subjective acute dose effects of intramuscular ketamine in healthy adults. Exp Clin Psychopharmacol. 2006;14(4):439-449. doi:10.1037/1064-1297.14.4.439
21. Nagels A, Kirner-Veselinovic A, Krach S, Kircher T. Neural correlates of S-ketamine induced psychosis during overt continuous verbal fluency. Neuroimage. 2011;54(2):1307-1314. doi:10.1016/j.neuroimage.2010.08.021
22. D'Souza DC, Ahn K, Bhakta S, et al. Nicotine Fails to Attenuate Ketamine-Induced Cognitive Deficits and Negative and Positive Symptoms in Humans: Implications for Schizophrenia. Biol Psychiatry. 2012;72(9):785-794. doi:10.1016/j.biopsych.2012.05.009
23. Ebert A, Haussleiter IS, Juckel G, Brüne M, Roser P. Impaired facial emotion recognition in a ketamine model of psychosis. Psychiatry Res. 2012;200(2-3):724-727. doi:10.1016/j.psychres.2012.06.034
24. Carter LP, Kleykamp BA, Griffiths RR, Mintzer MZ. Cognitive effects of intramuscular ketamine and oral triazolam in healthy volunteers. Psychopharmacology (Berl). 2013;226(1):53-63. doi:10.1007/s00213-012-2883-x
25. Koychev I, William Deakin JF, El-Deredy W, Haenschel C. Effects of Acute Ketamine Infusion on Visual Working Memory: Event-Related Potentials. Biol Psychiatry Cogn Neurosci Neuroimaging. 2017;2(3):253-262. doi:10.1016/j.bpsc.2016.09.008
26. Becker B, Steffens M, Zhao Z, et al. General and emotion-specific neural effects of ketamine during emotional memory formation. Neuroimage. 2017;150:308-317. doi:10.1016/j.neuroimage.2017.02.049
27. Morrison RL, Fedgchin M, Singh J, et al. Effect of intranasal esketamine on cognitive functioning in healthy participants: a randomized, double-blind, placebo-controlled study. Psychopharmacology (Berl). 2018;235(4):1107-1119. doi:10.1007/s00213-018-4828-5

Supplementary Table 2. Cognitive tests and related cognitive domains measured in included studies

	Cognitive Test	Cognitive Domain Measured	Follow-up points
Single-dose ketamine studies			
Permoda-Osip et al. (2015)	Stroop test	Attention, executive function	Day 3
	Trails Making Test (TMT)	Processing speed (Part A), executive function (Part B)	
Murrough et al. (2015)	TMT-A, category fluency test, Brief Assessment of Cognition in Schizophrenia (BACS)– Symbol coding	Processing speed	Week 1
	Wechsler Memory Scale (WMS) – Spatial Span	Working Memory	
	Letter-Number Sequencing	Working Memory	
	Hopkins Verbal Learning Test (HVLT)	Verbal Memory	
	Brief Visuospatial Memory Test (BVMT)	Visual Memory	
	Neuropsychological Assessment Battery (NAB) – mazes	Problem Solving	
Grunenbaum et al. (2017)	Simple & Choice Reaction Time	Reaction time	Day 1
	TMT-A, Wechsler Adult Intelligence Scale (WAIS) – digit symbol coding, Stroop test	Processing speed	
	Continuous Performance Test (CPT) – identical pairs, Stroop test	Attention	
	Buschke Selective Reminding Test (SRT)	Global Memory	
	Brief Visual Retention Test (BVRT)	Visual memory	
	A not B test, N-back test	Working memory	
	Controlled Oral Word Association Test (COWAT)	Verbal fluency	
	Go/No-Go test, Time production test, Stroop test	Executive function	
Chen et al. (2018)	Working memory task	Working memory	Day 3, Week 2
	Go/No-Go test	Executive function	
Repeated-dose ketamine studies			
Shiroma et al. (2014)	Identification task	Attention	Week 1, 2, 3, 4
	N-back test	Working memory	
	Groton Maze Learning Test (GML)	Spatial memory	
	Groton Maze Chase Test, Detection task	Processing speed	
	Continuous Paired Associative Learning Task (CPAL), one card learning task, GML –delayed recall	Visual memory	
	International Shopping List Task (ISL)	Verbal memory	
	Set-shifting task	Executive function	
Zhou et al. (2018)	BACS – Symbol coding, category fluency, TMT Part A	Processing Speed	Day 1, day 14
	WMS – Spatial Span, Letter-Number Sequencing	Working memory	
	HVLT	Verbal memory	
	BVMT	Visual memory	
Wajs et al. (2020)	Simple Reaction Time – detection task	Processing speed	28 days after start of treatment; week 20, 32, and 44 follow-up
	Identification task	Attention	
	One card learning task	Visual memory	
	N-back test	Working memory	
	Groton Maze Learning Test	Spatial memory	
	HVLT	Verbal memory	
Ketamine adjunct to electroconvulsive therapy studies			
Loo et al. (2012)	Medical College of Georgia Complex Figures	Visuospatial function	Day 1-3, Month 1
	HVLT	Verbal memory	
	COWAT	Verbal fluency	
	Symbol Digit Modalities Test (SDMT), Woodcock Johnson Cross-Out Test	Processing speed	
	Autobiographical Memory Interview – Short form (AMI-SF)	Autobiographical memory	
Anderson et al. (2017)	HVLT	Verbal memory	After last session, month 1 and 4
	COWAT	Verbal fluency	
	AMI-SF	Autobiographical memory	
	Medical College of Georgia Complex Figures	Visuospatial function	
	WAIS – digit span	Attention, working memory	
Chen et al. (2017)	Wechsler Memory Scale-Chinese Revision (WMS-RC)	Global memory	Day 1
	Mini Mental State Exam (MMSE)	Global cognition	
Altinay et al. (2019)	Montreal Cognitive Assessment (MoCA)	Global cognition	After last session
	COWAT	Verbal fluency	

Ketamine anesthesia for electroconvulsive therapy studies			
McDaniel et al. (2006)	MMSE – Short term memory item	Short-term memory	≥2 days
Yoosefi et al. (2014)	MMSE	Global cognition	Day 3-7, Month 1
Rybakowski et al. (2016)	BVRT	Visual memory	Day 2-4
	Rey-Osterrieth complex figure test	Visuospatial function	
	WAIS – digit span	Attention, working memory	
	Rey Auditory Verbal Learning Test (RAVLT)	Verbal memory	
	Verbal fluency test	Verbal fluency	
	Stroop Test	Attention, executive function, processing speed	
Zhong et al. (2016)	Verbal fluency test	Verbal fluency	Day 2-3
	WAIS – Digit symbol coding, TMT Part A	Processing speed	
	WAIS – digit span	Attention, working memory	
	Wisconsin Card Sorting Test (WCST), TMT Part B	Executive function	
	Tower of Hanoi	Problem solving	
	Visual regeneration test	Visual memory	
Carspecken et al. (2018)	MoCA	Global cognition	Day 3
Jagtiani et al. (2019)	MMSE	Global cognition	Hour 6

Supplementary Table 3. Grading of Recommendations, Assessment, Development and Evaluations (GRADE) Criteria[42,43]



Appendix 1. Search Strategy

OVID (example for MEDLINE database):

1. exp Depressive Disorder, Major/
2. exp Bipolar Disorder/
3. exp Depressive Disorder, Treatment-Resistant/
4. bipolar disorder*.tw.
5. bipolar depression*.tw.
6. manic depressive disorder*.tw.
7. manic depression*.tw.
8. bipolar affective disorder*.tw.
9. affective disorder*.tw.
10. refractory depression*.tw.
11. therapy resistant depression*.tw.
12. treatment refractory depression*.tw.
13. refractory depressive disorder*.tw.
14. treatment resistant depressive disorder*.tw.
15. treatment resistant depression*.tw.
16. major depressive disorder*.tw.
17. depression*.tw.
18. depressive disorder*.tw.
19. depress*.tw.
20. mood disorder*.tw.
21. exp Ketamine/
22. ketamine*.tw.
23. ci 581*.tw.
24. calypsol*.tw.
25. calipsol*.tw.
26. kalipsol*.tw.
27. ketalar*.tw.
28. ketamine hydrochloride*.tw.
29. ketanset*.tw.
30. ketaset*.tw.
31. r ketamine*.tw.
32. arketamine*.tw.
33. s ketamine*.tw.
34. esketamine*.tw.
35. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
36. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
37. 35 or 36
38. limit 37 to human

Cochrane Library:

1. MeSH descriptor: [Depressive Disorder, Major] explode all trees
2. MeSH descriptor: [Depressive Disorder, Treatment-Resistant] explode all trees
3. MeSH descriptor: [Bipolar Disorder] explode all trees
4. (bipolar disorder*):ti,ab,kw
5. (bipolar depression*):ti,ab,kw
6. (manic depressive disorder*):ti,ab,kw
7. (manic depression*):ti,ab,kw
8. (bipolar affective disorder*):ti,ab,kw
9. (affective disorder*):ti,ab,kw
10. (refractory depression*):ti,ab,kw
11. (therapy resistant depression*):ti,ab,kw
12. (treatment refractory depression*):ti,ab,kw
13. (refractory depressive disorder*):ti,ab,kw
14. (treatment resistant depressive disorder*):ti,ab,kw
15. (treatment resistant depression*):ti,ab,kw
16. (major depressive disorder*):ti,ab,kw
17. (depression*):ti,ab,kw
18. (depressive disorder*):ti,ab,kw
19. (depress*):ti,ab,kw
20. (mood disorder*):ti,ab,kw
21. MeSH descriptor: [Ketamine] explode all trees
22. (ketamine*):ti,ab,kw
23. (ci 581*):ti,ab,kw
24. (calypsol*):ti,ab,kw
25. calipsol*):ti,ab,kw
26. (kalipsol*):ti,ab,kw
27. (ketalar*):ti,ab,kw
28. (ketamine hydrochloride*):ti,ab,kw
29. (ketanset*):ti,ab,kw
30. (ketaset*):ti,ab,kw
31. (r ketamine*):ti,ab,kw
32. (arketamine*):ti,ab,kw
33. (s ketamine*):ti,ab,kw
34. (esketamine*):ti,ab,kw
35. (#1)OR(#2)OR OR(#3) OR(#4) OR(#5) OR(#6) OR(#7) OR(#8) OR(#9) OR(#10) OR(#11) OR(#12) OR(#13) OR(#14) OR(#15) OR(#16) OR(#17) OR(#18) OR(#19) OR(#20)
36. (#21)OR(#22)OR OR(#23) OR(#24) OR(#25) OR(#26) OR(#27) OR(#28) OR(#29) OR(#30) OR(#31) OR(#32) OR(#33) OR(#34)

Clinical trial registries searched

1. Australian Clinical Trials
2. Clinicaltrials.gov
3. International Standard Randomised Controlled Trials Number (ISRCTN)
4. International Clinical Trials Registry Platform (ICTRP)
5. European Union Clinical Trials Register