REVIEW

A review of ketamine's role in ECT and non-ECT settings

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Abstract: Up to 20% of depressed patients demonstrate treatment resistance to one or more adequate antidepressant trials, resulting in a disproportionately high burden of illness. Ketamine is a non-barbiturate, rapid-acting general anesthetic that has been increasingly studied in treatment resistant depression (TRD), typically at sub-anesthetic doses (0.5 mg/kg over 40 min by intravenous infusion). More recent data suggest that ketamine may improve response rates to electroconvulsive therapy (ECT) when used as an adjunct, but also as a sole agent. In the ECT setting, a dose of 0.8 mg/kg or greater of ketamine demonstrates improved reduction in depressive symptoms than lower doses; however, inconsistency and significant heterogeneity among studies exists. Clinical predictors of responses to ketamine have been suggested in terms of non-ECT settings. Ketamine does increase seizure duration in ECT, which is attenuated when concomitant barbiturate anesthetics are used. However, most studies are small, with considerable heterogeneity of the sample population and variance in dosing strategies of ketamine, ECT, and concomitant medications, and lack a placebo control, which limits interpretation. Psychotomimetic and cardiovascular adverse effects are reported with ketamine. Cardiovascular adverse effects are particularly relevant when ketamine is used in an ECT setting. Adverse effects may be mitigated with concurrent propofol; however, this adds complexity and cost compared to standard anesthesia. Long-term adverse effects are still unknown, but relevant, given recent class concerns for anesthetic and sedative agents.

Keywords: ketamine, ECT, anesthesia, major depressive disorder

Introduction

Major depressive disorder (MDD) is defined as "treatment-resistant" depression (TRD) if a patient does not respond to one or more adequate antidepressant trials. TRD occurs at rates of 12%–20% among all depressed patients, and is associated with a disproportionately high burden of illness compared with patients who respond to treatment.[1]

Ketamine is a non-barbiturate, rapid-acting general anesthetic with an onset of action within 30 s when given by intravenous (iv) injection at an anesthetic dose of 2 mg/kg (range=1–4.5 mg/kg).[2] Most randomized controlled trials (RCTs) report on ketamine's safety and efficacy in TRD, in a non-electroconvulsive therapy (ECT) setting, when administered by iv infusion at a dose of 0.5 mg/kg over 40 min.[3] A growing body of literature suggests that sub-anesthetic doses of ketamine may reduce the time between initiation of therapy and time to response and/or remission, in TRD, with or without concomitant ECT.[4] Ketamine may also improve the response rates to ECT when used concurrently as an adjunct.[4]

However, there are significant challenges associated with the use of ketamine in the treatment of TRD, including: short duration of antidepressant effect and abuse

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potential in a non-ECT setting; potentially reduced efficacy by concomitant anesthetics in an ECT setting; risk of cardio-vascular (hypertension, tachycardia) and psychotomimetic (hallucinations, anxiety) adverse effects; and drug–drug interactions.[3]

A consensus statement on the use of ketamine in the treatment of mood disorders has recently been released.[5] Overall, there are limited data concerning the role of ketamine in an ECT setting, for example, when used as an adjunct compared to being used alone, optimal dosing and route of administration, as well as other clinical indicators that may predict the successful use of ketamine in both ECT and non-ECT settings.[3,4]

The objectives of this review are to summarize the extant literature to identify: (1) differences in efficacy that may exist between different doses of ketamine when used alone or with various concomitant agents in an ECT setting; (2) the efficacy of doses other than 0.5 mg/kg, with or without concomitant agents, and through different routes of administration, in a non-ECT setting; and (3) clinical predictors of response to ketamine in both settings.

Methodology

The following databases were searched: Pubmed, Embase, PsycINFO (1987 to present), and MEDLINE (1946 to present). The following search terms were used: ketamine, N-methyl D-aspartate, NMDA antagonist, ECT, electro-convulsive therapy, electroshock therapy, major depres-sive disorder, major depression, MDD, treatment-resistant depressive disorder. Studies were included if they met the following criteria: language, English; publication status, published trials; design, RCT; intervention, ketamine administration alone without ECT for treatment of MDD, ketamine administration with other agents without ECT for treatment of MDD, ketamine administration as an anesthetic for ECT for treatment of MDD, ketamine administration as an anesthetic for ECT along with other agents for treatment of MDD; participants, diagnosis of MDD, TRD, psychotic TRD, bipolar depression.

Studies were excluded if they met the following criteria: (1) Studies of ketamine use in a non-ECT setting using 0.5 mg/kg iv infusion over 40 min, unless investigating clinical predictors for response or use in combination with other specified agents for treatment of TRD; (2) cross-over studies – due to the potential of carry-over effects; (3) studies that did not investigate ketamine as a treatment of depression; and (4) studies that did not report the efficacy of ketamine as one of the primary objectives.

Table 1 Criteria for level of evidence and line of treatment

Level of evidence	Criteria
1	Meta-analysis with narrow confidence intervals and/or 2 or more RCTs with adequate sample size, preferably PBO controlled
2	Meta-analysis with wide confidence intervals and/or 1 or more RCTs with adequate sample size
3	Small-sample RCTs or nonrandomized, controlled prospective studies or case series or high-quality retrospective studies
4	Expert opinion/consensus

Abbreviations: RCTs, randomized controlled trials; PBO, placebo.

The level of evidence for each study was assessed using prespecified criteria[6] (Table 1). The search generated 704 results, of which 26 studies met the inclusion criteria. Ten additional resources were used for background information purposes. Two additional studies were included from the bibliographies of relevant studies.

Intravenous ketamine in an ECT setting

A number of studies have investigated the use of ketamine, either alone or in addition to other anesthetic agents, and at various doses for induction of anesthesia in ECT (Table 2).[7–20]

When compared to control anesthesia, ketamine alone, or as an adjunctive agent to other anesthetics, significantly reduced depression severity in a number of studies.[7,8,10,14,18] Some studies have also shown an increased seizure duration if ketamine was used as a sole anesthetic, or in combination with other anesthetics, when compared to ketamine-free anesthesia.[9,10,21] Significant cognitive improvement was also seen with ketamine, especially in patients with higher cognitive impairment at baseline.[10] Several studies showed a more rapid response to ECT in patients receiving ketamine, despite the overall end effect being non-significant.[10,13] When considering dose-related efficacy, a majority of studies dem-onstrated efficacy with ketamine doses equal to or greater than 0.8 mg/kg, which may provide a signal for interpretation. One study, however, did not find a significant improvement in depressive symptoms when a dose of 2 mg/kg was used. Given the significant heterogeneity of studies, as well as a lack of high quality studies, conclusive results around dose-related efficacy were not possible. At best, this could be considered as a guide for future research.

In contrast, a few RCTs have not found ketamine to be superior to other anesthetics in depressive symptom reduction

Table 2 iv Ketamine in an ECT setting

Study	Objectives	Participants	Methods	Outcome measures	Results	Level of evidence
Jarventausta et al[7] (2013)	Effect of S-ketamine as an adjuvant to propofol anesthesia in ECT.	Adults (n=32) with recurrent, severe, or psychotic TRD. Baseline MADRS according to treatment group: (1) 36.9; (2) 37.3.	RCT: (1) S-ketamine 0.4 mg/kg iv bolus and then propofol, or (2) NS and propofol.	MADRS; speed of response. Rates of adverse effects.	No differences in magnitude and speed of response, numbers of ECT treatments, seizure thresholds, seizure durations and electrical doses.	3
Wang et al[8] (2012)	Effect of combined ketamine and propofol, for patients receiving a single ECT treatment.	Adults (n=48) with MDD. HDRS≥20. Baseline HDRS-17 according to treatment group: (1) 30.1; (2) 28.9; (3) 29.2.	RCT: (1) propofol 1.5 mg/kg iv; (2) ketamine 0.8 mg/kg iv; or (3) propofol 1.5 mg/kg iv plus ketamine 0.8 mg/kg iv.	HDRS scores 1 day before ECT and days 1, 2, 3, and 7 after ECT.	HDRS scores improved earlier with ketamine and propofol+ketamine, compared with propofol. Fewer adverse events with propofol+ketamine than with ketamine.	3
Yalcin et al[9] (2012)	Effect of ketamine, propofol, and ketofol on hemodynamic profile, duration of seizure activity, and recovery times for patients receiving single ECT treatment.	Adults (n=90) with MDD, and schizophrenia with depression.	RCT: (1) concomitant propofol; (2) ketamine; or (3) ketofol dosed at 10 mg increments until responsiveness to verbal command lost.	Hemodynamic profile, duration of seizure activity, and recovery times.	Motor seizure duration with propofol group was significantly decreased compared to ketamine and ketofol groups (29.3±5.1 s, 37.2±3.2 s, and 34±5.8 s, respectively; P<0.001).	3
Yoosefi et al[10] (2014)	Effects of thiopental and ketamine anesthesia in ECT.	Adult inpatients (n=31) with MDD and HDRS of ≥18. Baseline HDRS according to treatment group: (1) 23.6; (2) 22.86.	RCT: (1) ketamine 1–2 mg/kg iv, or (2) thiopental 2–3 mg/kg iv.	MMSE and HDRS before the 1st and 2nd ECT sessions as well as 3–7 days and 1 month after the 6th session.	Ketamine group showed longer seizure duration and significantly greater improvements in depressive symptoms only before the second ECT session (mean HDRS score: (1) 16.2; (2) 20.0; P=0.002). Significant cognitive improvements were demonstrated in the ketamine group (MMSE score at baseline 25.60 vs 27.82 1-month after 6th ECT).	3
Abdallah et al[11] (2012)	Effect of ketamine on antidepressant effects of ECT.	Adults (n=18) with MDD and BPD. Baseline HDRS according to treatment group: (1) 38.3±2.1; (2) 35.3±2.5.	RCT: (1) thiopental alone, or (2) thiopental plus ketamine 0.5 mg/kg iv for anesthesia before each ECT session.	HDRS at baseline and 24–72 h after the 1st and 6th ECT sessions.	No significant group effect or group-by-time interaction on HDRS scores.	3
Erdil et al[12] (2015)	Effect of an adjunctive sub-anesthetic dose of ketamine to sevoflurane, on seizure duration in ECT.	Adults (n=84) with MDD with no other major medical problems.	RCT: (1) SK, or (2) SS. Ketamine was administered as a 0.5 mg/kg iv bolus.	Duration of the motor seizure and EEG seizure duration.	Motor and EEG seizure durations were similar in both groups. MAP was significantly increased in both groups compared to BL: (1) 95.6 to peak of 119.8 mmHg; (2) 94.8 to peak of 115.6 mmHg. Heart rate increased significantly in both groups: (1) 77.3 to peak of 89.8 bpm; (2) 78.8 to peak of 91 bpm.	3

(Continued)

Table 2 (*Continued*)

Study	Objectives	Participants	Methods	Outcome measures	Results	Level of evidence
Salehi et al[13] (2015)	Effect of ketamine and sodium thiopental anesthesia during ECT.	Adults (n=160) with TRD (without other psychiatric disorders). Baseline HDRS according to treatment group: (1) 29.82±7.3; (2) 28.86±7.6.	DB, RCT: (1) ketamine 0.8 mg/kg iv, or (2) sodium thiopental 1–1.5 mg/kg iv. Number of ECT treatments=8.	HDRS-17 at baseline and after the end of ECT sessions 2, 4, 6, and 8.	HDRS score demonstrated a significant decreasing trend in both groups: (1) 8.32±5.17; (2) 10.53±7.87. Response was more rapid with ketamine.	2
Rybakowski et al[14] (2016)	Effect of ketamine anesthesia on antidepressant activity and cognition in ECT.	Adults with TRD (n=45). Mean HDRS-17=32 (no differences between groups). Mean duration of illness was 12.8 years.	DB RCT: (1) thiopental anesthesia only, (2) ketamine (1–1.5 mg/kg) at 2nd and 3rd ECT sessions, or (3) ketamine (1–1.5 mg/kg) at 2nd, 4th, 6th, 8th, and 10th sessions. Mean number of ECT treatments=10.8.	HDRS-17 after each ECT session. Cognitive function assessed with three categories of tests.	HDRS-17 scores decreased by: (1) 16.6, (2) 15.7, and (3) 21.8 points. Difference between groups (1) and (3) was statistically significant (P=0.0006). Verbal memory and phonological fluency in ketamine groups were markedly worsened.	3
Anderson et al[15] (2017)	Effect of adjunctive ketamine on cognitive and depressive symptoms in ECT.	Adult outpatients and inpatients (n=70) with severe MDD or BD (ECT in the previous 3 months was exclusionary). Baseline MADRS according to treatment group: (1) 31.8±7.4; (2) 35.2±8.4.	MC superiority RCT. 1:1 randomization: (1) ketamine (0.5 mg/kg) or (2) saline; with propofol or thiopental anesthesia. Mean number of ECT treatments=11.	Neuropsychological assessment using several tests. MADRS, CAS, CGI-S, CGI-I, QIDS-SR, and EQ-5D-3L.	No significant differences between the treatments in neuropsychological and efficacy measures.	3
Kuscu et al[16] (2015)	Effect of anesthesia with thiopental, ketamine, and ketamine-thiopental on depressive and anxiety symptoms in ECT.	Adults (n=58) with TRD (HDRS>17). Baseline scores according to treatment group: HDRS (1) 17.6±4.9; (2) 20.0±4.0; (3) 19.7±4.3. HAM-A (1) 10.2±4.3; (2) 12.3±4.8; (3) 13.1±5.7.	RCT: (1) thiopental 4 mg/kg iv; (2) ketamine 1 mg/kg; or (3) both administered pre-ECT. Total number of ECT treatments=8.	HDRS and HAM-A at baseline, after 3rd and 6th and last ECT treatments.	No statistical differences between the groups regarding HDRS scores. HAM-A scores were higher in ketamine groups: (1) 1.4±0.8; (2) 2.9±1.8; (3) 3.2±1.9 (P=0.017).	3
Fernie et al[17] (2017)	Effect of ketamine anesthesia on depressive and cognitive symptoms in ECT vs standard anesthesia.	Adults (n=40) with MDD, receiving ECT. Baseline scores according to treatment group: HDRS (1) 27.19±6.47; (2) 24.79±8.50; MADRS (1) 36.38±8.29; (2) 35.68±8.39.	DB RCT: (1) bolus ketamine up to 2 mg/kg, or (2) propofol up to 2.5 mg/kg.	HDRS-17 and MADRS before 1st, after 4th, at the end of treatment, and 1 month after the end of treatment.	No difference in the number of ECT treatments. No differences in change in symptom severity.	3
Zhong et al[18] (2016)	Effect of anesthetic and sub-anesthetic doses of ketamine on mood and cognitive symptoms in ECT.	Adults (n=90) with treatment resistant MDD or BD (other mental disorders, exclusionary).	RCT: (1) ketamine 0.8 mg/kg iv (K), (2) ketamine 0.5 mg/kg iv plus propofol 0.5 mg/kg iv (KP), or (3) propofol 0.8 mg/kg iv (P). Total number of ECT treatments=8.	HDRS-17, BPRS at baseline, after 1st, 2nd, 3rd, 4th, 6th, and 8th treatments.	K and KP groups showed statistically significant higher response rates after the 3rd ECT (HDRS-17=(1) 13.5±1.2; (2) 15.0±2.1 and (3) 16.5±1.9; P<0.001) and 4th ECT (HDRS-17=(1) 11.0±1.0; (2) 12.5±2.1; (3) 14.1±1.8; P<0.001).	3

Study	Aim	Baseline scores	Study design/intervention	Measures	Results	
		Baseline scores according to treatment group: HDRS-17 (1) 26.7±1.6; (2) 26.7±2.0; (3) 26.0±2.8. BPRS-18 (1) 35.47±4.167; (2) 36.53±5.164; (3) 36.93±6.142.			K group had a statistically significant higher remission rate compared to the KP and P groups after 8th ECT.	3
Rasmussen et al[19] (2014)	Effect of ketamine as an anesthetic agent for ECT.	Adults (n=38) with non-psychotic MDD, unipolar, or BD. Baseline scores according to treatment group: PHQ-9 (1) 17.57±6.96; (2) 15.98±7.54. HADS (1) 24.45±7.70; (2) 22.08±8.11.	RCT: (1) methohexital; or (2) ketamine as anesthetic during the first six treatments of ECT. Starting doses of 1.0 mg/kg were targeted for both agents and were individually adjusted.	PHQ-9, HADS, MMSE at baseline and after treatments 2, 4, and 6.	No significant difference in scores on either depression rating scale or in MMSE or post-treatment orientation scores.	3
Loo et al[20] (2012)	Effect of ketamine on depressive and cognitive symptoms with ECT.	Adult inpatients (n=51) with TRD, unipolar or bipolar (without current psychotic symptoms). Baseline MADRS according to treatment group: (1) 32.1±4.5; (2) 32.7±7.9.	DB, RCT: (1) ketamine 0.5 mg/kg iv; or (2) a PBO iv at the time of thiopentone anesthesia for ECT, for the whole ECT course.	MADRS prior to ECT, after 6 ECT treatments, 1–3 days after the end of the ECT course, and 1 month later.	No significant difference was found in MADRS scores between the groups over the whole course. A significant time-by-group interaction was found over the first week of treatment $(F_{(1, 40)}=4.555, P=0.039, \eta^2=102)$, indicating improvement in the ketamine group.	3

Abbreviations: iv, intravenous; ECT, electroconvulsive therapy; TRD, treatment resistant depression; MADRS, Montgomery-Asberg Depression Rating Scale; RCT, randomized controlled trial; NS, normal saline; MDD, major depressive disorder; HDRS, Hamilton Depression Rating Scale; MMSE, Mini Mental State Examination; BPD, bipolar disorder; SK, sevoflurane-ketamine; SS, sevoflurane-saline; DB, double-blind; EEG, electroencephalogram; MAP, mean arterial pressure; BL, baseline; bpm, beats per minute; BD, bipolar depression; MC, multi-center; CAS, Clinical Anxiety Scale; CGI-S, Clinical Global Impression-Severity; CGI-I, Clinical Global Impression-Improvement; QIDS-SR, Quick Inventory of Depressive Symptomatology-Self Report; EQ-5D-3L, third-level version of the EuroQol five-dimensional questionnaire; HAM-A, Hamilton Anxiety Scale; PHQ, Patient Health Questionnaire; HADS, Hospital Anxiety and Depression Scale; PBO, placebo.

or improved cognition,[15–17,19,20] even if the seizure duration was prolonged with ketamine.[11] The effect of ketamine on seizure duration varied between studies, with some demonstrating no difference between ketamine and controls.[20] Of note, most of the studies employed different methods of ECT administration, such as dose titration,[11] which could explain some of the observed differences in treatment efficacy.

Intravenous ketamine in a non-ECT setting

When used as a general anesthetic together with propofol and fentanyl for orthopedic surgery in patients with MDD, ketamine (1 mg/kg) demonstrated significant reductions in depressed mood, suicidal tendencies, somatic anxiety, and hypochondriasis (Table 3).[22–24]

Lenze et al[23] attempted to demonstrate the efficacy and safety of prolonged ketamine infusion (0.6 mg/kg/h over 96 h) vs a single dose (0.5 mg/kg for 40 min), both with co-administration of clonidine (0.3 mg twice daily) in patients with TRD. Although there was no difference in Montgomery-Asberg Depression Rating Scale (MADRS) scores between prolonged infusion and a single dose of ketamine, a more sustained antidepressant response (spearman correlation coefficient between S-ketamine concentration and MADRS change from baseline: 0.75 for 96-hour arm and 0.17 for 40-minute arm; $p<0.05$) was observed at 8 weeks following prolonged infusion. Li et al[24] compared single bolus ketamine at doses of 0.5 mg/kg and 0.2 mg/kg, and a single bolus of normal saline in patients with TRD. The investigators found no significant difference between the two ketamine treatment strategies, but both treatments were significantly more effective than placebo (PBO) (Hamilton Depression Rating Scale [HDRS] reduction of 37.8%, 38.2%, and 26.7%, respectively).

Ketamine with adjunctive agents in non-ECT setting

Three studies investigated adjunctive use of riluzole in patients receiving ketamine infusion (Table 4).[25–27]

Riluzole is a glutamatergic modulator postulated to induce a rapid response to ketamine, and to maintain remission without the potential psychotomimetic side effects associated with ketamine.[25] When dosed at 50 mg twice daily for 4 weeks following a single ketamine infusion (0.5 mg/kg) in patients with TRD, riluzole did not appear to significantly prolong the duration of response (time to relapse=17.2 days for riluzole; 9.8 days for PBO). However, the study was not adequately powered to show a difference between the two treatment groups. In another RCT, riluzole was administered at a daily dose of

100–200 mg following a ketamine infusion (0.5 mg/kg).[26] There was no significant difference in time-to-relapse with riluzole, when compared to PBO (24.4 days and 22.0 days, respectively). A combination of single iv dose of ketamine (0.5 mg/kg) and escitalopram (10 mg daily) was studied in patients with severe MDD.[27] Compared to escitalopram therapy alone, the combination group had a significantly higher response rate (92.3% vs 57.1%), remission rate (76.9% vs 14.3%), shorter time to response (HR=0.04 95% CI=0.01–0.22), and remission (HR=0.11, 95% CI=0.02–0.63).

Oral ketamine

Oral ketamine has been investigated as an antidepressant treatment in patients with mild-to-moderate depression and concomitant chronic pain (Table 5).[28] When compared to diclofenac, ketamine, dosed at 50 mg orally three times a day, showed significant improvement in HDRS (mean difference=2.85, 95% CI 0.54–5.16) and Hospital Anxiety and Depression Scale (HADS) scores (mean difference=0.75, 95% CI 0.18–1.32) at week 6 of treatment.

Intranasal ketamine

A recently conducted study compared three different doses of S-(+)-ketamine enantiomer (esketamine) (28 mg, 54 mg, and 84 mg) administered intranasally vs PBO, and found that all three doses significantly decreased MADRS in both phases of the studies.[29] However, in patients with severe MDD and at imminent risk of suicide, intranasal esketamine (84 mg), along with standard of care, was shown to be superior to PBO in reducing symptoms of depression.[30] These two studies are summarized in Table 6.

Adverse effects of ketamine

In contrast to most anesthetic agents that are typically hypotensive, ketamine increases heart rate and blood pressure via centrally mediated adrenergic response; and, while this may be useful in trauma or shock situations, the parasympathetic and sympathetic responses to ECT result in transient hypotension and bradycardia followed by hypertension and tachycardia. Ketamine anesthesia is, thus, associated with temporary increases in pulse rate and blood pressure (BP), with a median systolic and diastolic peak increase of 20%–25% from baseline. (2) Studies have reported a significant QTc interval prolongation (up to 20.7 ms) and an increase in mean arterial BP (range of 9.8–22.5 mmHg).[8,10,12,13,19,21] This may be clinically significant, considering that many psychotropics (antidepressants, antipsychotics, lithium) prolong QTc interval.

Table 3 iv Ketamine in a non-ECT setting

Study	Research objective	Participants	Methods/ intervention	Outcome assessment/ analysis	Results	Level of evidence
Kudoh et al[22] (2002)	Effect of ketamine anesthesia on postoperative outcomes following orthopedic surgery.	Adults (n=70) with MDD (Groups A and B on antidepressants for ≥1 year). Controls (n=25) without depression (Group C). All patients had orthopedic surgery. Baseline HDRS according to treatment group: (A) 12.7±5.4; (B) 12.3±6.0; (C) 4.2±1.7.	RCT: Groups A and C received 1.0 mg/kg of iv ketamine, 1.5 mg/kg iv propofol, and 2 mcg/kg iv fentanyl. Group B received 1.5 mg/kg iv propofol and 2 mcg/kg iv fentanyl.	HDRS score: 1 day before, and 1 and 3 days after surgery.	Depressive and pain symptoms decreased significantly in Group A vs B (HDRS=9.9±4.1 and 14.4±3.8; $P<0.001$).	3
Lenze et al[23] (2016)	Efficacy and safety of the prolonged (96 h) ketamine infusion vs single iv dose of ketamine, with co-administration of clonidine.	Adults (n=20) with TRD, and MADRS≥22 (patients with BD, lifetime psychotic disorder, and medical instability excluded). Baseline MADRS according to treatment group: (1) 31.9±5.9; (2) 34.0±3.8.	DB RCT: clonidine 0.1 mg po BID× 7 days prior to infusion, then 0.2 mg po BID×1 day, 0.3 mg po BID thereafter, and either: (1) ketamine 0.15 mg/kg/h iv×96 h with increases as tolerated BID until a target rate of 0.6 mg/kg/h; or (2) NS iv×95 h and then ketamine 0.5 mg/kg iv×40 min.	BPRS, clinical and adverse events checklist, MADRS, CGI-I.	Average rate of ketamine administration=0.52 mg/kg/h. No difference between arms in MADRS changes. BPRS score remained significantly higher for most of the infusion in prolonged treatment group. Significant relationship demonstrated between ketamine concentration and sustained response at 8 weeks in the prolonged treatment group. Spearman correlation coefficient between S-ketamine concentration and MADRS change from baseline: 0.75 for 96-hour arm and 0.17 for 40-minute arm; $p<0.05$.	3
Li et al[24] (2016)	Effects of ketamine on TRD.	Adults (n=48) with TRD (patients with major medical or neurological illnesses or SUD excluded). Baseline MADRS according to treatment group: (1) 22.6±5.8; (2) 20.9±5.6; (3) 22.8±3.9.	DB RCT: (1) ketamine 0.5 mg/kg iv; (2) ketamine 0.2 mg/kg iv; or (3) normal saline.	HDRS-17 and BPRS at baseline, 40, 80, 120, and 240 min.	Non-statistically significant HDRS-17 reduction in ketamine groups vs PBO at 240 min: (1) −37.8%, (2) −38.2%, (3) −26.7% ($P=0.537$).	3

Abbreviations: iv, intravenous; ECT, electroconvulsive therapy; MDD, major depressive disorder; HDRS, Hamilton Depression Rating Scale; RCT, randomized controlled trial; TRD, treatment resistant depression; MADRS, Montgomery-Asberg Depression Rating Scale; BD, bipolar depression; SUD, substance use disorder; DB, double-blind; po, per os; NS, normal saline; BPRS, Brief Psychiatric Rating Scale; CGI-I, Clinical Global Impression-Improvement; PBO, placebo.

Table 4 Ketamine with adjunctive agents in non-ECT setting

Study	Research objective	Participants	Methods/ intervention	Outcome assessment/ analysis	Results	Level of evidence
Ibrahim et al[25] (2012)	Effect of a single iv dose of ketamine in TRD, and effect of riluzole on depressive symptoms.	Adult inpatients (n=42) with MDD without psychotic features, MADRS>22 (patients with history of substance/ antidepressant induced hypomania or mania excluded). Baseline MADRS according to treatment group: (1) 32.7±3.7; (2) 32.7±5.7.	DB, RCT: all patients received a single open-label infusion of 0.5 mg/kg ketamine. At 4–6 h post-infusion, patients randomized to receive: (1) riluzole 100–200 mg po daily or (2) PBO for 4 weeks.	MADRS; HAM-D, BDI, VAS-depression, HAM-A, BPRS-positive symptoms, CADSS, YMRS, and SSI. Subjects were rated 60 min prior to infusion, at 40, 80, 120, and 230 min post-infusion, and then daily for the next 28 days.	No significant differences in all rating scales between riluzole and placebo groups.	3
Mathew et al[26] (2010)	Effect of riluzole in preventing post-ketamine relapse; and effect of pre-treatment with lamotrigine on ketamine's psychotomimetic adverse effects and antidepressant efficacy.	Adults (n=26) with TRD (IDS-C$_{30}$>32). Baseline MADRS=36.9±5.4; QIDS-SR$_{16}$=18.6±3.9; CGI-I=5.3±0.8.	RCT: two hours prior to iv ketamine, patients received lamotrigine 300 mg po or PBO po. Bolus ketamine 0.5 mg/kg iv infusion was administered 2 h later. Responders were randomized to: (1) riluzole 100–200 mg po daily or; (2) PBO for up to 32 days.	Efficacy: MADRS and QIDS-SR$_{16}$; CGI-I rating was used to guide riluzole dose adjustment.	Average improvement of 60%±32% (P<0.001) in MADRS at 24 h; average improvement of 62%±28% in QIDS-SR$_{16}$ (P<0.001). Lamotrigine and placebo pre-treatment groups did not significantly differ in any efficacy measure at the 24-, 48-, or 72-h rating. Riluzole did not protect against post-ketamine relapse in the first month. Lamotrigine did not attenuate psychotomimetic adverse effects, or improve antidepressant response.	3
Hu et al[27] (2016)	Effect of single-dose iv ketamine on escitalopram in MDD.	Adults (n=30) with severe MDD (HDRS-17≥24). Mean total MADRS=34.3±7.3; QIDS-SR=17.1±4.6.	DB RCT: (1) escitalopram 10 mg po daily and single dose of ketamine 0.5 mg/kg iv (EK); or (2) escitalopram 10 mg po daily and single dose of NS iv (E).	MADRS, QIDS-SR, BPRS, YMRS, CADSS at baseline, 1, 2, 4, 24, and 72 h, and 7, 14, 21, and 28 days.	At 4 weeks, EK group had a significantly higher response rate (≥50% in MADRS score reduction) (92.3% vs 57.1%; P=0.04), remission rate (MADRS score≤10) (76.9% vs 14.3%; P=0.001), shorter time to response (HR=0.04 95% CI=0.01–0.22, P<0.001) and remission (HR=0.11, 95% CI=0.02–0.63, P=0.01). YMRS scores increased significantly with ketamine augmentation at 1 (0.4±0.7; P=0.01) and 2 h (0.4±0.7; P=0.02).	3

Abbreviations: ECT, electroconvulsive therapy; iv, intravenous; TRD, treatment resistant depression; MDD, major depressive disorder; MADRS, Montgomery-Asberg Depression Rating Scale; DB, double-blind; RCT, randomized controlled trial; PBO, placebo; HAM-D, Hamilton Depression Rating Scale; BDI, Beck Depression Inventory; HAM-A, Hamilton Anxiety Scale; BPRS, Brief Psychiatric Rating Scale; CADSS, Clinician Administered Dissociative States Scale; YMRS, Young Mania Rating Scale; SSI, Scale for Suicidal Ideation; IDS, Inventory of Depressive Symptomatology; QIDS-SR, Quick Inventory of Depressive Symptomatology-Self Report; CGI-I, Clinical Global Impression-Improvement; po, per os; NS, normal saline; HDRS, Hamilton Depression Rating Scale.

Table 5 Oral ketamine

Study	Research objective	Participants	Methods/intervention	Outcome assessment/analysis	Results	Level of evidence
Jafarinia et al[28] (2016)	Effect of ketamine po vs diclofenac monotherapy on depressive symptoms in patients with chronic pain.	Adults (n=40) with chronic, persistent mild-to-moderate headache≥6 months, MDD with HDRS<19. (Patients with any antidepressant or ECT treatment in past 2 months, other mental disorders, substance dependence, severe depression, suicidal ideation excluded). Baseline scores according to treatment group: HDRS (1) 15±2.36; (2) 14.95±2.72. HADS (1) 9.05±1.60; (2) 9.45±1.47.	DB RCT: (1) ketamine 50 mg po TID; or (2) diclofenac 50 mg po TID for 6 weeks.	HDRS and HADS at baseline, week 3, and week 6.	Difference in HDRS scores not significant at week 3, significant at week 6 (reduction of (1) 6.95±3.86 and (2) 4.10±3.34; mean difference=2.85, 95% CI 0.54–5.16, P=0.017). Significant improvement in difference in HADS score at week 3 (decreased by: (1) 2.10±0.72 and (2) 1.05±1.10; mean difference=1.05, 95% CI 0.45–1.64, P=0.001) and week 6 (decreased by: (1) 2.85±1.04 and (2) 2.10±0.72; mean difference=0.75, 95% CI 0.18–1.32, P=0.012).	3

Abbreviations: po, per os; MDD, major depressive disorder; HDRS, Hamilton Depression Rating Scale; ECT, electroconvulsive therapy; HADS, Hospital Anxiety and Depression Scale; DB, double-blind; RCT, randomized controlled trial.

While ketamine preserves airway reflexes and spontaneous respirations versus other agents such as methohexital or propofol, because muscle relaxants (paralytics) must be used in ECT, ventilation still needs to be supported. Hypersalivation may be a problem, especially in patients without a secured airway. Increased muscle tone can occur and may manifest as tonic-clonic movements. Ketamine induces theta activity and suppresses alpha activity; an EEG study of 14 patients did not show any seizure activity, but epileptiform attacks have been reported.[2] Increased confusion, restlessness, headaches, fear, and derealization have also been observed as adverse effects of ketamine use in anesthesia.[7,13,14,19] Hallucinations or delusions were rarely observed.[7,11,19]

The S-ketamine enantiomer (esketamine) has a threefold to fourfold greater affinity for NMDA receptors than the R-ketamine enantiomer (arketamine), and has been associated with post-treatment disorientation and restlessness.[7] It has been reported that arketamine, compared to esketamine or racemic ketamine, may have a lower rate of adverse effects related to NMDA inhibition such as dissociation, dizziness, sensory, and perceptual deficits.[31] Additionally, rates of both cardiovascular and psychotomimetic effects appear to be lower if ketamine is used in combination with propofol, when compared to ketamine as a sole agent.[8,9]

The US Food and Drug Administration (FDA) has very recently issued new warnings about the safety of general anesthetic and sedative (benzodiazepine) drugs, based on animal studies showing prolonged exposure causes widespread loss of nerve cells in the developing brain.[32]

Clinical predictors of response to ketamine

One study has demonstrated ketamine's antidepressant effects to be more pronounced in individuals with TRD who had a family history of alcohol dependence in a first-degree relative.[33] Other clinical predictors of response to ketamine are summarized in Table 7.[34–36] A pooled analysis of National Institute of Mental Health (NIMH) data reported that this factor accounted for 22% variance in percent change of HDRS scores, and was the strongest single clinical predictor of response to ketamine.[33] This observation was further supported by a study conducted by Niciu et al,[34] where a single dose of iv ketamine (0.5 mg/kg) was administered followed by a flexible dose of riluzole (100–200 mg daily) or PBO for 4 weeks. Family history-positive patients had an extended delay in time-to-relapse by an average of 13.4 days. However, personal history of alcohol dependence did not predict

Table 6 Intranasal ketamine

Study	Research objective	Participants	Methods/ intervention	Outcome assessment/ analysis	Results	Level of evidence
Daly et al[29] (2016)	Effect of intranasal esketamine in patients with TRD.	Medically stable adults (n=67) with TRD, without psychotic features. IDS-C_{30} ≥34 (patients with BD, ID, Cluster B PD, psychotic disorder, PTSD, OCD, suicidality; history of non-response to esketamine, ketamine or ECT excluded). Baseline MADRS according to treatment group: (1) 35.0±5.2; (2) 31.3±3.8; (3) 33.2±6.3; (4) 35.0±4.2.	DB, MC, RCT. DB phase, randomized to receive: (1) intranasal PBO, (2) intranasal esketamine 28 mg; (3) intranasal esketamine 54 mg; or (4) intranasal esketamine 84 mg on days 1, 4, 11, and 16. OL phase, started with intranasal esketamine 56 mg every 3 days, with dose decrease or increase thereafter.	MADRS at BL, at the end of DB and OL endpoints. TEAEs, CADSS pre-dose, at 40 min and 2 h post dose.	All three esketamine doses superior to PL in DB phase, mean MADRS reduction compared to PBO: (2) 4.2±2.09, P=0.021; (3) 6.3±2.07, P=0.001; (4) 9.0±2.13, P<0.001. At the end OL phase (74 days), 64.7% of patients were responders (decrease in MADRS total score≥50%), 32.4% of patients met remission criteria (MADRS total score≤10).	3
Canuso et al[30] (2015)	Effect of intranasal esketamine and standard of care against intranasal PBO in MDD with suicidal symptoms.	Adults (n=68) with MDD and current suicidal ideation with intent, at imminent risk of suicide; MADRS≥22 pre-dose (patients with BPD, ID, antisocial, histrionic, and borderline PD, psychotic symptoms, OCD, or SUD excluded). Baseline MADRS according to treatment group: (1) 38.5±6.17; (2) 38.8±7.02.	DB, MC, RCT: (1) intranasal esketamine 84 mg; or (2) intranasal PBO administered twice weekly for 4 weeks (DB phase, days 1–25). Follow-up phase, weekly visits until day 53, then once every 2 weeks through day 81.	Efficacy: MADRS and CGJ-SR 4 h post-dose, day 2 and day 25. Safety: TEAEs, vital signs, and CADSS total score.	Esketamine treatment superior to PBO with significantly greater change from BL in MADRS at day 1 (mean difference=5.3±2.10, P=0.015) and day 2 (mean difference=7.2±2.85, P=0.015). Difference at day 25 was not significant (P=0.159). No statistically significant differences were observed in CGJ-SR.	3

Abbreviations: TRD, treatment resistant depression; IDS, Inventory of Depressive Symptomatology; BD, bipolar depression; ID, intellectual disability; PD, personality disorder; PTSD, post-traumatic stress disorder; OCD, obsessive compulsive disorder; ECT, electroconvulsive therapy; MADRS, Montgomery-Asberg Depression Rating Scale; DB, double-blind; MC, multi-center; RCT, randomized controlled trial; PBO, placebo; OL, open-label; BL, baseline; TEAE, treatment-emergent adverse event; CADSS, Clinician Administered Dissociative States Scale; PL, placebo; MDD, major depressive disorder; BPD, bipolar disorder; SUD, substance use disorder; CGJ-SR, Clinical Global Judgment of Suicide Risk.

Table 7 Clinical predictors of response to ketamine

Study	Research objective	Participants	Methods/intervention	Outcome assessment/analysis	Results	Level of evidence
Niciu et al[34] (2014)	Effect of a single ketamine infusion in subjects with FHP of an AUD in a 1st degree relative.	Adult patients (n=52) with a diagnosis of TRD without psychotic features; MADRS score of >22. Baseline rating scale scores: MADRS, FHP 31.4±4.6; FHN 34.1±4.7. HDRS, FHP 19.4±4.1; FHN 21.7±4.0.	RCT: all patients received a single 0.5 mg/kg ketamine infusion; 4–6 h later subjects were randomized to: (1) riluzole 100–200 mg po daily or (2) PBO twice daily for 4 weeks. Patients then divided to: FHP riluzole, FHP placebo, FHN riluzole, FHN placebo groups.	MADRS (daily), HDRS-17, BDI, SSI, YMRS.	FHP subjects had less depression when randomized to PBO ($F_{(1,50)}$=9.69, P=0.003), but not to riluzole ($F_{(1,48)}$=0.003, P=0.95).	3
Ionescu et al[35] (2014)	Effect of anxious depression on ketamine response.	Adults (n=26) from Ibrahim et al[25] study randomized to PBO; divided into anxious depression (baseline HDRS 22.5±4.9; MADRS 33.8±6.1) and non-anxious depression (baseline HDRS 19.6±2.8; MADRS 32.7±5.1).	As per Ibrahim et al.[25]	MADRS and HDRS daily; HDRS, anxiety/somatization factor score.	Patients with anxious depression had significantly lower scores on depression rating scales, and longer time to relapse. All significant time points had at least moderate differences (d>0.51). Similar analysis with the HDRS showed a significant main effect of group ($F_{(1,23)}$=6.80, P=0.02), but no significant interaction between group and time ($F_{(31,560)}$=1.39, P=0.08).	3
Murrough et al[36] (2015)	Effect of ketamine on cognition 7 days post-treatment, and baseline neurocognitive predictors of the antidepressant response to ketamine.	Adult inpatients (n=62) with recurrent TRD; current episode length of ≥2 years; score of ≥32 on IDS-C$_{30}$; and no other psychotropic medications. Baseline MADRS according to treatment group: (1) 32.5±6.0; (2) 31.0±5.1.	DB, RCT: (1) single iv infusion of ketamine at 0.5 mg/kg or (2) midazolam at 0.045 mg/kg.	MADRS at 48 and 72 h and 7 days post-infusion. Neurocognitive battery at baseline and at 7 days post-treatment.	Ketamine responders had significantly slower processing speed at baseline compared with ketamine non-responders ($F_{(1,45)}$=4.36, P=0.043).	3

Abbreviations: FHP, family history positive; AUD, alcohol use disorder; TRD, treatment resistant depression; MADRS, Montgomery-Asberg Depression Rating Scale; FHN, family history negative; HDRS, Hamilton Depression Rating Scale; RCT, randomized controlled trial; PBO, placebo; BDI, Beck Depression Inventory; SSI, Scale for Suicidal Ideation; YMRS, Young Mania Rating Scale; IDS, Inventory of Depressive Symptomatology; DB, double-blind; iv, intravenous.

response to ketamine. Mathew et al[26] found that responders to ketamine alone, or ketamine along with riluzole were, on average, 52.4 years old, whereas non-responders were 40.3 years old (*P*=0.01). A post hoc analysis of an RCT by Ionescu et al[35] showed that ketamine demonstrated greater efficacy in anxious TRD than in non-anxious TRD; the former group also remained in remission for longer. Finally, in terms of cognitive factors, patients with slower processing speed at baseline may have a better response to ketamine at 24 h post-infusion, as demonstrated by Murrough et al.[36]

Discussion

In an ECT setting, ketamine may accelerate initial response when used alone or in combination with non-barbiturate agents such as propofol, and at doses of equal to or higher than 0.8 mg/kg. Stronger conclusions around dose-related efficacy in the ECT setting would require further research with more rigorous trials, as well as a meta-analysis to account for the significant heterogeneity of the studies included. While most studies using doses equal to or higher than 0.8 mg/kg did demonstrate a significant reduction in depressive symptoms, this finding was not consistent among all studies, and limited our ability to draw a conclusion around this specific objective (Table 2). Propofol does appear to mitigate some of ketamine's adverse effects, including cardiotoxicity, psychotomimetic effects, vomiting, and recovery agitation, without reducing efficacy.[8,9] Ketamine, in turn, mitigates propofol-induced hypotension.[9] When combined with barbiturates such as thiopental, ketamine has not been shown to be effective in reducing depressive symptoms, likely due to the effects of barbiturates in attenuating seizures as a result of their anticonvulsant properties.[7,11,15,16] Ketamine may have a role as an adjunctive agent to a non-barbiturate anesthetic, or as a sole anesthetic to accelerate response in the severely ill and those at risk of suicide. While iv ketamine remains the main route of administration, a few studies have demonstrated promising results in non-ECT settings when using alternate routes, notably intranasal.[29,30]

Safety concerns in the setting of ECT include higher rates of hypertension, QTc interval prolongation, transient arrhythmias, confusion, or fear, with hallucinations upon awakening from anesthesia.[7–9,12,16,23,25] The rates of these effects appear to have a positive correlation with an increasing dose of ketamine, notably in the 0.8–2.0 mg/kg dosing range.[8,9,12,16,23,25] Ketamine use in patients with cardiovascular disease should be considered with caution, especially when used in an ECT setting. Ketamine should also be considered with caution in patients with a history of psychotic episodes, due to its potential psychotomimetic effects. Concomitant use of propofol may be considered to mitigate some of these adverse effects.[8] However, this does add to complexity and cost. It is important to note that most of these adverse effects are transient in nature, and subside shortly after completion of an ECT session.[7,15,18] Therefore, an individual risk–benefit analysis should be considered.

One of the biggest challenges in using ketamine for treatment of MDD appears to be the maintenance of response to ketamine.[23,25,26] There are concerns regarding the use of ketamine as a maintenance treatment, including: (1) lack of evidence supporting such use; (2) lack of long-term safety data; and (3) logistical difficulties associated with administration in an outpatient setting. Riluzole has thus far not shown a statistically significant difference over PBO in maintenance of the response induced by ketamine.[25,26] Although riluzole shows theoretical promise, larger and more rigorous RCTs will have to be carried out to investigate the hypothesis. Hu et al[27] demonstrated that a combination of ketamine with escitalopram was more efficacious in achieving and sustaining response and remission than escitalopram alone. This observation suggests that patients should be maintained on existing oral antidepressant therapy during and after receiving ketamine treatment. Lenze et al[23] found that prolonged ketamine infusion (96 h) may offer a more sustained antidepressant response. Safety concerns regarding such a prolonged infusion may be greater than with the standard total of six 40-min infusions, particularly given recent animal data demonstrating neurotoxicity with chronic sub-anesthetic iv doses of ketamine.[37] A study by Daly et al[29] demonstrated that administration of intranasal esketamine for up to 74 days may be an option to maintain response and remission. Self-administration of esketamine presents another concern in terms of risk for abuse. Ketamine remains a restricted drug in most jurisdictions. Tolerance, dependence, and withdrawal have been reported with long-term use.[2]

The studies investigating the clinical predictors of ketamine's efficacy in TRD are indeed interesting.[33] The evidence to date suggests that ketamine may potentially be more beneficial for patients with a history of a first-degree relative with alcohol dependence, patients suffering from anxious depression, patients with slower processing speed at baseline, patients suffering from depression and undergoing a surgery, and patients who are around 50 years of age.[26,34–36] It is important to note that, currently, such evidence may only be interpreted as signals, and further research is needed to better understand the clinical predictors of ketamine's efficacy in TRD.

Limitations

There are a few limitations to this literature review. A full meta-analysis was not performed, and only published English

language studies were included. The average level of evidence was 3; many studies were at high risk for bias, given the lack of blinding, and the majority had less than 50 participants. Small samples are underpowered to conclude a meaningful difference between treatment groups. Additionally, the populations included in these studies were heterogeneous and included patients with differing durations of illness and on different antidepressant treatments. Ketamine has been principally investigated in patients with chronic and severe depression who may have altered neurobiology and pharmacological responses, when compared to patients who are relatively early into their illness.[38,39] Therefore, the results cannot be generalized to all patients suffering from MDD, and it is important to recognize that even small changes in depressive symptoms may be more meaningful or accepted in a population of patients with very treatment-resistant depression. Studies also differed in ECT administration techniques and depression rating scales used. There are only limited data regarding validity of depression rating scales used more frequently than weekly, whereas changes in ketamine response may occur on an hourly to daily basis.[26] Some studies have also used PBO controls, but ketamine's psychotomimetic effects render full blinding difficult.[23,24,29,30] The majority of the studies allowed concomitant medications, which increases inter-patient variability, and exacerbates potential risk for specific interactions with ketamine. Finally, only short-term effects of ketamine have been explored, thus leaving the question of long-term safety unanswered. This is particularly relevant given the recent class warning for anesthetic and sedative agents.

Conclusion

Ketamine warrants consideration as an agent for use in an ECT setting and may accelerate response. However, the evidence is mixed, the effect is modest at best, and many questions regarding optimal dosing strategies remain unanswered. The long-term safety of ketamine is still unknown, and there are recent class concerns with respect to the use of most anesthetic agents. Ketamine may be more efficacious in patients with certain clinical predictors, but requires further investigation to confirm the same. It should be used with caution or avoided in certain patients with additional risk factors for cardiovascular or psychotomimetic adverse effects.

Additional rigorous, well-controlled, randomized, double-blinded studies are needed that would further explore different dosing strategies and routes of administration for ketamine in ECT and non-ECT settings, in order to address risks and benefits.

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