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Review article

Is ketamine an appropriate alternative to ECT for patients with treatment resistant depression? A systematic review

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ABSTRACT

Objective: Ketamine has repeatedly shown to have rapid and robust antidepressant effects in patients with treatment resistant depression (TRD). An important question is whether ketamine is as effective and safe as the current gold standard electroconvulsive therapy (ECT).
Methods: The literature was searched for trials comparing ketamine treatment with ECT for depression in the Pubmed/MEDLINE database and Cochrane Trials Library.
Results: A total of 137 manuscripts were identified, 6 articles were included in this review. Overall quality of the included studies was diverse with relevant risk of bias for some of the studies. Results suggest that ketamine treatment might give faster but perhaps less durable antidepressant effects. Side effects differed from ECT, in particular less cognitive impairment was apparent in ketamine treatment.
Limitations: The included studies have limited sample sizes, use different treatment protocols and in most trials, longer term follow up is lacking. Furthermore, allocation bias appears likely in the non-randomized trials.
Conclusions: Current available literature does not yet provide convincing evidence to consider ketamine as an equally effective treatment alternative to ECT in patients with TRD. There are indications for a more favourable short term cognitive side effect profile after ketamine treatment. Methodologically well-designed studies with larger sample sizes and longer follow up duration are warranted.

1. Introduction

Major depressive disorder (MDD) is a highly prevalent disorder accounting for a large proportion of disability worldwide. Unfortunately more than 30% of patients do not achieve remission after four trials of antidepressants (Gaynes et al., 2008). Treatment resistant depression (TRD) is associated with more somatic comorbidity, substance abuse and excess mortality, including through suicide (Mrazek et al., 2014; Nemeroff, 2007). Still, professional guidelines state electroconvulsive therapy (ECT) as the gold standard treatment for TRD, due to its proven high efficacy (Haq et al., 2015). ECT however entails certain disadvantages, the public attitude is not unreservedly positive and availability varies across regions, which may explain the relatively low application rate (Sackeim, 2017; Wilkinson et al., 2018). Furthermore, the procedure requires repeated anesthesia and there is a risk of serious cognitive problems. Fear of adverse cognitive effects is common among patients, and those with post-ECT memory impairment experience this as highly distressing (Verwijk et al., 2017). Sadly, TRD patients often relapse and require additional rounds of ECT sessions (Sackeim et al., 2001). In TRD treatment, there is a need for treatments at least equally effective to ECT with more acceptable side effect profiles and better capabilities for long-term relapse prevention.

The N-methyl-D-aspartate (NMDA) receptor antagonist ketamine has been in the center of attention in depression research for the past decades. Ketamine has repeatedly shown rapid and robust antidepressant effects in patients with MDD (Han et al., 2016; Kishimoto et al., 2016). Even in severe TRD patients, ketamine exerts positive effects (Ruberto et al., 2020). Side effects are generally mild and self-limiting (Short et al., 2018).

An important question is whether ketamine may serve as an effective

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and acceptable alternative to ECT for TRD patients. If so, this gives directories on where ketamine should end up in stepwise depression treatment algorithms. Therefore, the aim of this systematic review is to describe emerging literature on the direct comparison between ketamine treatment and ECT for TRD.

2. Methods

This review was conducted and reported according to the Preferred Reporting Items for Systematic Meta-Analyses (PRISMA) guidelines (Moher, 2009). A literature search in the Pubmed/MEDLINE database and Cochrane Trials Library was conducted on September 21st, 2020 with the keywords *ketamine* AND (*ECT* OR *electroconvulsive therapy*) AND (*compare* OR *comparison* OR *comparative*). No restrictions were set. Two investigators (JV and SS) independently reviewed the titles of the retrieved publications to select eligible studies. The bibliographies of relevant studies were manually searched to identify additional relevant reports. According to the Participants, Intervention, Comparison, Outcomes and Study design (PICOS) strategy, inclusion criteria were as following. Participants: patients with MDD. Intervention vs. Comparison: ketamine in any form (racemic, S-ketamine or R-ketamine), at any dose and frequency and in any route of administration vs. ECT. Outcomes: severity of depressive symptoms at post-ketamine or ECT treatment time points, assessed with standardized rating scales (e.g. Hamilton Depression Rating Scale (HDRS) or Montgomery Åsberg Depression Rating Scale (MADRS)). Secondary outcomes included assessments of depressive symptom severity at other time points (during treatment and at follow up), response and remission rates, cognitive assessment, tolerability and side effects. Study design: randomized controlled trials, controlled clinical trials, open label trials. Data extraction was performed by two investigators (JV and SS) independently. The following information was retrieved: characteristics of the study design, population, interventions and outcome measures. The corresponding authors of included studies were contacted to obtain additional information if relevant. The methodological quality of the included studies was independently assessed by two investigators (JV and SS) according to the Risk of Bias version 2 tool (RoB 2) (Sterne et al., 2019) and Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I tool) (Sterne et al., 2016). Furthermore, clinicaltrials.gov was searched for on-going studies.

3. Results

A total of 137 articles were identified, of which 129 were excluded because the article did not report on a clinical trial (n = 8) or no comparison between ketamine treatment and ECT was performed (n = 121). An additional two articles (Campion, 2015; Kellner et al., 2015) were excluded after full text assessment for the same reasons. A flowchart of the screening process is shown in Fig. 1.

Six articles reported on a trial comparing ketamine treatment with ECT and were included in the review. Among them are three single blind, randomized controlled trials that used blind raters to assess antidepressant efficacy (Ghasemi et al., 2014; Kheirabadi et al., 2019; Sharma et al., 2020). The other three articles describe the results of naturalistic open label studies (Allen et al., 2015; Basso et al., 2020; Loureiro et al., 2020). A detailed description of the included studies including the ECT procedures can be found in Table 1. Outcomes of the methodological quality evaluation can be found in Tables 2 and 3. Furthermore, searching clinicaltrials.gov yielded three on-going trials. Publications of the study protocol of two of these trials were identified with the systematic search (Mathew et al., 2019; Phillips et al., 2020).

Ghasemi et al. (2014) performed a single blind, randomized study in 18 patients with MDD and ECT indication, comparing three IV ketamine infusions of 0.5 mg/kg with brief pulse (BP) bilateral (BL) ECT on three

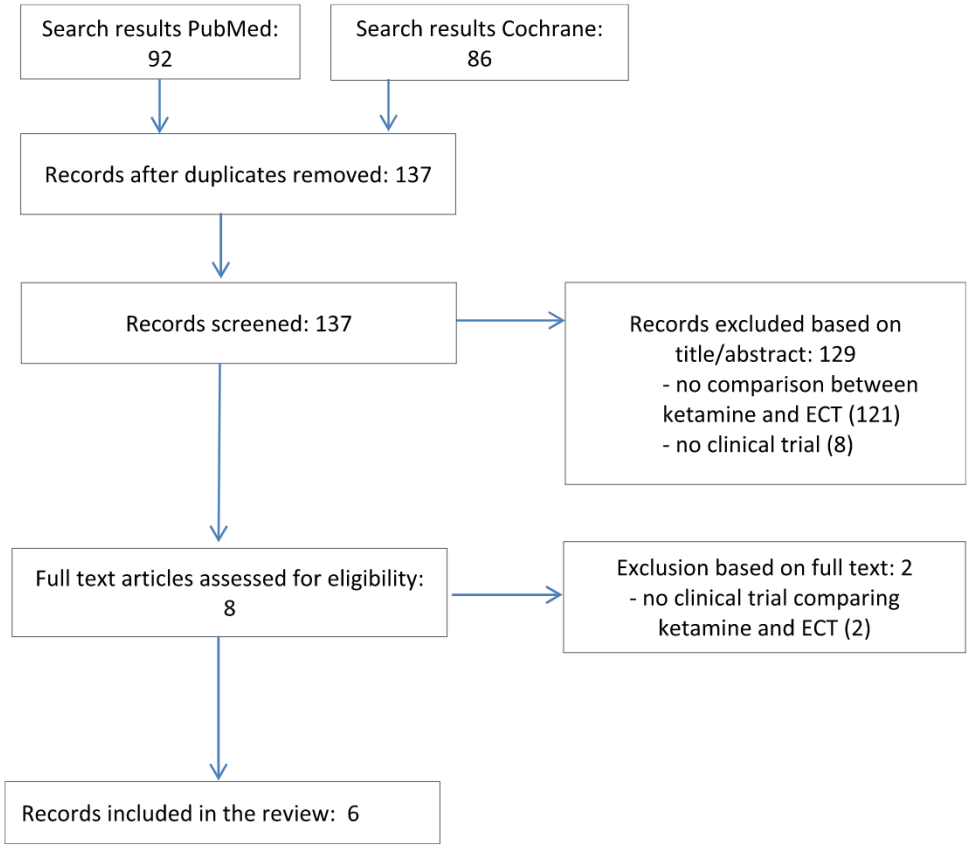

Fig. 1. PRISMA flowchart

Table 1
Included articles reporting on the comparison between ketamine treatment and ECT.

Study	Design	N	Subjects	Ketamine	ECT	Antidepressant effects	Other outcomes
Ghasemi et al. 2013	Blind, RCT	18	DSM-IV MDD without psychotic featuresECT candidates	Ketamine 0.5mg/kg IV (n=9)Three infusions every 48h	BP (1.0 ms) BL ECT with Thymatron DGx (n=9)Three sessions every 48h.Dose titration starting at 25.2 mC. Following sessions with electrical dose of 2.5 times ST. Electrical dose increased by 50% if seizure duration (not recorded by EEG) was less than 15s. Premedication: 0.5 mg atropine. Anaesthesia: thiopental 2-3 mg/kg and succinylcholine 0.5 mg/kg.	Ketamine vs. ECT after correction:HDRS scores: F5.80 = 4.80, p < 0.02.BDI scores: F5.80 = 2.74, p < 0.075.Post hoc analyses: Mean (SD) HDRS scores ketamine vs. ECT:- 1st treatment: 16.88 (6.58) vs. 31.44 (7.26), p = 0.000- 2nd treatment: 15.55 (6.54) vs. 24.55 (4.64), p = 0.004- 3rd treatment: 13.77 (6.98) vs. 19.44 (5.25), p = 0.074- 72h post-treatment: 10.11 (5.01) vs. 16.77 (4.81), p = 0.011- 1wk post-treatment: 9.55 (4.98) vs. 14 (4.9), p = 0.074Ketamine vs. ECT response rate:1st treatment: 77.78% vs. 11.11%2nd treatment: 77.78 vs. 22.22% 3rd treatment: 88.89% vs. 66.67%72h post-treatment: 100% vs. 88.89%1wk post-treatment: 100% vs. 88.89%	Safety: according to the authors both ketamine and ECT were well tolerated in all patients. No significant change in hemodynamic parameters.
Kheirabadi et al. 2019	Blind, RCT	32	MDDNo history of psychosisECT candidates	Ketamine 0.5mg/kg IV (n=16) Twice weekly up to complete remission	BL ECT with Thymatron DGx (n=16).Twice weekly up to complete remission.20–100% Of electric energy to induce generalized tonic–clonic seizures for at least 25s. Premedication: atropine 0.25 mg. Anaesthesia: thiopental 3 mg/kg, and succinylcholine 20 mg.	Mean HDRS scores (SD) ketamine (n=10) vs. ECT (n=12):-Baseline: 24.6 (2.4) vs. 26.1 (3.8), p = 0.3-At 1st session: 20.9 (2.4) vs. 24.5 (4.2), p = 0.6-At 2nd session: 19.1 (3.9) vs. 23.4 (4.4), p = 0.5-At 3rd session: 17.9 (3.1) vs. 21.9 (3.5), p = 0.8-At 4th session: 17.3 (3.3) vs. 19 (2.2), p = 0.4-At 5th session: 16.8 (4.4) vs. 16.6 (2.6), p = 0.3-At 6th session: 16.4 (4.1) vs. 14.7 (3.3), p = 0.6-1wk later: 16.9 (3.3) vs. 13.6 (3.1), p = 0.5-1 month later: 19.4 (1.5) vs. 12.9 (2.6), p = 0.3-2 months later: 21.1 (1.6) vs. 12.5 (2.9), p = 0.1-3 months later: 22.6 (1.8) vs. 13.9 (2.9), p = 0.4	Cognitive state was more favorable (not significant) in the ketamine group (p > 0.5). WMS ketamine vs. ECT:-Baseline 42.9 (8.2) vs. 50.3 (8.8), p = 0.8-1 wk later: 50.4 (8.4) vs. 47 (8.9), p = 0.5-1 month later: 49 (9.9) vs. 47.8 (9.5), p = 0.3Safety;Side effects ketamine group: dizziness (100%), headache (60%), blurry vision (60%), numbness of half body (60%), depersonalization (60%), vertigo (40%), diplopia (40%), nausea (30%), nystagmus (5%), increased respiration and heart rate (5%).Side effects ECT group: headache (100%), dizziness (92%), muscle pain (92%), nausea (75%), joint pain (50%), orientation disorder (33%), extended seizure (5%).
Sharma et al. 2020	Blind, RCT	26	Severe bipolar/unipolar depressionWith or without psychotic symptomsECT candidates	Ketamine 0.5mg/kg IV (n=12)Six alternate-day sessions	BP (1.5 ms) BF or RUL ECT with Niviqure (n=13) for 6 alternate-day sessions.ST titration. Following sessions with 1.5-2 times ST (n=9, BF ECT) or 6 times ST (n=4, RUL ECT). Anaesthesia: thiopental 2-4 mg/kg and succinylcholine 0.5-1 mg/kg.	Significant improvement on HDRS scores in both groups after treatment when compared to baseline (p < 0.001).In ECT group significantly faster and greater reduction in HDRS scores as compared to ketamine group (group*time interaction: F = 4.79; p < 0.001). Response ketamine vs. ECT:8/12 (66.67%) vs. 13/13 (100%) (p = 0.041) Remission ketamine vs ECT:6/12 (50%) vs. 12/13 (92.31%) (p = 0 .030)Faster response (log rank= 8.69, p < 0.01) and remission (log rank= 8.91, p < 0.01) with ECT compared to ketamine.	Cognition: significant improvement on the DSST variable of the B4ECTReCoDe compared to baseline (p = 0.017) in ketamine group, non-significant worsening in ECT group. No significant changes compared to baseline on the other variables in the ketamine and ECT groups. Safety: no variations in vital signs leading to any intervention.Ketamine group: transient dissociative symptoms (n = 5), drop out due to intolerable dissociative experience (n = 1). Mean CADSS score after each treatment was 2.4, 1.8, 3.6, 1.9, 1.8 respectively.ECT group: prolonged apnoea (n = 1), delayed motor recovery (n = 1).
Allen et al. 2015	Open label	35	DSM-IV recurrent unipolar MDD, TRD.	Ketamine 0.5mg/kg IV (n=18)Up	BP BL ECT with spECTrum 5000 M (MECTA Corporation; max. 1200mC) (n=17).Twice weekly,	Ketamine significantly reduced HDRS scores compared to baseline, F(2.3,	Response rate ketamine group: Infusion 1; after 2h: 76.5% Infusion 1; after 24h: 81.3%

(continued on next page)

Table 1 (*continued*)

			No family history of psychosis.	to 3 weekly infusions	5-12 sessions, median = 8.ST determined by a method of limits. Subsequent treatments at 1.5 times ST. Stimulus charge titrated upwards as required. Seizure durations documented by motor activity and EEG. Anaesthesia: methohexitone (0.75–1.0 mg/kg) and suxamethonium (0.5–1.0 mg/kg).	20.7) = 22.56, $p < 0.001$, partial eta squared = 0.72. HDRS scores significantly lower at all post-infusion time points compared to baseline ($p < 0.001$).Lower HDRS scores at T4 compared to T3 ($p = 0.01$). Lower HDRS scores at T6 compared to T5 ($p = 0.02$). ECT significantly reduced HDRS scores compared to baseline, t(17) = 4.15, p = 0.001, Cohen's d = 0.98.	Infusion 1; after 1 week: 46.7%Infusion 2; after 2h: 100%Infusion 2; after 1 week: 66.7%Infusion 3; after 2h: 90%Infusion 3: after 1 week: 60%Response rate after final ECT: 50%Safety: elevation of diastolic BP during infusion (n=1), unpleasant experience (n=2).
Basso et al. 2020	Open label	50	MDD, TRDNo history of psychosisECT candidates	Ketamine 0.5 mg/kg IV (n=25) Thrice weekly for 2 weeks. Mean number of infusions: 6.76 (SD = 1.23), range 6-9.	UBP (0.3 ms) RUL ECT with spECTrum 5000 Q (n=25). Thrice weekly for 4 weeks. Mean number of sessions 12.36 (SD = 1.75), range 9-16.ST titration. Voltage modified if patients showed no response or insufficient seizures (motor response < 20s or EEG < 30 s). Anaesthesia: propofol (approx.. 1.5 mg/ kg) or etomidate (approx. 0.75 mg/kg) and succinylcholine (approx. 0.75 mg/kg)	Mean MADRS (SD) scores ketamine vs. ECT:-T0: baseline: 26.40 (4.94) vs. 31.17 (7.28), p = 0.01-T1: after 3 infusions and 6 ECTs: 13.38 (5.27) vs. 19.52 (7.07)-T2: after 6 infusions and 12 ECTs: 13.40 (6.89) vs. 13.75 (7.69)Group * time interaction: F(1,43) = 6.93, p = .012, partial η2 = 0.139, n = 46, d = 0.80. MADRS scores reduced more from T0 to T1 with ketamine (M = −47.45%, SD = 23.43) than ECT (M = −34.86%, SD = 21.29). No significant difference in symptom reduction until T2 between groups (ECT: M = −55.70%, SD = 23.63, n = 22; ketamine: M = −49.88%, SD = 27.30, n = 24).	Cognitive assessment: differences in cognitive functioning with $p \leq .05$ were found in attention, verbal memory, and executive functions, with large effect sizes (all $d > 0.5$). No significant differences were found for immediate memory and visual memory.The difference regarding change on the composite score reflected a small effect (d = 0.40).
Loureiro et al. 2020	Open label	44	DSM-V MDD, moderate to severe depression, TRDNo current or past history of psychosis	Ketamine 0.5 mg/kg IV (n=27) Twice or thrice weekly for a total of four infusions.	UBP (0.3 ms) RUL ECT with spectrum 5000 Q (n = 17)48% switched to BL ECT (0.5 ms). Thrice weekly until maximal response or remission for at least a week. Mean number of sessions 14.ST titration.	Mean HDRS scores (SD) baseline vs. after treatment: Ketamine: 20.15 (4.70) 8.93 (4.46) T = 10.73, $p < 0.01$ECT: 21.41 (8.33) 15.35 (8.60) T = 3.07, $p < 0.01$	SHAPS scores significantly decreased after both ketamine and ECT ($p < 0.01$). DASS scores decreased significantly after ketamine only ($p < 0.01$).

BF bifrontal; BP brief pulse; DASS; Depression Anxiety Stress Scales; DSM-IV diagnostic and statistical manual of mental disorders fourth edition; DSST digit symbol substitution test; ECT electroconvulsive therapy; EEG electroencephalography; HDRS Hamilton Depression Rating Scale; M mean; MADRS Montgomery Asberg Depression Rating Scale; MDD major depressive disorder; N sample size; RCT randomized controlled trial; SHAPS Snaith-Hamilton Pleasure Scale; SD standard deviation; ST seizure threshold; TRD treatment resistant depression; UBP ultrabrief pulse; WMS Wechsler Memory Scale. Niviqure is an ECT device manufactured by Niviqure Meditech PVT. LTD., 311/2, 10th E Main Road, Jayanagar, 1 Block, Bangalore, India. spECTCrum 5000 M and 5000 Q are ECT devices manufactured by MECTA corporation 19799 SW 95th Ave Suite B, Tualatin, OR 97062, USA. Thymatron DGx is an ECT device manufactured by Somatics LLC, 910 Sherwood Terrace Ste 23, Lake Bluff, IL 60044, USA

Table 2
Risk of bias assessment of RCTs according to the Risk of Bias version 2 tool (RoB 2) (Sterne et al., 2019).

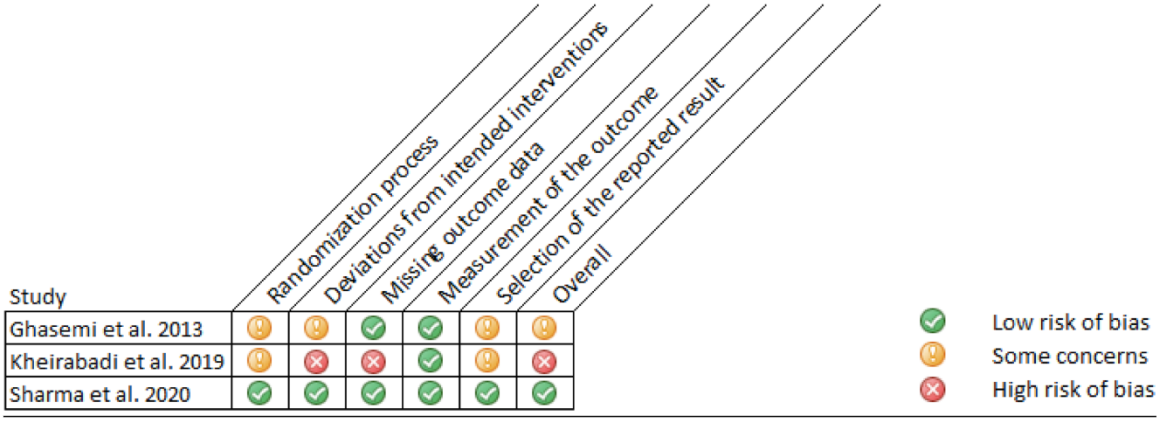

Table 3
Risk of bias assessment of non-RCTs according to the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I tool) (Sterne et al., 2016).

test days every 48 h. Authors did not describe treatment history and duration of current depressive episode of the included patients. Results showed that the mean Beck Depression Inventory (BDI) and Hamilton Depression Rating Scale-25 ($HDRS_{25}$) scores were significantly lower in patients receiving ketamine (n = 9) when compared to patients receiving ECT (n = 9) after the first and second treatment and after 72 h post-treatment. No significant differences between the groups were reported after the third treatment and at 1 week post-treatment. Mean scores and response rates can be found in Table 1. Both treatments were well tolerated in all patients and no clinically significant changes in hemodynamic parameters occurred. Limitations of this trial were the small number of patients, the short follow up duration and the fact that only three sessions of ECT were administered (with the first stimulus at the level of seizure threshold). ECT courses typically involve more than three sessions (6-12 treatments).

A second single blind, randomized trial was performed in 32 patients with MDD and ECT indication (Kheirabadi et al., 2019). Details on prior treatment steps and MDD duration were not provided. Sixteen patients received 0.5 mg/kg IV ketamine and 16 received BL ECT twice weekly up to complete remission of the depressive symptoms. Twelve patients in the ECT group and 10 patients in the ketamine group completed the trial and only the results of these patients were included in the analysis. Reasons for loss to follow-up were extended seizure duration (n = 1 in ECT group) and the patient's unwillingness to continue to participate (n = 3 in ECT and n = 6 in ketamine group). Patients in both groups improved, the mean HDRS score decreased with 8.2 points in the ketamine group and 11.4 points in the ECT group after five sessions.

Although not significantly different, ketamine users seemed to recover a bit faster (see Table 1 for scores) and there was a numerical benefit for ECT after 6 treatment sessions, with a mean decrease of 7.8 points on HDRS scores in the ECT group, compared to 4.5 points mean decrease in the ketamine group. The antidepressant effect in the ketamine group did not last; again, differences were not statistically significant, but the HDRS scores in the ketamine group gradually returned to baseline values within 3 months post treatment whereas the values in the ECT group after 3 months remained comparable to the first week post treatment. Differences in Wechsler Memory Scale (WMS) scores were also not statistically significant but the mean scores increased in the ketamine group whereas a decreasing pattern was found in the ECT group, which may be suggestive of a more favorable cognitive side effect profile for ketamine. Patients in the ketamine group suffered most often from dizziness, headache, blurred vision, and numbness to one side of the body and depersonalization, whereas the ECT group complained of muscle pain, joint pain and headache as well.

The study did not report how many ECT sessions were performed. It appears unlikely that all patients received only six sessions in total. It is therefore it unclear whether additional ECT sessions were performed prior to or around follow up time points. Further limitations of this study are the high drop-out rate without a dropout analysis and, as a result, groups with small sample sizes. Moreover, the authors stated that both the evaluator and the patients were blinded to the method of treatment, the latter appears unlikely considering the differences in treatment methods.

Another blind, randomized trial was published by Sharma et al. (2020). This trial compared the effects of right unilateral (RUL) or bifrontal (BF) ECT with 0.5 mg/kg IV ketamine infusion. Both interventions were applied in six alternate-day sessions in 26 patients with bipolar or unipolar depression, with or without psychotic symptoms. The patients had an average illness duration of 87.17 (ketamine group) and 85.23 (ECT group) months. Previous treatment with ECT was performed in 25.0% (ketamine group) and 38.5% (ECT group) of the patients. HDRS scores did not differ significantly between the two groups at baseline (ketamine group 23.33 vs. ECT group 25.15; p = 0.418). Compared to the ketamine group, patients in the ECT group showed greater reduction in the HDRS scores (group*time interaction: F = 4.79; p < 0.001) and achieved response (log rank = 8.69, p < 0.01) and remission (log rank = 8.91, p < 0.01) faster. Significant improvement in cognitive functions measured with the Battery for ECT Related Cognitive Deficits (B4ECT-ReCoDe) (Viswanath et al., 2013) was observed after ketamine treatment when compared to baseline (p = 0.017), whereas no significant difference was found in the ECT group. The study was performed in a small sample and 3 patients from the ketamine group dropped out because of dissociative effects (n = 1) and lack of efficacy (n = 2). In the ECT group, all patients showed response and 92.3% showed remission. These rates raise questions because they are remarkably higher than response and remission rates reported in currently available literature (Kellner et al., 2010; Sackeim et al., 2008). Another limitation of this trial was the use of two different ECT methods with RUL electrode placement in 4 patients and BF electrode placement in 9 patients, which might have influenced cognitive outcomes.

In the open label trial of Allen et al. (2015), 35 patients with unipolar TRD (failed to respond to at least two adequate trials of antidepressant medication) received up to 12 ECT sessions (n = 17) twice weekly or up to three 0.5 mg/kg IV ketamine infusions (n = 18) with a frequency of once a week. In the ECT group, patients received 5 – 12 sessions (median = 8). The majority of patients in the ketamine group received all 3 infusions (n = 10), 2 patients had 2 infusions and 5 patients only received 1 infusion. At all post-infusion time points (2h and 24h after each ketamine infusion and one week after the last infusion), mean HDRS scores were significantly lower when compared to baseline (in all cases p < 0.001). Mean HDRS scores post treatment in the ECT group were also significantly lower compared to baseline (p = 0.001). At 2h following the first ketamine infusion, a majority of patients (76.5%) reported response (50% or more reduction in HDRS score) and at 1 week post treatment, 60% reported response. Following the final ECT session, 50% of patients showed response. Seven patients discontinued ketamine sessions, reasons were elevation of diastolic blood pressure during infusion (n = 1), loss to follow-up (n = 1), unpleasant experience (n = 2) and work commitments (n = 1) after the first infusion and remission (n = 1) and lack of improvement (n = 1) after the second infusion. In the ECT group no patients discontinued. Limitations are that the study was not designed to compare the two treatments, but rather to investigate

the impact on serum brain-derived neurotrophic factor. In addition, the non-randomized, open label design is susceptible to selection bias. There is little information about patient selection and the baseline symptom severity was rather low compared to patients usually receiving ECT. Follow-up period was short. Furthermore, the 1 week interval between ketamine infusions may have negatively influenced antidepressant treatment potential and is an additional reason to interpret results cautiously.

Basso et al. (2020) treated 31 hospitalized patients with TRD (two or more insufficient antidepressant treatment trials in the current episode) with a 2-week series of ketamine infusions. Thirty-one age and gender matched patients who had received a 4-week course of ECT treatment were selected as matched controls. Patients who received three or less ketamine infusions (because of lack of efficacy (n = 3) or full remission (n = 1)) or more than 16 ECT sessions (n = 1) and patients with missing neurocognitive data (n = 1) were excluded, together with their matched control. This resulted in a final sample of 50 patients. At baseline, the patients treated with ketamine had significantly lower MADRS scores (M = 26.40, SD = 4.94) than those treated with ECT (M = 31.17, SD = 7.28) (p = 0.010) but their current episode was longer (in months: M = 30.30, SD = 22.24 vs. M = 15.05, SD = 11.20) (p = 0.009). The MADRS baseline scores were included as a covariate in the between-group analyses. At the mid treatment time point (six ECT sessions or three ketamine infusions), mean MADRS scores were more strongly reduced for patients treated with ketamine (M = -47.45%, SD = 23.43) than for those treated with ECT (M = -34.86%, SD = 21.29) ($p < 0.05$)). At the end of the treatment course, ketamine treatment was equally effective in symptom reduction compared to ECT (ECT: M = -55.70%, SD = 23.63; ketamine: M = - 49. 88%, SD = 27.30). Patients from the ketamine group showed significantly better neurocognitive test performance on the domains attention, verbal memory and executive function. Differences in the domains immediate memory and visual memory were not significant. The difference regarding change on the composite score had a small effect size (d = 0.40) favoring ketamine. Limitations of this study were the naturalistic design and lack of follow up assessments, and differences between the groups at baseline should be taken into account. Patients from the ketamine group were less severely depressed and none of them suffered from depression with psychotic symptoms, whereas 16% of the ECT group were diagnosed with depression with psychotic symptoms.

A third open label trial was performed by Loureiro et al. (2020) in 44 MDD patients receiving either ECT (N = 17) or IV ketamine 0.5 mg/kg (N = 27). Treatment sessions were 2-3 days apart with a total of 4 sessions in the ketamine group. ECT was continued until patients achieved maximal response or remission, the average number of sessions was 14. All patients started with RUL ECT, however 48% switched to BL ECT during the study. The patients had a moderate to severe depression for $\geq$ 6 months and failed $\geq$ 2 adequate antidepressant trials in the current depressive episode.

Mean HDRS scores decreased after both ECT (from 21.41 (SD 8.33) to 15.35 (SD 8.60), T = 3.07, $p < 0.01$) and ketamine treatment (from 20.15 (SD 4.70) to 8.93 (SD 4.46), T = 10.73, $p < 0.01$). No information on safety of the interventions was available. The study was designed to examine the neural underpinnings of emotion processing and did not directly compare antidepressant efficacy, side effects and tolerability of ketamine and ECT.

4. Discussion

Limited data is available on whether ketamine treatment may serve as a proper alternative to ECT in TRD treatment. Based on the few studies, no definite conclusions can be drawn. Results of the included studies do not point unanimously to one outcome. One of the three RCTs found significantly more improvement after ECT, whereas two RCTs found no significant differences between ECT and ketamine treatment. But, risk of bias evaluation raises concerns about the validity of the latter two studies. Several studies suggest that ketamine exerts a more rapid antidepressant effect than ECT (Basso et al., 2020; Ghasemi et al., 2014; Kheirabadi et al., 2019), but this was not found in the qualitatively best assessed RCT of Sharma et al. (2020), in which patients receiving ECT recovered more quickly. A faster antidepressant effect is potentially relevant since quick reduction of depressive symptoms can be essential for depressed patients. Future comparisons may untangle this question on differences in recovery speed between ECT and ketamine treatment and its clinical relevance.

Ketamine showed a more favorable neurocognitive side effect profile than ECT (Basso et al., 2020; Ghasemi et al., 2014; Kheirabadi et al., 2019). Of note, the only study (Kheirabadi et al., 2019) that included longer term follow up assessments reported less durability of ketamine's antidepressant effects when compared to ECT, but it was unclear if patients still received ECT around these follow up measurements whereas ketamine infusions had stopped. Maintaining the antidepressant effects of ketamine after treatment cessation is currently one of the most important challenges (Fourcade and Lapidus, 2016; Papakostas, 2020). However, this is not only a problem for ketamine treatment. Relapse rates within six months after ECT range from 39% (with continuation pharmacotherapy) to 84% (no continuation pharmacotherapy) (Sackeim et al., 2001). Strategies to maintain remission after ECT include use of an antidepressant as relapse prevention. This may also be highly relevant after ketamine treatment, although prolonged or even maintenance ketamine treatment has also been suggested for initial responders (Wajs et al., 2020). Studies on differences in treatment outcome between ECT and ketamine treatment after several months of follow up and further investigation in treatment strategies to prevent relapse is of utmost importance for clinical practice.

Currently available studies have considerable methodological limitations including small sample sizes and lack of longer term follow up assessments. Not only durability of antidepressant effects, but also potential long term side effects on cognition, urinary tract problems (Castellani, 2020) and risk of abuse (Bonnet, 2015) should be investigated. While the cognitive side effect profile of ketamine is more favorable than that of ECT during initial treatment, chronic usage of high ketamine doses can also result in memory impairment (Morgan et al., 2014). The need of prolonged maintenance treatment with ketamine could predispose patients to ketamine related bladder issues or addiction, a risk that should be taken into account in comparing ketamine treatment with ECT. Acute side effects during ketamine treatment that were reported include dizziness, headache, blurry vision, numbness of the body, depersonalization, vertigo, diplopia, and nausea. Furthermore, dissociative symptoms, elevation of blood pressure and an unpleasant experience were reasons for drop out. The impact of both acute and chronic adverse events resulting from ketamine treatment should be weighed against common side effects in ECT treatment such as cognitive impairment, muscle pain, joint pain, headache and risks associated with general anesthesia. How well patients tolerate and experience both treatments should be assessed systematically in future comparisons.

Another limitation is that the included studies used different ketamine treatment protocols (frequency and total amount of administrations) and ECT treatment differed in terms of frequency (twice vs. thrice weekly), electrode placement (bilateral, bifrontal and unilateral), stimulus width (brief pulse vs. ultra brief pulse), dose determination (1.5 vs 2.5 times seizure threshold) and medication used for anaesthesia, all of which could influence its antidepressant efficacy (Campion, 2015; Hoyer et al., 2014). Relatively low frequency of ketamine infusions, for example once weekly in the study by Allen et al. (Allen et al., 2015), may diminish antidepressant potential of the treatment. After one infusion, the time to relapse is on average one week (Andrade, 2017). A frequency of at least twice a week is probably more sufficient in maintaining the antidepressant efficacy of ketamine. The studies included here treated patients with relatively low levels of treatment resistance (two failed antidepressants) or did not elaborate on treatment resistance level, which makes extrapolation to clinical practice difficult. Future studies

comparing ECT and ketamine need to include TRD patients with high levels of treatment resistance corresponding to levels where ECT is the treatment of choice according to current guidelines. Providing detailed information on prior treatment history and depression severity is essential for proper interpretation of the results.

In addition, a double blind study design does not seem feasible for the comparison of ketamine and ECT, given the nature of these treatments. Three trials used a blind, randomized study design. In the open label and retrospective studies, it seems likely that allocation bias causes differences between the two treatment groups.

Lastly, the included studies differed in terms of in- and exclusion criteria. Including patients with bipolar depression or depression with psychotic symptoms could influence treatment results. Patients with psychotic symptoms were excluded in most studies except in the trial of Sharma et al. (2020), probably because of the risk for exacerbation of psychotic symptoms after ketamine administration (Veraart et al., 2021). ECT however seems to be particularly effective in patients with psychotic depression compared to depression without psychotic symptoms (van Diermen et al., 2018). Investigating differences in the predictive value for response between ketamine and ECT of these patient characteristics may pave the way towards more personalized medicine.

These results emphasize the urgent need for well-powered, randomized, controlled trials comparing ketamine to ECT treatment in patients with depression. Three on-going studies were identified through clinicaltrials.gov. The 'Canadian biomarker integration network in depression' study (CAN-BIND study, ClinicalTrials.gov Identifier: NCT03674671) (Phillips et al., 2020) aims to recruit 240 participants in a randomized, single blinded cross over trial. Patients from the ECT waiting list will be randomized to either 0.5 mg/kg IV ketamine or ECT thrice weekly. A Swedish study (ClinicalTrials.gov Identifier: NCT02659085) titled 'A randomized controlled non-inferiority trial comparing ketamine with ECT in patients with MDD' planned to enroll 198 inpatients with MDD in an open label trial comparing 0.5 mg/kg IV ketamine thrice weekly with ECT. The 'ECT vs. ketamine in patients with TRD' (ELEKT-D study, ClinicalTrials.gov Identifier: NCT03113968) (Mathew et al., 2019) aims to randomize 400 participants in an unblinded study comparing ECT thrice weekly with ketamine 0.5 mg/kg IV (modified if clinically warranted) twice weekly.

In conclusion, the results of trials comparing ketamine treatment with ECT should be interpreted with caution considering the discussed methodological limitations of the studies. Conclusions regarding the antidepressant efficacy, its durability and time to response are pending larger RCTs. Additional information on antidepressant efficacy and predictors of response is necessary, but the potentially more favorable cognitive side effect profile might be a future reason to consider ketamine as a treatment alternative to ECT for patients with depression.

Author statement

Jolien Veraart: conception and design, acquisition, analysis and interpretation of data, drafting, final approval and agreement to be accountable for all aspects of the work.

Sanne Smith-Apeldoorn: acquisition, analysis and interpretation of data, critical revision, final approval and agreement to be accountable for all aspects of the work.

Harm-Pieter Spaans: analysis and interpretation of data, critical revision, final approval and agreement to be accountable for all aspects of the work.

Jeanine Kamphuis: analysis and interpretation of data, critical revision, final approval and agreement to be accountable for all aspects of the work.

Robert Schoevers: analysis and interpretation of data, critical revision, final approval and agreement to be accountable for all aspects of the work.

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